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«ГОМЕЛЬСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ»

Кафедра внутренних болезней № 2 с курсом эндокринологии

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ИЗБРАННЫЕ ВОПРОСЫ ТЕРАПИИ

Учебно-методическое пособие
для студентов 4 курса факультета по подготовке специалистов
для зарубежных стран медицинских вузов

SELECTED TOPICS IN INTERNAL MEDICINE

Teaching workbook for the 4th year students
of the Faculty on preparation of experts for foreign countries
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В учебно-методическом пособии с позиции «доказательной медицины» отражены вопросы этиопатогенеза, алгоритмы диагностики и лечения основных заболеваний внутренних органов, изучаемых студентами 4 курса на цикле «Внутренние болезни».

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CONTENTS

THE LIST OF ABBREVIATIONS

ABU — asymptomatic bacteriuria
ACC — American College of Cardiology
ACE — angiotensin-converting enzyme
ACS — acute coronary syndrome
ACTH — adrenocorticotropic hormone
ADEM — acute disseminated encephalomyelitis
ADH — antidiuretic hormone
ADHF — acute decompensated heart failure
ADP — adenosine diphosphate
ADPKD — autosomal dominant polycystic kidney disease
AED — sautomatic external defibrillators
AF — atrial fibrillation
AHA — American Heart Association
AIP — autoimmune pancreatitis
AIH — autoimmune hepatitis
AKI — acute kidney injury
AKIN — Acute Kidney Injury Network
ALT — alanine aminotransferase
AMA — antimitochondrial antibody
ANA — antinuclear antibodies
ANCA — antineutrophil cytoplasmic antibody
anti-GBM — anti-glomerular basement membrane
ARA — antagonists AT1-receptors for angiotensin II
ARF — acute renal failure
ART — antiretroviral therapy
AST — aspartate aminotransferase
ATM — acute transverse myelitis
ATN — acute tubular necrosis
ATS — american Thoracic Society
apoE — apolipoprotein E
$AT_{1(2)}$ — angiotensin II type 1 (2)
ATP — adenosine triphosphate
BAL — bronchoalveolar lavage
BMI — body mass index
BNP — B-type natriuretic peptide
BPH — benign prostatic hypertrophy
BPP — bacteremic pneumococcal pneumonia
BUN — blood urea nitrogen
CABG — coronary artery bypass grafting
CAD — coronary artery disease
CAP — community-acquired pneumonia
CA-MRSA — community-acquired methicillin-resistant Staphylococcus aureus
CBC — complete blood count
CCK — cholecystokinin

CCK-8 — cholecystokinin-octapeptide
CETP — cholesteryl ester transfer protein
CF — cystic fibrosis
CHD — coronary heart disease
CIF — cotransport inhibitory factor
CKD — chronic kidney disease
CK-MB — creatine kinase MB
CMV — cytomegalovirus
CNS — central nervous system
COPD — chronic obstructive pulmonary disease
COX-2 — cyclooxygenase-2
C(P)-ANCA — cytoplasmic (perinuclear) pattern antineutrophil cytoplasmic antibody
CRF — chronic renal failure
CSF — cerebrospinal fluid
CT — computed tomography
cTnI (T) — cardiac-specific troponin I (T)
CVD — cardiovascular diseases
DIC — disseminated intravascular coagulation
DPT — diphtheria-pertussis-tetanus
DU — duodenal ulcer
EBV — Epstein-Barr virus
ECG — electrocardiogram
EGJ — esophagogastric junction
EGF — epidermal growth factor
ENaC — epithelial sodium channels
ERCP — endoscopic retrograde cholangiopancreatography
ESAs — erythropoiesis-stimulating agents
ESC — European Society of Cardiology
ESKD — end-stage kidney disease
ESRD — end-stage renal disease
ESWL — extracorporeal shockwave lithotripsy
EVCPP — endoventricular circular patch plasty
GBM — glomerular basement membrane
GERD — Gastro Esophageal Reflux Disease
GFR — glomerular filtration rate
GFR — glomerular filtration rate
GI — gastrointestinal
GGT — gamma glutamyltransferase
GN — glomerulonephritis
GRACE — Global Registry of Acute Coronary Events
GSL — glycosphingolipid
GU — gastric ulcer
HAP — hospital-acquired (or nosocomial) pneumonia
HAP — hospital-acquiredpneumonia
HBcAb — hepatitis B core antibody
HBsAb — hepatitis B surface antibody
HbsAg — hepatitis B surface antigen

HbsAg — hepatitis B surface antigen
HBV — hepatitis B virus
HDL — high density lipoprotein
HF — heart failure
HF — heart failure
HFSA — Heart Failure Society of America
H-FABP — heart-type fatty acid binding protein
HHC — hereditary hemochromatosis
HIV — human immunodeficiency virus
HOA — hypertrophic osteoarthropathy
hs-CRP — high sensitive C-reactive protein
HUS — hemolytic-uremic syndrome
ICD — implanted pacemaker or cardiac defibrillator
ICU — intensive care unit
IDL — intermediate density lipoprotein
IDSA — infectious Diseases Society of America
IDU — injection drug users
IHD — ischemic heart disease
IgG (A) — immunoglobulin G (A)
IL — interleukin
IL-8 — interleukin-8
IRAP — idiopathic recurrent acute pancreatitis
KDIGO — Kidney Disease Improving Global Outcomes
KDOQI — Kidney Disease Outcomes Quality Initiative
LCAT — lecithin-cholesterol acyltransferase
LDH — lactate dehydrogenase
LDL — low density lipoprotein
LES — lower esophageal sphincter
LFTs — liver function tests
LKMA — liver-kidney microsomal antibodies
LMWH — low-molecular-weight heparin
LPL — lipoprotein lipase
LPS — lipopolysaccharide
LV — left ventricular
LV — left ventricular
LVADs — left ventricular assist devices
LVEF — left ventricular ejection fraction
LVH — left ventricular hypertrophy
LVH — left ventricular hypertrophy
MALT — mucosa-associated lymphoid tissue
MI — myocardial infarction
MI — myocardial infarction
MPGN — membranoproliferative glomerulonephritis
MPO — myeloperoxidase
MRFIT — Multiple Risk Factor Intervention Trial
MRI — magnetic resonance imaging

MRSA — methicillin-resistant S. aureus
MRCP — magnetic resonance cholangiopancreatography
NASH — non-alcoholic steatohepatitis
NHANES I — First National Health and Nutrition Examination Survey
NKF — National Kidney Foundation
NO — nitric oxide
NOS — nitric oxide synthetase
NP — natriuretic peptide
NPT — nitrite production test
NSAID — snonsteroidal antiinflammatory drugs
NSAID — snonsteroidal anti-inflammatory drugs
NSTEMI — non-ST-segment elevation myocardial infarction
NYHA — New York Heart Association
PAD — peripheral arterial disease
PAF — platelet activating factor
PDT — pathogen-directed treatment
PCI — percutaneous coronary intervention
PCR — polymerase chain reaction
PEI — pancreatic exocrine insufficiency
PET — positron emission tomography
PFTs — pancreatic function tests
PGI2 — prostacyclin
pH_i — intracellular pH
PMN — polymorphonuclear neutrophils
PMNs — polymorphonuclear leukocytes
PRA — plasma renin activity
PSC — primary sclerosing cholangitis
PSGN — poststreptococcal glomerulonephritis
PSI — Pneumonia Severity Index
PSVT — supraventricular tachycardia, or paroxysmal
PTRA — percutaneous transluminal renal angioplasty
PTH — parathyroid hormone
PUD — peptic ulcer disease
RAS — renin-angiotensin system
RBC — red blood cell
RBF — renal blood flow
RIFLE — risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage
SAVER — surgical anterior ventricular endocardial restoration
SBP — spontaneous bacterial peritonitis
SCORE — Systemic Coronary Risk Evaluation
SCr — serum creatinine concentration
SECs — squamous epithelial cells
SLE — systemic lupus erythematosus

SMA — anti-smooth muscle antibodies
SOD — sphincter of Oddi dysfunction
SSA — sulfosalicylic acid
STEMI — ST-segment elevation myocardial infarction
SVT — supraventricular tachycardia, or paroxysmal
TAI — transcatheter arteriography/intervention
TIBC — total iron binding capacity
TIMI — thrombolysis in Myocardial Infarction
TINU — tubulointerstitial nephritis and uveitis
TGF — beta-transforming growth factor beta
TLR4 — toll-like receptor 4
TNFa — tumor necrosis factor alpha
TSH — thyroid stimulating hormone
TTP — thrombotic thrombocytopenic purpura
TxA2 — thromboxane A2
UC — ulcerative colitis
UCr — urine creatinine concentration
UFH — unfractionated heparin
UTI — urinary tract infection
VAP — ventilator-associated pneumonia
VLDL — very low density lipoprotein
VUR — vesicoureteral reflux
WBC — white blood cell
WPW — wolff-Parkinson-White syndrome
XPN — xanthogranulomatous pyelonephritis

INTRODUCTION

Medical practice is rapidly changing. Therefore clinical excellence may be achieved only by means of a constant educational process based on up-to-date scientific data. The cornerstone of the best medical practice is familiarity with current standards based on randomized controlled multicenter clinical trials and meta-analyses (so-called «evidence-based medicine»). For these reasons educational material in this manual was written in accordance with international clinical guidelines and well-recognized databases for medical professionals such as eMedicine, Medscape and UpToDate.

Patient as a central person of any diagnostic or therapeutic intervention must be informed by physician in understandable form about the nature of the procedure and the attendant risks and benefits. Patient informed consent is the base of compliance (adherence to treatment) and the way to success in fight against disease. Only open communication between the physician and the patient or family if he (she) agreed will help to arrange for emotional, physical, and spiritual support to maintain the quality of life even for very sick person. Fundamental principles of medicine must help for the practical doctors to assure the family members that everything possible has been done for the best interests of their sick relative.

This manual is written in accordance with the program of the course in internal diseases for the 4^{th} year medical students studying in Belarus. It focuses on major current problems in cardiology, gastroenterology, pulmonology and nephrology. For complit studing there are lectures and practical classes in clinics.

1. ARTERIAL HYPERTENSION

Definitions and introduction

Arterial hypertension (hypertension or high blood pressure) is a state of permanently elevated arterial blood pressure: systolic (140 mm Hg and above) and/or diastolic (90 mm Hg and above). Hypertension is an independent predisposing factor for heart failure, coronary artery disease, stroke, renal disease, and peripheral arterial disease.

There is one of the leading causes of the global burden of disease. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease, heart failure, ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease.

Medical concepts about the hazards of hypertension have been preoccupied with the diastolic blood pressure component since the beginning of the 20th century. Only lately has the focus shifted to systolic blood pressure and most recently, to pulse pressure. A major impediment to evaluation of the net impact of the components of the blood pressure on the structure and function of the heart and other vital organs is their high correlation with each other. The correlation between systolic blood pressure and pulse pressure is 0.90, making it extremely difficult to statistically dissociate their effects. Also, there appears to be an interaction with age such that diastolic pressure declines in importance as a CHD predictor as age advances, whereas the influence of systolic pressure increases. Recent Framingham Study investigation found that with increasing age there is a shift in importance from diastolic to systolic and finally to pulse pressure for prediction of CHD. From age 60 years on, diastolic pressure is negatively correlated with CHD incidence so that pulse pressure becomes superior to systolic pressure.

In the past it was argued that it was the underlying damaged stiff artery that was directly responsible for the increased CVD found to be associated with isolated systolic hypertension and increased pulse pressure. However, investigation by the Framingham Study many years ago suggested an effect of the systolic and pulse pressure taking arterial compliance into account. Contrary to the fears of many, trials demonstrated that antihypertensive treatment of isolated systolic hypertension actually reduces the risk of CVD, and does so rather promptly. There is mounting evidence supporting the contention that the cardiovascular hazards of hypertension involve large artery stiffness and early wave reflection as well as peripheral resistance. Until very recently the dominant concept of hypertension pathogenesis overemphasized vascular resistance and underestimated the influence of arterial stiffness. Despite the demonstrated efficacy of treating systolic hypertension, the reported poor blood pressure control is overwhelmingly due to failure to control the systolic component.

Classification

According of blood pressure level there are next categories (table 1):

Table 1 — Arterial blood pressure classification

Categories of blood pressure	Systolic blood pressure (mm Hg)	Diastolic blood pressure (mm Hg)	
Optimal	< 120		< 80
Normal	120–129		80–84
High normal	130–139		85–89
First degree hypertension	140–159	and/or	90–99
Second degree hypertension	160–179	and/or	100–109
Third degree hypertension	≥ 180	and/or	≥ 110
Isolated systolic hypertension	≥ 140	and/or	< 90

There are two forms of hypertension: primary (essential) and secondary. Essential hypertension comprises 90–95 % of hypertensive patients and has no clear cause. Secondary hypertension (5 to 10 % of cases of high-blood pressure) can often be a consequence of kidney disease, infectious and endocrine diseases and atherosclerosis.

Causes of secondary hypertension by age:

A. Age under 18 years:

1. Renal parenchymal disease (most common in under age <12 years):
   a. Glomerulonephritis.
   b. Vesicoureteral Reflux Nephropathy.
2. Aortic Coarctation.

B. Age 19 to 39 years:

1. Renal Artery Stenosis due to fibromuscular dysplasia.
2. Thyroid Disease.

C. Age 40 to 64 years:

1. Hyperaldosteronism.
2. Thyroid Disease.
3. Obstructive Sleep Apnea.
4. Cushing Syndrome.
5. Pheochromocytoma.

D. Age over 65 years:

1. Renal Artery Stenosis due to atherosclerotic disease.
2. Chronic Kidney Disease.
3. Hypothyroidism.

Causes: secondary hypertension in adults:

A. Medications

1. NSAIDs, glucocorticoids, adrenomimetics and others.

B. Primary Aldosteronism:

1. Most common treatable secondary cause of Hypertension.
2. Evaluate as cause in Refractory Hypertension where Hypokalemia or borderline low potassium.

C. Renovascular or renal parenchymal disease.
D. Pheochromocytoma.
E. Cushing's Disease.
F. Hyperparathyroidism.
G. Aortic Coarctation.
H. Sleep Apnea.
I. Thyroid Disease:
1. Hyperthyroidism causes systolic Hypertension.
2. Hypothyroidism causes diastolic Hypertension.

Pathophysiology

Cardiac output and peripheral resistance are the two determinants of arterial pressure. Cardiac output is determined by stroke volume and heart rate; stroke volume is related to myocardial contractility and to the size of the vascular compartment. Peripheral resistance is determined by functional and anatomic changes in small arteries and arterioles. Vascular volume is a primary determinant of arterial pressure over the long term. Sodium is predominantly an extracellular ion and is a primary determinant of the extracellular fluid volume. When NaCl intake exceeds the capacity of the kidney to excrete sodium, vascular volume initially expands and cardiac output increases. However, many vascular beds (including kidney and brain) have the capacity to auto regulate blood flow, and if constant blood flow is to be maintained in the face of increased arterial pressure, resistance within that bed must increase. The initial elevation of blood pressure in response to vascular volume expansion may be related to an increase of cardiac output; however, over time, peripheral resistance increases and cardiac output reverts toward normal. The effect of sodium on blood pressure is related to the provision of sodium with chloride; non chloride salts of sodium have little or no effect on blood pressure. As arterial pressure increases in response to a high NaCl intake, urinary sodium excretion increases and sodium balance is maintained at the expense of an increase in arterial pressure. The mechanism for this «pressure-natriuresis» phenomenon may involve a subtle increase in the glomerular filtration rate, decreased absorbing capacity of the renal tubules, and possibly hormonal factors such as atrial natriuretic factor. In individuals with an impaired capacity to excrete sodium, greater increases in arterial pressure are required to achieve natriuresis and sodium balance. NaCl-dependent hypertension may be a consequence of a decreased capacity of the kidney to excrete sodium, due either to intrinsic renal disease or to increased production of a salt-retaining hormone (mineralocorticoid) resulting in increased renal tubular reabsorption of sodium. Renal tubular sodium reabsorption also may be augmented by increased neural activity to the kidney. In each of these situations, a higher arterial pressure may be required to achieve sodium balance. Conversely, salt-wasting disorders are associated with low blood pressure levels. In about 80 % of these patients, vascular volume and hypertension can be controlled with adequate dialysis; in the other 20 %, the mechanism of hypertension is related to increased activity of the renin-angiotensin system and is likely to be responsive to pharmacologic blockade of renin-angiotensin. The autonomic nervous system maintains cardiovascular homeostasis via pressure, volume, and chemoreceptor signals. Adrenergic reflexes modulate blood pressure over the short term, and adrenergic function, in concert with hormonal and volume-related factors, contributes to the long-term regulation of arterial pressure. The three endogenous catechol amines are norepinephrine, epinephrine, and dopamine. All three play important roles in tonic and phasic cardiovascular regulation.

Pheochromocytoma is the most blatant example of hypertension related to increased catecholamine production, in this instance by a tumor. The renin-angiotensin-aldosterone system contributes to the regulation of arterial pressure primarily via the vasoconstrictor properties of angiotensin II and the sodium-retaining properties of aldosterone. Renin is an aspartyl protease that is synthesized as an enzymatically inactive precursor, prorenin. Most renin in the circulation is synthesized in the renal afferent renal arteriole. Prorenin may be secreted directly into the circulation or may be activated within secretory cells and released as active renin. Although human plasma contains two to five times more prorenin than renin, there is no evidence that prorenin contributes to the physiologic activity of this system. Once released into the circulation, active renin cleaves a substrate, angiotensinogen, to form an inactive decapeptide, angiotensin I. A converting enzyme, located primarily but not exclusively in the pulmonary circulation, converts angiotensin I to the active octapeptide, angiotensin II, by releasing the C-terminal histidyl-leucine dipeptide. The same converting enzyme cleaves a number of other peptides, including and thereby inactivating the vasodilator bradykinin. Acting primarily through angiotensin II type 1 (AT_1) receptors on cell membranes, angiotensin II is a potent pressor substance, the primary tropic factor for the secretion of aldosterone by the adrenal zona glomerulosa, and a potent mitogen that stimulates vascular smooth muscle cell and myocyte growth. Independent of its hemodynamic effects, angiotensin II may play a role in the pathogenesis of atherosclerosis through a direct cellular action on the vessel wall. An angiotensin II type 2 (AT_2) receptor has been characterized. It is widely distributed in the kidney and has the opposite functional effects of the AT_1 receptor. The AT_2 receptor induces vasodilation, sodium excretion, and inhibition of cell growth and matrix formation. Experimental evidence suggests that the AT_2 receptor improves vascular remodeling by stimulating smooth muscle cell apoptosis and contributes to the regulation of glomerular filtration rate. AT_1 receptor blockade induces an increase in AT_2 receptor activity. Renin-secreting tumors are clear examples of renin-dependent hypertension. In the kidney, these tumors include benign hemangiopericytomas of the juxtaglomerular apparatus and, infrequently, renal carcinomas, including Wilms' tumors. Renin-producing carcinomas also have been described in lung, liver, pancreas, colon, and adrenals. In these instances, in addition to excision and/or ablation of the tumor, treatment of hypertension includes pharmacologic therapies targeted to inhibit angiotensin II production or action. Renovascular hypertension is another renin-mediated form of hypertension. Obstruction of the renal artery leads to decreased renal perfusion pressure, thereby stimulating renin secretion. Over time, as a consequence of secondary renal damage, this form of hypertension may become less renin dependent. Angiotensinogen, renin, and angiotensin II are also synthesized locally in many tissues, including the brain, pituitary, aorta, arteries, heart, adrenal glands, kidneys, adipocytes, leukocytes, ovaries, testes, uterus, spleen, and skin. Angiotensin II in tissues may be formed by the enzymatic activity of renin or by other proteases, e.g., tonin, chymase, and cathepsins. In addition to regulating local blood flow, tissue angiotensin II is a mitogen that stimulates growth and contributes to modeling and repair. Excess tissue angiotensin II may contribute to atherosclerosis, cardiac hypertrophy, and renal failure and consequently may be a target for pharmacologic therapy to prevent target organ damage. Angiotensin II is the primary tropic factor regulating the synthesis and secretion of aldosterone by the zona glomerulosa of the adrenal cortex. Aldosterone synthesis is also dependent on potassium, and aldosterone secretion may be decreased in potassium-depleted individuals. Although acute elevations of adrenocorticotropic hormone (ACTH) levels also increase aldosterone secretion, ACTH is not an important tropic factor for the chronic regulation of aldosterone.Aldosterone is a potent mineralocorticoid that increases sodium reabsorp-

tion by amiloride-sensitive epithelial sodium channels (ENaC) on the apical surface of the principal cells of the renal cortical collecting duct. Electric neutrality is maintained by exchanging sodium for potassium and hydrogen ions. Consequently, increased aldosterone secretion may result in hypokalemia and alkalosis. Because potassium depletion may inhibit aldosterone synthesis, clinically, hypokalemia should be corrected before a patient is evaluated for hyperaldosteronism. Aldosterone also has effects on nonepithelial targets. Aldosterone and/or mineralocorticoid receptor activation induces structural and functional alterations in the heart, kidney, and blood vessels, leading to myocardial fibrosis, nephrosclerosis, and vascular inflammation and remodeling, perhaps as a consequence of oxidative stress. These effects are amplified by a high salt intake. In animal models, high circulating aldosterone levels stimulate cardiac fibrosis and left ventricular hypertrophy, and spironolactone (an aldosterone antagonist) prevents aldosterone-induced myocardial fibrosis. Pathologic patterns of left ventricular geometry also have been associated with elevations of plasma aldosterone concentration in patients with essential hypertension as well as in patients with primary aldosteronism. In patients with CHF, low-dose spironolactone reduces the risk of progressive heart failure and sudden death from cardiac causes by 30%. Owing to a renal hemodynamic effect, in patients with primary aldosteronism, high circulating levels of aldosterone also may cause glomerular hyperfiltration and albuminuria. These renal effects are reversible after removal of the effects of excess aldosterone by adrenalectomy or spironolactone. Increased activity of the renin-angiotensin-aldosterone axis is not invariably associated with hypertension. In response to a low-NaCl diet or to volume contraction, arterial pressure and volume homeostasis may be maintained by increased activity of the renin-angiotensin-aldosterone axis. Secondary aldosteronism (i.e., increased aldosterone secondary to increased renin-angiotensin), but not hypertension, also is observed in edematous states such as CHF and liver disease.

Several reflexes modulate blood pressure on a minute-to-minute basis. One arterial baroreflex is mediated by stretch-sensitive sensory nerve endings in the carotid sinuses and the aortic arch. The rate of firing of these baroreceptors increases with arterial pressure, and the net effect is a decrease in sympathetic outflow, resulting in decreases in arterial pressure and heart rate. This is a primary mechanism for rapid buffering of acute fluctuations of arterial pressure that may occur during postural changes, behavioral or physiologic stress, and changes in blood volume. However, the activity of the baroreflex declines or adapts to sustained increases in arterial pressure such that the baroreceptors are reset to higher pressures. Patients with autonomic neuropathy and impaired baroreflex function may have extremely labile blood pressures with difficult-to-control episodic blood pressure spikes associated with tachycardia.

Vascular mechanisms: vascular radius and compliance of resistance arteries are also important determinants of arterial pressure. Resistance to flow varies inversely with the fourth power of the radius, and consequently, small decreases in lumen size significantly increase resistance. In hypertensive patients, structural, mechanical, or functional changes may reduce the lumen diameter of small arteries and arterioles. Remodeling refers to geometric alterations in the vessel wall without a change in vessel volume. Hypertrophic (increased cell size, and increased deposition of intercellular matrix) or eutrophic vascular remodeling results in decreased lumen size and hence contributes to increased peripheral resistance. Apoptosis, low-grade inflammation, and vascular fibrosis also contribute to remodeling. Lumen diameter also is related to elasticity of the vessel. Vessels with a high degree of elasticity can accommodate an increase of volume with relatively little change in pressure, whereas in a semi rigid vascular system, a small increment in volume induces a relatively large increment of pressure. Hypertensive patients have stiffer arteries, and arteriosclerotic patients may have particularly high systolic blood pressures and wide pulse pressures as a consequence of decreased vascu-

lar compliance due to structural changes in the vascular wall. Recent evidence suggests that arterial stiffness has independent predictive value for cardiovascular events. Clinically, a number of devices are available to evaluate arterial stiffness or compliance, including ultrasound and magnetic resonance imaging (MRI).Ion transport by vascular smooth muscle cells may contribute to hypertension-associated abnormalities of vascular tone and vascular growth, both of which are modulated by intracellular pH (pH_i). Three ion transport mechanisms participate in the regulation of pH_i: (1) Na^+-H^+ exchange, (2) Na^+-dependent HCO_3^--Cl^- exchange, and (3) cation-independent $HCO_3^-Cl^-$ exchange. Based on measurements in cell types that are more accessible than vascular smooth muscle (e.g., leukocytes, erythrocytes, platelets, skeletal muscle), activity of the Na^+-H^+ exchanger is increased in hypertension, and this may result in increased vascular tone by two mechanisms. First, increased sodium entry may lead to increased vascular tone by activating Na^+-Ca^{2+} exchange and thereby increasing intracellular calcium. Second, increased pH_i enhances calcium sensitivity of the contractile apparatus, leading to an increase in contractility for a given intracellular calcium concentration. Additionally, increased Na^+-H^+ exchange may stimulate growth of vascular smooth muscle cells by enhancing sensitivity to mitogens. Vascular endothelial function also modulates vascular tone. The vascular endothelium synthesizes and releases a spectrum of vasoactive substances, including nitric oxide, a potent vasodilator. Endothelium-dependent vasodilation is impaired in hypertensive patients. This impairment often is assessed with high-resolution ultrasonography before and after the hyperemic phase of reperfusion that follows 5 minutes of forearm ischemia. Alternatively, endothelium-dependent vasodilation may be assessed in response to an intra-arterially infused endothelium-dependent vasodilator, e.g., acetylcholine. Endothelin is a vasoconstrictor peptide produced by the endothelium, and that orally active endothelin antagonists may lower blood pressure in patients with resistant hypertension. Currently, it is not known if the hypertension-related vascular abnormalities of ion transport and endothelial function are primary alterations or secondary consequences of elevated arterial pressure. Limited evidence suggests that vascular compliance and endothelium-dependent vasodilation may be improved by aerobic exercise, weight loss, and antihypertensive agents. It remains to be determined whether these interventions affect arterial structure and stiffness via a blood pressure–independent mechanism and whether different classes of antihypertensive agents preferentially affect vascular structure and function.

Risk Stratification

Prevention of complications by controlling cardio-vascular diseases (CVD) risk factors that accompany elevated blood pressure deserves a high priority because the risk of CVD is greatly influenced by the burden of associated risk factors. Multivariable risk formulations for quantifying the impact of a set of risk factors for development of CVD have been developed from Framingham Study data. The composite risk factor score derived from it corresponds to the probability of an event over 10 years. These estimated event rates when compared with average risk for same-aged persons provide absolute and relative risks. Cardiovascular risk stratification based on systolic and diastolic blood pressure levels, and prevalence of risk factors, asymptomatic organ damage, diabetes, chronic kidney disease stage, or symptomatic cardiovascular disease. The risk stratification presented as low, moderate, high, or very high refers to 10-year risk of CV mortality (absolute risk of dying from CVD within 10 years). According to US Joint National Committee (JNC) there are next groups of Cardiovascular Risk.

Risk Group A: Low Cardiovascular Risk

A. Criteria:

1. No Cardiovascular Risks (See Risk Group B).
2. No Target organ damage or Cardiovascular Disease.

B. Prehypertension (120-139 / 80-89):

1. Lifestyle Modification in Hypertension.

C. Stage 1 Hypertension (140-159 / 90-99):

1. Lifestyle Modification in Hypertension.
2. Consider Antihypertensive after up to 6–12 months:
   a. Hydrochlorothiazide — first choice in most patients.

D. Stage 2 Hypertension or greater (>159/99):

1. Lifestyle Modification in Hypertension.
2. Hypertension Combination Therapy.

Risk Group B: Moderate Cardiovascular Risk

A. Criteria:

1. Tobacco Abuse.
2. Dyslipidemia.
3. Renal Insufficiency.
4. Patient age over 60 years.
5. Male gender of postmenopausal women.
6. Cardiovascular Family History.
7. No Diabetes Mellitus.
8. No Target organ damage or Cardiovascular Disease.

B. Prehypertension (120-139 / 80-89):

1. Lifestyle Modification in Hypertension.

C. Stage 1 Hypertension (140-159 / 90-99):

1. Lifestyle Modification in Hypertension.
2. Antihypertensive (e.g. Hydrochlorothiazide).

D. Stage 2 Hypertension or greater (>159/99):

1. Lifestyle Modification in Hypertension.
2. Hypertension Combination Therapy.

Risk Group C: High Cardiovascular Risk

A. Criteria:

1. Target organ damage or Cardiovascular Disease:
   a. Left Ventricular Hypertrophy.
   b. Angina or prior Myocardial Infarction.
   c. Prior coronary revascularization.
   d. Cerebrovascular Accident (Stroke or CVA).
   e. Transient Ischemic Attack (TIA).

f. Nephropathy or Chronic Kidney Disease.
g. Peripheral Vascular Disease.
h. Retinopathy.
2. Cardiovascular Risks (See Risk Group B)

B. Prehypertension (120-139 / 80-89) or greater:

1. Lifestyle Modification in Hypertension.
2. Antihypertensive.
3. Hypertension Combination Therapy if > 20/10 over goal.

Management

A critical step in preventing and treating high blood pressure is a healthy lifestyle. You can lower your blood pressure with the following lifestyle changes:

- Losing weight if you are overweight or obese.
- Quitting smoking.
- Eating a healthy diet, including the DASH diet (eating more fruits, vegetables, and low fat dairy products, less saturated and total fat).
- Reducing the amount of sodium in your diet to less than 1,500 milligrams a day if you have high blood pressure. Healthy adults should try to limit their sodium intake to no more 2,300 milligrams a day (about 1 teaspoon of salt).
- Getting regular aerobic exercise (such as brisk walking at least 30 minutes a day, several days a week).
- Limiting alcohol to two drinks a day for men, one drink a day for women.

In addition to lowering blood pressure, these measures enhance the effectiveness of high blood pressure drugs.

If such changings of life style do not give normalization of blood pressure or risc is hight, it is nessessary to start with drugs to treat high blood pressure. There are several types of drugs used to treat high blood pressure, including:

- Angiotensin-converting enzyme (ACE) inhibitors. These medications help relax blood vessels by blocking the formation of a natural chemical that narrows blood vessels. People with chronic kidney disease may benefit from ACE inhibitors as one of their medications.
- Angiotensin II receptor blockers (ARBs). These medications help relax blood vessels by blocking the action, not the formation, of a natural chemical that narrows blood vessels. People with chronic kidney disease may benefit from ARBs as one of their medications.
- Calcium channel blockers. These medications help relax the muscles of your blood vessels. Some slow your heart rate. Calcium channel blockers may work better for older people and blacks than do ACE inhibitors alone.
- Thiazide (hydrochlorthiazide) and thiazide-like diuretics (chlorthalidone or indapamide). Diuretics, sometimes called water pills, are medications that act on your kidneys to help your body eliminate sodium and water, reducing blood volume.

• Beta adrenoblockers. Today this group is the fifth of choice. These medications reduce the workload on heart – prolonged diastolic period (rest and blood circulation of the heart), causing heart to beat slower and with less force.

• Alpha adrenoblockers. These medications reduce nerve impulses to blood vessels, reducing the effects of natural chemicals that narrow blood vessels.

• Alpha-beta blockers. In addition to reducing nerve impulses to blood vessels, alpha-beta blockers slow the heartbeat to reduce the amount of blood that must be pumped through the vessels.

• Central-acting agents. These medications prevent brain from signaling nervous system to increase heart rate and narrow blood vessels.

• Vasodilators. These medications work directly on the muscles in the walls of arteries.

• Aldosterone antagonists. Examples are spironolactone and eplerenone. These drugs block the effect of a natural chemical that can lead to salt and fluid retention, which can contribute to high blood pressure.

• One medicine can reduce high blood pressure (hypertension) to the target level in less than half of cases. It is common to need two or more different medicines to reduce high blood pressure to a target level. In about a third of cases, three medicines or more are needed to get blood pressure to the target level. True combination medications are usually one pill that contains two types of prescription medication. This can be beneficial because it's easier to remember to take one pill instead of two, and some medications are less expensive when combined into a single drug.

Recommendations for Management of Hypertension, 2014. Evidence-Based Guideline for the Management of High Blood Pressure in Adults — Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8):

• Recommendation 1:

— In the general population aged ≥60 years, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) ≥ 150 mm Hg or diastolic blood pressure (DBP) ≥ 90 mm Hg and treat to a goal SBP < 150 mm Hg and goal DBP < 90 mm Hg. (Strong Recommendation — Grade A).

• Corollary Recommendation:

— In the general population aged ≥ 60 years, if pharmacologic treatment for high BP results in lower achieved SBP (eg, < 140 mm Hg) and treatment is well tolerated and without adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert Opinion — Grade E)

• Recommendation 2:

— In the general population < 60 years, initiate pharmacologic treatment to lower BP at DBP ≥ 90 mm Hg and treat to a goal DBP < 90 mm Hg. (For ages 30–59 years, Strong Recommendation — Grade A; For ages 18–29 years, Expert Opinion — Grade E).

• Recommendation 3:

— In the general population < 60 years, initiate pharmacologic treatment to lower BP at SBP ≥ 140 mm Hg and treat to a goal SBP < 140 mm Hg. (Expert Opinion — Grade E).

• Recommendation 4:

— In the population aged ≥ 18 years with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg and treat to goal SBP < 140 mm Hg and goal DBP < 90 mm Hg. (Expert Opinion — Grade E).

• Recommendation 5:

— In the population aged ≥ 18 years with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg and treat to a goal SBP < 140 mm Hg and goal DBP < 90 mm Hg. (Expert Opinion — Grade E).

• Recommendation 6:

— In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation — Grade B).

• Recommendation 7:

— In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (For general black population: Moderate Recommendation — Grade B; for black patients with diabetes: Weak Recommendation — Grade C).

• Recommendation 8:

— In the population aged ≥ 18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. (Moderate Recommendation — Grade B).

• Recommendation 9:

— The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an ACEI and an ARB together in the same patient. If goal BP cannot be reached using only the drugs in recommendation 6 because of a contraindication or the need to use more than 3 drugs to reach goal BP, antihypertensive drugs from other classes can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed. (Expert Opinion — Grade E).

2. ATHEROSCLEROSIS AND ANGINA PECTORIS

Definitions and introduction

Cardiovascular diseases (CVD) includes four major areas:

• Coronary heart disease (CHD) manifested by sudden cardiac death, angina pectoris, myocardial infarction (MI) and post-MI cardio sclerosis, heart failure (HF), and arrhythmias. The prevalence of coronary artery disease (CAD)(synonym — coronary heart disease — CHD) is approximately one-third to one-half that of total CVD. General principle — atherosclerosis must be responsible for practically all cases of ischemic heart disease (IHD).

- Cerebrovascular disease manifested by stroke and transient ischemic attack.
- Peripheral arterial disease manifested by intermittent claudication.
- Aortic atherosclerosis and thoracic or abdominal aortic aneurysm.

Last three so-called «noncoronary athery atherosclerosis».

Many of the important risk factors for cardiovascular disease are modifiable by specific preventive measures. These included smoking, dyslipidemia, arterial hypertension, diabetes, abdominal obesity, stressed psychosocial factors, low daily consumption of fruits and vegetables, regular alcohol consumption in high doses, and low level of physical activity. Female sex and old age (include posmenopausalperiod for women), family history of CHD in young agesare not prevented cardiovascular risk factors promote coronary disease.Individual prognostic risk factors may be count by SCORE tables (Systemic Coronary Risk Evaluation).

Atherosclerosis is a disease of large and medium-sized muscular arteries and is characterized by the following:

- Endothelial dysfunction: several studies have found that coronary artery endothelial dysfunction and increased vascular oxidative stress predict long-term progression of atherosclerosis and an increased incidence of cardiovascular events. Endothelium-derived relaxing factor, a thiolated form of nitric oxide (NO) is the most potent vasodilator.
- Vascular inflammation.
- Buildup of lipids, cholesterol, calcium, and cellular debris within the intima of the vessel wall.

The classification of lipoproteins

There are five major lipoproteins, each of which has a different function:

Chylomicrons are very large particles that carry dietary lipid. They are associated with a variety of apolipoproteins, including A-I, A-II, A-IV, B-48, C-I, C-II, C-III, and E.

Very low density lipoprotein (VLDL) carries endogenous triglycerides and to a lesser degree cholesterol. The major apolipoproteins associated with VLDL are B-100, C-I, C-II, C-III, and E.

Intermediate density lipoprotein (IDL) carries cholesterol esters and triglycerides. It is associated with apolipoproteins B-100, C-III, and E.

Low density lipoprotein (LDL) carries cholesterol esters and is associated with apolipoprotein B-100.

High density lipoprotein — High density lipoprotein (HDL) also carries cholesterol esters. It is associated with apolipoproteins A-I, A-II, C-I, C-II, C-III, D, and E.

Apolipoproteins — Understanding the major functions of the different apolipoproteins is important clinically, because defects in apolipoprotein metabolism lead to abnormalities in lipid handling.

The assembly and secretion of apolipoprotein B containing lipoproteins in the liver and intestines is dependent upon microsomal triglyceride transfer protein which transfers lipids to apolipoprotein B. In one study, apolipoprotein B and microsomal transfer protein genes were expressed in the human heart, strongly suggesting that the heart synthesizes and secretes apolipoprotein B containing lipoproteins. This may represent a pathway of «reverse triglyceride transport» by which the cardiac myocytes can unload surplus fatty acids not required for fuel.

A-I — Structural protein for HDL; activator of lecithin-cholesterol acyltransferase (LCAT).

A-II — Structural protein for HDL; activator of hepatic lipase.

A-IV — Activator of lipoprotein lipase (LPL) and LCAT.

B-100 — Structural protein for VLDL, IDL, LDL, and Lp(a); ligand for the LDL receptor; required for assembly and secretion of VLDL.

B-48 — Contains 48 percent of B-100; required for assembly and secretion of chylomicrons; does not bind to LDL receptor.

C-I — Activator of LCAT.

C-II — Essential cofactor for LPL.

C-III — Interferes with apo-E mediated clearance of triglyceride-enriched lipoproteins by cellular receptors; inhibits triglyceride hydrolysis by lipoprotein lipase and hepatic lipase; interferes with normal endothelial function.

D — May be a cofactor for cholesteryl ester transfer protein (CETP).

E — Ligand for hepatic chylomicron and VLDL remnant receptor, leading to clearance of these lipoproteins from the circulation; ligand for LDL receptor. There are three different apo E alleles in humans: E2, which has cysteine residues at positions 112 and 158; E3, which occurs in 60 to 80 percent of Caucasians and has cysteine at position 112 and arginine at position 158; and E4, which has arginine residues at positions 112 and 158. These alleles encode for a combination of apo E isoforms that are inherited in a codominant fashion. Compared to apo E3, apo E2 has reduced affinity and apo E4 has enhanced affinity for the LDL (apo B/E) receptor. These isoforms are important clinically because apo E2 is associated with familial dysbetalipoproteinemia (due to less efficient clearance of VLDL and chylomicrons) and apo E4 is associated with an increased risk of hypercholesterolemia and coronary heart disease(CHD). Apo(a) — Structural protein for Lp(a); inhibitor of plasminogen activation on Lp(a).

Clinical classification of dyslipidemias

The major classes of dyslipidemia are classified according to the Fredrickson phenotype:

- Fredrickson phenotype I — serum concentration of chylomicrons elevated; triglycerides concentrations are elevated to > 99th percentile.
- Fredrickson phenotype IIa — serum concentration of LDL cholesterol elevated; the total cholesterol concentration is > 90th percentile. Concentrations of triglyceride and/or apolipoprotein B may also be ≥ 90th percentile.
- Fredrickson phenotype IIb — serum concentrations of LDL and VLDL cholesterol elevated; total cholesterol and/or triglycerides may be ≥ 90th percentile and apolipoprotein B ≥ 90th percentile.
- Fredrickson phenotype III — serum concentration of VLDL remnants and chylomicrons elevated; total cholesterol and triglycerides > 90th percentile.
- Fredrickson phenotype IV — serum concentrations of VLDL elevated; total cholesterol may be > 90th percentile and may also see triglyceride concentrations > 90th percentile or low HDL.
- Fredrickson phenotype V — elevated serum concentrations of chylomicrons and VLDL; triglycerides > 99th percentile.

The following lipid and lipoprotein abnormalities are associated with increased coronary risk:

- Elevated total cholesterol and elevated LDL-cholesterol.

- Low HDL-cholesterol.
- Increased total-to-HDL-cholesterol ratio.
- Hypertriglyceridemia.
- Increased non-HDL-cholesterol.
- Increased Lp(a).
- Increased apolipoprotein B.
- Small, dense LDL particles.
- Different genotypes of apolipoprotein E (apoE) influence cholesterol and triglyceride levels as well as the risk of CHD.

Atherosclerotic process starts with fatty streaks that are first seen in adolescence; these lesions progress into plaques in early adulthood, and culminate in thrombotic occlusions and coronary events in middle age and later life. Atherosclerotic buildup results in the following:

- Plaque formation.
- Vascular remodeling.
- Acute (unstable plaque) and chronic (stable plaque) luminal obstruction.
- Abnormalities of blood flow.
- Diminished oxygen supply to target organs.

The signs and symptoms of noncoronary atherosclerosis are highly variable. Patients with mild atherosclerosis may present with clinically important symptoms and signs of disease. However, many patients with anatomically advanced disease may have no symptoms and experience no functional impairment. Signs and symptoms of noncoronary atherosclerosis that affect different organ systems include the following:

- Central nervous system: Stroke, reversible ischemic neurologic deficit, transient ischemic attack.
- Peripheral vascular system: Intermittent claudication, impotence, nonhealing ulceration and infection of the extremities.
- Gastrointestinal vascular system: Mesenteric angina characterized by epigastric or periumbilical postprandial pain–may be associated with hematemesis, hematochezia, melena, diarrhea, nutritional deficiencies, and weight loss; abdominal aortic aneurysm that is typically asymptomatic (sometimes pulsatile) until the dramatic, and often fatal, signs and symptoms of rupture.
- Target organ failure: Occult or symptomatic visceral ischemia.

Diagnosis

Examination findings of noncoronary atherosclerosis are highly variable but may provide objective evidence of extracellular lipid deposition, stenosis or dilatation of large muscular arteries, or target organ ischemia or infarction, such as the following:

- Hyperlipidemia: Xanthelasma and tendon xanthomata.
- Cerebrovascular disease: Diminished carotid pulses, carotid artery bruits, and focal neurologic deficits.

• Peripheral vascular disease: Decreased peripheral pulses, peripheral arterial bruits, pallor, peripheral cyanosis, gangrene, and ulceration.

• Abdominal aortic aneurysm: Pulsatile abdominal mass, peripheral embolism, and circulatory collapse.

• Atheroembolism: Livedo reticularis, gangrene, cyanosis, ulceration, digital necrosis, GI bleeding, retinal ischemia, cerebral infarction, and renal failure.

Laboratory testing:

• Lipid profile.

• Blood glucose and hemoglobin A1c.

Imaging studies:

• Ultrasonography: For evaluating brachial artery reactivity and carotid artery intima-media thickness (measures of vessel wall function and anatomy, respectively).

• Artherio(aorto) — contrast radiography.

• Intravascular ultrasonography: Generally considered the criterion standard for the anatomic study of the vessel wall (provides images of the thickness and the acoustic density of the vessel wall).

• Magnetic resonance imaging.

• Nuclear perfusion imaging with single-photon emission computed tomography (SPECT) scanning or positron emission tomography (PET) scanning.

Management

The prevention and treatment of all localization atherosclerosis require risk factor control, including the medical management of hypertension, hyperlipidemia and dyslipidemia, diabetes mellitus, and cigarette habituation.

Pharmacotherapy: the following medications may be used in the management of noncoronary atherosclerosis:

• HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme) reductase inhibitors (eg, pravastatin, simvastatin, lovastatin, fluvastatin, atorvastatin, rosuvastatin, pitavastatin).

• Fibric acid derivatives (eg, fenofibrate).

• Omega-3 polyunsaturated fatty acids.

• In case of familial hypercholesterolemia treatment options include combination drug therapy, although drug therapy alone often is inadequate because of the relative or absolute deficiency of hepatic LDL receptors. Lipid apheresis is an effective means of reducing circulating lipid levels. Liver transplantation has been performed on young patients with severe disease.

Instrumental and surgical treatment:

• Endoarterioectomy and tromboextraction.

• Artery bypass grafting (ABG) and shunting.

• Artery plastic and stenting.

• Resection and plastic of aortic aneurism.

• Occlusion of arterial aneurism.

Initially thought to be a chronic, slowly progressive, degenerative disease, atherosclerosis is a disorder with periods of activity and quiescence. Coronary artery calcification detected by computed tomography can be used to quantify the amount of calcium present in the coronary arteries of a given patient. The coronary calcium score correlates with the risk of cardiovascular events in both asymptomatic and symptomatic patients.The prognosis in patients with atherosclerosis depends on the following factors:

- Presence of inducible ischemia.
- Left ventricular function.
- Presence of arrhythmias.
- Revascularization potential (complete vs incomplete).
- Aggressiveness of risk alteration.
- Compliance with medical therapy.

The prognosis of atherosclerosis also depends on systemic burden of disease, the vascular bed(s) involved, and the degree of flow limitation. Wide variability is noted, and clinicians appreciate that many patients with critical limitation of flow to vital organs may survive many years, despite a heavy burden of disease. Conversely, MI or sudden cardiac death may be the first clinical manifestation of atherosclerotic cardiovascular disease in a patient who is otherwise asymptomatic with minimal luminal stenosis and a light burden of disease. Much of this phenotypic variability is likely to be determined by the relative stability of the vascular plaque burden. Plaque rupture and exposure of the thrombogenic lipid core are critical events in the expression of this disease process and determine the prognosis. The ability to determine and quantify risk and prognosis in patients with atherosclerosis is limited by the inability to objectively measure plaque stability and other predictors of clinical events.

Angina pectoris is the result of myocardial ischemia caused by an imbalance between myocardial blood supply and oxygen demand. It is a common presenting symptom, typically — retrosternal chest pain or discomfort (pressure, heaviness, squeezing, burning, or choking sensation). In some casespain localized primarily in the epigastrium, back, neck, jaw, or shoulders (so-called «atypical forms of angina pectoris»). Pain precipitated by exertion, eating, exposure to could, or emotional stress, lasting for about 1–5 minutes and relieved by rest or nitroglycerin. Pain intensity that does not change with respiration, cough, or change in position. Angina decubitus (a variant of angina pectoris that occurs at night while the patient is recumbent) may occur.Coronary spasm can also reduce blood flow through the coronary arteries. Prinzmetal angina is defined as resting angina associated with ST-segment elevation caused by focal coronary artery spasm. Although most patients with Prinzmetal angina have underlying fixed coronary lesions, some have angiographically normal coronary arteries. Several mechanisms have been proposed for Prinzmetal angina: focal deficiency of nitric oxide production, hyperinsulinemia, low intracellular magnesium levels, smoking cigarettes, and using cocaine.

Ambulatory ECG monitoring has shown that silent ischemia is a common phenomenon among patients with established coronary artery disease. The exact mechanism(s) for silent ischemia is not known. However, autonomic dysfunction (especially in patients with diabetes), a higher pain threshold in some individuals, and the production of excessive quantities of endorphins are among the more popular hypotheses.

The syndrome that includes angina pectoris, ischemialike ST-segment changes on ECG and/or myocardial perfusion defects during stress testing, and angiographically normal coronary arteries is referred to as syndrome X. Most patients with this syndrome are postmenopausal women, and they usually have an excellent prognosis. Syndrome X is believed to be caused by microvascular angina. Multiple mechanisms may be responsible for this syndrome, including impaired endothelial dysfunction, increased release of local vasoconstrictors, fibrosis and medial hypertrophy of the microcirculation, abnormal cardiac adrenergic nerve function, and/or estrogen deficiency.

Myocardial ischemia can also be the result of factors affecting blood composition, such as reduced oxygen-carrying capacity of blood, as is observed with severe anemia, or elevated levels of carboxyhemoglobin. The latter may be the result of inhalation of carbon monoxide in a closed area or of long-term smoking.

For most patients with stable angina, physical examination findings are normal. A positive Levine sign suggests angina pectoris.

According to Canadian Cardiovascular Society there are four functional classes of stable angina pectoris (table 2).

Table 2 — Classification of angina severity according to the Canadian Cardiovascular Society

Class	Level of symptoms
I	'Ordinary activity does not cause angina'
	Angina with strenuous or rapid or prolonged exertion only
II	'Slight limitation of ordinary activity'
	Angina on walking or climbing stairs rapidly, walking uphill or exertion after meals, in cold weather, when under emotional stress, or only during the first few hours after awakening
III	'Marked limitation of ordinary physical activity'
	Angina on walking one or two blocks on the level or one flight of stairs at a normal pace under normal conditions (equivalent to 100–200 m.)
IV	'Inability to carry out any physical activity without discomfort' or 'angina at rest'

Diagnosis of angina pectoris

Laboratory tests:

- Complete blood count (CBC).
- Chemistry panel with lipid profile.
- Blood glucose and hemoglobin A_{1C} (HbA_{1C}) measurement: appropriate in patients with diabetes mellitus.
- C-reactive protein level.
- Serum markers of biomarkers of cardiomyocyte injury.

Instrumental studies:

- ECG (including exercise with ECG monitoring and ambulatory ECG monitoring).
- Echocardiography.

- Velocity probes.
- Coronary angiography.
- Chest radiography, X-ray and nuclear imaging: computed tomography, magnetic resonance tomography, SPECT, PET etc.

Management of angina pectoris

Life style changing:

- Encouragement of smoking cessation
- Treatment of risk factors (eg, arterial hypertension, diabetes mellitus, obesity, hyperlipidemia)

Pharmacologic therapy:

- Treatment of dyslipidemia.
- Nitrates.
- Beta blockers.
- Calcium channel blockers.
- Ivabradin.
- Antiplatelet agents for acute coronary events: aspirin, clopidogrel, glycoprotein IIb/IIIa inhibitors.
- Other Therapies.

Nitrates: the organic nitrates are a valuable class of drugs in the management of angina pectoris. Their major mechanisms of action include systemic venodilation with concomitant reduction in left ventricular end-diastolic volume and pressure, thereby reducing myocardial wall tension and oxygen requirements; dilation of epicardial coronary vessels; and increased blood flow in collateral vessels. When metabolized, organic nitrates release nitric oxide (NO) that binds to guanylyl cyclase in vascular smooth muscle cells, leading to an increase in cyclic guanosine monophosphate, which causes relaxation of vascular smooth muscle. Nitrates also exert antithrombotic activity by NO-dependent activation of platelet guanylyl cyclase, impairment of intraplatelet calcium flux, and platelet activation.The absorption of these agents is most rapid and complete through the mucous membranes. For this reason, nitroglycerin is most commonly administered sublingually in tablets of 0.4 or 0.6 mg. Patients with angina should be instructed to take the medication both to relieve angina and also approximately 5 min before stress that is likely to induce an episode. The value of this prophylactic use of the drug cannot be overemphasized.Nitrates improve exercise tolerance in patients with chronic angina and relieve ischemia in patients with unstable angina as well as patients with Prinzmetal's variant angina. A diary of angina and nitroglycerin use may be valuable for detecting changes in the frequency, severity, or threshold for discomfort that may signify the development of unstable angina pectoris and/or herald an impending myocardial infarction.

Long-Acting Nitrates: none of the long-acting nitrates are as effective as sublingual nitroglycerin for the acute relief of angina. These organic nitrate preparations can be swallowed, chewed, or administered as a patch or paste by the transdermal route. They can provide effective plasma levels for up to 24 h, but the therapeutic response is highly variable. Different preparations and/or administration during the daytime should be tried only to prevent discomfort while avoiding side effects such as headache and dizziness. Individual dose titration is important to prevent side effects. To minimize the effects of tolerance, the minimum effective dose should be used and a minimum of 8 h each day kept free of the drug to restore any useful response(s).

Beta-Adrenergic Blockers: these drugs represent an important component of the pharmacologic treatment of angina pectoris. They reduce myocardial oxygen demand by inhibiting the increases in heart rate, arterial pressure, and myocardial contractility caused by adrenergic activation. Beta blockade reduces these variables most strikingly during exercise but causes only small reductions at rest. Long-acting beta-blocking drugs or sustained-release formulations offer the advantage of once-daily dosing. The therapeutic aims include relief of angina and ischemia. These drugs also can reduce mortality and reinfarction rates in patients after myocardial infarction and are moderately effective antihypertensive agents.Relative contraindications include asthma and reversible airway obstruction in patients with chronic lung disease, atrioventricular conduction disturbances, severe bradycardia, Raynaud's phenomenon, and a history of mental depression. Side effects include fatigue, reduced exercise tolerance, nightmares, impotence, cold extremities, intermittent claudication, bradycardia (sometimes severe), impaired atrioventricular conduction, left ventricular failure, bronchial asthma, worsening claudication, and intensification of the hypoglycemia produced by oral hypoglycemic agents and insulin. Reducing the dose or even discontinuation may be necessary if these side effects develop and persist. Since sudden discontinuation can intensify ischemia, the doses should be tapered over 2 weeks. Beta blockers with relative $Beta_1$-receptor specificity such as metoprolol and atenolol may be preferable in patients with mild bronchial obstruction and insulin-requiring diabetes mellitus.

Calcium Channel Blockers: calcium channel blockers are coronary vasodilators that produce variable and dose-dependent reductions in myocardial oxygen demand, contractility, and arterial pressure. These combined pharmacologic effects are advantageous and make these agents as effective as beta blockers in the treatment of angina pectoris. They are indicated when beta blockers are contraindicated, poorly tolerated, or ineffective. Verapamil and diltiazem may produce symptomatic disturbances in cardiac conduction and bradyarrhythmias. They also exert negative inotropic actions and are more likely to aggravate left ventricular failure, particularly when used in patients with left ventricular dysfunction, especially if the patients are also receiving beta blockers. Although useful effects usually are achieved when calcium channel blockers are combined with beta blockers and nitrates, individual titration of the doses is essential with these combinations. Variant (Prinzmetal's) angina responds particularly well to calcium channel blockers (especially members of the dihydropyridine class), supplemented when necessary by nitrates.Verapamil ordinarily should not be combined with beta blockers because of the combined adverse effects on heart rate and contractility. Diltiazem can be combined with beta blockers in patients with normal ventricular function and no conduction disturbances. Amlodipine and beta blockers have complementary actions on coronary blood supply and myocardial oxygen demands. Whereas the former decreases blood pressure and dilates coronary arteries, the latter slows heart rate and decreases contractility. Amlodipine and the other second-generation dihydropyridine calcium antagonists (nicardipine, isradipine, long-acting nifedipine, and felodipine) are potent vasodilators and are useful in the simultaneous treatment of angina and hypertension. Short-acting dihydropyridines should be avoided because of the risk of precipitating infarction, particularly in the absence of concomitant beta-blocker therapy.

Antiplatelet Drugs: aspirin is an irreversible inhibitor of platelet cyclooxygenase and thereby interferes with platelet activation. Chronic administration of 75–325 mg orally per day has been shown to reduce coronary events in asymptomatic adult men over age 50, patients with chronic stable angina, and patients who have or have survived unstable angina and myocardial infarction. There is a dose-dependent increase in bleeding when aspirin is used chronically. It is preferable to use an enteric-coated formulation in the range of 81–162 mg/d. Administration of this drug should be considered in all patients with IHD in the absence of ga-

strointestinal bleeding, allergy, or dyspepsia. Clopidogrel (300–600 mg loading and 75 mg/d) is an oral agent that blocks P2Y12 ADP receptor–mediated platelet aggregation. It provides benefits similar to those of aspirin in patients with stable chronic IHD and may be substituted for aspirin if aspirin causes the side effects listed above. Clopidogrel combined with aspirin reduces death and coronary ischemic events in patients with an acute coronary syndrome and also reduces the risk of thrombus formation in patients undergoing implantation of a stent in a coronary artery. Alternative antiplatelet agents that block the P2Y12 platelet receptor such as prasugrel have been shown to be more effective than clopidogrel for prevention of ischemic events after placement of a stent for an acute coronary syndrome but are associated with an increased risk of bleeding. Although combined treatment with clopidogrel and aspirin for at least a year is recommended in patients with an acute coronary syndrome treated with implantation of a drug-eluting stent, studies have not shown any benefit from the routine addition of clopidogrel to aspirin in patients with chronic stable IHD.

Other Therapies: The angiotensin-converting enzyme (ACE) inhibitors are widely used in the treatment of survivors of myocardial infarction, patients with hypertension or chronic IHD including angina pectoris, and those at high risk of vascular diseases such as diabetes. The benefits of ACE inhibitors are most evident in IHD patients at increased risk, especially if diabetes mellitus or LV dysfunction is present, and those who have not achieved adequate control of blood pressure and LDL cholesterol on beta blockers and statins. However, the routine administration of ACE inhibitors to IHD patients who have normal LV function and have achieved blood pressure and LDL goals on other therapies does not reduce the incidence of events and therefore is not cost-effective. Despite treatment with nitrates, beta blockers, or calcium channel blockers, some patients with IHD continue to experience angina, and additional medical therapy is now available to alleviate their symptoms. Ranolazine, a piperazine derivative, may be useful for patients with chronic angina despite standard medical therapy. Its antianginal action is believed to occur via inhibition of the late inward sodium current (I_{Na}). The benefits of I_{Na} inhibition include limitation of the Na overload of ischemic myocytes and prevention of Ca^{2+} overload via the Na^{+}–Ca^{2+} exchanger. A dose of 500–1000 mg orally twice daily is usually well tolerated. Ranolazine is contraindicated in patients with hepatic impairment or with conditions or drugs associated with QT_c prolongation and when drugs that inhibit the CYP3A metabolic system (e.g., ketoconazole, diltiazem, verapamil, macrolide antibiotics, HIVprotease inhibitors, and large quantities of grapefruit juice) are being used.Another class of agents open ATP-sensitive potassium channels in myocytes, leading to a reduction of free intracellular calcium ions. The major drug in this class is nicorandil, which typically is administered orally in a dose of 20 mg twice daily for prevention of angina.

Instrumental and surgical treatment:

- Coronary artery bypass grafting (CABG).
- Percutaneous coronary intervention (PCI).
- Combination of CABG and PCI.

Revascularization therapy (ie, coronary revascularization) can be considered in the following:

- Patients with left main artery stenosis greater than 50 %.
- Patients with 2- or 3-vessel disease and left ventricular (LV) dysfunction.
- Patients with poor prognostic signs during noninvasive studies.
- Patients with severe symptoms despite maximum medical therapy.

3. ACUTE CORONARY SYNDROME

Definitions and introduction

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to presentations found in non-ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina. Most cases of ACS occur from disruption of a previously non severe lesion (an atherosclerotic lesion that was previously hemodynamically insignificant yet vulnerable to rupture). The vulnerable plaque is typified by a large lipid pool, numerous inflammatory cells, and a thin, fibrous cap. Elevated demand can produce ACS in the presence of a high-grade fixed coronary obstruction, due to increased myocardial oxygen and nutrition requirements, such as those resulting from exertion, emotional stress, or physiologic stress (eg, from dehydration, blood loss, hypotension, infection, thyrotoxicosis, or surgery). ACS without elevation in demand requires a new impairment in supply, typically due to thrombosis and/or plaque hemorrhage. The major trigger for coronary thrombosis is considered to be plaque rupture caused by the dissolution of the fibrous cap, the dissolution itself being the result of the release of metalloproteinases (collagenases) from activated inflammatory cells. This event is followed by platelet activation and aggregation, activation of the coagulation pathway, and vasoconstriction.

The role of platelets in ACS: platelets play an important role in cardiovascular disease both in the pathogenesis of atherosclerosis and in the development of acute thrombotic events. Their importance in coronary disease and in acute coronary syndromes is indirectly confirmed by the benefit of antiplatelet agents (particularly aspirin, clopidogrel, and the glycoprotein IIb/IIIa inhibitors) in these disorders. Both superficial and deep intimal injury disrupt the intact endothelium, which normally prevents the adherence of platelets by the production of the antiplatelet agents nitric oxide and prostacyclin. Disruption of the endothelium also exposes collagen. These factors lead to the adherence of platelets to the subendothelium, both directly and via von Willebrand factor, and, subsequently, to platelet activation. Platelet adhesion is mediated by the binding of platelet receptors to a number of arterial wall receptors, including subendothelial collagen (whose corresponding platelet receptor is Gp Ia/IIa), von Willebrand factor (Gp Ib/IX and Gp IIb/III), and fibrinogen (Gp IIb/IIIa). Binding of platelets to these structural proteins in concert with the action of soluble receptor-mediated stimulants, such as thrombin, adenosine diphosphate (ADP), and thromboxane A2 (TxA2), induces platelet activation. This process involves the mobilization of calcium from intracellular stores, the activation of several intracellular kinases, and the release of arachidonic acid from membrane phospholipids, resulting in the generation of TxA2. Platelet activation produced in vivo is enhanced by circulating catecholamines. Platelet aggregation results from conversion of the IIb/IIIa receptor to a form that can bind adhesive proteins. This process is normally opposed by the secretion of nitric oxide and of prostacyclin (PGI2), another product of arachidonic acid metabolism, from the vascular endothelium. During and after aggregation, platelets release many substances that can induce further platelet accumulation and activation, vasoconstriction, thrombosis, and mitogenesis, including ADP, serotonin, platelet-derived growth factor, fibroblast growth factor, platelet factor 4, and ß-thromboglobulin. Platelet-released serotonin normally causes vasodila-

tion; however, it can induce vasoconstriction in the presence of damaged or abnormal (dysfunctional) endothelium. Activated platelets also release nitric oxide. This response may prevent an excessive response by inhibiting platelet recruitment to the growing thrombus.

Coronary artery thrombosis is the final pathogenic mechanism of acute ischemic events, including myocardial infarction and sudden death. There are complex interactions among the atherosclerotic artery, endothelial injury and dysfunction, vasospasm, and platelet activation. Plaque rupture exposes thrombogenic subendothelial components, leading to platelet deposition and activation.The following observations are compatible with the importance of platelet thrombus formation in acute ischemic syndromes:

• Thrombus formation within a coronary vessel is the acute precipitating event in most unstable ischemic coronary syndromes, as documented by angiographic and pathologic studies. Among patients with sudden death due to coronary thrombosis, the thrombi typically have a layered appearance indicative of episodic growth. Episodic growth may alternate with intermittent fragmentation of the thrombus, leading to distal embolization of both thrombus and platelet aggregates and microinfarction.

• Aggregating platelets form the core of the growing thrombotic mass (white thrombus) at the disrupted plaque; the associated reduction in blood flow promotes upstream and/or downstream propagation of fibrin and red blood cell and leukocyte rich red thrombus. Both subendothelial tissue factor and activated platelets themselves serve as stimuli for thrombin generation. Platelets provide a membrane surface for the assembly of procoagulants, two of which (factors V and VIII) are released with activation. Persistent thrombotic occlusion of the coronary vessel leads to acute myocardial infarction.

• Increased platelet-derived thromboxane A2 and other prothrombotic prostaglandin metabolites have been found in patients with acute myocardial infarction and unstable angina, providing biochemical support for platelet activation as the cause of these events. One prospective study, for example, found a phasic increase in the excretion of thromboxane A2 metabolites in 84 percent of episodes of unstable angina.

• Patients with unstable angina have elevated levels of P-selectin, an integral membrane protein involved in platelet adhesion. Pulsatile shear stress, as occurs in stenotic arteries, can cause platelet aggregation via an increased expression of P-selectin. Hydrodynamic shear stress, resulting from plaque rupture, can activate platelets and cause both platelet aggregation (via glycoprotein IIb/IIIa and von Willebrand factor) and platelet-mediated neutrophil aggregation via upregulation of P-selectin. Although levels of P-selectin decrease during the first month after treatment, levels remain higher than normal even with therapy with glycoprotein IIb/IIIa inhibitors, suggesting continued platelet activation. This finding is consistent with serial angioscopic studies showing persistence of complex yellow plaque and thrombus after successful reperfusion at one month and later.

• Aggregating platelets from patients with acute coronary syndromes produce less nitric oxide than those from patients with stable or no angina. Why this might occur is not known, but impaired nitric oxide production can enhance platelet aggregation and thrombus formation.

• Despite treatment with platelet inhibitors, patients with acute cardiovascular events have enhanced platelet reactivity even at baseline.

These findings are consistent with another platelet-related factor believed to contribute to cardiovascular thrombosis, which is the presence of larger, more reactive platelets in patients with acute ischemic events. The increase in platelet size, which is in compensation for a persistent decrease in platelet count, results from the ongoing consumption of platelets in unstable angina; this is not seen in an acute myocardial infarction. In addition, platelets from patients with unstable angina, as determined by studying platelet aggregability ex vivo, are hyperaggregable. These effects promote thrombus growth, limitation of blood flow, and acute ischemia. Platelet

reactivity is altered by a number of environmental factors, such as age, serum cholesterol, diabetes, catecholamine levels, cigarette smoking, and alcohol consumption.

Polymorphisms of platelet glycoprotein receptor genes: The functions of the platelet glycoprotein receptors have been described above. It has been suggested that polymorphisms in these receptors are a risk factor for coronary artery thrombosis, although data from Framingham suggest that these polymorphisms contribute minimally to platelet function. Associations have been described for Gp IIIa polymorphisms and Gp Ia/IIa polymorphisms.

Interaction of thrombosis and inflammation: The mechanism of action of most platelet inhibitors is inhibition of fibrinogen-dependent platelet-platelet association.Platelets are also involved in the inflammatory response and produce proinflammatory mediators such as platelet-derived growth factor, platelet factor 4, and transforming growth factor-beta, as well as CD40 ligand. Patients with acute coronary syndromes have increased interactions between platelets (homotypic aggregates) and between platelets and leukocytes/neutrophils (heterotypic aggregates). These latter aggregates form when platelets are activated and adhere to circulating leukocytes or neutrophils. Accumulating information suggests that inflammation plays an important role during the thrombotic phase of acute coronary syndromes. Leukocytes and neutrophils bind to platelets via P-selectin and beta-2-integrin, a process that requires platelet production of platelet-activating factor. Leukocytes in turn may be able to enhance platelet aggregation, and the relationship between platelet-dependent thrombosis and inflammation is also governed, in part, by the platelet-surface receptor CD40 and its binding of CD40 ligand. These interactions suggest a mechanism for the coupling of thrombosis and inflammation during cardiac ischemia.

Classification

Classification is based on ECG changes and presence or absence of cardiac markers in blood. Distinguishing NSTEMI and STEMI is useful because prognosis and treatment are different.

Unstable angina (acute coronary insufficiency, preinfarction angina, intermediate syndrome) is defined as:

- Rest angina that is prolonged (usually > 20 min).
- New-onset angina of at least class 3 severity in the Canadian Cardiovascular Society (CCS) classification (see Table 2).
- Increasing angina, ie, previously diagnosed angina that has become distinctly more frequent, more severe, longer in duration, or lower in threshold (eg, increased by ≥ 1 CCS class or to at least CCS class 3).

Also, ECG changes such as ST-segment depression, ST-segment elevation, or T-wave inversion may occur during unstable angina but are transient. Of cardiac markers, CK is not elevated but cardiac troponin, particularly when measured using high-sensitivity troponin tests (hs-cTn), may be slightly increased. Unstable angina is clinically unstable and often a prelude to MI or arrhythmias or, less commonly, to sudden death.

Non-ST-segment elevation MI (NSTEMI, subendocardial MI) is myocardial necrosis (evidenced by cardiac markers in blood; troponin I or troponin T and CK will be elevated) without acute ST-segment elevation or Q waves. ECG changes such as ST-segment depression, T-wave inversion, or both may be present.

ST-segment elevation MI (STEMI, transmural MI) is myocardial necrosis with ECG changes showing ST-segment elevation that is not quickly reversed

by nitroglycerin or showing new left bundle branch block. Q waves may be present. Cardiac markers, troponin I or troponin T, and CK are elevated.

Diagnosis

Symptoms reported by patients with ACS include the following:

- Palpitations.
- Pain, which is usually described as pressure, squeezing, or a burning sensation across the precordium and may radiate to the neck, shoulder, jaw, back, upper abdomen, or either arm.
- Exertional dyspnea that resolves with pain or rest.
- Diaphoresis from sympathetic discharge.
- Nausea from vagal stimulation.
- Decreased exercise tolerance.

Physical findings can range from normal to any of the following:

- Hypotension: Indicates ventricular dysfunction due to myocardial ischemia, MI, or acute valvular dysfunction.
- Hypertension: May precipitate angina or reflect elevated catecholamine levels due to anxiety or to exogenous sympathomimetic stimulation.
- Diaphoresis.
- Pulmonary edema and other signs of left heart failure.
- Extracardiac vascular disease.
- Jugular venous distention.
- Cool, clammy skin and diaphoresis in patients with cardiogenic shock.
- A third heart sound (S_3) and, frequently, a fourth heart sound (S_4).
- A systolic murmur related to dynamic obstruction of the left ventricular outflow tract.
- Rales on pulmonary examination (suggestive of left ventricular dysfunction or mitral regurgitation).

Potential complications include the following:

- Pulmonary edema.
- Myocardial necrosis with rupture of the papillary muscle, left ventricular free wall (with heart tamponade), and ventricular septum.

Guidelines for the management of non-ST-segment elevation ACS of the European Society of Cardiology (ESC) include the use of the CRUSADE risk score (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA (American College of Cardiology and American Heart Association guidelines).

In the emergency setting, ECG is a very important diagnostic test for ACS. ECG changes that may be seen during anginal episodes include the following:

- Transient ST-segment elevations or not.
- Dynamic T-wave changes: Inversions, normalizations, or hyperacute changes.

• ST depressions: These may be junctional, downsloping, or horizontal.

In the emergency setting, laboratory studiesof cardiomyocyte injury are most important tests for MI diagnose. Cardiac injury can be defined as the disruption of normal cardiac myocyte membrane integrity resulting in the loss into the extracellular space (including blood) of intracellular constituents including detectable levels of a variety of biologically active cytosolic and structural proteins such as troponin, creatine kinase, myoglobin, heart-type fatty acid binding protein, and lactate dehydrogenase. Injury is usually is considered irreversible (cell death), but definitive proof that cell death is an inevitable consequence of the process is not available.When a sufficient number of myocytes have died (myocyte necrosis) or lost function, acute clinical disease is apparent; examples included MI or myocarditis.

Cardiac-specific troponin T (cTnT) and cardiac-specific troponin I (cTnI) have amino-acid sequences different from those of the skeletal muscle forms of these proteins. These differences permitted the development of quantitative assays for cTnT and cTnI with highly specific monoclonal antibodies. Since cTnT and cTnI are not normally detectable in the blood of healthy individuals but may increase after STEMI to levels > 20 times higher than the upper reference limit (the highest value seen in 99 % of a reference population not suffering from MI), the measurement of cTnT or cTnI is of considerable diagnostic usefulness, and they are now the preferred biochemical markers for MI. The cardiac troponins are particularly valuable when there is clinical suspicion of either skeletal muscle injury or a small MI that may be below the detection limit for creatine phosphokinase (CK) and its MB isoenzyme (CKMB) measurements, and they are, therefore, of particular value in distinguishing unstable angina from NSTEMI. Levels of cTnI and cTnT may remain elevated for 7–10 days after STEMI.

CK rises within 4–8 h and generally returns to normal by 48–72 h. An important drawback of total CK measurement is its lack of specificity for STEMI, as CK may be elevated with skeletal muscle disease or trauma, including intramuscular injection. The MB isoenzyme of CK has the advantage over total CK that it is not present in significant concentrations in extracardiac tissue and, therefore, is considerably more specific. However, cardiac surgery, myocarditis, and electrical cardioversion often result in elevated serum levels of the MB isoenzyme. A ratio (relative index) of CKMB mass: CK activity > 2.5 suggests but is not diagnostic of a myocardial rather than a skeletal muscle source for the CKMB elevation.

Myoglobin is a ubiquitous heme protein that is rapidly released from damaged tissue because of its small size. Due to its early appearance in the serum, myoglobin was postulated to be a useful adjunct to either troponin or creatine kinase MB (CK-MB) for the early diagnosis of MI. With contemporary, highly sensitive troponin assays and the use of the 99th percentile or 10 percent coefficient of variation cut off, troponin is elevated prior to elevations in myoglobin. Thus, there is little advantage for the use of myoglobin as a marker of early injury unless an insensitive troponin assay is being employed. In addition there are several limitations to the use of serum myoglobin for the diagnosis of acute MI. First, the rapid release and

metabolism of myoglobin can result in an undulating or «staccato» pattern characterized by increases and decreases in serum myoglobin concentration that can lead to clinical confusion. Another problem is that myoglobin lacks specificity for the heart. Serum concentrations are elevated after injury to a variety of tissues (particularly skeletal muscle), after recent cocaine use, and in patients with impaired renal function due to decreased clearance. Because of these limitations and absence of any advantage over troponins, myoglobin should not be routinely measured in patients with suspected MI.

Heart-type fatty acid binding protein (H-FABP) is a low molecular weight protein that behaves similarly to myoglobin in its kinetics and release. However, in contrast to myoglobin, there is more fatty acid binding protein in heart compared to skeletal muscle, making this a potentially more specific test.

Lactate dehydrogenase (LD, formerly abbreviated LDH) was commonly used in the past in combination with aspartate aminotransferase (AST or SGOT) and CK-MB to diagnose an acute MI.LD consists of M (muscle) and H (heart) subunits that give rise to five isoenzymes. The heart primarily contains LD1 and some LD2. Red cells, kidney, stomach, and pancreas are other important sources of LD1. In contrast, LD5 predominates in skeletal muscle and liver.LD activity rises to abnormal levels approximately 10 hours after the onset of MI, peaks at 24 to 48 hours, and remains elevated for six to eight days. However, since troponins are more specific than LD and remain elevated for five to ten days, current recommendations suggest that LD no longer has a role in the diagnosis of MI.

While there are theoretical advantages of the biomarkers myoglobin, heart-type fatty acid binding protien, and lactate dehydrogenase, none of these is superior to troponin for the diagnosis of or prognosis after cardiac injury.Recommended using cardiac troponins in preference to CK-MB for diagnostic and prognostic purposes. It is unnecessary to obtain both values. Cardiac troponins I and T are equally useful.

The nonspecific reaction to myocardial injury is associated with polymorphonuclear leukocytosis, which appears within a few hours after the onset of pain and persists for 3–7 days (so-called «necrotic resorbs syndrome»); the white blood cell count often reaches levels of 12,000–15,000/L. The erythrocyte sedimentation rate rises more slowly than the white blood cell count, peaking during the first week and sometimes remaining elevated for one or two weeks.

Laboratory studies that may be helpful include the following:

- Serum markers of biomarkers of cardiomyocyte injury.
- Complete blood count.
- Basic metabolic panel.

Diagnostic imaging modalities that may be useful include the following:

- Echocardiography.
- Coronaroangiography.
- Chest radiography.
- Myocardial perfusion imaging.
- Computed tomography, including CT coronary angiography.

Management of ACS (NSTEMI)

Initial therapy focuses on the following:

- Stabilizing the patient's condition.
- Relieving ischemic pain.
- Providing anticoagulant therapy.

Pharmacologic anti-ischemic therapy includes the following:

- Nitrates (for symptomatic relief).
- Beta blockers (eg, metoprolol): These are indicated in all patients unless contraindicated.

Pharmacologic antithrombotic therapy includes the following:

- Aspirin.
- Clopidogrel.
- Prasugrel.
- Ticagrelor.
- Glycoprotein IIb/IIIa receptor antagonists (abciximab, eptifibatide, tirofiban).

Pharmacologic anticoagulant therapy includes the following:

- Unfractionated heparin (UFH).
- Low-molecular-weight heparin (LMWH; dalteparin, nadroparin, enoxaparin).
- Factor Xa inhibitors (rivaroxaban, fondaparinux).

Thienopyridines:

Clopidogrel

Clopidogrel is an oral thienopyridine prodrug that irreversibly inhibits the adenosine diphosphate receptor on the platelet, resulting in a reduction in platelet aggregation through a different mechanism than aspirin. It is effective for patients with both NSTEMI and STEMI.

Prasugrel

Prasugrel is an oral thienopyridine prodrug that irreversably binds to the ADP receptor to inhibit platelet aggregation. Prasugrel may be associated with a reduction in combined event rate (cardiovascular mortality, nonfatal infarction, and nonfatal stroke) with no benefit in mortality compared to clopidogrel but with an overall resultant increase in major bleeding (as compared to clopidogrel) when administered after angiography to patients with NSTEMI undergoing PCI. Risk factors associated with a higher rate of bleeding with prasugrel use are age ≥75 years, previous stroke or TIA, and body weight less than 60 kg. Small improvements in combined event rate (cardiovascular mortality, nonfatal infarction, and nonfatal stroke) and/or mortality are observed when prasugrel (compared to clopidogrel) is administered before or after angiography to patients with NSTEMI and STEMI managed with PCI. Prasugrel (60 mg oral loading dose) may be substituted for clopidogrel after angiography in patients determined to have non-ST-segment elevation ACS or STEMI who are more than 12 hours after symptom onset prior to planned PCI (Class IIa, LOE B). There is no direct evidence for the use of prasugrel in the ED or prehospital settings. In patients who are not at high risk for bleeding, administration of prasugrel (60-mg oral loading dose) prior to angiography in patients determined to have STEMI ≤ 12 hours after the initial symptoms may be substituted for administration of clopido-

grel (Class IIa, LOE B). Prasugrel is not recommended in STEMI patients managed with fibrinolysis or NSTEMI patients before angiography.

Glycoprotein IIb/IIIa Inhibitors

The use and efficacy of glycoprotein IIb/IIIa receptor inhibitors for treatment of patients with UA/NSTEMI has been well established. These trials were conducted prior to contemporary conservative and invasive strategies, and ongoing questions have been investigated concerning their timing (eg, upsteam initiation) and use combined with other contemporary agents (eg, clopidogrel). Two recent studies do not support the routine use of upstream GP IIb/IIIa inhibitors. Other studies have documented benefit largely in patients who have elevated cardiac troponin and a planned invasive strategy or specific subsets such as those patients with diabetes or significant ST-segment depression on the presenting ECG. The current evidence supports a selective strategy for the use of GP IIb/IIIa inhibitors in the use of dual platelet inhibitor treatment of patients with planned invasive strategy taking into consideration the ACS risk of the patient and weighing this against the potential bleeding risk. There is no current evidence supporting the routine use of GP IIb/ IIIa inhibitor therapy prior to angiography in patients with STEMI and use of these agents upstream is uncertain. Use of GP IIb/ IIIa inhibitors should be guided by local interdisciplinary review of ongoing clinical trials, guidelines, and recommendations.

β-Adrenergic Receptor Blockers

Controversy surrounds the administration of β-adrenergic receptor blockers in the setting of ACS. Several studies have shown reduced mortality and decreased infarct size with early IV β-blocker use. Early β-blocker administration may help prevent dangerous arrhythmias and reduce reinfarction, but there is an increased incidence of cardiogenic shock.

Recent evidence shows no particular benefit to the IV administration of β-blockers on either mortality, infarct size, prevention of arrhythmias, or reinfarctionThere may be, however, a statistically significant short-term benefit to 6-week mortality when IV β-blockers were given to low-risk (ie, Killip Class I) patients. IV β-blockers may also be beneficial for NSTEMI. One study suggested that the earlier the IV β-blockers were administered, the greater the effect seen on infarct size and mortality. Of note, none of the papers reviewed showed that β-blockers caused irreversible harm when given early in the development of suspected ACS. Balancing the evidence overall for non-ST-segment elevation ACS patients, current ACC/AHA Guidelines recommend β-blockers be initiated orally within the first 24 hours after hospitalization. Contraindications to β-blockers are moderate to severe LV failure and pulmonary edema, bradycardia (< 60 bpm), hypotension (SBP < 100 mm Hg), signs of poor peripheral perfusion, second-degree or third-degree heart block, or reactive airway disease.

Heparins

Heparin is an indirect inhibitor of thrombin that has been widely used in ACS as adjunctive therapy for fibrinolysis and in combination with aspirin and other platelet inhibitors for the treatment of non-ST-segment elevation ACS. UFH has several disadvantages, including (1) the need for IV administration; (2) the requirement for frequent monitoring of the activated partial thromboplastin time (aPTT); (3) an unpredictable anticoagulant response in individual patients; and (4) heparin can also stimulate platelet activation, causing thrombocytopenia. Because of the limitations of heparin, newer preparations of LMWH have been developed.

Enoxaparin

Eleven in-hospital randomized clinical trials, and additional studies (including 7 meta-analyses) document similar or improved composite outcomes (death, MI, and/or recurrent angina or recurrent ischemia or revascularization) when enoxaparin was administered instead of UFH to patients with non-ST-segment elevation ACS with an increase in the proportion of patients with minor bleeding complications.

Fondaparinux

There was similar or improved outcomes of combined end points (death, MI, urgent revascularization) without increased bleeding when fondaparinux was administered in-hospital rather than UFH in patients with non-ST-segment elevation ACS. Fondaparinux was associated with increased risk of catheter thrombosis in PCI.

Bivalirudin

No benefit in combined outcome was observed when bivalirudin was administered in hospital compared to UFH in patients with non-ST-segment elevation ACS, however less bleeding was observed with bivalirudin and no renal dosing is required.

Treatment Recommendations for UA/NSTEMI

For in-hospital patients with NSTEMI managed with a planned initial conservative approach, either fondaparinux (Class IIa, level of evidens (LOE) - B) or enoxaparin (Class IIa, LOE A) are reasonable alternatives to UFH or placebo. For in-hospital patients with NSTEMI managed with a planned invasive approach, either enoxaparin or UFH are reasonable choices (Class IIa, LOE A). Fondaparinux may be used in the setting of PCI, but requires co-administration of UFH and does not appear to offer an advantage over UFH alone (Class IIb, LOE A). For in-hospital patients with NSTEMI and renal insufficiency, bivalirudin or UFH may be considered (Class IIb, LOE A). For in-hospital patients with NSTEMI and increased bleeding risk, where anticoagulant therapy is not contraindicated, fondaparinux (Class IIa, LOE B) or bivalirudin (Class IIa, LOE A) are reasonable and UFH may be considered (Class IIb, LOE C) There is no specific evidence for or against anticoagulant use in NSTEMI in the prehospital setting.

Unfractionated Heparin Versus Low-Molecular-Weight Heparin With Fibrinolysis in STEMI

Nine randomized clinical trials and additional studies (including one meta-analyses) document similar or improved composite outcomes (death, MI, and/or recurrent angina or recurrent ischemia or revascularization) when enoxaparin was administered instead of UFH to patients with STEMI undergoing fibrinolysis. This must be balanced against an increase in intracranial hemorrhage in patients >75 years of age who received enoxaparin documented in one of these randomized controlled trials. One randomized clinical trial demonstrated superiority in clinical outcomes when fondaparinux was compared to UFH in patients treated with fibrinolysis.There is insufficient evidence to provide a recommendation on bivalirudin, nadroparin, reviparin, or parnaparin for use in STEMI patients undergoing fibrinolysis.

Enoxaparin

For patients with STEMI managed with fibrinolysis in the hospital, it is reasonable to administer enoxaparin instead of UFH (Class IIa, LOE A). In addition, for prehospital patients with STEMI managed with fibrinolysis, adjunctive enoxaparin instead of UFH may be considered (Class IIb, LOE A). Patients initially treated with enoxaparin should not be switched to UFH and vice versa because of increased risk of bleeding (Class III, LOE C). In younger patients < 75 years the initial dose of enoxaparin is 30 mg IV bolus followed by 1 mg/kg SC every 12 hours (first SC dose shortly after the IV bolus) (Class IIb, LOE A). Patients ≥ 75 years may be treated with 0.75 mg/kg SC enoxaparin every 12 hours without an initial IV bolus (Class IIb, LOE B). Patients with impaired renal function (creatinine clearance < 30 mL/min) may be given 1 mg/kg enoxaparin SC once daily (Class IIb, LOE B). Patients with known impaired renal function may alternatively be managed with UFH (Class IIb, LOE B).

Fondaparinux

Fondaparinux (initially 2.5 mg IV followed by 2.5 mg SC once daily) may be considered in the hospital for patients treated specifically with non-fibrin-specific thrombolytics (ie, streptokinase), pro-

vided the creatinine is < 3 mg/dL (Class IIb, LOE B). There are insufficient data to recommend other LMWH or bivalirudin over UFH in patients treated with fibrinolysis in STEMI.

Unfractionated Heparin Versus Low-Molecular-Weight Heparin With PPCI in STEMI

Two registry studies and other studies demonstrated similar or improved outcomes when enoxaparin was compared to UFH in patients undergoing PPCI combined with a GP IIb/IIIa antagonist and thienopyridine inhibitor.

One large clinical trial demonstrated better outcomes in terms of acute cardiac events and bleeding using fondaparinux and PPCI. Thrombus formation on catheter material in patients on fondaparinux, however, required the addition of UFH during PCI.

Two large randomized clinical trials resulted in less bleeding and a short- and long-term reduction in cardiac events and overall mortality with bivalirudin compared to UFH plus a glycoprotein inhibitor in patients with STEMI and PPCI. For patients with STEMI undergoing contemporary PCI (ie, additional broad use of glycoprotein IIb/IIIa inhibitors and a thienopyridine) enoxaparin may be considered a safe and effective alternative to UFH (Class IIb, LOE B). Patients initially treated with enoxaparin should not be switched to UFH and vice versa to avoid increased risk of bleeding. Fondaparinux may be considered as an alternative to UFH, however, there is an increased risk of catheter thrombi with fondaparinux alone. Additional UFH (50 to 100 U/kg bolus) may help to avoid this complication (Class IIb, LOE B), but using these two agents is not recommended over UFH alone. For fondaparinux and enoxaparin it is necessary to adjust the dose in patients with renal impairment. Bivalirudin may be considered as an alternative to UFH and GP IIb/IIIa inhibitors (Class IIb, LOE A).

Calcium Channel Blockers

There is little evidence that calcium channel blocking agents can be safely used as an alternative or additional therapy to β-blockers when the later are contraindicated or their maximum dose has been achieved. Calcium channel blocking agents have not been shown to reduce mortality after acute MI, and in certain patients with cardiovascular disease there are data to suggest that they are harmful. β-blockers have been used much more broadly, have a much safer profile, and appear to be a more appropriate choice for patients presenting with myocardial infarction compared to calcium channel blockers.

ACE Inhibitor Therapy

ACE Inhibitors and ARBs in the Hospital

ACE inhibitor therapy has improved survival rates in patients with AMI, particularly when started early after the initial hospitalization. Evidence from 7 large clinical trials, 2 meta-analyses, and 10 minor trials documents consistent improvement in mortality when oral ACE inhibitors are administered in the hospital setting to patients with AMI with or without early reperfusion therapy. In these studies ACE inhibitors were not administered in the presence of hypotension (SBP < 100 mm Hg or ≥ 30 mm Hg below baseline). The beneficial effects are most pronounced in patients with anterior infarction, pulmonary congestion, or LV ejection fraction < 40 %.Administration of an oral ACE inhibitor is recommended within the first 24 hours after onset of symptoms in STEMI patients with pulmonary congestion or LV ejection fraction < 40 %, in the absence of hypotension (SBP < 100 mm Hg or ≥ 30 mm Hg below baseline) (Class I, LOE A). Oral ACE inhibitor therapy can also be useful for all other patients with AMI with or without early reperfusion therapy (Class IIa, LOE B). IV administration of ACE inhibitors is contraindicated in the first 24 hours because of risk of hypotension (Class III, LOE C). In conclusion, although ACE inhibitors and ARBs have been shown to reduce long-term risk of mortality in patients suffering an AMI, there is insufficient evidence to support the routine initiation of ACE inhibitors and ARBs in the prehospital or ED setting (Class IIb, LOE C).

HMG Coenzyme A Reductase Inhibitors (Statins)

A variety of studies documented consistent reduction in indicators of inflammation and complications such as reinfarction, recurrent angina, and arrhythmias when statin treatment is administered within a few days after onset of an ACS. There is little data to suggest that this therapy should be initiated within the ED; however, early initiation (within 24 hours of presentation) of statin therapy is recommended in patients with an ACS or AMI (Class I, LOE C). If patients are already on statin therapy, continue the therapy (Class IIb, LOE C).

An increase in short-term mortality and incidence of major adverse cardiac events have been reported with discontinuation of statin treatment in ACS patients at hospital admission. Statins should not be discontinued during the index hospitalization unless contraindicated (Class III, LOE C). Pretreatment with statins in patients undergoing elective percutaneous angioplasty for stable angina or hemodynamicaly stable ACS has been shown to significantly reduce biomarkers of myocardial necrosis or inflammation compared to placebo when given between 3 and 7 days prior to the procedure. Furthermore, pretreatment with atorvastatin 80 mg 12 hours before and an additional 40 mg immediately before PCI for NSTEMI or documented ischemia has been shown to significantly decrease the 30 day composite of death, MI, and unplanned revascularization compared to placebo in a prospective randomized trial. There were no deaths in any of the two groups and the primary end point was driven by periprocedural myocardial infarction in concordance to the previously published studies. In conclusion, intensive (target LDL values optimally < 70 mg/dL) statin treatment should be initiated within the first 24 hours after onset of an ACS event (eg, immediately after hospital admission) in all patients presenting with any form of ACS unless strictly contraindicated (eg, by proven intolerance) (Class I, LOE A). It is reasonable to use statin pretreatment for patients who will be undergoing elective or urgent angioplasty in order to decrease perioperative myocardial infarction. There are no reports on risk or safety considerations of early initiation of statin treatment in ACS.

Glucose-Insulin-Potassium

Although glucose-insulin-potassium (GIK) therapy was formerly thought to reduce the chance of mortality during AMI by several mechanisms, recent clinical trials found that GIK did not show any benefit in STEMI. At this time there is little evidence to suggest that this intervention is helpful (Class IIb, LOE C).

Current guidelines for patients with moderate- or high-risk ACS include the following:

- Early invasive approach.
- Concomitant antithrombotic therapy, including aspirin and clopidogrel, as well as UFH or LMWH.

Due to considerable variability in patient outcomes across the ACS spectrum, a systematic assessment of probability of adverse events may help inform the most appropriate therapy. Several ACS risk prediction tools have been devised, with the Global Registry of Acute Coronary Events (GRACE) score considered the most robust. The increased availability of percutaneous coronary intervention (PCI) as a treatment option for ACS combined with an expanding case mix and emphasis on quality assurance have triggered the creation of PCI specific prognostic models.

The following mnemonic may useful in educating patients with CAD regarding treatments and lifestyle changes necessitated by their condition:

- A = Aspirin and antianginals
- B = Beta blockers and blood pressure (BP)
- C = Cholesterol and cigarettes
- D = Diet and diabetes
- E = Exercise and education

Myocardial infarction and acute coronary syndrome.

Cardiologists now know that in many cases (perhaps more than half), the plaque that ruptures and results in the clinical acute coronary events is less than 50 % occlusive. These so-called «vulnerable plaques», as compared with stable plaques, consist of a large lipid core, inflammatory cells, and thin, fibrous caps that are subjected to greater biomechanical stress, thus leading to rupture that perpetuates thrombosis and acute coronary events.

Nonatherosclerotic causes of myocardial infarction include the following:

- Coronary occlusion secondary to vasculitis.
- Ventricular hypertrophy (eg, left ventricular hypertrophy, idiopathic hypertrophic subaortic stenosis, underlying valve disease).
- Coronary artery emboli, secondary to cholesterol, air, or the products of sepsis.
- Congenital coronary anomalies.
- Coronary trauma.
- Primary coronary vasospasm (variant angina).
- Drug use (eg, cocaine, amphetamines, ephedrine).
- Arteritis.
- Coronary anomalies, including aneurysms of coronary arteries.
- Factors that increase oxygen requirement, such as heavy exertion, fever, or hyperthyroidism.
- Factors that decrease oxygen delivery, such as hypoxemia of severe anemia.
- Aortic dissection, with retrograde involvement of the coronary arteries.
- Infected cardiac valve through a patent foramen ovale.
- Significant gastrointestinal bleed.

In addition, myocardial infarction can result from hypoxia due to carbon monoxide poisoning or acute pulmonary disorders. Infarcts due to pulmonary disease usually occur when demand on the myocardium dramatically increases relative to the available blood supply.

Although rare, pediatric coronary artery disease may be seen with Marfan syndrome, Kawasaki disease, Takayasu arteritis, progeria, and cystic medial necrosis.

Imaging studies, such as contrast chest CT scans or transesophageal echocardiograms, should be used to differentiate myocardial infarction from aortic dissection in patients in whom the diagnosis is in doubt. Stanford type A aortic

dissections may dissect in a retrograde fashion causing coronary blockage and dissection, which may result in myocardial infarction. In one study, 8 % of patients with Stanford type A dissections had ST elevation on ECG.

Myocardial infarction induced by chest trauma has also been reported, usually following severe chest trauma such as motor vehicle accidents and sports injuries.

Myocardial infarction, commonly known as a heart attack, is the irreversible necrosis of heart muscle secondary to prolonged ischemia. This usually results from an imbalance in oxygen supply and demand, which is most often caused by plaque rupture with thrombus formation in a coronary vessel, resulting in an acute reduction of blood supply to a portion of the myocardium. Although the clinical presentation of a patient is a key component in the overall evaluation of the patient with myocardial infarction, many events are either "silent" or are clinically unrecognized, evidencing that patients, families, and health care providers often do not recognize symptoms of a myocardial infarction. The appearance of cardiac markers in the circulation generally indicates myocardial necrosis and is a useful adjunct to diagnosis.

Myocardial infarction is considered part of a spectrum referred to as acute coronary syndrome (ACS). The ACS continuum representing ongoing myocardial ischemia or injury consists of unstable angina, non–ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Patients with ischemic discomfort may or may not have ST-segment or T-wave changes denoted on the ECG. ST elevations seen on the ECG reflect active and ongoing transmural myocardial injury. Without immediate reperfusion therapy, most persons with STEMI develop Q waves, reflecting a dead zone of myocardium that has undergone irreversible damage and death. Those without ST elevations are diagnosed either with unstable angina or NSTEMI-differentiated by the presence ofcardiac enzymes. Both these conditions may or may not have changes on the surface ECG, including ST-segment depression or T-wave morphological changes.

Coronary thrombolysis and mechanical revascularization have revolutionized the primary treatment of acute myocardial infarction, largely because they allow salvage of the myocardium when implemented early after the onset of ischemia.

The modest prognostic benefit of an opened infarct-related artery may be realized even when recanalization is induced only 6 hours or more after the onset of symptoms, that is, when the salvaging of substantial amounts of jeopardized ischemic myocardium is no longer likely. The opening of an infarct-related artery may improve ventricular function, collateral blood flow, and ventricular remodeling, and it may decrease infarct expansion, ventricular aneurysm formation, left ventricular dilatation, late arrhythmia associated with ventricular aneurysms, and mortality. One third of patients who experience STEMI die within 24 hours of the onset of ischemia, and many of the survivors experience significant morbidity. However, a steady decline has occurred in the mortality rate from STEMI over the last several decades. Acute myocardial in-

farction is associated with a 30 % mortality rate; half of the deaths occur prior to arrival at the hospital. An additional 5–10 % of survivors die within the first year after their myocardial infarction. Approximately half of all patients with a myocardial infarction are rehospitalized within 1 year of their index event. Overall, prognosis is highly variable and depends largely on the extent of the infarct, the residual left ventricular function, and whether the patient underwent revascularization.

Myocardial hibernation and stunning: after the occurrence of 1 or more ischemic insults, impaired wall motion is often transient (myocardial stunning) or prolonged (myocardial hibernation). These phenomena occur because of the loss of essential metabolites such as adenosine, which is needed for adenosine triphosphate (ATP)-dependent contraction. Hibernation, a persisting wall-motion abnormality that is curable with revascularization, must be differentiated from permanent, irreversible damage or completed infarct.

Better prognosis is associated with the following factors:

- Successful early reperfusion (STEMI goals: patient arrival to fibrinolysis infusion within 30 minutes OR patient arrival to percutaneous coronary intervention within 90 minutes).
- Preserved left ventricular function.
- Short-term and long-term treatment with beta-blockers, aspirin, and ACE inhibitors.

Poorer prognosis is associated with the following factors:

- Increasing age.
- Diabetes.
- Previous vascular disease (ie, cerebrovascular disease or peripheral vascular disease).
- Elevated Thrombolysis in Myocardial Infarction (TIMI) risk score for unstable angina/NSTEMI (7 factors: Age ≥ 65 y, ≥ 3 risk factors for cardiac disease, previous coronary disease, ST segment deviation ≥ 0.5 mm, ≥ 2 episodes of angina in last 24 h, aspirin use within prior wk, and elevated cardiac enzyme levels).
- Delayed or unsuccessful reperfusion.
- Poorly preserved left ventricular function (the strongest predictor of outcome).
- Evidence of congestive heart failure (Killip classification ≥II) or frank pulmonary edema (Killip classification ≥III) – see on Table 3.
- Elevated B-type natriuretic peptide (BNP) levels.
- Elevated high sensitive C-reactive protein (hs-CRP), a nonspecific inflammatory marker.
- Secretory-associated phospholipase A2 activity is related to atherosclerosis and predicts all-cause mortality in elderly patients; it also predicts mortality or MI in post-MI patients.

Table 3 — Modified from Killip T, Classification and Mortality Rate of Acute MI*

Class	PAO_2**	Clinical Description	Hospital Mortality Rate
I	Normal	No clinical evidence of left ventricular (LV) failure	3–5 %
II	Slightly reduced	Mild to moderate LV failure	6–10 %
III	Abnormal	Severe LV failure, pulmonary edema	20–30 %
IV	Severely abnormal	Cardiogenic shock: hypotension, tachycardia, mental obtundation, cool extremities, oliguria, hypoxia	> 80 %

* Determined by repeated examination of the patient during the course of illness.
** Determined while the patient is breathing room air.

Diagnosis

The electrocardiogram (ECG) is an important and sometimes central tool used to establish the diagnosis of myocardial ischemia or infarction. New abnormalities in the ST segment and T waves represent myocardial ischemia and may be followed by the formation of Q waves. However, the electrocardiogram may be normal or nonspecific in a patient with either ischemia or infarction. The findings on the ECG depend upon several characteristics of the ischemia or infarction including:

- Duration — hyperacute/acute versus evolving/chronic.
- Size — amount of myocardium affected.
- Localization — anterior versus inferior-posterior.

An acute myocardial infarction (MI) presents with a current of injury pattern characterized by elevation of the ST segment in different leads, depending upon the location of the MI. The earliest change, which is not frequently seen, is symmetric, hyperacute T waves (defined as amplitude more than 50 percent of the R wave in the same lead) in at least two contiguous leads. The ST segment elevates with the following appearance:

- Initially there is elevation of the J point and the ST segment retains its concave configuration.
- Over time the ST segment elevation becomes more pronounced and the ST segment changes its morphology, becoming more convex or rounded upward.
- The ST segment may eventually become indistinguishable from the T wave; the QRS-T complex can actually resemble a monophasic action potential.
- An initial Q wave develops and there is a loss of R wave amplitude as the ST segment becomes elevated.

An abnormal Q wave is any Q wave in leads V1 to V3 or a Q wave ≥30 msec in leads I, II, aVL, aVF, or V4 to V6; the Q wave must be present in any two contiguous leads and ≥ 1 mm in depth. Over time, there is evolution of these ECG changes: the ST segment gradually returns to the isoelectric baseline; the R wave amplitude becomes markedly reduced; the Q wave deepens; and the T wave be-

comes inverted. These changes generally occur within the first two weeks after the event; however, in some patients they occur within a few hours of presentation.

The electrocardiographic changes that occur in patients who sustain a non-ST elevation MI are different: the ST and T waves changes is variable. ECG examples of STE/NSTE ACS see on Figures 1, 2:

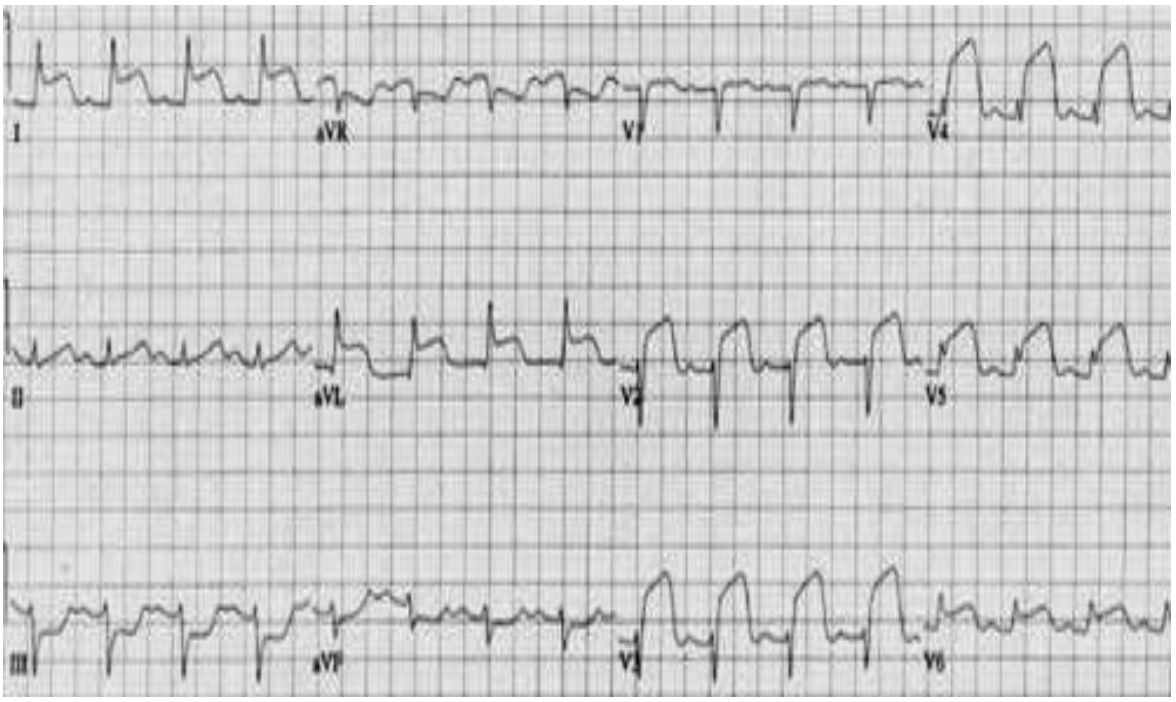

Figure 1 — STE ACS (MI)

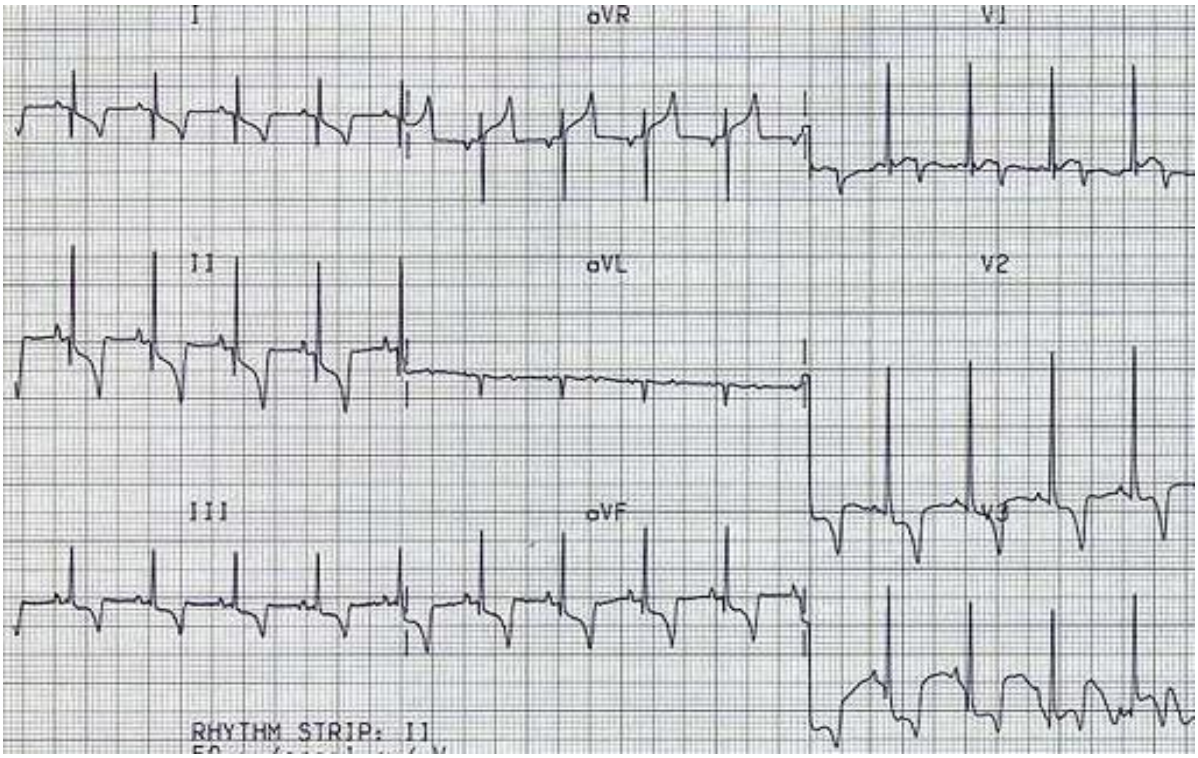

Figure 2 — NSTE ACS

The leads affected by these changes depend upon the location of the MI. See Table 4.

Table 4 — ECG-leads changes depend upon the localisation of MI

The localisation of MI	ECG-leads with specific changes	
	direct	reciprocal
Anterior wall of LV*	V1-V6	II, III, aVF
Anterioseptal of LV	V1-V2	II, III, aVF
Anterioapical of LV	V3-V4	II, III, aVF
Anteriolateral of LV	I, aVL, V5-V6	II, III, aVF
Lateral of LV	I, aVL	II, III, aVF
Inferior wall of LV	II, III, aVF	I, aVL, V1-V3
Posterior wall of LV	V7-V9 + (additional leads)	I, V1-V3, V3R
RV**	V1, V3R-V4R	V7-V9

Abbreviations: *LV — left ventrical, **RV — right ventrical.

- An acute anterior wall MI presents with the changes in some or all of the precordial chest leads V1-V6. Reciprocal ECG changes occasionally are observed during the initial period of the acute infarction, presenting most often as depressions of the ST segments in the inferior leads (II, III, and aVF).
- An acute anteroseptal transmural MI presents with the changes in leads V1-V2. Reciprocal ECG changes occasionally are observed during the initial period of the acute infarction, presenting as depressions of the ST segments in the inferior (II, III, aVF) or lateral leads (I, aVL, V5 and V6).
- An acute anteroapical transmural MI presents with the changes in leads V3 and V4. Reciprocal ECG changes occasionally are observed during the initial period of the acute infarction, presenting as depressions of the ST segment in the inferior leads (II, III, aVF).
- An acute anterolateral transmural MI presents with the changes in leads V5 and V6, often in association with changes in leads I and aVL. Reciprocal ECG changes occasionally are observed during the initial period of the acute infarction, presenting as depressions of the ST segment in the inferior leads (II, III, aVF), and in some cases in leads V1 and V2.
- An acute lateral transmural myocardial infarction presents with the changes confined to leads I and aVL. Reciprocal ECG changes occasionally are observed during the initial period of the acute infarction, presenting as ST segment depressions in the inferior leads (II, III and aVF) or leads V1 and V2.
- An acute inferior wall transmural myocardial infarction presents with the changes in leads II, II, and aVF. Reciprocal ECG changes occasionally are observed during the initial period of the acute infarction, presenting with ST segment depressions in leads V1 to V3, I, or aVL. The ST segment changes in the precordial leads are not reciprocal in some cases, but represent true posterior wall involvement (which may be diagnosed by ST elevation in leads V7 to V9) or involvement of the right ventricle (which may be diagnosed by ST elevations in right precordial chest leads).

Management ACS with MI

For patients with chest pain, prehospital care includes the following:

- Intravenous access, supplemental oxygen, pulse oximetry.
- Immediate administration of aspirin en route.
- Nitroglycerin for active chest pain, given sublingually or by spray.
- Telemetry and prehospital ECG, if available.

Emergency department and inpatient care.

Initial stabilization of patients with suspected myocardial infarction and ongoing acute chest pain should include administration of sublingual nitroglycerin if patients have no contraindications to it. The American Heart Association (AHA) recommends the initiation of beta blockers to all patients with STEMI (unless beta blockers are contraindicated). Evidence suggests a benefit from the use of beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and statins. If STEMI is present, the decision must be made quickly as to whether the patient should be treated with thrombolysis or with primary percutaneous coronary intervention (PCI). Although patients presenting with no ST-segment elevation are not candidates for immediate thrombolytics, they should receive anti-ischemic therapy and may be candidates for PCI urgently or during admission.

Critical care units have reduced early mortality rates from acute myocardial infarction by approximately 50 % by providing immediate defibrillation and by facilitating the implementation of beneficial interventions. These interventions include the administration of IV medications and therapy designed to do the following:

- Limit the extent of myocardial infarction.
- Salvage jeopardized ischemic myocardium.
- Recanalize infarct-related arteries.

Secondary prevention: various secondary preventive measures are at least partly responsible for the improvement in the long-term mortality and morbidity rates after STEMI. Long-term treatment with an antiplatelet agent (usually aspirin 150–160 mg orally daily) after STEMI is associated with a 25 % reduction in the risk of recurrent infarction, stroke, or cardiovascular mortality (36 fewer events for every 1000 patients treated). An alternative antiplatelet agent that may be used for secondary prevention in patients intolerant of aspirin is clopidogrel (75 mg orally daily). ACE inhibitors or ARBs and, in appropriate patients, aldosterone antagonists should be used indefinitely by patients with clinically evident heart failure, a moderate decrease in global ejection fraction, or a large regional wall motion abnormality to prevent late ventricular remodeling and recurrent ischemic events.The chronic routine use of oral beta-adrenoceptor blockers for at least two years after STEMI is supported by well-conducted, placebo-controlled trials. Finally, risk factors for atherosclerosis should be discussed with the patient, and, when possible, favorably modified.

Complicated MI: Infarction of ≥ 40 % of the LV myocardium usually results in cardiogenic shock and carries a high mortality rate. Of those who developed shock, patients with ST-segment elevation developed shock significantly earlier than patients without ST-segment elevation. Cardiogenic shock and congestive heart failure are not contraindications to fibrinolysis, but PCI is preferred if the patient is at a facility with PCI capabilities. Based on the results of the SHOCK trial ACC/AHA guidelines note that PPCI is reasonable in those who develop shock within 36 hours of symptom onset and who are suitable candidates for revascularization that can be performed within 18 hours of the onset of shock. Although the benefits in the SHOCK trial were observed only in patients ≤ 75 years of age, selected elderly patients also appear to benefit from this strategy. The guidelines also support the use of hemodynamic support with intra-aortic balloon counterpulsation (IABP) in this setting as part of aggressive medical treatment. The IABP works synergistically with fibrinolytic agents in this setting, and the benefits observed with early revascularization strategy in the SHOCK trial were also obtained in the setting of IABP support. The use of PPCI for patients with cardiogenic shock has increased over time and contributes to the observed decrease in hospital mortality. The majority of survivors following cardiogenic shock experience a good quality of life, and the early mortality benefit with revascularization is sustained over time. In hospitals without PCI facilities, fibrinolytic administration needs to be considered with prompt transfer to a tertiary care facility where adjunct PCI can be performed if cardiogenic shock or ongoing ischemia ensues. The ACC/AHA STEMI guidelines recommend a door-to-departure time of ≤ 30 minutes for transfer to a PCI-capable center.

4. HEART FAILURE

Definitions and introduction

Heart failure (HF) is a clinical syndrome that occurs in patients who, because of an inherited or acquired abnormality of cardiac structure and/or function, develop a constellation of clinical symptoms (dyspnea and fatigue) and signs (edema and rales) that lead to frequent hospitalizations, a poor quality of life, and a shortened life expectancy.

Aging of the population and prolongation of the lives of cardiac patients by modern therapeutic innovations has led to an increasing prevalence of HF. Despite improvements in therapy, the mortality rate in patients with HF has remained unacceptably high, making early detection of susceptible persons who would benefit from preventive measures imperative. The overall prevalence of HF in the adult population in developed countries is 2 %. Investigations using echocardiography have found that only 50 percent of participants with left ventricular dysfunction are symptomatic. HF prevalence follows an exponential pattern, rising with age, and affects 6–10 % of people over age 65.The incidence of HF, like the prevalence, increases with age. In the Framingham Study, the incidence approximately doubled over each successive decade of life, rising more steeply with age in women than in men. The annual incidence in men rose from 2 per 1000 at age 35 to 64 years to 12 per 1000 at age 65 to 94 years. Because the increase in risk with age is balanced by the decreased life expectancy with older age, the lifetime likelihood of developing HF is approximately 20 percent at all ages above 40.

Epidemiologically, the impact of the various predisposing conditions for HF is best determined by the population attributable risk (PAR) that takes into account both the hazard ratio and the prevalence of the predisposing condition in the population. As an example, the First National Health and Nutrition Examination Survey (NHANES I) of 13,643 men and women who were followed for 19 years found that the risk factors for HF and their population attributable risk (PAR) were as follows:

- Coronary heart disease — relative risk 8.1; overall PAR 62 percent, 68 percent in men and 56 percent in women.
- Cigarette smoking — relative risk 1.6, PAR 17 percent.
- Hypertension — relative risk 1.4, PAR 10 percent.
- Overweight — relative risk 1.3, PAR 8 percent; the importance of obesity was also demonstrated in a long-term follow-up from the Framingham Heart Study which estimated that approximately 11 percent of cases of HF in men and 14 percent in women are attributable to obesity alone.
- Diabetes — relative risk 1.9, PAR 3 percent.
- Valvular heart disease — relative risk 1.5, PAR 2 percent; however, valve disease is an increasingly common cause of HF at older ages, with calcific aortic stenosis being the most common disorder requiring surgery.

As demonstrated by the above observations, ischemic cardiomyopathy is the most common cause of HF due to systolic dysfunction in Western countries. Ischemic cardiomyopathy is diagnosed in patients with HF who have had a myocardial infarction or have evidence of hibernating myocardium or, on angiography, severe coronary disease. In contrast, patients with single vessel disease who have no evidence of myocardial infarction or revascularization have a similar prognosis as those with nonischemic cardiomyopathy. It was suggested that such patients should be classified as nonischemic cardiomyopathy, at least for prognostic purposes.

Hypertension increases the risk of HF at all ages. Data from the Framingham Heart Study found that, after age 40, the lifetime risk of developing HF was twice as high in subjects with a blood pressure $\geq$ 160/100 mmHg compared to < 140/90 mmHg. The risk of developing HF increases with the degree of blood pressure elevation. However, even moderate elevations contribute to risk in the long term. The average blood pressure of hypertensive candidates for HF in the Framingham Study was only 150/90 mmHg.

Whether due to hypertension, coronary disease, valve disease, or diabetes, left ventricular hypertrophy (LVH) is a prominent feature of evolving HF. Among patients with HF in the general population, antecedent evidence of LVH is present in approximately 20 percent by ECG and 60 to 70 by echocardiogram. The risk of HF of any cause increases progressively in relation to the left ventricular mass with no discernible separation of compensatory from pathologic hypertrophy. Each method of demonstrating left ventricular hypertrophy (ECG, chest film, or echocardiogram) independently predicts HF. As a result, persons having any combination of them have a greater risk than those with any one alone.

The most common conditions associated with diastolic dysfunction are aging, hypertension, diabetes mellitus, left ventricular hypertrophy, coronary disease, and infiltrative cardiomyopathies. Patients with HF and preserved systolic function tend to be older and overweight, more often women, and have renal dysfunction, concentric left ventricular hypertrophy, and higher systolic blood pressure compared to patients with HF due to systolic dysfunction.

The signs and symptoms of HF are in part due to compensatory mechanisms utilized by the body in an attempt to repair the primary deficit in the car-

diac output. Well-recognized neurohumoral adaptations, such as activation of the renin-angiotensin-aldosterone and sympathetic nervous systems and antidiuretic hormone (vasopressin) by the low output state, can contribute to maintenance of perfusion of vital organs in two ways:

- Maintenance of systemic pressure by vasoconstriction, resulting in redistribution of blood flow to vital organs.
- Restoration of cardiac output by increasing myocardial contractility and heart rate and by expansion of the extracellular fluid volume.

HF is also associated with alterations in a host of autocrine and paracrine signaling systems, many of which are involved in mediating inflammation, including nitric oxide (NO), inflammatory cytokines, chemokines and cyclooxygenase. The physiologic and clinical significance of these changes is complex and less well understood.

Nitric oxide: nitric oxide is enzymatically formed from L-arginine by three isoforms of nitric oxide synthetase (NOS): neuronal-type (nNOS, NOS1), cytokine-inducible NOS (iNOS, NOS2), and the endothelial-type (eNOS, NOS3). These enzymes differ markedly in their localization and function. Many cell types, most notably endothelial cells, constitutively express eNOS, generating relatively low levels of NO that are under tight control by regulatory factors. In contrast, iNOS is normally not expressed, but when induced by inflammatory cytokines can generate large amounts of NO far in excess of those made by eNOS. There may be alterations in all three isoforms of NOS in HF.Chronic HF is associated with arterial endothelial dysfunction and impaired endothelium-dependent, flow-mediated dilation; the mechanism is probably a reduction in NO synthesis via eNOS as well as a decrease in endothelial release of and response to NO. In contrast, venous endothelial function and tone and basal and stimulated NO release from the venous capacitance bed is preserved.There is evidence for increased free radical formation in HF, and it is possible that these species inactivate NO. Support for this hypothesis comes from one study in which vitamin C improved endothelial function in patients with HF in association with an increased availability of NO. The level of NOS activity in the failing human myocardium is variable, likely reflecting the multiple types of NOS and the heterogeneity of myocardial failure. Increased levels of activity of eNOS and nNOS, and increased NO production, have been observed within myocytes from patients with HF due to either an ischemic or nonischemic dilated cardiomyopathy. The expression of iNOS, in particular, appears to correlate with the level of tumor necrosis factor alpha (TNFa).

Nitric oxide may exert either beneficial or detrimental effects in the myocardium:

- In an animal model of myocardial infarction, the presence of eNOS limits left ventricular dysfunction and remodeling, in part by decreasing myocyte hypertrophy in the noninfarcted myocardium.
- Another animal study found that nitric oxide production lowers myocyte energy production by directly affecting mitochondrial function. While this effect may limit energy availability, it may also reduce the generation of reactive oxygen radicals in the mitochondria.
- Nitric oxide can also affect basal myocardial function and can impair the inotropic response to beta-adrenergic receptor stimulation.

The localization of NOS within the myocyte may also be disrupted in HF. In a study of nNOS expression in human hearts explanted at transplantation, there was a significant in-

crease in sarcolemmal nNOS and a concomitant decrease in nNOS associated with the sarcoplasmic reticulum. This translocation of nNOS within failing heart muscle cells could contribute to the pathogenesis of HF by reducing calcium stores in the sarcoplasmic reticulum and increasing inhibition of the cell membrane L-type calcium channel, both effects that would reduce the availability of calcium to the contractile apparatus.Inducible nitric oxide synthase gene expression and local nitric oxide production may also be increased within skeletal muscle of patients with HF. This response could contribute to a reduction in contractile performance and muscle wasting.

Cytokines: HF is often characterized by increases in circulating proinflammatory cytokines (TNFa, interleukin (IL)-6, IL-1-beta, and IL-2) and their soluble receptor or receptor antagonists that become more pronounced as myocardial function deteriorates. In addition, increased production of proinflammatory cytokines and other inflammatory markers may identify patients at increased risk of developing HF in the future. The clinical significance of elevated cytokine levels in HF remains uncertain. A cause-and-effect relationship may contribute since, as will be described below, excess TNFa and IL-6 may have a deleterious effects on cardiac function.

Tumor necrosis factor-alpha: plasma TNFa concentrations are often elevated in patients with HF. Plasma TNFa increases with disease severity, being directly correlated with NYHA functional class. An increase in TNFa may predict both the prognosis in patients with HF and the development of HF in patients without the disease.Among patients with HF, the source of TNFa may in part be the heart itself. Although the nonfailing heart does not express TNFa, significant amounts are expressed by the failing human heart. The stimuli for cardiac TNFa expression are not well understood. Passive stretch alone can increase expression in cardiac myocytes, and, in humans, pressure and volume overload due to aortic stenosis or mitral regurgitation are associated with increased plasma TNFa and other cytokine concentrations. However, inflammation is also likely to be important since increased TNFa production by peripheral blood mononuclear cells is also predictive of risk. Cytokine activation may be a marker for chronic inflammation. One possible mechanism is increased exposure to endotoxin due to altered gut permeability in patients with edema.Experimental studies suggest that local production of TNFa may have toxic effects on the myocardium, which could explain the association of TNFa with an adverse prognosis.

Interleukin-6: as with TNFa, IL-6 production is increased in patients in HF and may contribute to disease progression.. Higher plasma levels of IL-6 at baseline significantly associated with enhanced mortality.The increase in plasma IL-6 is at least in part derived from the peripheral circulation, where the rate of production varies with the severity of the HF. The rate of cytokine activation can be reduced by optimal medical therapy but persistently high IL-6 levels are associated with increased mortality. It is possible that elevated IL-6 contributes to the decline in cardiac function.As with TFNa, plasma IL-6 also may predict the development of HF.

Chemokines (chemotactic cytokines) are a family of low molecular weight proteins that are potent chemoattractants of monocytes and may modulate the formation of reactive oxygen species and cytokines. Chemokines specific for neutrophils, called CXC chemokines, are distinguished from other chemokines by a protein motif in which the first two cysteines are separated by one amino acid. CXC chemokines are produced by many different cell types, including endothelial cells, platelets, neutrophils, T lymphocytes, and monocytes. The CXC cytokines include IL-8 (previously known as neutrophil activating peptide 1), neutrophil activating peptide-2 (NAP-2), and GRO-alpha. The levels were directly related to the severity of HF evaluated both clinically and hemodynamically. Activated monocytes and platelets may contribute to the elevated levels of CXC chemokines.

Cyclooxygenase-2 (COX-2), which is induced in many cells in response to cytokines, such as TNFa, and ischemia, is an enzyme that catalyzes the conversion of arachidonic acid to prostaglandins and thromboxane A2. COX-2 may play an important role in myocardial inflammation and injury. In one study, myocardial tissue from patients with end-stage heart failure had significant expression of COX-2 in myocytes and inflammatory cells within the area of fibrotic scar, but not in areas of normal myocardium; COX-2 expression was not seen in the myocardium of normal controls.

Myeloperoxidase (MPO) is a leukocyte-derived enzyme that can produce a cascade of reactive oxidative species, which may lead to lipid peroxidation, scavenging of nitric oxide, and nitric oxide synthase inhibition. Plasma MPO levels are elevated in patients with chronic systolic HF. Elevated plasma MPO has been associated with an increased likelihood of more advanced HF and may be predictive of a higher rate of adverse clinical outcomes.

Adrenomedullin is a peptide that was originally isolated from human pheochromocytoma cells; it has an amino acid sequence that is similar to human calcitonin gene-related peptide, a potent vasodilator. In addition to vasodilatory effects on the vasculature, adrenomedullin and its binding sites have been found in the heart and adrenomedullin enhances myocardial contractility via a cyclic AMP-independent mechanism. This suggests that adrenomedullin may play a role in the compensatory mechanisms in HF.Supporting this hypothesis is the observation that circulating levels of adrenomedullin are elevated in patients with HF and are correlated with the degree of left ventricular function and elevation in pulmonary artery pressure. Levels are especially increased in those with evidence of diastolic dysfunction and a restrictive left ventricular filling pattern. An infusion of adrenomedullin causes rapid and long-lasting arterial vasodilation in normal subjects; these actions, which are mediated by a nitric oxide-dependent mechanism, are attenuated in patients with HF. However, even this lesser degree of arterial vasodilation is sufficient to increase the cardiac index and reduce the pulmonary capillary wedge pressure.An elevated plasma adrenomedullin concentration is an independent predictor of a poor outcome in patients with ischemic cardiomyopathy. Carvedilol reduced the risk of death or heart failure only in those with supramedian levels of serum adrenomedullin to rates comparable to those with inframedian values.

Cotransport inhibitory factor (CIF) is a nondigitalis-like natriuretic factor that acts like loop diuretic drugs and inhibits the furosemide-sensitive sodium-potassium-chloride cotransport system. In contrast to ANP, CIF seems to regulate long-term renal sodium excretion. CIF plasma and urinary activities are increased in patients with HF and while they change in parallel with ANP and are correlated with the decrease in LVEF, the increase in plasma CIF is twice as great as those of plasma ANP.

HF is caused by any condition which reduces the efficiency of the myocardium, or heart muscle, through damage or overloading. As such, it can be caused by as diverse an array of conditions as myocardial infarction (in which the heart muscle is starved of oxygen and dies), hypertension (which increases the force of contraction needed to pump blood) and amyloidosis (in which protein is deposited in the heart muscle, causing it to stiffen). Over time these increases in workload will produce changes to the heart itself. Reduced force of contraction, due to overloading of the ventricle. In health, increased filling of the ventricle results in increased force of contraction (by the Frank–Starling law of the heart) and thus a rise in cardiac output. In heart failure this mechanism fails, as the ventricle is loaded with blood to the point where heart muscle contraction becomes less efficient. This is due to reduced ability to cross-link actin and myosin filaments in over-stretched

heart muscle. A reduced stroke volume, as a result of a failure of systole, diastole or both. Increased end systolic volume is usually caused by reduced contractility. Decreased end diastolic volume results from impaired ventricular filling — as occurs when the compliance of the ventricle falls (i.e. when the walls stiffen). As the heart works harder to meet normal metabolic demands, the amount cardiac output can increase in times of increased oxygen demand (e.g. exercise) is reduced. This contributes to the exercise intolerance commonly seen in heart failure. This translates to the loss of one's cardiac reserve. The cardiac reserve refers to the ability of the heart to work harder during exercise or strenuous activity. Since the heart has to work harder to meet the normal metabolic demands, it is incapable of meeting the metabolic demands of the body during exercise.

Increased heart rate, stimulated by increased sympathetic activity in order to maintain cardiac output. Initially, this helps compensate for heart failure by maintaining blood pressure and perfusion, but places further strain on the myocardium, increasing coronary perfusion requirements, which can lead to worsening of ischemic heart disease. Sympathetic activity may also cause potentially fatal arrhythmias.

Hypertrophy (an increase in physical size) of the myocardium, caused by the terminally differentiated heart muscle fibres increasing in size in an attempt to improve contractility. This may contribute to the increased stiffness and decreased ability to relax during diastole.

Enlargement of the ventricles, contributing to the enlargement and spherical shape of the failing heart. The increase in ventricular volume also causes a reduction in stroke volume due to mechanical and contractile inefficiency.

The general effect is one of reduced cardiac output and increased strain on the heart. This increases the risk of cardiac arrest (specifically due to ventricular dysrhythmias), and reduces blood supply to the rest of the body. In chronic disease the reduced cardiac output causes a number of changes in the rest of the body, some of which are physiological compensations, some of which are part of the disease process:

Arterial blood pressure falls. This destimulates baroreceptors in the carotid sinus and aortic arch which link to the nucleus tractus solitarius. This center in the brain increases sympathetic activity, releasing catecholamines into the blood stream. Binding to alpha-1 receptors results in systemic arterial vasoconstriction. This helps restore blood pressure but also increases the total peripheral resistance, increasing the workload of the heart. Binding to beta-1 receptors in the myocardium increases the heart rate and make contractions more forceful, in an attempt to increase cardiac output. This also, however, increases the amount of work the heart has to perform.

Increased sympathetic stimulation also causes the hypothalamus to secrete vasopressin (also known as antidiuretic hormone or ADH), which causes fluid retention at the kidneys. This increases the blood volume and blood pressure.

Reduced perfusion (blood flow) to the kidneys stimulates the release of renin — an enzyme which catalyses the production of the potent vasopressor angiotensin.

Angiotensin and its metabolites cause further vasocontriction, and stimulate increased secretion of the steroid aldosterone from the adrenal glands. This promotes salt and fluid retention at the kidneys, also increasing the blood volume.

The chronically high levels of circulating neuroendocrine hormones such as catecholamines, renin, angiotensin, and aldosterone affects the myocardium directly, causing structural remodelling of the heart over the long term. Many of these remodelling effects seem to be mediated by transforming growth factor beta (TGF-beta), which is a common downstream target of the signal transduction cascade initiated by catecholamines and angiotensin II, and also by epidermal growth factor (EGF), which is a target of the signaling pathway activated by aldosterone.

Reduced perfusion of skeletal muscle causes atrophy of the muscle fibres. This can result in weakness, increased fatigueability and decreased peak strength — all contributing to exercise intolerance.

The increased peripheral resistance and greater blood volume place further strain on the heart and accelerates the process of damage to the myocardium. Vasoconstriction and fluid retention produce an increased hydrostatic pressure in the capillaries. This shifts the balance of forces in favour of interstitial fluid formation as the increased pressure forces additional fluid out of the blood, into the tissue. This results in edema (fluid build-up) in the tissues. In right-sided heart failure this commonly starts in the ankles where venous pressure is high due to the effects of gravity (although if the patient is bed-ridden, fluid accumulation may begin in the sacral region.) It may also occur in the abdominal cavity, where the fluid build-up is called ascites. In left-sided heart failure edema can occur in the lungs — this is called cardiogenic pulmonary edema. This reduces spare capacity for ventilation, causes stiffening of the lungs and reduces the efficiency of gas exchange by increasing the distance between the air and the blood. The consequences of this are shortness of breath, orthopnea and paroxysmal nocturnal dyspnea.

The symptoms of heart failure are largely determined by which side of the heart fails. The left side pumps blood into the systemic circulation, whilst the right side pumps blood into the pulmonary circulation. Whilst left-sided heart failure will reduce cardiac output to the systemic circulation, the initial symptoms often manifest due to effects on the pulmonary circulation. In systolic dysfunction, the ejection fraction is decreased, leaving an abnormally elevated volume of blood in the left ventricle. In diastolic dysfunction, end-diastolic ventricular pressure will be high. This increase in volume or pressure backs up to the left atrium and then to the pulmonary veins. Increased volume or pressure in the pulmonary veins impairs the normal drainage of the alveoli and favors the flow of fluid from the capillaries to the lung parenchyma, causing pulmonary edema. This impairs gas exchange. Thus, left-sided heart failure often presents with respiratory symptoms: shortness of breath, orthopnea and paroxysmal nocturnal dyspnea.

In severe cardiomyopathy, the effects of decreased cardiac output and poor perfusion become more apparent, and patients will manifest with cold and clammy extremities, cyanosis, claudication, generalized weakness, dizziness, and syncope.

The resultant hypoxia caused by pulmonary edema causes vasoconstriction in the pulmonary circulation, which results in pulmonary hypertension. Since the right ventricle generates far lower pressures than the left ventricle (approximately 20 mmHg versus around 120 mmHg, respectively, in the healthy individual) but nonetheless generates cardiac output exactly equal to the left ventricle, this means that a small increase in pulmonary vascular resistance causes a large increase in amount of work the right ventricle must perform. However, the main mechanism by which left-sided heart failure causes right-sided heart failure is actually not well understood. Some theories invoke mechanisms that are mediated by neurohormonal activation. Mechanical effects may also contribute. As the left ventricle distends, the intraventricular septum bows into the right ventricle, decreasing the capacity of the right ventricle.

Systolic dysfunction:

HF caused by systolic dysfunction is more readily recognized. It can be simplistically described as failure of the pump function of the heart. It is characterized by a decreased ejection fraction (less than 45 %). The strength of ventricular contraction is attenuated and inadequate for creating an adequate stroke volume, resulting in inadequate cardiac output. In general, this is caused by dysfunction or destruction of cardiac myocytes or their molecular components. In congenital diseases such as Duchenne muscular dystrophy, the molecular structure of individual myocytes is affected. Myocytes and their components can be damaged by inflammation (such as in myocarditis) or by infiltration (such as in amyloidosis). Toxins and pharmacological agents (such as ethanol, cocaine, and amphetamines) cause intracellular damage and oxidative stress. The most common mechanism of damage is ischemia causing infarction and scar formation. After myocardial infarction, dead myocytes are replaced by scar tissue, deleteriously affecting the function of the myocardium. On echocardiogram, this is manifest by abnormal or absent wall motion.

Because the ventricle is inadequately emptied, ventricular end-diastolic pressure and volumes increase. This is transmitted to the atrium. On the left side of the heart, the increased pressure is transmitted to the pulmonary vasculature, and the resultant hydrostatic pressure favors extravassation of fluid into the lung parenchyma, causing pulmonary edema. On the right side of the heart, the increased pressure is transmitted to the systemic venous circulation and systemic capillary beds, favoring extravassation of fluid into the tissues of target organs and extremities, resulting in dependent peripheral edema.

Diastolic dysfunction

Heart failure caused by diastolic dysfunction is generally described as the failure of the ventricle to adequately relax and typically denotes a stiffer ventri-

cular wall. This causes inadequate filling of the ventricle, and therefore results in an inadequate stroke volume. The failure of ventricular relaxation also results in elevated end-diastolic pressures, and the end result is identical to the case of systolic dysfunction (pulmonary edema in left heart failure, peripheral edema in right heart failure). Diastolic dysfunction can be caused by processes similar to those that cause systolic dysfunction, particularly causes that affect cardiac remodeling. Diastolic dysfunction may not manifest itself except in physiologic extremes if systolic function is preserved. The patient may be completely asymptomatic at rest. However, they are exquisitely sensitive to increases in heart rate, and sudden bouts of tachycardia (which can be caused simply by physiological responses to exertion, fever, or dehydratation, or by pathological tachyarrhythmias such as atrial fibrillation with rapid ventricular response) may result in flash pulmonary edema. Adequate rate control (usually with a pharmacological agent that slows down AV conduction such as a calcium channel blocker or a beta-blocker) is therefore key to preventing decompensation.Left ventricular diastolic function can be determined through echocardiography by measurement of various parameters such as the E/A ratio (early-to-atrial left ventricular filling ratio), the E (early left ventricular filling) deceleration time, and the isovolumic relaxation time.

Classification

There are many different ways to categorize heart failure, including:

- The side of the heart involved (left heart failure versus right heart failure). Left heart failure compromises aortic flow to the body and brain. Right heart failure compromises pulmonic flow to the lungs. Mixed presentations are common, especially when the cardiac septum is involved.
- Whether the abnormality is due to insufficient contraction (systolic dysfunction), or due to insufficient relaxation of the heart (diastolic dysfunction), or to both.
- Whether the problem is primarily increased venous back pressure (preload), or failure to supply adequate arterial perfusion (afterload).
- Whether the abnormality is due to low cardiac output with high systemic vascular resistance or high cardiac output with low vascular resistance (low-output heart failure vs. high-output heart failure).
- The degree of functional impairment conferred by the abnormality (as reflected in the New York Heart Association Functional Classification).
- The degree of coexisting illness: i.e. heart failure/systemic hypertension, heart failure/pulmonary hypertension, heart failure/diabetes, heart failure/renal failure, etc.

Functional classification generally relies on the New York Heart Association functional classification. The classes (I-IV) are:

Class I: no limitation is experienced in any activities; there are no symptoms from ordinary activities.

Class II: slight, mild limitation of activity; the patient is comfortable at rest or with mild exertion.

Class III: marked limitation of any activity; the patient is comfortable only at rest.

Class IV: any physical activity brings on discomfort and symptoms occur at rest.

This score documents severity of symptoms, and can be used to assess response to treatment. While its use is widespread, the NYHA score is not very reproducible and doesn't reliably predict the walking distance or exercise tolerance on formal testing. In its 2001 guidelines the AmericanCollege of Cardiology/American Heart Association working group introduced four stages of heart failure:

Stage A: Patients at high risk for developing HF in the future but no functional or structural heart disorder.

Stage B: a structural heart disorder but no symptoms at any stage.

Stage C: previous or current symptoms of heart failure in the context of an underlying structural heart problem, but managed with medical treatment.

Stage D: advanced disease requiring hospital-based support, a heart transplant or palliative care.

The ACC staging system is useful in that Stage A encompasses «pre-heart failure» — a stage where intervention with treatment can presumably prevent progression to overt symptoms. ACC Stage A does not have a corresponding NYHA class. ACC Stage B would correspond to NYHA Class I. ACC Stage C corresponds to NYHA Class II and III, while ACC Stage D overlaps with NYHA Class IV.

Signs of left-sided HF: common respiratory signs are tachypnea (increased rate of breathing) and increased work of breathing (non-specific signs of respiratory distress). Rales or crackles, heard initially in the lung bases, and when severe, throughout the lung fields suggest the development of pulmonary edema (fluid in the alveoli). Cyanosis which suggests severe hypoxemia, is a late sign of extremely severe pulmonary edema.Additional signs indicating left ventricular failure include a laterally displaced apex beat (which occurs if the heart is enlarged) and a gallop rhythm (additional heart sounds) may be heard as a marker of increased blood flow, or increased intra-cardiac pressure. Heart murmurs may indicate the presence of valvular heart disease, either as a cause (e.g. aortic stenosis) or as a result (e.g., mitral regurgitation) of the heart failure.

Signs of right-sided HF: physical examination can reveal pitting peripheral edema, ascites, and hepatomegaly. Jugular venous pressure is frequently assessed as a marker of fluid status, which can be accentuated by eliciting hepatojugular reflux. If the right ventricular pressure is increased, a parasternal heave may be present, signifying the compensatory increase in contraction strength.

Biventricular failure: dullness of the lung fields to finger percussion and reduced breath sounds at the bases of the lung may suggest the development of a pleural effusion (fluid collection in between the lung and the chest wall). Though it can occur in isolated left- or right-sided heart failure, it is more common in bi-

ventricular failure because pleural veins drain both into the systemic and pulmonary venous system. When unilateral, effusions are often right sided.

Diagnosis

Symptoms: HF symptoms are traditionally and somewhat arbitrarily divided into «left» and «right» sided, recognizing that the left and right ventricles of the heart supply different portions of the circulation. However, heart failure is not exclusively backward failure (in the part of the circulation which drains to the ventricle).There are several other exceptions to a simple left-right division of heart failure symptoms. Left sided forward failure overlaps with right sided backward failure. Additionally, the most common cause of right-sided heart failure is left-sided heart failure. The result is that patients commonly present with both sets of signs and symptoms.

Left-sided failure: backward failure of the left ventricle causes congestion of the pulmonary vasculature, and so the symptoms are predominantly respiratory in nature. Backward failure can be subdivided into failure of the left atrium, the left ventricle or both within the left circuit. The patient will have dyspnea (shortness of breath) on exertion (dyspnée d'effort) and in severe cases, dyspnea at rest. Increasing breathlessness on lying flat, called orthopnea, occurs. It is often measured in the number of pillows required to lie comfortably, and in severe cases, the patient may resort to sleeping while sitting up. Another symptom of heart failure is paroxysmal nocturnal dyspnea a sudden nighttime attack of severe breathlessness, usually several hours after going to sleep. Easy fatigueability and exercise intolerance are also common complaints related to respiratory compromise. «Cardiac asthma» or wheezing may occur. Compromise of left ventricular forward function may result in symptoms of poor systemic circulation such as dizziness, confusion and cool extremities at rest.

Right-sided failure: backward failure of the right ventricle leads to congestion of systemic capillaries. This generates excess fluid accumulation in the body. This causes swelling under the skin (termed peripheral edema or anasarca) and usually affects the dependent parts of the body first (causing foot and ankle swelling in people who are standing up, and sacral edema in people who are predominantly lying down). Nocturia (frequent nighttime urination) may occur when fluid from the legs is returned to the bloodstream while lying down at night. In progressively severe cases, ascites (fluid accumulation in the abdominal cavity causing swelling) and hepatomegaly (enlargement of the liver) may develop. Significant liver congestion may result in impaired liver function, and jaundice and even coagulopathy (problems of decreased blood clotting) may occur.

The diagnosis of HF is relatively straightforward when the patient presents with classic signs and symptoms of HF; however, the signs and symptoms of HF are neither specific nor sensitive. Accordingly, the key to making the diagnosis is to have a high index of suspicion, particularly for high-risk patients. When

these patients present with signs or symptoms of HF, additional laboratory testing should be performed.

Framingham criteria: by the Framingham criteria, diagnosis of congestive heart failure (heart failure with impaired pumping capability) requires the simultaneous presence of at least 2 of the following major criteria or 1 major criterion in conjunction with 2 of the following minor criteria. Major criteria:

- Cardiomegaly on chest radiography.
- S3 gallop (a third heart sound)
- Acute pulmonary edema.
- Paroxysmal nocturnal dyspnea.
- Crackles on lung auscultation.
- Central venous pressure of more than 16 cm H2O at the right atrium.
- Jugular vein distension.
- Positive abdominojugular test.
- Weight loss of more than 4.5 kg in 5 days in response to treatment (sometimes classified as a minor criterium).

Minor criteria:

- Tachycardia of more than 120 beats per minute.
- Nocturnal cough.
- Dyspnea on ordinary exertion.
- Pleural effusion.
- Decrease in vital capacity by one third from maximum recorded.
- Hepatomegaly.
- Bilateral ankle edema.

Minor criteria are acceptable only if they can not be attributed to another medical condition such as pulmonary hypertension, chronic lung disease, cirrhosis, ascites, or the nephrotic syndrome. The Framingham Heart Study criteria are 100 % sensitive and 78 % specific for identifying persons with definite congestive heart failure.

Laboratory Testing: patients with new-onset HF and those with chronic HF and acute decompensation should have a complete blood count, a panel of electrolytes, blood urea nitrogen, serum creatinine, hepatic enzymes, and a urinalysis. Selected patients should have assessment for diabetes mellitus (fasting serum glucose or oral glucose tolerance test), dyslipidemia (fasting lipid panel), and thyroid abnormalities (thyroid-stimulating hormone level).

Biomarkers: circulating levels of natriuretic peptides are useful adjunctive tools in the diagnosis of patients with HF. Both B-type natriuretic peptide (BNP) and N-terminal pro-BNP, which are released from the failing heart, are relatively sensitive markers for the presence of HF with depressed EF; they also are elevated in HF patients with a preserved EF, albeit to a lesser degree. However, it is important to recognize that natriuretic peptide levels increase with age and renal

impairment, are more elevated in women, and can be elevated in right HF from any cause. Levels can be falsely low in obese patients and may normalize in some patients after appropriate treatment. At present, serial measurements of BNP are not recommended as a guide to HF therapy. Other biomarkers, such as troponin T and I, C-reactive protein, TNF receptors, and uric acid, may be elevated in HF and provide important prognostic information. Serial measurements of one or more biomarkers ultimately may help guide therapy in HF, but they are not currently recommended for this purpose.

Electrocardiogram (ECG): a routine 12-lead ECG is recommended. The major importance of the ECG is to assess cardiac rhythm and determine the presence of LV hypertrophy or a prior MI (presence or absence of Q waves) as well as to determine QRS width to ascertain whether the patient may benefit from resynchronization therapy (see below). A normal ECG virtually excludes LV systolic dysfunction.

Chest X-Ray: a chest x-ray provides useful information about cardiac size and shape, as well as the state of the pulmonary vasculature, and may identify noncardiac causes of the patient's symptoms. Although patients with acute HF have evidence of pulmonary hypertension, interstitial edema, and/or pulmonary edema, the majority of patients with chronic HF do not. The absence of these findings in patients with chronic HF reflects the increased capacity of the lymphatics to remove interstitial and/or pulmonary fluid.

Assessment of LV Function: noninvasive cardiac imaging is essential for the diagnosis, evaluation, and management of HF. The most useful test is the two-dimensional (2-D) echocardiogram/Doppler, which can provide a semiquantitative assessment of LV size and function as well as the presence or absence of valvular and/or regional wall motion abnormalities (indicative of a prior MI). The presence of left atrial dilation and LV hypertrophy, together with abnormalities of LV diastolic filling provided by pulse-wave and tissue Doppler, is useful for the assessment of HF with a preserved EF. The 2-D echocardiogram/Doppler is also invaluable in assessing RV size and pulmonary pressures, which are critical in the evaluation and management of cor pulmonale (see below). Magnetic resonance imaging (MRI) also provides a comprehensive analysis of cardiac anatomy and function and is now the gold standard for assessing LV mass and volumes. MRI also is emerging as a useful and accurate imaging modality for evaluating patients with HF, both in terms of assessing LV structure and for determining the cause of HF (e.g., amyloidosis, ischemic cardiomyopathy, hemochromatosis).The most useful index of LV function is the EF (stroke volume divided by end-diastolic volume). Because the EF is easy to measure by noninvasive testing and easy to conceptualize, it has gained wide acceptance among clinicians. Unfortunately, the EF has a number of limitations as a true measure of contractility, since it is influenced by alterations in afterload and/or preload. Nonetheless, with the exceptions indicated above, when the EF

is normal (> 50 %), systolic function is usually adequate, and when the EF is significantly depressed (< 30–40 %), contractility is usually depressed.

Exercise Testing: treadmill or bicycle exercise testing is not routinely advocated for patients with HF, but either is useful for assessing the need for cardiac transplantation in patients with advanced HF. A peak oxygen uptake (V_{o2}) < 14 mL/kg per min is associated with a relatively poor prognosis. Patients with a V_{o2} < 14 mL/kg per min have been shown, in general, to have better survival when transplanted than when treated medically.

HF resembles but should be distinguished from conditions in which there is circulatory congestion secondary to abnormal salt and water retention but in which there is no disturbance of cardiac structure or function (e. g., renal failure) and noncardiac causes of pulmonary edema (e. g., acute respiratory distress syndrome). In most patients who present with classic signs and symptoms of HF, the diagnosis is relatively straightforward. However, even experienced clinicians have difficulty differentiating the dyspnea that arises from cardiac and pulmonary causes. In this regard, noninvasive cardiac imaging, biomarkers, pulmonary function testing, and chest x-ray may be useful. A very low BNP or N-terminal pro-BNP may be helpful in excluding a cardiac cause of dyspnea in this setting. Ankle edema may arise secondary to varicose veins, obesity, renal disease, or gravitational effects. When HF develops in patients with a preserved EF, it may be difficult to determine the relative contribution of HF to the dyspnea that occurs in chronic lung disease and/or obesity.

Management

Management focuses on improving the symptoms and preventing the progression of the disease. Reversible causes of the heart failure also need to be addressed: (e.g. infection, alcohol ingestion, anemia, thyrotoxicosis, arrhythmia, hypertension). Treatments include lifestyle and pharmacological modalities.

Acute decompensated heart failure (ADHF) is a common and potentially fatal cause of acute respiratory distress. The clinical syndrome is characterized by the development of dyspnea, often associated with accumulation of fluid within the lung's interstitial and alveolar spaces, which is the result of acutely elevated cardiac filling pressures (cardiogenic pulmonary edema). ADHF can also present as elevated left ventricular filling pressures and dyspnea without pulmonary edema. ADHF is most commonly due to left ventricular (LV) systolic or diastolic dysfunction, with or without additional cardiac pathology, such as coronary artery disease or valve abnormalities. However, a variety of conditions or events can cause pulmonary edema due to an elevated pulmonary capillary wedge pressure in the absence of heart disease, including primary fluid overload (eg, due to blood transfusion), severe hypertension and severe renal disease.

Major Society Guidelines: the following recommendations are generally in agreement with those published in the American College of Cardiology/American Heart Association (ACC/AHA)

heart failure guidelines and in the Heart Failure Society of America (HFSA) guidelines for ADHF. Similar recommendations were provided in European Society of Cardiology (ESC) guidelines for acute heart failure. Additional recommendations are provided in the Society of Chest Pain Centers recommendations for the acute heart failure patient. As noted in HFSA guidelines, hospital admission is recommended for patients with ADHF with the following clinical conditions:

- Evidence of severely decompensated HF including hypotension, worsening renal function, or altered mentation. This is also supported by the ACC/AHA focused update, which recommends that patients with rapid decompensation and hypoperfusion associated with decreasing urine output or other manifestations of shock should receive rapid intervention to improve systemic perfusion.
- Dyspnea at rest, which is typically reflected by resting tachypnea and less commonly reflected by oxygen saturation < 90 percent.
- Hemodynamically significant arrhythmia including new onset of atrial fibrillation with rapid ventricular response.
- Acute coronary syndromes.

Hospitalization should be considered for patients with ADHF with the following clinical conditions:

- Worsened congestion, even if without dyspnea.
- Signs and symptoms of pulmonary or systemic congestion, even in the absence of weight gain.
- Major electrolyte disturbance.
- Associated comorbid conditions such as pneumonia, pulmonary embolus, diabetic ketoacidosis, or symptoms suggestive of transient ischemic attack or stroke.
- Repeated ICD firings.
- Previously undiagnosed HF with signs and symptoms of systemic or pulmonary congestion.

Monitoring: patients who are admitted to the hospital for the management of ADHF are at risk for hemodynamic instability and arrhythmias, so close monitoring is necessary. The HFSA guidelines recommend more than daily monitoring of vital signs (including orthostatic blood pressure) and at least daily monitoring of weight, fluid intake and output, symptoms and signs of congestion, serum electrolytes, BUN, and serum creatinine, and oxygen saturation until stable. Serum potassium and magnesium levels should be monitored at least daily, and more frequent monitoring may be required when diuresis is rapid. Routine tests include blood glucose, troponin, complete blood count, and the INR if warfarin is used. Evaluation of BNP or NT-proBNP, liver function tests, and urinalysis is frequently indicated and arterial blood gas testing is occasionally indicated (eg, to detect carbon dioxide retention). Telemetry is usually continued for at least 24 to 48 hours. This may be discontinued once the patient's hemodynamics, medication regimen, and electrolytes are stable.

Documentation of effective diuresis: ADHF is associated with an exceptionally high rate of readmissions, which is due in part to inadequate fluid removal during the initial admission. Persistent congestion may be difficult to discern and accurate intake and output assessments are often difficult to maintain. Daily assessment of patient weight may be the most effective method for documenting effective diuresis. For accurate comparisons, daily measurements should use the same scale and should be performed at the same time each day, usually in the morning, prior to eating and after voiding. Weight comparisons may require adjustment for variations in food intake. Hemodynamic monitoring: in patients with adequate acoustic windows, echocardiography may provide a noninvasive means of estimating filling pressures.

The HFSA guidelines recommend the following treatment goals for patients admitted for ADHF:

- Improve symptoms, especially congestion and low-output symptoms.

- Restore normal oxygenation.
- Optimize volume status.
- Identify etiology.
- Identify and address precipitating factors.
- Optimize chronic oral therapy.
- Minimize side effects.
- Identify patients who might benefit from revascularization.
- Identify patients who might benefit from device therapy.
- Identify risk of thromboembolism and need for anticoagulant therapy.
- Educate patients concerning medications and self management of HF.
- Consider and, where possible, initiate a disease-management program.

Treatment goals for acute versus chronic HF: it is important to distinguish the management of ADHF from that of chronic HF. The treatment of chronic HF, particularly when due to systolic dysfunction, is built around therapies that have been shown to reduce long-term mortality and improve symptoms (eg, ACE inhibitors and beta blockers).In contrast, the goals of the initial management of ADHF are hemodynamic stabilization, support of oxygenation and ventilation, and symptom relief. Some of the cornerstones of chronic HF therapy should not be added or should be used with caution in ADHF (eg, beta blockers), particularly during the period of initial stabilization. Such therapies may be initiated or titrated upward later in a patient's course.

Chronic HF should be viewed as a continuum that is composed of four interrelated stages. Stage A includes patients who are at high risk for developing HF but do not have structural heart disease or symptoms of HF (e.g., patients with diabetes mellitus or hypertension). Stage B includes patients who have structural heart disease but do not have symptoms of HF (e.g., patients with a previous MI and asymptomatic LV dysfunction). Stage C includes patients who have structural heart disease and have developed symptoms of HF (e.g., patients with a previous MI with dyspnea and fatigue). Stage D includes patients with refractory HF requiring special interventions (e.g., patients with refractory HF who are awaiting cardiac transplantation). In this continuum, every effort should be made to prevent HF not only by treating the preventable causes of HF (e.g., hypertension) but also by treating the patient in stages B and C with drugs that prevent disease progression (e.g., ACE inhibitors and beta blockers) and by symptomatic management of patients in stage D.

Defining an Appropriate Therapeutic Strategy for Chronic HF

Once patients have developed structural heart disease, their therapy depends on their NYHA functional classification. Although this classification system is notoriously subjective and has large interobserver variability, it has withstood the test of time and continues to be widely applied to patients with HF. For patients who have developed LV systolic dysfunction but remain asymptomatic (class I), the goal should be to slow disease progression by

blocking neurohormonal systems that lead to cardiac remodeling. For patients who have developed symptoms (class II–IV), the primary goal should be to alleviate fluid retention, lessen disability, and reduce the risk of further disease progression and death. These goals generally require a strategy that combines diuretics (to control salt and water retention) with neurohormonal interventions (to minimize cardiac remodeling).

Management of HF with Depressed Ejection Fraction (< 40 %): clinicians should aim to screen for and treat comorbidities such as hypertension, CAD, diabetes mellitus, anemia, and sleep-disordered breathing, as these conditions tend to exacerbate HF. HF patients should be advised to stop smoking and to limit alcohol consumption to two standard drinks per day in men or one per day in women. Patients suspected of having an alcohol-induced cardiomyopathy should be urged to abstain from alcohol consumption indefinitely. Extremes of temperature and heavy physical exertion should be avoided. Certain drugs are known to make HF worse and should be avoided. For example, nonsteroidal anti-inflammatory drugs, including cyclooxygenase 2 inhibitors, are not recommended in patients with chronic HF because the risk of renal failure and fluid retention is markedly increased in the presence of reduced renal function or ACE inhibitor therapy. Patients should receive immunization with influenza and pneumococcal vaccines to prevent respiratory infections. It is equally important to educate the patient and family about HF, the importance of proper diet, and the importance of compliance with the medical regimen. Supervision of outpatient care by a specially trained nurse or physician assistant and/or in specialized HF clinics has been found to be helpful, particularly in patients with advanced disease.

Surgical treatment of HF: options for surgical management of patients with end-stage, refractory systolic heart failure are more limited. Heart transplantation or complex «heart-lungs» transplantation remains the ultimate treatment for end-stage heart failure, but the persistent shortage of donor hearts, contraindications due to recipient comorbidities, and transplant complications limit the utility of this approach. Thus, heart transplantation is not an option for most patients with end-stage heart failure. Other surgical approaches to end-stage heart failure continue to evolve. Although large randomized trials are unusual in this field, important steps have been made over the past 10 to 15 years, as discussed below. However, the use of any of these approaches remains highly individualized. Current strategies include:

- Coronary revascularization in selected patients with ischemic cardiomyopathy and hibernating myocardium.
- Left ventricular assist devices (LVADs) as a bridge to heart transplantation or as permanent circulatory assistance, also referred to as destination therapy. The use of these devices is discussed elsewhere.
- Mitral valve repair in selected patients with dilated cardiomyopathy. Despite significant functional improvement, no survival benefit has been demonstrated.
- Reconstructive cardiac surgery in patients with large akinetic or dyskinetic regions can help improve left ventricular structure and function but a uniform clinical benefit has not been established.

Coronary revascularization: coronary heart disease causes irreversible as well as reversible left ventricular dysfunction. Myocardial segments involved in MI may subsequently recover, either spontaneously or after revascularization, and left ventricular ejection fraction (LVEF) may improve markedly, and even normalize, in subsets of patients following successful revascularization. The recoverable or viable myocardium has been termed «hibernating» myocardium when the ischemia is chronic and «stunned» myocardium when the insult is transient.

Mitral valve repair: some degree of mitral regurgitation is almost always present in patients with severe systolic dysfunction, regardless of etiology. In this setting, mitral incompetence is a consequence of mitral annular dilation, electromechanical dyssynchrony, and changes in the subvalvular geometry. Although it is usually functional in nature, the regurgitant flow imposes a hemodynamic load on the left ventricle, leading to eccentric hypertrophy and dilatation that increases the degree of mitral regurgitation in a vicious cycle. Treatment of functional mitral regurgitation should focus on optimizing medical therapy of heart failure and when appropriate, cardiac resynchronization therapy. In selected patients, mitral valve repair, in which the subvalvular apparatus including the chordal and papillary muscles, is left intact, can lead to reduced ventricular size, improvements in LVEF, and improved symptoms of heart failure. However, observational data suggest that these benefits are not associated with improved survival. Some investigators advocate combined mitral valve repair and left ventricular reconstruction in patients with heart failure and significant mitral regurgitation. Methods for percutaneous mitral valve repair to treat mitral regurgitation are under investigation.

Left ventricular reconstruction: left ventricular reconstruction or volume reduction procedures were developed as potential alternatives to cardiac transplantation. This strategy grew out of earlier experience with ventricular aneurysmectomy. The procedure can produce more normal left ventricular geometry and improve left ventricular systolic function but a beneficial impact on clinical status and long-term survival has not been established.In the setting of systolic heart failure, the ventricular cavity size enlarges to maintain stroke volume with associated changes in ventricular geometry (the ventricle becomes less ellipsoid and more spherical). Increases in ventricular cavity size (without adequate compensatory hypertrophy) result in increases in wall stress as governed by Laplace's law (stress = (pressure x radius) ÷ (2 x wall thickness)). Increased wall stress stimulates processes that lead to further ventricular dilatation and systolic dysfunction. Thus changes in size and geometry are thought to lead to progressive left ventricular dysfunction and worsening heart failure. Surgical removal or exclusion of portions of dysfunctional myocardium and/or infarcted territories can return the left ventricle to a more normal cavity volume/mass ratio and geometry. Based upon Laplace's law, reduction in internal cavity dimensions leads to reduced end-systolic and end-diastolic wall stress. In this way, cardiac work efficiency may be improved, which theoretically could improve the symptoms of heart failure. Limited evidence has shown some ventricular functional improvement following surgical reconstruction and the degree of myocardial fibrosis and myocyte hypertrophy appear to be inversely correlated with improvements in left ventricular function after partial ventriculectomy. In addition, neurohormonal activation may be reduced by left ventricular reconstruction. However, data on clinical benefit are limited and a mortality benefit has not been proven.

Dor procedure: left ventricular aneurysmectomy has been offered as an option for selected patients with symptomatic aneurysms which have been defined as including those associated with heart failure, angina pectoris, systemic embolization, and/or malignant ventricular tachyarrhythmias. The Dor procedure, also called endoventricular circular patch plasty (EVCPP) or endoventricular patch reconstruction, is an approach to surgical reconstruction in the setting of postinfarction aneurysm formation.

SAVER procedure: a modification of the Dor procedure, surgical anterior ventricular endocardial restoration (SAVER), is performed on the dilated, remodeled ventricle after anterior MI and consists of exclusion of noncontracting segments from the ventricular cavity.

Mechanical inhibition of dilation: the Acorn CorCap device is a knitted polyester sock that is drawn up and anchored over the ventricles in order to limit left ventricular dilation and remodeling and improve LVEF.

Largely abandoned procedures

Batista procedure: as originally described, the Batista procedure, or partial left ventriculectomy (or partial left ventricular resection), involved the removal of a section of the left ventricular free wall, between both papillary muscles and extending from the apex to the mitral annulus. An improvement in heart failure and LVEF was thought to result from a reduction in peak wall stress and possibly a more uniform pattern of left ventricular contraction and relaxation. Current practice guidelines note that partial left ventriculectomy is not recommended in nonischemic cardiomyopathy.

Cardiomyoplasty, also referred to as «dynamic cardiomyoplasty», is a surgical therapy for dilated cardiomyopathy in which the latissimus dorsi muscle is wrapped around the heart and paced during ventricular systole. Postoperative observations suggested that progressive left ventricular dilation could be slowed in some patients by the diastolic «girdling» effect of the muscle wrap.Early enthusiasm was driven by improvements in functional capacity and ventricular remodeling, but long-term outcome data were limited. A large, randomized clinical trial of cardiomyoplasty in NYHA class III patients was prematurely terminated because of poor enrollment and modest clinical benefit. These data suggested that those who could survive the operation did not need it, and those who did need it could not survive it. For these reasons, cardiomyoplasty is no longer performed for the management of heart failure.

Prevention of HF requires early detection and treatment of predisposing conditions and of high-risk candidates by internists and general practitioners.

Risk factor reduction.The high risk for HF associated with hypertension, diabetes, coronary disease, and obesity identify these as priority areas for preventive efforts. As an example, major hypertension trials clearly indicate that treating hypertension reduces the risk of HF. The impact of healthy lifestyle habits (normal body weight, not smoking, regular exercise (five or more times per week), moderate alcohol intake (5 or more drinks/week), consumption of breakfast cereals, and consumption of fruits and vegetables), reduce salt consumption, on heart failure risk was examined in a study of 20,900 men from the Physicians' Health Study. The analysis revealed that healthy lifestyle habits were associated with lower lifetime risk, with highest risk (21 percent) in men adhering to none of the six lifestyle factors (21 percent) and the lowest risk (10 percent) in men adhering to four or more of these factors.

5. HEART RHYTHM DISORDERS DEFINITION AND OVERVIEW

Definitions and introduction

A heart rhythm disorder is an abnormal variation from the normal heartbeat. Heart rhythm disorders involve abnormalities of one or more of the following: heart rate, regularity of beats, sites where electrical impulses originate, or sequence of activation of heartbeats. Heart rhythm disorder is also referred to as an arrhythmia.

The primary function of the heart is to supply blood and nutrients to the body. The regular beating, or contraction, of the heart moves the blood throughout the body. Each heartbeat is controlled by electrical impulses traveling through the heart. In the normal heart these electrical impulses occur in regular intervals. When something goes wrong with the heart's electrical system, the heart does not beat regularly. The irregular beating results in a heart rhythm disorder, or arrhythmia.

The electrical system regulating heartbeat consists of:

- The sinoatrial, or SA, node is located in the right atrium. It provides the main control and is the source of each beat. The SA node also keeps up with the body's overall need for blood and increases the heart rate when necessary, such as during exercise, emotional excitement, or illness such as fever. The SA node is sometimes called the «natural pacemaker» of the heart.
- Atrioventricular, or AV node. Electrical impulses leave the SA node and travel through special conducting pathways in the heart to the other controller, the AV node. The purpose of the AV node is to provide a pathway for impulses from the atria to the ventricles. It also creates a delay in conduction from the atria to the ventricle. This causes the atria to contract first and allow the ventricles to fill with blood before they contract themselves. The delay ensures proper timing so that the lower chambers of the heart (ventricles) have time to fill completely before they contract.

Normally, the heart beats about 60 to 100 times a minute. This state is called «normal sinus rhythm» or «normal rhythm» or «normal heartbeat». Depending upon the needs of the body, it may beat faster (sinus tachycardia) due to stress or slower (sinus bradycardia) such as during sleep.

Arrhythmias electrophysiological mechanizms:

Re-entry

Re-entry is a common cause of arrhythmias. A prerequisite for re-entry is the presence of two pathways with differing conduction velocities that connect two points, in this case the atria with the ventricles. The signal splits in two at arrival, but no arrhythmia is initiated as the slow signal becomes extinct when it meets the fast signal. However, after an extrasystole the fast pathway is still refractory and conduction is by the slow pathway, resulting in a prolongation of the PR interval. The signal that reaches the His by the slow pathway may find the fast pathway conducting and return to the atria, resulting in an echo beat. This may set in motion a re-entry pathway through the AV node resulting in AV nodal tachycardia. Ventricular tachycardia and AV-nodal re-entry are typical examples. Re-entry can occur when a conduction path is partly slowed down. As

a result of this, the signal is conducted by both a fast and a slow pathway. During normal sinus rhythm this generally does not cause problems, but when an extrasystole follows rapidly upon the previous beat, the fast pathway is sometimes still refractory and cannot conduct the signal.

Now the following sequence results in re-entry:

1. The atrial signal coming from above is conducted by the slow pathway.

2. As the signal, going through the slow pathway, reaches the end of the fast pathway, it finds this pathway able to conduct.

3. The signal is conducted through the fast pathway up to the beginning of the slow pathway, which by that time is able to conduct.

4. This circle is perpetuated and a signal generator is created. In the case of AV-nodal re-entry this will typically generate a signal at a frequency of 180–250 bpm.

Triggered Activity

Triggered activity (TA) is defined by impulse initiation caused by afterdepolarizations (membrane potential oscillations that occur during or immediately following a preceding AP). Afterdepolarizations occur only in the presence of a previous AP (the trigger), and when they reach the threshold potential, a new AP is generated. This may be the source of a new triggered response, leading to self-sustaining TA.

Based on their temporal relationship, 2 types of afterpolarizations are described: early afterdepolarizations (EADs) occur during phase 2 or 3 of the AP, and delayed afterdepolarizations (DADs) occur after completion of the repolarization phase.

Delayed Afterdepolarization-Induced Triggered Activity

A DAD is an oscillation in membrane voltage that occurs after completion of repolarization of the AP (during phase 4).

These oscillations are caused by a variety of conditions that raise the diastolic intracellular Ca^{2+} concentration, which cause Ca^{2+} mediated oscillations that can trigger a new AP if they reach the stimulation threshold. As the cycle length decreases, the amplitude and rate of the DADs increases, and therefore is expected to initiate arrhythmias triggered when DADs increase the heart rate (either spontaneously or during pacing). In fact, the amplitude and number of triggered responses are direct functions of both the rate and duration of overdrive pacing (easier to induce with continued stimulation). When overdrive pacing is performed, the TA can slow until it stops, or when it is not rapid enough to terminate the triggered rhythm it can cause overdrive acceleration, in contrast to overdrive suppression seen with automatic rhythms. Toxic concentration of digitalis was the first observed cause of DAD. This occurs via inhibition of the Na/K pump, which promotes the release of Ca^{2+} from the sarcoplasmic reticulum. Clinically, digoxin toxic bidirectional fascicular tachycardia is felt to be an example of TA. Catecholamines can cause DADs by causing intracellular Ca^{2+} overload via an increase in $I_{Ca\text{-}L}$and theNa^{+}-Ca^{2+} exchange current, among other mechanisms. Ischemia-induced DADs are thought to be mediated by the accumulation of lysophosphoglycerides in the ischemic tissue,with subsequent elevation in Na^{+} and Ca^{2+}. Abnormal sarcoplasmic reticulum function (e.g. mutations in ryanodine receptor) can also lead to intracellular Ca^{2+} overload, facilitating clinical arrhythmias, such as catecholaminergic polymorphic VT. A critical factor for the development of DADs is the duration of the AP. Longer APs are associated with more Ca^{2+} overload and facilitate DADs. Therefore, drugs that prolong AP (eg, Class IA antiarrhythmic agents) can occasionally increase DAD amplitude. Triggered arrhythmias induced by

DADs may be terminated by single stimuli; therefore, other electrophysologic features are needed to distinguish them from the reentrant tachycardias. The rate dependency of the coupling interval may be useful, because in most cases of DAD-induced arrhythmias the shorter the cycle of stimulation, the shorter the coupling interval to the induced arrhythmia. This is in contrast to the inverse relationship seen in reentrant arrhythmias, where the shorter the coupling intervals of the initiating stimuli, the longer the coupling interval of the first arrhythmia beat. Since this is not always the case, other electrophysiologic properties must be taken into account. Adenosine has been used as a test for the diagnosis of DADs. Adenosine reduces the Ca^{2+}inward current indirectly by inhibiting effects on adenylate cyclase and cyclic adenosine monophosphate. Thus, it may abolish DADs induced by catecholamines, but does not alter DADs induced by Na^{+}/K^{+} pump inhibition. The interruption of VT by adenosine points toward catecholamine-induced DADs as the underlying mechanism. Clinical examples: atrial tachycardia, digitalis toxicity-induced tachycardia, accelerated ventricular rhythms in the setting of acute myocardial infarction, some forms of repetitive monomorphic VT, reperfusion-induced arrhythmias, right ventricular outflow tract VT, exercise-induced VT (e.g. catecholaminergic polymorphic VT).

Early Afterdepolarization-Induced Triggered Activity

The EADs are oscillatory potentials that occur during the AP plateau (phase 2 EADs) or during the late repolarization (phase 3 EADs).

Both types may appear during similar experimental conditions, but they differ morphologically as well as in the underlying ionic mechanism. Phase 2 EADs appear to be related to $I_{ca\text{-}L}$ current, while phase 3 EADs may be the result of electronic current across repolarization or the result of low. The plateau of the AP is a period of high membrane resistance and little current flow. Consequently, small changes in either repolarizing or depolarizing currents can have profound effects on the AP duration and profile. As a wide variety of agents and conditions can result in a decreased outward current or increased inward current (so shifting the normal outward current), they can establish the conditions necessary for EADs. A fundamental condition underlying the development of EADs is AP prolongation, which manifests on the surface electrocardiogram (ECG) as QT prolongation. Some antiarrhythmic agents, principally class IA and III drugs, may become proarrhythmic because of their therapeutic effect of prolonging the AP. Many other drugs can predispose to the formation of EADs, particularly when associated with hypokalemia and/or bradycardia, additional factors that result in prolongation of the APD Catecholamines may enhance EADs by augmenting Ca^{2+} current, however the resultant increase in heart rate along with the increase in K^{+} current effectively reduces the APD and thus abolishes EADs. An EAD-mediated TA appears to be the underlying cause of arrhythmias that develop in the setting of long QT syndrome. While the true mechanism of these arrhythmias is still debated, it is accepted that enhanced repolarization dispersion seen in the syndrome can create a proarrhythmic substrate. In such an electrophysiologic milieu an EAD can initiate the tachycardia. Early afterdepolarization-triggered arrhythmias are rate dependent, and in general the EAD amplitude increases at a slow rate. Therefore, this type of TA is not expected to follow premature stimulation (which is associated with an acceleration of repolarization that decreases the EAD amplitude), with the exception of a long compensatory pause following a premature stimulus, which can be even more important than bradycardia in initiating «torsades de pointes».

Classification

There is no universal classification of arrhythmias. There are many types of arrhythmias, and they are classified by some investigators by where they begin

in the heart (the atria, AV node, or the ventricles). Others classify arrhythmias as one of four types — premature beats, supraventricular, ventricular, and bradyarrhythmias. Generally speaking, those that do not originate from the ventricles are called supraventricular arrhythmias while those that come from the ventricles are called ventricular arrhythmias. The arrhythmias that can often lead to death in minutes are ventricular fibrillation and ventricular tachycardia. Although others may also cause death, these two arrhythmias can quickly and severely alter the heart's ability to effectively pump blood. Immediate electrocardioversion to put the heart back into a more effective rhythm that allows the heart to pump blood effectively can be life-saving.Arrhythmia may be classified by rate (tachycardia, bradycardia), mechanism (automaticity, reentry, triggered) or duration (isolated premature beats; couplets; runs, that is 3 or more beats; non-sustained (less then 30 seconds) or sustained (over 30 seconds). It is also appropriate to classify by site of origin:

Atrial

- Sinus bradycardia.
- Premature Atrial Contractions (PACs).
- Wandering Atrial Pacemaker.
- Atrial tachycardia.
- Multifocal atrial tachycardia.
- Supraventricular tachycardia (SVT).
- Atrial flutter.
- Atrial fibrillation (Afib).

Junctional arrhythmias

- AV nodal reentrant tachycardia.
- Junctional rhythm.
- Junctional tachycardia.
- Premature junctional contraction.

Ventricular.

- Premature ventricular contractions (PVCs), sometimes called ventricular extra beats (VEBs).
- Premature ventricular beats occurring after every normal beat are termed «ventricular bigeminy».
- PVCs that occur at intervals of 2 normal beats to 1 PVC are termed «PVCs in trigeminy».
- Three premature ventricular grouped together is termed a «run of PVCs»; in general, runs lasting longer than three beats are referred to as ventricular tachycardia.
- Accelerated idioventricular rhythm.
- Monomorphic Ventricular tachycardia.
- Polymorphic ventricular tachycardia.
- Ventricular fibrillation.

The following are some of the more commonly encountered arrhythmias, starting with the supraventricular arrhythmias:

- Premature atrial contractions, sometimes called PAC or APC, or premature supraventricular contractions: This happens when another part of the atria sends an electrical impulse soon after the previous beat, causing the heart to contract earlier than expected. This arrhythmia is a very common occurrence in all ages and usually is not serious.
- Supraventricular tachycardia, or paroxysmal SVT or PSVT: SVT occurs when any structure above the ventricle (usually the atria or the AV node) produces a regular, rapid electrical impulse resulting in a rapid heartbeat.
- Sick sinus syndrome: Irregular electrical impulses generated by the SA node cause a slower-than-normal heart rate (sometimes alternating with rapid heart rates if the electrical impulses switch to a high rate).
- Wolff-Parkinson-White (WPW) syndrome: This is an arrhythmia people are born with because they have extra electrical pathways leading from the atrium to the ventricle that can cause tachycardia and particular types of rapid arrhythmias.
- Atrial fibrillation: This is a common condition caused by electrical impulses discharged at a rapid rate from many different areas of the atria. It usually causes a fast and irregular heartbeat.
- Atrial flutter: This condition is caused by a rapid discharge from a single place in the right atrium. Typically, the right atrium produces electrical impulses at a rate of 300 beats per minute, but only every other beat is conducted through the AV node, meaning that the ventricular rate is classically about 150 beats per minute.

Arrhythmias arising in the ventricle (ventricular arrhythmias) are more likely to be found in people with more serious heart disease but may also be found in healthy individuals.

Premature ventricular complex or PVC: This electrical impulse starts in the ventricle causing the heart to beat earlier than expected. Usually, the heart returns to its normal rhythm right away.

Ventricular tachycardia: Fast and usually regular impulses come from the ventricles and cause a very rapid heart rate. This is usually a life-threatening tachycardia and needs immediate medical attention, possibly electrical shock or defibrillation that can stop or override these impulses.

Ventricular fibrillation: Electrical impulses arise from the ventricles in a fast and disordered sequence. The resulting uncoordinated contractions cause the heart to quiver (appearing like a bag of worms) and lose the ability to beat and pump blood, leading to immediate cardiac arrest; electrical shock therapy may be life-saving.

Bradyarrhythmias produce heart rates that are too slow to allow enough blood to be pumped during either time of demand (stress or increased activity) or even during normal activity. Bradyarrhythmias are usually slower than 60 beats per minute. For example, patients may become dizzy and pass out when they try to stand up because not enough blood is pumped into the brain.

Heart Rhythm Disorders Causes

Among individuals without known heart disease, arrhythmias are generally random, isolated occurrences that do not carry any significance. However, an

evaluation by a physician is advised if a person notices any unusual or abnormal heart beats, especially if they reoccur or are sustained. A variety of heart diseases cause arrhythmias. Heart disease can refer to patients with coronary artery disease, heart valve problems, heart failure, or disorders with heart conduction, or high blood pressure. Remember, however, that having an arrhythmia does not necessarily mean that a person has heart disease. Arrhythmias have many causes; sometimes the cause of an arrhythmia is never determined, other times the cause may be easy to determine and treat. Sometimes, conditions other than heart disease may cause or aggravate arrhythmias. These conditions include the following:

- Infection or fever.
- Physical or emotional stress.
- Diseases such as anemia or thyroid disease.
- Drugs and other stimulants, such as caffeine, tobacco, alcohol, cocaine, amphetamines, and certain over-the-counter and prescription medications, including medicine used to treat arrhythmias.
- Certain arrhythmias can be genetically determined such as Wolff-Parkinson-White (WPW) syndrome.

Diagnosis

Heart rhythm disorders symptoms: Many arrhythmias cause no or minimal symptoms. Other people, however, can actually feel the arrhythmia when it happens. Common symptoms include the following:

- Palpitations, feeling «skipped beats».
- Thumping or fluttering in the chest.
- Sensation of the heart racing.

In addition, some can experience symptoms that are more generalized, including the following:

- Feeling faint or tired.
- Light-headedness or passing out (syncope).
- Shortness of breath.
- Chest pain or discomfort.

On the other hand, people may feel many of the sensations described above and have no arrhythmias whatsoever. These symptoms may be due to anxiety, stress, or other causes besides an abnormal heartbeat. Most people have noticed their heart racing, a fluttering in the chest, or a sensation that the heart skipped a beat. If this happens once, or very infrequently, with no other symptoms, it is usually not serious and medical care is usually not needed. However, any questions or concerns should be discussed with a health care professional. If the person is prescribed a medication, the health care professional should also be notified if a recommended treatment does not alleviate the symptoms. More serious symptoms should be evaluated immediately at the nearest hospital emergency department. These symptoms include:

- Any unexplained shortness of breath.

- Loss of consciousness.
- Light-headedness or feeling faint.
- Feeling that the heart is beating too slowly or too quickly.
- Chest pain with normal activity.
- Chest pain with any of the above symptoms.

Evaluation of rhythm disorders usually requires a detailed discussion of symptoms and a physical exam with a health care professional. In addition, an electrocardiogram (ECG) is mandatory to establish the exact type of arrhythmia. If the rhythm disturbance is present while the ECG is being recorded, the problem may be identified immediately. Otherwise, more specialized testing may be required. A 24-hour (or longer) recording of the heartbeat is often necessary to detect any rhythm problem that occurs daily but not constantly. (For examples of EKGs of various arrhythmias, the reader is urged to see the references provided in this introductory article). However, if the arrhythmia is even more infrequent, an event recorder may be used. These recorders can be hand-held machines that are activated by the patient whenever he or she feels symptoms. These event recorders can be worn for variable amounts of time from days to weeks in order to detect changes in the heart's rhythm. Some recorders are placed surgically under the skin and left there for up to 1 year. An ultrasound of the heart, called an echocardiogram, is often used for an evaluation of the structure and function of the heart that may help identify underlying causes that lead to arrhythmias. In general, arrhythmias in children are diagnosed with most of the same tests that are used in adults.

Management

Arrhythmias can be frightening, but in many cases, especially in younger patients with normal underlying hearts, they are not life-threatening and can be effectively treated with medications. Supraventricular arrhythmias are very common in middle-aged and elderly adults. The older a person becomes, the more likely they are to experience an arrhythmia, especially atrial fibrillation. Many supraventricular arrhythmias are temporary and not serious, especially if no underlying heart disease is present. These arrhythmias can be a response to normal activities or emotions. Even if an arrhythmia has a serious underlying cause, the arrhythmia itself may not be dangerous. The underlying problem can often be treated effectively.

The treatment of arrhythmias varies depending on the presence or absence of symptoms, how frequent the arrhythmia occurs, and the seriousness of any underlying heart condition. The majority of arrhythmias are either not treated or are treated with medications taken by mouth. Some arrhythmias must be treated emergently with electrocardioversion or the patient will die. For others, the treatment may range from vagal maneuvers (for example, the Valsalva, a maneuver of breath holding and bearing down) to medication to more advanced surgical procedures, such as an internal implanted pacemaker or cardiac defibrillator (ICD).

Sometimes, no treatment is necessary because the arrhythmia resolves. Except in life-threatening emergencies, a person should have a detailed discussion of the tests and treatment options with the health care professional to be clear about the tests and potential treatment options before any tests or surgery is done. This discussion should include the risks and benefits the patient may have if they choose to have or not have specific treatments or surgical procedures done.

Heart rhythm disorders medications: the choice and use of medications depends on the specific type of arrhythmia present. Although detailed discussion about this is beyond the scope of this article, the reader is encouraged to click onto the links to the predominant arrhythmias to determine the common medications and common surgical methods used to treat these heart beat disorders. Although some arrhythmias may require some special uses of medications (for example, IV adenosine for PSVT), most utilize various beta-blockers and calcium channel blockers to control fast rates. Although atropine may be used for a short time to speed up heart rates, usually the treatment will be a pacemaker.

Electrical and surgical treatments: the most common electrical and surgical treatments are listed as follows:

Electrical: these include pacemakers and defibrillators (several types including ones that can either pace, defibrillate, or even cardiovert manually) and automatic external defibrillators (AEDs) that are available to the public, and function with external sources of electricity.

Ablation: this technique is done by surgically placing small probes that can destroy tissue and then are removed once the tissue is altered. (Technically, ablation — which kills cells found usually in the atria, thus stopping arrhythmia-generating cells — may be done with hot or cold probes.) This is sometimes termed a modified MAZE procedure.

Surgical implants: these are pacemakers that regulate heartbeat rates by either including extra beats if the heartbeat is too slow or «overdrive pacing» if the rate is too fast (for example, ventricular tachycardia); defibrillators that detect and then interrupt ventricular fibrillation; and devices that can both pace and defibrillate, all of which are surgically implanted and battery-powered.

Surgery: this is open-heart surgery (termed MAZE surgery or MAZE procedure) where small cuts are made in the heart tissue to induce scar formation that blocks electrical impulses or removes cells causing impulses (currently infrequently done).

Electrical cardioversion is most often used in emergencies, although patients with certain arrhythmias who are stable may have electrical cardioversion done non-emergently. Most of the surgical procedures (implants) are done in patients whose arrhythmias are under medical control (temporarily or longer-term).

Heart rhythm disorders follow-up: follow-up is usually done with the primary care professional and often with a heart specialist (cardiologist). The patient is monitored for effectiveness of treatment, recurrence of symptoms or arrhythmia, side effects of medication, additional routine testing, and overall condi-

tion. For those requiring pacemakers, follow-up on a regular basis is mandatory. Patients are advised to make all follow-up appointments and should not attempt to change their medications without first consulting their doctor(s).

Atrial fibrillation

Atrial fibrillation (AF) is a common arrhythmia, particularly in patients with underlying heart disease. Among patients with both HF and AF, there are several possible relationships:

- Acute HF can precipitate AF due to increases in left atrial pressure and wall stress.
- AF can cause acute HF, particularly if the ventricular response is rapid.
- AF may be chronic and not directly related to the acute HF decompensation.

It is usually difficult to determine whether AF is the cause or result of ADHF. A reliable history of palpitations that clearly precede the decompensation suggests but does not prove that AF was the cause of the pulmonary edema. The treatment of AF depends upon whether or not it is associated with significant hemodynamic instability and whether or not it is believed to be the precipitant of HF decompensation.

In some patients with AF and ADHF, effective treatment of pulmonary edema results in slowing of the ventricular rate or spontaneous reversion of the arrhythmia. If AF persists, it is treated in the same fashion as AF in other situations.

Rate control is often the preferred initial strategy for the following reasons:

- Because acute HF can precipitate AF, cardioversion prior to the resolution of acute HF will often be followed by early recurrence of AF.
- AF is often a chronic condition that is not contributing to the acute decompensation.

However, if a rate control strategy is selected, the negative inotropic effects of beta-blockers and nondihydropyridine calcium channel blockers can be problematic in patients with systolic dysfunction. For this reason, short-acting IV formulations of such drugs (eg, esmolol or diltiazem) are often used. In addition, digoxin is also potentially useful in this setting, although its use has lessened considerably due to toxicity issues and slow onset of action. Amiodarone can be considered.

Restoration of sinus rhythm should be considered in the following settings:

- If AF is associated with hypotension or evidence of cardiogenic shock.
- If AF is clearly the cause for pulmonary edema.
- If the response to effective therapy of pulmonary edema is slow or suboptimal.

Heparin should be started prior to cardioversion, if possible.

Ventricular arrhythmia: ventricular tachycardia during pulmonary edema is usually life threatening. As a result, prompt electrical cardioversion or defibrillation is required. If the arrhythmia recurs after reversion, antiarrhythmic therapy, particularly with amiodarone may be effective. The development of ventricular fibrillation mandates prompt resuscitation.

Antiarrhythmic drugs

Antiarrhythmic drugs comprise many different drug classes and have several different mechanisms of action. Furthermore, some classes and even some specific drugs within a class are effective with only certain types of arrhythmias. Therefore, attempts have been made to classify the different antiarrhythmic drugs so by mechanism. Although different classification schemes have been proposed, the first scheme (Vaughan-Williams) is still the one that most physicians use when speaking of antiarrhythmic drugs. The following Table 4 shows the Vaughan-Williams classification and the basic mechanism of action associated with each class. Note that Class I drugs are further broken down into subclasses because of subtle, yet important differences in their effects on action potentials. Clicking on the «Class» or «Basic Mechanism» will take you to a page describing the drugs that comprise that class.

The Vaughan-Williams Classification of Antiarrhythmic Drugs see above (Table 5).

Table 5 — Vaughan-Williams Classification of Antiarrhythmic Drugs

Class	Basic Mechanism	Comments
I	sodium-channel blockade	Reduce phase 0 slope and peak of action potential
IA	— moderate	Moderate reduction in phase 0 slope; increase APD; increase ERP
IB	— weak	Small reduction in phase 0 slope; reduce APD; decrease ERP
IC	— strong	Pronounced reduction in phase 0 slope; no effect on APD or ERP
II	beta-blockade	Block sympathetic activity; reduce rate and conduction
III	potassium-channelblockade	Delay repolarization (phase 3) and thereby increase action potential duration and effective refractory period
IV	calcium-channelblockade	Block L-type calcium-channels; most effective at SA and AV nodes; reduce rate and conduction

Abbreviations: APD, action potential duration; ERP, effective refractory period; SA, sinoatrial node; AV, atrioventricular node.

6. GASTROESOPHAGEAL REFLUX DISEASE

Definitions and introduction

Due to the broad spectrum of conditions attributable to reflux, there is little agreement as to what constitutes typical gastroesophageal reflux disease (GERD). In general terms, GERD is applied to patients with symptoms suggestive of reflux or complications thereof, but not necessarily with esophageal inflammation. The Montreal Classification defines GERD as «a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications». The cardinal symptoms associated with GERD are heartburn and regurgitation. However, complications from GERD can arise even in patients who lack these typical symptoms.

The primary event in the pathogenesis ofgastroesophageal reflux disease GERD is movement of gastric juice from the stomach into the esophagus. The three dominant pathophysiologic mechanisms causing gastroesophageal junction incompetence are:

- Transient lower esophageal sphincter relaxations (tLESRs).
- A hypotensive lower esophageal sphincter (LES).
- Anatomic disruption of the gastroesophageal junction, often associated with a hiatal hernia.

The evolving concept is that the dominant mechanism varies as a function of disease severity with tLESRs predominating with mild disease and mechanisms associated with a hiatus hernia and/or a weak sphincter predominating with more severe disease. The relatively recent availability of esophageal impedance testing, which can detect reflux irrespective of pH, discern reflux of gas from liquid, and determine the distribution of refluxate, will likely help determine the impact of these variables on the clinical features of GERD.Transient lower esophageal sphincter relaxations account for essentially all reflux events in individuals with a normal LES pressure at the time of reflux. There are several major differences between tLESRs and swallow-induced LES relaxation: tLESRs occur without an associated pharyngeal contraction, are unaccompanied by esophageal peristalsis, and persist for longer periods (> 10 sec) than do swallow-induced LES relaxations.It has become increasingly clear that tLESRs are the physiological mechanism of belching. The frequency of tLESRs is greatly increased by distension of the stomach or by assuming an upright posture. Furthermore, a tLESR is an integrated motor response involving not only LES relaxation, but also crural diaphragmatic inhibition, esophageal shortening by contraction of its longitudinal muscle, and contraction of the costal diaphragm. That tLESRs are an active, vagally mediated reflex, rather than the result of forceful gastric distention, was demonstrated by both a combined endoscopic/manometric study and a combined manometric/fluoroscopic study showing that sphincter relaxation (evident manometrically) always preceded actual esophagogastric junction opening.One hypothesis is that a primary determinant of reflux disease is not an increased number of tLESRs, rather an increased proportion of tLESRs that are associated with acid reflux as opposed to only gas venting. Such a progression could be caused by increased compliance of the EGJ as a consequence of weakening/dilatation of the diaphragmatic hiatus. Increased compliance leads to an increased luminal cross-sectional area during opening that in turn results in an increased volume of reflux and a reduced ability to limit refluxate to gas. Different investigators have documented acid reflux during as many as 93 percent or as few as 9 to 15 percent of tLESRs.

Hypotensive lower esophageal sphincter: the LES is a 3 to 4 cm long segment of tonically contracted smooth muscle at the distal end of the esophagus. LES tonic contraction is a property of both the muscle itself and of its extrinsic innervation. Normal resting tone of the LES varies from 10 to 30 mmHg, being least in the post-cibal period and greatest at night.Only a minority of individuals with GERD have a grossly hypotensive LES (< 10 mmHg) when determined during fasting measurements. There are, however, a host of factors that can reduce LES pressure: gastric distension, cholecystokinin, various foods (fat, chocolate, caffeine, alcohol), smoking, and many drugs. Thus, many patients have periods of gross LES hypotension as a result of foods, drugs, or habits.

Gastroesophageal reflux can occur with diminished LES pressure either by strain-induced reflux or free reflux:

- Strain-induced reflux occurs when a hypotensive LES is overcome and «blown open» by an abrupt increase of intraabdominal pressure. Manometric data suggest that stress reflux is relatively unusual unless the LES pressure is less than 4 mmHg.

• During free reflux a fall in intraesophageal pH occurs without identifiable change in either intragastric or LES pressure. Free reflux is observed only when LES pressure is within 0 to 4 mmHg of intragastric pressure.

Hiatal hernia and the diaphragmatic sphincter: the diaphragm as well as the LES contributes to gastroesophageal sphincter competence, making it more accurate to think of the composite as esophagogastric junction (EGJ) pressure. Recordings of LES pressure usually exhibit inspiratory increases as a result of contraction of the diaphragmatic crus that encircles the LES. Observations of the antireflux mechanism during maneuvers such as leg raising and abdominal compression suggest a «pinchcock» effect of crural contraction that augments the antireflux barrier. The crural diaphragmatic component of EGJ pressure is most relevant in patients with hiatal hernia, in whom this component may be impaired.However, a study examining the correlation between GERD, hiatus hernia, LES pressure, and crural diaphragm function as quantified by the magnitude of EGJ pressure augmentation during inspiration found that function of the crural diaphragm was most strongly correlated with GERD. Furthermore, the associations between GERD and hiatus hernia or LES pressure no longer achieved statistical significance after considering the effect of inspiratory augmentation in multivariate analysis, suggesting both effects were largely mediated by associated crural diaphragm dysfunction.

The susceptibility to reflux under circumstances of abrupt increases of intraabdominal pressure (eg, during bending or coughing) depends upon both the instantaneous LES pressure and the diaphragmatic sphincter. Patients with hiatus hernia can have progressive disruption of the diaphragmatic sphincter. Therefore, although neither condition (hiatus hernia or hypotensive LES) alone results in severe incompetence; the two conditions interact with each other in more than an additive fashion. The severity of esophagitis correlates with the size of the hiatal hernia. Two other factors also appear to be important in patients with reflux associated with a hiatus hernia. A hiatus hernia is associated with a reduced threshold for eliciting tLESRs in response to gastric distension. It is also associated with malfunction of the gastroesophageal barrier during periods of low LES pressure, during normal swallow-associated LES relaxation, and during deep inspiration or straining.

Obesity: obesity is a risk factor for GERD, erosive esophagitis, and esophageal adenocarcinoma. The mechanisms by which this occurs are incompletely understood.Several studies have evaluated the relationship between obesity and GERD but comparison among them is limited by variable definitions used and differences in study design. One of the most comprehensive studies included a total of 285 patients in whom anthropometric variables were correlated with findings on manometry. There was a significant correlation of body mass index and waist circumference with intragastric pressure and the gastroesophageal pressure gradient. Obesity was also associated with disruption of the esophagogastric junction leading to a hiatal hernia and increased esophageal acid exposure. Obesity, particularly abdominal obesity, has also been associated with increased reflux symptoms.Extending on these findings, another report found obesity to be associated with both an increased frequency of tLESRs and an increased proportion of tLESRs associated with acid reflux during the postprandial period in subjects without hiatus hernia or clinical evidence of GERD. These findings suggest that LES dysfunction might be an important mediator of the pathogenesis of obesity-related GERD. Even moderate weight gain in women of normal weight was potentially associated with exacerbation of symptoms.

Pregnancy and exogenous estrogen: heartburn occurs in 30 to 50 percent of pregnancies. It is due to both mechanical and intrinsic factors that adversely affect lower esophageal sphincter tone. Estrogen replacement therapy in postmenopausal women also appears to modestly increase the risk of heartburn.

Esophageal acid clearance: following reflux, the period that the esophageal pH remains less than 4 is called the acid clearance time. Esophageal acid clearance begins with emptying

the refluxed fluid from the esophagus by peristalsis and is completed by titration of the residual acid by swallowed saliva. Approximately 7 mL of saliva will neutralize 1 mL of 0.1 N HCl, with 50 percent of the neutralizing capacity being attributable to salivary bicarbonate. The normal rate of salivation is about 0.5 mL/min; maneuvers that increase salivation (eg, oral lozenges or gum chewing) will hasten acid clearance while circumstances of diminished salivation (eg, sleep) will delay it.Prolongation of esophageal acid clearance occurs in about one-half of patients with esophagitis. A review of a large data set of 24-hour esophageal pH recordings suggested that individuals with known hiatal hernias tended to have the most prolonged recumbent acid clearance times. The two major causes of this problem are impaired esophageal emptying and impaired salivary function. Abnormal acid clearance improves with an erect posture, suggesting that gravity compensates for impaired fluid emptying.

Esophageal emptying in GERD: two mechanisms of impaired esophageal emptying have been identified:

- Peristaltic dysfunction, resulting in either failed or hypotensive (< 30 mmHg) peristaltic contractions. Peristaltic dysfunction becomes more common with increasing severity of esophagitis. Whether peristaltic dysfunction associated with peptic esophagitis is reversible is disputed. Most likely, acute dysfunction associated with active esophagitis is partially reversible, while chronic dysfunction associated with stricturing or extensive fibrosis is not.
- «Re-reflux» associated with hiatal hernias which also impairs esophageal emptying. Scintiscanning and pH recording concurrent with fluoroscopy demonstrate «re-reflux» from the hernia sac during swallowing. This occurs only with «nonreducing» hernias that are evident between swallows and during peristalsis-induced esophageal shortening. In one report, for example, retrograde flow or «re-reflux» was seen with almost 50 percent of test swallows in patients with nonreducing hernias, impairing both esophageal emptying and esophageal acid clearance.

The potential for re-reflux may be aggravated by the presence of an «acid pocket» in the most proximal gastric cardia that escapes the buffering effects of food and remains highly acidic during the postprandial period. The net result is much greater acid exposure just above the squamocolumnar junction compared to 5 cm proximal to it, likely explaining the propensity of the distal area to develop mucosal erosions.

Salivary function in GERD: reduced salivation or diminished salivary neutralizing capacity also prolongs acid clearance. Diminished salivation during sleep, for example, explains why reflux events during sleep or immediately prior to going to sleep are associated with markedly prolonged acid clearance times. In addition, chronic xerostomia is associated with prolonged esophageal acid exposure and esophagitis. However, the only large scale analysis of salivary function in GERD found no difference between the resting salivary function of the esophagitis patients and controls.

Cigarette smokers have prolonged esophageal acid clearance times due to hyposalivation. In one report, for example, smokers without symptoms of reflux disease were found to have acid clearance times 50 percent longer than those of nonsmokers; furthermore, the salivary titratable base content of the smokers was only 60 percent of the age-matched nonsmokers.

Mechanisms of and defenses against esophageal injury: the development of esophagitis in GERD on a cellular level is due to hydrogen ion diffusion into the mucosa, leading to cellular acidification and necrosis. As noted above, reflux, impaired esophageal emptying, and diminished salivary function contribute to increased exposure of the esophagus to acid. In contrast, esophagitis is less clearly related to increased gastric acid secretion in GERD patients. This was demonstrated in a study which compared gastric acid and pepsin secretion in 115 patients with endoscopically-graded esophagitis to 508 age- and disease-matched controls without esophagitis; there were no differences between the two groups. A caveat to this is that reduced acid secretion as can be seen with chronic H. pylori gastritis may be somewhat protective against GERD.

Pepsin, bile acids, trypsin, and food hyperosmolality increase the susceptibility of the esophageal mucosa to acid injury. Pepsin and bile acids have been subjected to the most scrutiny. At pH 2, pepsin disrupts the histologic integrity of the mucosal barrier, increases hydrogen ion permeability, and causes hemorrhage. In contrast, an esophagus exposed to a pepsin perfusate at pH 7.5 followed by a solution at pH 2 without pepsin shows minimal mucosal disruption or changes in permeability. Thus, pepsin's ability to cause mucosal injury is pH dependent, with maximal enzyme activity below pH 3.Bile acids have been implicated in the development of esophagitis primarily in patients with increased duodenogastric reflux following gastric surgery. However, bile acids are not as important as acid and pepsin.

Epithelial defense: the esophageal mucosa possesses several morphologic and physiologic defenses against cellular acidification. Conceptually, epithelial defenses can be subdivided into preepithelial, epithelial, and postepithelial factors.Preepithelial defenses (surface mucous and bicarbonate that maintain a significant pH gradient between lumen and cell surface) are poorly developed in the esophagus; as a result, the pH gradient in the mucus layer is minimal or nil.Although the esophageal epithelium contains a few submucosal glands that secrete bicarbonate into the submucosa, mucosa, and lumen, the main defense against acid injury is the epithelial barrier itself. The esophageal mucosa is a relatively «tight» epithelium, resistant to ionic movements at the intercellular as well as the cellular level because of the tight junctions and the lipid rich matrix in the intercellular space. This mucosa can retard hydrogen ion penetration in the face of ion gradients of greater than 5 pH units.

The importance of tight junctions has been demonstrated by the luminal and serosal application of low molecular weight markers of paracellular permeability. When applied luminally, the paracellular movement of these markers was restricted to the first few layers of the stratum corneum by tight junctions; when applied serosally, they permeated freely through the basal cell and stratum spinosum layers and were retarded only within seven to nine cell layers of the lumen. These observations illustrate the vulnerability of the esophageal mucosa to injury once the superficial cell layers have been lost. A histomorphometric correlate of increased paracellular permeability is the presence of dilated intercellular spaces, evident in transmission electron microscopy. Detailed analyses suggest this to be a sensitive and reversible marker for a reflux injured esophagus. Further defense of the esophageal epithelium is provided by hydrogen ion extrusion. Two pH-activated acid extruding processes are located on esophageal membranes: a Na/H exchanger; and a sodium dependent Cl/HCO3 exchanger. Once extruded, the hydrogen ions are buffered by extracellular bicarbonate in equilibrium with the blood. Thus, blood flow is the main postepithelial defense, interacting with epithelial factors to protect against acid injury. In addition to providing nutrients for metabolic activity, blood flow increases in response to luminal acid, delivering more bicarbonate to the intercellular space. Finally, when the epithelial cells are no longer able to maintain intracellular pH, they lose the ability to volume regulate and cellular edema ensues. Esophageal acid injury also stimulates cell proliferation, which is observed in biopsy specimens as thickening of the basal cell layer of the epithelium.

Esophageal hypersensitivity: despite careful evaluation, some patients who have typical reflux-like symptoms do not have pathologic reflux documented by endoscopy or 24-hour pH studies. The symptoms of these hypersensitive patients are similar to those with GERD. The cause of heartburn in patients with normal esophageal acid exposure is uncertain but may be related to heightened esophageal sensitivity (also called visceral hyperalgesia). This is analogous to the visceral hyperalgesia described in a variety of other disorders including noncardiac chest pain, functional dyspepsia, and irritable bowel syndrome.

Epidemiology

Epidemiologic estimates regarding the prevalence of GERD are based upon the assumption that heartburn and/or regurgitation is the indicator of the disease.

However, patients with objective evidence of GERD (such as esophagitis or Barrett's esophagus) do not always have heartburn. A systematic review identified 15 epidemiological studies of GERD that fulfilled strict quality criteria. GERD prevalence (as defined by at least weekly heartburn and/or acid regurgitation) was 10 to 20 percent in the Western world and about 5 percent in Asia. The incidence in the Western world was approximately 5 per 1000 person years. The Montreal Working Group concluded that in population-based studies, mild symptoms occurring two or more days a week, or moderate to severe symptoms occurring more than one day a week, are often considered troublesome. However, in clinical practice, it is the patient who should determine if their reflux symptoms are troublesome.

Diagnosis

Clinical manifestations: the most common symptoms of GERD are heartburn (or pyrosis), regurgitation, and dysphagia. In addition, a variety of extra-esophageal manifestations have been described including bronchospasm, laryngitis, and chronic cough.

Heartburn is typically described as a burning sensation in the retrosternal area (behind the breastbone), most commonly experienced in the postprandial period.

Regurgitation is defined as the perception of flow of refluxed gastric content into the mouth or hypopharynx. Patients typically regurgitate acidic material mixed with small amounts of undigested food.

Dysphagia is common in the setting of long-standing heartburn and, in patients with erosive esophagitis, can resolve following treatment with a proton pump inhibitor. Slowly progressive dysphagia for solids with episodic esophageal obstruction is suggestive of a peptic stricture. Other, more common, causes of dysphagia are esophageal inflammation, eosinophilic esophagitis, and impaired peristalsis. The most dreaded cause of dysphagia is esophageal cancer, either adenocarcinoma arising from Barrett's metaplasia or squamous cell carcinoma.

Other symptoms of GERD include chest pain, water brash, globus sensation, odynophagia, and nausea.

GERD-related chest pain may mimic angina pectoris, and is typically described as squeezing or burning, located substernally and radiating to the back, neck, jaw, or arms, lasting anywhere from minutes to hours, and resolving either spontaneously or with antacids. It usually occurs after meals, awakens patients from sleep, and may be exacerbated by emotional stress. The preponderance of patients with reflux-induced chest pain also have typical reflux symptoms.

Water brash or hypersalivation is a relatively unusual symptom in which patients can foam at the mouth, secreting as much as 10 mL of saliva per minute in response to reflux.

Globus sensation is the almost constant perception of a lump in the throat (irrespective of swallowing), which has been related to GERD in some cases.

Odynophagia is an unusual symptom of GERD but, when present, usually indicates an esophageal ulcer.

Nausea is infrequently reported with GERD but may be a consideration in patients with otherwise unexplained symptoms. In one report, nausea resolved after therapy for GERD in 10 patients who previously had intractable symptoms.

GERD needs to be distinguished from infectious esophagitis, pill esophagitis, eosinophilic esophagitis, peptic ulcer disease, non-ulcer dyspepsia, biliary tract disease, coronary artery disease, and esophageal motor disorders. Symptoms alone do not reliably distinguish among these disorders. Similarly, the severity and duration of symptoms correlate poorly with the severity of esophagitis.

Unexplained chest pain should be evaluated with an electrocardiogram and exercise stress test prior to a gastrointestinal evaluation. The remaining elements of the differential diagnosis can be evaluated by endoscopy or biliary tract ultrasonography. The findings on endoscopy vary with the cause of the symptoms:

- Infectious esophagitis is circumferential and tends to involve the proximal esophagus far more frequently than does reflux esophagitis. The ulcerations seen in peptic esophagitis are usually irregularly shaped or linear, multiple, and distal, whereas infectious ulcers are multiple and punctate.
- Pill-induced ulcerations are usually singular and deep, occurring at points of stasis.
- Both infectious and pill esophagitis are accompanied by odynophagia, which is atypical of peptic esophagitis.

Diagnostic evaluation: it is neither necessary nor practical to initiate a diagnostic evaluation in every patient with heartburn. Endoscopy with biopsy should be done at presentation for patients with an esophageal GERD syndrome with troublesome dysphagia. Biopsies should target any areas of suspected metaplasia, dysplasia, or, in the absence of visual abnormalities, normal mucosa (at least five samples to evaluate for eosinophilic esophagitis). Endoscopy should also be done to evaluate patients with a suspected esophageal GERD syndrome who have not responded to an empirical trial of twice daily PPI therapy.For patients who require diagnostic evaluation, potentially useful tests are endoscopy and ambulatory pH monitoring, each of which provides distinct but related information.

Esophagoscopy (with biopsy when necessary) should be the initial evaluation of suspected GERD because it provides a mechanism for detecting, stratifying, and managing the esophageal manifestations of GERD. However, the absence of endoscopic features of GERD does not exclude the diagnosis. Some patients with initial negative endoscopies will develop mucosal lesions during follow-up examinations. In addition, symptoms may be due to esophageal hypersensitivity. Finally, the accuracy of endoscopy for the diagnosis of GERD is subject to observer variability. It is likely that these considerations will also apply to use of the esophageal Pillcam (a video capsule that is swallowed and transmits images to a receiver) that has been approved for diagnosis of esophageal disease. The interoperator variability of endoscopy in assessing the severity of peptic esophagitis spawned many endoscopic grading schemes; of the more than 80 proposed schemes, the two most dominant will be described.

Ambulatory esophageal pH monitoring: ambulatory pH monitoring is useful for confirming gastroesophageal reflux disease in those with persistent symptoms (whether typical or atypical) who do not have evidence for mucosal damage on endoscopy, particularly if a trial of acid suppression has failed. It can also be used to monitor the adequacy of treatment in those with continued symptoms. Ambulatory pH monitoring can be done with either a trans-nasally placed catheter or a wireless, capsule shaped device that is affixed to the distal esophageal mucosa. In each case, the pH sensor is coupled with compact, portable data loggers, and computerized data analysis. The catheter type pH electrode is positioned 5 cm above the manometrically defined upper limit of the lower esophageal sphincter. In the case of the wireless device, the pH capsule is attached 6 cm proximal to the endoscopically defined squamocolumnar junction. Tests are traditionally conducted for a 24 hour period with patients advised to consume an unrestricted diet. However, in the case of the wireless device, studies can be conducted for two to four days, varying the dietary and/or therapeutic circumstances between days if desired. The current consensus is to consider the percentage time with the intraesophageal pH below 4 as the most useful outcome measure in discriminating between physiologic and pathologic esophageal reflux. Although symptom association is essential when evaluating atypical or sporadic symptoms, a direct one-to-one correlation between reflux events and symptoms rarely exists, leading to several proposed methods for quantifying the reflux-symptom relationship. However, none of the proposed symptom evaluation schemes has been validated prospectively against an independent parameter of diagnostic accuracy such as antireflux therapy with a symptomatic response. An additional, more recently described indication is measurement of gastric pH. In this setting, the distal electrode is placed 10 cm below the lower esophageal sphincter in the stomach with the pH values from this electrode being recorded similarly to those from the intraesophageal electrode. This technique monitors the distal esophageal pH and also assesses the efficacy of acid suppression achieved by various pharmaceuticals. The latter may be important for patients with continued symptoms despite treatment with acid suppression. However, abnormal esophageal acid exposure in patients taking a proton pump inhibitor twice daily is unlikely. Ambulatory pH monitoring is also used for the detection of pathologic reflux associated with supra-esophageal complications such as reflux laryngitis or cough. However, there has been no consensus on the pH criteria that should be used for defining pathologic reflux in this setting. One study suggested that a pH decrease of more than 2 pH units in the pharynx, occurring during esophageal acidification, and reaching a nadir of less than pH 4 units in less than 30 seconds was optimal for distinguishing patients with suspected regurgitation from healthy controls.

Esophageal manometry is of minimal use in the diagnosis of GERD. One possible exception is for the evaluation of peristaltic function before antireflux surgery to exclude major motor disorders.

The Bernstein test is useful to determine symptom correlation with esophageal acidification in patients without endoscopic evidence of esophagitis. The test is

done by alternately infusing saline or 0.1 N HCl at a rate of 6 to 8 mL/min into the mid-esophagus via a nasogastric tube or manometric assembly. A positive test is defined as reproduction of the patient's symptoms with acid perfusion but not with saline. This test is ideal for determining acid sensitivity.However, for reasons that are not entirely clear, acid sensitivity during the Bernstein test does not correlate well with «spontaneous» periods of acid sensitivity during reflux episodes as assessed during ambulatory pH monitoring. Thus, acid sensitivity during the Bernstein test does not necessarily prove that symptoms are due to esophageal acid sensitivity in patients with symptoms of reflux.

Radiologic techniques: double contrast barium swallow examinations can identify early stages of reflux esophagitis by a granular or nodular appearance of the mucosa of the distal third of the esophagus with numerous ill-defined, 1 to 3 mm lucencies. A variety of other changes may also be seen:

- Thickening of the longitudinally oriented esophageal folds may occur, with folds wider than 3 mm categorized as abnormal. These folds may be quite tortuous, mimicking varices.
- Shallow ulcers and erosions are recognized on double contrast radiographs as tiny collections of barium in the distal esophagus near the gastroesophageal junction, sometimes surrounded by a radiolucent halo of edematous mucosa.
- The appearance of a smooth, tapered area of concentric narrowing in the distal esophagus, 1 to 4 cm in length and 0.2 to 2.0 cm in diameter is virtually pathognomonic of a benign peptic stricture. However, many peptic strictures have an asymmetric appearance with puckering of one wall of the stricture due to eccentric scarring.

Radiography versus endoscopy: double contrast barium swallow examinations are of limited use in the management of GERD because of its limited sensitivity in patients with milder forms of GERD. Radiologic evaluation is most useful in the detection of peptic stricture. When data from barium radiography and endoscopy were compared, the diagnostic accuracy of radiography was 25 percent with mild esophagitis, 82 percent with moderate esophagitis, and 99 percent with severe esophagitis. The demonstration of reflux of barium during the study is of dubious significance since it can be provoked in 25 to 71 percent of symptomatic patients compared to 20 percent of normal controls.

Histology: even though the esophagus may appear endoscopically normal, it is not necessarily histologically normal. A review of the literature suggested that about two-thirds of patients who have symptoms of GERD but have no visible endoscopic findings (ie, nonerosive reflux disease) have histologic evidence of esophageal injury that responds to acid suppression. The most consistently observed histologic findings was dilatation of the intercellular spaces seen on transmission electron microscopy.

Classification

Historically, the most widely referenced grading of esophagitis is the Savary-Miller classification:

• Grade I exhibits one or more supravestibular, non-confluent reddish spots, with or without exudate.

• Grade II demonstrates erosive and exudative lesions in the distal esophagus that may be confluent, but not circumferential.

• Grade III is characterized by circumferential erosions in the distal esophagus, covered by hemorrhagic and pseudomembranous exudate.

• Grade IV is defined by the presence of chronic complications such as deep ulcers, stenosis, or scarring with Barrett's metaplasia.

Despite its widespread use, the Savary-Miller grading scheme has its limitations. Because it includes all complications, grade IV esophagitis is ambiguous. This has led to modifications which either offer subdivisions of grade IV or relegate metaplasia to grade V. With so many proposed modifications, grades IV and V no longer have any widely accepted meaning.

Los Angeles classification: in this grading scheme, a mucosal break refers to an area of slough adjacent to more normal mucosa in the squamous epithelium with or without overlying exudate:

• Grade A — one or more mucosal breaks each ≤ 5 mm in length.

• Grade B — at least one mucosal break > 5 mm long, but not continuous between the tops of adjacent mucosal folds.

• Grade C — at least one mucosal break that is continuous between the tops of adjacent mucosal folds, but which is not circumferential.

• Grade D — mucosal break that involves at least three-fourths of the luminal circumference.

From a clinical perspective, the multitude of esophagitis grading schemes makes the interpretation of an endoscopic report impossible unless the specific findings are detailed. Thus, the most practical alternative is a detailed description of the specific findings. If a classification system is to be used, it is imperative that the scheme be specified.

Response to antisecretory therapy: a symptomatic response to antisecretory therapy with proton pump inhibitors or H_2 antagonists is frequently considered to support the presumptive diagnosis of GERD.

Mamagement

Treatment of GERD involves a stepwise approach. The goals are to control symptoms, to heal esophagitis, and to prevent recurrent esophagitis or other complications. The treatment is based on lifestyle modification and control of gastric acid secretion through medical therapy with antacids or proton pump inhibitors or surgical treatment with corrective antireflux surgery.

Nonpharmacotherapy: lifestyle modifications used in the management of GERD include the following:

• Losing weight (if overweight).

• Avoiding alcohol, chocolate, citrus juice, and tomato-based products.

• Avoiding peppermint, coffee, and possibly the onion family.

- Eating small, frequent meals rather than large meals.
- Waiting 3 hours after a meal to lie down.
- Refraining from ingesting food (except liquids) within 3 hours of bedtime.
- Elevating the head of the bed 8 inches.
- Avoiding bending or stooping positions.

Pharmacotherapy: the following medications are used in the management of GERD:

- H_2 receptor antagonists (eg, ranitidine, cimetidine, famotidine, nizatidine).
- Proton pump inhibitors (eg, omeprazole, lansoprazole, rabeprazole, esomeprazole, pantoprazole).
- Prokinetic agents (eg, aluminum hydroxide).
- Antacids (eg, aluminum hydroxide, magnesium hydroxide).

Surgical options: transthoracic and transabdominal fundoplications are performed for GERD including partial (anterior or posterior) and circumferential wraps. Open and laparoscopic techniques may be used. Placement of a device to augment the lower esophageal sphincter is another surgical option. Indications for fundoplication include the following:

- Patients with symptoms that are not completely controlled by proton pump inhibitors.
- Patients with well-controlled reflux disease who desire definitive, one-time treatment.
- The presence of Barrett esophagus.
- The presence of extraesophageal manifestations.
- Young patients.
- Poor patient compliance with regard to medications.
- Postmenopausal women with osteoporosis.
- Patients with cardiac conduction defects.
- Cost of medical therapy.

In refractory cases or when complications related to reflux disease are identified (eg, stricture, aspiration, airway disease, Barrett esophagus), surgical treatment (fundoplication) is typically necessary. The surgical morbidity and mortality is higher in patients who have complex medical problems in addition to gastroesophageal reflux.

7. DYSPEPSIA

Definitions and introduction

Dyspepsia is defined as chronic or recurrent pain or discomfort centered in the upper abdomen. Discomfort is defined as a subjective negative feeling that is nonpainful, and can incorporate a variety of symptoms including early satiety or upper abdominal fullness.

Dyspepsia is a common complaint in clinical practice; therefore, its management should be based on the best evidence. Dyspepsia has often been loosely defined; the most widely applied definition of dyspepsia is the Rome Working Teams formulation, namely chronic or recurrent pain or discomfort centered in the upper abdomen. Predominant epigastric pain or discomfort helps to distinguish dyspepsia from GERD; in the latter the dominant complaint is typically heartburn or acid regurgitation but there may be a distinct epigastric component that is confusing. Frequent reflux symptoms (twice a week or more) probably impair quality of life and are generally considered to identify GERD until proven otherwise. Clinical trials in dyspepsia have used various definitions and have often not distinguished obvious GERD from dyspepsia, making interpretation of treatment responses problematic.

Diagnosis

Discomfort has been defined by the Rome Working Teams as a subjective negative feeling that is nonpainful, and has been considered to incorporate a variety of symptoms including early satiety, bloating, upper abdominal fullness, or nausea. However, bloating is most typically a symptom of IBS and may not be located in the upper abdomen exclusively. Nausea can be secondary to a variety of nonabdominal conditions. Hence, neither bloating nor nausea alone should be considered to identify dyspepsia. Belching alone is also an insufficient symptom to identify dyspepsia and can be secondary to air swallowing, although it is commonly present with epigastric pain or discomfort.

Dyspeptic patients more than 55 yr old, or those with alarm features (bleeding, anemia, early satiety, unexplained weight loss (> 10 % body weight), progressive dysphagia, odynophagia, persistent vomiting, a family history of gastrointestinal cancer, previous esophagogastric malignancy, previous documented peptic ulcer, lymphadenopathy, or an abdominal mass) should undergo prompt endoscopy to rule out peptic ulcer disease, esophagogastric malignancy, and other rare upper gastrointestinal tract disease.

In patients aged 55 yr or younger with no alarm features, the clinician may consider two approximately equivalent management options: (i) test and treat for H. pylori using a validated noninvasive test and a trial of acid suppression if eradication is successful but symptoms do not resolve or (ii) an empiric trial of acid suppression with a proton pump inhibitor (PPI) for 4–8 wk. The test-and-treat option is preferable in populations with a moderate to high prevalence of H. pylori infection (≥ 10 %), whereas the empirical PPI strategy is preferable in low prevalence situations.

Some anxious patients may need the reassurance afforded by endoscopy. On the other hand, repeat EGD is not recommended once a firm diagnosis of functional dyspepsia has been made, unless completely new symptoms or alarm features develop. Repeat EGD is otherwise unlikely to ever be cost-effective.

Grades of evidence:

Early endoscopy for alarm symptoms: C.

Test-and-treat strategy for H. pylori: A.

Acid suppression therapy: A.

Reassurance after endoscopy: C.

Additional diagnostic testing over and above EGD has a low yield in dyspepsia, at least in primary care. Studies applying abdominal ultrasonography in dyspepsia have reported few abnormalities aside from asymptomatic cholelithiasis that needs no intervention.

However, the symptom criteria used to define functional dyspepsia have generally been broader than recommended by the Rome Committees.

Management

A number of management options are available to the clinician in younger patients with no alarm features with uninvestigated dyspepsia.

A wait-and-see strategy of patient reassurance and education, with use of over-the-counter antacids, H_2-blockers, or PPIs and reevaluation can be considered, particularly in primary care. Another strategy worth considering is prescription of empirical full-dose or high-dose antisecretory therapy, reserving further evaluation for those who are either unresponsive or have an early symptomatic relapse after ceasing medication. Empiric antisecretory therapy was the backbone of the guideline proposed by the American College of Physicians and is still widely applied in practice. A third approach applies H. pylori test-and-treat as the initial strategy, currently most widely recommended around the world. Here, young patients without alarm features are tested for H. pylori infection. If H.pylori is detected, empiric antibiotic therapy is prescribed in an attempt to eradicate the infection; H. pylori-negative patients are treated with empiric antisecretory therapy initially. A modification of the H.pylori test-and-treat strategy is to either prescribe empiric antisecretory therapy first and reserve H. pylori testing later for failures, or apply empiric antisecretory therapy after H. pylori eradication fails to relieve symptoms. A final approach is to perform prompt EGD for all patients with dyspepsia. The best option remains under debate, but new data are available to help guide a rational decision.

There is empiric evidence from a management trial of prompt endoscopy in older patients that this is the strategy of first choice. There is only limited and unconvincing evidence that endoscopy leads to improved patient satisfaction scores in dyspepsia. Other studies have suggested that patients with dyspepsia are reassured by EGD and may require fewer prescriptions, although the duration of reassurance is not established. Dyspeptic patients who seek medical attention are more concerned about the possible seriousness of their symptoms and are more likely to be concerned about underlying cancer. Health anxiety has been shown to lead to a cycle of repeated medical consultations.

There are several potential disadvantages of prompt endoscopy for all dyspeptic patients that need to be carefully considered. Endoscopy is invasive and although the risks of this procedure in relatively healthy patients are very low, the issue of the risk-benefit ratio needs careful weighing, particularly as the procedure is very unlikely to identify an unexpected structural cause in a young patient with no alarm features. Finding esophagitis, the most likely structural abnormality, may often not lead to a change in management. Moreover, the high prevalence of dyspepsia means that a general recommendation to perform endoscopies on all patients would be very costly and would overwhelm endoscopy services. Furthermore, it is contentious that prompt EGD provides any direct benefits despite some positive studies quoted above. A syste-

matic review concluded that most data failed to support the view that endoscopy alone improves patient outcome in dyspepsia compared with other empiric strategies.

In H. pylori-negative cases with uninvestigated dyspepsia and no alarm features, an empiric trial of acid suppression for 4–8 wk is recommended first-line therapy.

Grade of evidence: A

If initial acid suppression fails after 2–4 wk, it is reasonable to step up therapy, although this is based on expert opinion only; this may require changing drug class or dosing.

Grade of evidence: C

In patients who do respond to initial therapy, it is recommended that treatment be stopped after 4–8 wk and if symptoms recur, another course of the same treatment is justified. There are no data on long-term self-directed therapy in this condition, although this may be worth considering in some patients.

Grade of evidence: C

The widespread availability of PPIs has resulted in this class of agents frequently being prescribed as initial empiric therapy in uninvestigated dyspepsia in place of H_2 receptor antagonists.

A meta-analysis of several large studies has demonstrated a short course of PPI therapy compared with a H_2-receptor antagonist, alginate, or placebo in primary care provides better symptomatic outcomes. There are limited data that prokinetic therapy employed as an empiric strategy may be efficacious in uninvestigated dyspepsia. A randomized trial in H. pylori-negative dyspepsia demonstrated that cisapride had low efficacy and was inferior to acid suppression. Moreover, cisapride is no longer available because of rare toxicity from QT_C prolongation and sudden death. There have been no trials of metoclopramide, tegaserod or domperidone in the management of uninvestigated dyspepsia.

There are only very limited data comparing empiric H. pylori treatment versus empiric PPI therapy.

Once a diagnosis of functional dyspepsia is confirmed by a negative endoscopy, an empiric trial of therapy is commonly prescribed. However, the benefits of all therapies in this condition have been questioned. Many patients do not require medication for dyspepsia after they have had reassurance and education. It is therefore important for the clinician to explain the meaning of the symptoms and their benign nature. Ascertaining why a patient with long-standing symptoms has presented on this occasion for care can be helpful, as this may identify those who have fears of an underlying serious disease or specific psychological distress that can be addressed. Potential precipitating factors in dyspepsia remain poorly defined. High-fat meals should be avoided; eating frequent and smaller meals throughout the day can sometimes be helpful. Specific foods that precipitate symptoms can be avoided. Food intolerance is uncommon, however, and food allergy very rare. Follow-up of the patient helps determine the natural history and allows further correction of faulty ideas and provides reassurance that can be very helpful in long-term management.

Antacids and sucralfate were not superior to placebo in functional dyspepsia based on a Cochrane review. However, a recent trial of simethicone has suggested potential benefit compared with placebo, and in another study equivalence with cisapride.

Eradication of H. pylori in functional dyspepsia is controversial. Moreover, H. pylori eradication in those with documented functional dyspepsia may help prevent ulcer disease, although convincing evidence is not available.

The benefit of other treatments remains uncertain. Drugs that relax the gastric fundus (*e.g.*, tegaserod, cisapride, sumatriptan, buspirone, clonidine, some SSRIs, nitric oxide donors) may theoretically improve some dysmotility-like dyspepsia (*e.g.*, early satiety) but adequate randomized controlled trials are lacking. Antidepressants are also of uncertain efficacy in functional dyspepsia but are often prescribed. There are insufficient data on the use of tricyclic antidepressants such as amitryptyline in dyspepsia, but small studies have suggested benefit; however, the beneficial effect of low-dose amitryptyline seen in functional dyspepsia was not related to changes in perception of gastric distension. An increased tolerance to aversive visceral sensations may play a role in the therapeutic effect. There are limited data with the SSRIs. Psychological therapies are promising, particularly hypnotherapy, but more data are needed in larger patient populations before these can be recommended for routine use.

8. ACUTE AND CHRONIC GASTRITIS

Definitions and introduction

Injury to the gastric mucosa is associated with epithelial cell damage and regeneration. The term gastritis is used to denote inflammation associated with mucosal injury. However, epithelial cell injury and regeneration are not always accompanied by mucosal inflammation. This distinction has caused considerable confusion since gastritis is often used to describe endoscopic or radiologic characteristics of the gastric mucosa rather than specific histologic findings. Epithelial cell damage and regeneration without associated inflammation is properly referred to as «gastropathy». The causes, natural history, and therapeutic implications of gastropathy differ from gastritis:

- Gastropathy is usually caused by irritants such as drugs (eg, nonsteroidal anti-inflammatory agents), alcohol, bile reflux, hypovolemia, and chronic congestion.
- Gastritis is usually due to infectious agents (such as Helicobacter pylori) and autoimmune and hypersensitivity reactions.

Helicobacter pylori-associated gastritis: the ability of H. pylori to cause acute gastritis was demonstrated most clearly after healthy volunteers ingested the organisms and developed a mild illness (consisting of epigastric pain, nausea, and vomiting without fever) associated with acute inflammatory changes on gastric biopsy. Despite the high prevalence of chronic H. pylori gastritis, few examples of spontaneous acute infection have been recognized. This is not surprising since the majority of patients who develop dyspeptic complaints (which may signal acute infection) are not immediately investigated; furthermore, the initial infection occurring in the community probably produces few or no symptoms in the majority of individuals.

Endoscopic and histopathologic features — the endoscopic appearance of acute H. pylori gastritis is variable and, in severe cases, can resemble lymphoma or carcinoma. Early after infection, Helicobacter pylori gastritis preferentially involves the gastric antrum. Histologic changes of acute Helicobacter pylori gastritis include intense neutrophilic infiltration of the mucous neck re-

gion and lamina propria. When severe, pit abscesses occur, along with mucin loss, erosion of the juxtaluminal cytoplasm, and desquamation of surface foveolar cells. Both the neutrophils and the bacteria are responsible for destruction of the epithelium. Acute gastritis almost always evolves into active chronic gastritis unless treated with appropriate antibiotics.

The major clinical associations with chronic H. pylori gastritis are peptic ulcer disease and, less commonly, gastric cancer and MALT lymphoma. An association between chronic H. pylori infection and dyspepsia remains controversial. A definitive histopathologic diagnosis of H. pylori infection depends upon the demonstration of the typical spiral shaped bacilli on a biopsy specimen. During treatment, Helicobacter pylori bacteria may lose their typical spiral shape and assume new forms, including U-shaped, rod-like, and coccoid forms. The coccoid forms appear as round basophilic dots, 0.4 to 1.2 μm in diameter. Proton pump inhibitors and other hypochlorhydric states facilitate survival of non-Helicobacter pylori bacteria, such that the presence of gastric organisms (including cocci) does not confirm the presence of Helicobacter infection. In such cases, the distinction requires immunohistochemistry for Helicobacter pylori. H. pylori organisms reside primarily in the unstirred layer of gastric mucus, adjacent to epithelial cells at the mucosal surface and in gastric pits. Gastric glands are usually not involved. The epithelial localization reflects the affinity of H. pylori organisms for gastric mucous cells. H. pylori organisms do not attach to small intestinal or other gastric epithelial cell types. The organisms can be detected in both the antrum and the body of the stomach in the majority of infected patients. The following represents the approximate frequency of H. pylori localization within the stomach, based upon the collective experience of several investigators:

- Antrum and body — 80 percent.
- Antrum only — 8 percent.
- Body only — 10 percent.

The first two patterns are associated with Helicobacter pylori and the last pattern is associated with Helicobacter pylori infection, modified by PPIs or marked atrophy and intestinal metaplasia. The usual natural history of Helicobacter pylori gastritis is of an antral predominant early stage of infection with only minimal corpus involvement. This stage is associated with an exaggerated gastrin response, precipitating an increase in acid secretion, enough to cause duodenal ulcers in some patients. With continued inflammation, gastrin producing cells are gradually lost, precipitating a fall in acid secretion and the development of atrophy with intestinal metaplasia. These changes facilitate the proximal migration of the bacteria, leading to corpus gastritis. Thus, the natural history of Helicobacter pylori gastritis is of diffuse antral inflammation spreading to the corpus, resulting in an atrophic front of advancing corpus injury with concomitant reduction in acid secretion. This scenario is accelerated with low acid secretion states such as chronic therapy with PPIs. However, this evolution is not inevitable since it can be modified by treatment. Patients in whom Helicobacter pylori colonization is heaviest in the gastric body may differ from those with antral predominant infection.

Histopathologic diagnosis of Helicobacter pylori: in current practice, noninvasive testing (eg, serology or stool antigen assay) is generally used to establish the diagnosis of H. pylori infection. A major role for histopathology is in diagnosing H. pylori infection in patients taking a proton pump inhibitor (PPI). PPIs can reduce the sensitivity of some of the noninvasive assays, an effect that may be due to the antimicrobial activity of these drugs. Histopathology is also used for the establishment of gastritis and for the detection of associated abnormalities such as intestinal metaplasia and mucosa-associated lymphoid tissue (MALT).The variable distribution of H. pylori in the stomach, and the attenuated growth observed during treatment with PPIs has implications for optimal sites and the number of biopsy specimens (recommended 4–5) that should be obtained to establish the diagnosis of Helicobacter pylori: lesser and greater curvature of the mid antrum, lesser and greater curvature of the mid body and one from stomach angle (lesser curvature).

Staining: although it is frequently possible to identify H. pylori in standard hematoxylin and eosin preparations, this type of staining is unreliable and is not advised. A variety of better staining methods for H. pylori are available:

- The quick Giemsa method is easy to use, inexpensive, and gives consistent results. It is the preferred method in many laboratories.
- Immunostaining techniques are also available, and are highly sensitive and reliable. They have a particular advantage in patients partially treated for Helicobacter pylori gastritis, a setting that can result in atypical (including coccoid) forms, which may mimic bacteria or cell debris on hematoxylin and eosin preparations.
- Silver stains (such Warthin-Starry and Genta methods), which were crucial to the original demonstration of H. pylori, are expensive and the results are not always reliable.

Mucosal changes: the inflammatory changes in chronic H. pylori gastritis have been well described. Acute and chronic inflammatory cells are concentrated in the upper part of the mucosa, beginning just below the surface epithelium and giving the appearance of superficial gastritis, particularly in oxyntic mucosa. This pattern is so characteristic that the observer can suspect H. pylori gastritis even at the lowest magnifications.The chronic inflammatory elements in H. pylori gastritis primarily consist of lymphocytes and plasma cells, scattered macrophages, and often increased eosinophils. Lymphoid follicles are frequently present. They represent an immune response to the bacteria and their presence provides a useful marker for Helicobacter pylori infection. Similarly, a prominence of plasma cells is a valuable clue to H. pylori infection. The acute (active) inflammatory component consists of neutrophilic infiltration of the surface and foveolar epithelium and the lamina propria, usually in scattered foci, with the frequent presence of small pit abscesses. The intensity of the inflammation varies among patients and sometimes from specimen to specimen in the same patient. Active inflammation is somewhat more common in antral than in oxyntic H. pylori infection. Although casual observation reveals no obvious relation between the numbers of organisms and the severity of the active or chronic inflammation, a correlation with active gastritis has been described.

VAC A: most Helicobacter pylori strains secrete the vacuolating cytotoxin Vac A. The toxin inserts itself onto the epithelial cell membrane and forms a hexameric anion-selective, voltage-dependent channel through which bicarbonate and organic anions can be released, possibly providing Helicobacter pylori bacteria with their nutrients. Vac A also inhibits T-lymphocyte activation.

Cytotoxin associated gene A: histopathologic changes in H. pylori gastritis correlate with the presence of an H. pylori-derived cytotoxic protein encoded for by a gene called cytotoxin associated gene A (CagA). CagA toxin correlates with a number of features that suggest a more severe form of infection, including:

- A larger number of H. pylori organisms.
- A greater degree of acute and chronic inflammation.
- More severe epithelial injury.
- A higher likelihood of associated peptic ulceration (duodenal and gastric).
- An increased risk for developing gastric gland atrophy, intestinal metaplasia, and gastric adenocarcinoma.

The deleterious effects of the cagA protein may in part be mediated by its ability to upregulate epithelial synthesis of interleukin-8 (IL-8), which promotes acute inflammation by mobilizing neutrophils. Another potentially important pathogenic characteristic associated with cagA-producing H. pylori strains is the ability to activate neutrophils in the absence of opsonization. This capability (demonstrated by the initiation of an oxidative burst within neutrophils exposed to organisms) correlates well with the severity of mucosal inflammation, and presence of peptic ulceration. The pathogenicity of cagA positive strains also appears to correlate with the number of repeat DNA sequences in the 3' region; strains with more than three repeat regions have been associated with enhanced histologic injury.

Significance of lymphoid follicles: lymphoid follicles represent an immune response to the organism, and are composed of aggregates of lymphocytes and other lymphoid cells associated with a central germinal center made up of larger, paler mononuclear cells. They appear within one week after the onset of acute H. pylori infection, and are uncommon in non-H. pylori-infected gastric mucosa. The number of lymphoid follicles correlates with the titer of serum IgG anti-H. pylori antibodies. Lymphoid follicles accompanying H. pylori gastritis are involved in the genesis of primary gastric lymphoma. The pathogenesis may involve stimulation of B cells with the ability for unsuppressed proliferation by activated T cells within the follicles.

Autoimmune gastritis

This corpus-restricted gastritis is associated with circulating autoantibodies against the microsomes of parietal cells as well as intrinsic factor. Intrinsic factor plays a key role in the absorption of vitamin B_{12}, and gastric acid is important for absorption of iron. Destruction of the cells producing hydrochloric acid and intrinsic factor, respectively, results in hypochlorhydria and a reduction in pepsin activity within gastric juices and may lead to pernicious or iron deficiency anemia. The finding of a low pepsinogen I level in the serum is a sensitive and specific indicator of gastric atrophy. Endoscopically, the mucosa of the corpus is thinner than normal. Often a reduction or absence of rugal folds and small mucosal elevations due to the presence of islands of intestinal metaplasia are seen. In the florid phase microscopy reveals a dense infiltrate of lymphocytes and plasma cells involving the entire thickness of the corpus mucosa with destruction of the oxyntic glands. As atrophy sets in, the mucosa shows a marked reduction of these glands, reduced inflammation and increasing degrees of intestinal and pyloric metaplasia. Metaplasia refers to replacement of normal gastric epithelium by modified cells of intestinal or pyloric variety. The hypo-/achlorhydria cause physiological hypergastrinaemia, which in turn stimulates proliferation of neuroendocrine cells and can lead to development of neuroendocrine tumours (‘carcinoids’). These tumours are relatively innocuous, in contrast to the less common solitary, sporadic type which is more aggressive.

Chemical (reactive) gastropathy

Chemical gastropathy was recommended as the preferred term to synonyms such as chemical gastritis, type C gastritis and reactive gastropathy, and refers to endoscopic and histological changes caused by chemical injury to the gastric mucosa.

Chemical agents commonly associated with mucosal damage include:

• Medications, particularly NSAIDs, but also drugs such as PPIs, iron, kayexalate, colchicine, antineoplastics and corticosteroids. NSAIDs cause mucosal damage by reducing prostaglandin synthesis. Second-generation and selective NSAIDs and COX-2 inhibitors are better tolerated by the gastric mucosa. Endoscopically, long-term users of NSAIDs may show mucosal erythema, congestion, erosions and ulcers. Histologically the mucosa reveals oedema, foveolar hyperplasia, smooth-muscle proliferation, regeneration and, on occasion, erosion with a relatively mild inflammatory cell response.

• Duodenopancreatic (bile) reflux is seen particularly in patients with a Billroth II partial gastrectomy. A chronic gastritis with marked foveolar hyperplasia, which may be cystic or polypoid, develops proximal to the stoma.

• Acids, alkalis and large quantities of alcohol. Most of these cause extensive severe, necrotising lesions.

Classification

Most classification systems distinguish acute, short-term from chronic, long-term disease. The terms acute and chronic are also used to describe the type of inflammatory cell infiltrate. Acute inflammation is usually associated with neutrophilic infiltration, while chronic inflammation is usually characterized by mono-

nuclear cells, chiefly lymphocytes, plasma cells and macrophages. In 1990 the Sydney system was developed as a guideline for the classification and grading of gastritis by a group of international experts in Sydney, Australia. See on Table 6.

Table 6 — Sydney classification for chronic gastritis (modified)

Feature	Definition	Grading Guidelines
Chronic inflammation	Increased lymphocytes and plasma cells in the lamina propria	Mild, moderate, or severe increase in density
Activity	Neutrophilic infiltrates of the lamina propria, pits, or surface epithelium	Less than one third of pits and surface infiltrated = mild; one third to two thirds = moderate; more than two thirds = severe
Atrophy	Loss of specialized glands from either antrum or corpus	Mild, moderate, or severe loss
Intestinal metaplasia	Intestinal metaplasia of the epithelium	Less than one third of mucosa involved = mild; one third to two thirds = moderate; more than two thirds = severe

This system combines topographical, morphological and aetiological information (detection of H. pylori) into a scheme that helps generate a reproducible and clinically useful diagnosis. Four years later this system was updated and subsequently modified to improve the criteria for evaluating atrophy. It recommends that at least five biopsy specimens (two from the greater and lesser curvatures of the corpus, one from the incisura angularis and two from the larger and lesser curvatures of the antrum) with mucosa and muscularis mucosae represented in each biopsy be evaluated. In practice, however, pathologists are usually asked to make a diagnosis on one or two biopsy specimens as most types of gastritis can be diagnosed without extensive tissue sampling.

The Sydney System for the classification of gastritis emphasized the importance of combining topographical, morphological, and etiological information into a schema that would help to generate reproducible and clinically useful diagnoses. To reappraise the Sydney System 4 years after its introduction, a group of gastrointestinal pathologists from various parts of the world met in Houston, Texas, in September 1994. The aims of the workshop were (a) to establish an agreed terminology of gastritis; (b) to identify, define, and attempt to resolve some of the problems associated with the Sydney System. TThe Sydney System was revised at the Houston Gastritis Workshop. Overall, the principles and grading of the Sydney System were only slightly modified, the grading being aided by the provision of a visual analogue scale. The terminology of the final classification has been improved to emphasize the distinction between the atrophic and nonatrophic stomach; the names used for each entity were selected because they are generally acceptable to both pathologists and gastroenterologists. In addition to the main categories and atrophic and nonatrophic gastritis, the special or distinctive forms are described and their respective diagnostic criteria are provided.

Operative Link on Gastritis Assessment (OLGA)) develops a histological staging system for gastric inflammatory diseases that would meet the same objec-

tives as the hepatitis staging system. The OLGA system uses the biopsy sampling protocol and the visual analogue scales recommended by the Houston-updated Sydney system. In the OLGA staging system, gastric atrophy is considered to be the histological lesion representative of disease progression. Gastritis stage results from combining the extent of atrophy scored histologically with the topography of atrophy identified through biopsy mapping. It has been also suggested that the diagnostic report include information about the probable aetiology.

Special or distinctive forms of gastritis:

Lymphocytic gastritis

A diagnosis of lymphocytic gastritis can only be made on histology, but many patients have the endoscopic features of varioliform gastritis with mucosal nodules, chronic persistent erosions and thickened mucosal folds. The disease is characterised by an infiltrate of lymphocytes in the lamina propria with large numbers of lymphocytes among the epithelial cells lining the surface and foveolae.

The aetiology remains uncertain, although an allergic or autoimmune pathogenesis is proposed. Lymphocytic gastritis may be found in association with coeliac disease (gluten-sensitive enteropathy), Menetrier's disease (hypertrophic gastropathy characterised by a hypertrophic gastric mucosa with convoluted, thickened mucosal folds and protein-losing enteropathy), as an abnormal response to HP infection or NSAID use, or in association with lymphocytic/collagenous colitis. Treatment is steroids and management of any underlying cause.

Collagenous gastritis

This is a rare entity characterised by a thickened subepithelial band of collagen and chronic inflammatory infiltrate in the gastric mucosa, similar to that seen in collagenous colitis. The disease may be limited to the stomach, then usually in children and young adults presenting with anaemia due to gastric bleeding, and demonstrate focal nodularity of the gastric mucosa on endoscopy. It may also be found in adults with collagenous colitis and present with a chronic watery diarrhoea.

Eosinophilic gastritis

Eosinophilic gastritis and gastroenteritis may affect all age groups and present with failure to thrive (in children), abdominal pain, irritability, gastric dysmotility, vomiting, diarrhoea, dysphagia and (in severe cases) protein-losing enteropathy. Many patients are atopic and have increased serum total IgE and food-specific IgE, as well as blood eosinophilia. This entity is characterised by eosinophil-rich inflammation of all or a portion of the GI tract wall. Gastroscopy may reveal antral mucosal swelling and redness with narrowing of the pylorus and diminished peristalsis. Improvement after elimination of certain foods from the diet supports an allergic aetiology. Parasites and drug reactions are a much less common cause.

Granulomatous gastritis

This group of conditions is characterised by multiple granulomas in the gastric mucosa and has a long list of possible causes. This includes infections

such as tuberculosis and histoplasmosis, foreign body reaction directed against postoperative sutures or food trapped in ulcers, tumours such as mucus-producing adenocarcinomas and lymphomas, as well as systemic granulomatous diseases such as sarcoidosis, Crohn's disease and Wegener's granulomatosis.

Vascular gastropathy

Vascular gastropathy refers to a group of disorders characterised by distinct alterations in the gastric mucosal blood vessels and a paucity or absence of inflammation.

• Gastric antral vascular ectasia (GAVE or 'watermelon stomach') is a rare condition of unknown aetiology. Endoscopy shows longitudinal mucosal folds with ectatic vessels converging from the proximal antrum into the pylorus. Histology reveals marked dilated mucosal capillaries, some of which may be thrombosed, and features of reactive gastropathy. Patients may present with occult bleeding, melaena, haematemesis and anaemia.

• Portal hypertensive gastropathy is seen in patients with portal hypertension who may present with gastric haemorrhage due to dilatation, congestion and proliferation of mucosal blood vessels, most prominent in the proximal stomach. The endoscopic appearance may resemble snake skin, cherry red spots or have a mosaic pattern. Decompression of the portal hypertension by means of bypass surgery reduces the risk of haemorrhage.

From gastritis to cancer:

Based on extensive epidemiological and pathological cohort studies, Pelayo Correa proposed a paradigm of gastric carcinogenesis that has become known as Correa's cascade. In this model, chronic gastritis progressively evolves to atrophy and intestinal metaplasia. In some subjects the metaplastic epithelium undergoes further genomic and phenotypic disarrangements (dysplasia) and may progress to invasive neoplasia. Recently, the paradigm has been modified to insert H. pylori at the beginning of the sequence. Although this model is validated and widely accepted, there is still a wide discordance in the histopathological recognition of two of its crucial steps: atrophy and dysplasia.

Management

Symptoms treatment — see «Dyspepsia management». Endoscopic management of atrophic gastritis is very important for early detection and treatment of gastric neoplasia. H. pylori-associated gastritis and may respond to eradication of H. pylori infection according to Maastricht Consensuns IV. Regimens available:

• The triple treatment including PPI-clarithromycin and amoxicillin or metronidazole proposed at the first Maastricht conference1 to treat H. pylori infection has become universal since it was recommended by all the consensus conferences held around the world. However, the most recent data show that this combination has lost some efficacy and often allows the cure of only a maximum of 70 % of the patients, which is less than the 80 % rate aimed for at the beginning and far below what should be expected for an infectious disease.

• While no new drug has been developed for this indication, a number of studies have been carried out in recent years using different combinations of known

antibiotics. Most data were obtained with the so-called ‘sequential treatment’ which includes a 5-day period with PPI amoxicillin, followed by a 5-day period with PPI-clarithromycin-metronidazole (or tinidazole).

- It was also proposed that the three antibiotics should be taken simultaneously together with a PPI (non-bismuth quadruple therapy).
- There was also a renewal of the old recipe — that is, the bismuth-containing quadruple therapy following the development of a gallenic formulation including bismuth salts, tetracycline and metronidazole in the same pill.
- Other treatment — treatment of complications (Vit. B12 deficiency anemia, iron deficiency anemia and others).
- Special forms of gastritis (granulematosus, eosinophilic) needs patogenic treatment (immunosupressors, antiallergic drugs etc.).

Management of Helicobacter pylori infection according to the Maastricht IV/ Florence Consensus Report. Summary of treatment strategies see on Table 7.

Table 7 — Summary of treatment strategies

Statement	Level of evidence	Grade of recommendation
Proton pump inhibitor (PPI)-clarithromycin containing triple therapy without prior susceptibility testing should be abandoned when the clarithromycin resistance rate in the region is over 15–20 %	5	D
In areas of low clarithromycin resistance, clarithromycin- containing treatments are recommended for first-line empirical treatment. Bismuth-containing quadruple treatment is also an alternative	1a	A
In areas of high clarithromycin resistance, bismuth-containing quadruple treatments are recommended for first-line empirical treatment. If this regimen is not available sequential treatment or a non-bismuth quadruple treatment is recommended	1a	A
The use of high-dose (twice a day) PPI increases the efficacy of triple therapy	1b	A
Extending the duration of PPI-clarithromycin-containing triple treatment from 7 to 10–14 days improves the eradication success by approximately 5 % and may be considered	1a	A
PPI-clarithromycin-metronidazole (PCM) and PPI-clarithromycin-amoxicillin (PCA) regimens are equivalent	1a	A
Certain probiotics and prebiotics show promising results as an adjuvant treatment in reducing side effects	5	D
PPI-clarithromycin-containing treatments do not need to be adapted to patient factors except for dosing	5	D
After failure of a PPI-clarithromycin containing therapy, either a bismuth containing quadruple therapy of Levofloxacin containing triple therapy are recommended.	1a	A
Rising rates of Levofloxacin resistance should be taken into account	2b	B
After failure of second-line treatment, treatment should be guided by antimicrobial susceptibility testing whenever possible	4	A

9. PEPTIC ULCERS

Definitions and introduction

Peptic ulcers are defects in the gastrointestinal mucosa that extend through the muscularis mucosae. They persist as a function of the acid or peptic activity in gastric juice. Peptic ulcer disease (PUD) is an important cause of morbidity and health care costs. The natural history of peptic ulcer ranges from resolution without intervention to the development of complications with the potential for significant morbidity and mortality, such as bleeding and perforation.

Epidemiology: the time trends in the epidemiology of peptic ulcer reflect complex, multifactorial etiologies. Peptic ulcer was rare before the 1800s. The pathology of GU was first described in 1835; during the late 1800s the prominent form was gastric ulcers in young women. DU were rare until about 1900 and then became a prevalent condition during the first half of the twentieth century. However, in developed countries the mortality from peptic ulcer has fallen dramatically for birth cohorts born after the turn of the twentieth century. It is now evident that the epidemiology of peptic ulcer largely reflects environmental factors, primarily H. pylori infection, NSAID use, and smoking. However, these environmental factors do not tell the whole story of the time trends and the birth-cohort effect for peptic ulcer. In particular, H. pylori was a prevalent human infection well before the late 1800s, so that this infection per se cannot explain the rise in ulcer prevalence and shift from GU to DU.The influence of environmental factors on the pattern of gastritis may be a key variable in these birth-cohort effects. At the end of the 19th century (and currently in many developing countries) H. pylori infection was characterized by pangastritis involving the gastric antrum and body and leading to acid hyposecretion, which predisposed to gastric cancer and GU. In contrast, DU is associated with antral-predominant gastritis that spares the acid-secreting body, but is negatively associated with more or severe body gastritis and with gastric cancer. The reason is that DU requires a permissive level of acid secretion which cannot be achieved in the face of moderate body gastritis, whereas gastric cancer is associated with hypochlorhydria. Although still controversial, this dramatic shift in pattern of ulcer disease and of H. pylori-induced gastritis appeared to reflect environmental factors, which changed markedly during this period, rather than genetic bacterial or host factors, which appeared unchanged. One theory suggests that during the early 1900s improved transportation and refrigeration decreased the need for food preservatives and supported a rapid change in diet across the emerging developed nations. The most evident change was from a seasonal diet, in which salt was used as a preservative, to a diet with fresh fruits and vegetables available all year. Furthermore, improved hygiene and overall health in developed countered was associated with reduced rates of childhood infections, which may decrease susceptibility to the pangastritic spread of H. pylori. Estimates of the annual incidence of peptic ulcer disease range from 0.1

to 0.3 percent. A systematic review of the worldwide literature estimated that the annual incidence ranged from 0.1 to 0.19 percent for physician-diagnosed PUD and 0.01 to 0.17 percent when based upon hospitalized patients. Ulcer incidence increases with age for both DU and GU, but DU emerges two decades earlier than GU, particularly in males.The disease burden varies based upon the presence of H. pylori. The ulcer incidence in H. pylori-infected individuals is about 1 percent per year, a rate that is 6 to 10-fold higher than for uninfected subjects.The lifetime prevalence is also higher in H. pylori-positive subjects (approximately 10 to 20 percent compared to 5 to 10 percent in the general population).

Etiology: peptic ulcer disease is associated with two major factors: Helicobacter pylori infection; and the consumption of nonsteroidal antiinflammatory drugs (NSAIDs). There are also a number of other defined mechanisms for peptic ulcer that are much less common but becoming more evident as the prevalence of H. pylori declines in developed countries.

Several factorsare associated with a transient increase in ulcer disease:

- The incidence of H. pylori below age 50 is falling dramatically in developed countries due in part to improved hygiene and socioeconomic conditions. However, the prevalence of H. pylori infection remains high for older individuals and in certain predisposed subpopulations.
- NSAID use increases as a function of age and is an independent risk factor for ulcers. In addition, older subjects are more likely to develop complications from NSAID ulcers and to suffer increased morbidity and mortality from these complications because of comorbidities.
- Smoking clearly exacerbates at least H. pylori associated ulcer disease. The decline in smoking in younger individuals, particularly males, and increase in women, may be a factor in the declining male/female ratio of ulcer disease. Smoking does not appear to be a factor in the ulcer complications found in older women or in NSAID-related ulcers.
- Other factors, such as the extreme psychological stress or associated with traumatic events.

Pathophysiology: considering the acid-peptic environment of the stomach and the noxious agents that are ingested, ulcers are surprisingly uncommon, illustrating the importance of protective mechanisms that govern gastric mucosal function and repair. Primary malfunction of these secretory, defense, or repair mechanisms is a very uncommon cause of ulcer, if it occurs at all. Most ulcers occur when the normal mechanisms are disrupted by superimposed processes such as H. pylori infection and the ingestion of NSAIDs.

There are a number of risk factors for ulcer disease, such as smoking and increased acid and decreased duodenal bicarbonate secretion. Although these factors are almost certainly of pathogenic relevance, the extent to which these three mechanisms distinguish the small subset with H. pylori exposure that develop ulcers from the similarly-exposed majority who remain ulcer-free has not been established.Mucosal damage from trauma, acid-peptic activity, and

exposure to environmental toxins occurs in everyone everyday, and the gastrointestinal mucosa has a remarkable ability to repair itself. Chronic peptic ulcers, which are focal mucosal lesions that persist or recur over time, usually in the same location, are the exception.

Gastric acid hypersecretion: although only a small proportion of DU subjects have true acid hypersecretion, high-normal or modestly elevated values appear to be a defining characteristic of patients with DU, whether or not they are infected with H. pylori.Among H. pylori-positive subjects with DU, three factors appear to contribute to the high-normal or high levels of acid secretion:

- A subset has hypergastrinemia that is H. pylori-dependent, since cure of the infection leads to a decrease in acid secretion.
- A subset has an H. pylori-independent drive to acid secretion, possibly related to vagal hyperactivity.
- DU patients generally have sparing of their acid-secreting gastric body from gastritis and atrophy, leaving the parietal cell mass intact and capable of producing robust levels of acid secretion.

Relative hypergastrinemia is seen in H. pylori-infected subjects with or without DU; the causal elements appear to be suppression of somatostatin, rather than an increase in gastrin-secreting cells. The abnormality in acid secretion seen in DU subjects is linked to the predisposition in the host, rather than directly to H. pylori infection. The defective regulation of acid secretion in DU appears to be related to impaired control of inhibitory mechanisms, although defective inhibitory regulation is also seen in people without DU. The abnormalities in gastrin and somatostatin secretion and most abnormalities of acid secretion normalize within one year of H. pylori eradication.Ulcer recurrence following successful H. pylori eradication may be more common than previously expected. A small study found higher basal and pentagastrin-stimulated acid secretion in patients with recurrent ulcers following successful H. pylori eradication, compared to patients without recurrent ulcers.Among H. pylori-negative subjects, a subset has acid hypersecretion without hypergastrinemia. The mechanisms of acid hypersecretion in these patients have not been defined. One study of six patients with non-HP, non-NSAID DU found increased gastrin response to a meal (but not fasting hypergastrinemia) and increased peak gastric acid secretion. Some subjects with non-HP, non-NSAID hypersecretion may have a component of muscarinic-dependent, vagal hyperactivity, although this element is difficult to quantify. In the absence of H. pylori or gastrinoma, fasting hypergastrinemia is only rarely found in hypersecretory DU patients, sometimes linked to antral G cell hyperfunction. Taken together, these data indicate that increased acid secretion is an important factor in some patients with ulcer recurrences following successful H. pylori eradication and in some patients with non-HP, non-NSAID DU. The combination of increased gastric acid secretion and reduced duodenal bicarbonate secretion lowers the pH in the duodenum, which promotes the development of gastric metaplasia (ie, the presence of gastric epithelium in the first portion of the duodenum).H. pylori infection in areas of gastric metaplasia induces duodenitis and enhances the susceptibility to acid injury, thereby possibly predisposing to DU. A study that followed 181 pts with endoscopy-negative, non-ulcer dyspepsia and found that duodenal colonization by H. pylori was a highly significant predictor of the subsequent development of DU.

Excess acid secretion in gastrinoma patients is also associated with marked gastric metaplasia in the duodenum. Thus, metaplasia can be related to chronic injury can occur independently of H. pylori infection. Although it is possible that duodenal gastric metaplasia is simply a consequence of duodenal injury from acid or H. pylori, it is an attractive hypothesis that chronic, local duodenal mucosal injury ulcer actually predisposes to focal development of DU.

Gastric ulcer: GU occurring in the stomach proximal to the distal antrum and prepyloric region is usually associated with low-normal or low acid secretion, reflecting a low normal parietal cell mass. These findings correspond to the encroachment of oxyntic mucosa by ad-

vancing antritis and oxyntic gland atrophy. In contrast to GU involving the gastric body, patients with ulcers in the distal antrum or GU associated with concurrent DU have normal or even increased levels of acid secretion.

Genetic, environmental, and psychological risk factors: the familial aggregation of both DU and GU appeared distinct: first-degree relatives of patients with DU have a threefold increase in the prevalence of DU but not GU; in contrast, relatives of patients with GU have a threefold increase in the prevalence of GU but not DU. Hyperpepsinogenemia was proposed as a marker of autosomal dominant inheritance of predisposition to peptic ulcer. Subsequent follow-up of these same subjects revealed that this pattern of hyperpepsinogenemia was in fact due to familial clustering of H. pylori infection.

Host factors appear to be important in predisposing to H. pylori infection and to disease outcomes, such as DU and gastric cancer. However, the number of emerging candidates is daunting and no studies have yet determined the universality of any single finding. Some of the variability may be due to different genetic makeup of the study populations and the relatively small size of the studies. However, it is likely that multiple host factors interact with multiple bacterial factors, making this area challenging to investigate and to integrate. Genetic polymorphism related to synergy between host (TNF alpha promoter) and bacterial (induced by contact with epithelium, or the iceA1 gene) factors have been related to DU in children.In the setting of H. pylori infection host polymorphisms involving the cytokine IL-1- beta, but not IL-6, are linked to DU, probably related to effects of H. pylori-associated inflammation and acid secretion.Although IL-1-beta has been reported to have cytoprotective effects, it remains to be determined whether cytokine polymorphisms influence PUD in patients with other forms of PUD. Genetic polymorphism relating to cyclooxygenase-1 and PG production is another factor to consider. An association has been reported between peptic ulcer and several indirect «genetic» markers. Blood groups O and A, the Lewis phenotype Le (a + b-), and non-secretors of ABH in particular, have been associated for increased risk of peptic ulcers. However, other studies have failed to find any association of blood group O with H. pylori infection or with peptic ulcer. Thus, the relation between Lewis antigen expression, H. pylori attachment, and peptic ulcer disease is unclear.

Factors that influence the course of peptic ulcer: a number of risk factors potentially impact the rate of ulcer healing, complications, and the tendency for recurrence.

Characteristics of the patient: there are several characteristics of the patient that may influence ulcer healing.Ulcers in older patients may heal more slowly than in younger individuals. Older patients are also more likely to bleed, rebleed, require more transfusions, and have a prolonged hospital stay, probably due to the presence of comorbid illness.Patients with simultaneous DU and GU may have delayed healing and a more complicated course.Patients who first develop ulcer complications in the hospital (stress ulcer) respond poorly to medical and surgical therapy. Stress ulcers are clearly related to pathophysiologic disturbances provoked by the underlying medical or surgical illness; they do poorly unless the underlying disease remits or responds to therapy. Despite a report that H. pylori-positive patients have an increased change of demonstrating marked mucosal injury, there is no evidence that stress ulcers are related to H. pylori infection.

Smoking: studies primarily performed in the pre-H. pylori era found that smoking had an important facilitative role for peptic ulcer disease. Smokers were more likely to develop ulcers, and the ulcers were more difficult to treat and were associated with a higher rate of recurrence. However, smoking does not appear to be a risk factor for ulcer relapse once H. pylori has been eradicated. Many mechanisms have been proposed to underlie the deleterious effects of smoking on mucosal aggressive and protective factors. As an example, smoking and chronic nicotine treatment stimulated basal acid output to a greater extent in smokers with DU history, compared to smokers without a DU history. The general wisdom is that smoking is a risk factor for PUD before, but not after H. pylori eradication.

Alcohol: alcohol in high concentrations damages the gastric mucosal barrier to hydrogen ions and is associated with acute gastric mucosal lesions characterized by mucosal hemorrhages. Alcohol also stimulates acid secretion. In addition, contents of alcoholic beverages other than alcohol are also strong stimulants of acid secretion.Despite these acute effects, there is no evidence that alcohol intake causes or exacerbates chronic peptic ulcer disease. Modest alcohol consumption may even promote ulcer healing. In contrast, alcohol abuse interferes with patient compliance and ulcer healing.

Diet: folklore has incriminated dietary indiscretion as a cause of ulcers. Although certain foods, beverages, and spices cause dyspepsia, there are no convincing data that such specific foods cause, perpetuate, or reactivate peptic ulcers. There are, however, some data that implicate dietary factors may influence peptic ulcer pathogenesis. Dietary factors have been hypothesized to account for some of the regional variation of ulcer disease, possibly related to toxins generated with storage of certain foods or from protective effects of certain foods. Other dietary factors also may be protective. Dietary insufficiency of essential fatty acids has been proposed as a pathogenic factor in DU, possibly resulting in depletion of mucosal prostanoids. It has also been suggested that an increase in dietary polyunsaturated fatty acids was protective against H. pylori. Supporting evidence for these hypotheses remains weak. Fatty acids had no effect on either colonization of the stomach by H. pylori or antral prostaglandin levels. However, high consumption of fruits and vegetables, dietary fiber, and vitamin A were associated with a reduced risk of ulcer disease.Coffee is a strong stimulant of acid secretion and produces dyspepsia in many individuals, which often results from enhanced esophageal reflux. Caffeine is not the only variable, because decaffeination does not reduce these effects of coffee. Despite these observations, there is no evidence that coffee consumption is a risk factor for ulcer disease, although increased consumption may be associated with a higher rate of infection with H. pylori. Clinical experience indicates that food intolerances are common in patients with DU and other acid-peptic and functional gastrointestinal disorders. These symptoms appear to reflect sensitivities to substances in foods; there is no evidence that they are related directly to ulcer formation. Food intolerances are common and highly variable in the general population making rigorous investigation challenging. Although frequently advised in the past, there is no evidence that dietary manipulations, such as a bland diet, enhance healing. Frequent feedings, justified on the basis that small meals cause less gastric distension, may lead instead to more sustained stimulation of acid secretion. Bedtime snacks stimulate nocturnal acid secretion. Milk was a mainstay of symptomatic therapy for peptic ulcer because of its soothing nature, until it was shown to be a strong acid secretagogue, largely because of its calcium and protein content. Milk stimulates more acid secretion than it buffers and is not an effective antacid. Nevertheless, it appears to reduce acute acid-induced damage in rats, to protect against cysteamine-induced acute DU in mice, and, after four days, to reduce histamine-stimulated acid secretion in rats. Human milk contains potentially protective factors, including growth factors, surface active phospholipids, and prostaglandin E2. Thus, it is possible that milk has antiulcer actions that override the stimulation of acid secretion. Thus, despite a lack of scientific validation, use of milk should not be discouraged in patients who find it beneficial, as long as they realize that there is no known therapeutic benefit.

Psychologic factors: the importance of psychodynamic factors in the genesis of peptic ulcer remains controversial despite decades of study. Investigation of the psychodynamic aspects of ulcer disease has been hampered for a variety of reasons:

- It is difficult to define ulcer occurrence and recurrence and to achieve adequate sampling and blinding. Many retrospective studies are based on self-report about the ulcer history, which could lead to bias favoring association with psychosocial factors.
- The pathogenesis of ulcer disease is multifactorial, and psychodynamic factors are likely to play a role only in a subset of ulcer patients, which remains undefined.

• Psychological stress is difficult to measure. Stressful events are only part of the picture; the level of distress also reflects the patient's perception of the stressful event, interpretation of implications, and coping mechanisms.

• Psychodynamic factors need to be correlated with pathophysiologic mechanisms relating to known variables of importance, such as infection with H. pylori, adequate acid secretory mass, smoking, and NSAID use.

Second, several studies have established that peptic ulcer complications become much more prevalent during periods of natural disaster or societal catastrophe. Stress, anxiety, and depression were also observed to impair endoscopic healing and to promote relapse of endoscopically diagnosed ulcers.The effects of stress seem to be reversible; patients who develop an ulcer following traumatic life events, but who are psychologically stable, tend to do well after the stress has resolved.The pathophysiological mechanisms accounting for the effects of stress on the ulcer formation have not been defined. These effects could be mediated by both altered behaviors and by altered physiology. Pathogenic mechanisms for peptic ulcer are multifactorial, a fact that confounds unraveling the link between psychosocial factors and ulcerogenesis. As example, stress increases acid secretion, but the effects are more prominent in patients with DU, compared to controls. As a result, one must consider not only the stressor, but the individual's physiological and psychosocial response to the stress; deleterious effects may only be evident in a subset of predisposed individuals.Lastly, finding a relationship between psychosocial factors and ulcer disease does not establish causality. In some cases, psychological features may be the result, not the cause of the disease process.

Diagnosis

Clinical manifestations of peptic ulcers: a pragmatic definition of «dyspepsia» is the presence of symptoms that the clinician suspects are coming from the upper gastrointestinal (GI) tract. Peptic ulcers can present with any of the three dyspeptic symptom patterns:

• Ulcer-like or acid dyspepsia (burning pain; epigastric hunger-like pain; relief with food, antacids, and/or antisecretory agents).

• Food-provoked dyspepsia or indigestion (postprandial epigastric discomfort and fullness, belching, early satiety, nausea, and occasional vomiting).

The «classic» pain of duodenal ulcers (DU) occurs when acid is secreted in the absence of a food buffer. Food is usually well emptied by two to three hours after meals, but food-stimulated acid secretion persists for three to five hours; thus, classic DU symptoms occur two to five hours after meals. Symptoms also classically occur at night, between about 11 PM and 2 AM, when the circadian stimulation of acid secretion is maximal. The ability of alkali, food, and antisecretory agents to produce relief suggests a role for acid in symptom generation. Thus, «acid dyspepsia» is a fitting term.

Silent ulcers: frequently, peptic ulcers are asymptomatic. Between 43 and 87 percent of patients with bleeding peptic ulcers present without antecedent dyspepsia or other heralding GI symptoms. Ulcer perforation also frequently occurs without antecedent symptoms. This «silent» presentation may be more frequent in elderly patients and possibly in individuals consuming nonsteroidal antiinflammatory drugs (NSAIDs). Consistent with these findings, patients with a

history of bleeding peptic ulcers had low levels of background GI symptoms and symptomatic responses to a nutrient meal that were comparable to healthy controls and much less than symptomatic ulcer patients.

Predictive value of symptoms: in patients with peptic ulcers, there is often a poor correlation of the presence of endoscopic ulceration with symptoms. Longitudinal studies have shown that as many as 40 percent of patients with endoscopically healed ulcers have persistent symptoms, while 15 to 44 percent of those who become symptom-free still have an ulcer crater at endoscopy. Thus, the disappearance of symptoms does not guarantee ulcer healing, nor does the persistence of symptoms consistently predict the presence of an ulcer crater.In patients with uninvestigated dyspepsia, symptoms do not accurately predict the presence or absence of organic disease. In one study, a clinical diagnosis of peptic ulcer disease had a positive likelihood ratio for the presence of endoscopic peptic ulceration of 2.2 to 2.9, whereas a clinical diagnosis of no peptic ulcer disease had a negative likelihood ratio of 0.45 to 0.48. However, clinical diagnoses have very poor predictive value for two reasons: symptoms are nonspecific and overlapping and the pre-test prevalence of peptic ulcer disease among patients with undiagnosed dyspepsia in developed countries has dropped to as low as 4 to 9 percent. Despite this low accuracy of the clinical diagnosis of organic disease, emphasize a point made above: a detailed clinical history helps clinicians to discriminate between symptoms coming from the upper or lower GI tract versus symptoms of cardiac, pulmonary, or fibromuscular origin, thereby guiding diagnosis and treatment.

Diagnosis of peptic ulcer disease: there are two major considerations in diagnosis of peptic ulcer disease (PUD): determining whether dyspeptic symptoms are due to PUD and determining the specific etiology of an ulcer discovered by endoscopy or radiography. Symptoms alone cannot reliably distinguish PUD from other causes of dyspepsia. The diagnosis is generally established by upper endoscopy, although the need to pursue a definitive diagnosis depends upon the clinical setting. As an example, establishing a definitive diagnosis is always required in patients with gastrointestinal bleeding or other alarm symptoms (such as early satiety, dysphagia, weight loss, occult gastrointestinal bleeding, or otherwise unexplained anemia). By contrast, empiric testing for H. pylori may be appropriate in young patients without alarm symptoms.

Endoscopy is the most accurate diagnostic test for PUD. Sensitivity of endoscopy depends in part upon the location of the ulcer, the experience of the endoscopist, and the «gold» standard used.

Experienced endoscopists detect about 90 percent of gastroduodenal lesions found by a second endoscopist, by radiography, or at surgery.Benign ulcers have smooth, regular, rounded edges, with a flat, smooth ulcer base often filled with exudate. By contrast, the following features are suggestive of malignancy on endoscopy or radiography:

- The ulcerated mass protrudes into the lumen.
- The folds surrounding the ulcer crater are nodular, clubbed, fused, or stop short of the ulcer margin.
- The margins are overhanging, irregular, or thickened.

Multiple biopsies of gastric ulcers (GUs) are necessary, and should be performed even for lesions with a benign endoscopic appearance since benign-appearing ulcers may harbor malignancy. The chance of malignancy is greater in large GUs, but cancer can be found in lesions less than 1 cm. The optimal number of biopsies has been debated and probably depends upon the technique; four jumbo biopsies of the ulcer margin are equivalent to six to seven regular-sized biopsies, the number shown to detect the vast majority of cancers.Repeat endoscopy after treatment has been advocated to confirm healing of GUs to ensure that the lesions are benign. However, with the decreasing incidence of gastric cancer in developed countries, the increased use of nonsteroidal antiinflammatory drugs, and the concern over the costs of care, this practice standard has been questioned. A few cautions are necessary:

- The observation that the patient becomes asymptomatic on treatment does not reliably exclude malignancy. It is important to identify the patient with gastric cancer in the absence of alarm symptoms because the cancer is more likely to be at an early stage.
- If follow-up endoscopy is performed, biopsy of the ulcer bed should be done, even if the ulcer has healed; malignancy or high grade dysplasia is occasionally detected in «healed» ulcers.
- Endoscopy appears to be less sensitive for detecting esophageal and gastric cancer when the patient is taking antisecretory agents.

Barium radiography: with the advances and availability of endoscopy over the last 30 years, upper gastrointestinal radiography has been relegated to a limited role in the diagnosis of PUD. However, it still continues to be performed in patients who are not eligible or unwilling to undergo endoscopy, or where endoscopy is unavailable.A definitive radiographic diagnosis of peptic ulcer requires demonstration of barium within an ulcer niche, which is generally round or oval and may be surrounded by a smooth mound of edema. Secondary changes include folds radiating to the crater, and deformities in the region secondary to spasm, edema, and scarring. The incisura can be found encircling a GU due to the secondary spasm of circular muscle. Secondary signs of DU include deformity of the duodenal bulb that may be evidenced by flattening of the superior or inferior fornices, eccentricity of the pyloric channel, pseudodiverticula, or exaggerated outpouching of recesses at the base of the bulb.In the presence of deformity of the duodenal bulb, edema of the folds, or postoperative deformity, ulcer craters become much more difficult to detect. Shallow lesions < 0.5 cm in diameter are also difficult to detect reliably. False positive results occur when barium is trapped between folds. Thus, it is important to document that the configuration of a suspected crater is constant on multiple X-ray views.The sensitivity of barium radiography for detecting ulcers reflects the technique, skill, and interest of the radiologist, and the ability of the patient to cooperate. Success also depends upon the size and location of the ulcer. Because of the shift from endoscopy over the past 25 years, there are few radiologists with expertise at upper gastrointestinal radiography. Thus, accuracy in practice will likely not achieve the standards that have reported in earlier studies.Single contrast radiographic techniques miss as many as 50 percent of DUs. In contrast, in experienced hands about 80 percent of DUs can be detected with procedures using double contrast, compression, or hypotonic duodenography. The optimal technique appears to be a combined «biphasic» approach, including spot views during vigorous compression with the bulb filled with barium to improve the detection of anterior ulcers, and double contrast to improve the detection of posterior ulcers. The detection of GUs also varies considerably as a function of technique.

Radiographic differentiation of benign versus malignant lesions: although benign GUs are more frequently found on the lesser curvature at the incisura, they can occur anywhere, as can gastric cancers. Thus, location is of little value in predicting the presence or absence of malignancy. In contrast, several other features suggest the presence of gastric cancer on radiography:

- An ulcer within a definitive mass protruding into the lumen.

• Effaced, interrupted, fused, or nodular mucosal folds as they approach the margin of the crater.

• Negative irregular filling defects in the ulcer crater, although an irregular base also may result from the presence of blood clots, granulation tissue, or other debris.

The only definitive way to rule out malignancy is direct inspection with adequate biopsy. However, the following radiographic signs of benignancy may be useful:

• Radiation of smooth, symmetric mucosal folds to the edge of the ulcer crater or to a smooth mound of edema (ulcers should not be considered radiologically benign without an en face view demonstrating this feature).

• A smooth translucent band or collar surrounding the ulcer crater, suggesting edema (differentiation from an infiltrating mass with central ulceration is critical).

• Hampton's sign, which is a radiolucent line about 1 mm in width that rims the mouth of the ulcer crater, resulting from undermining of normal mucosa (reliable, if present, but insensitive).

• An incisura or indentation on the opposite wall due to edema and spasm of circular muscle.

• Extension of a crater outside the contour of the gastric lumen.

Helicobacter pylori testing: when an ulcer is discovered by endoscopy or radiography, it is important to determine if H. pylori is present before treating with antibiotics. At endoscopy, a biopsy for urease testing will be highly accurate and inexpensive. Because the pretest prevalence of H. pylori is high in the setting of a demonstrated ulcer (especially in the absence of use of NSAIDs), a negative test should be followed by a second test to confirm the absence of H. pylori. Breath or stool antigen testing for H. pylori are appropriate alternatives if noninvasive testing is needed.

Diagnostic approach with established ulcers: certain diagnostic considerations apply to patients with identified ulcer disease. If the patient has a DU, it is initially necessary only to establish H. pylori status, as indicated above. Biopsy of the DU is only indicated for refractory ulcers or lesions that are suggestive of malignancy. By contrast, all GU warrant thorough biopsy at the first endoscopy. The necessity of follow-up endoscopy and biopsy for GU to ensure healing and to exclude malignancy is a clinical decision that rests on the adequacy of the initial biopsies and the patient's risk for gastric malignancy.

Differential diagnosis: peptic ulcers must be differentiated from other disorders that cause symptoms in the upper abdomen and ulcerative lesions of the stomach and duodenum that are secondary to diseases involving the gastroduodenal mucosal itself. The specific causes of ulcerative lesions of the stomach and duodenum must be identified whenever possible, since effective therapy is available for many cases secondary to other specific causes. Some of these conditions can be diagnosed by gross and histologic assessment of the gastric mucosa and are described below. In addition, a variety of other conditions are associated with peptic ulcers, which may or may not be detectable by biopsy or visual inspection.

Functional dyspepsia: the most common type of dyspepsia encountered in primary care and gastroenterology practice is functional (idiopathic) dyspepsia, also referred to as nonulcer dyspepsia. Although developed by an international committee for research purposes, the following definition of functional dyspepsia (Rome criteria) has clinical utility:

• The presence of symptoms thought to originate in the gastroduodenal region, in the absence of any organic, systemic, or metabolic disease that is likely to

explain the symptoms (eg, acid-peptic or neoplastic disease of the stomach, esophagus or duodenum, or disease of the pancreas or hepatobiliary system).

- Symptoms include epigastric discomfort or pain, postprandial fullness, and early satiation
- Patients with a past history of documented chronic peptic ulcer disease should not be classified as having functional dyspepsia at least until the relationship between these entities is clarified.

There are no diagnostic tests for functional dyspepsia, and, as noted above, it is not possible to clinically distinguish ulcer from nonulcer dyspepsia. As a result, the diagnosis is made upon the exclusion of other causes of dyspepsia.

Gastric carcinoma: it is important to differentiate between gastric carcinoma and peptic ulcer at an early stage, when the cancer is operable and potentially curable. Gastric malignancy infrequently causes chronic dyspepsia. However, the possibility should be considered, particularly in patients over 45 to 55 years of age and in those who have the following «alarm symptoms» or risk factors:

- Unintended weight loss.
- Bleeding.
- Anemia.
- Dysphagia.
- Odynophagia.
- Hematemesis.
- A palpable abdominal mass or lymphadenopathy.
- Persistent vomiting.
- Unexplained iron deficiency anemia.
- Family history of upper gastrointestinal cancer.
- Previous gastric surgery.
- Jaundice.

Although early gastric cancer is usually asymptomatic, it can present with dyspepsia that is indistinguishable from symptoms due to peptic ulcers. New onset of symptoms or a recent change in pattern should raise concern for possible neoplasia. In general, compared with advanced disease, early gastric cancer has fewer associated symptoms and a much better prognosis. The alarm signs or symptoms suggestive of invasive disease, such as anemia or weight loss, occurred less frequently (5 to 15 percent and 4 to 40 percent, respectively). Unfortunately, alarm symptoms are not accurate predictors of underlying pathology. However, they probably increase the chance of finding organic disease and should be sought and appropriately evaluated. Cancers missed on endoscopy have been associated with alarm symptoms. Other neoplastic processes can mimic peptic ulcers, presenting with dyspepsia or ulcers, such as gastric lymphoma; leiomyosarcoma; primary gastric and metastatic malignant melanoma; and metastatic renal cell carcinoma. Duodenal carcinoma is very uncommon, but can occasionally present with gastrointestinal bleeding or as an apparently be-

nign ulcer. However, most cases present as a mass lesion rather an ulcer. Localized duodenal lymphoma can also mimic a duodenal ulcer and respond to ulcer therapy for a period of time.

Drug-induced dyspepsia: numerous drugs can cause dyspepsia, epigastric distress, nausea, or vomiting. These include NSAIDs, with or without ulceration, theophylline, and digitalis. Caffeine, coffee, alcohol, and smoking can also contribute to symptoms.

Management

Treatment: the following points should be considered when treating peptic ulcer disease (PUD):

- All patients with PUD should receive antisecretory therapy. In patients with uncomplicated H. pylori ulcers, the proton pump inhibitor given along with the antibiotic regimen is usually adequate to induce healing.
- Patients with PUD should be tested for H. pylori, keeping in mind that PPIs, bismuth, many antibiotics, as well as upper GI bleeding, may lead to false-negative test results. In the face of a known ulcer (high pre-test prevalence), H. pylori is only confidently excluded if two appropriately performed tests are negative, with no exposure to the above mentioned four suppressive factors in the two weeks before testing.
- Patients with H. pylori should be treated with a goal of H. pylori eradication.
- Antisecretory therapy is the mainstay of therapy in uninfected patients, and is appropriate for maintenance therapy in selected cases.
- It is essential to withdraw potential offending or contributing agents such as NSAIDs, cigarettes, and excess alcohol.
- In non-H. pylori, non-NSAID ulcers, every effort should be made to address other contributing factors whenever possible, such as treating medical comorbidities, poor nutritional status, ischemia, and acid hypersecretion.
- There is no evidence that addressing stressful psychosocial situations and psychological comorbidity benefits treatment outcomes; in fact, one older study suggested that cognitive psychotherapy increased relapse rates. On the other hand, it is important to keep in mind that patients with active psychosocial issues may be predisposed to recurrence or persistence of symptoms and ulcers. Furthermore, psychosocial issues should be addressed since they can have other deleterious health consequences.
- No firm dietary recommendations are necessary, though patients should avoid foods that precipitate dyspepsia.

Eradication of H. pylori: all patients with peptic ulcers who are infected with H. pylori should undergo therapy to eradicate the organism. This recommendation is based upon overwhelming data indicating that H. pylori eradication reduces ulcer recurrence. It has been suggested that pretreatment with a proton pump inhibitor could decrease the efficacy of Helicobacter pylori eradication. However, the data clearly show no change in eradication rates or ulcer recurrence at one year in patients treated with proton pump inhibitors prior to anti-H. pylori therapy.

Treatment regimens: multiple regimens have been evaluated for H. pylori therapy. Eradication rates with the original bismuth triple regimens (bismuth, metronidazole, and either tetracycline or amoxicillin) are in the range of 75 to 90 percent. The optimal therapeutic regimen has not yet been defined. Treatment should be effective, but considerations such as cost, side effects, and ease of administration must also be taken into account.

Treatment of H. pylori in patients on NSAIDs: the relationship between H. pylori and NSAIDs is controversial and complex and may be related to whether the patient is a new ("naïve") or a chronic user of NSAIDs. In naïve NSAID users, H. pylori appears to be a significant risk factor for complicated ulcers. Furthermore, there appears to be a benefit from screening naïve NSAID users at the start of therapy for H. pylori and eradicating the organism before starting NSAID treatment. By contrast, with established NSAID users who present with ulcer complications and evidence of H. pylori infection, eradicating H. pylori infection does not appear to reduce the high risk of ulcer complications if NSAIDs are continued.Eradicating H. pylori infection may also lower the risk of ulcer recurrence in patients on low-dose aspirin. However, treatment of such patients with a PPI in addition to the eradication of H. pylori can significantly reduce the risk of recurrent ulcer complications.Thus, the available data support H. pylori testing and treatment prior to starting NSAIDs. It is appropriate to look for H. pylori and eradicate it following presentation of any clinical ulcer. However, if patients are going to continue NSAIDs or aspirin, they must be treated with a regimen that reduces the risk of further ulcer complications, such as PPIs.

Antisecretory therapy after H. pylori eradication: patients with uncomplicated, small (< 1 cm) duodenal ulcers or gastric ulcers who have received adequate treatment for H. pylori probably do not need any further therapy directed at ulcer healing, as long as they are asymptomatic following therapy. This recommendation is based upon data indicating that eradication of H. pylori without concurrent acid suppression therapy heals most duodenal ulcers and gastric ulcers. There are no firm guidelines regarding the continuation of antisecretory medication after H. pylori eradication in patients who had complications due to PUD. There is evidence suggesting that elimination of H. pylori alone is sufficient. However, this only applies to compliant patients with confirmed H. pylori eradication, in the absence of continued NSAID use. In addition, treatment with H. pylori eradication alone should only be considered for patients with small or moderate size ulcers that can be expected to heal rapidly.Two consensus panels have recommended maintenance acid suppression following H. pylori eradication in patients with a complicated duodenal ulcers. Such patients should also undergo follow-up endoscopy at least 4 to 12 weeks after the completion of H. pylori therapy to assess ulcer healing and eradication of the infection; therapy can be stopped only if complete healing has occurred and persistent H. pylori infection can be excluded.Patients without complicated ulcers who have other markers of increased risk (such as giant ulcers > 2 cm, densely fibrosed ulcer beds, or a protracted prior history) also warrant treatment with antisecretory agents, at least until both cure of H. pylori infection and ulcer healing have been confirmed. Prolonged antisecretory therapy can certainly be justified in patients who are considered to be at high risk, since no studies have had the power to define the optimal management in these patients. Patients with intermediate sized ulcers (1 to 2 cm) are probably at some increased risk for slow healing, as noted previously. Some risk of recurrence or exacerbation may be due to the rebound acid hypersecretion that accompanies discontinuation of potent antisecretory agents, especially after a prolonged course of treatment. Although the magnitude varies and the clinical significance has not been firmly established, tapering the PPI and then stepping down to an H_2 receptor antagonist for two to three months deserves consideration in high-risk patients.

Initial approach to ulcers not due to H. pylori: common causes of H. pylori-negative ulcers are false-negative testing for H. pylori and undiscovered consumption of NSAIDs. However, some patients will have ulcers that are not related to H. pylori or NSAIDS.In the face of a known peptic ulcer, a single positive test (invasive or noninvasive) is sufficient to diagnose H. pylori infection. However, with a known ulcer a single negative test is not sufficient to exclude it, so additional H. pylori

testing is necessary in patients with PUD and negative H. pylori testing. The pretest probability of H. pylori in patients with gastric ulcers is 60 to 80 percent, so a single negative test for H. pylori has about an 80 percent NPV (ie, 20 percent of negative results would be false negatives). In patients with gastric ulcers, multiple biopsies of the ulcer margin are generally indicated to exclude malignancy. In addition, at least three biopsies of the antrum are justified for urease testing for H. pylori, and, if negative, histology. The absence of inflammation provides solid evidence for the true absence of H. pylori. If a gastric ulcer were discovered on radiography or found at endoscopy but H. pylori status was not determined, noninvasive testing for H. pylori is appropriate. However, if adequate biopsies of a gastric ulcer were not obtained, endoscopy is indicated to exclude malignancy.

Antisecretory therapy: antisecretory therapy is warranted in patients with PUD who are truly not infected with H. pylori. Proton pump inhibitors are more effective than H_2 receptor antagonists (H_2RAs), though full-dose H_2RAs do provide effective initial therapy. Although there are differences between therapies, they are of little clinical importance in uncomplicated ulcers; cost has become an important factor in choosing a therapeutic regimen. Combining conventional antiulcer agents (eg, PPIs and H_2RAs) adds to cost without enhancing healing and is not recommended; taking these classes of agents at the same time may actually attenuate PPI action. Studies of the various agents used to treat ulcers have shown the following:

- All H_2 receptor antagonists (ranitidine, famotidine, and nizatidine) are associated with healing rates of 70 to 80 percent for duodenal ulcers after four weeks, and 87 to 94 percent after eight weeks of therapy. Split dose, evening, and nighttime therapy are all effective.
- Proton pump inhibitors, including omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole, are effective in inducing ulcer healing. Daily doses of omeprazole from 20 to 40 mg produced duodenal ulcer healing rates of 63 to 93 percent at two weeks, and of 80 to 100 percent at four weeks. Omeprazole (20 mg daily) produces more rapid healing than standard doses of H_2RAs in most, but not all studies. Combining data from eight trials comparing 20 mg of omeprazole to 300 mg of ranitidine, omeprazole had a 14 percent advantage at two weeks and a 9 percent advantage at four weeks. Thus, omeprazole heals duodenal ulcers more rapidly than standard doses of H_2RAs, but the advantage after four weeks of therapy is small.
- Omeprazole at doses of 20 to 40 mg daily produces numerically greater gastric ulcer healing than H_2RAs, but the rate of early healing of gastric ulcers is not accelerated by omeprazole to the same extent as that found with duodenal ulcers.
- Although antacids and sucralfate are in general superior to placebo in healing duodenal ulcers, efficacy has not been established for gastric ulcers or for either NSAID ulcers or non-H. pylori, non-NSAID ulcers.
- Misoprostol enhances duodenal ulcer healing compared with placebo at doses of 400 to 800 mcg daily. However, prostaglandin analogs have no advantage over antisecretory agents for ulcer healing and are not indicated for this purpose.

Antisecretory drugs can be discontinued after four to six weeks in patients with uncomplicated ulcers who are asymptomatic. Although some progressive

healing occurs with longer treatment periods, the advantages relative to further increasing treatment costs in patients who are asymptomatic and uncomplicated are debatable. Some patients are at increased risk for recurrence, especially those in whom the underlying cause of the ulcer cannot be reversed. Such patients may benefit from maintenance therapy with an antisecretory drug.

Follow-up after initial therapy for peptic ulcer:

Patients with uncomplicated duodenal ulcers who have been treated do not need further endoscopy or radiography unless symptoms persist or recur.

Gastric ulcers: there are no prospective outcome data and no clear consensus to guide management with respect to appropriate follow-up in patients with gastric ulcers and the literature is filled with divergent views and recommendations. Repeat endoscopy with biopsy has been advocated to confirm gastric ulcer healing as a means of ensuring that the lesions are benign. However, with the decreasing incidence of gastric cancer in developed countries, the increased use of NSAIDs, and the concern over the costs of care, this practice standard has been questioned. Overall, the risk of finding gastric cancer on follow-up endoscopy of an apparently benign gastric ulcer varies from about 0.8 to 4.3 percent. However, if an experienced endoscopist judges the gastric ulcer to be benign and if initial biopsies are adequate and negative for malignancy and dysplasia, the yield of follow-up studies is low and the cost of every cancer discovered will be high. Many cases of carcinoma masquerading as benign ulcers occur because biopsies were inadequate or dysplasia or neoplasia was missed in the initial biopsy.It must be emphasized that an «adequate» approach is to obtain at least four jumbo biopsies from the ulcer margin or seven regular biopsies and one from the base, if the ulcer is not too deep. These biopsies must contain adequate tissue for the pathologist; many biopsies taken even by experienced endoscopists contain only mucus or blood, which of course do not rule out malignancy.In the absence of guiding data or consensus, there is a wide range of standard practice. Our approach is to not repeat an upper endoscopy on patients with benign-appearing gastric ulcers that have been adequately biopsied with no evidence of malignancy or dysplasia on biopsies. In patients at high-risk for malignancy perform a follow-up endoscopy (with biopsies of the ulcer if still present) after six weeks of therapy. High-risk gastric ulcers include the following:

- Occurrence in ethnic groups raised in endemic areas, or a family history of gastric cancer.
- The absence of recent NSAID use.
- The presence of H. pylori, particularly if associated with gastric atrophy.
- Age greater than 50 years.
- The absence of either a concomitant duodenal ulcer or a prior history of duodenal ulcer (duodenal ulcers require higher acid secretion, which is incompatible with the pangastritis typical of most gastric cancers).
- Giant ulcers (> 2 to 3 cm).
- The absence of a protracted ulcer history. Although there will be exceptions, the longer the ulcer history, the lower the risk that a gastric ulcer is cancer. Gastric ulcers require acid and gastric cancer usually develops in the setting of atrophic pangastritis.

Maintenance therapy should be considered to prevent recurrence in high-risk subgroups, defined by a history of complications, frequent recurrences, or refractory, giant, or severely fibrosed ulcers. In such patients who are also infected with H. pylori, maintenance therapy should be continued at least until cure of the infection has been confirmed, and possibly longer. Long-term maintenance therapy is indicated in high-risk patients who fail H. pylori eradication or who have H. pylori-negative ulcers. Maintenance antisecretory therapy is effective in reducing duodenal ulcer recurrences and complications. Typical recurrence rates are 20 to

25 percent over a 12-month period in patients who take H_2RAs versus 60 to 90 percent for placebo. Maintenance doses of H_2RAs are as follows:

- Ranitidine 150 mg at bedtime.
- Famotidine 20 mg at bedtime.
- Nizatidine 150 mg at bedtime.

PPIs also prevent duodenal ulcer recurrences if used in adequate doses.

Gastric ulcers: the highest risk of recurrence occurs in the first three to six months of maintenance therapy. Antisecretory therapy appears to remain effective for more than five years; recurrence rates after this time period are lower than in the first year of therapy. Patients followed for these prolonged periods on H_2 receptor antagonists include many individuals with a history of complications or those initially referred for ulcer surgery. Approximately three-quarters of these patients did well clinically on maintenance doses in one report: one-quarter remained asymptomatic and ulcer-free, and one-half had one or more relapses that responded to full-dose H_2 receptor antagonist therapy.

There are no data from controlled trials regarding the appropriate duration of maintenance therapy. For uncomplicated recurrent disease, stopping therapy after two years is reasonable, while a five-year course may be more appropriate for complicated disease. If the causal factor can be confidently reversed (eg, H. pylori infection eradicated or NSAIDs discontinued), then requirements for maintenance are markedly reduced.

There are four major complications of peptic ulcer disease:

- Bleeding.
- Perforation.
- Penetration.
- Obstruction.

Despite improvements in the medical management and the lower overall incidence of peptic ulcer disease, the incidence of potentially life-threatening ulcer complications has not declined. There are important time trends embedded within this stable overall rate of complications: the dramatic decline in the prevalence of Helicobacter pylori; an increased use of nonsteroidal antiinflammatory drugs (NSAIDs); and an increased rate of ulcer complications related to NSAID use, especially in the elderly. As a result of these trends, ulcer complications are on the rise in older patients and are declining in younger individuals. Data are limited regarding the relative frequency of the various complications; estimates suggest that they occur at a rate of approximately 1 to 2 percent per ulcer patient per year of follow-up. The complications can be identified from hospitalization data, but the denominator of the peptic ulcer patients at risk is difficult to determine.Complications can occur in patients with peptic ulcer of any etiology. Giant ulcers and pyloric channel ulcers may be associated with a higher rate of complications.

There are no known pathophysiologic factors that predispose to the development or recurrence of complications, although some common themes emerge:

- Patients with a history of complicated ulcer disease are more prone to experiencing another complication.
- Most complicated ulcers are chronic and fibrosed, penetrating deeply into the wall to form a dense fibrotic scar that is slow to heal, erodes blood vessels, or reaches the serosa.

• Comorbid disease increases mortality.

• A prolonged ulcer history is common among patients with complicated ulcers.

However, some patients have few or no symptoms until complications develop, despite an obviously scarred, chronic ulcer. In addition, some complicated ulcers, especially when linked to NSAID use or developing in hospitalized patients (stress ulcers), are acute and occur without dense fibrosis or a prolonged ulcer history.

Bleeding: upper gastrointestinal (UGI) bleeding secondary to peptic ulcer is a common medical condition that results in high patient morbidity and medical care costs, although it appears to be becoming a less common cause of UGI bleeding.UGI bleeding commonly presents with hematemesis (vomiting of blood or coffee-ground-like material) and/or melena (black, tarry stools). Hematochezia (passage of maroon or bright red blood or blood clots per rectum), usually a sign of a lower GI source, can be seen when UGI bleeding is massive. A nasogastric tube lavage which yields blood or coffee-ground-like material confirms UGI bleeding and can help predict the risk of a high-risk lesion; however, lavage may not yield blood or coffee-ground-like material if bleeding has ceased or arises beyond a closed pylorus.The initial evaluation of the patient with UGI bleeding involves an assessment of hemodynamic stability and the necessity for fluid resuscitation. Endoscopy is then the procedure of choice for the diagnosis and treatment of active UGI bleeding and for the prevention of rebleeding.

The majority of patients with UGI bleeding due to peptic ulcer disease will stop bleeding spontaneously and most will not rebleed during hospitalization. However, a subgroup of patients with severe UGI bleeding from ulcers is at high risk for recent hemorrhage. Gastroduodenal ulcers can be stratified into high versus low risk for rebleeding by the presence or absence of stigmata of ulcer hemorrhage.

The major endoscopic predictors of persistent or recurrent bleeding include:

• Active bleeding during endoscopy — 90 percent recurrence.

• Visible vessel — 50 percent recurrence.

• An adherent clotthat are not easily removed endoscopically (eg, with irrigation or gentle suctioning of the clot away from the ulcer crater to reveal the underlying stigmata) — 25 to 30 percent recurrence

Endoscopic therapy: ulcers with a clean base or a flat pigmented spot are at low risk of rebleeding and should not be treated endoscopically. There are several different types of endoscopic treatment for bleeding peptic ulcers: thermal coagulation, injection therapy, hemostatic clips, fibrin sealant (or glue), argon plasma coagulation, and combination therapy. At least methods conclusion about methods to control bleeding:

• Compared with epinephrine, further bleeding was reduced significantly by other monotherapies (eg, thermal coagulation) or epinephrine combined with another modality.

• Clips were more effective than epinephrine alone, but not different than other therapies.

• The efficacy of endoscopic therapies for clots was uncertain.

Thermal coagulation achieves acute hemostasis and prevents rebleeding by coaptive coagulation of the underlying artery in the ulcer base.

Injection therapy with absolute alcohol (98 percent, total volume < 1.0 mL) or epinephrine (1:10,000 dilution) is inexpensive and effective for acute hemostasis. A potential advantage of epinephrine injection is that it is easy to administer, can help slow or stop bleeding,

and can reduce bleeding incited by mechanical hemostasis. During active bleeding it can produce a cleaner field permitting targeted treatment of the bleeding site. Addition of a sclerosant (eg, ethanolamine) confers no advantage over injection with epinephrine alone. However, the rebleeding rate is high (approximately 18 percent) if epinephrine injections alone are performed.Injection of saline causes local tamponade, which can be effective in achieving hemostasis. However, saline injection alone was less effective at preventing recurrent bleeding compared to bipolar electrocoagulation.

Fibrin sealant: a relatively new approach involves the use of endoscopically injected fibrin sealant to achieve initial hemostasis and decrease the rate of rebleeding from peptic ulcers.

Endoclips: the endoscopic application of hemoclips (endoclips) provides an alternative to the hemostatic methods described above. Once applied, the clips achieve hemostasis in a manner similar to surgical ligation. Although experience is relatively limited compared with other hemostatic methods, the available data suggest that endoclips are as safe as other hemostatic methods, and can be considered as an option for patients with ulcer bleeding. Placement of an endoclip can also be of value even if an ulcer is not amenable to endoscopic therapy since it may serve as a radiologic marker for subsequent interventional radiology.

Argon plasma coagulation (APC) has a theoretical disadvantage for the treatment of bleeding ulcers since it does not permit tamponade.

Second-look endoscopy: the International Consensus Recommendations for the management of patients with nonvariceal upper gastrointestinal bleeding do not recommend routine use of second-look endoscopy. The guidelines note that while older data support the use of second-look endoscopy, many of the trials did not use contemporary management strategies, and more recent studies have not shown a benefit. However, the guidelines also suggest that patients at particularly high-risk for rebleeding may benefit from second-look endoscopy.

Acid suppression: a meta-analysis of randomized controlled trials evaluating PPIs for bleeding ulcers (with or without endoscopic therapy) found a significant and consistent reduction in the risk of rebleeding and the need for surgery; there was no effect on mortality.

Most studies evaluated intravenous omeprazole. Although the efficacy of intravenous formulations of other PPIs has not been studied extensively, they are probably acceptable alternatives when given in doses that are known to inhibit gastric acid secretion. Oral dosing of PPIs may also be an option and is less expensive. A combined analysis of five studies evaluating oral dosing (with or without endoscopic therapy) found a significant reduction in the risk of rebleeding and surgery. A controlled trial involving patients at high risk for rebleeding suggested that patients treated with injection therapy may also benefit from oral omeprazole. A meta-analysis that included seven randomized trials patients who had received endoscopic treatment for a bleeding ulcer compared rebleeding rates, the need for surgical intervention, and mortality between patients receiving high-dose omeprazole or pantoprazole (both given as an 80 mg bolus followed by 8 mg/h) and patients receiving non-high-dose omeprazole or pantoprazole (with oral doses ranging from 80 to 160 mg/day and IV doses ranging from 20 to 80 mg/day). There were no differences in any of the outcomes between the two groups. The International Consensus Recommendation, which suggests that patients with high-risk stigmata receive an intravenous bolus of a PPI followed by a continuous infusion. A meta-analysis concluded that there was a possible minor benefit with intravenous H_2 antagonists in bleeding gastric ulcers but no benefit with duodenal ulcers. The relative efficacy of the proton pump inhibitors may be due to their superior ability to maintain a gastric pH at a level above 6.0, and thus protect an ulcer clot from fibrinolysis. It is unlikely that an intravenous proton pump inhibitor would be of significant benefit in patients who do not have active bleeding, or other high-risk stigmata for recurrent bleeding (such as a visible ves-

sel or adherent clots); in such patients the risk of recurrent bleeding is low. The goal of treatment in these patients (following resuscitation) should be directed at healing the ulcers and eliminating precipitating factors (such as H. pylori and NSAIDs).

Somatostatin and octreotide: somatostatin or its long-acting analogue octreotide have a theoretical benefit in bleeding ulcer disease because they reduce splanchnic blood flow, inhibit gastric acid secretion, and may have gastric cytoprotective effects. A clinical benefit has been described in ulcer bleeding but because of the effectiveness of endoscopic therapy, its role is generally limited to settings in which endoscopy is unavailable or as a means to help stabilize patients before definitive therapy can be performed.

Refractory bleeding: although the majority of bleeding ulcers can be controlled endoscopically, some patients have refractory bleeding. Gastric ulcers along the lesser curvature and duodenal bulbar ulcers in the posterior wall appeared to be at greater risk for severe bleeding or rebleeding compared with ulcers in other locations because of their proximity to large underlying arteries (left gastric and posterior gastroduodenal arteries). In addition, patients who presented with active hemorrhage, shock, and the lowest hemoglobin concentrations did less well than those without these risk factors. Factors that did not predict outcome of endoscopic therapy were a history of nonsteroidal antiinflammatory drug (NSAID) or aspirin use, coagulopathy, previous peptic ulceration, and concomitant cardiorespiratory disease. Severe bleeding, active bleeding, fresh blood in the stomach and large ulcers were independent risk factors for therapeutic failure after injection of epinephrine plus heater probe treatment.

Interventions such as surgery or angiography are indicated in patients who have active bleeding that is not stopped or slowed down significantly with endoscopic therapy. The patient is referred for surgery if the bleeding persists or rebleeding occurs after two therapeutic endoscopies. This approach was supported by a controlled trial. Conclusion for angiography or surgery for acute nonvariceal upper gastrointestinal bleeding:

- Endoscopy is the best initial diagnostic and therapeutic procedure.
- Surgery and transcatheter arteriography/intervention (TAI) are equally effective following failed therapeutic endoscopy, but TAI should be considered particularly in patients at high risk for surgery.
- TAI is less likely to be successful in patients with impaired coagulation.
- TAI is the best technique for treatment of bleeding into the biliary tree or pancreatic duct.

In addition to failure of endoscopic therapy, other indications for surgery for peptic ulcer hemorrhage include:

- Hemodynamic instability despite vigorous resuscitation (more than a three unit transfusion).
- Recurrent hemorrhage after initial stabilization (with up to two attempts at obtaining endoscopic hemostasis).
- Shock associated with recurrent hemorrhage.
- Continued slow bleeding with a transfusion requirement exceeding three units per day.

Secondary or relative indications for surgery include rare blood type, difficult crossmatch, refusal of transfusion, shock on presentation, advanced age, se-

vere comorbid disease, and chronic gastric ulcer as the origin of hemorrhage. These criteria also apply to elderly patients in whom prolonged resuscitation, large volume transfusion, and periods of hypotension are poorly tolerated.Surgical treatments for peptic ulcer disease include oversewing of the artery with truncal vagotomy and pyloroplasty, antrectomy, and gastrojejunostomy (Billroth procedure), and highly selective vagotomy. Emergency surgery for bleeding peptic ulcer disease involves oversewing of the ulcer (to ligate the bleeding artery) plus truncal vagotomy (to decrease acid secretion) and pyloroplasty (drainage procedure). More time consuming procedures, such as highly selective vagotomy, can be performed either at standard laparotomy or laparoscopically for non-emergency ulcer surgery.

The risk of recurrent ulceration and bleeding depends upon characteristics of the ulcer, use of endoscopic therapy, and the extent to which risk factors such as use of NSAIDs and H. pylori infection. Maintenance therapy with acid suppression may be required for patients at high risk of recurrence.

Perforation: duodenal, antral, and gastric body ulcers account for 60, 20, and 20 percent of perforations due to peptic ulcer, respectively. One-third to one-half of perforated ulcers are associated with NSAID use; these usually occur in elderly patients.The association between HP and perforated ulcer remains controversial. H. pylori and NSAIDs are both independent causes of ulcer perforation. Ulcer perforation should be suspected in patients with a history of peptic ulcer symptoms who develop the sudden onset of severe, diffuse abdominal pain. Some patients who experience a perforation have no history of a peptic ulcer, although a detailed history reveals ulcer symptoms in the majority of cases. The exception may be older individuals with NSAID-induced perforation who often deny preceding ulcer symptoms.

Three phases of a perforated ulcer are:

- In the initial phase (within two hours of onset), abdominal pain is usually sudden, sometimes even producing collapse or syncope. Localization is usually epigastric, but it quickly becomes generalized. This catastrophic onset reflects bathing of the peritoneal cavity with acidic fluid that probably releases vasoactive mediators which underlie the physiologic response. Tachycardia, a weak pulse, cool extremities, and a low temperature are characteristic features. The stage may last only a few minutes or up to two hours. The severity of the onset depends upon how much fluid is released; if juice is confined by fibrosis, symptoms may be much less severe. Pain may radiate to the top of the right or both shoulders. Abdominal rigidity begins to develop.
- In the second phase (usually 2 to 12 hours after onset), abdominal pain may lessen and an inexperienced observer may be led to believe that the patient is getting better. Pain is usually generalized, often markedly worse upon movement, and the abdomen consistently displays marked board-like rigidity. There may be obliteration of liver dullness due to peritoneal air. The pelvic peritoneum, palpated at rectal examination, is often tender due to irritation from collected inflammatory fluid. Right lower quadrant tenderness may develop from fluid moving down the gutter.
- In the third phase (usually > 12 hours after onset), increasing abdominal distention is noted, but abdominal pain, tenderness, and rigidity may be less evident. Temperature elevation and hypovolemia due to third-spacing develop. Acute collapse occurs as peritonitis advances.

Rapid diagnosis is essential since the prognosis is excellent within the first six hours, but deteriorates to probable death with more than a 12-hour delay. The history and physical examination provide essential clues; perforation is largely a clinical diagnosis. The presence of free air is highly indicative of perforated DU, although about 10 to 20 percent of patients with a perforated DU will not have free air. If free air is found, no other diagnostic studies are necessary. Leakage of water soluble contrast is a useful confirmatory test when necessary. With diagnostic uncertainty, CT or ultrasound can be useful to detect small amounts of free air or fluid. In a small proportion of cases, free fluid will be the only clue indicating perforation on imaging studies.

Nonoperative management, including intravenous fluids, nasogastric suction, antibiotics, and antisecretory drugs, may be successful in some patients in whom the leak seals quickly in response to medical management. The antibiotic regimen should cover enteric gram negative rods, anaerobes, and mouth flora. A regimen of ampicillin, metronidazole, and either a third generation cephalosporin or a fluoroquinolone is often used pending operative findings and culture results.The efficacy of initial medical therapy compared to immediate laparotomy with surgical repair was evaluated in a randomized trial of 83 patients with a perforated peptic ulcer. Only 11 of 40 patients in the conservative therapy group had no clinical improvement after 12 hours and required surgery; thus, emergency surgery was prevented in more than 70 percent of patients. The two groups did not differ significantly in terms of morbidity or mortality. However, the hospital stay was 35 percent longer in the group treated conservatively and patients over 70 years old were less likely to respond to conservative treatment. The authors concluded that an initial period of nonoperative treatment with careful observation was safe in younger patients under age 70.

In patients who require surgery, simple patch closure or truncal vagotomy with pyloroplasty (incorporating the perforation) have been the traditional procedures employed for perforated duodenal ulcers. Perforated gastric ulcers are associated with a higher mortality; distal gastrectomy is the preferred approach in these patients unless they are at unacceptably high risk because of advanced age, comorbid disease, intraoperative instability, or severe peritoneal soilage. Patch closure alone is associated with postoperative gastric obstruction in approximately 15 percent of cases. Laparoscopic repair appears to be a reasonable option.

Penetration: ulcer penetration refers to penetration of the ulcer through the bowel wall without free perforation and leakage of luminal contents into the peritoneal cavity. Surgical series suggest that penetration occurs in 20 percent of ulcers, but only a small proportion of penetrating ulcers become clinically evident. Penetration occurs in descending order of frequency into the pancreas, gastrohepatic omentum, biliary tract, liver, greater omentum, mesocolon, colon, and vascular structures.Antral and duodenal ulcers can penetrate into the pancreas. Penetration can also involve pyloric or prepyloric ulcers penetrating the duodenum, eventually leading to a gastroduodenal fistula evident as a «double» pylorus. A long-standing ulcer history is common but not invariable in patients who develop penetration. Penetration often comes to attention because of a change in symptoms or involvement of adjacent structures. The change in symptom pattern may be gradual or sudden; it usually involves a loss of cyclicity of the pain with meals, and loss of food and antacid relief. The pain typically be-

comes more intense, of longer duration, and is frequently referred to the lower thoracic or upper lumbar region.The diagnosis of penetrating ulcer is suspected clinically when an ulcer in the proper region is found. Mild hyperamylasemia can develop with posterior penetration of either gastric or duodenal ulcer, but clinical pancreatitis is uncommon. Penetration can be associated with a wide array of uncommon complications including perivisceral abscess, erosion into vascular structures leading to exsanguinating hemorrhage (aortoenteric fistula), or erosion into the cystic artery. Rare biliary tract complications include erosion into the biliary tree with choledochoduodenal fistula, extrahepatic obstruction, or hematobilia. Fistulization into the pancreatic duct has also been reported with penetrating duodenal ulcer.Gastrocolic fistulae are seen with greater curvature gastric ulcers, particularly marginal ulcers. Typical features of this complication include pain, weight loss, and diarrhea; feculent vomiting is an uncommon, but diagnostic symptom. A duodenocolic fistula can also occur. No rigorous studies are available to guide the management of penetrating ulcers. One can assume that management should follow the intensive measures outlined for refractory ulcers.

Gastric outlet obstruction: gastric outlet obstruction is the least frequent ulcer complication. Most cases are associated with duodenal or pyloric channel ulceration, with gastric ulceration accounting for only 5 percent of cases. As peptic ulcer has become less frequent, malignancy has emerged as a prominent cause of gastric outlet obstruction, despite the lower overall rates of gastric cancer. Obstruction accounted for 10 to 30 percent of patients undergoing ulcer surgery in past series, but this proportion appears to be dropping relative to bleeding and perforation. Some of this decrease may be due to more effective endoscopic and medical management, including the ability to identify and reverse underlying causes. Several elements can contribute to the development of gastric outlet obstruction:

- Rapidly reversible elements include spasm, edema, inflammation, and pyloric dysmotility related to the ulcer or inflammatory changes.
- Fibrosis, scarring, and deformity underlie slowly reversible or irreversible obstruction.
- Gastric atony, which develops after prolonged obstruction, contributes to gastric retention.

Symptoms of gastric retention include early satiety, bloating, indigestion, anorexia, nausea, vomiting, epigastric pain, and weight loss. The presence of recognizable food more than 8 to 12 hours after eating was uncommon, but highly suggestive of gastric retention. The presence of succussion splash on abdominal examination several hours after eating or drinking is a useful clue, when present. The average duration of symptoms was one month, although one-third had symptoms for longer than three months. Patterns drawn from surgical series are useful, but the presentation in a general medical setting may be different. Important variables include the patient's response to these symptoms, age, comorbid conditions, and general health status. A subset of patients with chronic organic disease (peptic ulcer in particular) has visceral hyposensitization; thus, high-

grade outlet obstruction may be present in these individuals without perceived gastric distress. Appetite and food intake may be preserved in association with delayed, large volume vomiting of undigested food. Conversely, some patients may have minimal or intermittent obstruction, but complain of considerable pain and indigestion.

Diagnosis and differential diagnosis: the first decision is determining whether the symptoms are due to gastric retention and whether outlet obstruction is the underlying cause. Measuring gastric residual and performing a saline load test can establish the diagnosis of mechanical outlet obstruction. Definitive diagnosis of gastric pathology must await gastric cleansing, decompression, and correction of fluid and electrolyte abnormalities. Endoscopic inspection and biopsy are indicated in suspected cases of gastric outlet obstruction and usually provide a definitive diagnosis of the underlying pathology, especially for excluding malignancy. Conventional upper gastrointestinal radiography can provide useful information, but is often not definitive. A CT or surgery may be required if there is a heightened suspicion for malignancy and biopsies are unrevealing.

Management: the initial step in the management of presumed gastric outlet obstruction is to confirm the diagnosis of gastric retention (eg, measure the gastric residual and if less than about 250 to 300 cc perform a saline load test). If gastric retention is confirmed, the nasogastric tube should be replaced by a large bore Ewald tube and the stomach lavaged to remove debris. The nasogastric tube should then be reinserted, good function confirmed, and intermittent suction continued for three to five days to decompress the stomach while intravenous fluid and electrolytes are administered. Prolonged vomiting and poor fluid intake may lead to prerenal azotemia, hyponatremia, and a hypokalemic metabolic alkalosis. Intravenous saline will restore the volume status and urine output; potassium chloride should also be administered as indicated. Intravenous proton pump inhibitor treatment should be used to reduce volume requirements, control gastric pH, and facilitate ulcer healing, although there have been no formal studies of such treatment. Careful assessment of nutritional status is required; intravenous hyperalimentation should be considered in malnourished patients. Approximately one-half of cases of gastric outlet obstruction due to peptic ulcer and associated spasm, edema, inflammation, or pyloric dysmotility respond initially to this regimen, although some initial responders may eventually require surgery or endoscopic dilatation. Repeating the saline load test can gauge progress; a residual volume below 200 mL suggests resolution. Management is simplified in cases which appear due to spasm, edema, inflammation, or associated pyloric dysmotility rather than malignancy or dense scarring. However, even cases with a good clinical response require endoscopy and biopsy to exclude malignancy, diagnose ulcer disease, and determine if H. pylori is present.Once the patient has been stabilized and gastric outlet obstruction has been confirmed, the next steps are to identify and treat the underlying cause of the obstruction. The benefit of antisecretory therapy has not been established for

the acute or long-term management of ulcer obstruction, but medical management should include these agents. However, if the underlying cause of ulcer disease has not been reversed, H_2 receptor antagonists, especially at maintenance doses, are unlikely to control the obstruction. Full dose intravenous antisecretory therapy is warranted during gastric decompression. After the patient resumes oral intake and is emptying liquids, use of an H_2 receptor antagonist syrup provides one option. Since all five of the proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole) use enteric-coated formulations, good emptying of solids is required for effective drug delivery; their oral use is therefore limited until the obstruction has resolved and motility has recovered. Antisecretory therapy with H_2 receptor antagonists or proton pump inhibitors is indicated for long-term management of patients who have had a gastric outlet obstruction due to peptic ulcer. When H. pylori infection is present and treated, full dose antisecretory medication should probably be continued until successful cure of the infection has been confirmed and antral-duodenal deformity has resolved. Although not documented in controlled studies, in some cases the combination of curing H. pylori infection, continued antisecretory therapy, and time will eventually reverse antral-duodenal deformity and the high tendency for recurrent obstruction.

Endoscopic balloon dilatation: endoscopic balloon dilatation is useful for patients who do not respond to initial medical therapy, although repeated sessions are necessary in some cases. Dilatation can be accomplished by using endoscopy and a TTS (through the scope) balloon, or by using a balloon placed over a guidewire positioned under fluoroscopic guidance. Advancing the wire well past the stricture and using 6 to 8 cm balloons stabilizes balloon placement during dilatation. Balloon dilatation should be monitored by a pressure gauge, sustained for one minute, and repeated three to four times. Successful dilatation is usually confirmed by pulling the balloon through the strictured segment, although failure to accomplish this does not preclude a successful procedure. Using dilute contrast medium to fill the balloon allows progress to be followed fluoroscopically; a waist forms initially during dilatation, but is effaced during balloon distention. Symptoms are usually considerably improved with successful dilatation to 12 mm. There may be an advantage to postponing dilatation beyond 15 mm until after a period medical management.Long duodenal strictures are the most difficult to dilate. Stepwise dilatation for tight obstruction will probably lower the risk of perforation. Nevertheless, because of the risk of perforation, patients should be appropriately prepared for surgery before dilatation, and monitored closely after dilatation before resuming oral intake. An immediate post-procedure Gastrografin study is an appropriate precaution to detect perforation in a timely fashion.

Recommendations regarding surgical therapy: in the past, patients with gastric outlet obstruction due to peptic ulcer traditionally were sent to surgery if they failed to respond to three days of nasogastric suction. However, in cases where the cause can be reversed (eg, H. pylori or NSAIDs), a more conservative approach deserves consideration. Gastric outlet obstruction is not an emergency; both endoscopic or surgical intervention should be delayed until the patient has been stabilized and fluid and electrolyte balance restored. Delays are also appropriate if the patient's nutritional status is compromised (an albumin less than 2.8 in general is a strong predictor of a poor surgical outcome) or if the stomach is markedly dilated (postoperative gastric

atony appears more likely and may be prevented by preoperative decompression). Before surgery is contemplated, endoscopy with biopsy is required to identify the cause of the obstruction. If the pyloric channel can be identified and a balloon passed, dilatation is an appropriate option in experienced hands. A gastrograffin study may be helpful to define the anatomy of the pylorus before dilatation. If the pylorus can be opened sufficiently to allow the patient to tolerate a liquid diet, especially when an underlying cause can be reversed, then continuing medical treatment is a reasonable option as long as gastric function is carefully monitored to ensure that retention does not recur. Cases that clearly warrant surgery are ones where the pylorus is obstructed and cannot be safely dilated, or where the obstruction persists or recurs during medical management.When surgery is necessary, inflammation and scarring may prevent safe antrectomy, which would otherwise be an excellent choice since it resects the ulcer and relieves the obstruction. In these instances, truncal vagotomy and gastrojejunostomy may be the preferred approach. Placement of a feeding jejunostomy tube at the time of surgery is usually recommended, because of both preoperative malnutrition and the risk of delayed postoperative gastric emptying. Concerning sequelae of surgery include gastric dysmotility and symptoms persisting beyond the early postoperative period in the absence of mechanical obstruction. Estimates of postoperative gastric dysfunction range from 10 to 50 percent. The outcome will vary depending upon patient selection, the preoperative status, and surgical technique.

10. LIVER DISEASES

Definitions and introduction

Although the term «liver function tests» (LFTs) is commonly used, it is imprecise since many of the tests reflecting the health of the liver are not direct measures of its function. Furthermore, the commonly used liver function tests may be abnormal even in patients with a healthy liver. The most common laboratory measures classified as LFTs include the enzyme tests (principally the serum aminotransferases, alkaline phosphatase, and gamma glutamyl transpeptidase), tests of synthetic function (principally the serum albumin concentration and prothrombin time), and the serum bilirubin, which measures the liver's ability to detoxify metabolites and transport organic anions into bile.The term «liver function tests» will be used to denote these tests throughout this discussion unless particular tests are specified. There are two aminotransferases: alanine aminotransferase (ALT, formerly called SGPT), and aspartate aminotransferase (AST, formerly called SGOT). The sensitivity and specificity of the serum aminotransferases (particularly serum ALT) for discriminating those with and without liver disease depends upon the cutoff values chosen to define an abnormal test. ALT levels correlate with the degree of trunk fat, and the cutoff values should be adjusted for gender and body mass index. In addition, cutoff levels for recognition of liver disease differ based on the reference used at the specific laboratory.

Diagnosis

The physical examination should focus upon findings suggesting the presence of liver disease. Specific findings may provide clues toward diagnosis of an underlying cause:

- Temporal and proximal muscle wasting suggest longstanding diseases.
- Stigmata of chronic liver disease include spider nevi, palmar erythema, gynecomastia, caput medusae.
- Dupuytren's contractures, parotid gland enlargement, and testicular atrophy are commonly seen in advanced Laennec's cirrhosis and occasionally in other types of cirrhosis.
- An enlarged left supraclavicular node (Virchow's node) or periumbilical nodule (Sister Mary Joseph's nodule) suggest an abdominal malignancy.
- Jugular venous distension, a sign of right sided heart failure, suggests hepatic congestion.
- A right pleural effusion, in the absence of clinically apparent ascites, may be seen in advanced cirrhosis.

The abdominal examination should focus on the size and consistency of the liver, the size of the spleen (a palpable spleen is enlarged), and should include an assessment for ascites (usually by determining whether there is a fluid wave or shifting dullness). Patients with cirrhosis may have an enlarged left lobe of the liver (which can be felt below the xiphoid) and an enlarged spleen (which is most easily appreciated with the patient in the right lateral decubitus position). A grossly enlarged nodular liver or an obvious abdominal mass suggests malignancy. An enlarged tender liver could be viral or alcoholic hepatitis or, less often, an acutely congested liver secondary to right-sided heart failure. Severe right upper quadrant tenderness with respiratory arrest on inspiration (Murphy's sign) suggests cholecystitis or, occasionally, ascending cholangitis. Ascites in the presence of jaundice suggests either cirrhosis or malignancy with peritoneal spread.

Laboratory testing: a critical step in guiding the evaluation is determining the overall pattern of the abnormal LFTs, which can be broadly divided into two categories:

- Patterns predominantly reflecting hepatocellular injury.
- Patterns predominantly reflecting cholestasis.

Patients with a hepatocellular process generally have a disproportionate elevation in the serum aminotransferases compared with the alkaline phosphatase, while those with a cholestatic process have the opposite findings. The serum bilirubin can be prominently elevated in both hepatocellular and cholestatic conditions and therefore is not necessarily helpful in differentiating between the two. The serum albumin and a prothrombin time should be obtained to assess liver function. A low albumin suggests a chronic process such as cirrhosis or cancer, while a normal albumin suggests a more acute process such as viral hepatitis or choledocholithiasis. An elevated prothrombin time indicates either vitamin K deficiency due to prolonged jaundice and malabsorption of vitamin K or significant hepatocellular dysfunction. The failure of the prothrombin time to

correct with parenteral administration of vitamin K indicates severe hepatocellular injury. The presence of bilirubin in the urine reflects direct hyperbilirubinemia and therefore underlying hepatobiliary disease. In contrast to conjugated bilirubin, unconjugated bilirubin is tightly bound to albumin; as a result, it is not filtered by the glomerulus and present in the urine unless there is underlying renal disease. Conjugated bilirubin may be found in the urine when the total serum bilirubin concentration is normal because the renal reabsorptive capacity for conjugated bilirubin is low and the methods used can detect urinary bilirubin concentrations as low as 0.05 mg/dL (0.9 mmol/L). Thus, bilirubinuria may be an early sign of liver disease.

Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. It is generally considered to be irreversible in its advanced stages at which point the only option may be liver transplantation. However, reversal of cirrhosis (in its earlier stages) has been documented in several forms of liver disease following treatment of the underlying cause. Patients with cirrhosis are susceptible to a variety of complications and their life expectancy is markedly reduced.

Management

Common patterns of lft abnormalities: the laboratory evaluation of patients with chronic (defined as six months or greater), mild elevation (defined approximately as less than four times the upper limit of normal) of one or both of the aminotransferases is best achieved in a stepwise fashion to eliminate unnecessary testing. On the other hand, it is sometimes convenient for patients (particularly in the referral setting) if several blood tests are obtained simultaneously since they can be processed on the same sample, thereby eliminating a return visit for additional testing. Furthermore, the order of the testing may change if the history and physical examination raise the pretest probability of a particular diagnosis. Thus, the steps outlined below are meant to be general guidelines.

Step one: the first step should be to identify medications and supplements that can cause elevation of the serum aminotransferases, to assess for alcohol use, and to test for viral hepatitis B and C, hemochromatosis, and fatty liver.

Medications: almost any medication can cause an elevation of liver enzymes. Common causes include nonsteroidal anti-inflammatory drugs, antibiotics, statins, antiepileptic drugs, and antituberculous drugs. In addition, herbal preparations and illicit drug use may also be the cause. Questioning should also include nonprescription medications; acetaminophen, for example, can cause aminotransferase elevation among healthy adults even when taken in recommended doses. A careful history and review of laboratory data are critical for identifying a medication as the cause of elevated serum aminotransferases. However, the diagnosis of drug-induced liver injury can be difficult. The relationship to drug ingestion and toxicity is not always clear; patients may be taking multiple medications, making identification of the offending agent difficult,

and the development of abnormal LFTs can occasionally be delayed, obscuring its relationship to hepatotoxicity. In addition, patients may have concomitant diseases (such as alcoholism), which can produce similar clinical and laboratory abnormalities. Features suggesting drug toxicity include lack of illness prior to ingesting the drug, clinical illness or biochemical abnormalities developing after beginning the drug, and improvement after the drug is withdrawn. If an immunologic reaction is suspected, the illness will generally recur upon reintroduction of the offending substance. However, rechallenge is not advised.If the identified medication is essential to the patient's well-being and no suitable substitute is available, the clinician needs to make a risk-benefit analysis to determine if a drug should be continued despite the aminotransferase elevation. A liver biopsy is occasionally necessary to determine the nature and severity of liver injury.

Alcohol abuse: the diagnosis of alcohol abuse can be difficult because many patients conceal this information. Several short questionnaires are of assistance in detecting occult alcohol abuse. In addition, the diagnosis is supported by an AST to ALT ratio of 2:1 or greater. In a study of hundreds of patients who had liver biopsy confirmed liver disorders, more than 90 percent of the patients whose AST to ALT ratio was two or greater had alcoholic liver disease. The percentage increased to greater than 96 percent when the ratio was greater than three. However, subsequent studies have revealed that the AST/ALT ratio may also be occasionally elevated in an alcoholic pattern in patients with nonalcoholic steatohepatitis, and is frequently elevated in an alcoholic pattern in patients with hepatitis C who have developed cirrhosis. Several other patterns of laboratory abnormalities may also be supportive of the diagnosis of alcohol abuse:

- A twofold elevation of the gamma glutamyltransferase (GGT) in patients whose AST to ALT ratio is greater than 2:1 strongly suggests alcohol abuse. However, an elevated GGT by itself is insufficiently specific to establish the diagnosis.
- It is rare for the AST to be greater than eightfold elevated and even less common for the ALT to be greater than fivefold elevated. The ALT may even be normal even in patients with severe alcoholic liver disease.

Hepatitis B: the proper initial testing for patients suspected of having chronic hepatitis B includes:

- Hepatitis B surface antigen (HBsAg).
- Hepatitis B surface antibody (HBsAb).
- Hepatitis B core antibody (HBcAb).

Patients who are surface antigen and core antibody positive are chronically infected and additional testing (hepatitis B «e» antigen and «e» antibody and a hepatitis B DNA (HBV DNA)) is indicated. A positive HBsAb and HBcAb indicates immunity to hepatitis B and another cause of aminotransferase elevation should be sought. The presence of a positive HBV DNA in the presence or absence of the «e» antigen indicates viral replication. A positive HBV DNA and a negative «e» antigen indicates that the patient has a precore mutant of hepatitis B.

Both of these situations warrant further evaluation with a liver biopsy and possible treatment. A positive hepatitis B surface antigen with a negative HBV DNA and a negative «e» antigen suggests that the patient is a carrier of hepatitis B and in a non-replicative state. The presence of a carrier state does not explain elevated aminotransferases, and another cause needs to be sought.

Hepatitis C: the actual sequence of diagnostic testing in an individual patient depends upon the clinical setting. Initial evaluation typically begins with an antibody test. Subsequent testing depends upon the clinical setting.

Hereditary hemochromatosis (HHC) is a common genetic disorder. Population screening has shown that the frequency of heterozygotes is about 10 percent in Caucasian populations in the United States and western Europe, with a frequency of about 5 per 1000 (0.5 percent) for the homozygous state. Screening should begin with a fasting serum iron and total iron binding capacity (TIBC), which permits the calculation of the iron or transferrin saturation (serum iron/TIBC). An iron saturation of greater than 45 percent warrants obtaining a serum ferritin. Ferritin should not be obtained as an initial test because it is an acute phase reactant and therefore less specific than the iron saturation. A serum ferritin concentration of greater than 400 ng/mL in men and 300 ng/mL in women further supports the diagnosis of HHC. A liver biopsy should be performed if screening tests suggest iron overload to quantify hepatic iron and to assess the severity of liver injury, and genetic testing should be done. A hepatic iron index (hepatic iron concentration in micromoles per gram dry weight divided by the patient's age) greater than 1.9 is consistent with homozygous HHC. A liver biopsy is not necessary for patients less than 40 years of age with genotypically defined hemochromatosis (C282Y homozygous) with normal liver function tests.Genetic testing has not replaced liver biopsy in the diagnosis of HHC. Not every patient who is homozygous for the HFE mutation has iron overload and not every patient with HHC has the identified HFE mutation. Thus, the biopsy may still be required to identify iron overload in some patients and is critical to determine the amount of fibrosis. Patients with HHC and cirrhosis continue to have a high risk of developing hepatocellular carcinoma even with depletion of body iron stores. These patients need to be identified and screened appropriately.

Hepatic steatosis and an associated condition, non-alcoholic steatohepatitis (NASH), may present solely with mild elevations of the serum aminotransferases, which are usually less than fourfold elevated. NASH is a condition more common in women and associated with obesity and type 2 diabetes mellitus.The initial evaluation to identify the presence of fatty infiltration of the liver is radiologic imaging including ultrasound, computed tomographic imaging, or magnetic resonance imaging. Ultrasonography has a lower sensitivity than CT or MRI scanning, but is less expensive. Thus, in a patient in whom there is a high pretest probability of steatosis and tests for hepatitis B, C, and HHC are unremarkable, the least expensive test to look for steatosis is ultrasonography.

Step two: the next set of tests should look for non-hepatic causes of elevated aminotransferases, which include principally muscle disorders and thyroid disease. Much less common causes are occult celiac disease and adrenal insufficiency.

Muscle disorders: elevated serum aminotransferases may be caused by disorders that affect organs other than the liver, most commonly striated muscle. Serum AST and ALT may both be elevated with muscle injury. Their ratio depends in part upon when they are assessed relative to the muscle injury. Immediately after muscle injury, the AST/ALT ratio is generally greater than three, but approaches one within a few days because of a faster decline in the serum AST. Conditions that can cause this include subclinical inborn errors of muscle metabolism, acquired muscle disorders (such as polymyositis), seizures, and heavy exercise (such as long distance running). If striated muscle is the source of increased aminotransferases, serum levels of creatine kinase, LDH, and aldolase will be elevated at least to the same degree. The creatine kinase or aldolase levels should be determined if other more common hepatic conditions have been ruled out.

Thyroid disorders can produce elevated aminotransferases by unclear mechanisms. An assay for thyroid stimulating hormone (TSH) is a reasonable screening test for hypothyroidism while a full set of thyroid function tests should be checked if hyperthyroidism is suspected.

Celiac disease: several reports have described elevated serum aminotransferases in patients with undiagnosed celiac disease. Serum aminotransferases returned to normal in all but one patient one year following a gluten free diet. The diagnosis of celiac disease is suggested by appropriate antibody screening with serum antiendomysial IgA or anti tissue transglutaminase IgA antibodies.

Adrenal insufficiency: aminotransferase elevation (1.5 to 3 times the upper limit of normal) has been described in patients with adrenal insufficiency (due to Addison's disease or secondary causes), including those without obvious clinical features of the disorder. Aminotransferases normalize within one week following appropriate treatment.

Anorexia nervosa has been associated with aminotransferase elevation by mechanisms that are not well understood.

Step three: the next set of tests is aimed at identifying rarer liver conditions:

Autoimmune hepatitis (AIH) is a condition found primarily in young to middle-aged women. The diagnosis is based upon the presence of elevated serum aminotransferases, the absence of other causes of chronic hepatitis, and features (serological and pathological) suggestive of AIH.A useful screening test for AIH is the serum protein electrophoresis (SPEP). More than 80 percent of patients with autoimmune hepatitis will have hypergammaglobulinemia. A greater than twofold polyclonal elevation of the immunoglobulins supports the diagnosis. Additional tests commonly ordered include antinuclear antibodies (ANA), anti-smooth muscle antibodies (SMA), and liver-kidney microsomal antibodies (LKMA). A reasonable approach to diagnosing autoimmune hepatitis is to start with an SPEP. An

ANA and SMA should be obtained in patients who have a polyclonal increase in gamma globulin. Elevated gamma globulins and high titer autoantibodies should prompt a liver biopsy to confirm the diagnosis of AIH. Patients (especially young women) with negative viral serologies and persistently elevated aminotransferases greater than 100 u/L should undergo liver biopsy even in the absence of elevated gamma globulins and autoantibodies. If the biopsy is consistent with chronic active hepatitis, patients should receive a trial of corticosteroids since approximately 20 percent of patients with steroid responsive hepatitis will not have a positive ANA or SMA at the time of presentation.

Wilson disease, a genetic disorder of biliary copper excretion, may cause elevated aminotransferases in asymptomatic patients. While the prevalence of Wilson disease is very low, it is a treatable liver disease and needs to be identified. Patients usually present between ages 5 to 25. However, the range of ages in cases reports spans from age 3 to 80. The initial screening test for Wilson disease is a serum ceruloplasmin, which will be reduced in approximately 85 percent of patients. Patients should also be examined by an ophthalmologist for Kayser-Fleischer rings. If the ceruloplasmin is normal and Kayser-Fleischer rings are absent, but there is still a suspicion of Wilson disease, the next test is a 24-hour urine collection for quantitative copper excretion. A value of greater than 100 mcg/day is suggestive of the diagnosis. The diagnosis is usually confirmed by a liver biopsy for quantitative copper. Patients with Wilson disease have liver copper levels of greater than 250 mcg/gm of dry weight. While the gene responsible for Wilson disease has been identified, the number of disease specific mutations is so great that molecular diagnosis is not yet feasible except in family members of a proband with a known mutation.

Alpha-1 antitrypsin deficiency is an uncommon cause of chronic liver disease in adults. Decreased levels of alpha-1 antitrypsin can be detected either by direct measurement of serum concentrations or by the absence of the alpha-1 peak on a serum protein electrophoresis. However, serum concentrations of alpha-1 antitrypsin can be increased in response to inflammation resulting in a falsely negative test. As a result, obtaining an alpha-1 antitrypsin phenotype is probably the most cost-effective test. In adults, alpha-1 antitrypsin deficiency should be suspected in patients who have a history of emphysema either at a young age or out of proportion to their smoking history.

Adult bile ductopenia is a rare inherited condition that presents with elevated aminotransferases. In mild forms, patients are asymptomatic, while in more serious forms, patients have pruritus and elevations of plasma alkaline phosphatase. The diagnosis is based upon liver biopsy findings. In the healthy liver, there are approximately 1.5 to 2 bile ducts cut in cross section per portal triad. Some patients respond to ursodeoxycholic acid (12 to 15 mg/kg body weight per day). Such patients have normalization of the plasma aminotransferases and generally do not progress to cirrhosis. By contrast, in the severe form,

the disease progresses despite treatment, and patients may eventually require liver transplantation.

Step four: a liver biopsy is often considered in patients in whom all of the above testing has been unyielding. However, in some settings, the best course may be observation. Recommend observation only in patients in whom the ALT and AST are less than twofold elevated and no chronic liver condition has been identified by the above noninvasive testing. Recommend a liver biopsy in patients in whom the ALT and AST are persistently greater than twofold elevated. While it remains unlikely that the biopsy will provide a diagnosis or lead to changes in management, it is often reassuring to the patient and clinician to know that there is no serious disorder.

Isolated hyperbilirubinemia occurs principally in two settings:

- Overproduction of bilirubin.
- Impaired uptake, conjugation, or excretion of bilirubin.

The initial step in evaluating a patient with an isolated elevated hyperbilirubinemia is to fractionate the bilirubin to determine whether the hyperbilirubinemia is predominantly conjugated or unconjugated. An increase in unconjugated bilirubin in serum results from either overproduction, impairment of uptake, or impaired conjugation of bilirubin. An increase in conjugated bilirubin is due to decreased excretion into the bile ductules or backward leakage of the pigment.

Unconjugated hyperbilirubinemia: indirect hyperbilirubinemia may be observed in a number of disorders. These can be divided into disorders associated with bilirubin overproduction (such as hemolysis and ineffective erythropoiesis) and disorders related to impaired hepatic uptake/conjugation of bilirubin (such as Gilbert's disease, Crigler-Najjar syndrome, and the effects of certain drugs).

Hemolysis can usually be detected by obtaining a reticulocyte count, haptoglobin, and examining the peripheral smear. Hemolytic disorders that cause excessive heme production may be either inherited or acquired. Inherited disorders include spherocytosis, sickle cell anemia, and deficiency of red cell enzymes such as pyruvate kinase and glucose-6-phosphate dehydrogenase. In these conditions, the serum bilirubin rarely exceeds 5 mg/dL. Higher levels may occur when there is coexistent renal or hepatocellular dysfunction or in acute hemolysis such as a sickle cell crisis. Acquired hemolytic disorders include microangiopathic hemolytic anemia (eg, hemolytic-uremic syndrome), paroxysmal nocturnal hemoglobinuria, and immune hemolysis. Ineffective erythropoiesis occurs in cobalamin, folate, and iron deficiencies.

Impaired hepatic uptake or conjugation of bilirubin should be considered in the absence of hemolysis. This is most commonly caused by certain drugs (including rifampicin and probenecid) which diminish hepatic uptake of bilirubin, or Gilbert's syndrome (a common genetic disorder associated with unconjugated hyperbilirubinemia). Much less commonly, indirect hyperbilirubinemia can be

caused by two other genetic disorders: Crigler-Najjar syndrome, types I and II.Gilbert's syndrome affects approximately 3 to 7 percent of the population, with white males predominating over females by a ratio of 2 to 7:1. Impaired conjugation of bilirubin is due to reduced bilirubin UDP glucuronosyl transferase activity. Affected patients have mild unconjugated hyperbilirubinemia with serum levels almost always less than 6 mg/dL. The serum levels may fluctuate and jaundice is often identified only during periods of illness or fasting. In an otherwise healthy adult with mildly elevated unconjugated hyperbilirubinemia and no evidence of hemolysis, the presumptive diagnosis of Gilbert's syndrome can be made without further testing.

Crigler Najjar type I is an exceptionally rare condition found in neonates and is characterized by severe jaundice (bilirubin > 20 mg/dL) and neurologic impairment due to kernicterus. Crigler-Najjar type II is somewhat more common than type I. Patients live into adulthood with serum bilirubin levels that range from 6 to 25 mg/dL. Bilirubin UDP glucuronosyl transferase activity is typically present but greatly reduced. Bilirubin UDP glucuronosyl transferase activity can be induced by the administration of phenobarbital, which can reduce serum bilirubin levels in these patients.

Conjugated hyperbilirubinemia: elevated conjugated hyperbilirubinemia is found in two rare inherited conditions: Dubin-Johnson syndrome and Rotor syndrome. Patients with both conditions present with asymptomatic jaundice typically in the second decade of life. The defect in Dubin-Johnson syndrome is altered excretion of bilirubin into the bile ducts, while Rotor syndrome appears to be due to defective hepatic storage of bilirubin. Dubin-Johnson and Rotor syndrome should be suspected in patients with mild hyperbilirubinemia (with a direct-reacting fraction of approximately 50 percent) in the absence of other abnormalities of standard liver function tests. Normal levels of serum alkaline phosphatase and gamma-glutamyltranspeptidase help to distinguish these conditions from disorders associated with biliary obstruction. Differentiating between these syndromes is possible but clinically unnecessary due to their benign nature.

Isolated elevation of the alkaline phosphatase and/or gamma glutamyl transpeptidase: serum alkaline phosphatase is derived predominantly from the liver and bones, although other sources may contribute to serum levels in some settings. Women in the third trimester of pregnancy, for example, have elevated serum alkaline phosphatase due to an influx into blood of placental alkaline phosphatase. Individuals with blood types O and B can have elevated serum alkaline phosphatase after eating a fatty meal due to an influx of intestinal alkaline phosphatase. Infants and toddlers occasionally display transient marked elevations of alkaline phosphatase in the absence of detectable bone or liver disease. There are also reports of a benign familial occurrence of elevated serum alkaline phosphatase due to intestinal alkaline phosphatase. Alkaline phosphatase levels also vary with age. Alkaline phosphatase levels are generally higher in children and adolescents because of phy-

siological osteoblastic activity. Levels may be up to three times higher than in healthy adults, with maximum levels in infancy and adolescence, coinciding with periods of maximum bone growth velocity. Also, the normal serum alkaline phosphatase gradually increases from age 40 to 65, particularly in women. The normal alkaline phosphatase for an otherwise healthy 65-year-old woman is more than 50 percent higher than a healthy 30-year-old woman.

The first step in the evaluation of an elevated alkaline phosphatase is to identify its source. If it is not available, either a 5'-nucleotidase or GGT should be obtained. These tests are usually elevated in parallel with the alkaline phosphatase in liver disorders but are not increased in bone disorders. An elevated serum alkaline phosphatase with a normal 5'-nucleotidase or GGT should prompt an evaluation for bone diseases. Initial testing for alkaline phosphatase of hepatic origin — chronic cholestatic or infiltrative liver diseases should be considered in patients in whom the alkaline phosphatase is determined to be of liver origin and persists over time. The most common causes include partial bile duct obstruction, primary biliary cirrhosis (PBC), primary sclerosing cholangitis, adult bile ductopenia, and certain drugs such as androgenic steroids and phenytoin. Infiltrative diseases include sarcoidosis, other granulomatous diseases, and less often unsuspected cancer metastatic to the liver. Initial testing should include a right upper quadrant ultrasound (which can assess the hepatic parenchyma and bile ducts) and an antimitochondrial antibody (AMA), which is highly suggestive of PBC. The presence of biliary dilatation suggests obstruction of the biliary tree. In patients with biliary dilatation or choledocholithiasis cholangiography (either MRCP or ERCP depending upon the clinical setting and degree of suspicion for a stone) should be done to identify the cause of obstruction and to allow for an intervention such as stone removal or stent placement. Patients with a positive AMA should have a liver biopsy to verify the diagnosis of PBC. A liver biopsy and either an ERCP or magnetic resonance cholangiopancreatogram (MRCP) if the AMA and ultrasound are both negative and the alkaline phosphatase is persistently more than 50 percent above normal for more than six months. If the alkaline phosphatase is less than 50 percent above normal, all of the other liver tests are normal, and the patient is asymptomatic, suggest observation alone since further testing is unlikely to influence management.

Gamma glutamyl transpeptidase (GGT) is found in hepatocytes and biliary epithelial cells. In normal full-term neonates, serum GGT activity is six to seven times the upper limit of the adult reference range; levels decline and reach adult levels by 5 to 7 months of age. GGT is sensitive for detecting hepatobiliary disease, but its usefulness is limited by its lack of specificity. Elevated levels of serum GGT have been reported in a wide variety of clinical conditions, including pancreatic disease, myocardial infarction, renal failure, chronic obstructive pulmonary disease, diabetes, and alcoholism. High serum GGT values are also found in patients taking medications such as phenytoin and barbiturates. Suggest

GGT be used to evaluate elevations of other serum enzyme tests (eg, to confirm the liver origin of an elevated alkaline phosphatase or to support a suspicion of alcohol abuse in a patient with an elevated AST and an AST:ALT ratio of greater than 2:1). An elevated GGT with otherwise normal liver tests should not lead to an exhaustive work-up for liver disease.

Evaluation of patients with simultaneous elevation of several lfts: it is helpful to attempt to divide this group of patients into those with a predominantly hepatocellular process and those with a predominantly cholestatic process, although the distinction is not always possible. Patients with a predominantly cholestatic pattern may be further divided into those with intra- or extrahepatic cholestasis. The degree of aminotransferase elevation can occasionally help in differentiating between hepatocellular and cholestatic processes. While ALT and AST values less than eight times normal may be seen in either hepatocellular or cholestatic liver disease, values 25 times normal or higher are seen primarily in hepatocellular diseases. On the other hand, patients with jaundice from cirrhosis may have normal or only slight elevations of the aminotransferases.

Predominantly hepatocellular pattern with jaundice: common hepatocellular diseases that can cause jaundice include viral and toxic hepatitis (including drugs, herbal therapies and alcohol) and end-stage cirrhosis from any cause. Wilson disease should be considered in young adults.Autoimmune hepatitis predominantly occurs in young to middle-aged women (although it may affect men and women of any age) and should particularly be considered in patients who have other autoimmune diseases.Alcoholic hepatitis can be differentiated from viral and toxin related hepatitis by the pattern of the serum aminotransferases. Patients with alcoholic hepatitis typically have an AST:ALT ratio of at least 2:1. The AST rarely exceeds 300 U/L. In contrast, patients with acute viral hepatitis and toxin related injury severe enough to produce jaundice typically have aminotransferases greater than 500 U/L with the ALT greater than or equal to the AST.Patients with acute viral hepatitis can develop jaundice. Appropriate testing for suspected acute viral hepatitis includes a:

- Hepatitis A IgM antibody.
- Hepatitis B surface antigen.
- Hepatitis B core IgM antibody.
- Hepatitis C viral RNA.

Patients with acute hepatitis C are usually asymptomatic. As a result, acute hepatitis C is an uncommon cause of acute viral hepatitis that is clinically evident. Nevertheless, testing for acute HCV is reasonable and should be performed by requesting an assay for serum hepatitis C viral RNA since hepatitis C antibody may take weeks to months to become detectable.

Toxic hepatitis: drug induced hepatocellular injury can be classified either as predictable or unpredictable. Predictable drug reactions are dose-dependent and affect all patients who ingest a toxic dose of the drug in question. The clas-

sic example is acetaminophen hepatotoxicity. Unpredictable, or idiosyncratic, drug reactions are not dose dependent and occur in a minority of patients. Virtually any drug can cause an idiosyncratic reaction. As discussed above, features suggesting drug toxicity include lack of illness prior to ingesting the drug, clinical illness or biochemical abnormalities developing after beginning the drug, and improvement after the drug is withdrawn.Environmental toxins are also an important cause of hepatocellular injury. Examples include industrial chemicals such as vinyl chloride, herbal preparations containing pyrrolizidine alkaloids (Jamaica bush tea), and the mushrooms Amanita phalloides or verna containing highly hepatotoxic amatoxins.

Shock liver (ischemic hepatitis): patients who have a prolonged period of systemic hypotension (such as following a cardiac arrest or patients with severe heart failure) may develop ischemic injury to several organs including the liver. Striking increases in serum aminotransferases (exceeding 1000 IU/L or 50 times the upper limit of normal) and lactic dehydrogenase may be seen. Patients may also develop jaundice, hypoglycemia, and hepatic synthetic dysfunction. The majority of patients have concomitant deterioration of renal function. The prognosis depends mostly upon the underlying condition. Hepatic function usually returns to normal within several days of the acute episode.

Wilson disease: patients with Wilson disease can occasionally present with acute and even fulminant hepatitis. The diagnosis should be considered in patients younger than 40, particularly those who have concomitant hemolytic anemia.

Patients with autoimmune hepatitis can present with acute and even fulminant hepatitis. The diagnosis is established by the clinical setting, exclusion of other causes, serologic testing, and in some cases a liver biopsy.

Clinical manifestations: patients with cirrhosis may present in a variety of ways. They may have stigmata of chronic liver disease discovered on routine physical examination. They may have undergone laboratory or radiologic testing or an unrelated surgical procedure that incidentally uncovered the presence of cirrhosis.They may present with decompensated cirrhosis, which is characterized by the presence of dramatic and life-threatening complications, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis (SBP), or hepatic encephalopathy.Some patients never come to clinical attention. In older reviews, cirrhosis was diagnosed at autopsy in up to 30 to 40 percent of patients.

The history should include questioning about risk factors for chronic liver disease including a history of hepatitis, alcohol consumption, diabetes mellitus, use of illicit drugs (by injection or inhalation), transfusions, family history of liver disease, travel, and the presence of autoimmune diseases (including inflammatory bowel disease, rheumatoid arthritis and thyroid disease). The review of systems should include questioning related to fatigue, easy bruisability, lower extremity edema, fever, weight loss, diarrhea, pruritus, increasing abdominal girth, and confusion or sleep disturbance (possibly indicating encephalopathy).

Physical findings: a number of physical findings have been described in patients with cirrhosis:

Spider angiomata (also referred to as spider telangiectasias) are vascular lesions consisting of a central arteriole surrounded by many smaller vessels. They are most frequently found on the trunk, face, and upper limbs. The body (the central arteriole) can be seen pulsating when compressed with a glass slide. Blood fills the central arteriole first before traveling to the peripheral tips of each leg after blanching. There are usually multiple radiating «legs» and surrounding erythema that may encompass the entire lesion or only its central portion.While their pathogenesis is incompletely understood, they are believed to result from alterations in sex hormone metabolism. Acquired spider angiomata are not specific for cirrhosis since they may also be seen during pregnancy and in patients with severe malnutrition. They can also be seen in otherwise healthy people, who usually have fewer than three small lesions. As a general rule, the number and size of spider angiomata correlate with the severity of liver disease. Patients with numerous and large spider angiomata may be at increased risk for variceal hemorrhage.

Palmar erythema is an exaggeration of the normal speckled mottling of the palm, and is also believed to be caused by altered sex hormone metabolism. It is most frequently found on the thenar and hypothenar eminences while sparing the central portions of the palm. Palmar erythema is not specific for liver disease and can be seen in association with pregnancy rheumatoid arthritis, hyperthyroidism, and hematological malignancies.

Nail changes: Muehrcke's nails are paired horizontal white bands separated by normal color. The exact pathogenesis is unknown but it is believed to be caused by hypoalbuminemia. They are not specific for cirrhosis since they may also be seen in other conditions associated with a low serum albumin, such as the nephrotic syndrome.Terry's nails can also be seen in patients with cirrhosis. The proximal two-thirds of the nail plate appears white whereas the distal one-third is red. This finding is also believed to be secondary to a low serum albumin.

Clubbing and hypertrophic osteoarthropathy: clubbing is present when the angle between the nail plate and proximal nail fold is greater than 180 degrees. When severe, the distal finger has a drum stick appearance. Hypertrophic osteoarthropathy (HOA) is a chronic proliferative periostitis of the long bones that can cause considerable pain. Clubbing is more common in biliary causes of cirrhosis (particularly primary biliary cirrhosis) while hypertrophic osteoarthropathy can be seen with various causes of liver disease. Neither feature is specific for liver disease. The pathogenesis of clubbing and hypertrophic osteoarthropathy are not well understood. The most frequent cause of HOA is lung cancer, which should be sought in the appropriate setting. Pathogenesis and disease associations are further discussed elsewhere.

Dupuytren's contracture results from the thickening and shortening of the palmar fascia, which causes flexion deformities of the fingers. Pathologically, it

is characterized by fibroblastic proliferation and disorderly collagen deposition with fascial thickening. The pathogenesis is unknown but may be related to free radical formation generated by the oxidative metabolism of hypoxanthine.It is relatively common in patients with alcoholic cirrhosis in whom it may be found in as many as a third of patients. However, it can also be seen in several other conditions including in workers exposed to repetitive handling tasks or vibration, and those with diabetes mellitus, reflex sympathetic dystrophy, cigarette smoking and alcohol consumption, and Peyronie's disease.

Gynecomastia is defined histologically as a benign proliferation of the glandular tissue of the male breast and clinically by the presence of a rubbery or firm mass extending concentrically from the nipple. Fat deposition without glandular proliferation is termed pseudogynecomastia (often seen in obese men). These two entities can be distinguished by having the patient lie on his back with his hands behind his head. The examiner then places his or her thumb and forefinger on each side of the breast, and slowly brings them together.Up to two-thirds of patients with cirrhosis have gynecomastia. It is possibly caused by increased production of androstenedione from the adrenals, enhanced aromatization of androstenedione to estrone, and increased conversion of estrone to estradiol. Men may also develop other features reflecting feminization such as loss of chest or axillary hair and inversion of the normal male pubic hair pattern. Gynecomastia can be seen in a variety of conditions other than cirrhosis.

Hypogonadism is manifested by impotence, infertility, loss of sexual drive, and testicular atrophy. It is a feature seen predominantly in patients with alcoholic cirrhosis and hemochromatosis. More than one mechanism appears to be involved. In some cases, primary gonadal injury appears to be more prominent, as suggested by increased serum FSH and LH concentrations, while in others suppression of hypothalamic or pituitary function appears to have a primary role, as suggested by serum LH concentrations that are not elevated. The toxic effects of alcohol or iron may also contribute to its development.

Hepatomegaly: the cirrhotic liver may be enlarged, normal sized, or small. While the presence of a palpable liver may indicate liver disease, a non-palpable liver does not exclude it. When palpable, the cirrhotic liver has a firm and nodular consistency.

Splenomegaly is common especially in patients with cirrhosis from nonalcoholic etiologies. It is believed to be caused primarily by congestion of the red pulp as the result of portal hypertension. However, splenic size does not correlate well with portal pressures, suggesting that other factors may be contributing. The differential diagnosis of splenomegaly includes several other disorders.

Ascites is the accumulation of fluid in the peritoneal cavity. The accuracy of physical findings is variable depending in part upon the amount of fluid present, the technique used to examine the patient, and the clinical setting (eg, detection may be more difficult in patients who are obese).

Caput medusa: the veins of the lower abdominal wall normally drain inferiorly into the iliofemoral system while the veins of the upper abdominal wall drain superiorly into the veins of the thoracic wall and axilla. When portal hypertension occurs as the result of cirrhosis, the umbilical vein, normally obliterated in early life, may open. Blood from the portal venous system may be shunted through the periumbilical veins into the umbilical vein and ultimately to the abdominal wall veins, causing them to become prominent. This appearance has been said to resemble the head (caput) of the mythical Gorgon Medusa.Dilated abdominal veins can also be seen in the inferior vena cava syndrome and the superior vena cava syndrome (if obstruction includes the azygous system). In these conditions, collateral veins tend to be more prominent in the lateral aspect of the abdominal wall. One maneuver that has been proposed to distinguish vena caval obstruction from portal hypertension is to pass the finger along dilated veins located below the umbilicus to strip them of blood and determine the direction of blood flow during refilling. In portal-systemic collateral veins, the blood flow should be directed inferiorly away from the umbilicus in contrast to vena caval collateral vein flow in which the flow should be cephalad. However, the actual ability of this maneuver to discriminate between the two is poor since in both conditions the dilated veins may lack valves and thus have bidirectional blood flow.

The Cruveilhier-Baumgarten murmur is a venous hum that may be auscultated in patients with portal hypertension. It results from collateral connections between the portal system and the remnant of the umbilical vein. It is best appreciated when the stethoscope is placed over the epigastrium. The murmur is augmented by maneuvers which increase intraabdominal pressure such as the Valsalva maneuver and diminished by applying pressure on the skin above the umbilicus.

Fetor hepaticus: a sweet, pungent smell to the breath of a patient with cirrhosis may occasionally be encountered. It is caused by increased concentrations of dimethylsulphide, the presence of which suggests underlying severe portal-systemic shunting.

Jaundice is a yellow coloring of the skin and mucus membranes that results from increased serum bilirubin. It is usually not detectable until the bilirubin is greater than 2 to 3 mg/dL. The hyperbilirubinemia may also cause the urine to appear dark colored (so-called «beer» or «coca-cola» color).

Yellow discoloration to the skin can also be caused by excessive consumption of carotene (such as in patients who consume large quantities of carrots). Yellowing of the skin in carotenemia can be distinguished from jaundice by the absence of yellow discoloration in the sclera in the former.

Asterixis (bilateral but asynchronous flapping motions of outstretched, dorsiflexed hands) is seen in patients with hepatic encephalopathy, which describes the spectrum of potentially reversible neuropsychiatric abnormalities seen in patients with liver dysfunction. Asterixis may also be seen in patients with uremia and severe heart failure.

Miscellaneous: patients with cirrhosis may also present with a diverse range of signs and symptoms that reflect the pivotal role that the liver has in the homeostasis of many different bodily functions. They may also have features suggesting the underlying cause of cirrhosis such as cryoglobulinemia from hepatitis C, diabetes mellitus and arthropathy in patients with hemochromatosis, and extrahepatic autoimmune diseases (such as hemolytic anemia or thyroiditis) in patients with autoimmune hepatitis. Other general features that may be seen include:

- Constitutional symptoms such as weakness, fatigue, anorexia, and weight loss and features suggesting malnutrition.
- Pigment gallstones resulting from hemolysis.
- Parotid gland enlargement (probably due to alcohol, not cirrhosis per se). Enlargement is usually secondary to fatty infiltration, fibrosis, and edema rather than a hyperfunctioning gland.
- Diabetes mellitus is seen in 15 to 30 percent of patients with cirrhosis. It may be particularly common in patients with chronic hepatitis C. The pathogenesis is likely related to insulin resistance and an inadequate secretion of insulin from the beta cells of the pancreas. Diabetes may also be seen in patients with hemochromatosis.

Physical assessment for hepatomegaly: the liver is the largest internal organ in humans and typically spans 21 to 23 cm horizontally and 14 to 17 cm vertically. The size of the normal liver varies depending upon sex, height, and body habitus. Physical examination of the liver can be helpful for assessing its shape and consistency or whether there is tenderness of the liver edge. It is less useful for assessing its size since assessment of liver size by physical examination correlates poorly with radiologic assessment. Nevertheless, the liver span can be estimated using percussion techniques or the scratch test. The scratch test uses auscultation while lightly scratching the skin. The intensity of the scratching sound increases when the liver is encountered with the scratching finger. A normal liver span in the mid-clavicular line by physical examination is 7 to 10 cm.In healthy people, the liver is generally not palpable because it lies posterior to the rib cage. By contrast, an enlarged liver can often be palpated below the costal margin. However, there are exceptions in which a normal-sized liver can be palpated below the costal margin including patients with emphysema, a thin-body habitus, the presence of a hypertrophied caudate lobe (such as seen in patients with Budd-Chiari syndrome), or Riedel's lobe (an anatomical variant in which there is an extension of the right-lobe downward and lateral toward the gallbladder).

Laboratory findings: the presence of cirrhosis is sometimes suggested by laboratory abnormalities. In today's medical practice, it is common for panels of serum chemistries to be sent for screening or evaluation of specific complaints. Although the term «liver function tests» (LFTs) is commonly used, it is imprecise since many of the tests reflecting the health of the liver are not direct measures of its function. The most common laboratory measures classified as LFTs

include the enzyme tests (principally the serum aminotransferases, alkaline phosphatase, and gamma glutamyl transpeptidase), the serum bilirubin, and tests of synthetic function (principally the serum albumin concentration and prothrombin time).Certain abnormalities discovered on routine cell counts and chemistries can suggest the presence of advanced liver disease while providing clues to its severity and etiology. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are usually moderately elevated. AST is more often elevated than ALT. However, normal aminotransferases do not preclude a diagnosis of cirrhosis. Most forms of chronic hepatitis other than alcohol have a ratio of AST/ALT less than one. However, as chronic hepatitis progresses to cirrhosis, the ratio of AST to ALT may reverse.

Alkaline phosphatase: alkaline phosphatase is usually elevated but less than two to three times the upper normal limit. Higher levels may be seen in patients with primary sclerosing cholangitis and primary biliary cirrhosis.

Gamma-glutamyl transpeptidase (GGT) levels correlate reasonably well with alkaline phosphatase in liver disease. Levels of GGT are typically much higher in chronic liver disease from alcohol than other causes. This may be the result of alcohol inducing hepatic microsomal GGT or alcohol causing GGT to leak from hepatocytes.

Bilirubin levels may be normal in well compensated cirrhosis. However, they rise as the cirrhosis progresses. In patients with primary biliary cirrhosis, a rising serum bilirubin portends a poor prognosis.

Albumin is synthesized exclusively in the liver. Albumin levels fall as the synthetic function of the liver declines with worsening cirrhosis. Thus, serum albumin levels can be used to help grade the severity of cirrhosis. Hypoalbuminemia is not specific for liver disease since it may be seen in many other medical conditions such as congestive heart failure, the nephrotic syndrome, protein losing enteropathy, or malnutrition.

Globulins tend to be increased in patients with cirrhosis. This may be secondary to shunting of bacterial antigens in portal venous blood away from the liver to lymphoid tissue which induces immunoglobulin production. Marked elevations of IgG may be a clue to the presence of autoimmune hepatitis. Increased levels of IgM are present in 90 to 95 percent of patients with primary biliary cirrhosis.

Serum sodium: hyponatremia is common in patients with cirrhosis with ascites and is related to an inability to excrete free water. This results primarily from high levels of anti-diuretic hormone secretion. Hyponatremia often becomes severe as cirrhosis progresses to end-stage liver disease.

Hematologic abnormalities: patients with cirrhosis commonly have a number of hematologic abnormalities, including disorders of coagulation and varying degrees of cytopenia. Thrombocytopenia is the most common first hematologic abnormality while leukopenia and anemia develop later in the disease course.

Anemia is usually multifactorial in origin; acute and chronic gastrointestinal blood loss, folate deficiency, direct toxicity due to alcohol, hypersplenism, bone marrow suppression (as in hepatitis-associated aplastic anemia), the anemia of chronic disease (inflammation), and hemolysis may all contribute.

Thrombocytopenia is mainly caused by portal hypertension with attendant congestive splenomegaly. An enlarged spleen can result in temporary sequestration of up to 90 percent of the circulating platelet mass. However, this uncommonly results in platelet counts less than 50,000/mL, and, unless complicated by coexisting coagulopathy, is rarely a clinical problem. Decreased thrombopoietin levels may also contribute to thrombocytopenia.

Leukopenia and neutropenia are due to hypersplenism with splenic margination.

Coagulation defects: most of the proteins involved in the coagulation process are produced in the liver. Thus, worsening coagulopathy correlates with the severity of hepatic dysfunction. In addition to deficiency of coagulant proteins, patients may develop varying degrees of DIC, fibrinolysis, vitamin K deficiency, dysfibrinogenemia, and thrombocytopenia, all of which may contribute to bleeding.

Prothrombin time: the liver is involved in the synthesis of many of the proteins required for normal clotting. Thus, the prothrombin time reflects the degree of hepatic synthetic dysfunction. The prothrombin time increases as the ability of a cirrhotic liver to synthesize clotting factors diminishes.

Other liver function tests: the ability of the liver to transport organic anions and metabolize drugs has led to the development of a multitude of tests to assess the function of the liver. None is used routinely in clinical practice.

Serological markers of hepatic fibrosis are currently being examined to help predict the presence of cirrhosis without the need for liver biopsy. None is sufficiently accurate for routine clinical use.

Radiographic findings: although radiographic findings can occasionally suggest the presence of cirrhosis, they are not adequately sensitive or specific for use as a primary diagnostic modality. The major utility of radiography in the evaluation of the cirrhotic patient is in its ability to detect complications of cirrhosis such as ascites, hepatocellular carcinoma, and hepatic or portal vein thrombosis. In rare instances, radiographic findings suggest the etiology of cirrhosis. A hypertrophied caudate lobe discovered on CT scanning, for example, suggests Budd-Chiari syndrome. Decreased signal intensity on MRI may indicate iron overload from hereditary hemochromatosis.

Ultrasonography is routinely used during the evaluation of the cirrhotic patient. It is noninvasive, well tolerated, widely available, and provides valuable information. In advanced cirrhosis, the liver may appear small and nodular. Surface nodularity and increased echogenicity with irregular appearing areas are consistent with cirrhosis but can also be seen with hepatic steatosis. There is typically atrophy of the right lobe and hypertrophy of the caudate or left lobes. Investigators have attempted to use the ratio of the width of the caudate lobe to the

width of the right lobe as an ultrasonographic criterion for the diagnosis of cirrhosis. However, the sensitivity is poor.Ultrasonography may be used as a screening test for hepatocellular carcinoma and portal hypertension. The finding of nodules on ultrasonography warrants further evaluation since benign and malignant nodules can have similar ultrasonographic appearance. Findings of portal hypertension include an increased diameter of the portal vein and the presence of collateral veins. Ultrasonography is also useful for detecting splenomegaly, ascites, and portal vein thrombosis.

«Stiffness» measurement: increasing scarring of the liver is associated with increasing «stiffness» of the tissue. A sonographic technique to assess liver stiffness has been developed (Fibroscan, EchoSens, Paris, France). A vibration of mild amplitude and low frequency is transmitted through the liver inducing an elastic shear wave that propagates through the tissue. A pulse-echo ultrasound follows the propagation of the wave; the harder the tissue (and hence the more dense the fibrosis) the faster the wave propagates. Initial assessment of the device suggests that it has excellent test characteristics in patients with advanced fibrosis. The test is limited in patients with obesity, narrow intercostal spaces, and ascites. Further validation studies are needed to clarify its role.

Computed tomography is not routinely used in the diagnosis and evaluation of cirrhosis. It provides similar information to ultrasonography, but at the expense of radiation and contrast exposure. CT findings may suggest the presence of cirrhosis, but they are not diagnostic.

Magnetic resonance imaging: the role of magnetic resonance imaging (MRI) in the diagnosis of cirrhosis is unclear. Despite much enthusiasm about the potential of MRI in the evaluation of the cirrhotic patient, its use today is limited by expense, patient intolerability, and the ability to obtain information provided by MRI through other means.MRI may also reveal iron overload and provide an estimate of the hepatic iron concentration. MR angiography is more sensitive than ultrasonography in diagnosing complications of cirrhosis such as portal vein thrombosis.

Nuclear studies: radionuclide testing can be useful in suggesting the diagnosis of cirrhosis. 99mTc sulfur colloid is normally taken up by cells of the reticuloendothelial system. In patients with cirrhosis, there may be heterogeneity in the uptake of 99mTc sulfur colloid by the liver and increased uptake by the spleen and bone marrow. The exact sensitivity and specificity of these findings in making the diagnosis of cirrhosis is unknown. Given the widespread use of the other imaging modalities discussed above, this test is seldom performed in clinical practice.

Diagnosis: the gold standard for diagnosis of cirrhosis is examination of an explanted liver at autopsy or following liver transplantation during which the architecture of the entire liver can be appreciated. In clinical practice, cirrhosis is diagnosed with a liver biopsy during which a sample of the liver is obtained by ei-

ther a percutaneous, transjugular, laparoscopic, or radiographically-guided fine-needle approach depending upon the clinical setting. Serologic and radiographic methods to diagnose cirrhosis continue to be studied but none has yet supplanted liver histology as the gold standard. The sensitivity of a liver biopsy for cirrhosis is in the range of 80 to 100 percent depending upon the method used, and the size and number of specimens obtained. However, liver biopsy is not necessary if the clinical, laboratory, and radiologic data strongly suggest the presence of cirrhosis. An example would be a patient with ascites, severe coagulopathy, and a shrunken nodular appearing liver on ultrasonography. In addition to demonstrating that cirrhosis is present, a liver biopsy can sometimes suggest the cause. This is especially true for metabolic causes of cirrhosis such as hereditary hemochromatosis, NASH, Wilson's disease, and alpha-1 antitrypsin deficiency.

Determining the cause of cirrhosis: while many causes of chronic liver injury can lead to cirrhosis, a specific etiology can usually be determined by the history combined with serologic and histologic evaluation. The two most common causes in the United States are alcoholic liver disease and hepatitis C, which together account for almost one-half of those undergoing transplantation. The proportion of patients with cirrhosis without an apparent cause (cryptogenic cirrhosis) is declining. In 1960, nearly a third of all cases of cirrhosis were considered cryptogenic compared to 10 to 15 percent today. The proportion may be declining further since it is becoming increasingly apparent that many such patients may actually have had unrecognized nonalcoholic steatohepatitis (NASH). Determination of the etiology of cirrhosis is important since it may influence treatment decisions, counseling of family members, and help predict complications. As examples:

- Patients with cirrhosis related to autoimmune hepatitis may have clinical and histologic improvement (including regression of fibrosis) when treated with corticosteroids justifying the use of corticosteroids even in those with advanced disease.
- Phlebotomy decreases complications of portal hypertension in patients with cirrhosis who have hereditary hemochromatosis.
- Prophylactic measures (such as lamivudine or hepatitis B immune globulin) are required in patients undergoing transplantation for cirrhosis related to hepatitis B.
- Family members of patients diagnosed with hemochromatosis or Wilson's disease may require genetic counseling and screening. Appropriate preventive measures and advice can be discussed with family members of patients with chronic viral hepatitis or alcoholic cirrhosis.
- The risk for hepatocellular carcinoma is higher in patients with cirrhosis from viral hepatitis or hemochromatosis compared to patients with autoimmune hepatitis or NASH.

Morphologic classification: cirrhosis was historically classified morphologically as micronodular, macronodular, or mixed. Micronodular cirrhosis, cha-

racterized by nodules less than 3 mm in diameter, was believed to be caused by alcohol, hemochromatosis, cholestatic causes of cirrhosis, and hepatic venous outflow obstruction. Macronodular cirrhosis, characterized by various sized nodules larger than 3 mm, was believed to be secondary to chronic viral hepatitis.Although important from a historical perspective, the morphological classification system has a number of limitations and has thus largely been abandoned. First, it is relatively nonspecific with regard to etiology. Second, the morphologic appearance of the liver may change as the liver disease progresses; micronodular cirrhosis usually progresses to macronodular cirrhosis. Third, serological markers available today are more specific than morphological appearance of the liver for determining the etiology of cirrhosis. As an example, antimitochondrial antibodies have a specificity of 98 percent for primary biliary cirrhosis. Finally, accurate assessment of liver morphology can only be achieved at surgery, laparoscopy, or autopsy, while in today's clinical practice there are less invasive means to make an etiologic diagnosis.

Testing for specific diseases: the order and selection of specific tests for determining the cause of cirrhosis should be guided by the available information from the history, physical examination, and laboratory and radiologic tests, which may point toward a diagnosis.

Alcoholic liver disease: documenting chronic alcohol abuse is the most important aspect of diagnosing alcoholic liver disease, although it is often denied by the patient. Patients with concurrent alcoholic hepatitis may present with fever, hepatomegaly, jaundice, and anorexia. Alcoholic hepatitis is also associated with the classical laboratory findings of a disproportionate elevation of AST (aspartate aminotransferase, SGOT) compared to ALT (alanine aminotransferase, SGPT), with both values usually being less than 300 IU/L. This ratio is generally greater than 2.0, a value that is rarely seen in other forms of liver disease. Liver biopsy, if performed, may reveal the typical findings of alcoholic hepatitis, including liver cell necrosis, Mallory bodies, infiltration by neutrophils, and a perivenular distribution of inflammation. Alcoholic fibrosis, like the hepatitis lesion, first appears in the pericentral zone and then progresses to panlobular fibrosis in those who continue to drink.

Chronic hepatitis C virus infection: the diagnostic tests for hepatitis C virus (HCV) infection consist of serologic assays that detect antibody to hepatitis C and molecular assays that detect or quantify HCV RNA. A liver biopsy can be helpful for establishing the severity of disease and evaluating for contributing causes such as alcohol.

Chronic hepatitis B virus (HBV) infection is a much less common cause of cirrhosis than hepatitis C. The diagnosis of chronic HBV infection is based upon the detection of HBsAg more than four to six months after initial infection. Additional tests for HBV replication — HBeAg and serum HBV DNA— should be performed to determine if the patient should be considered for antiviral therapy.

Nonalcoholic steatohepatitis (NASH) is a disorder diagnosed by liver biopsy. The biopsy findings are indistinguishable from those of alcoholic hepatitis described above but the patient lacks a history of significant alcohol consumption. The liver disease is stable in most patients but a minority progress to cirrhosis.

Primary biliary cirrhosis: patients with primary biliary cirrhosis (PBC) may be asymptomatic or present with a history of fatigue, pruritus, and skin hyperpigmentation that is not due to jaundice. The physical examination typically reveals hepatomegaly and less often splenomegaly. Laboratory tests reveal pronounced elevations in the serum alkaline phosphatase concentration, which is of hepatic origin; affected patients may also have striking elevations in the serum cholesterol concentration while hyperbilirubinemia is not seen until late in the course of the disease. Modest elevations in serum bilirubin that persists for more than three to six months imply a poor prognosis; such patients should be referred for liver transplantation even in the absence of life-threatening complications related to cirrhosis. Antimitochondrial antibodies are the serologic hallmark of PBC. Liver biopsy is usually confirmatory rather than diagnostic. The pathognomonic florid bile duct lesion is uncommonly seen in percutaneous needle biopsies of the liver. The continuous assault on the bile duct epithelial cells leads to their gradual destruction and eventual disappearance.Imaging tests or cholangiography are not needed in most patients. Endoscopic retrograde cholangiography is typically normal or shows narrow caliber bile ducts in PBC, and is helpful in the patient in whom the antimitochondrial antibody test is negative and the possibility of primary sclerosing cholangitis or a carcinoma of the bile duct or pancreas exists.

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease of the liver and bile ducts that is frequently progressive. The clinical presentation is that of a cholestatic liver disease, including pruritus, steatorrhea, fat soluble vitamin deficiencies, and metabolic bone disease. Complications are common, including dominant biliary strictures, cholangitis, cholelithiasis, cholangiocarcinoma, and colon cancer. There is a strong association between PSC and inflammatory bowel disease, particularly ulcerative colitis (UC) but also Crohn's disease. The incidence of UC in patients approaches 90 percent when rectal and sigmoid biopsies are routinely obtained. The diagnosis is best established by contrast cholangiography, which reveals a characteristic picture of diffuse, multifocal strictures and focal dilation of the bile ducts, leading to a beaded appearance. The term «primary» is used to distinguish PSC from other conditions that may lead to a similar clinical and cholangiographic syndrome. These include choledocholithiasis, cholangiocarcinoma, bacterial cholangitis, prior biliary surgery, intraarterial floxuridine, and acquired immunodeficiency syndrome associated cholangiopathy.PSC is also associated with a number of immunologic abnormalities, none of which is diagnostic. These include an elevated serum IgM concentration in 50 percent and several autoantibodies. The most common are anti-smooth muscle and antinuclear antibodies, and antibodies directed against cytoplasmic and nuclear antigens of neutrophils.

Autoimmune hepatitis: establishing the diagnosis of autoimmune hepatitis is particularly important because therapy with prednisone with or without azathioprine is beneficial. Many patients, even those with established cirrhosis, respond when treatment is initiated.A characteristic laboratory feature of autoimmune hepatitis, although not universally present, is an elevation in serum globulins, particularly gamma globulins. This hyperglobulinemia is generally associated with circulating autoantibodies, which are particularly helpful in identifying autoimmune hepatitis. There are two major types of autoimmune hepatitis which are characterized by specific autoantibodies: antinuclear, anti-smooth muscle, antiactin antibodies and/or ANCA in type 1; and anti-LKM-1 and anti-ALC-1 (anti-liver cytosol) antibodies in type 2. On occasion, antimitochondrial antibodies occur in association with antinuclear and/or smooth muscle antibodies. The diagnosis of autoimmune hepatitis can be difficult to establish because the characteristic autoantibodies may be present and the liver biopsy reveals characteristic but nonspecific changes such as a portal mononuclear cell infiltrate which invades the sharply demarcated hepatocyte boundary (limiting plate) surrounding the portal triad; plasma cells are often seen in the inflammatory infiltrate. Given the possible difficulties in diagnosis, some clinicians will initiate a trial of corticosteroids in patients with a compatible picture and no other apparent cause of cirrhosis, particularly if the serum aminotransferases are elevated and prominent hyperglobulinemia is present.

Hereditary hemochromatosis: the presence of hereditary hemochromatosis (HH) may be suspected if there is a family history of cirrhosis or if the patient also has skin hyperpigmentation, diabetes mellitus, pseudogout, and/or a cardiomyopathy.Signs of iron overload are also typically present in HH. A fasting transferrin saturation of $\geq$ 60 percent in men and $\geq$ 50 percent in women will detect about 90 percent of patients with homozygous HH. However, many investigators have advocated using a «cutoff» value of 45 percent for both men and women, which will lead to fewer patients being missed (at the expense of leading to the identification of more false positives).Increased iron also stimulates the hepatic production and release of ferritin. As a result, a plasma ferritin concentration above 300 ng/mL in men and 200 ng/mL in women provides further support for the diagnosis of iron overload. An elevated plasma ferritin is generally less sensitive than the transferrin saturation in screening for HH because a greater degree of iron overload is required to raise the ferritin concentration.However, an elevation in the plasma ferritin and increased iron saturation can also be seen in patients with a variety of liver diseases. Thus, other tests are required to confirm the diagnosis in patients who present with cirrhosis. This can be achieved in one of three ways: genetic testing, which is now available; liver biopsy; and the response to quantitative phlebotomy. In the absence of genetic testing, liver biopsy is usually required to confirm the diagnosis of homozygous HH; heterozygotes do not develop cirrhosis in the absence of some other

type of liver disease (eg, viral hepatitis, nonalcoholic steatohepatitis). Parenchymal iron loading can be demonstrated by Perls' Prussian blue staining of a liver biopsy, and fibrosis can be detected if it exists. The hepatic tissue can also be directly analyzed for iron content which must be performed meticulously to detect nonheme iron. The hepatic iron content is preferably reported as micromoles of iron per gram dry weight of liver. Normal values are less than 36 μmol/g, while values above 71 μmol/g are highly suggestive of homozygous HH. This value can be divided by the subject's age in years to give the hepatic iron index (HII); a value ≥ 1.9 is also highly suggestive of homozygous HH.

Other causes of cirrhosis are much less common but should be considered in the appropriate clinical setting. As an example, Wilson's disease is an autosomal recessive disorder which should be suspected in any patient who has a personal or family history of cirrhosis at a young age or who presents with fulminant hepatic failure under the age of 45. The diagnosis is usually established by the findings of a low serum ceruloplasmin concentration (present in 95 percent of patients) and increased hepatic copper content on liver biopsy, a finding that can also be seen in cholestatic liver diseases such as primary biliary cirrhosis and primary sclerosing cholangitis. Alpha-1 antitrypsin (AAT) deficiency is also an autosomal recessive disorder which can cause cirrhosis in children and in 10 to 15 percent of adults who may also have chronic obstructive pulmonary disease. The first step in an individual suspected of having AAT deficiency is measurement of serum AAT concentrations. Phenotyping should be saved for individuals who have a low or borderline AAT concentration; this test requires skill and experience, so care should be taken to select a laboratory that can provide these features.

Treatment

Chronic Viral Hepatites

Antiviral therapy has several major goals, including the following:

- To decrease viral replication or eradicate.
- To prevent progression of disease.
- To decrease the prevalence of cirrhosis.
- To decrease the frequency of HCC as a complication of cirrhosis.
- To ameliorate symptoms, such as fatigue and joint pain.
- To treat extrahepatic complications of HCV infection, such as cryoglobulinemia or glomerulonephritis.

IFN has been the drug of choice for the treatment of hepatitis C for more than 2 decades. It is often used in combination with another drug, ribavirin. Successful IFN-based therapy, resulting in an SVR, can improve the natural history of chronic hepatitis C and may reduce the risk of HCC in patients with HCV-induced cirrhosis. IFN-based therapy appears to reduce the rate of fibrosis progression in patients with HCV infection. Agents currently approved by the FDA for the treatment of HCV infection include the following:

- IFN alfa-2b.
- IFN alfa-2a.
- Consensus IFN, also known as IFN alfacon-1 (discontinued from market in September 2013).
- Ribavirin, which is used in combination with IFN.

The addition of a large, inert polyethylene glycol (PEG) molecule to a therapeutic molecule (eg, IFN) can delay the clearance of the therapeutic molecule from the bloodstream.

Newer therapeutic agents

It is likely that the ongoing development of direct-acting antiviral drugs (DAAs) will improve treatment options for patients infected with hepatitis C. More than 2 dozen DAAs are being studied in clinical trials. These drugs, previously known as specifically targeted antiviral therapy for HCV drugs (STAT-C drugs), target different aspects of the HCV life cycle and thus fall into different categories, as follows:

- Nucleoside NS5B polymerase inhibitors.
- Nonnucleoside NS5B polymerase inhibitors.
- NS5A inhibitors.
- NS4B inhibitors.
- Viral entry inhibitors.
- NS3/4a protease inhibitors, such as telaprevir and boceprevir.

Treatment of patients coinfected with HBV and HDV has not been well studied. Multiple small studies have demonstrated that patients with HBV-HDV coinfection are less responsive to IFN therapy than patients with HBV infection alone. Treatment with PEG-IFN alfa-2b produced HDV RNA negativity in only 17–19 % of patients. Lamivudine appears to be ineffective against HBV-HDV coinfection.

Alcohol-related liver disease

Abstinence is the most effective means to prevent alcohol-related liver injury. In addition, several drugs have been studied to improve rates of abstinence, but none is used routinely.

Guidelines for the long-term management of alcoholic liver disease emphasize strict abstinence and possible use of pharmacologic therapy with counseling to prevent relapse. The guidelines also recommend nutritional therapy in patients with alcoholic cirrhosis. Such patients should receive frequent interval feedings, emphasizing a snack at nighttime and morning feeding to improve nutritional balance. Standard vitamin supplementation according to the recommended daily allowances is recommended, especially for thiamine and B vitamins. Guidelines from the American Association for the Study of Liver Diseases and the American College of Gastroenterology suggest multiple feedings, emphasizing breakfast and a nighttime snack, with a regular oral diet at higher-than-usual dietary intake (1.2 to 1.5 g/kg for protein and 35 to 40 kcal/kg for energy).

Complementary medicines:

Silymarin, the active ingredient in milk thistle, is thought to have antioxidant properties and has been proposed as a treatment for alcoholic liver disease. However, a systematic review concluded that the methodological quality of many of the studies was low and overall found no significant benefit in patients with alcoholic liver disease.

Polyunsaturated lecithin (PUL) is extracted from soybeans and is a constituent of cell membranes. Its mechanism of action is unknown; one possible mechanism is an alteration in collagenase activity. PUL appears to improve histology and reduce activation of hepatic stellate cells in baboons with alcoholic liver injury. A large multicenter trial in humans is now underway. An attractive aspect of this medication is its excellent side effect profile since the compound is a normal cellular constituent.

S-adenosylmethionine: a number of studies have evaluated the efficacy of s-adenosylmethionine, a glutathione precursor, in the treatment of alcoholic liver disease. Although a potential reduction on mortality has been suggested in some of the reports, a systematic review that included eight placebo-controlled trials found no significant benefit.

Metadoxine: a combination of two antioxidants, pyridoxine and pyrrolidone (metadoxine), has been approved for the treatment of alcoholic liver disease in some countries. Studies in humans and animals demonstrated that it was associated with improvement in biochemical and histologic parameters. A controlled trial included 136 alcoholics diagnosed with fatty liver who were randomly assigned to metadoxine (1500 mg/day) or placebo for three months. At the end of the study, there was significant improvement in liver function tests in both groups, although improvement was observed more rapidly in those randomized to metadoxine. The percentage of patients with persistent hepatic steatosis as assessed by ultrasound was also significantly lower in the metadoxine group (28 versus 70 percent). This benefit was observed in those who abstained from alcohol as well as patients who continued to drink, although the degree of improvement was less in the latter group. Further studies are needed to better clarify the significance of these observations on other clinical endpoints.

The combination of N-acetylcysteine (NAC), an antioxidant, with prednisolone has been studied but may not be more effective than prednisolone alone.

Pentoxifylline: the observation that tumor necrosis factor (TNF) levels are increased in patients with alcoholic hepatitis provided a rationale for the study of pentoxifylline (an inhibitor of TNF synthesis) in alcoholic hepatitis. Although the available data are variable with regard to its efficacy, it may be an acceptable option in patients with severe disease, particularly those with a contraindication to glucocorticoids. A guideline issued by the American Association for the Study of Liver Diseases and the American College of Gastroenterology suggests pentoxifylline (400 mg orally three times daily for four weeks) as an alternative to glu-

cocorticoids in patients with severe alcoholic hepatitis (Maddrey score ≥ 32), especially if there are contraindications to glucocorticoids.

Hepatic regeneration therapy: although hepatic regeneration therapy has considerable promise, treatment should be limited to controlled clinical trials.

Liver transplantation

Indices of prognosis: the presence of liver failure manifested by coagulopathy, jaundice, and/or encephalopathy is a poor prognostic indicator, usually indicating the presence of little hepatic functional reserve.

Maddrey's discriminant function: disease severity and mortality risk in patients with alcoholic hepatitis may be estimated by using a discriminant function formula (MDF, also known as the Maddrey score) calculated as follows:

Discriminant function = (4.6 × [prothrombin time - control PT]) + (serum bilirubin)

where PT refers to the prothrombin time and the bilirubin concentration is measured in units of mg/dL (this can be converted from bilirubin concentrations expressed as micromol/L by dividing by 17). A value greater than 32 is associated with a high short-term mortality and has been used to determine the need for glucocorticoids in patients with severe alcoholic hepatitis.

The Model for End-Stage Liver Disease (MELD) score is a statistical model predicting survival in patients with cirrhosis. The score is based upon the serum bilirubin, creatinine, and INR.

The Glasgow alcoholic hepatitis score (GAH) is a multivariate model predicting mortality in alcoholic hepatitis that includes age, serum bilirubin (at day one and days six to nine), blood urea nitrogen, prothrombin time, and peripheral white blood cell count. A benefit from glucocorticoids was observed only in patients with a score ≥ 9. Compared with the MDF and MELD scores, one comparative study found the GAH score was less sensitive for predicting one-month and three-month mortality.

A prognostic scoring system (the Lille model) has been proposed for predicting mortality in patients with severe alcoholic hepatitis who have been treated with glucocorticoids. The model, which combines six variables (age, renal insufficiency (Cr > 1.3 or creatinine clearance < 40), albumin, prothrombin time, bilirubin, and evolution of bilirubin at day seven), performed better than the Child-Pugh score, discriminant function, or Glasgow score in predicting survival at six months.

Autoimmune hepatitis

Patients with serum aminotransferase levels greater than 10-fold the upper limit of normal should be treated. Patients with more modest elevations in aminotransferase and/or serum gamma globulin levels should also be treated if they are symptomatic and/or have significant interface hepatitis. Treatment is warranted in patients with histologic features of bridging necrosis or multiacinar necrosis. The presence of interface hepatitis without bridging necrosis or multiacinar necrosis on histologic examination may warrant treatment but does not compel it. Treatment may not be indicated in patients with inactive cirrhosis, preexistent comorbid conditions, or drug intolerances.

Initial therapy recommend for patients with autoimmune hepatitis who are eligible for treatment based upon the indications above receive treatment with immunosuppressive/immunomodulator therapy (Grade 1A). Corticosteroids are the mainstay of therapy. However, steroid-sparing with azathioprine or 6-MP is

used frequently. Possible starting therapy with corticosteroids alone unless there are significant contraindications (Grade 2C). Because combination therapy can result in fewer glucocorticoid side effects, azathioprine or 6-MP can be added if clinical and biochemical remission is not achieved in the initial three months of therapy. The treatment should be continued until remission, treatment failure, or the development of drug toxicity (Grade 2B). The optimal endpoint is to achieve sustained remission without the need for drug therapy, an endpoint achievable in 10 to 40 percent of patients. Remission is generally not observed before 12 months. Approximately 65 and 80 percent of patients achieve remission by 18 months and 3 years, respectively. The probability of remission decreases after two years. Patients who are refractory to or intolerant of immunosuppressive therapy and develop end stage liver disease require liver transplantation.

AMA positive autoimmune hepatitis treatment is usually initiated with 20 to 30 mg of prednisone (or its equivalent) per day. Younger patients with severe disease may sometimes require higher doses, which are associated with an increased risk of major side effects. In older patients, who may tolerate steroid side effects poorly, initial therapy using a combination of a glucocorticoids and azathioprine may be preferable.

The goal of therapy should be to obtain normal serum aminotransferase levels and histologic improvement. Normalization of serum aminotransferases usually occurs rapidly (often within one month), and within six months in almost all patients who are destined to respond. Once normal serum aminotransferases are established, patients are maintained on the lowest dose of corticosteroids possible to maintain normal values. In some cases (usually after one to two years) therapy may be withdrawn without subsequent relapse. Azathioprine may be effective as maintenance monotherapy although. Ursodeoxicholic acid (UDCA) 13 mg/kg per day alone may improve serum biochemical values. However, it is unclear if UDCA mitigates the necroinflammatory process and retards progression of the disease. It has been suggested that combining UDCA and corticosteroids has a synergistic effect. The role of other drugs is even less well defined. Corticosteroids alone are unlikely to result in clinical, biochemical, and histologic remission. Regimens that include corticosteroids with azathioprine may be more effective than corticosteroids alone. In children with refractory autoimmune liver disease, rescue therapy with mycophenolate mofetil appears to be less effective in those with autoimmune sclerosing cholangitis than in autoimmune hepatitis.

Wilson's disease

Patients with Wilson's disease require lifelong therapy. Discontinuation of therapy can lead to the development of fulminant hepatic failure. Treatment should be given in two phases: removing the tissue copper that has accumulated and then preventing reaccumulation. In asymptomatic patients identified through screening, should be treated with a chelating agent (such as penicillamine or trien-

tine) or with zinc (Grade 1B). Evolving consensus has been to use trientine because of its relatively favorable side-effect profile. Copper balance should be monitored regularly in such patients by obtaining a 24 hour urine collection and by estimating nonceruloplasmin bound copper. Symptomatic patients should be treated with a chelating agent (penicillamine or trientine) until stable. As noted above, trientine may be preferred, especially in patients with neurologic symptoms, since it appears to be less likely to exacerbate them. Patients typically require one to five years of higher-dose treatment after which they can be transitioned to maintenance therapy. Prior to the transition, patients should be clinically well, have normal serum aminotransferases, and hepatic synthetic function, nonceruloplasmin-bound copper in the normal range, and 24 hour urinary copper repeatedly in the range of 200 to 500 mcg (3 to 8 micromoles) per day.

Oral zinc interferes with the absorption of copper, providing a rationale for its use in Wilson's disease. Zinc induces metallothionein (an endogenous chelator of metals) in enterocytes, which has a greater affinity for copper than for zinc, causing it to bind luminal copper and thereby preventing its entry into the circulation. The bound copper is excreted fecally during normal turnover of enterocytes. Copper secreted from saliva and gastric and intestinal secretions is also bound, thereby further enhancing a negative copper balance. Zinc may also induce hepatic metallothionein. There are several forms of oral zinc salts, which probably have similar abilities to interfere with copper absorption, but differ in their tolerability. Zinc acetate causes the least gastrointestinal side-effects while gluconate is more tolerable than sulfate. The dose of zinc acetate in adults and older children is a total of 150 mg daily given in three divided doses. Twice daily dosing is also effective in patients who cannot comply with three times daily dosing.

Patients who have decompensated liver disease should be considered for liver transplantation.

11. PYELONEPHRITIS

Definitions and introduction

Urinary tract infections (UTIs) are common, especially in young children and sexually active women. By convention, UTI is defined as an infection either of the lower tract (acute cystitis) or upper tract (acute pyelonephritis and other renal infections). Despite the upper tract involvement in acute pyelonephritis, most episodes are generally considered to be uncomplicated. A complicated urinary tract infection, whether localized to the lower or upper tract, is associated with an underlying condition that increases the risk of failing therapy (such as obstruction, urologic dysfunction, or a multiply-resistant uropathogen). It is difficult to determine whether a patient with pyelonephritis or cystitis has a complicated or uncomplicated infection. However, an uncomplicated urinary tract infection is generally defined as

one occurring in a healthy, ambulatory nonpregnant woman; all other urinary tract infections may be considered complicated. Multiple factors are associated with complicated urinary tract infection that generally warrants both a broader spectrum antimicrobial for empiric therapy and, infrequently, consideration of surgical intervention. Acute pyelonephritis also must be distinguished from chronic pyelonephritis. Chronic pyelonephritis is an uncommon cause of chronic tubulointerstitial disease due to recurrent infection, such as infection in association with a chronically obstructing kidney stone, or vesicoureteral reflux (VUR).

Acute pyelonephritis is a potentially organ- and/or life-threatening infection that often leads to renal scarring. An episode of acute pyelonephritis may lead to significant renal damage (acute renal failure); abscess formation (eg, nephric, perinephric); sepsis; or sepsis syndrome, septic shock, and multiorgan system failure. Acute pyelonephritis develops in 20–30 % of pregnant women with untreated asymptomatic bacteriuria (ABU) (2–9.5 %), most often during the late second and early third trimesters. The incidence of pyelonephritis in infants and children is difficult to ascertain because of the infrequency of typical symptoms. Up to 25 % of children with UTI and no signs or symptoms of pyelonephritis do have bacteria demonstrable in the upper urinary tract. No racial predilection of pyelonephritis has been demonstrated. Pyelonephritis is significantly more common in females than in males, although this difference narrows considerably with increasing age, especially in patients aged 65 years and older. In females, pyelonephritis shows a trimodal distribution, with an elevated incidence in girls aged 0–4 years, a peak in women 15–35 years of age, and a gradual increase after age 50 years to another peak at 80 years of age. In males, the age distribution of pyelonephritis is bimodal. Males also demonstrate a peak incidence of pyelonephritis at 0–4 years of age. Rates gradually increase after 35 years of age and peak at 85 years of age.

Patogenesis: acute pyelonephritis results from bacterial invasion of the renal parenchyma. Bacteria usually reach the kidney by ascending from the lower urinary tract. In all age groups, episodes of bacteriuria occur commonly, but most are asymptomatic and do not lead to infection. The development of infection is influenced by bacterial factors and host factors. Bacteria may also reach the kidney via the bloodstream. Hematogenous sources of gram-positive organisms, such as Staphylococcus, are intravenous drug abuse and endocarditis.

Experimental evidence suggests that hematogenous spread of gram-negative organisms to the kidney is less likely unless an underlying problem exists, such as an obstruction. Little or no evidence supports lymphatic spread of uropathogens to the kidney. Most bacterial data are derived from research with Escherichia coli, which accounts for 70–90 % of uncomplicated UTIs and 21–54 % of complicated UTIs (ie, UTIs that are secondary to anatomic or functional abnormalities that impair urinary tract drainage; are associated with metabolic disorders; or involve unusual pathogens). A subset of E. coli, the uropathogenic E. coli (UPEC), also termed extraintestinal pathogenic E. coli (ExPEC), accounts for most clinical isolates from UTIs.UPEC derives commonly from the phylogenetic groups B2 and D, which express

distinctive O, K, and H antigens. UPEC genes encode several postulated virulence factors (VFs), including adhesins, siderophores, protectins, and toxins, as well as having the metabolic advantage of synthesizing essential substances.

Adhesins have specific regions that attach to cell receptor epitopes in a lock-and-key fashion. Mannose-sensitive adhesins (usually type 1 fimbriae) are present on essentially all E. coli. They contribute to colonization (eg, bladder, gut, mouth, vagina) and possibly pathogenesis of infection; however, they also attach to polymorphonuclear neutrophils (PMNs), leading to bacterial clearance.Mannose-resistant adhesins permit the bacteria to attach to epithelial cells, thereby resisting the cleansing action of urine flow and bladder emptying. They also allow the bacteria to remain in close proximity to the epithelial cell, enhancing the activity of other VFs. The P fimbriae family of adhesins is epidemiologically associated with prostatitis, pyelonephritis (70–90 % of strains), and sepsis. This family of adhesins is associated with less than 20 % of asymptomatic bacteriuria (ABU) strains. The AFA/Dr family is associated with diarrhea, UTI, and particularly pyelonephritis in pregnancy. The S/F1C family is associated with neonatal meningitis and UTI. Siderophores are involved in iron uptake, an essential element for bacteria, and possibly adhesion. Protectins and their contributions to virulence include the following:

- Lipopolysaccharide (LPS) coatings: resist phagocytosis.
- Tra T and Iss: resist action of complement.
- Omp T: cleave host defense proteins (eg, immunoglobulins).

Toxins, which affect various host cell functions, include the following:

- Alpha-hemolysin.
- Cytotoxic necrotizing factor-1.
- Cytolethal distending toxin.
- Secreted autotransporter toxin.

No single VF is sufficient or necessary to promote pathogenesis. Apparently, multiple VFs are necessary to ensure pathogenesis, although adhesins play an important role. As noted above, UPEC account for most uncomplicated pyelonephritis cases and a significant portion of complicated pyelonephritis cases.

The following microorganisms are also commonly isolated:

- Staphylococcus saprophyticus.
- Klebsiella pneumoniae.
- Proteus mirabilis.
- Enterococci.
- S aureus.
- Pseudomonas aeruginosa.
- Enterobacter species.

This is the same spectrum of organisms cultured in cystitis. In 10–15 % of symptomatic cystitis cases, cultures using routine methods remain negative, although the symptoms typically respond to antibiotic therapy. In some cases, cultures using selective media have grown Gardnerella vaginalis, Mycoplasma hominis, and Ureaplasma urealyticum. These data cannot be extended to acute pyelonephritis, but they do illustrate the difficulties in isolating the causative organism.

Evidence suggests that the pathogenesis of pyelonephritis takes a 2-step path. First, UPEC attaches to the epithelium and triggers an inflammatory response involving at least 2 receptors, glycosphingolipid (GSL) and Toll-like receptor 4 (TLR4). In the mouse model, GSL is the primary receptor and TLR4 is recruited and is an important receptor for the release of chemokines. When TLR4 is genetically absent, an asymptomatic carrier state develops in the infected mice. Second, as a result of the inflammatory response, chemokines (eg, interleukin-8 (IL-8), which is chemotactic for PMNs) are released and attach to the neutrophil-activating chemokine receptor 1 (CXCR1), allowing PMNs to cross the epithelial barrier into the urine. In children prone to pyelonephritis, for example, CXCR1 expression has been shown to be significantly lower than in control subjects. Several other host factors militate against symptomatic UTI. Phagocytosis of bacteria in urine is maximized at pH 6.5-7.5 and osmolality of 485 mOsm; values deviating from these ranges lead to significantly reduced or absent phagocytosis. Other important factors are the flushing action of urine flow in the ureter and bladder, the inhibition of attachment of type 1 fimbriae E. coli to uroepithelial cells by tubular cell–secreted Tamm-Horsfall protein, and the inhibition of attachment by some surface mucopolysaccharides on the uroepithelial cells.

Complicated UTI is an infection of the urinary tract in which the efficacy of antibiotics is reduced because of the presence of one or more of the following:

- Structural abnormalities of the urinary tract.
- Functional abnormalities of the urinary tract.
- Metabolic abnormalities predisposing to UTIs.
- Unusual pathogens.
- Recent antibiotic use.
- Recent urinary tract instrumentation.

Obstruction is the most important factor. It negates the flushing effect of urine flow; allows urine to pool (urinary stasis), providing bacteria a medium in which to multiply; and changes intrarenal blood flow, affecting neutrophil delivery. Obstruction may be extrinsic or intrinsic. Extrinsic obstruction occurs with chronic constipation (particularly in children), prostatic swelling/mass (eg, hypertrophy, infection, cancer), and retroperitoneal mass. Intrinsic obstruction occurs with bladder outlet obstruction, cystocele, fungus ball, papillary necrosis, stricture, and urinary stones. With increasing size of stone, the probability of stone passage decreases while the probability of obstruction increases. Nonetheless, stones as small as 2 mm have resulted in obstruction, while 8-mm stones have occasionally passed spontaneously.Infectious stones, urease stones, or triple-phosphate stones composed of magnesium ammonium phosphate or struvite and apatite account for 10–15 % of all urinary stones. They develop secondary to the action of urea-splitting organisms and can grow rapidly and branch out (ie, staghorn calculi). If left untreated, staghorn calculi will destroy the kidney and may cause the death of the patient. Complications include azotemia, hydropyonephrosis, perinephric abscess, pyelonephritis (severe or end-stage), sepsis, and xanthogranulomatous pyelonephritis. Incomplete bladder emptying may be related to medication (eg, anticholinergics). The spermicide nonoxynol-9 inhibits the growth of lactobacilli. Lactobacilli produce hydrogen peroxide, which protects

the vaginal ecosystem against pathogens. Frequent sexual intercourse causes local mechanical trauma to the urethra in both partners.

Atrophic vaginal mucosa in postmenopausal women predisposes to the colonization of urinary tract pathogens and UTIs because of the higher pH (5.5 vs 3.8) and the absence of lactobacilli. Bacterial prostatitis (acute or chronic) produces bacteriuria, whereas nonbacterial prostatitis and pelviperineal pain syndrome (prostadynia) do not.

Complications of obstruction with superimposed infection include hydronephrosis, pyonephrosis, urosepsis, and xanthogranulomatous pyelonephritis. Additionally, the pathogens can sequester in the struvite stones, protected from the host's immune system. Proteus species are the most common urea-splitting organisms. E. coli, Klebsiella, Pseudomonas, and Staphylococcus can also produce urease, however, and are sometimes involved in staghorn calculus formation.

Pregnancy produces hormonal and mechanical changes that predispose the woman to upper urinary traction infections. Hydroureter of pregnancy, secondary to both hormonal and mechanical factors, manifests as dilatation of the renal pelvis and ureters (greater on the left than on the right), with the ureters containing up to 200 mL of urine. Progesterone decreases ureteral peristalsis and increases bladder capacity. The enlarging uterus displaces the bladder, contributing to urinary stasis. Complicated UTI can result from one or more diverse factors.

Diabetes mellitus produces autonomic bladder neuropathy, glucosuria, leukocyte dysfunction, microangiopathy, and nephrosclerosis; additionally, it leads to recurrent bladder instrumentation secondary to the neuropathy. Complicated UTIs in patients who have diabetes mellitus include the following:

- Renal and perirenal abscess.
- Emphysematous pyelonephritis.
- Emphysematous cystitis.
- Fungal infections.
- Xanthogranulomatous pyelonephritis.
- Papillary necrosis.

Diagnosis

The classic presentation in patients with acute pyelonephritis is as follows:

- Fever — This is not always present, but when it is, it is not unusual for the temperature to exceed 103 °F (39.4 °C)
- Costovertebral angle pain — Pain may be mild, moderate, or severe; flank or costovertebral angle tenderness is most commonly unilateral over the involved kidney, although bilateral discomfort may be present
- Nausea and/or vomiting — These vary in frequency and intensity, from absent to severe; anorexia is common in patients with acute pyelonephritis

Gross hematuria (hemorrhagic cystitis), unusual in males with pyelonephritis, occurs in 30–40 % of females, most often young women, with the disorder.

Symptoms of acute pyelonephritis usually develop over hours or over the course of a day but may not occur at the same time. If the patient is male, elderly, or a child or has had symptoms for more than 7 days, the infection should be considered complicated until proven otherwise. The classic manifestations of acute pyelonephritis observed in adults are often absent in children, particularly neonates and infants. In children aged 2 years or younger, the most common signs and symptoms of urinary tract infection (UTI) are as follows:

- Failure to thrive.
- Feeding difficulty.
- Fever.
- Vomiting.

Elderly patients may present with typical manifestations of pyelonephritis, or they may experience the following:

- Fever.
- Mental status change.
- Decompensation in another organ system.
- Generalized deterioration.

In the outpatient setting, pyelonephritis is usually suggested by a patient's history and physical examination and supported by urinalysis results. Urine specimens can be collected through the following methods:

- Clean catch.
- Urethral catheterization.
- Suprapubic needle aspiration.

Urinalysis can include the following:

- Dipstick leukocyte esterase test (LET) — Helps to screen for pyuria.
- Nitrite production test (NPT) — To screen for bacteriuria.
- Examination for hematuria (gross and microscopic) and proteinuria.

Urine culture is indicated in any patient with pyelonephritis, whether treated in an inpatient or outpatient setting, because of the possibility of antibiotic resistance.

Imaging studies that may be used in assessing acute pyelonephritis include the following:

- Computed tomography (CT) scanning — To identify alterations in renal parenchymal perfusion; alterations in contrast excretion, perinephric fluid, and nonrenal disease; gas-forming infections; hemorrhage; inflammatory masses; and obstruction.
- Magnetic resonance imaging (MRI) — To detect renal infection or masses and urinary obstruction, as well as to evaluate renal vasculature.
- Ultrasonography — To screen for urinary obstruction in children admitted for febrile illnesses and to examine patients for renal abscesses, acute focal bacterial nephritis, and stones (in xanthogranulomatous pyelonephritis).
- Scintigraphy — To detect focal renal abnormalities.
- CT and MR urography — Used in the evaluation of hematuria.

Management

Antibiotic therapy is essential in the treatment of acute pyelonephritis and prevents progression of the infection. Urine culture and sensitivity testing should always be performed, and empirical therapy should be tailored to the infecting uropathogen.Patients presenting with complicated pyelonephritis should be managed as inpatients and treated empirically with broad-spectrum parenteral antibiotics.

Outpatient care: outpatient treatment is appropriate for patients who have an uncomplicated infection that does not warrant hospitalization. Patients presenting with acute pyelonephritis can be treated with a single dose of a parenteral antibiotic followed by oral therapy, provided that they are monitored within the first 48 hours.

Inpatient care: inpatient care includes the following:

- Supportive care.
- Monitoring of urine and blood culture results.
- Monitoring of comorbid conditions for deterioration.
- Maintenance of hydration status with IV fluids until hydration can be maintained with oral intake.
- IV antibiotics until defervescence and significant symptomatic improvement occur; convert to an oral regimen tailored to urine or blood culture results.

Surgery: in addition to antibiotics, surgery may be necessary to treat the following manifestations of acute pyelonephritis:

- Renal cortical abscess (renal carbuncle): Surgical drainage (if patients do not respond to antibiotic therapy); other surgical options are enucleation of the carbuncle and nephrectomy.
- Renal corticomedullary abscess: Incision and drainage, nephrectomy.
- Perinephric abscess: Drainage, nephrectomy.
- Calculi-related urinary tract infection (UTI): Extracorporeal shockwave lithotripsy (ESWL) or endoscopic, percutaneous, or open surgery.
- Renal papillary necrosis: CT scan — guided drainage or surgical drainage with debridement.
- Xanthogranulomatous pyelonephritis: Nephrectomy.
- Timely diagnosis and management of acute pyelonephritis has a significant impact on the outcome. Any patient with acute pyelonephritis who deteriorates suddenly or does not respond to conventional therapy may have a complication, resistant organism, or unrecognized comorbidity.
- Pyelonephritis causes considerable morbidity, but these data can only be extrapolated from the morbidity data for acute lower urinary tract infections. Specifically, acute cystitis in women produces approximately 6.1 days with symptoms, 2.4 days of restricted activity, 1.2 days that the patient is unable to work or attend class, and 0.4 days bedridden.
- For patients with pyelonephritis who have an organ-threatening infection, the follow-up examination is important to be sure that the patient is progressing satisfactorily and that recovery is complete. Failure to diagnose these complications in a timely fashion could predispose the patient to a poor outcome. Pregnant patients with pyelonephritis are at significant risk for premature labor.
- Mortality is higher in patients older than 65 years; it is also higher with septic shock, bedridden status, and immunosuppression. In men, mortality is also increased with use of antibiotics during the previous month. Morbidity (prolonged hospital stay) in both men and

women is increased with a change in initial treatment, diabetes mellitus, and long-term indwelling catheter.

Chronization ofrenal inflammation and fibrosis induced by recurrent or persistent renal infection, vesicoureteral reflux, or other causes of urinary tract obstruction. Chronic pyelonephritis is associated with progressive renal scarring, which can lead to end-stage renal disease — ESRD. Factors that may affect the pathogenesis of chronic pyelonephritis are as follows:

- The sex of the patient and his or her sexual activity.
- Pregnancy, which may lead to progression of renal injury with loss of renal function.
- Genetic factors.
- Bacterial virulence factors.
- Neurogenic bladder dysfunction.

Complications of chronic pyelonephritis can also include the following:

- Proteinuria.
- Focal glomerulosclerosis.
- Progressive renal scarring leading to end-stage renal disease.
- Xanthogranulomatous pyelonephritis(XPN) — May occur in approximately 8.2 % of cases and in 25 % of patients with pyonephrosis; XPN can be confused with renal cancer.
- Pyonephrosis — May occur in cases of obstruction.
- Progressive renal scarring (reflux nephropathy).

12. GLOMERULONEPHRITIS

Definitions and introduction

A large body of clinical, immunopathologic, and experimental data support the thesis that most forms of human glomerulonephritis (GN) result from immunologic mechanisms. The etiologic agents in human GN are largely unknown with the exception of infectious agents, such as beta streptococci in poststreptococcal GN, or hepatitis C virus in cryoglobulinemic membranoproliferative glomerulonephritis (MPGN). It is likely that most precipitating factors, such as infections, and drug and toxin exposures, initiate similar immune responses that result in GN via shared common pathways. The nature of the immune responses which lead to GN, and the individuals who develop them, are strongly influenced by immunogenetic phenotypes.

Bright initially described acute glomerulonephritis (GN) in 1927. Acute poststreptococcal glomerulonephritis (PSGN) is the archetype of acute GN. Acute nephritic syndrome is the most serious and potentially devastating form of the various renal syndromes. Acute GN comprises a specific set of renal diseases in which an immunologic mechanism triggers inflammation and proliferation of glomerular tissue that can result in damage to the basement

membrane, mesangium, or capillary endothelium. Hippocrates originally described the manifestation of back pain and hematuria, which lead to oliguria or anuria. With the development of the microscope, Langhans was later able to describe theese pathophysiologic glomerular changes.Acute GN is defined as the sudden onset of hematuria, proteinuria, and red blood cell (RBC) casts. This clinical picture is often accompanied by hypertension, edema, azotemia (ie, decreased glomerular filtration rate (GFR), and renal salt and water retention. Acute GN can be due to a primary renal disease or to a systemic disease.

GN represents 10–15 % of glomerular diseases. Variable incidence has been reported, in part because of the subclinical nature of the disease in more than half the affected population. Despite sporadic outbreaks, the incidence of PSGN has fallen over the past few decades. Factors responsible for this decline may include better health care delivery and improved socioeconomic conditions.GN comprises 25–30 % of all cases of end-stage renal disease (ESRD). About one fourth of patients present with acute nephritic syndrome. Most cases that progress do so relatively quickly, and end-stage renal failure may occur within weeks or months of the onset of acute nephritic syndrome. Asymptomatic episodes of PSGN exceed symptomatic episodes by a ratio of 3-4:1. Geographic and seasonal variations in the prevalence of PSGN are more marked for pharyngeally associated GN than for cutaneously associated disease.

Postinfectious GN can occur at any age but usually develops in children. Most cases occur in patients aged 5–15 years; only 10 % occur in patients older than 40 years. Outbreaks of PSGN are common in children aged 6–10 years. Acute nephritis may occur at any age, including infancy. Acute GN predominantly affects males (2:1 male-to-female ratio). Postinfectious GN has no predilection for any racial or ethnic group. A higher incidence (related to poor hygiene) may be observed in some socioeconomic groups.

Etiology: The causal factors that underlie acute GN can be broadly divided into infectious and noninfectious groups.The most common infectious cause of acute GN is infection by Streptococcus species (ie, group A, beta-hemolytic). Two types have been described, involving different serotypes:

- Serotype 12 — Poststreptococcal nephritis due to an upper respiratory infection, occurring primarily in the winter months.
- Serotype 49 — Poststreptococcal nephritis due to a skin infection, usually observed in the summer and fall and more prevalent in southern regions of the United States.

PSGN usually develops 1-3 weeks after acute infection with specific nephritogenic strains of group A beta-hemolytic streptococcus. The incidence of GN is approximately 5–10 % in persons with pharyngitis and 25 % in those with skin infections. Nonstreptococcal postinfectious GN may also result from infection by other bacteria, viruses, parasites, or fungi. Bacteria besides group A streptococci that can cause acute GN include diplococci, other streptococci, staphylococci, and mycobacteria. Salmonella typhosa, Brucella suis, Treponema pallidum, Corynebacterium bovis, and actinobacilli have also been identified. Cytomegalovirus (CMV), coxsackievirus, Epstein-Barr virus (EBV), hepatitis B virus (HBV), rubella, rickettsiae (as in scrub typhus), and mumps virus are accepted as viral causes only if it can be documented that a recent group A beta-hemolytic streptococcal infection did not occur. Acute GN has been documented as a rare complication of hepatitis A.Attributing glomerulonephritis to a parasitic or fungal etiology requires the exclusion of a streptococcal infection. Identified organisms include Coccidioides immitis and the following parasites: Plasmodium malariae, Plasmodium falciparum, Schistosoma mansoni, Toxoplasma gondii, filariasis, trichinosis, and trypanosomes.

Noninfectious causes of acute GN may be divided into primary renal diseases, systemic diseases, and miscellaneous conditions or agents. Multisystem systemic diseases that can cause acute GN include the following:

• Vasculitis (eg, Wegener granulomatosis) — This causes glomerulonephritis that combines upper and lower granulomatous nephritides).

• Collagen-vascular diseases (eg, systemic lupus erythematosus (SLE)) — This causes glomerulonephritis through renal deposition of immune complexes).

• Hypersensitivity vasculitis — This encompasses a heterogeneous group of disorders featuring small vessel and skin disease.

• Cryoglobulinemia — This causes abnormal quantities of cryoglobulin in plasma that result in repeated episodes of widespread purpura and cutaneous ulcerations upon crystallization.

• Polyarteritis nodosa — This causes nephritis from a vasculitis involving the renal arteries.

• Henoch-Schönlein purpura — This causes a generalized vasculitis resulting in glomerulonephritis.

• Goodpasture syndrome — This causes circulating antibodies to type IV collagen and often results in a rapidly progressive oliguric renal failure (weeks to months).

Primary renal diseases that can cause acute GN include the following:

• Membranoproliferative glomerulonephritis (MPGN) — This is due to the expansion and proliferation of mesangial cells as a consequence of the deposition of complements. Type I refers to the granular deposition of C3; type II refers to an irregular process.

• Berger disease (IgG-immunoglobulin A (IgA) nephropathy) — This causes GN as a result of diffuse mesangial deposition of IgA and IgG.

• «Pure» mesangial proliferative GN.

• Idiopathic rapidly progressive glomerulonephritis — This form of GN is characterized by the presence of glomerular crescents. Three types have been distinguished: Type I is an antiglomerular basement membrane disease, type II is mediated by immune complexes, and type III is identified by antineutrophil cytoplasmic antibody (ANCA).

Miscellaneous noninfectious causes of acute GN include the following:

• Guillain-Barré syndrome.

• Irradiation of Wilms tumor.

• Diphtheria-pertussis-tetanus (DPT) vaccine.

• Serum sickness.

• Epidermal growth factor receptor activation and possibly to its inhibitor cetuximab.

• Glomerular lesions in acute GN are the result of glomerular deposition or in situ formation of immune complexes. On gross appearance, the kidneys may be enlarged up to 50 %. Histopathologic changes include swelling of the glomerular tufts and infiltration with polymorphonucleocytes (see Histologic Findings). Immunofluorescence reveals deposition of immunoglobulins and complement.

• Except in PSGN, the exact triggers for the formation of the immune complexes are unclear. In PSGN, involvement of derivatives of streptococcal proteins has been reported. A streptococcal neuraminidase may alter host immunoglobulin G (IgG). IgG combines with host antibodies. IgG/anti-IgG immune complexes are formed and then collect in the glomeruli. In addition, eleva-

tions of antibody titers to other antigens, such as antistreptolysin O or antihyaluronidase, DNAase-B, and streptokinase, provide evidence of a recent streptococcal infection.

Structural and functional changes: acute GN involves both structural changes and functional changes. Structurally, cellular proliferation leads to an increase in the number of cells in the glomerular tuft because of the proliferation of endothelial, mesangial, and epithelial cells. The proliferation may be endocapillary (ie, within the confines of the glomerular capillary tufts) or extracapillary (ie, in the Bowman space involving the epithelial cells). In extracapillary proliferation, proliferation of parietal epithelial cells leads to the formation of crescents, a feature characteristic of certain forms of rapidly progressive GN. Leukocyte proliferation is indicated by the presence of neutrophils and monocytes within the glomerular capillary lumen and often accompanies cellular proliferation. Glomerular basement membrane thickening appears as thickening of capillary walls on light microscopy. On electron microscopy, this may appear as the result of thickening of basement membrane proper (eg, diabetes) or deposition of electron-dense material, either on the endothelial or epithelial side of the basement membrane. Electron-dense deposits can be subendothelial, subepithelial, intramembranous, or mesangial, and they correspond to an area of immune complex deposition. Hyalinization or sclerosis indicates irreversible injury. These structural changes can be focal, diffuse or segmental, or global. Functional changes include proteinuria, hematuria, reduction in GFR (ie, oligoanuria), and active urine sediment with RBCs and RBC casts. The decreased GFR and avid distal nephron salt and water retention result in expansion of intravascular volume, edema, and, frequently, systemic hypertension.

Poststreptococcal glomerulonephritis

Streptococcal M-protein was previously believed to be responsible for PSGN, but the studies on which this belief was based have been discounted. Nephritis-associated streptococcal cationic protease and its zymogen precursor (nephritis-associated plasmin receptor (NAPlr)) have been identified as a glyceraldehyde-3-phosphate dehydrogenase that functions as a plasmin(ogen) receptor. Immunofluorescence staining of the renal biopsy tissues with anti-NAPlr antibody revealed glomerular NAPlr deposition in early-phase acute PSGN, and glomerular plasmin activity was almost identical to NAPlr deposition in renal biopsy tissues of acute PSGN patients. These data suggest that NAPlr may contribute to the pathogenesis of acute PSGN by maintaining plasmin activity. Antibody levels to NAPR are elevated in streptococcal infections (of group A, C, and G) associated with GN but are not elevated in streptococcal infections without GN, whereas anti-streptolysin-O titers are elevated in both circumstances. These antibodies to NAPR persist for years and perhaps are protective against further episodes of PSGN. In a study in adults, the 2 most frequently identified infectious agents were streptococci (27.9 %) and staphylococci (24.4 %).

The prognosis depends on the underlying disease and the overall health of the patient. Most epidemic cases follow a course ending in complete patient recovery (as many as 100 %). The mortality of acute GN in the most commonly affected age group, pediatric patients, has been reported at 0–7 %.Sporadic cases of acute nephritis often progress to a chronic form. This progression occurs in as many as 30 % of adult patients and 10 % of pediatric patients. GN is the cause of chronic renal failure in 25 %. The condition is characterized by irreversible and progressive glomerular and tubulointerstitial fibrosis, ultimately leading to a reduction in

the glomerular filtration rate (GFR) and retention of uremic toxins. If disease progression is not halted with therapy, the net results are chronic kidney disease (CKD), end-stage renal disease (ESRD), and cardiovascular disease. The diagnosis of CKD can be made without knowledge of the specific cause. At the later stages of glomerular injury, biopsy results cannot help distinguish the primary disease. Histology and clues to the etiology are often derived from other systemic diseases (if present). Considerable cause-specific variability is observed in the rate at which acute glomerulonephritis progresses to chronic glomerulonephritis. The progression from acute glomerulonephritis to chronic glomerulonephritis is variable, depending to a considerable extent on the cause of the condition. Whereas complete recovery of renal function is the rule for patients with poststreptococcal glomerulonephritis, several other glomerulonephritides, such as immunoglobulin A (IgA) nephropathy, often have a relatively benign course, and many do not progress to ESRD. Progression patterns may be summarized as follows:

- Rapidly progressive glomerulonephritis or crescentic glomerulonephritis — About 90 % of patients progress to ESRD within weeks or months.
- Focal segmental glomerulosclerosis: — about 80 % of patients progress to ESRD in 10 years; patients with the collapsing variant (malignant focal segmental glomerulosclerosis) have a more rapid progression; this form may be idiopathic or related to HIV infection.
- Membranous nephropathy — About 20–30% of patients with membranous nephropathy progress to chronic renal failure (CRF) and ESRD in 10 years.
- Membranoproliferative glomerulonephritis: — About 40 % of patients with membranoproliferative glomerulonephritis progress to CRF and ESRD in 10 years.
- IgA nephropathy — About 10 % of patients with IgA nephropathy progress to CRF and ESRD in 10 years.
- Poststreptococcal glomerulonephritis — About 1–2 % of patients with poststreptococcal glomerulonephritis progress to CRF and ESRD; older children who present with crescentic glomerulonephritis are at greatest risk.
- Lupus nephritis — Overall, about 20 % of patients with lupus nephritis progress to CRF and ESRD in 10 years; however, patients with certain histologic variants (eg, class IV) may have a more rapid decline.

Pathophysiology: reduction in nephron mass from the initial injury reduces the GFR. This reduction leads to hypertrophy and hyperfiltration of the remaining nephrons and to the initiation of intraglomerular hypertension. These changes occur in order to increase the GFR of the remaining nephrons, thus minimizing the functional consequences of nephron loss. The changes, however, are ultimately detrimental because they lead to glomerulosclerosis and further nephron loss. In early renal disease (stages 1-3), a substantial decline in the GFR may lead to only slight increases in serum creatinine levels. Azotemia (ie, a rise in blood urea nitrogen (BUN) and serum creatinine levels) is apparent when the GFR decreases to less than 60–70 mL/min. In addition to a rise in BUN and creatinine levels, the substantial reduction in the GFR results in the following:

- Decreased production of erythropoietin, thus resulting in anemia.
- Decreased production of vitamin D, resulting in hypocalcemia, secondary hyperparathyroidism, hyperphosphatemia, and renal osteodystrophy.
- Reduction in acid, potassium, salt, and water excretion, resulting in acidosis, hyperkalemia, hypertension, and edema.
- Platelet dysfunction, leading to increased bleeding tendencies.

Accumulation of toxic waste products (uremic toxins) affects virtually all organ systems. Azotemia occurring with the signs and symptoms listed above is known as uremia. Uremia occurs at a GFR of approximately 10 mL/min. Some of these toxins (eg, BUN, creati-

nine, phenols, and guanidines) have been identified, but none has been found to be responsible for all the symptoms.

Treatment

Discontinuation of the potential causative agent is a mainstay of therapy, and immunosuppressive therapy has been employed if there is no subsequent improvement in kidney function.

Most original research focuses on acute poststreptococcal glomerulonephritis (PSGN). Treatment of PSGN is mainly supportive, because there is no specific therapy for renal disease. When acute GN is associated with acute infection, the underlying infections must be treated (antibiotics in case of acute PSGN).

Membranous nephropathy (MN) is often idiopathic but may also be caused by drugs and underlying diseases. For patients who remain at low risk of progression over a six-month period, recommend continued observation rather than administering immunosuppressive therapy (Grade 1B). Such patients should be periodically monitored every three months for two years and twice yearly thereafter to assess for disease progression that might warrant therapy. For patients who remain at moderate risk for progression and do not continue to show a progressive decline in proteinuria at six months, recommend the initiation of immunosuppressive therapy rather than continued observation (Grade 1B). For moderate risk patients with a progressive decline in protein excretion over this period that remains above 4 g/day, we suggest immunosuppressive therapy rather than continued observation (Grade 2C). However, some clinicians would continue to withhold immunosuppressive therapy beyond six months in such patients who are doing well. If immunosuppressive therapy is administered, recommend either a cytotoxic-based or calcineurin inhibitor-based regimen rather than other therapies (Grade 1B). The choice between a cytotoxic-based or calcineurin inhibitor-based regimen depends primarily upon clinician and patient preference, after a thorough discussion of the potential benefits and risks. As an example, calcineurin inhibitor-based therapy may be preferred among those who elect to avoid toxicity of cytotoxic agents, such as the risk of decreased fertility. If a cytotoxic-based therapy is chosen, recommend a cyclophosphamide-based regimen rather than chlorambucil because of a lower rate of side effects (Grade 1B). If a calcineurin-based therapy is chosen, the administration of either cyclosporine or tacrolimus is largely based upon patient preference. As an example, tacrolimus may be preferred among those who wish to avoid some of the side effects commonly observed with cyclosporine, such as hirsutism or gingival hypertrophy. Patients treated with either a cyclophosphamide or a calcineurin inhibitor-based regimen are considered unresponsive if a substantial reduction in proteinuria (30 to 50 percent from peak levels) is not observed after four to six months of therapy. Among those who do not respond to initial treatment with a cyclophosphamide or a calcineurin inhibitor-based regimen, we suggest treatment with the other regimen (Grade 2C). The dosing regimens are the same as those described for initial therapy, as tolerated. For patients initially

treated with cytotoxic therapy, we usually wait three to six months after the cessation of cytotoxic therapy before initiating a calcineurin inhibitor, unless the patient has severe symptoms or a rise in serum creatinine. For patients who remain at high risk of progression over a three-month observation period and have normal or near normal renal function (defined as a creatinine clearance above 80 mL/min), recommend the initiation of immunosuppressive therapy rather than continued observation (Grade 1B). With immunosuppressive therapy, recommend either a cytotoxic-based or calcineurin inhibitor-based regimen rather than other therapies (Grade 1B). The choice between a cyclophosphamide-based or calcineurin inhibitor-based regimen depends principally upon clinician and patient preference. As an example, calcineurin inhibitor-based therapy may be preferred among those who elect to avoid toxicity of cytotoxic agents, such as the risk of reduced fertility. Among patients considered to be at high risk because of reduced renal function that is considered due to MN, recommend the initiation of immunosuppressive therapy without delay with either a cyclophosphamide-based or a calcineurin inhibitor-based regimen rather than other therapies (Grade 1B). The choice between these regimens depends primarily upon clinician and patient preference, after a thorough discussion of the potential benefits and risks. Dose adjustments may be needed for patients with impaired renal function.

Better not use immunosuppressive therapy in patients with substantial chronic interstitial fibrosis and/or vascular disease, unless these findings can be explained by concurrent disease (eg, hypertension, diabetes). Such findings would be unlikely to be due to MN if they were present on the initial biopsy.

Rituximab can be considered after a careful evaluation of the potential risks and benefits of further immunosuppression. A clinically relevant response may be less likely in patients with a creatinine clearance below 75 mL/min per 1.73 m^2.

Most cases of acute interstitial nephritis (AIN) are allergic reactions as suggested by the following: the majority of the immune reactions are directly to drugs or drug-induced antigens; systemic manifestations of hypersensitivity are often present; AIN is not a dose-dependent phenomenon and only a small percentage of patients develop the condition; AIN typically improves following cessation of the drug; and AIN may rapidly recur with accidental re-exposure to the drug or a closely related antigen. Given these considerations, the most important aspect of therapy of AIN is cessation of the potentially offending agent (or treatment of the underlying infection). Immunosuppressive therapy has been employed to treat AIN that persists despite discontinuation of the offending agent. Given the potential for benefit and the relative safety of short-term therapy, reasonable to treat patients with corticosteroids if they do not have significant improvement in the serum creatinine within three to seven days after discontinuation of the offending agent. In such cases, a renal biopsy is preferred to confirm AIN, as well as to exclude other possible diseases or interstitial nephritis with significant chronic damage (eg, marked interstitial fibrosis, tubular atrophy, and minim-

al or no acute inflammation), in which case immunosuppressive therapy might not be indicated. An empiric trial of glucocorticoid therapy is a reasonable alternative in patients with a strongly suggestive history of acute drug-induced AIN when kidney biopsy is not feasible. Approach is to administer prednisone at a dose of 1 mg/kg per day (to a maximum of 40 to 60 mg) for a minimum of one to two weeks, beginning a gradual taper after the serum creatinine has returned to or near baseline, for a total therapy duration of two to three months. Most patients will improve in the first one to two weeks. In patients with more severe acute renal failure, therapy may be initiated with intravenous methylprednisolone (0.5 to 1 g/day for three days).

There is limited experience with treating AIN in patients who are glucocorticoid-dependent (ie, relapse during the prednisone taper), glucocorticoid-resistant (as with NSAID-induced disease), or cannot tolerate glucocorticoids. There are case reports and small series using mycophenolate mofetil (MMF) and cyclosporine. MMF may be considered only in patients who are glucocorticoid-dependent, glucocorticoid-resistant, or unable to tolerate glucocorticoid therapy and have biopsy-proven AIN.

13. CHRONIC KIDNEY DISEASE

Definitions and classification

The definitions and classification of chronic kidney disease (CKD) guidelines were introduced by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (KDOQI) in 2002, and were subsequently adopted with minor modifications by the international guideline group Kidney Disease Improving Global Outcomes (KDIGO) in 2004. These CKD guidelines shifted the concept of kidney disease from that of an uncommon life-threatening condition requiring care by nephrologists to that of a common condition with a range of severity meriting attention by general internists, and demanding strategies for prevention, early detection, and management. The guidelines had a major effect on clinical practice, research, and public health, but also generated substantial controversy.

Controversies addressed by the new guidelines: in 2009, KDIGO convened a Controversies Conference to address key areas of controversy and review data on more than 1.5 million individuals from 45 cohorts that was assembled by the CKD Prognosis Consortium. Conference attendees recommended, by at least a two-thirds majority vote, that the previous KDOQI and KDIGO definitions of CKD be retained, but that the classification be modified to include the cause of disease and albuminuria staging.

Chronic kidney disease (CKD) is a common condition in which there is a loss of kidney function over time. CKD is associated with an increased risk of cardiovascular disease and chronic renal failure.

Causes of CKD include the following:

- Diabetic kidney disease.
- Hypertension.
- Vascular disease.
- Glomerular disease (primary or secondary).
- Cystic kidney diseases.
- Tubulointerstitial disease.
- Urinary tract obstruction or dysfunction.
- Recurrent kidney stone disease.
- Congenital (birth) defects of the kidney or bladder.
- Unrecovered acute kidney injury.

Vascular diseases that can cause CKD include the following:

- Renal artery stenosis.
- Cytoplasmic pattern antineutrophil cytoplasmic antibody (C-ANCA)–positive and perinuclear pattern antineutrophil cytoplasmic antibody (P-ANCA)–positive vasculitides.
- ANCA-negative vasculitides.
- Atheroemboli.
- Hypertensive nephrosclerosis.
- Renal vein thrombosis.

Primary glomerular diseases include the following:

- Membranous nephropathy.
- Alport syndrome.
- Immunoglobulin A (IgA) nephropathy.
- Focal and segmental glomerulosclerosis (FSGS).
- Minimal change disease.
- Membranoproliferative glomerulonephritis (MPGN).
- Complement-related diseases (eg, atypical hemolytic-uremic syndrome (HUS), dense deposit disease).
- Rapidly progressive (crescentic) glomerulonephritis.

Secondary causes of glomerular disease include the following:

- Diabetes mellitus.
- Systemic lupus erythematosus.
- Rheumatoid arthritis.
- Mixed connective tissue disease.
- Scleroderma.
- Wegener granulomatosis.
- Mixed cryoglobulinemia.
- Endocarditis.
- Hepatitis B and C.
- Syphilis.
- Human immunodeficiency virus (HIV).
- Parasitic infection.

- Heroin use.
- Gold.
- Penicillamine.
- Amyloidosis.
- Light-chain deposition disease.
- Neoplasia.
- Thrombotic thrombocytopenic purpura (TTP).
- Shiga-toxin or Streptococcus pneumoniae – related HUS.
- Henoch-Schönlein purpura.
- Reflux nephropathy.

Causes of tubulointerstitial disease include the following:

- Drugs (eg, sulfonamides, allopurinol).
- Infection (viral, bacterial, parasitic).
- Sjögren syndrome.
- Tubulointerstitial nephritis and uveitis (TINU) syndrome.
- Chronic hypokalemia.
- Chronic hypercalcemia.
- Sarcoidosis.
- Multiple myeloma cast nephropathy.
- Heavy metals.
- Radiation nephritis.
- Polycystic kidneys.
- Cystinosis and other inherited diseases.

Urinary tract obstruction may result from any of the following:

- Benign prostatic hypertrophy.
- Urolithiasis (kidney stones).
- Urethral stricture.
- Tumors.
- Neurogenic bladder.
- Congenital (birth) defects of the kidney or bladder.
- Retroperitoneal fibrosis.

Pathophysiology: a normal kidney contains approximately 1 million nephrons, each of which contributes to the total glomerular filtration rate (GFR). In the face of renal injury (regardless of the etiology), the kidney has an innate ability to maintain GFR, despite progressive destruction of nephrons, as the remaining healthy nephrons manifest hyperfiltration and compensatory hypertrophy. This nephron adaptability allows for continued normal clearance of plasma solutes. Plasma levels of substances such as urea and creatinine start to show measurable increases only after total GFR has decreased to 50 %.The plasma creatinine value will approximately double with a 50 % reduction in GFR. For example, a rise in plasma creatinine from a baseline value of 0.6 mg/dL to 1.2 mg/dL in a patient, although still within the adult reference range, actually represents a loss of 50 % of functioning nephron mass. The hyperfiltration and hypertrophy of residual nephrons, although beneficial for the reasons noted, has been hypothesized to represent a major cause of progressive renal dysfunction. The increased glome-

rular capillary pressure may damage the capillaries, leading initially to secondary focal and segmental glomerulosclerosis (FSGS) and eventually to global glomerulosclerosis. This hypothesis is supported by studies of five-sixths nephrectomized rats, which develop lesions identical to those observed in humans with CKD. Factors other than the underlying disease process and glomerular hypertension that may cause progressive renal injury include the following:

- Systemic hypertension.
- Nephrotoxins (eg, nonsteroidal anti-inflammatory drugs (NSAIDs), intravenous contrast media).
- Decreased perfusion (eg, from severe dehydration or episodes of shock).
- Proteinuria (in addition to being a marker of CKD).
- Hyperlipidemia.
- Hyperphosphatemia with calcium phosphate deposition.
- Smoking.
- Uncontrolled diabetes.

Aging and renal function: the biologic process of aging initiates various structural and functional changes within the kidney. Renal mass progressively declines with advancing age, and glomerulosclerosis leads to a decrease in renal weight. Histologic examination is notable for a decrease in glomerular number of as much as 30–50 % by age 70 years. The GFR peaks during the third decade of life at approximately 120 mL/min/1.73 m^2; it then undergoes an annual mean decline of approximately 1 mL/min/y/1.73 m^2, reaching a mean value of 70 mL/min/1.73 m^2 at age 70 years. Ischemic obsolescence of cortical glomeruli is predominant, with relative sparing of the renal medulla. Juxtamedullary glomeruli see a shunting of blood from afferent to efferent arterioles, resulting in redistribution of blood flow favoring the renal medulla. These anatomic and functional changes in renal vasculature appear to contribute to an age-related decrease in renal blood flow. Renal hemodynamic measurements in aged humans and animals suggest that altered functional response of the renal vasculature may be an underlying factor in diminished renal blood flow and increased filtration noted with progressive renal aging. The vasodilatory response is blunted in the elderly when compared to younger patients. However, the vasoconstrictor response to intrarenal angiotensin is identical in young and older human subjects. A blunted vasodilatory capacity with appropriate vasoconstrictor response may indicate that the aged kidney is in a state of vasodilatation to compensate for the underlying sclerotic damage. Given the histologic evidence for nephronal senescence with age, a decline in the GFR is expected. However, a wide variation in the rate of GFR decline is reported because of measurement methods, race, gender, genetic variance, and other risk factors for renal dysfunction.

Genetics: most cases of CKD are acquired rather than inherited, although CKD in a child is more likely to have a genetic or inherited cause. Well-described genetic syndromes associated with CKD include autosomal dominant polycystic kidney disease (ADPKD) and Alport syndrome. Other examples of specific single-gene or few-gene mutations associated with CKD include Dent disease, nephronophthisis, and atypical hemolytic uremic syndrome (HUS).

APOL1 gene: More recently, researchers have begun to identify genetic contributions to increased risk for development or progression of CKD.

FGF-23 gene: Circulating levels of the phosphate-regulating hormone fibroblast growth factor 23 (FGF-23) are affected by variants in the FGF23 gene.

Single-nucleotide polymorphisms associated with variation in GFR found that development of albuminuria was associated mostly with an SNP in the SHROOM3 gene.

Immune-system and RAS genes: a number of genes have been associated with the development of ESRD. Many of these genes involve aspects of the immune system (eg, CCR3, IL1RN, IL4).

Unsurprisingly, polymorphisms in genes involving the renin-angiotensin system (RAS) have also been implicated in predisposition to CKD.

Hyperkalemia: the ability to maintain potassium excretion at near-normal levels is generally maintained in CKD, as long as aldosterone secretion and distal flow are maintained. Another defense against potassium retention in patients with CKD is increased potassium excretion in the gastrointestinal tract, which also is under control of aldosterone. Hyperkalemia usually does not develop until the GFR falls to less than 20–25 mL/min/1.73 m², at which point the kidneys have decreased ability to excrete potassium. Hyperkalemia can be observed sooner in patients who ingest a potassium-rich diet or have low serum aldosterone levels. Common sources of low aldosterone levels are diabetes mellitus and the use of ACE inhibitors or NSAIDs. Hyperkalemia in CKD can be aggravated by an extracellular shift of potassium, such as occurs in the setting of acidemia or from lack of insulin.

Hypokalemia is uncommon but can develop in patients with very poor intake of potassium, gastrointestinal or urinary loss of potassium, or diarrhea or in patients who use diuretics.

Metabolic acidosis often is a mixture of normal anion gap and increased anion gap In CKD, the kidneys are unable to produce enough ammonia in the proximal tubules to excrete the endogenous acid into the urine in the form of ammonium. In stage 5 CKD, accumulation of phosphates, sulfates, and other organic anions are the cause of the increase in anion gap. Metabolic acidosis has been shown to have deleterious effects on protein balance, leading to the following:

- Negative nitrogen balance.
- Increased protein degradation.
- Increased essential amino acid oxidation.
- Reduced albumin synthesis.
- Lack of adaptation to a low-protein diet.

Hence, metabolic acidosis is associated with protein-energy malnutrition, loss of lean body mass, and muscle weakness. The mechanism for reducing protein may include effects on adenosine triphosphate (ATP) – dependent ubiquitin proteasomes and increased activity of branched-chain keto acid dehydrogenases. Metabolic acidosis also leads to an increase in fibrosis and rapid progression of kidney disease, by causing an increase in ammoniagenesis to enhance hydrogen excretion. In addition, metabolic acidosis is a factor in the development of renal osteodystrophy, because bone acts as a buffer for excess acid, with resultant loss of mineral. Acidosis may interfere with vitamin D metabolism, and patients who are persistently more acidotic are more likely to have osteomalacia or low-turnover bone disease.

Salt- and water-handling abnormalities: salt and water handling by the kidney is altered in CKD. Extracellular volume expansion and total-body volume overload results from failure of sodium and free-water excretion. This generally becomes clinically manifested when the GFR falls to less than 10–15 mL/min/1.73 m², when compensatory mechanisms have become exhausted. As kidney function declines further, sodium retention and extracellular volume expansion lead to peripheral edema and, not uncommonly, pulmonary edema and hypertension. At a higher GFR, excess sodium and water intake could result in a similar picture if the ingested amounts of sodium and water exceed the available potential for compensatory excretion. Tubulointerstitial renal diseases represent the minority of cases of CKD. However, it is important to note that such diseases often cause fluid loss rather than overload. Thus, despite moderate or severe reductions in GFR, tubulointerstitial renal diseases may manifest first as polyuria and volume depletion, with inability to concentrate the urine. These symptoms may

be subtle and require close attention to be recognized. Volume overload occurs only when GFR reduction becomes very severe.

Anemia: normochromic normocytic anemia principally develops from decreased renal synthesis of erythropoietin, the hormone responsible for bone marrow stimulation for red blood cell (RBC) production. The anemia starts early in the course of the disease and becomes more severe as, with the shrinking availability of viable renal mass, the GFR progressively decreases. No reticulocyte response occurs. RBC survival is decreased, and bleeding tendency is increased from the uremia-induced platelet dysfunction. Other causes of anemia in CKD include the following:

- Chronic blood loss: Uremia-induced platelet dysfunction enhances bleeding tendency.
- Secondary hyperparathyroidism.
- Inflammation.
- Nutritional deficiency.
- Accumulation of inhibitors of erythropoiesis.

Bone disease: renal bone disease is a common complication of CKD. It results in skeletal complications (eg, abnormality of bone turnover, mineralization, linear growth) and extraskeletal complications (eg, vascular or soft-tissue calcification). Different types of bone disease occur with CKD, as follows:

- High-turnover bone disease from high parathyroid hormone (PTH) levels.
- Low-turnover bone disease (adynamic bone disease).
- Defective mineralization (osteomalacia).
- Mixed disease.
- Beta-2-microglobulin–associated bone disease.

Bone disease in children is similar but occurs during growth. Therefore, children with CKD are at risk for short stature, bone curvature, and poor mineralization («renal rickets» is the equivalent term for adult osteomalacia). CKD-mineral and bone disorder (CKD-MBD) involves biochemical abnormalities related to bone metabolism. CKD-MBD may result from alteration in levels of serum phosphorus, PTH, vitamin D, and alkaline phosphatase. Secondary hyperparathyroidism develops in CKD because of the following factors:

- Hyperphosphatemia.
- Hypocalcemia.
- Decreased renal synthesis of 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D, or calcitriol).
- Intrinsic alteration in the parathyroid glands, which gives rise to increased PTH secretion and increased parathyroid growth.
- Skeletal resistance to PTH.

Calcium and calcitriol are primary feedback inhibitors; hyperphosphatemia is a stimulus to PTH synthesis and secretion.

Hyperphosphatemia and hypocalcemia: phosphate retention begins in early CKD; when the GFR falls, less phosphate is filtered and excreted, but because of increased PTH secretion, which increases renal excretion, serum levels do not rise initially. As the GFR falls toward CKD stages 4-5, hyperphosphatemia develops from the inability of the kidneys to excrete the excess dietary intake. Hyperphosphatemia suppresses the renal hydroxylation of inactive 25-hydroxyvitamin D to calcitriol, so serum calcitriol levels are low when the GFR is less than 30 mL/min/1.73 m². Increased phosphate concentration also effects PTH concentration by its direct effect on the parathyroid glands (posttranscriptional effect). Hypocalcemia develops primarily from decreased intestinal calcium absorption because of low plasma calcitriol levels. It also possibly results from increased calcium-phosphate binding, caused by elevated serum phosphate levels.

Increased PTH secretion: Low serum calcitriol levels, hypocalcemia, and hyperphosphatemia have all been demonstrated to independently trigger PTH synthesis and secretion. As these stimuli persist in CKD, particularly in the more advanced stages, PTH secretion becomes maladaptive, and the parathyroid glands, which initially hypertrophy, become hyperplastic. The persistently elevated PTH levels exacerbate hyperphosphatemia from bone resorption of phosphate.

Skeletal manifestations: if serum levels of PTH remain elevated, a high−bone turnover esion, known as osteitis fibrosa, develops. This is one of several bone lesions, which as a group are commonly known as renal osteodystrophy and which develop in patients with severe CKD. Osteitis fibrosa is common in patients with ESRD.The prevalence of adynamic bone disease in the United States has increased, and it has been described before the initiation of dialysis in some cases. The pathogenesis of adynamic bone disease is not well defined, but several factors may contribute, including high calcium load, use of vitamin D sterols, increasing age, previous corticosteroid therapy, peritoneal dialysis, and increased level of N-terminally truncated PTH fragments. Low-turnover osteomalacia in the setting of CKD is associated with aluminum accumulation. It is markedly less common than high-turnover bone disease. Another form of bone disease is dialysis-related amyloidosis, which is now uncommon in the era of improved dialysis membranes. This condition occurs from beta-2-microglobulin accumulation in patients who have required chronic dialysis for at least 8–10 years. It manifests with cysts at the ends of long bones.

Staging of CKD: the different stages of CKD form a continuum. The Kidney Disease Outcomes Quality Initiative (KDOQI) classification of the stages of CKD is as follows:

- Stage 1: Kidney damage with normal or increased GFR (> 90 mL/min/1.73 m^2).
- Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m^2).
- Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m^2).
- Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m^2).
- Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m^2 or dialysis).

In stage 1 and stage 2 CKD, reduced GFR alone does not clinch the diagnosis, because the GFR may in fact be normal or borderline normal. Other markers of kidney damage, including abnormalities in the composition of blood or urine or structural abnormalities visualized by imaging studies, establish the diagnosis in such cases. Hypertension is a frequent sign of CKD but should not by itself be considered a marker of it, because elevated blood pressure is also common among people without CKD. In an update of its CKD classification system, the National Kidney Foundation (NKF) advised that GFR and albuminuria levels be used together, rather than separately, to improve prognostic accuracy in the assessment of CKD. More specifically, the guidelines recommended the inclusion of estimated GFR and albuminuria levels when evaluating risks for overall mortality, cardiovascular disease, end-stage kidney failure, acute kidney injury, and the progression of CKD. Referral to a kidney specialist was recommended for patients with a very low GFR (< 15 mL/min/1.73 m²) or very high albuminuria (>300 mg/24 h). Patients with stages 1-3 CKD are frequently asymptomatic. Clinical manifestations resulting from low kidney function typically appear in stages 4–5.

Albuminuria: the three albuminuria stages follow familiar definitions of «normal», «high» (formerly microalbuminuria), and «very high» (formerly macroalbuminuria and nephrotic range) albuminuria:

A1 — ACR <30 mg/g (< 3.4 mg/mmol).

A2 — ACR 30 to 300 mg/g (3.4 to 34.0 mg/mmol).

A3 — ACR >300 mg/g (>34.0 mg/mmol).

Diagnosis

Signs and symptoms: patients with CKD stages 1–3 (GFR > 30 mL/min/1.73 m²) are generally asymptomatic. Typically, it is not until stages 4–5 (GFR < 30 mL/min/ 1.73 m²) that endocrine/metabolic derangements or disturbances in water or electrolyte balance become clinically manifest. Signs of metabolic acidosis in stage 5 CKD include the following:

- Protein-energy malnutrition.
- Loss of lean body mass.
- Muscle weakness.

Signs of alterations in the way the kidneys are handling salt and water in stage 5 include the following:

- Peripheral edema.
- Pulmonary edema.
- Hypertension.

Anemia in CKD is associated with the following:

- Fatigue.
- Reduced exercise capacity.
- Impaired cognitive and immune function.
- Reduced quality of life.
- Development of cardiovascular disease.
- New onset of heart failure or the development of more severe heart failure.
- Increased cardiovascular mortality.

Other manifestations of uremia in end-stage renal disease (ESRD), many of which are more likely in patients who are being inadequately dialyzed, include the following:

- Pericarditis: Can be complicated by cardiac tamponade, possibly resulting in death.
- Encephalopathy: Can progress to coma and death.
- Peripheral neuropathy.
- Restless leg syndrome.
- Gastrointestinal symptoms: Anorexia, nausea, vomiting, diarrhea.
- Skin manifestations: Dry skin, pruritus, ecchymosis.
- Fatigue, increased somnolence, failure to thrive.
- Malnutrition.
- Erectile dysfunction, decreased libido, amenorrhea.
- Platelet dysfunction with tendency to bleed.

Screen adult patients with CKD for depressive symptoms; self-report scales at initiation of dialysis therapy reveal that 45 % of these patients have such symptoms, albeit with a somatic emphasis.

Laboratory studies used in the diagnosis of CKD can include the following:

- Complete blood count (CBC).

- Basic metabolic panel
- Urinalysis.
- Serum albumin levels: Patients may have hypoalbuminemia due to urinary protein loss or malnutrition.
- Lipid profile: Patients with CKD have an increased risk of cardiovascular disease.

Evidence of renal bone disease can be derived from the following tests:

- Serum phosphate.
- 25-hydroxyvitamin D.
- Alkaline phosphatase.
- Intact parathyroid hormone (PTH) levels.

In certain cases, the following tests may also be ordered as part of the evaluation of patients with CKD:

- Serum and urine protein electrophoresis: Screen for a monoclonal protein possibly representing multiple myeloma.
- Antinuclear antibodies (ANA), double-stranded DNA antibody levels: Screen for systemic lupus erythematosus.
- Serum complement levels: Results may be depressed with some glomerulonephritides.
- Cytoplasmic and perinuclear pattern antineutrophil cytoplasmic antibody (C-ANCA and P-ANCA) levels: Positive findings are helpful in the diagnosis of Wegener granulomatosis and polyarteritis nodosa; P-ANCA is also helpful in the diagnosis of microscopic polyangiitis.
- Anti-glomerular basement membrane (anti-GBM) antibodies: Presence is highly suggestive of underlying Goodpasture syndrome.
- Hepatitis B and C, human immunodeficiency virus (HIV), Venereal Disease Research Laboratory (VDRL) serology: Conditions associated with some glomerulonephritides.

Imaging studies that can be used in the diagnosis of CKD include the following:

- Renal ultrasonography: Useful to screen for hydronephrosis, which may not be observed in early obstruction, or for involvement of the retroperitoneum with fibrosis, tumor, or diffuse adenopathy; small, echogenic kidneys are observed in advanced renal failure.
- Retrograde pyelography: Useful in cases with high suspicion for obstruction despite negative renal ultrasonograms, as well as for diagnosing renal stones.
- Computed tomography (CT) scanning: Useful to better define renal masses and cysts usually noted on ultrasonograms; also the most sensitive test for identifying renal stones.
- Magnetic resonance imaging (MRI): Useful in patients who require a CT scan but who cannot receive intravenous contrast; reliable in the diagnosis of renal vein thrombosis.

• Renal radionuclide scanning: Useful to screen for renal artery stenosis when performed with captopril administration; also quantitates the renal contribution to the GFR.

Biopsy: percutaneous renal biopsy is generally indicated when renal impairment and/or proteinuria approaching the nephrotic range are present and the diagnosis is unclear after appropriate workup.

Management

Early diagnosis and treatment of the underlying cause and/or institution of secondary preventive measures is imperative in patients with CKD. These may slow, or possibly halt, progression of the disease. The medical care of patients with CKD (see Treatment) should focus on the following:

• Slowing or halting the progression of CKD.

• Treating the pathologic manifestations of CKD.

• Timely planning for long-term renal replacement therapy, including dialysis and transplantation.

The medical care of patients with CKD should focus on the following:

• Delaying or halting the progression of CKD: Treatment of the underlying condition, if possible, is indicated.

• Treating the pathologic manifestations of CKD.

• Timely planning for long-term renal replacement therapy.

The pathologic manifestations of CKD should be treated as follows:

• Anemia: When the hemoglobin level is below 10 g/dL, treat with erythropoiesis-stimulating agents (ESAs), which include epoetin alfa and darbepoetin alfa.

• Hyperphosphatemia: Treat with dietary phosphate binders and dietary phosphate restriction.

• Hypocalcemia: Treat with calcium supplements with or without calcitriol.

• Hyperparathyroidism: Treat with calcitriol or vitamin D analogues.

• Volume overload: Treat with loop diuretics or ultrafiltration.

• Metabolic acidosis: Treat with oral alkali supplementation.

• Uremic manifestations: Treat with long-term renal replacement therapy (hemodialysis, peritoneal dialysis, or renal transplantation).

Indications for renal replacement therapy include the following:

• Severe metabolic acidosis.

• Hyperkalemia.

• Pericarditis.

• Encephalopathy.

• Intractable volume overload.

• Failure to thrive and malnutrition.

• Peripheral neuropathy.

• Intractable gastrointestinal symptoms.

• In asymptomatic patients, a GFR of 5-9 mL/min/1.73 m², irrespective of the cause of the CKD or the presence or absence of other comorbidities.

Prognosis: patients with chronic kidney disease (CKD) generally experience progressive loss of kidney function and are at risk for end-stage renal disease (ESRD). The rate of progression depends on age, the underlying diagnosis, the success of implementation of secondary preventive measures, and the individual patient. Timely initiation of chronic renal replacement therapy is imperative to prevent the uremic complications of CKD that can lead to significant morbidity and death.

14. ACUTE KIDNEY INJURY

Definitions and introduction

Acute kidney injury (AKI) or acute renal failure (ARF) is defined as an abrupt or rapid decline in renal filtration function.This condition is usually marked by a rise in serum creatinine concentration or by azotemia (a rise in blood urea nitrogen (BUN) concentration). However, immediately after a kidney injury, BUN or creatinine levels may be normal, and the only sign of a kidney injury may be decreased urine production. A rise in the creatinine level can result from medications (eg, cimetidine, trimethoprim) that inhibit the kidney's tubular secretion, while a rise in the BUN level can also occur without renal injury, resulting instead from such sources as gastrointestinal (GI) or mucosal bleeding, steroid use, or protein loading. Therefore, a careful inventory must be taken before concluding that a kidney injury is present.

Pathophysiology: the driving force for glomerular filtration is the pressure gradient from the glomerulus to the Bowman space. Glomerular pressure depends primarily on renal blood flow (RBF) and is controlled by the combined resistances of renal afferent and efferent arterioles. Regardless of the cause of AKI, reductions in RBF represent a common pathologic pathway for decreasing glomerular filtration rate (GFR). The etiology of AKI consists of 3 main mechanisms: prerenal, intrinsic, and obstructive. In prerenal failure, GFR is depressed by compromised renal perfusion. Tubular and glomerular function remains normal. Intrinsic renal failure includes diseases of the kidney itself, predominantly affecting the glomerulus or tubules, which are associated with the release of renal afferent vasoconstrictors. Ischemic renal injury is the most common cause of intrinsic renal failure. Patients with chronic kidney disease may also present with superimposed AKI from prerenal failure and obstruction, as well as intrinsic renal disease. Obstruction of the urinary tract initially causes an increase in tubular pressure, which decreases the filtration driving force. This pressure gradient soon equalizes, and maintenance of a depressed GFR then depends on renal efferent vasoconstriction.

Depressed RBF eventually leads to ischemia and cell death. This may happen before frank systemic hypotension is present and is referred to as normotensive ischemic AKI. The initial ischemic insult triggers a cascade of events, including production of oxygen free radicals, cytokines and enzymes; endothelial activation and leukocyte adhesion; activation of coagulation; and initiation of apoptosis. These events continue to cause cell injury even after restoration of RBF. Tubular cellular damage results in disruption of tight junctions between

cells, allowing back leak of glomerular filtrate and further depressing effective GFR. In addition, dying cells slough off into the tubules, forming obstructing casts, which further decrease GFR and lead to oliguria. During this period of depressed RBF, the kidneys are particularly vulnerable to further insults; this is when iatrogenic renal injury is most common. The following are common combinations:

- Radiocontrast agents, aminoglycosides, or cardiovascular surgery with preexisting renal disease (eg, elderly, diabetic, jaundiced patients).
- Angiotensin-converting enzyme (ACE) inhibitors with diuretics, small- or large-vessel renal arterial disease.
- NSAIDs with chronic heart failure, hypertension, or renal artery stenosis.

Acute tubular necrosis

Frank necrosis is not prominent in most human cases of ATN and tends to be patchy. Less obvious injuries include the following:

- Loss of brush borders.
- Flattening of the epithelium.
- Detachment of cells.
- Formation of intratubular casts.
- Dilatation of the lumen.

Although these changes are observed predominantly in proximal tubules, injury to the distal nephron can also be demonstrated. In addition, the distal nephron may become obstructed by desquamated cells and cellular debris.

Apoptosis: in contrast to necrosis, the principal site of apoptotic cell death is the distal nephron. During the initial phase of ischemic injury, loss of integrity of the actin cytoskeleton leads to flattening of the epithelium, with loss of the brush border, loss of focal cell contacts, and subsequent disengagement of the cell from the underlying substratum.

Inflammatory response: many endogenous growth factors that participate in the process of regeneration following ischemic renal injury have not been identified. However, administration of growth factors exogenously has been shown to ameliorate and hasten recovery from AKI. Depletion of neutrophils and blockage of neutrophil adhesion reduce renal injury following ischemia, indicating that the inflammatory response is responsible, in part, for some features of ATN, especially in postischemic injury after transplant.

Vasoconstriction: intrarenal vasoconstriction is the dominant mechanism for reduced GFR in patients with ATN. The mediators of this vasoconstriction are unknown, but tubular injury seems to be an important concomitant finding. Urine backflow and intratubular obstruction (from sloughed cells and debris) are causes of reduced net ultrafiltration. The importance of this mechanism is highlighted by the improvement in renal function that follows relief of such intratubular obstruction. In addition, when obstruction is prolonged, intrarenal vasoconstriction is prominent in part due to the tubuloglomerular feedback mechanism, which is thought to be mediated by adenosine and activated when there is proximal tubular damage and the macula densa is presented with increased chloride load. Apart from the increase in basal renal vascular tone, the stressed renal microvasculature is more sensitive to potentially vasoconstrictive drugs and otherwise-tolerated changes in systemic blood pressure. The vasculature of the injured kidney has an impaired vasodilatory response and loses its autoregulatory behavior. This latter phenomenon has important clinical relevance because the frequent reduction in systemic pressure during intermittent hemodialysis may provoke additional damage that can delay recovery from ATN. Often, injury results in atubular glomeruli, where the glomerular function is preserved, but the lack of tubular outflow precludes its function.

Isosthenuria: a physiologic hallmark of ATN is a failure to maximally dilute or concentrate urine (isosthenuria). This defect is not responsive to pharmacologic doses of vasopressin. The injured kidney fails to generate and maintain a high medullary solute gradient, because the accumulation of solute in the medulla depends on normal distal nephron function. Failure to excrete concentrated urine even in the presence of oliguria is a helpful diagnostic clue in distinguishing prerenal from intrinsic renal disease. In prerenal azotemia, urine osmolality is typically more than 500 mOsm/kg, whereas in intrinsic renal disease, urine osmolality is less than 300 mOsm/kg.

Restoration of renal blood flow and associated complications: recovery from AKI is first dependent upon restoration of RBF. Early RBF normalization predicts better prognosis for recovery of renal function. In prerenal failure, restoration of circulating blood volume is usually sufficient. Rapid relief of urinary obstruction in postrenal failure results in a prompt decrease of vasoconstriction. With intrinsic renal failure, removal of tubular toxins and initiation of therapy for glomerular diseases decreases renal afferent vasoconstriction.Once RBF is restored, the remaining functional nephrons increase their filtration and eventually undergo hypertrophy. GFR recovery depends on the size of this remnant nephron pool. If the number of remaining nephrons is below a critical threshold, continued hyperfiltration results in progressive glomerular sclerosis, eventually leading to increased nephron loss. A vicious cycle ensues; continued nephron loss causes more hyperfiltration until complete renal failure results. This has been termed the hyperfiltration theory of renal failure and explains the scenario in which progressive renal failure is frequently observed after apparent recovery from AKI.

Classification

Categories of AKI: AKI may be classified into 3 general categories, as follows:

- Prerenal — As an adaptive response to severe volume depletion and hypotension, with structurally intact nephrons.
- Intrinsic — In response to cytotoxic, ischemic, or inflammatory insults to the kidney, with structural and functional damage.
- Postrenal — From obstruction to the passage of urine.

Prerenal AKI represents the most common form of kidney injury and often leads to intrinsic AKI if it is not promptly corrected. Volume loss can provoke this syndrome; the source of the loss may be GI, renal, or cutaneous (eg, burns) or from internal or external hemorrhage. Prerenal AKI can also result from decreased renal perfusion in patients with heart failure or shock (eg, sepsis, anaphylaxis). Several classes of medications can induce prerenal AKI in volume-depleted states, including ACE inhibitors and angiotensin receptor blockers (ARBs), which are otherwise safely tolerated and beneficial in most patients with chronic kidney disease. Aminoglycosides, amphotericin B, and radiologic contrast agents may also do so. Arteriolar vasoconstriction leading to prerenal AKI can occur in hypercalcemic states, as well as with the use of radiocontrast agents, NSAIDs, amphotericin, calcineurin inhibitors, norepinephrine, and other pressor agents. The hepatorenal syndrome can also be considered a form of prerenal AKI, because functional renal failure develops from diffuse vasoconstriction in vessels supplying the kidney. To summarize, volume depletion can be caused by the following:

- Renal losses — Diuretics, polyuria.
- GI losses — Vomiting, diarrhea.
- Cutaneous losses — Burns, Stevens-Johnson syndrome.
- Hemorrhage.

- Pancreatitis.

Decreased cardiac output can be caused by the following:

- Heart failure.
- Pulmonary embolus.
- Acute myocardial infarction.
- Severe valvular disease.
- Abdominal compartment syndrome — Tense ascites.

Systemic vasodilation can be caused by the following:

- Sepsis.
- Anaphylaxis.
- Anesthetics.
- Drug overdose.

Afferent arteriolar vasoconstriction can be caused by the following:

- Hypercalcemia.
- Drugs — NSAIDs, amphotericin B, calcineurin inhibitors, norepinephrine, radiocontrast agents.
- Hepatorenal syndrome.

Diseases that decrease effective arterial blood volume include the following:

- Hypovolemia.
- Heart failure.
- Liver failure.
- Sepsis.

Renal arterial diseases that can result in AKI include renal arterial stenosis, especially in the setting of hypotension or initiation of ACE inhibitors or ARBs. Renal artery stenosis typically results from atherosclerosis or fibromuscular dysplasia, but is also a feature of the genetic syndromes type 1 neurofibromatosis, Williams syndrome, and Alagille syndrome. Patients can also develop septic embolic disease (eg, from endocarditis) or cholesterol emboli, often as a result of instrumentation or cardiovascular surgery.

Intrinsic AKI: structural injury in the kidney is the hallmark of intrinsic AKI; the most common form is ATN, either ischemic or cytotoxic. Glomerulonephritis can be a cause of AKI and usually falls into a class referred to as rapidly progressive (RP) glomerulonephritis. Glomerular crescents (glomerular injury) are found in RP glomerulonephritis on biopsy; if more than 50 % of glomeruli contain crescents, this usually results in a significant decline in renal function. Although comparatively rare, acute glomerulonephritides should be part of the diagnostic consideration in cases of AKI. To summarize, vascular (large- and small-vessel) causes of intrinsic AKI include the following:

- Renal artery obstruction — Thrombosis, emboli, dissection, vasculitis.
- Renal vein obstruction — Thrombosis.
- Microangiopathy — TTP, HUS, disseminated intravascular coagulation (DIC), preeclampsia.
- Malignant hypertension.
- Scleroderma renal crisis.
- Transplant rejection.
- Atheroembolic disease.

Glomerular causes include the following:

- Anti-glomerular basement membrane (GBM) disease — As part of Goodpasture syndrome or renal limited disease.

• Anti-neutrophil cytoplasmic antibody — associated glomerulonephritis (ANCA-associated glomerulonephritis) — Wegener granulomatosis, Churg-Strauss syndrome, microscopic polyangiitis.

• Immune complex glomerulonephritis — Lupus, postinfectious glomerulonephritis, cryoglobulinemia, primary membranoproliferative glomerulonephritis.

Tubular etiologies may include ischemia or cytotoxicity. Cytotoxic etiologies include the following:

• Heme pigment — Rhabdomyolysis, intravascular hemolysis.

• Crystals — Tumor lysis syndrome, seizures, ethylene glycol poisoning, megadose vitamin C, acyclovir, indinavir, methotrexate.

• Drugs — Aminoglycosides, lithium, amphotericin B, pentamidine, cisplatin, ifosfamide, radiocontrast agents.

Interstitial causes include the following:

• Drugs — Penicillins, cephalosporins, NSAIDs, proton-pump inhibitors, allopurinol, rifampin, indinavir, mesalamine, sulfonamides.

• Infection — Pyelonephritis, viral nephritides.

• Systemic disease — Sjögren syndrome, sarcoid, lupus, lymphoma, leukemia, tubulonephritis, uveitis.

Postrenal AKI: mechanical obstruction of the urinary collecting system, including the renal pelvis, ureters, bladder, or urethra, results in obstructive uropathy or postrenal AKI. Causes of obstruction include the following:

• Stone disease.

• Stricture.

• Intraluminal, extraluminal, or intramural tumors.

• Thrombosis or compressive hematoma.

• Fibrosis.

If the site of obstruction is unilateral, then a rise in the serum creatinine level may not be apparent, because of preserved function of the contralateral kidney. Nevertheless, even with unilateral obstruction a significant loss of GFR occurs, and patients with partial obstruction may develop progressive loss of GFR if the obstruction is not relieved. Bilateral obstruction is usually a result of prostate enlargement or tumors in men and urologic or gynecologic tumors in women. Patients who develop anuria typically have obstruction at the level of the bladder or downstream to it. To summarize, causes of postrenal AKI include the following:

• Ureteric obstruction — Stone disease, tumor, fibrosis, ligation during pelvic surgery.

• Bladder neck obstruction — Benign prostatic hypertrophy (BPH), cancer of the prostate (CA prostate or prostatic CA), neurogenic bladder, tricyclic antidepressants, ganglion blockers, bladder tumor, stone disease, hemorrhage/clot.

• Urethral obstruction — Strictures, tumor, phimosis.

• Intra-abdominal hypertension — Tense ascites.

• Renal vein thrombosis.

Diseases causing urinary obstruction from the level of the renal tubules to the urethra include the following:

• Tubular obstruction from crystals — Eg, uric acid, calcium oxalate, acyclovir, sulfonamide, methotrexate, myeloma light chains.

• Ureteral obstruction — Retroperitoneal tumor, retroperitoneal fibrosis (methysergide, propranolol, hydralazine), urolithiasis, or papillary necrosis.

• Urethral obstruction — Benign prostatic hypertrophy; prostate, cervical, bladder, or colorectal carcinoma; bladder hematoma; bladder stone; obstructed Foley catheter; neurogenic bladder; stricture.

Patients who develop AKI can be oliguric or nonoliguric, can have a rapid or slow rise in creatinine levels, and may have qualitative differences in urine solute concentrations and cellular content. (Approximately 50–60 % of all causes of AKI are nonoliguric.) This lack of a uniform clinical presentation reflects the variable nature of the injury. Classifying AKI as oliguric or nonoliguric on the basis of daily urine excretion has prognostic value. Oliguria is defined as a daily urine volume of less than 400 mL and has a worse prognosis, except in pre-renal injury. Anuria is defined as a urine output of less than 100 mL/day and, if abrupt in onset, suggests bilateral obstruction or catastrophic injury to both kidneys. Stratification of renal injury along these lines helps in diagnosis and decision-making (eg, timing of dialysis) and can be an important criterion for patient response to therapy.

RIFLE classification system: In 2004, the Acute Dialysis Quality Initiative work group set forth a definition and classification system for acute renal failure, described by the acronym RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function, and End-stage kidney disease). Investigators have since applied the RIFLE system to the clinical evaluation of AKI, although it was not originally intended for that purpose. AKI research increasingly uses RIFLE. When the failure classification is achieved by UO criteria, the designation of RIFLE-F_O is used to denote oliguria.The initial stage, risk, has high sensitivity; more patients will be classified in this mild category, including some who do not actually have renal failure. Progression through the increasingly severe stages of RIFLE is marked by decreasing sensitivity and increasing specificity.

Acute Kidney Injury Network (AKIN) classification system has developed specific criteria for the diagnosis of AKI. The AKIN defines AKI as abrupt (within 48 hours) reduction of kidney function, manifested by any 1 of the following:

- An absolute increase in serum creatinine of 0.3 mg/dL or greater ($\geq$ 26.4 μmol/L).
- A percentage increase in serum creatinine of 50 % or greater (1.5-fold from baseline).
- A reduction in urine output, defined as less than 0.5 mL/kg/h for more than 6 hours.

Diagnosis

Signs and symptoms in patients with AKI:

- Livido reticularis, digital ischemia, butterfly rash, palpable purpura: Systemic vasculitis.
- Maculopapular rash: Allergic interstitial nephritis.
- Track marks (ie, intravenous drug abuse): Endocarditis.

Eye examination may reveal the following:

- Keratitis, iritis, uveitis, dry conjunctivae: Autoimmune vasculitis.
- Jaundice: Liver diseases.
- Band keratopathy (ie, hypercalcemia): Multiple myeloma.
- Signs of diabetes mellitus.
- Signs of hypertension.
- Atheroemboli: Retinopathy.

Examination of the patient's ears may reveal the following signs:

- Hearing loss: Alport disease and aminoglycoside toxicity.
- Mucosal or cartilaginous ulcerations: Wegener granulomatosis.

Cardiovascular examination may reveal the following:

- Irregular rhythms (ie, atrial fibrillation): Thromboemboli.
- Murmurs: Endocarditis.
- Pericardial friction rub: Uremic pericarditis.
- Increased jugulovenous distention, rales, S_3: Heart failure.

The following signs of AKI may be discovered during an abdominal examination:

- Pulsatile mass or bruit: Atheroemboli.
- Abdominal or costovertebral angle tenderness: Nephrolithiasis, papillary necrosis, renal artery thrombosis, renal vein thrombosis.
- Pelvic, rectal masses; prostatic hypertrophy; distended bladder: Urinary obstruction.
- Limb ischemia, edema: Rhabdomyolysis.

Pulmonary examination may reveal the following:

- Rales: Goodpasture syndrome, Wegener granulomatosis.
- Hemoptysis: Wegener granulomatosis.

The following tests can aid in the diagnosis and assessment of AKI:

- Kidney function studies: Increased levels of blood urea nitrogen (BUN) and creatinine are the hallmarks of renal failure; the ratio of BUN to creatinine can exceed 20:1 in conditions that favor the enhanced reabsorption of urea, such as volume contraction (this suggests prerenal AKI).
- Complete blood count.
- Peripheral smear.
- Serologic tests: These may show evidence of conditions associated with AKI, such as schistocytes in disorders such as hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura.
- Fractional excretion of sodium and urea.
- Bladder pressure: Patients with a bladder pressure above 25 mm Hg should be suspected of having AKI caused by abdominal compartment syndrome.
- Ultrasonography: Renal ultrasonography is useful for evaluating existing renal disease and obstruction of the urinary collecting system.
- Aortorenal angiography: Can be helpful in establishing the diagnosis of renal vascular diseases, such as renal artery stenosis, renal atheroembolic disease, atherosclerosis with aortorenal occlusion, and certain cases of necrotizing vasculitis (eg, polyarteritis nodosa).
- Renal biopsy: Can be useful in identifying intrarenal causes of AKI.

Management

Maintenance of volume homeostasis and correction of biochemical abnormalities remain the primary goals of AKI treatment and may include the following measures:

- Correction of fluid overload with furosemide.
- Correction of severe acidosis with bicarbonate administration, which can be important as a bridge to dialysis.
- Correction of hyperkalemia.
- Correction of hematologic abnormalities (eg, anemia, uremic platelet dysfunction) with measures such as transfusions and administration of desmopressin or estrogens.

Dietary changes are an important facet of AKI treatment. Restriction of salt and fluid becomes crucial in the management of oliguric renal failure, wherein the kidneys do not adequately excrete either toxins or fluids.Pharmacologic treatment of AKI has been attempted on an empiric basis, with varying success rates.

Long-term prognosis: in contrast to previous belief, it is now known that survivors of AKI do not universally have a benign course. On long-term follow-up (1–10 years), approximately 12.5 % of survivors of AKI are dialysis dependent; rates range widely, from 1–64 %, depending on the patient population. From 19–31 % of survivors experience partial recovery of kidney function and have chronic kidney disease.

15. FUNCTIONAL GALLBLADDER AND SPHINCTER OF ODDI DISODERS

Definitions and introduction

These criteria (known as the «Rome criteria») specify three subsets of functional gallbladder and sphincter of Oddi disorders:

- Functional gallbladder disorder.
- Functional biliary sphincter of Oddi disorder.
- Functional pancreatic sphincter of Oddi disorder.

A great deal has been written about the sphincter of Oddi and its dysfunction, but the literature is often difficult to interpret because of differences in nomenclature. The terms papillary stenosis, sclerosing papillitis, biliary spasm, biliary dyskinesia, and postcholecystectomy syndrome have been used synonymously with sphincter of Oddi dysfunction (SOD). Despite this source of confusion, two separate pathologic entities are widely recognized based upon their distinct pathogenic mechanisms.

Sphincter of Oddi stenosis is an anatomic abnormality associated with narrowing of the SO. It can result from any process leading to inflammation or scarring, such as pancreatitis, passage of a gallstone through the papilla, intraoperative trauma, infection, and adenomyosis. Sphincter of Oddi stenosis is associated with abnormal SO motility and elevated basal pressure.

Sphincter of Oddi dyskinesia refers to a functional disturbance of the SO, leading to intermittent biliary obstruction. The cause of SO dyskinesia is not well understood. Spasm and relaxation of the SO can be induced pharmacologically with agents known to affect smooth

muscle function (such as nitroglycerin), suggesting that the spasm may be influenced by local hormonal or neurologic disturbance.

Anatomy: the sphincter of Oddi is a muscular structure that encompasses the confluence of the distal common bile duct and the pancreatic duct as they penetrate the wall of the duodenum. The sphincter of Oddi (SO) is composed of small circular and longitudinal muscular segments that are approximately 6 to 10 mm in total length and are contained mostly within the wall of the duodenum. The muscle fibers surround the intraduodenal segment of the common bile duct and the ampulla of Vater. A circular aggregate of muscle fibers known as the sphincter choledochus (or sphincter of Boyden) maintains resistance to bile flow, and thereby permits filling of the gallbladder during fasting and prevents retrograde reflux of duodenal contents into the biliary tree. A separate structure, called the sphincter pancreaticus, encircles the distal pancreatic duct. The muscle fibers of the sphincter pancreaticus are interlocked with those of the sphincter choledochus in a figure eight pattern. Although the pancreatic and biliary sphincter portions of the SO can be distinguished anatomically, their manometric features are similar and a direct anatomic and manometric correlation has not been established.The muscle fibers of the SO function independently from those of the duodenal musculature. The motility of the SO is complex and not completely understood, but is known to vary in the fasting and fed states.During fasting, SO motility is integrated with the migrating motor complex (MMC), permitting coordinated release of bile into the duodenum. Myoelectrical potentials within the SO increase during phase one of the MMC, reach a maximum during phase three, and then decrease rapidly.During the fed state, myoelectrical potentials within the SO vary depending upon the type and quantity of nutrients ingested and may be influenced by endogenous hormones such as cholecystokinin.

Clinical manifestations and diagnosis: by «Rome criteria» SOD has been associated with two clinical syndromes: biliary pain and idiopathic recurrent acute pancreatitis (IRAP).

IRAP is defined as two or more attacks of well documented acute pancreatitis of unclear cause despite an exhaustive work-up (laboratory and noninvasive imaging) with complete resolution of clinical and laboratory findings between attacks.

The guidelines stress that patients with upper abdominal pain who do not meet the Rome symptom-based criteria should not be submitted to ERCP or other invasive procedures. Those who fulfill the criteria should be assessed initially with noninvasive procedures and eventually with therapeutic trials that will more likely identify the majority of patients whose pain is not biliopancreatic in origin and will therefore not require further investigation.

The following are the Rome criteria for functional gallbladder and sphincter of Oddi disorders. In order to fulfill the Rome criteria, all of the following conditions must be met:

- Pain located in the epigastrium and/or right upper quadrant.
- Episodes lasting 30 minutes or longer.
- Recurrent symptoms occurring at different intervals (not daily).
- The pain builds up to a steady level.
- The pain is moderate to severe enough to interrupt the patients' daily activities or lead to an emergency department visit.
- The pain is not relieved by bowel movements.
- The pain is not relieved by postural change.

- The pain is not relieved by antacids.
- Exclusion of other structural disease that would explain the symptoms.

Supportive criteria include:

- Pain associated with nausea and vomiting.
- Pain radiating to the back and/or right infrasubscapular region.
- Pain awakening the patient from sleep in the middle of the night.

The following are the Rome criteria for functional gallbladder disorder:

- Criteria for functional gallbladder and sphincter of Oddi disorders are fulfilled.
- Gallbladder is present.
- Normal liver enzymes, conjugated bilirubin, and amylase/lipase.
- Functional biliary sphincter of Oddi disorder — The following are the Rome III criteria for functional biliary sphincter of Oddi disorder:
- Criteria for functional gallbladder and sphincter of Oddi disorder are fulfilled.
- Normal amylase/lipase.

Supportive criteria include elevated serum aminotransferases, alkaline phosphatase or conjugated bilirubin temporally related to at least two pain episodes.

Functional pancreatic sphincter of Oddi disorder: the following are the Rome criteria for functional pancreatic sphincter of Oddi disorder:

- Criteria for functional gallbladder and sphincter of Oddi disorder are fulfilled.
- Elevated amylase/lipase.

Classification

Biliary SOD: the presence of biliary SOD has been based upon a variety of parameters, including dilation of the common bile duct, provocation tests, hepatobiliary scintigraphy, and a classification system.

Otherwise unexplained dilation of the common bile duct on ultrasound is associated with SOD and may predict a favorable response to sphincterotomy in patients with other clinical evidence of biliary obstruction (eg, pain, abnormal liver function tests). However, common bile duct dilation (more than 6 mm) may be observed in up to one-third of patients after cholecystectomy. Furthermore, the size of the common bile duct increases with age. As a result, dilation of the common bile duct alone is insufficient evidence for establishing the diagnosis of SOD. It should be considered in the context of symptoms, liver and pancreatic biochemical tests, and a history of multiple gallbladder stones or past removal of common bile duct stones. In most instances, mild dilation is an incidental finding warranting only observation. To increase the specificity of common bile duct diameter measurement for determining SOD, several provocation tests have been developed that use either a fatty meal (fatty meal ultrasonography) or cholecystokinin to increase bile flow. In patients who have normal SO function, the bile duct diameter remains constant or decreases following stimulation; an increase of more than 2 mm is considered to be abnormal. Hepatobiliary scintigraphy using technetium-99m labeled dyes can provide a standardized, semiquantitative assessment of delayed biliary drainage in patients whose gallbladder is absent. Scintigraphy should have only a supportive role in the evaluation of suspected SOD.

Classification systems: several investigators have constructed criteria by which the likelihood of finding SOD and its response to treatment can be predicted. The best studied classification system for biliary SOD (known as the Milwaukee Biliary Group Classification) is based upon the number of laboratory, clinical, and radiologic features suggesting SOD in an individual patient. The original Milwaukee classification recognizes three groups of patients who have biliary type pain without an identifiable cause prior to manometry:

- Type I patients fulfill all of three criteria: (a) pain associated with abnormal serum aminotransferases (ALT and AST more than two times normal on at least two occasions); (b) a dilated common bile duct more than 10 mm on ultrasound or 12 mm on ERCP; and (c) delayed drainage of contrast from the common bile duct after more than 45 minutes in the supine position).
- Type II patients have one or two of the above criteria.
- Type III patients have none of the above criteria.

The Rome III consensus statement revised the Milwaukee Biliary Group Classification to make it more applicable to clinical practice and, whenever possible, avoid invasive procedures such as ERCP. Thus, the revised system emphasizes noninvasive methods to evaluate common bile duct diameter instead of contrast drainage times:

- Type I patients present with biliary-type pain; abnormal aminotransferases, bilirubin or alkaline phosphatase > 2 times normal values documented on two or more occasions and a dilated bile duct greater than 8 mm diameter on ultrasound. Approximately 65 to 95 percent of these patients have manometric evidence of biliary SOD.
- Type II patients present with biliary-type pain and one of the previously mentioned laboratory or imaging abnormalities. Approximately 50 to 63 percent of these patients have manometric evidence of biliary SOD.
- Type III patients complain only of recurrent biliary-type pain and have none of the previously mentioned laboratory or imaging criteria. Approximately 12 to 59 percent of these patients have manometric evidence of biliary SOD.

Pancreatic SOD: tests of SOD involving the pancreatic segment of the SO have focused on pancreatic outflow obstruction due to SO stenosis.

Provocation tests for evaluating pancreatic SOD are based upon a similar principle as provocation tests for biliary SOD. An increase in pancreatic duct diameter following secretin stimulation of more than 1.5 mm (assessed by transabdominal ultrasound, CT or MRI) lasting for more than 30 minutes is considered to be pathologic. The addition of endoscopic ultrasound to the secretin stimulation test has been attempted to improve accuracy. The results suggested excellent negative and positive predictive values, but poor overall sensitivity for this test. Results were compared to conventional manometry where the diagnosis was based upon a mean basal pressure of > 40 mm Hg. Results were also correlated with long-term outcomes with or without endoscopic sphincterotomy. Secretin MRCP was useful in predicting abnormal manometry and response to endotherapy in patients with suspected type II SOD, but

was insensitive to predicting abnormal manometry in patients with suspected type III SOD. Further studies are needed.

A classification system similar to the Milwaukee Biliary Group Classification has been developed for pancreatic SOD, although it is not as widely used as the classification system for biliary SOD. Pancreatic-type pain as defined by Rome III criteria SOD is virtually indistinguishable from biliary-type pain. This updated classification for presumptive SOD recognizes three groups of patients who have recurrent pancreatitis and/or typical pancreatic pain of uncertain etiology:

- Type I patients have all three of the following criteria: (a) pain; (b) a dilated pancreatic duct (greater than 6 mm in the head and more than 5 mm in the body); and (c) serum amylase or lipase level greater than 1.5 times the upper limit of normal on at least one occasion.
- Type II patients have pain plus one other criterion.
- Type III patients only have pain.

Diagnosis

Sphincter of Oddi manometry (SOM) remains the gold standard for diagnosis of SOD. Patients with SO dysfunction have been divided into two groups based upon manometric findings:

- Patients with structural alterations of the SO zone (stenosis).
- Patients with functional abnormalities (dyskinesia).

Patients with stenosis are identified by an abnormally elevated basal SO pressure (> 40 mmHg), which is the most widely clinically accepted diagnostic finding for SOD. Patients with SO dyskinesia may also have elevated basal SO pressure. However, in contrast to SO stenosis, the elevated pressure decreases dramatically following amyl nitrite inhalation or glucagon bolus injection, which relaxes smooth muscles. Other manometric characteristics of this group are: rapid SO contraction frequency (> 7/min) or tachyodia, an excess in retrograde phasic contractions (> 50 percent), and a substantial basal SO pressure increase (paradoxical response) following administration of cholecystokinin-octapeptide (CCK-8). Manometric findings in patients with SO dyskinesia are less well reproduced upon repeat measurement compared to patients with SO stenosis.

Although SO manometry remains the gold standard for diagnosis of SOD, it is invasive, technically demanding, and has several limitations.

Biliary-type pain: the most reliable finding predicting a favorable response to sphincterotomy in patients with biliary-type pain is elevated basal pressure.

Pancreatitis: manometric findings in patients with idiopathic recurrent pancreatitis suggest that impedance to flow of pancreatic secretions may cause pancreatitis. Stenting of the hypertensive pancreatic duct segment should be considered after biliary sphincterotomy in patients with SOD.The most practical sequence after excluding the traditional causes of pancreatitis include: liver and pancreatic biochemical tests followed by transabdominal ultrasound, EUS and/or MRCP and then ERCP with bile analysis and SO manometry as needed.

Treatment

The goal of treating patients with symptomatic SO dysfunction is to eliminate pain and/or recurrent pancreatitis by improving the impaired flow of biliary and pancreatic secretions into the duodenum, which can be accomplished by pharmacologic, endoscopic, and surgical approaches. Drugs that cause smooth muscle relaxation may be beneficial in patients with SOD. Calcium channel blockers and nitrates have been best studied, although the data are sparse. Although calcium channel blockers and nitrates may have a role in some patients, side effects are common, and, in one series, pharmacologic therapy was ineffective in approximately 50 percent of patients. Ursodeoxycholic acid: some studies have implicated biliary microlithiasis in the pathogenesis of postcholecystectomy pain.

Endoscopic therapy: the biliary or pancreatic segment of the sphincter of Oddi can be severed using electrocautery during endoscopic retrograde cholangiopancreatography (ERCP). It should be performed by an experienced, capable endoscopist who has demonstrated good outcomes by sufficient patient follow-up.

In patients with biliary pain, biliary sphincterotomy has the greatest benefit for those who have elevated basal SO pressures (greater than 40 mmHg). There is general consensus that patients with type I biliary SOD likely have papillary stenosis and benefit from endoscopic biliary sphincterotomy without the need for preceding SOM. Type II patients generally undergo SOM and those with elevated basal biliary sphincter pressures undergo endoscopic sphincterotomy. Type III biliary SOD patients are the most difficult to diagnose and manage. Due to a lack of objective findings, it is difficult to differentiate type III SOD from disorders that are unrelated to the sphincter of Oddi, such as irritable bowel syndrome and chronic functional abdominal pain. Thus, type III patients are best managed by gastroenterologists with expertise in SOD. Endoscopic pancreatic sphincterotomy may benefit patients with pancreatitis thought to be due to SOD. However, some patients required repeat sphincterotomy for recurrent SO stenosis. Pancreatitis is also a potential complication of sphincterotomy. The risk may be greater after pancreatic than after biliary sphincterotomy and most often occurs in patients with pancreatic sphincter hypertension. Placement of a pancreatic stent following biliary sphincterotomy may reduce the incidence of pancreatitis in these patients. A problem with pancreatic duct stenting is the requirement for another procedure to remove the stent. Nasopancreatic drainage may be an alternative, permitting noninvasive removal of the drain following recovery.

Botulinum toxin injection: endoscopic injection of botulinum toxin for biliary sphincter of Oddi dysfunction has been used successfully by some groups to determine if a symptomatic response might predict a successful outcome to subsequent sphincterotomy.

Electroacupuncture: a potential therapeutic role for electroacupuncture was suggested in a pilot study in which an acupoint on the right lateral tibia (GB34) was stimulated, resulting in a significant decrease in basal pressure, amplitude, duration, and frequency of phasic contractions. The inhibition of SO contractili-

ty was accompanied by an increase in plasma CCK levels. All changes reverted to baseline upon discontinuation of stimulation. The clinical relevance of these observations remains to be determined.

Surgery: biliary and pancreatic sphincterotomy can also be accomplished by a transduodenal surgical approach. Surgical sphincterotomy has two potential advantages compared to standard endoscopic approaches.

Surgery allows for greater precision in performing the sphincterotomy. With endoscopic sphincterotomy it is difficult to sever the transampullary septum without risking duodenal perforation. As a result, endoscopic sphincterotomy may not completely relieve pancreatic duct obstruction. Endoscopic sphincterotomy of the biliary segment of the SO also may not affect the pancreatic duct segment at all. These problems are both overcome by performing the sphincterotomy surgically. Surgery may reduce the chance of recurrent stenosis due to scarring.

16. CHOLANGITIS

Definitions and introduction

Acute cholangitis is a clinical syndrome characterized by fever, jaundice, and abdominal pain that develops as a result of stasis and infection in the biliary tract.

Cholangitis was first described by Charcot as a serious and life-threatening illness; however, it is now recognized that the severity can range from mild to life-threatening.

Pathogenesis: acute cholangitis is caused primarily by bacterial infection. The organisms typically ascend from the duodenum; hematogenous spread from the portal vein is a rare source of infection.The most important predisposing factor for acute cholangitis is biliary obstruction and stasis secondary to biliary calculi or benign stricture. Chronic biliary obstruction raises the intrabiliary pressure, a central pathogenetic event in the development of acute cholangitis. High pressure promotes the migration of bacteria from the portal circulation into the biliary tract and subsequent colonization. It also favors migration of bacteria from bile into the systemic circulation, resulting in a higher incidence of septicemia. One study, for example, demonstrated a significant correlation between biliary and serum levels of endotoxins and the clinical severity of acute cholangitis.In addition, increased biliary pressure adversely affects a number of host defense mechanisms including:

- Hepatic tight junctions.
- Kupffer cells.
- Bile flow.
- IgA production.

Mechanism of bacterial entry into the biliary tract: the sphincter of Oddi normally forms an effective mechanical barrier to duodenal reflux and ascending bacterial infection. The continuous flushing action of bile plus the bacteriostatic activity of bile salts also help to maintain bile sterility. Secretory IgA and biliary mucous probably function as antiadherent factors, preventing bacterial colonization. When the barrier mechanism is disrupted, as occurs after endoscopic sphincterotomy, choledochal surgery, or biliary stent insertion, pathogenic bacteria enter the biliary system at high concentrations. Thus, cholangitis frequently develops after endoscopic or percutaneous manipulation with incomplete biliary drainage or as a late complication of stent blockage. However, bacteria can also pass spontaneously through the sphincter of

Oddi in small numbers. The presence of a foreign body, such as a stone or stent, can then act as a nidus for bacterial colonization. Bile taken from patients without obstruction is sterile or nearly sterile. In comparison, approximately 70 percent of all patients with gallstones have evidence of bacteria in the bile. Patients with common duct stones have a higher probability of bile culture positivity than those with gallstones in the gallbladder or cystic duct. Bacteria can also be cultured from gallstones. In one study, for example, 80 percent of brown pigment stones were culture positive, and 84 percent showed scanning electron microscopic evidence of bacterial structures. The organisms recovered in culture were typical of those seen in cholangitis (enterococci — 40 percent; Escherichia coli — 17 percent; Klebsiella spp — 10 percent), although the ratio of enterococci and E. coli was inverted from that usually found in infected bile. Some features of bacteria that may enhance pathogenicity in this setting include:

- External pili in Gram negative Enterobacteriaceae, which facilitate attachment to foreign surfaces such as a stone or stent.
- A glycocalyx matrix composed of exopolysaccharides produced by bacteria which protect the organisms from host defense mechanisms and may hinder penetration of antibiotics.
- Bacteriology — Culture of bile, ductal stones, and blocked biliary stents are positive in over 90 percent of cases, yielding a mixed growth of gram negative and gram positive bacteria. The most common bacteria isolated are of colonic origin.
- Escherichia coli is the major gram negative bacterium isolated (25 to 50 percent), followed by Klebsiella (15 to 20 percent) and Enterobacter species (5 to 10 percent).
- The most common gram positive bacteria are Enterococcus species (10 to 20 percent).
- Anaerobes, such as Bacteroides and Clostridia, are usually present as a mixed infection. They are rarely the sole infecting organisms and it is not clear if they play a role in acute cholangitis. Recovery of anaerobes appears to be more common after repeated infections or surgery on the biliary tree. The frequency of anaerobic infection is underestimated by standard culture techniques.

Diagnosis

Clinical manifestations: the classic triad of Charcot (fever, right upper quadrant pain, and jaundice) occurs in only 50 to 75 percent of patients with acute cholangitis. Confusion and hypotension can occur in patients with suppurative cholangitis, producing Reynold's pentad, which is associated with significant morbidity and mortality. Hypotension may be the only presenting symptom in elderly patients or those on corticosteroids, while septic shock in severe cases can lead to multiorgan failure. The differential diagnosis includes:

- Biliary leaks.
- Liver abscess.
- Infected choledochal cysts.
- Oriental cholangiohepatitis (hepatolithiasis).
- Cholecystitis.
- Mirizzi syndrome.
- Right lower lobe pneumonia/empyema.

Laboratory tests: routine laboratory tests typically reveal an elevated white blood cell count with neutrophil predominance, and a cholestatic pattern of liver function test abnormalities with elevations in the serum alkaline phosphatase,

gammaglutamyl transpeptidase (GGT), and bilirubin (predominantly conjugated) concentration. Serum amylase can be increased to three to four times normal, suggesting an associated pancreatitis. However, a pattern of acute hepatocyte necrosis can be seen in which the aminotransferases may be as high as 1000 IU/L. This pattern reflects microabscess formation in the liver. Liver biopsy in such cases shows neutrophils in the cholangioles with small abscesses and associated hepatocyte necrosis. Blood cultures should be performed in all patients in whom cholangitis is suspected. Cultures should also be obtained from bile or stents removed at ERCP (endoscopic retrograde cholangiopancreatography). Antibiotic therapy should be directed at any organisms isolated from these cultures.

Recommend ultrasonography as the first imaging study in patients suspected of having cholangitis to look for CBD dilatation and stones. However, ultrasonography may be negative when only small stones are present in the bile ducts (which occurs in 10 to 20 percent of cases), and with acute obstruction when the bile duct has not yet had time to dilate. Ultrasonography should be followed by endoscopic retrograde cholangiopancreatography (ERCP) both to confirm the diagnosis and to intervene therapeutically with sphincterotomy, stone extraction, or stent insertion. Occlusive cholangiography should not be performed in patients with acute suppurative cholangitis since it can promote the development of septicemia. Magnetic resonance cholangiopancreatography (MRCP) is a newer technique for the evaluation of CBD stones, particularly in the patient who is postcholecystectomy or in whom ERCP was unsuccessful or failed to completely delineate ductal abnormalities. In the presence of a dilated CBD, this test has a 90 to 95 percent concordance with ERCP in diagnosing CBD stones over 1 cm in diameter. If cholangitis is not severe and the risks of ERCP are high, then MRCP may be useful, especially if no stones are demonstrated. If, however, Charcot's triad is present, a therapeutic ERCP with drainage of the obstruction should not be delayed. Endoscopic ultrasound provides another means to visualize common duct stones. While its role remains unclear, it may be useful in patients in whom ERCP was unsuccessful or undesirable (such as pregnant women) and those at increased risk for ERCP.

Management

The mainstays of therapy are antibiotics and establishment of biliary drainage. Other general measures include fluids to maintain urine output, correction of coagulopathy, and frequent monitoring of vital signs for evidence of sepsis. In cases of suspected sepsis, monitoring for multiorgan failure from endotoxemia is essential.

Antibiotics: there are little data and no consensus opinions regarding the best initial antibiotic regimen for cholangitis. Beta lactam-based therapy appears to be as effective as treatment with ampicillin and gentamicin with less toxicity. Fluoroquinolones appear to have relatively high rates of biliary excretion, and one study found that ciprofloxacin may be as effective as triple therapy with cef-

tazidime, ampicillin and metronidazole.Empiric antibiotic therapy for ascending cholangitis should include broad-spectrum parenteral antibiotics based upon the probable source of infection until culture results are available.

Biliary drainage: eighty percent of patients with acute cholangitis will respond to conservative management and antibiotic therapy. Biliary drainage can then be performed on an elective basis. In 15 to 20 percent of cases, cholangitis fails to settle over the first 24 hours with conservative therapy alone, requiring urgent biliary decompression. Indications for urgent biliary decompression include:

- Persistent abdominal pain.
- Hypotension despite adequate resuscitation.
- Fever greater than 39 °C (102 ºF).
- Mental confusion, which is a predictor of poor outcome.

Establishment of biliary drainage: biliary drainage can be achieved by ERCP, a direct percutaneous approach, or open surgical decompression. Endoscopic sphincterotomy with stone extraction and/or stent insertion is now the treatment of choice for establishing biliary drainage in acute cholangitis. Common bile duct stones can be removed successfully in 90 to 95 percent of patients after sphincterotomy. Prior to injection of contrast, many endoscopists aspirate the bile duct to remove bile and pus in attempt to decompress the biliary system and reduce the risk of inducing bacteremia with contrast injection.Endoscopic drainage is associated with a significantly lower overall rate of mortality and morbidity compared with surgical decompression (4.7 to 10 percent versus 10 to 50 percent, respectively). As mentioned above, occlusive cholangiography should not be performed in patients with acute suppurative cholangitis since it can promote the development of septicemia.In patients with underlying coagulopathy, which prevents a sphincterotomy, those in whom drainage is inadequate due to the presence of large stones, or those who are too ill to leave the intensive care unit and undergo the procedure with fluoroscopy, drainage can be achieved by insertion of a nasobiliary catheter. This procedure permits active decompression of the CBD by aspiration and provides a route for irrigation of the biliary system. However, the catheters can become dislodged, particularly in elderly or confused patients. An internal stent may be another option with a lower risk of dislodgement, although it does not permit injection of contrast or irrigation. A controlled trial suggested that an internal stent permitted adequate drainage even when performed without a sphincterotomy.Stones more than 2 cm in diameter generally require lithotripsy for fragmentation prior to removal. Intrahepatic stones can sometimes be removed with choledochoscopy depending upon their size, number, and location. Percutaneous drainage can be considered when ERCP is unavailable, unsuccessful or contraindicated. A percutaneous cholecystostomy tube may be an option in patients with an intact gallbladder.

Role of surgery: emergency surgery for acute cholangitis has largely been replaced by nonoperative biliary drainage. Once the acute cholangitis is controlled, patients with difficult ductal stones may undergo surgical exploration of the CBD for

stone removal. Elective surgery carries a very low morbidity and mortality compared with emergency surgery. If emergent surgery is needed due to failure of a nonsurgical drainage procedure, choledochotomy with placement of a large-bore T tube carries a lower mortality compared to cholecystectomy with CBD exploration.

17. CHRONIC PANCREATITIS

Definitions and introduction

Chronic pancreatitis is commonly defined as a continuing, chronic, inflammatory process of the pancreas, characterized by irreversible morphologic changes.

Pathophysiology

Whatever the etiology of chronic pancreatitis, pancreatic fibrogenesis appears to be a typical response to injury. This involves a complex interplay of growth factors, cytokines, and chemokines, leading to deposition of extracellular matrix and fibroblast proliferation. In pancreatic injury, local expression and release of transforming growth factor beta (TGF-beta) stimulates the growth of cells of mesenchymal origin and enhances synthesis of extracellular matrix proteins, such as collagens, fibronectin, and proteoglycans.

Evidence indicates involvement of distinct chemokines in the initiation and perpetuation of chronic pancreatitis.

Etiology

The cause of chronic pancreatitis usually is metabolic in nature. The proposed pathologic mechanisms of chronic pancreatitis are as follows:

- Intraductal plugging and obstruction — Eg, ethanol (ETOH) abuse, stones, tumors.
- Direct toxins and toxic metabolites — These act on the pancreatic acinar cell to stimulate the release of cytokines, which stimulate the stellate cell to produce collagen and to establish fibrosis; cytokines also act to stimulate inflammation by neutrophils, macrophages, and lymphocytes (eg, ETOH, tropical sprue).
- Oxidative stress — Eg, idiopathic pancreatitis.
- Necrosis-fibrosis — Recurrent acute pancreatitis that heals with fibrosis.
- Ischemia — From obstruction and fibrosis; important in exacerbating or perpetuating disease rather than in initiating disease.
- Autoimmune disorders — chronic pancreatitis has been found in association with other autoimmune diseases, such as Sjögren syndrome, primary biliary cirrhosis, and renal tubular acidosis.
- Secondary forms of autoimmune chronic pancreatitis are associated with primary biliary cirrhosis, primary sclerosing cholangitis, and Sjögren syndrome.

While alcohol greatly influences the understanding of its pathophysiology because it is the most common etiology (60–70 %), approximately 20–30 % of cases are idiopathic and 10 % of cases are due to rare diseases.

Diagnosis

Signs and symptoms: for most patients with chronic pancreatitis, abdominal pain is the presenting symptom. The patient experiences intermittent attacks of severe pain, often in the mid-abdomen or left upper abdomen and occasional-

ly radiating in a bandlike fashion or localized to the midback. The pain may occur either after meals or independently of meals, but it is not fleeting or transient and tends to last at least several hours. Other symptoms associated with chronic pancreatitis include diarrhea and weight loss.

Diagnosis is based on tests of pancreatic structure and function.

Imaging tests

Imaging studies such as abdominal radiography and CT scanning can show inflammation or calcium deposits of the pancreas or changes to the pancreatic ducts. Pancreatic calcifications, often considered pathognomonic of chronic pancreatitis, are observed in approximately 30 % of cases.

Endoscopic retrograde cholangiopancreatography

The endoscopic retrograde cholangiopancreatography (ERCP) test provides the most accurate visualization of the pancreatic ductal system and has been regarded as the criterion standard for diagnosing chronic pancreatitis. It combines the use of endoscopy and fluoroscopy to visualize and treat problems of the bile and pancreatic ducts.

Magnetic resonance cholangiopancreatography

MRCP provides information on the pancreatic parenchyma and adjacent abdominal viscera, and it uses heavily T2-weighted images to visualize the biliary and pancreatic ductal system. This procedure is relatively safe, reasonably accurate, noninvasive, fast, and very useful in planning surgical or endoscopic intervention.

Endoscopic ultrasonography

The most predictive endosonographic feature of chronic pancreatitis is the presence of stones. Other suggestive features include the following:

- Visible side branches.
- Cysts.
- Lobularity.
- An irregular main pancreatic duct.
- Hyperechoic foci and strands.
- Dilation of the main pancreatic duct.
- Hyperechoic margins of the main pancreatic duct.

Management

Treatment is typically directed at the underlying cause of the pancreatitis and to relieve pain and malabsorption.

Pain relief: pancreatic enzyme supplementation may be helpful in reducing pain. The hypothesis is that stimulation of the pancreas by food causes pain. Cholecystokinin (CCK) is one of the possible mediators of this response. When exogenous pancreatic enzymes are taken with a meal, CCK-releasing factors are degraded and CCK release in response to a meal is reduced. This decreases pancreatic stimulation and pain.

If conventional medical therapy is unsuccessful and the patient has severe, intractable pain, celiac ganglion blockade can be considered. This approach tries to alleviate pain by modifying afferent sensory nerves in the celiac plexus, using agents that anesthetize, reduce inflammation, or destroy nerve fibers.

Endoscopic therapy aimed at decompressing an obstructed pancreatic duct can be associated with pain relief in some patients. The rationale for this approach is based on the hypothesis that ductal hypertension due to strictures of the main pancreatic duct leads to pain.

Surgery: the choice of operation depends on the clinical problem and the preoperative assessment of the abnormality. In general, the approach aims either to improve pancreatic duct drainage or to resect the diseased organ. Data suggest that surgical drainage of the pancreatic duct is more effective than endoscopic drainage in patients with obstruction of the pancreatic duct due to chronic pancreatitis. In patients with a dilated pancreatic duct, a Roux-en-Y side-to-side pancreaticojejunostomy is indicated. If the disease is limited to the head of the pancreas, a Whipple operation (pancreaticoduodenectomy) can produce good results. Chronic pancreatitis is commonly defined as a continuing, chronic, inflammatory process of the pancreas, characterized by irreversible morphologic changes. This chronic inflammation can lead to chronic abdominal pain and/or impairment of endocrine and exocrine function of the pancreas. Chronic pancreatitis usually is envisioned as an atrophic fibrotic gland with dilated ducts and calcifications. However, findings on conventional diagnostic studies may be normal in the early stages of chronic pancreatitis, as the inflammatory changes can be seen only by histologic examination.

By definition, chronic pancreatitis is a completely different process from acute pancreatitis. In acute pancreatitis, the patient presents with acute and severe abdominal pain, nausea, and vomiting. The pancreas is acutely inflamed (neutrophils and edema), and the serum levels of pancreatic enzymes (amylase and lipase) are elevated. Full recovery is observed in most patients with acute pancreatitis, whereas in chronic pancreatitis, the primary process is a chronic, irreversible inflammation (monocyte and lymphocyte) that leads to fibrosis with calcification. The patient with chronic pancreatitis clinically presents with chronic abdominal pain and normal or mildly elevated pancreatic enzyme levels. When the pancreas loses its endocrine and exocrine function, the patient presents with diabetes mellitus and steatorrhea.

Autoimmune pancreatitis

Autoimmune pancreatitis (AIP) is a rare disorder of presumed autoimmune etiology that is associated with characteristic clinical, histologic, and morphologic findings. AIP can occur as a primary pancreatic disorder or in association with other diseases of presumed autoimmune etiology including primary sclerosing cholangitis (PSC), primary biliary cirrhosis, retroperitoneal fibrosis, rheumatoid arthritis, sarcoidosis, and Sjögren's syndrome. AIP has been referred to by a variety of names including sclerosing pancreatitis, tumefactive pancreatitis, and nonalcoholic destructive pancreatitis, depending in part upon the specific pathologic findings and the presence of extrapancreatic manifestations. However, it is generally believed that the pathologic heterogeneity may reflect different stages or manifestations of the same disease.Among patients with AIP, IgG4 positive plasma cells are considered a marker for the disease and can be detected in the pancreas and a variety of other tissues. In addition, serum IgG4 levels are elevated to more than two times the upper limit of normal in most patients.

Clinical manifestations: a number of clinical features have been described that may reflect different stages of autoimmune pancreatitis. The manifestations occur in the pancreas, biliary tract, and other organs.

Pancreatic manifestations: a variety of manifestations related to the pancreas and biliary tract have been described in patients with AIP:

- A pancreatic mass that can be confused with pancreatic carcinoma or lymphoma.
- Mild abdominal pain with or without attacks of acute pancreatitis and chronic pancreatitis.
- Pancreatic duct strictures.
- Peripancreatic vascular complications are rare.

Biliary tract manifestations: the most common presentation of AIP is obstructive jaundice. The term IgG4-associated cholangitis (IAC) has been proposed for the biliary tract manifestations of AIP. An obstructive pattern of liver function tests (ie, a disproportionately elevated serum alkaline phosphatase and minimally elevated serum aminotransferases) is commonly seen in patients with biliary tract involvement. These features can also be seen in patients with pancreatic cancer or cholangiocarcinoma.

Other manifestations: a number of other organs can be involved in patients with AIP. These include the salivary glands (Sjögren's syndrome), bile duct strictures, lung nodules, autoimmune thyroiditis, and kidney (interstitial nephritis with an IgG4-positive plasma cell infiltrate and IgG4 deposits in the tubular basement membrane).

Distinct clinical profiles: types 1 and 2 AIP are defined by histologic patterns. These types also have distinct clinical profiles.

Diagnosis: AIP should be considered in the differential diagnosis of patients presenting with the varied symptoms referable to the pancreas and biliary tract described above, particularly in those with other autoimmune conditions. Although AIP is rare, correct diagnosis can help avert the consequences of progressive disease and unnecessary surgery. An important part of the differential diagnosis is distinguishing AIP from pancreatic cancer.A pancreatic biopsy is usually required to establish the diagnosis.The presence of immunostaining for IgG4 in plasma cell infiltrates in both the pancreas and extrapancreatic tissues provides support for the diagnosis.The diagnostic criteria proposed by the Mayo Clinic (the «HISORT» criteria) include the presence of one or more of the following:

- Diagnostic Histology.
- Characteristic Imaging on computed tomography and/or pancreatography.
- Elevated serum IgG4 levels on Serologic testing.
- Other organ involvement.
- Response of pancreatic and extrapancreatic manifestations to glucocorticoid therapy.

Histology of AIP:

- A lymphoplasmacytic sclerosing pancreatitis OR more than 10 IgG4 positive cells with at least two of the following: periductal lymphoplasmacytic infiltrate, obliterative phlebitis, and acinar fibrosis (type 1)
- Idiopathic duct centric pancreatitis OR a granulocytic epithelial lesion in the pancreatic duct with minimal IgG4 positive cells in the pancreatic parenchyma (type 2).

Imaging: AIP is usually first suggested by an imaging test such as contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI). The main findings that are diagnostic or highly suggestive of AIP are a diffusely enlarged pancreas with featureless borders and delayed enhancement with or without a capsule-like rim. In contrast, findings that are highly suggestive or diagnostic of pancreatic cancer include a low density mass, dilatation and/or cutoff of the pancreatic duct, and distal pancreatic atrophy.

Endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP) may reveal a narrowed main and dorsal pancreatic duct; diffuse, irregular narrowing of the pancreatic duct (beaded appearance), or a focal stricture of the pancreatic duct, proximal or distal common bile duct; or irregular narrowing of the intrahepatic ducts.A stricture in the common bile duct or the finding of a lesion in the head of the pancreas often prompts consideration of malignancy. Thus, it may not be possible to distinguish AIP from pancreatic cancer based solely upon imaging tests.

Endoscopic ultrasonography and transabdominal ultrasonography have also been evaluated in patients with AIP.

Distinction from PSC: certain cholangiographic features may help distinguish AIP from primary sclerosing cholangitis (PSC), which has similar clinical features and, in a small proportion of patients, elevations in serum IgG4 that are less pronounced than those in AIP. In one report, band-like strictures, a beaded or pruned-tree appearance, and diverticulum-like formation were more frequent in PSC. By contrast, segmental strictures, long strictures with prestenotic dilation, and strictures of the distal common bile duct were more common in AIP.Another distinguishing feature is that AIP but not PSC typically responds to glucocorticoid therapy.

Serologic testing for IgG4 is an important component of evaluating a patient suspected of having autoimmune pancreatitis. IgG4 accounts for only 5 to 6 percent of the total serum IgG in healthy subjects. Serum concentrations of IgG4 that are ≥ 2 times the upper limit of normal (140 mg/dL) are diagnostic or highly suggestive of AIP, but may not rule out pancreatic cancer. This cutoff was chosen because values less than twice the upper limit of normal (serum IgG4 ≤ 280 mg/dL) are seen in up to 10 percent of individuals with pancreatic cancer.

Antibodies against plasminogen-binding protein (Anti-PBP): a serologic marker has been identified that is present in most patients with autoimmune pancreatitis. However, these antibodies were also may present in patients with pancreatic cancer. As a result, it cannot be used to distinguish between these two diseases.

Treatment of autoimmune pancreatitis (AIP) is based upon observational data, since there have been no randomized controlled trials. Comparison among studies can be difficult because of heterogeneous patient groups, use of different diagnostic criteria, and definitions of response. Despite these limitations, most patients respond to glucocorticoid therapy. AIP often responds to glucocorticoids, both improving clinical manifestations and potentially preventing complications. In most reports, one-half to two-thirds of patients responded to glucocorticoids but about 25 percent required a second course of treatment, while a smaller proportion needed continuous treatment.

Immunomodulatory drugs: limited data suggest that immunomodulatory drugs (azathioprine has been best studied) are effective in patients' flare while still treated with glucocorticoids or relapse when glucocorticoids are given. Treatment with rituximab, a monoclonal antibody, was reported but further data are required before such an approach can be recommended.

Alcoholic chronic pancreatitis

Excessive alcohol consumption is the most common cause of pancreatitis, accounting for about 60 % of all cases. In the affected gland, alcohol appears to increase protein secretion from acinar cells while decreasing fluid and bicarbonate production from ductal epithelial cells. The resulting viscous fluid results in proteinaceous debris becoming inspissated within the lumen, causing ductular obstruction, upstream acinar atrophy, and fibrosis. GP2, which is secreted from the acinar cell and is homologous to a protein involved in renal tubular casts, is an integral component of these ductal plugs. Lithostathine (formerly called pancreatic stone protein), which also is produced by acinar cells, accounts for about 5 % of secretory protein and inhibits the growth of calcium carbonate crystals. Abnormal lithostathine S1, whether inherited or acquired through trypsin digestion, appears to play a role in stone formation; it is insoluble at the neutral

pH of pancreatic juice and is the major constituent of pancreatic stones. A competing theory suggests that the persistent demands of metabolizing alcohol (and probably other xenobiotics, such as drugs, tobacco smoke, environmental toxins, and pollution) cause oxidative stress within the pancreas and may lead to cellular injury and organ damage, especially in the setting of malnutrition. Oxidative and nonoxidative pathways metabolize ethanol. Alcohol dehydrogenase oxidatively metabolizes ethanol first to acetaldehyde and then to acetate. When the alcohol concentration increases, cytochrome P-450 2E1 is induced to meet the metabolic demands. Although these reactions occur principally in the liver, further increases in ethanol concentration induce pancreatic cytochrome P-450 2E1, and the level of acetate within the pancreas begins to approach that observed in the liver. Reactive oxygen species produced by this reaction may overwhelm cellular defenses and damage important cellular processes. Although nonoxidative metabolism of ethanol is a minor pathway, the fatty acid ethyl esters produced by this reaction may cause cellular injury and are synthesized in the pancreas to a greater extent than in other organ systems. Because fewer than 5–10 % of people with alcoholism develop chronic pancreatitis, another factor or factors must place these individuals at risk. Researchers have studied genetic polymorphisms of ethanol-oxidizing enzymes, but to date, none have correlated with a susceptibility to alcohol-induced pancreatitis. A mutation in the gene encoding the serine protease inhibitor, Kazal type 1, has been identified in patients with chronic pancreatitis. The N34S mutation was detected in 5.8 % of 274 patients with alcoholic chronic pancreatitis, compared with 1.0 % of people with alcoholism without pancreatitis. Although all patients were heterozygous for the mutation, it provides evidence for abnormalities in the pancreatic protease/protease inhibitor system playing a role in the pathogenesis of alcoholic chronic pancreatitis.

Hereditary pancreatitis

Several inherited disorders also are considered metabolic in origin. Hereditary pancreatitis is an autosomal dominant disorder with an 80 % penetrance, accounting for about 1 % of cases. Research of families with hereditary pancreatitis has led to the identification of several mutations in the cationic trypsinogen gene on chromosome 7. These mutations apparently render the activated enzyme resistant to second-line proteolytic control mechanisms. Mutations were found in the pancreatic secretory serine protease inhibitor Kazal type 1 (SPINK1) gene in 18 of 96 patients with idiopathic or hereditary chronic pancreatitis.

Cystic fibrosis in pancreatitis: cystic fibrosis, one of the most common genetic abnormalities, is an autosomal recessive disorder accounting for a small percent of patients with chronic pancreatitis. The cystic fibrosis transmembrane regulator (CFTR) gene transcribes a protein important in regulating chloride transport across cellular membranes.

Several hundred mutations of the CFTR gene have been identified, and the clinical manifestation of any given mutation depends on how severely it affects the protein's ability to regulate chloride transport. Different mutations in CFTR are associated with different functional statuses of the exocrine pancreas. Specific CFTR genotypes are significantly associated with pancreatitis. Patients with genotypes associated with mild phenotypic effects have a greater risk of developing pancreatitis than do patients with genotypes associated with moderate-severe phenotypes.

Idiopathic chronic pancreatitis

This form of chronic pancreatitis accounts for approximately 30% of cases. It has been arbitrarily divided into early onset and late-onset forms. While the cause of idiopathic chronic pancreatitis is not yet known, some evidence points to atypical genetic mutations in CFTR, cationic trypsinogen, and other proteins.

Congenital abnormalities in chronic pancreatitis: congenital abnormalities, such as pancreas divisum and annular pancreas divisum, are uncommon (even rare) causes of chronic pancreatitis and usually require an additional factor to induce chronic pancreatitis. For example, while pancreas divisum usually does not cause chronic pancreatitis, patients with divisum

and minor papilla stenosis are at risk. In these patients, clear evidence of disease exists in the dorsal pancreas, whereas the ventral pancreas is normal histologically.

Acquired obstructive chronic pancreatitis

Acquired obstructive forms typically result from blunt abdominal trauma or accidents involving motor vehicles, bicycles, horses, or, on occasion, severe falls. In these cases, the pancreas is whiplashed against the spine, causing trauma to the ductal system and resulting in a stricture close to the surgical genu. In rare instances, chronic inflammatory conditions affecting the duodenum, or primarily the duodenal papilla, can induce fibrosis and papillary stenosis in a subset of patients, leading to chronic pancreatitis.

Other additional causes of chronic pancreatitis include the following:

- Hyperlipidemia (usually type I and type V) — However, hyperlipidemia usually presents with repeated attacks of acute pancreatitis.
- Hypercalcemia due to hyperparathyroidism — Now is a rare cause of chronic pancreatitis, probably because automation of serum chemistries reveals hypercalcemia before it results in pancreatitis.
- Nutritional, or tropical, chronic pancreatitis — Rare in the United States, but an important cause of disease in other parts of the world
- Medications — An infrequent, or possibly underrecognized, cause of chronic pancreatitis.
- Obstruction of the flow of pancreatic juice can cause chronic pancreatitis. Obstructive forms account for less than 10 % of cases and may be congenital or acquired.

Prognosis

The prognostic factors associated with chronic pancreatitis are age at diagnosis, smoking, continued use of alcohol, and the presence of liver cirrhosis.

The overall survival rate is 70 % at 10 years and 45 % at 20 years. In an international study, 559 deaths occurred among patients with chronic pancreatitis, compared with an expected number of 157, which creates a standard mortality ratio of 3.6. Taking the opposite view, the 10-year mortality rate is 30 %, and the 20-year mortality rate is 55 %. The risk of developing pancreatic cancer is approximately 4 % at 20 years.

The most common complications of chronic pancreatitis are pseudocyst formation and mechanical obstruction of the duodenum and common bile duct. Less frequent complications include pancreatic ascites or pleural effusion, splenic vein thrombosis with portal hypertension, and pseudoaneurysm formation of the splenic artery.

Pseudocyst

A pseudocyst is a collection of pancreatic juice enclosed by a wall of fibrous or granulation tissue. It arises as a consequence of acute pancreatitis, pancreatic trauma, or chronic pancreatitis. The clinical challenge is to diagnose a cystic pancreatic structure correctly as a pseudocyst. As many as 5 % of cysts are retention cysts, another 5 % of these cysts are either congenital in origin or acquired (as in von Hippel-Lindau syndrome), and 10 % are neoplastic in origin (mucinous vs serous cyst). Pseudocysts develop in approximately 10 % of patients with chronic pancreatitis. They develop as a result of ductal disruptions rather than from peripancreatic fluid accumulations that lead to pseudocyst formation in the setting of acute pancreatitis. Pseudocysts may be single or multiple and can be small or large, and they can be located either within or outside of the pancreas. Most pseudocysts communicate with the pancreatic ductal system and contain high concentrations of digestive enzymes. The walls of pseudocysts are formed by adjacent structures, such as the stomach, transverse mesocolon, gastrocolic omentum, and pancreas. The lining of pancreatic pseudocysts consists of fibrous and granulation tissue; the lack of an epithelial lining distinguishes pseudocysts from true cystic lesions

of the pancreas. Most pseudocysts are asymptomatic. They can, however, produce a wide range of clinical problems, depending upon the location and extent of the fluid collection. Expansion of the pseudocyst can produce abdominal pain, duodenal or biliary obstruction, vascular occlusion, or fistula formation into adjacent viscera, the pleural space, or pericardium. Spontaneous infection with abscess formation can occur. Pancreatic ascites and pleural effusion can result from disruption of the pancreatic duct, leading to fistula formation to the abdomen or chest, or rupture of a pseudocyst with tracking of pancreatic juice into the peritoneal cavity or pleural space. The indications for drainage of pseudocysts include rapid enlargement, compression of surrounding structures, pain, or signs of infection. Endoscopic retrograde pancreatograms may be helpful prior to drainage to rule out a stricture of the pancreatic duct, which can lead to persistent drainage from the pseudocyst.

Bile obstruction and duodenal obstruction

Symptomatic obstruction of the bile duct and/or duodenum develops in 5–10 % of patients with chronic pancreatitis. Postprandial pain and early satiety are characteristic of duodenal obstruction, while pain and abnormal liver function test results (including hyperbilirubinemia) are suggestive of a bile duct stricture. These complications are most commonly seen in patients with dilated pancreatic ducts; they are either due to inflammation and fibrosis in the head of the pancreas or are the result of a pseudocyst. Drainage of an obstructing pseudocyst can be accomplished surgically by gastrojejunostomy or choledochoenterostomy. Endoscopic stenting may be helpful for benign bile duct strictures.

Additional complications of chronic pancreatitis

Diabetes mellitus is a late manifestation in about one third of patients. The tendency to develop ketoacidosis is low. The presence of the splenic vein at the posterior surface of the pancreas predisposes it to thrombosis from adjacent pancreatic inflammation. Patients who are affected can develop gastric varices as a result of associated portal hypertension. Splenectomy is usually curative for patients who develop bleeding from gastric varices. Pseudoaneurysm is rare, but it can be deadly complication. Affected vessels, including the splenic, hepatic, gastroduodenal, and pancreaticoduodenal arteries, are in close proximity to the pancreas. Surgery for bleeding pseudoaneurysms is challenging and associated with high morbidity and mortality.

18. IRRITABLE BOWEL SYNDROME

Definitions and introduction

Irritable bowel syndrome (IBS) is a functional GI disorder characterized by abdominal pain and altered bowel habits in the absence of specific and unique organic pathology, although microscopic inflammation has been documented in some patients.

Population-based studies estimate the prevalence of irritable bowel syndrome at 10–20 % and the incidence of irritable bowel syndrome at 1–2 % per year. Irritable bowel syndrome (IBS) is a functional GI disorder characterized by abdominal pain and altered bowel habits in the absence of specific and unique organic pathology. Osler coined the term mucous colitis in 1892 when he wrote of a disorder of mucorrhea and abdominal colic with a high incidence in patients

with coincident psychopathology. Since that time, the syndrome has been referred to by sundry terms, including spastic colon, irritable colon, and nervous colon. In the past, irritable bowel syndrome has been considered a diagnosis of exclusion; however, it is no longer considered a diagnosis of exclusion, but it does have a broad differential diagnosis. No specific motility or structural correlates have been consistently demonstrated; however, experts suggest the use of available guidelines can minimize testing and aid in diagnosis.

Pathophysiology

Traditional theories regarding pathophysiology may be visualized as a 3-part complex of altered GI motility, visceral hyperalgesia, and psychopathology. A unifying mechanism is still unproven.

Altered GI motility includes distinct aberrations in small and large bowel motility. The myoelectric activity of the colon is composed of background slow waves with superimposed spike potentials. Colonic dysmotility in irritable bowel syndrome manifests as variations in slow-wave frequency and a blunted, late-peaking, postprandial response of spike potentials. Patients who are prone to diarrhea demonstrate this disparity to a greater degree than patients who are prone to constipation. Small bowel dysmotility manifests in delayed meal transit in patients prone to constipation and in accelerated meal transit in patients prone to diarrhea. In addition, patients exhibit shorter intervals between migratory motor complexes (the predominant interdigestive small bowel motor patterns). Current theories integrate these widespread motility aberrations and hypothesize a generalized smooth muscle hyperresponsiveness. They describe increased urinary symptoms, including frequency, urgency, nocturia, and hyperresponsiveness to methacholine challenge. Visceral hyperalgesia is the second part of the traditional 3-part complex that characterizes irritable bowel syndrome. Enhanced perception of normal motility and visceral pain characterizes irritable bowel syndrome. Rectosigmoid and small bowel balloon inflation produces pain at lower volumes in patients than in controls. Notably, hypersensitivity appears with rapid but not with gradual distention. Patients who are affected describe widened dermatomal distributions of referred pain. Sensitization of the intestinal afferent nociceptive pathways that synapse in the dorsal horn of the spinal cord provides a unifying mechanism.

Psychopathology is the third aspect. Associations between psychiatric disturbances and irritable bowel syndrome pathogenesis are not clearly defined. Patients with psychological disturbances relate more frequent and debilitating illness than control populations. Patients who seek medical care have a higher incidence of panic disorder, major depression, anxiety disorder, and hypochondriasis than control populations. A study has suggested that patients with irritable bowel syndrome may have suicidal ideation and/or suicide attempts strictly as a result of their bowel symptoms. Clinical alertness to depression and hopelessness is mandatory. This is underscored by another study that revealed that patient complaints that relate to

functional bowel disorders may be trivialized. An Axis I disorder coincides with the onset of GI symptoms in as many as 77 % of patients. A higher prevalence of physical and sexual abuse has been demonstrated in patients with irritable bowel syndrome. Whether psychopathology incites development of irritable bowel syndrome or vice versa remains unclear.

Microscopic inflammation has been documented in some patients. This concept is groundbreaking in that irritable bowel syndrome had previously been considered to have no demonstrable pathologic alterations. Both colonic inflammation and small bowel inflammation have been discovered in a subset of patients with irritable bowel syndrome, as well as in patients with inception of irritable bowel syndrome after infectious enteritis (postinfectious irritable bowel syndrome). Risk factors for developing postinfectious irritable bowel syndrome include longer duration of illness, the type of pathogen involved, smoking, female gender, an absence of vomiting during the infectious illness, and young age. Laparoscopic full-thickness jejunal biopsy samples revealed infiltration of lymphocytes into the myenteric plexus and intraepithelial lymphocytes in a subset of patients in one study. Neuronal degeneration of the myenteric plexus was also present in some patients. Patients with postinfectious irritable bowel syndrome may have increased numbers of colonic mucosal lymphocytes and enteroendocrine cells. Enteroendocrine cells in postinfectious irritable bowel syndrome appear to secrete high levels of serotonin, increasing colonic secretion and possibly leading to diarrhea. Small bowel bacterial overgrowth has been heralded as a unifying mechanism for the symptoms of bloating and distention common to patients with irritable bowel syndrome. This has led to proposed treatments with probiotics and antibiotics. The fecal microflora also differs among patients with irritable bowel syndrome versus controls. A sophisticated molecular analysis suggested an alteration in the patterns and the contents of gut bacteria.

Postulated etiologies of irritable bowel syndrome

Abnormal transit profiles and an enhanced perception of normal motility may exist. Up to one third of patients with irritable bowel syndrome may have altered colonic transit. Delayed colonic motility may be more common in patients with constipation-predominant irritable bowel syndrome than in healthy controls. Similarly, accelerated colonic transit may be more common in patients with diarrhea-predominant disease than in healthy controls. Local histamine sensitization of the afferent neuron causing earlier depolarization may occur.

Causes related to enteric infection

Colonic muscle hyperreactivity and neural and immunologic alterations of the colon and small bowel may persist after gastroenteritis. Psychological comorbidity independently predisposes the patient to the development of postinfectious irritable bowel syndrome. Psychological illness may create a proinflammatory cytokine milieu, leading to irritable bowel syndrome through an undefined mechanism after acute infection.

Infection with Giardia lamblia has been shown to lead to an increased prevalence of irritable bowel syndrome, as well as chronic fatigue syndrome. In a historic cohort study of patients with G lamblia infection as detected by stool cysts, the prevalence of irritable bowel syndrome was 46.1 % as long as 3 years after exposure, compared with 14 % in controls.

Central neurohormonal mechanisms

Abnormal glutamate activation of N- methyl-D-aspartate (NMDA) receptors, activation of nitric oxide synthetase, activation of neurokinin receptors, and induction of calcitonin gene-related peptide have been observed. The limbic system mediation of emotion and autonomic response enhances bowel motility and reduces gastric motility to a greater degree in patients who are affected than in controls. Limbic system abnormalities, as demonstrated by positron emission tomography, have been described in patients with irritable bowel syndrome and in those with major depression. The hypothalamic-pituitary axis may be intimately involved in the origin. Motility disturbances correspond to an increase in hypothalamic corticotropin-releasing factor (CRF) production in response to stress. CRF antagonists eliminate these changes.

Additional etiologic factors

Bloating and distention may also occur from intolerance to dietary fats. Reflex-mediated small bowel gas clearance is more impaired by ingestion of lipids in patients with irritable bowel syndrome than in patients without the disorder. Studies of elimination and challenge diets have suggested that poorly absorbed short-chain carbohydrates, in the form of fructose and fructans, may create symptoms among patients with irritable bowel syndrome, as measured by a visual analogue scale. Research suggests that neuronal degeneration and myenteric plexus lymphocytosis may exist in the proximal jejunum. Additionally, colonic lymphocytosis and enteroendocrine cell hyperplasia have been demonstrated in some patients.

Epidemiology

Population-based studies estimate the prevalence of irritable bowel syndrome at 10–20 % and the incidence of irritable bowel syndrome at 1–2 % per year. Of people with irritable bowel syndrome, approximately 10–20 % seek medical care. An estimated 20–50 % of gastroenterology referrals relate to this symptom complex. The incidence is markedly different among countries. American and European cultures demonstrate similar frequencies of irritable bowel syndrome across racial and ethnic lines. However, within the United States, survey questionnaires indicate a lower prevalence of irritable bowel syndrome in Hispanics in Texas and Asians in California. Populations of Asia and Africa may have a lower prevalence of irritable bowel syndrome. The role of different cultural influences and varying health care–seeking behaviors is unclear. In Western countries, women are 2–3 times more likely to develop irritable bowel syndrome than men, although males represent 70–80 % of patients with irritable bowel syn-

drome in the Indian subcontinent. Women seek health care more often, but the irritable bowel syndrome–specific influence of this occurrence remains unknown. Other factors, such as a probably greater incidence of abuse in women, may confound interpretation of this statistic. Patients often retrospectively note the onset of abdominal pain and altered bowel habits in childhood. Approximately 50 % of people with irritable bowel syndrome report symptoms beginning before they were aged 35 years. The development of symptoms in people older than 40 years does not exclude irritable bowel syndrome but should prompt a closer search for an underlying organic etiology.

Diagnosis

Manifestations of IBS are as follows:

- Altered bowel habits.
- Abdominal pain.
- Abdominal distention.

Altered bowel habits in IBS may have the following characteristics:

- Constipation variably results in complaints of hard stools of narrow caliber, painful or infrequent defecation, and intractability to laxatives.
- Diarrhea usually is described as small volumes of loose stool, with evacuation preceded by urgency or frequent defecation.
- Postprandial urgency is common, as is alternation between constipation and diarrhea.
- Characteristically, one feature predominates in a single patient, but significant variability exists among patients.

Abdominal pain in IBS is protean, but may have the following characteristics:

- Pain frequently is diffuse without radiation.
- Common sites of pain include the lower abdomen, specifically the left lower quadrant.
- Acute episodes of sharp pain are often superimposed on a more constant dull ache.
- Meals may precipitate pain.
- Defecation commonly improves pain but may not fully relieve it.
- Pain from presumed gas pockets in the splenic flexure may masquerade as anterior chest pain or left upper quadrant abdominal pain.

Additional symptoms consistent with irritable bowel syndrome are as follows:

- Clear or white mucorrhea of a noninflammatory etiology.
- Dyspepsia, heartburn.
- Nausea, vomiting.
- Sexual dysfunction (including dyspareunia and poor libido).
- Urinary frequency and urgency have been noted.
- Worsening of symptoms in the perimenstrual period.
- Comorbid fibromyalgia.
- Stressor-related symptoms.

Symptoms not consistent with irritable bowel syndrome should alert the clinician to the possibility of an organic pathology. Inconsistent symptoms include the following:

- Onset in middle age or older.
- Acute symptoms (irritable bowel syndrome is defined by chronicity).
- Progressive symptoms.
- Nocturnal symptoms.
- Anorexia or weight loss.
- Fever.
- Rectal bleeding.
- Painless diarrhea.
- Steatorrhea.
- Lactose and/or fructose intolerance.
- Gluten intolerance.

The Rome criteria for the diagnosis of irritable bowel syndrome require that patients have had recurrent abdominal pain or discomfort at least 3 days per month during the previous 3 months that is associated with 2 or more of the following:

- Relieved by defecation.
- Onset associated with a change in stool frequency.
- Onset associated with a change in stool form or appearance.

Supporting symptoms include the following:

- Altered stool frequency.
- Altered stool form.
- Altered stool passage (straining and/or urgency).
- Mucorrhea.
- Abdominal bloating or subjective distention.

Four bowel patterns may be seen with irritable bowel syndrome. These patterns include the following:

- IBS-D (diarrhea predominant).
- IBS-C (constipation predominant).
- IBS-M (mixed diarrhea and constipation).
- IBS-A (alternating diarrhea and constipation).

Management

A comprehensive history, a physical examination, and tailored laboratory and radiographic studies can establish a diagnosis of irritable bowel syndrome in most patients. The American College of Gastroenterologists does not recommend laboratory testing or diagnostic imaging in patients younger than 50 years with typical IBS symptoms and without the following «alarm features»:

- Weight loss.

- Iron deficiency anemia.
- Family history of certain organic GI illnesses (eg, inflammatory bowel disease, celiac sprue, colorectal cancer).

Screening studies to rule out disorders other than IBS include the following:

- Complete blood count with differential to screen for anemia, inflammation, and infection.
- A comprehensive metabolic panel to evaluate for metabolic disorders and to rule out dehydration/electrolyte abnormalities in patients with diarrhea.
- Stool examinations for ova and parasites, enteric pathogens, leukocytes, Clostridium difficile toxin, and possibly Giardia antigen.

History-specific studies include the following:

- Hydrogen breath testing to exclude bacterial overgrowth in patients with diarrhea to screen for lactose and/or fructose intolerance.
- Tissue transglutaminase antibody testing and small bowel biopsy in IBS-D to diagnose celiac disease.
- Thyroid function tests.
- Serum calcium testing to screen for hyperparathyroidism.
- Erythrocyte sedimentation rate and C-reactive protein measurement are nonspecific screening tests for inflammation.

Management of irritable bowel syndrome consists primarily of providing psychological support and recommending dietary measures. Pharmacologic treatment is adjunctive and should be directed at symptoms.

Dietary measures may include the following:

- Fiber supplementation may improve symptoms of constipation and diarrhea.
- Polycarbophil compounds (eg, Citrucel, FiberCon) may produce less flatulence than psyllium compounds (eg, Metamucil).
- Judicious water intake is recommended in patients who predominantly experience constipation.
- Caffeine avoidance may limit anxiety and symptom exacerbation.
- Legume avoidance may decrease abdominal bloating.
- Lactose and/or fructose should be limited or avoided in patients with these contributing disorders.

Although evidence is mixed regarding long-term improvement in GI symptoms with successful treatment of psychiatric comorbidities, the American College of Gastroenterology has concluded the following:

- Psychological interventions, cognitive-behavioral therapy, dynamic psychotherapy, and hypnotherapy are more effective than placebo.
- Relaxation therapy is no more effective than usual care.

Pharmacologic agents used for management of symptoms in IBS include the following:

- Anticholinergics (eg, dicyclomine, hyoscyamine).
- Antidiarrheals (eg, diphenoxylate, loperamide).
- Tricyclic antidepressants (eg, imipramine, amitriptyline).

- Prokinetics.
- Bulk-forming laxatives.
- Serotonin receptor antagonists (eg, alosetron).
- Chloride channel activators (eg, lubiprostone).
- Guanylate cyclase C (GC-C) agonists (eg, linaclotide).
- Antispasmodics (eg, peppermint oil, pinaverium, trimebutine, cimetropium/dicyclomine).

19. ULCERATIVE COLITIS

Definitions and introduction

Ulcerative colitis (UC) is one of the 2 major types of inflammatory bowel disease (IBD), along with Crohn disease. Unlike Crohn disease, which can affect any part of the gastrointestinal (GI) tract, UC characteristically involves the large bowel. Ulcerative colitis is more common in the Western and Northern hemispheres; the incidence is low in Asia and the Far East.

Histocompatibility human leukocyte antigen (HLA)-B27 is identified in most patients with ulcerative colitis, although this finding is not causally associated with the condition and the finding of HLA-B27 does not imply a substantially increased risk for ulcerative colitis. Ulcerative colitis might also be influenced by diet, although diet is thought to play a secondary role. Food or bacterial antigens might exert an effect on the already damaged mucosal lining, which has increased permeability. Ulcerative colitis is a lifelong illness that has a profound emotional and social impact on affected patients. Grossly, the colonic mucosa appears hyperemic, with loss of the normal vascular pattern. The mucosa is granular and friable. Frequently, broad-based ulcerations cause islands of normal mucosa to appear polypoid, leading to the term pseudopolyp. The bowel wall is thin or of normal thickness, but edema, the accumulation of fat, and hypertrophy of the muscle layer may give the impression of a thickened bowel wall. The disease is largely confined to the mucosa and, to a lesser extent, the submucosa. Muscle-layer and serosal involvement is very rare; such involvement is seen in patients with severe disease, particularly toxic dilatation, and reflects a secondary effect of the severe disease rather than primary ulcerative colitis pathogenesis. Early disease manifests as hemorrhagic inflammation with loss of the normal vascular pattern; petechial hemorrhages; and bleeding. Edema is present, and large areas become denuded of mucosa. Undermining of the mucosa leads to the formation of crypt abscesses, which are the hallmark of the disease.

Environmental factors also play a role. For example, sulfate-reducing bacteria, which produce sulfides, are found in large numbers in patients with ulcerative colitis, and sulfide production is higher in patients with ulcerative colitis than in other people. Sulfide production is even higher in patients with active ulcerative colitis than in patients in remission. The bacterial microflora is altered in patients with active disease. A decrease in Klebsiella species is seen in the ileum of patients relative to controls. This difference disappears after proctocolectomy.

Nonsteroidal anti-inflammatory drug (NSAID) use is higher in patients with ulcerative colitis than in control subjects, and one third of patients with an exacerbation of ulcerative colitis report recent NSAID use. This finding leads some to recommend avoidance of NSAID use in patients with ulcerative colitis.

Other factors that may be associated with ulcerative colitis include the following:

- Vitamins A and E, both considered antioxidants, are found in low levels in as many as 16 % of children with ulcerative colitis exacerbation.
- Psychological and psychosocial stress factors can play a role in the presentation of ulcerative colitis and can precipitate exacerbations.
- Smoking is negatively associated with ulcerative colitis. This relationship is reversed in Crohn disease.
- Milk consumption may exacerbate the disease.

Diagnosis

Patients with UC predominantly complain of the following:

- Rectal bleeding.
- Frequent stools.
- Mucous discharge from the rectum.
- Tenesmus (occasionally).
- Insidious onset.
- Lower abdominal pain and severe dehydration from purulent rectal discharge (in severe cases, especially in the elderly).

In some cases, UC has a fulminant course marked by the following:

- Severe diarrhea and cramps.
- Fever.
- Leukocytosis.
- Abdominal distention.

UC is associated with various extracolonic manifestations, as follows:

- Uveitis.
- Pyoderma gangrenosum.
- Pleuritis.
- Erythema nodosum.
- Ankylosing spondylitis.
- Spondyloarthropathies.

Other conditions associated with UC include the following:

- Primary sclerosing cholangitis (PSC).
- Recurrent subcutaneous abscesses unrelated to pyoderma gangrenosum.
- Multiple sclerosis.
- Immunobullous disease of the skin.

Physical findings are typically normal in mild disease, except for mild tenderness in the lower left abdominal quadrant. In severe disease, the following may be observed:

- Fever.
- Tachycardia.
- Significant abdominal tenderness.
- Weight loss.

The severity of UC can be graded as follows:

- *Mild:* Bleeding per rectum, fewer than 4 bowel motions per day.
- *Moderate:* Bleeding per rectum, more than 4 bowel motions per day.
- *Severe:* Bleeding per rectum, more than 4 bowel motions per day, and a systemic illness with hypoalbuminemia (< 30 g/L).

The diagnosis of ulcerative colitis is best made with endoscopy and mucosal biopsy for histopathology. Laboratory studies are helpful to exclude other diagnoses and assess the patient's nutritional status, but serologic markers can assist in the diagnosis of inflammatory bowel disease. Radiographic imaging has an important role in the workup of patients with suspected inflammatory bowel disease and in the differentiation of ulcerative colitis from Crohn disease by demonstrating fistulae or the presence of substantial coexisting more proximal small bowel disease in a patient who turns out to actually have Crohn disease. The initial treatment for ulcerative colitis includes corticosteroids, anti-inflammatory agents, antidiarrheal agents, and rehydration. Surgery is considered if medical treatment fails or if a surgical emergency develops.

Laboratory studies are useful principally in excluding other diagnoses and assessing the patient’s nutritional status. They may include the following:

- Serologic markers: eg, antineutrophil cytoplasmic antibodies (ANCA), anti-Saccharomyces cerevisiae antibodies ASCA).
- Complete blood count (CBC).
- Comprehensive metabolic panel.
- Inflammation markers: eg, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP).
- Stool assays.

Diagnosis is best made with endoscopy and biopsy, on which the following are characteristic:

- Abnormal erythematous mucosa, with or without ulceration, extending from the rectum to part or all of the colon.
- Uniform inflammation, without intervening areas of normal mucosa (skip lesions tend to characterize Crohn disease).
- Contact bleeding may also be observed, with mucus identified in the lumen of the bowel.

The extent of disease is defined by the following findings on endoscopy:

- Extensive disease: Evidence of UC proximal to the splenic flexure.
- Left-side disease: UC present in the descending colon up to, but not proximal to, the splenic flexure.
- Proctosigmoiditis: Disease limited to the rectum with or without sigmoid involvement.

Imaging modalities that may be considered include the following:

- Plain abdominal radiography.
- Double-contrast barium enema examination.

• Cross-sectional imaging studies (eg, ultrasonography, magnetic resonance imaging, computed tomography).
• Radionuclide studies.
• Angiography.

Management

Medical treatment of mild UC includes the following:
• Mild disease confined to the rectum: Topical mesalazine via suppository (preferred).
• Left-side colonic disease: A mesalazine suppository and an oral aminosalicylate (oral mesalazine is preferred to oral sulfasalazine).
• Systemic steroids, when disease does not quickly respond to aminosalicylates.
• Oral budesonide.
• After remission, long-term maintenance therapy (eg, once-daily mesalazine).
Medical treatment of acute, severe UC may include the following:
• Hospitalization.
• Intravenous high-dose corticosteroids.
• Alternative induction medications: cyclosporine, tacrolimus, infliximab, adalimumab, golimumab.
Indications for urgent surgery include the following:
• Toxic megacolon refractory to medical management.
• Fulminant attack refractory to medical management.
• Uncontrolled colonic bleeding.
Indications for elective surgery include the following:
• Long-term steroid dependence.
• Dysplasia or adenocarcinoma found on screening biopsy.
• Disease present 7–10 years.

Surgical options include the following:
• Total colectomy (panproctocolectomy) and ileostomy.
• Total colectomy.
• Ileoanal pouch reconstruction or ileorectal anastomosis.
• In an emergency, subtotal colectomy with end-ileostomy.

Prognosis

Ulcerative colitis may result in disease-related mortality. However, overall mortality is not increased in patients with ulcerative colitis, as compared with the general population. An increase in mortality may be observed among elderly patients with the disease. Mortality is also increased in patients who develop complications (eg, shock, malnutrition, anemia). Evidence suggests that mortality is increased in patients with ulcerative colitis who undergo any form of medical or surgical intervention. Involvement of the muscularis propria in the most severe cases can lead to damage to the nerve plexus, resulting in colonic dysmotility, dilation, and eventual infarction and gangrene, a condition termed toxic megacolon. This condition is characterized by a thin-walled, large, dilated colon that may eventually become perforated. Chronic disease is associated with pseudopolyp formation in about 15–20 % of cases. Chronic and severe cases can be associated with areas of precancerous changes, such as carcinoma in

situ or dysplasia. The most common cause of death of patients with ulcerative colitis is toxic megacolon. Colonic adenocarcinoma develops in 3–5 % of patients with ulcerative colitis, and the risk increases as the duration of disease increases. The risk of colonic malignancy is higher in cases of pancolitis and in cases in which onset of the disease occurs before the age of 15 years. Benign stricture rarely causes intestinal obstruction.

20. CROHN DISEASE

Definitions and introduction

Crohn disease is an idiopathic, chronic inflammatory process of the gastrointestinal tract that can affect any part of the tract from the mouth to the anus. Individuals with this condition often experience periods of symptomatic relapse and remission. Crohn disease is believed to be the result of an imbalance between proinflammatory and anti-inflammatory mediators. Although genetic susceptibility, luminal antigenic drive, and environmental triggers are also important factors, animal models demonstrate that no single factor is sufficient to induce intestinal inflammation. Approximately 30 % of Crohn disease cases involve the small bowel, particularly the terminal ileum, another 20 % involve only the colon, and 45% involve both the small bowel and colon.

Epidemiology

Once considered rare in the pediatric and black populations, Crohn disease is recognized with increasing frequency in children of all ages and in individuals of varying ethnicities. Within Europe and North America, a north-to-south gradient in the frequency of IBD in populations is present. This difference in incidence correlates with the highest frequency of IBD in temperate climates and more industrialized parts of the world, such as Western Europe and North America. As new regions assume Western cultural practices, an increased prevalence of ulcerative colitis is usually found approximately 1 decade before the observed increase in Crohn disease. The overall incidence of Crohn disease in Europe is about 5.6 per 100,000 inhabitants (7.0 per 100,000 person-years in northern centers vs 3.9 in southern centers). In most Western European countries, the incidence has stabilized or slightly increased. Increases are reported from some high-incidence areas (eg, Denmark and Sweden). Earlier studies from the 1980s reported an incidence of 4.1 per 100,000 person-years, whereas data for 2003-2005 indicate an incidence of 8.6 per 100,000 person-years. Incidence figures in Asia range from 0.5 to 4.2 cases per 100,000 persons. The lowest recorded rates of new cases appear to be in South Africa (0.3-2.6 cases per 100,000 persons) and Latin America (0-0.03 cases per 100,000 persons). A systematic review revealed that the highest prevalence for Crohn disease in North America was 319 per 100,000 persons, compared with 322 per 100,000 persons in Europe. The highest annual incidence figures were 20.2 per 100,000 person-years in North America, 12.7 per 100,000 person-years in Europe, and 5.0 per 100,000 person-years in Asia and the Middle East. In time-trend analyses, 75% of the epidemiologic studies showed statistically significant increases in the incidence of Crohn disease over time.

Age-, sex-, and race-related demographics

The age of onset of Crohn disease has a bimodal distribution. The first peak occurs between the ages of 15 and 30 years (late adolescence and early adulthood), and the second oc-

curs mainly in women between the ages of 60 and 70 years. However, most cases begin before age 30 years, and approximately 20–30 % of all patients with Crohn disease are diagnosed before age 20 years. A greater proportion of colonic and distal Crohn disease has been diagnosed in older patients, whereas younger patients have predominantly ileal disease. In general, the frequency of IBD is similar in males and females, with some studies showing a very slight female predominance. The rate of Crohn disease is 1.1–1.8 times higher in women than in men. This pattern is reversed with pediatric IBD, which has a higher incidence in boys than in girls (pediatric male-to-female ratio, ~1.6:1). Crohn disease is reported to be more common in white patients than in black patients and rare in Asian and Hispanic children. Approximately 20 % of all IBD patients are of black descent. Rates are higher in people of Jewish descent, particularly in Ashkenazi Jews and Jews of middle European origin as compared with Sephardic or eastern European Jews.

Pathophysiology

Chronic inflammation from T-cell activation leading to tissue injury is implicated in the pathogenesis of Crohn disease. After activation by antigen presentation, unrestrained responses of type 1 T helper (Th1) cells predominate in Crohn disease as a consequence of defective regulation. Th1 cytokines such as interleukin (IL)-12 and TNF-α stimulate the inflammatory response. Inflammatory cells recruited by these cytokines release nonspecific inflammatory substances, including arachidonic acid metabolites, proteases, platelet activating factor, and free radicals, which result in direct injury to the intestine. Microscopically, the initial lesion starts as a focal inflammatory infiltrate around the crypts, followed by ulceration of superficial mucosa. Later, inflammatory cells invade the deep mucosal layers and, in that process, begin to organize into noncaseating granulomas (see the image below). The granulomas extend through all layers of the intestinal wall and into the mesentery and the regional lymph nodes. Although granuloma formation is pathognomonic of Crohn disease, its absence does not exclude the diagnosis. Macroscopically, the initial abnormality consists of hyperemia and edema of the involved mucosa. Later, discrete superficial ulcers form over lymphoid aggregates and are seen as red spots or mucosal depressions. These can become deep, serpiginous ulcers located transversely and longitudinally over an inflamed mucosa, giving the mucosa a cobblestone appearance. The lesions are often segmental, being separated by healthy areas, and are often referred to as skip lesions. Bowel obstruction is caused initially by significant edema of the mucosa and associated spasm of the bowel. Obstruction is intermittent and can often be reversed by means of conservative measures and anti-inflammatory agents. With further disease progression, the obstruction becomes chronic because of fibrotic scarring, luminal narrowing, and stricture formation. Fistulae may be enteroenteral, enterovesical, enterovaginal, or enterocutaneous. The inflammation extending through the bowel wall may also involve the mesentery and surrounding lymph nodes. Creeping fat may be seen when the mesentery wraps around the bowel surface (see the following image). Serosal inflammation causes adhesions; thus, free perforations are less common in Crohn disease than in other inflammatory bowel conditions.

Etiology

The exact cause of Crohn disease remains unknown. Genetic, microbial, immunologic, environmental, dietary, vascular, and psychosocial factors have been implicated, as have smoking and use of oral contraceptives and nonsteroidal anti-inflammatory agents (NSAIDs). Patients may inherit susceptibility for an aberrant immunologic response to 1 or more of these provoking factors. Interaction between the predisposing genetic factors, environmental factors, host factors, and triggering event is likely necessary for the disease to develop. Studies have found compelling evidence for an inheritable risk for the development of

Crohn disease. However, classic mendelian inheritance is not seen. Most of the genes thought to be involved in the development of the disease play a role in mucosal immunity, and their products are found on the mucosal barrier epithelium. When the genetics of Crohn disease were first investigated, a strong association was found with chromosome 16 (IBD1 gene), which led to the identification of 3 single nucleotide polymorphisms (SNPs), 2 missense and 1 frameshift, in the NOD2 gene (now called CARD15), the first gene clearly identified as a susceptibility gene for Crohn disease.

NOD2/CARD15 is a polymorphic gene involved in the innate immune system. Of its more than 60 variations, 3 play a role in 27 % of patients with Crohn disease, primarily in those with ileal disease. Subsequent studies suggest that CARD15 genotype is associated not only with the onset of disease but also with its natural history. A study in a German and Norwegian cohort showed that patients with 1 of the 3 identified risk alleles for CARD15 were more likely to have either ileal or right-colon disease. Another early genome-wide association study (GWAS) looked at Jewish and non-Jewish case-control cohorts and identified 2 SNPs in the IL23R gene, which encodes 1 subunit of the IL-23 receptor protein. Interestingly, this study also described the promising nature of certain therapies that block the function of IL-23. Further research suggested that one particular polymorphism in the IL23R gene showed the strongest association in a German population. However, another study found that the Arg381Gln substitution is associated with childhood onset of IBD in Scotland. Numerous other loci have been identified as conferring susceptibility to Crohn disease. Several large studies found multiple susceptibility loci and confirmed earlier findings. In a meta-analysis of 3 GWASs, 526 SNPs from 74 distinct genomic loci were found. In addition to loci that have been previously discussed, 21 new loci were found that were associated with an increased risk of developing Crohn disease. Among the new loci were some very interesting implications, including the genes CCR6, IL12B, STAT3, JAK2, LRRK2, CDKAL1, and PTPN22. Most of these genes are involved in signal transduction in certain immune function, as well as genes involved more directly with immune function. The interlectin gene (ITLN1) is expressed in the small bowel and colon and is involved in recognition of certain microorganisms in the intestine. Other GWASs found associations between susceptibility to Crohn disease and polymorphisms in genes associated with the intestinal milieu. One study, involving nearly 20,000 SNPs in 735 individuals with Crohn disease, found an association in the ATG16L1 gene, which encodes the autophagy-related 16-like protein involved in the autophagosome pathway that processes intracellular bacteria. SNPs in other autophagy genes have also been associated with susceptibility to Crohn disease, as in one study examining at 2 polymorphisms that flanked the IRGM gene and that may be in the regulatory material for the gene. Subsequently, various other loci have been implicated in the autophagy pathway as being associated with Crohn disease, with mounting evidence that the autophagosome pathway is very important in the pathogenesis of the disease. Studies have also provided strong support for IBD susceptibility genes on chromosome 5p13.1, which is a gene desert but does modulate expression of the PTGER4 gene. A murine PTGER4 knockout model has been studied and found to exhibit significant susceptibility to severe colitis. A large genomic study of multiple diseases confirmed many of the findings found in earlier studies and identified several additional loci of interest for Crohn disease. A locus at 3p21 is located within the *BSN* gene, which encodes a brain-specific scaffold protein involved in neurotransmitter release. However, the MST1 gene is located nearby and encodes a macrophage stimulation gene, and the authors felt that this represented a more plausible explanation for the association. A locus at 10q24.2 is located near the *NKX2-3* gene, which is a homeodomain-containing transcription factor. Disruption of the homologous gene in a murine model resulted in defective development of the intestine. The investigators hypothesized that changes to expression of this gene could alter the migration of

lymphocytes in the intestine and change its inflammatory response. The last locus discussed in this model is immediately upstream of the PTPN2 on chromosome 18p11 and encodes a T cell protein tyrosine phosphatase, which is a negative regulator of inflammation. Infectious agents such as Mycobacterium paratuberculosis, Pseudomonas species, and Listeria species have all been implicated in the pathogenesis of Crohn disease, suggesting that the inflammation seen with the disease is the result of a dysfunctional, but appropriate, response to an infectious source. Interleukins and TNF-α have also been implicated in the disease process. Crohn disease is characterized by a Th1 cellular immune response pattern that leads to production of IL-12, TNF-α, and interferon gamma. TNF-α has been shown to play a critical role in the inflammation in this disease. Increased production of TNF-α by macrophages in patients with Crohn disease results in increased concentrations of TNF-α in the stool, blood, and mucosa.

Environmental influences such as tobacco use seem to have an effect on Crohn disease. Smoking has been shown to double the risk of Crohn disease, whereas the risk of developing ulcerative colitis is lower in people who smoke than in those who have never smoked or in those who stopped smoking before their diagnosis.

It has been suggested that a diet high in fatty foods may increase the risk of Crohn disease. Concerns about the measles vaccine and the development of the disease have proved to be unfounded. Although appendectomy has been suggested to be protective in ulcerative colitis, it is not a protective factor in Crohn disease.

Diagnosis

The characteristic presentation is abdominal pain and diarrhea, which may be complicated by intestinal fistulization or obstruction. Unpredictable flares and remissions characterize the long-term course. In addition, individuals can experience rectal bleeding, fever, weight loss, malnutrition, bone loss, and vitamin deficiencies. Psychosocial issues (eg, depression, anxiety, and coping difficulty) are common. Pediatric patients may also experience psychological issues regarding quality of life and body image. Laboratory data for Crohn disease are nonspecific and are of value principally in assisting with management. However, various imaging modalities can aid in diagnosis and management; the choice among them depends upon the clinical question being asked. Plain radiography or computed tomography (CT) of the abdomen and pelvis can assess for bowel obstruction or pelvic intra-abdominal abscesses. Small bowel follow-through (SBFT) studies are being supplanted by CT enterography or magnetic resonance (MR) enterography, which is better able to distinguish inflammation from fibrosis. Magnetic resonance imaging (MRI) of the pelvis or endoscopic (transrectal) ultrasonography can identify perianal fistula anatomy and activity and determine the presence or absence of pelvic and perianal abscesses. Endoscopic visualization and biopsy are essential in the diagnosis of Crohn disease. Colonoscopy is done to assess for colonic or terminal ileal disease. Upper GI endoscopy may be used to diagnose esophageal or gastroduodenal disease and is recommended for all children, regardless of the presence or absence of upper GI symptoms.

Examination for Crohn disease includes the following:

- Vital signs: Normal, but possible presence of tachycardia in anemic or dehydrated patients; possible chronic intermittent fever.

- Gastrointestinal: May vary from normal to those of an acute abdomen; assess for rectal sphincter tone, gross rectal mucosa abnormalities, presence of hematochezia.
- Genitourinary: May include presence of skin tags, fistulae, ulcers, abscesses, and scarring in perianal region; nephrolithiasis, hydronephrosis, and enterovesical fistulae.
- Musculoskeletal: Possible arthritis and arthralgia, particularly in large joints.
- Dermatologic: May show pallor or jaundice, mucocutaneous or aphthous ulcers, erythema nodosum, and pyoderma gangrenosum.
- Ophthalmologic: May reveal episcleritis; possible uveitis.
- Growth delay: Decreased growth velocity (eg, height), pubertal delay.
- Hematologic: Hypercoagulable state.

Laboratory Tests

Although laboratory results for Crohn disease are nonspecific and are of value principally for facilitating disease management, they may also be used as surrogate markers for inflammation and nutritional status and to screen for deficiencies of vitamins and minerals. Routine laboratory studies include the following:

- CBC count.
- Chemistry panel.
- Liver function tests.
- Inflammatory markers.
- Stool studies.
- Serologic tests.

Imaging modalities used for Crohn disease include the following:

- Plain abdominal radiography.
- Barium contrast studies (eg, small bowel follow-through, barium enema, enteroclysis).
- CT scanning of the abdomen.
- CT enterography or magnetic resonance enterography: Replacing small bowel follow-through studies.
- MRI of the pelvis.
- Abdominal and/or endoscopic ultrasonography.
- Nuclear imaging (eg, technetium-99m hexamethyl propylene amine oxime, indium-111).
- Fluorine-18-2-fluoro-2-deoxy-D-glucose scanning combined with positron emission tomography or CT scanning.

The following procedures may help in the evaluation of Crohn disease:

- Endoscopic visualization and biopsy (eg, upper gastrointestinal endoscopy, esophagogastroduodenoscopy, endoscopic retrograde cholangiopancreatography).
- Colonoscopy, ileocolonoscopy.
- Small bowel enteroscopy.
- Interventional radiology: For percutaneous drainages of abscesses.

Management

The general goals of treatment are as follows:

- To achieve the best possible clinical, laboratory, and histologic control of the inflammatory disease with the least adverse effects from medication.
- To permit the patient to function as normally as possible.
- In children, to promote growth with adequate nutrition; the unique problems encountered in the pediatric population necessitate a medical approach that promotes clinical improvement and reverses growth failure with minimal toxicity.

Therapy is typically administered in a "step-up" approach, in which patients with mild disease are treated with 5-aminosalicylic acid (5-ASA), antibiotics, and nutritional therapy. If the patient does not respond to this approach or if the disease is more severe than was initially thought, corticosteroid and immunomodulatory therapy with 6-mercaptopurine (6-MP) or methotrexate is attempted. Finally, biologic and surgical therapies, at the tip of the treatment pyramid, are used. A subpopulation of patients with risk factors for complicated disease and rapid progression may benefit from a "top-down" approach. This approach involves early and aggressive use of tumor necrosis factor (TNF) antagonists, which may alter the natural history of the disease, improve treatment response, and decrease the need for steroid therapy.

The characteristic presentation in Crohn disease is abdominal pain and diarrhea, which may be complicated by intestinal fistulization or obstruction. Unpredictable flares and remissions characterize the long-term course. Other signs and symptoms in Crohn disease may include the following:

- Rectal bleeding.
- Fever.
- Weight loss, anorexia.
- Nausea, vomiting
- Malnutrition, vitamin deficiencies.
- Generalized fatigability.
- Bone loss.
- Psychosocial issues (eg, depression, anxiety, and coping difficulty); pediatric patients may also experience psychological issues regarding quality of life and body image.
- Growth failure in pediatric patients: May precede gastrointestinal symptoms by years.

Medications used in the treatment of Crohn disease include the following:

- 5-Aminosalicylic acid derivative agents (eg, mesalamine rectal, mesalamine, sulfasalazine, balsalazide).
- Corticosteroids (eg, prednisone, methylprednisolone, budesonide, hydrocortisone, prednisolone).

- Immunosuppressive agents (eg, mercaptopurine, methotrexate, tacrolimus).
- Monoclonal antibodies (eg, infliximab, adalimumab, certolizumab pegol, natalizumab).
- Antibiotics (eg, metronidazole, ciprofloxacin).
- Antidiarrheal agents (eg, loperamide, diphenoxylate-atropine).
- Bile acid sequestrants (eg, cholestyramine, colestipol).
- Anticholinergic agents (eg, dicyclomine, hyoscyamine, propantheline).

Surgery

Unlike ulcerative colitis, Crohn disease has no surgical cure. Most patients with Crohn disease require surgical intervention during their lifetime. Surgical management of the terminal ileum, ileocolon, and/or upper gastrointestinal tract may include the following:

- Resection of the affected bowel.
- Ileocolostomy or proximal loop ileostomy.
- Drainage of any septic foci with later definitive resection.
- Strictureplasty.
- Bypass.
- Endoscopic dilatation of symptomatic, accessible strictures.

Surgical management of the colon may include the following:

- Subtotal or total colectomy with end ileostomy (laparoscopic or open approach).
- Segmental or total colectomy with or without primary anastomosis.
- Total proctocolectomy or proctectomy with stoma creation.

Prognosis

Crohn disease is a chronic inflammatory condition with an indolent course. Appropriate medical and surgical therapy helps patients to have a reasonable quality of life, with an overall good prognosis and an extremely low risk of a fatal outcome. The risk of surgery at 5-year intervals after diagnosis is as follows:

- 5 years after diagnosis — The cumulative probability of having only 1 surgical procedure is 37 %; 2 or more surgical procedures, 12%; and no surgical procedures, 51 %.
- 10 years after diagnosis — The cumulative probability of having only 1 surgical procedure is 39 %; 2 or more surgical procedures, 23 %; and no surgical procedures, 39 %.
- 15 years after diagnosis — The cumulative probability of having only 1 surgical procedure is 34 %; 2 or more surgical procedures, 36 %; and no surgical procedures, 30 %.

Patients with proximal small bowel disease have a higher risk of mortality than those who have ileal or ileocecal disease. The excess mortality may be ascribed to complications of Crohn disease. Acute Crohn disease of the terminal ileum is often discovered during laparotomy for suspected appendicitis and has an excellent prognosis. The acute episode is usually treated conservatively, and as many as two thirds of patients may show no subsequent evidence of regional enteritis.

21. PNEUMONIA

Definitions and classification

Pneumonia — x-ray based diagnosis of acute lungs inflammation caused by infection.

Pneumonia types:

• Hospital-acquired (or nosocomial) pneumonia (HAP) is pneumonia that occurs 48 hours or more after admission and did not appear to be incubating at the time of admission.

• Ventilator-associated pneumonia (VAP) is a type of HAP that develops more than 48 to 72 hours after endotracheal intubation.

• Healthcare-associated pneumonia (HCAP) is defined as pneumonia that occurs in a non-hospitalized patient with extensive healthcare contact, as defined by one or more of the following:

— Intravenous therapy, wound care, or intravenous chemotherapy within the prior 30 days.

— Residence in a nursing home or other long-term care facility.

— Hospitalization in an acute care hospital for two or more days within the prior 90 days.

— Attendance at a hospital or hemodialysis clinic within the prior 30 days.

Epidemiology: HAP is the leading cause of death among hospital-acquired infections, with estimates of HAP-associated mortality ranging from 20 to 50 percent. Most cases of HAP occur outside of intensive care units. However, the highest risk for HAP is in patients on mechanical ventilation (ie, VAP).

The pathogenesis of HAP, VAP, and HCAP is related to the number and virulence of microorganisms entering the lower respiratory tract and the response of the host (eg, mechanical, humoral, and cellular host defenses). The primary route of infection of the lungs is through microaspiration of organisms that have colonized the oropharyngeal tract (or, to lesser extent, the gastrointestinal tract). Approximately 45 percent of healthy subjects aspirate during sleep, and an even higher proportion of severely ill patients aspirate routinely. Although frequently regarded as partially protective, the presence of an endotracheal tube permits the aspiration of oropharyngeal material or bacteria of gastrointestinal origin. Depending upon the number and virulence of the organisms reaching the lung, pneumonia may ensue.Hospitalized patients often become colonized with microorganisms acquired from the hospital environment, and as many as 75 percent of severely ill patients will be colonized within 48 hours. The most common mechanism of infection in mechanically ventilated patients is direct contact with environmental reservoirs, including respiratory devices and contaminated water reservoirs. Such contamination frequently occurs despite rigorous cleaning of ventilator equipment because disposable tubing used in respiratory circuits or tracheostomy or endotracheal tubes may become contaminated in the process of routine nursing care or via the (contaminated) hands of hospital personnel.In addition, the near sterility of the stomach and upper gastrointestinal tract may be disrupted by alterations in gastric pH due to illness, medications, or enteric feedings. For this reason, much attention has been paid to the possible adverse effect of ulcer prophylaxis regimens that raise the gastric pH. Less frequently, pneumonia results from inhalation of infectious aerosols or from bacteremia originating in a distant focus.

Microbiology: HAP, VAP, and HCAP may be caused by a wide variety of pathogens and can be polymicrobial. Common pathogens include aerobic gram-negative bacilli (eg, Escherichia coli, Klebsiella pneumoniae, Enterobacter spp, Pseudomonas aeruginosa, Acinetobacter spp) and gram-positive cocci (eg, Staphylococcus aureus, including methicillin-resistant S. aureus (MRSA), Streptococcus spp). Nosocomial pneumonia due to viruses or fungi is significantly less common, except in the immunocompromised patient. The infecting flora in patients with VAP included MSSA, MRSA, P. aeruginosa, Stenotrophomonas maltophilia, Acinetobacter, and other spp. However, a study performed anaerobic cultures using protective brush specimens and bronchoalveolar lavage fluid from 185 patients with possible VAP identified only one anaerobic organism, nonpathogenic Veillonella spp. This suggests that the practice of including anaerobic coverage in the treatment of VAP is unnecessary.The clinical and microbiologic features of HCAP are more similar to HAP and VAP than to CAP but the incidence of specific pathogens varies with the population studied. The incidence of S. aureus in the HCAP and HAP groups were comparable and significantly higher than in the CAP group. The rate of MRSA infection was also higher in HCAP and HAP patients compared to CAP. Besides S. aureus, P. aeruginosa was the only other pathogen with a significant occurrence.

MDR risk factors: the etiology of HAP, VAP, and HCAP depends upon whether the patient has risk factors for multidrug resistant (MDR) pathogens. The frequency of specific MDR pathogens varies among hospitals, specific hospital units, and patient populations including those with recent exposure to antibiotics. An awareness of the susceptibility patterns of the nosocomial pathogens within a given healthcare setting is important for appropriate empiric antimicrobial therapy. The frequency of MDR bacteria as etiologic agents of HAP is increasing, especially among patients in ICUs.Host risk factors for infection with MDR pathogens include:

- Receipt of antibiotics within the preceding 90 days.
- Current hospitalization of ≥5 days.
- High frequency of antibiotic resistance in the community or in the specific hospital unit.
- Immunosuppressive disease and/or therapy.

Patients with HCAP are at variable risk for infection due to MDR pathogens. In a recent review of studies of HCAP published since the development of the guidelines, specific risk factors for MDR pathogens associated with HCAP included hospitalization for ≥2 days during the preceding 90 days, severe illness, antibiotic therapy in the past 6 months, poor functional status as defined by activities of daily living score, and immune suppression. The risk factor of long-term care facility (LTCF) residence applies specifically to those who have more severe illness, prior antibiotic therapy in the preceding six months, or poor functional status as defined by activities of daily living score.

Principles of diagnosis

The clinical diagnosis of HAP, VAP, and HCAP is difficult in part because the clinical findings are nonspecific. The guidelines concluded that HAP, VAP, or HCAP should be suspected in patients with a new or progressive infiltrate on lung imaging as well as clinical characteristics such as:

- Fever.
- Purulent sputum.
- Leukocytosis.
- Decline in oxygenation.

The presence of a new or progressive radiographic infiltrate plus at least two of the three clinical features (fever > 38 ºC, leukocytosis or leukopenia, and purulent secretions) represents a clinically relevant combination of criteria for starting empiric antimicrobial therapy. When findings at autopsy are used as a standard of reference, this combination of findings resulted in 69 percent sensitivity and 75 percent specificity for pneumonia.

Principles of treatment

Multidrug resistance (MDR) in gram-negative bacilli, which are an important cause of HAP, VAP, and HCAP, is variably defined as resistance to at least two, three, four, or eight of the antibiotics typically used to treat infections with these organisms.

Panresistance refers to those gram-negative organisms with diminished susceptibility to all of the antibiotics recommended for the empiric treatment of VAP, including, cefepime, ceftazidime, imipenem, meropenem, piperacillin-tazobactam, ciprofloxacin, and levofloxacin.

Spesiality of different pneumonia forms:

Pneumococcal pneumonia

The pneumococcus (Streptococcus pneumoniae) is the most common agent leading to hospitalization in all age groups. Pneumococcal pneumonia is the paradigm of classic lobar bacterial pneumonia.Although S. pneumoniae is the most common cause of community-acquired pneumonia (CAP), many studies have reported isolation of the organism in only 5 to 18 percent of cases. The rate of isolation increases when more invasive methods are used for obtaining specimens, such as transtracheal aspiration, which eliminates contaminating oropharyngeal flora. It is currently believed that many culture-negative cases of CAP are caused by pneumococcus. The following observations support this belief:

- The sputum culture is negative in about 50 percent of patients with concurrent pneumococcal bacteremia.
- A discriminant functional analysis, in which cases of unknown etiology were evaluated according to the clinical characteristics of S. pneumoniae, Mycoplasma pneumoniae, or other organisms, predicted that the majority of cases were due to pneumococcus.
- A majority of cases of unknown etiology respond to treatment with penicillin.
- Studies using transtracheal aspiration show high yields of S. pneumoniae.
- S. pneumoniae accounts for 66 percent of bacteremic pneumonias.

There has been a resurgence of outbreaks of pneumococcal pneumonia, particularly in chronic care facilities and involving antibiotic resistant strains. Risk factors:

- Alcohol abuse.
- Smoking.
- Asthma.
- Hyposplenism or splenectomy.
- Immunocompromised host.

Additional risk factors include:

- Homelessness.
- Incarceration.
- Pregnancy.
- Crack cocaine use.

Nasopharyngeal colonization: pneumococci are acquired by aerosol or inhalation, leading to colonization of the nasopharynx. Colonization is present in 40 to 50 percent of healthy adults and persists for four to six weeks. Carriage may involve more than one serotype at a time. Disease occurs most frequently upon acquisition of a serotype different from those with which an individual may be colonized. Pneumococcal carriage is more common in smokers than non-smokers. Colonization with pneumococcus is more common in children than adults and young children are responsible for the majority of new serotypes introduced into a household. Asymptomatic pneumococcal colonization in children has been implicated as a reservoir for penicillin- or antibiotic-resistant strains. Prolonged courses of antibiotics may increase the likelihood of colonization with antibiotic-resistant S. pneumoniae.

Mechanisms of pulmonary infection: the pneumococcus is acquired in the nasopharynx and is carried asymptomatically in approximately 40 to 50 percent of individuals at any point in time. Invasive disease, defined by the isolation of S. pneumoniae from a normally sterile site (eg, blood, cerebrospinal fluid, but not sputum), most commonly occurs upon acquisition of a new serotype, typically after an incubation period of one to three days.The development of pneumococcal pneumonia becomes more likely when the dose of inhaled or aspirated pneumococci overwhelms the host defense system in the respiratory tract. Pneumococci are presumably aerosolized from the nasopharynx to the alveolus where they enter alveolar type II cells. This process involves bacterial binding to the receptor for platelet activating factor (PAF), a key pulmonary chemokine. This attachment occurs through bacterial display of surface localized choline, a chemical constituent shared between the bacteria and the human chemokine PAF. Choline has been found on the surface of many pulmonary pathogens, suggesting a common motif for disease at this body site. The host innate defense element C-reactive protein binds to choline and opsonizes these pathogens if they pass from the lungs into the bloodstream. Thus, choline is useful in attaching to the lung but detrimental to the organism in the bloodstream. The pneumonic lesion progresses as pneumococci multiply in the alveolus and invade the alveolar epithelium. Pneumococci pass from alveolus to alveolus through the pores of Cohn, thereby creating inflammation and consolidation strictly along lobar compartments. The center of the spreading lesion shows more advanced inflammation than the edges.The evolution of the consolidated lung was first described by Laennec in 1838:

- Newly involved regions demonstrate engorgement of alveolar capillaries with frothy, serous, blood-tinged fluid in the alveolar spaces. This lesion can be recapitulated by instillation of heat-killed pneumococci into the lung and therefore, may result from the host response to the pneumococcal cell wall.
- The engorgement stage rapidly progresses to red hepatization characterized by a dry, granular, dark red lung surface and alveoli filled with copious, clotted inflammatory exudate. A distinctive feature of the exudate is its "freshness" in that erythrocytes and leukocytes are intact and a fibrin network extends from one alveolus into the next through the pores of Cohn. Pneumococci are intact and alive. Bronchoalveolar lavage fluid contains high amounts of tumor necrosis factor, interleukin-6 and nitric oxide, reflective of strong recruitment of leukocytes to the infected focus. There is little tissue destruction or necrosis during this process, however, perhaps explaining why the patient and lung architecture may often recover fully from these lesions. Infrequently, infection with S. pneumoniae can lead to a necrotizing pneumonia.
- As red hepatization progresses over two to three days, leukocytes pack into the alveoli, erythrocytes are lysed, and epithelial cells degenerate, leading to grey hepatization. Dying pneumococci release the pore-forming toxin pneumolysin that contributes to this stage.
- In the presence of antibody, pneumococci are opsonized by leukocytes and begin to be cleared. Consolidation is still prominent when defervescence occurs. An abrupt disappearance of fever, termed «crisis», is particularly common in children.

• Resolution results in a jelly-like consistency to the lung with a slimy, yellowish exudate. A key feature marking this stage is the involvement of mononuclear cells in the exudate. Absorption of the exudate is remarkably efficient with little organization or permanent scarring.

Clinical manifestations: classically, the patient with pneumococcal pneumonia becomes ill abruptly with fever, chills, cough and pain in the side, often so severe as to limit respiratory movements. This classical presentation, however, typically occurs in younger patients. With increasing age of the population, older patients are more frequently infected with pneumococcal pneumonia, and exhibit fewer symptoms.Tachypnea and increasing systemic toxicity follow initial symptom onset. The degree of distress is not directly related to the extent of pulmonary pathology, suggesting that hypoxia is not the cause of these symptoms, although hypoxia and cyanosis may develop in severe cases.Presentation may differ for patients with bacteremia (bacteremic pneumococcal pneumonia-BPP). Pneumococcal pneumonia may present atypically, especially in the elderly where confusion or delirium may be an initial manifestation. Infrequently, jaundice may occur, leading the clinician to suspect hepatobiliary disease.

The classic description of the sputum in lobar pneumococcal pneumonia is «rusty», due to mixed blood cells and hemoglobin in the sputum, as described in a 1939 text by Heffron.

Auscultatory findings of crepitant rales and bronchial tubular breath sounds are highly localized to the involved segment or lobe. These findings may disappear at the height of consolidation and reappear on resolution (redux crepitus). Consolidation is associated with physical findings of dullness on percussion, egophony, and whispered pectoriloquy.

In addition to classic lobar pneumonia (alveolar infection leading to consolidation of the greater part or all of one or more lobes, typically with air bronchograms), pneumococci can cause bronchopneumonia (infection of the bronchi with a more segmental pattern and without air bronchograms). The prevalence of these two disease patterns differs by serotype, suggesting that underlying pneumococcal components may contribute to variations in disease progression. Lobar pneumonia is associated with serotypes 1, 2, 3, 5, 7 and 8 and bronchopneumonia is associated with serotypes 3, 7, 8, 10, 18, and 20 in adults.

Spectrum of illness: Pneumococcal pneumonia may cause mild disease, but there is a wide range in severity, including patients with overwhelming sepsis in whom the mortality rate may be greater than 25 percent. However, for those who survive the infection, there is usually complete recovery of normal pulmonary function.

Complications: potential complications of pneumococcal pneumonia include bacteremia with metastatic infection, and pulmonary complications of parapneumonic effusion, empyema, necrotizing pneumonia, and lung abscess. Complications that were prevalent in the preantibiotic era (endocarditis, septic arthritis, peritonitis, pericarditis, and meningitis) are now relatively uncommon.Risk factors for a complicated course include older age, preexisting lung disease, immunodeficiency or AIDS and, importantly, acquisition of a nosocomial infection. The risk of overwhelming pneumococcal sepsis is increased in splenectomized patients, since the spleen is a principal site for clearance of this bacterium.In addition to complications related to the acute infection, the stress, hypoxemia, and inflammation associated with pneumococcal pneumonia may precipitate acute cardiac events.

Bacteremia with seeding of other organs was seen in 25 percent of cases in the 1960s, but is much less common now, occurring in less than 1 percent of patients.

Pulmonary complications: pleural effusions secondary to pneumococcal pneumonia are common and are usually sterile parapneumonic effusions. Empyema complicates approximately 5 percent of cases of patients with bacteremic pneumococcal pneumonia. Rarely, pneumococcal infection of the lung results in a lung abscess or necrotizing pneumonia. In some cases, there is polymicrobial infection with S. pneumoniae and anaerobic bacteria. It is likely that the latter account for the necrotizing pneumonia.

Acute cardiac events: community-acquired pneumonia, particularly pneumococcal pneumonia, has been associated with acute cardiac events that may result from cardiac stress, hypoxemia, and inflammation.

Diagnosis: the history, physical findings, and the finding of an opacity on chest radiograph, usually establish the diagnosis of pneumonia. Although lobar consolidation is suggestive of bacterial pneumonia, radiographs cannot reliably differentiate bacterial from nonbacterial pneumonia. The utility of sputum Gram stain and culture remains a source of controversy, and most patients with community-acquired pneumonia are treated empirically. Nevertheless, when a proper sputum sample is obtained, a Gram stain may give immediate etiologic information and is useful. The finding of a predominant organism (eg, gram-positive diplococci) may support the etiology of the pneumonia as pneumococcus.

Guidelines for the treatment of CAP, recommend blood cultures for patients with CAP requiring admission to the hospital under the following circumstances:

- Intensive care admission.
- Cavitary infiltrates.
- Leukopenia.
- Active alcohol abuse.
- Chronic severe liver disease.
- Asplenia.
- Positive pneumococcal urine antigen test.
- Pleural effusion.

Pneumococcal urinary antigen: the need for improved speed and accuracy in the diagnosis of pneumonia has led to the development of a urinary assay for pneumococcal cell wall components. The reported sensitivity ranges from 70 to 90 percent, with a specificity of 80 to 100 percent in adults with pneumonia. The specificity is lower in the setting of nasopharyngeal carriage without infection, and appears to be increased in patients with bacteremia or severe infection.

Polymerase chain reaction (PCR) tests for detecting pneumococcal autolysin or pneumolysin have been developed.

Treatment: the majority of patients with community-acquired pneumonia are treated empirically with a regimen that includes coverage against the pneumococcus.

Suspected pneumococcal pneumonia: in some cases, the clinical picture (rapid onset of fever, chills, and cough with a lobar pneumonia) and Gram's stain are strongly suggestive of pneumococcal infection. However, the presence of pneumococcus should be confirmed by a positive blood culture or urinary antigen test prior to narrowing the spectrum of antibiotic coverage.

Penicillin-susceptible strains: penicillin-sensitive strains can be treated with beta-lactam antibiotics: penicillin, penicillin derivatives or second generation cephalosporins; intravenous medication should be given for patients who require hospitalization, are hypotensive, are vomiting, or have evidence of complications.Third generation cephalosporins offer the convenience of less frequent dosing, but are more expensive than older penicillin and penicillin derivatives. First generation cephalosporins should not be used to treat pneumococcal pneumonia because of poor penetrance into the CSF, thereby increasing the risk for developing pneumococcal meningitis.

Strains with reduced susceptibility: pneumococcal strains with intermediate or full resistance to penicillin are increasing in incidence worldwide. However, studies have not conclusively shown a worse outcome for patients with pneumococcal pneumonia resistant to beta-lactams but treated with these agents. Thus, most concur with guidelines that patients with pneumococcal pneumonia caused by strains with reduced susceptibility, especially those not highly resistant, can be treated with beta-lactams. S. pneumoniae antibiotic resistance may be associated with in-

creased mortality and morbidity; thus, strategies to control resistance through appropriate antimicrobial use need to be encouraged. Comorbidities may be higher in patients with non-susceptible organisms, and use of concordant or discordant therapy did not differentially affect survival. For patients with pneumonia and concomitant meningitis, vancomycin should be added to initial beta-lactam therapy, pending results of antibiotic sensitivity.

Bacteremic pneumonia: although a number of studies cite bacteremia as a risk factor for a poorer outcome or complications, in the absence of critical illness, recommendations for choice and duration of therapy for bacteremic versus nonbacteremic pneumococcal pneumonia do not differ.

Therapy for critical illness: although there is no clear theoretic rationale for the advantage of combination therapy, suggest combination therapy for the subset of patients who are critically ill and require intensive care management. Additionally, other supportive measures for this population should be considered. Careful monitoring and glycemic control are indicated for all patients requiring intensive care intervention. Patients with evidence of shock require early goal-directed fluid resuscitation.

Duration of therapy: there is limited evidence on which to base recommendations regarding the appropriate duration of antibiotic therapy. Therapy is generally continued for five to seven days for uncomplicated disease or until the patient is afebrile for three to five days in more severe cases. It should be noted, however, that some patients with pneumococcal pneumonia have a low-grade fever (≤ 38 ºC) for several days, despite clinical improvement. The duration of combination therapy in patients with severe bacteremic pneumococcal disease is also unclear, but usually should not exceed three to five days followed by appropriate monotherapy for the remainder of the course. In patients who are improving on therapy, suggest switching from combination therapy to monotherapy once susceptibilities are known, which is usually two to three days after cultures are obtained. Patients with bacteremic pneumococcal disease should receive a total of 10 to 14 days of antimicrobial therapy.

Eradication of carriage: in some situations, such as outbreak settings, it may be important to eradicate nasopharyngeal carriage. Following features of the pneumonia associated with mortality:

- Bilateral disease.
- Suspected aspiration.
- Shock.
- HIV infection.
- Renal failure.
- Pneumonia severity index (PSI).

There was no independent association between initial antimicrobial regimen and mortality (beta-lactam monotherapy versus macrolide monotherapy versus beta-lactam plus macrolide versus fluoroquinolone monotherapy or other combination), except for those with a higher PSI score. Additionally, comorbid conditions are a significant predictor of poor outcome in bacteremic pneumococcal disease. Multivariate analysis identified the following independent predictors of death:

- Age > 65 years.
- Residence in a nursing home.
- Presence of chronic lung disease.
- Need for mechanical ventilation.
- High acute physiology and chronic health (APACHE).

No comorbidities or recent antibiotic use in other cases of CAP — For uncomplicated CAP in patients who do not require hospitalization, have no significant comorbidities and/or

use of antibiotics within the last three months, and where there is not a high prevalence of macrolide-resistant strains, recommend any one of the following oral regimens:

- Azithromycin (500 mg on day one followed by four days of 250 mg a day); 500 mg a day for three days, or 2 g single dose (microsphere formulation) are acceptable alternative regimens.
- Clarithromycin XL (two 500 mg tablets once daily) for five days or until afebrile for 48 to 72 hours.
- Doxycycline (100 mg twice a day) for 7 to 10 days.

There is concern that widespread use of fluoroquinolones in outpatients will promote the development of fluoroquinolone-resistance among respiratory pathogens (as well as other colonizing pathogens) and may lead to an increased incidence of C. difficile colitis. In addition, empiric use of fluoroquinolones should not be used for patients at risk for Mycobacterium tuberculosis without an appropriate assessment for tuberculosis infection. The administration of a fluoroquinolone in patients with tuberculosis has been associated with a delay in diagnosis, increase in resistance, and poor outcomes. Because of these concerns, the use of fluoroquinolones is discouraged in ambulatory patients with CAP without comorbid conditions or recent antimicrobial use, unless it is known that there is a high prevalence of high-level macrolide-resistant S. pneumoniae in the local community.

Although erythromycin is the least expensive macrolide, this drug rarely use for three reasons: multiple daily doses over several days are required; compliance is limited by gastrointestinal side effects, as well as dosing; and there is a risk of sudden cardiac death due to QT interval prolongation, particularly when other drugs metabolized by CYP3A4 are taken concurrently.

Comorbidities or recent antibiotic use: the presence of significant comorbidities (ie, chronic obstructive pulmonary disease (COPD), liver or renal disease, cancer, diabetes, chronic heart disease, alcoholism, asplenia, or immunosuppression), and/or use of antibiotics within the prior three months, increases the risk of infection with more resistant pathogens. Recommend one of the following oral regimens for such patients:

- A respiratory fluoroquinolone (gemifloxacin 320 mg daily, levofloxacin 750 mg daily, or moxifloxacin 400 mg daily) for a minimum of five days.
- Combination therapy with a beta-lactam effective against S. pneumoniae (high-dose amoxicillin, 1 g three times daily or amoxicillin-clavulanate 2 g twice daily or cefpodoxime 200 mg twice daily or cefuroxime 500 mg twice daily) PLUS either a macrolide (azithromycin 500 mg on day one followed by four days of 250 mg a day or clarithromycin 250 mg twice daily or clarithromycin XL 1000 mg once daily) or doxycycline (100 mg twice daily). Treatment should be continued for a minimum of five days.
- These regimens are also appropriate where there is a high prevalence of «high-level» macrolide-resistant S. pneumoniae, even in the absence of comorbidity or recent antimicrobial use.

Pathogen-directed therapy: once the etiology of CAP has been identified using reliable microbiologic methods, antimicrobial therapy should be directed at that pathogen.

Combination therapy: several retrospective, observational studies have suggested that treatment with macrolides as part of an initial combination regimen (usually with a cephalosporin) for patients who require hospitalization is associated with decreased mortality and/or shorter hospital stay than treatment with a cephalosporin alone.

Vaccination: patients with CAP should be appropriately vaccinated for influenza and pneumococcal infection. Screening for influenza vaccination status is warranted during influenza season (eg, from October through March in the northern hemisphere) in all patients. Screening for pneumococcal vaccination status is warranted in patients age 65 or older or with other indications for vaccination. Vaccination can be performed during outpatient treatment.

Smoking cessation should be a goal for patients with CAP who smoke.

Indications for hospitalization: determination of whether a patient with CAP can safely be treated as an outpatient or requires hospitalization is essential before selecting an antibiotic

regimen. Severity of illness is the most critical factor in making this determination, but other factors should also be taken into account. These include ability to maintain oral intake, likelihood of compliance, history of substance abuse, cognitive impairment, living situation, and patient functional status. Summarized briefly, prediction rules have been developed to assist in the decision of site of care for CAP. The most commonly used prediction rules are the Pneumonia Severity Index (PSI) and CURB-65. The PSI is better studied and validated, but requires a more complicated assessment. CURB-65 uses five prognostic variables:

- Confusion (based upon a specific mental test or disorientation to person, place, or time).
- Blood urea nitrogen > 7 mmol/L (20 mg/dL).
- Respiratory rate > 30 breaths/minute.
- Blood pressure (BP)- systolic < 90 mmHg or diastolic < 60 mmHg.
- Age > 65 years.

That patients with a CURB-65 score of 0 to 1, were at low risk and could probably be treated as outpatients. Those with a score of 2 should be admitted to the hospital, and those with a score of 3 or more should be assessed for ICU care, particularly if the score was 4 or 5. A simplified version (CRB-65), which does not require testing for blood urea nitrogen, may be appropriate for decision-making in primary care practitioners' offices. With either version, admission to the hospital is recommended if one or more points are present.

Treatment of community-acquired pneumonia in adults who require hospitalization. Empiric therapy: antibiotic therapy is typically begun on an empiric basis, since the causative organism is not identified in an appreciable proportion of patients. In addition, the clinical features and chest radiographic findings are not sufficiently specific to determine etiology and influence treatment decisions. The Gram stain of respiratory secretions can be useful for directing the choice of initial therapy if performed on a good quality sputum sample and interpreted by skilled examiners using appropriate criteria. Benefit from a pathogen-directed approach to treatment, particularly for moderate to severe CAP, may emerge as rapid diagnostic tests become more widely available. However, there has been some concern that narrowing the coverage spectrum of antibiotics when a specific pathogen is identified may undertreat patients who have concurrent infection with atypical organisms. Pathogen-directed treatment (PDT) must be based upon microbiologic studies (rapid diagnostic tests) or clinical presentation. Despite the general use of empiric therapy, testing for a microbial diagnosis is important in clinical or epidemiologic settings suggesting possible infection with an organism that requires treatment different from standard empiric regimens. These include Legionella species, influenza A and B or avian influenza, community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA).

The selection of antimicrobial regimens for empiric therapy is based upon a number of factors, including:

- The most likely pathogen(s).
- Clinical trials proving efficacy.
- Risk factors for antimicrobial resistance.
- Medical comorbidities, which may influence the likelihood of a specific pathogen and may be a risk factor for treatment failure.

Additional factors that may affect the choice of antimicrobial regimen include the potential for inducing antimicrobial resistance, pharmacokinetic and pharmacodynamic properties, safety profile, and cost. The effectiveness of empiric antimicrobial regimens may be decreased by the emergence of newly recognized pathogens, such as community-associated methicillin-resistant Staphylococcus aureus (CA-MRSA). With respect to patients who require hospitalization but not admission to an intensive care unit (ICU), the most frequently isolated pathogens are Streptococcus pneumoniae, respiratory viruses (eg, influenza, parainfluenza,

respiratory syncytial virus), and, less often, Mycoplasma pneumoniae, Haemophilus influenzae, Chlamydophila pneumoniae, and Legionella. The distribution is different in patients with CAP who require admission to an ICU. S. pneumoniae is most common but Legionella, gram-negative bacilli, and Staphylococcus aureus are also important. Community-associated MRSA typically produces a necrotizing pneumonia with high morbidity and mortality. Risk factors for CAP due to gram-negative bacilli include previous antibiotic therapy, immunosuppression, pulmonary comorbidity (eg, cystic fibrosis, bronchiectasis, or repeated exacerbations of chronic obstructive pulmonary disease that require frequent glucocorticoid and/or antibiotic use), probable aspiration, and multiple medical comorbidities (eg, diabetes mellitus, alcoholism). The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines on the management of community-acquired pneumonia recommend empiric antibiotic therapy directed against P. aeruginosa in patients with gram-negative bacilli on Gram stain, since such a regimen will also cover other gram-negative bacilli, such as Klebsiella pneumoniae.

For hospitalized patients on the general wards, the IDSA/ATS guidelines recommend an antipneumococcal fluoroquinolone (eg, levofloxacin, moxifloxacin) or the combination of a beta-lactam plus a macrolide.

For patients with severe CAP requiring intensive care unit (ICU) admission, the IDSA/ATS guidelines recommend a beta-lactam (ceftriaxone, cefotaxime, ampicillin-sulbactam) plus either intravenous azithromycin or an antipneumococcal fluoroquinolone unless there is concern for Pseudomonas or methicillin-resistant S. aureus (MRSA) infection. If Pseudomonas is a concern, an antipseudomonal agent (piperacillin-tazobactam, imipenem, meropenem, or cefepime) PLUS an antipseudomonal fluoroquinolone (ciprofloxacin or high-dose levofloxacin) should be used. If MRSA is a concern, either vancomycin or linezolid should be added.

Treatment regimens: antibiotic recommendations for hospitalized patients with CAP are divided by the site of care (ICU or non-ICU). Most hospitalized patients are initially treated with an intravenous regimen. However, many patients without risk factors for severe pneumonia can be treated with oral therapy, especially with highly bioavailable agents such as the fluoroquinolones.

Hospitalized patients with CAP are initially treated with empiric antibiotic therapy. When the etiology of CAP has been identified based upon reliable microbiologic methods, and there is no laboratory or epidemiologic evidence of coinfection, treatment regimens may be simplified and directed to that pathogen. The results of diagnostic studies that provide identification of a specific etiology within 24 to 72 hours can be useful for guiding continued therapy.

For patients admitted to a general ward, suggest one of the following regimens:

Combination therapy with ceftriaxone (1 to 2 g IV daily), cefotaxime (1 to 2 g IV every eight hours), or ampicillin-sulbactam (1.5 to 3 g IV every six hours) plus a macrolide — azithromycin (500 mg IV or orally daily) or clarithromycin (two 500 mg tablets once daily). Doxycycline (100 mg orally or IV twice daily) may be used as an alternative to a macrolide. Oral therapy with a macrolide or doxycycline is appropriate only for selected patients without evidence of or risk factors for severe pneumonia. Monotherapy with a respiratory fluoroquinolone given either IV or orally except as noted (levofloxacin 750 mg daily or moxifloxacin 400 mg daily).

Empiric therapy of patients requiring admission to an ICU are more likely to have risk factors for resistant pathogens, including community-associated MRSA and Legionella spp.In patients without risk factors for or microbiologic evidence of Pseudomonas aeruginosa or MRSA, recommend intravenous combination therapy with a potent anti-pneumococcal beta-lactam (ceftriaxone 2 g daily, cefotaxime 2 g every eight hours, or ampicillin-sulbactam 1.5 to 3 g every six hours) PLUS either an advanced macrolide (azithromycin 500 mg daily) or a respiratory fluoroquinolone (levofloxacin 750 mg daily or moxifloxacin 400 mg daily). In patients (particularly those with bronchiectasis or COPD and frequent antimicrobial or glucocor-

ticoid use) who may be infected with Pseudomonas aeruginosa or other resistant pathogens, therapy should include agents effective against the pneumococcus, P. aeruginosa, and Legionella spp. Acceptable regimens include combination therapy with a beta-lactam antibiotic and a fluoroquinolone, such as the following regimens:

- Piperacillin-tazobactam (4.5 g every six hours) OR.
- Imipenem (500 mg IV every six hours) OR.
- Meropenem (1 g every eight hours) OR.
- Cefepime (2 g every eight hours) OR.
- Ceftazidime (2 g every 8 hours).

PLUS

- Ciprofloxacin (400 mg every 8 hours) OR.
- Levofloxacin (750 mg daily).

For beta-lactam allergic patients, options include: aztreonam (2 g every 6 hours) plus levofloxacin (750 mg daily); or aztreonam plus moxifloxacin plus an aminoglycoside.The fluoroquinolones may be administered orally when the patient is able to take oral medications. The dose of levofloxacin is the same when given intravenously and orally, while the dose of ciprofloxacin is 750 mg orally twice daily.

If the Gram stain suggests S. aureus, recommend treatment for MRSA with the addition of vancomycin (15 mg/kg every 12 hours, adjusted for renal function) or linezolid (600 mg intravenously twice daily) until the results of culture and susceptibility testing are known. Also suggest empiric therapy of MRSA in patients with severe CAP who have risk factors for community-acquired (CA)-MRSA (prior antimicrobial therapy or recent influenza-like illness). Linezolid may be given orally when the patient is able to receive oral medications. If MRSA is not isolated, coverage for this organism should be discontinued.

Although community-acquired MRSA (CA-MRSA) is typically susceptible to more antibiotics than HA-MRSA, optimal treatment is not well-defined. Vancomycin or linezolid is recommended, although there is a lack of data regarding therapy of this disease. CA-MRSA as the cause of CAP should be suspected when pneumonia develops in a person known to be colonized with CA-MRSA or in those with risk factors for CA-MRSA colonization (eg, contact sport participants, injection drug users, those living in crowded conditions, men who have sex with men, prisoners). CA-MRSA pneumonia should also be suspected in young, previously healthy adults with a recent influenza-like illness. Factors associated with rapid mortality include infection with influenza, the need for ventilator or inotropic support, onset of respiratory distress syndrome, hemoptysis, and leukopenia.

Duration of therapy: based upon the available data, agree with the recommendation of the IDSA/ATS guidelines that patients with CAP should be treated for a minimum of five days. Before stopping therapy, the patient should be afebrile for 48 to 72 hours, breathing without supplemental oxygen (unless required for preexisting disease), and have no more than one clinical instability factor: defined as heart rate (HR) > 100 beats/min, respiratory rate (RR) > 24 breaths/min, and systolic blood pressure (SBP) ≤ 90 mmHg). Longer durations of therapy are needed in the following settings:

- If the initial therapy was not active against the subsequently identified pathogen.
- If extrapulmonary infection is identified.
- If the patient has documented P. aeruginosa or S. aureus pneumonia, or pneumonia caused by some unusual and less common pathogens (eg, Burkholderia pseudomallei, fungus).

The duration of therapy in these patients should be individualized based upon the clinical response to treatment and patient comorbidities.

Follow-up chest radiograph: chest x-ray findings usually clear more slowly than clinical manifestations. Routine chest x-rays for follow-up of CAP patients who are responding clinically are unnecessary.

The most common causes of treatment failure are lack of or delayed response by the host despite appropriate antibiotics and infection with an organism that is not covered by the initial antibiotic regimen. Patient-related factors include severity of illness, neoplasia, aspiration pneumonia, and neurologic disease, while lack of responsiveness to initial therapy may be due to drug-resistant organisms, unusual pathogens (eg, Legionella spp, Pneumocystis jirovecii (formerly P. carinii) or Mycobacterium tuberculosis), or an infectious complication, such as postobstructive pneumonia, empyema, abscess, or superimposed nosocomial pneumonia.In addition, treatment failure may be wrongly presumed when the infiltrates are responding slowly but the patient has developed a superimposed problem. These include noninfectious entities, such as drug fever, malignancy, interstitial lung disease (eg, bronchiolitis obliterans organizing pneumonia), inflammatory conditions, or heart failure, or a hospital-acquired infection of another body system (eg, intravascular catheter infection, urinary tract infection due to an indwelling urinary catheter, or Clostridium difficile infection). Treatment failure may also be incorrectly diagnosed in patients who have repeat sputum cultures that grow a new pathogen. The upper airway of hospitalized patients receiving antibiotics may become colonized, particularly with gram-negative bacilli and S. aureus, and may be misinterpreted as contributing to the pneumonia. Thus, repeat sputum cultures should be interpreted with caution.

Risk factors for nonresponse in hospitalized patients with CAP:

- Multilobar pneumonia.
- Pneumonia caused by Legionella or gram-negative organisms.
- Pneumonia Severity Index (PSI) > 90.
- Treatment with an antimicrobial agent to which the causative organism was not susceptible.

When evaluating a patient who is not responding to therapy, the initial approach may include repeating the history (including travel and pet exposures to look for unusual pathogens), chest x-ray, and sputum and blood cultures. If this is unrevealing, then further diagnostic procedures, such as chest CT, bronchoscopy, and, lung biopsy can be performed.

Chest CT can detect pleural effusion, lung abscess, or central airway obstruction, all of which can cause treatment failure. It may also detect noninfectious causes such as bronchiolitis obliterans organizing pneumonia. Since empyema and parapneumonic effusion can contribute to nonresponse, thoracentesis should be performed in all nonresponding patients with significant pleural fluid accumulation.

Bronchoscopy can evaluate the airway for obstruction due to a foreign body or malignancy, which can cause a postobstructive pneumonia. Protected brushings and bronchoalveolar lavage (BAL) may be obtained for microbiologic and cytologic studies; in some cases, transbronchial biopsy may be helpful. The microbiologic evaluation of the nonresponding patient can be complicated by the effect of the initial antimicrobial therapy that may reduce the yield of pathogen isolation, or select for colonization with resistant organisms. In addition, BAL may reveal evidence of noninfectious disorders or, if there is a lymphocytic rather than neutrophilic alveolitis, viral or Chlamydophila infection.

Thoracoscopic or open lung biopsy may be performed if all of these procedures are nondiagnostic and the patient continues to be ill. The advent of thoracoscopic procedures has significantly reduced the need for open lung biopsy, and its associated morbidity.

Management: failure to respond to antibiotics usually results in one or more of the following: patient transfer to a higher level of care; further diagnostic testing; and escalation of or change in treatment.

Appropriate antibiotic therapy significantly improves survival for patients with hospital-acquiredpneumonia(HAP), ventilator-associatedpneumonia (VAP),and healthcare-associated pneumonia(HCAP). However, establishing the diagnosis of pneumonia in such patients can

be difficult, especially those on mechanical ventilation in whom clinical, radiologic, and microbiologic findings can be due to numerous etiologies besides pneumonia. The difficulty in diagnosis may lead to overtreatment with its attendant risks of superinfection and antibiotic toxicity. When therapy is given, antimicrobial selection should be based upon risk factors for MDR pathogens, including recent antibiotic therapy (if any), the resident flora in the hospital or ICU, the presence of underlying diseases, and available culture data (interpreted with care). For patients with risk factors for MDR pathogens, empiric broad-spectrum, multidrug therapy is recommended. Once the results of pretherapy cultures are available, therapy should be narrowed based upon the susceptibility pattern of the pathogens identified.The implementation of recommendations to assess a patient's status 72 hours after the initiation of therapy and to discontinue antibiotics or narrow the regimen (deescalate therapy) based upon appropriate culture results may reduce the selective pressure for antimicrobial resistance.

Specific antimicrobial considerations: in critically ill patients, in those receiving antibiotics prior to the onset of pneumonia, and in institutions where these pathogens are frequent, coverage of methicillin-resistant S. aureus (MRSA), P. aeruginosa, and antibiotic-resistant gram-negative bacilli, such as Acinetobacter spp, and Legionella should be considered.

If MRSA is a frequent nosocomial pathogen in the institution, linezolid or vancomycin is a necessary first choice for anti-staphylococcal coverage, but should be discontinued if MRSA is not isolated.

The ATS/IDSA guidelines on HAP, VAP, and HCAP recommended either linezolid or vancomycin for infections due to MRSA. The usual doses are:

- Linezolid — 600 mg twice daily intravenously (or orally if or when the patient is able to receive oral medications).
- Vancomycin — 15 to 20 mg/kg (based on actual body weight) intravenously every 8 to 12 hours for patients with normal renal function, with a target serum trough concentration of 15 to 20 mg/L. In seriously ill patients, a loading dose of 25 to 30 mg/kg can be used to facilitate rapid attainment of the target trough concentration.

Gram-negative pathogens(especially Pseudomonas): the best rationale for the use of combination therapy is to provide a greater spectrum of activity when there is risk for MDR pathogens (eg, if the pathogen is resistant to one agent it may be susceptible to the other). Other commonly cited reasons for combination therapy include the potential for synergistic efficacy as well as the potential to reduce the emergence of resistance.

In ICU settings in which extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae are found, cephalosporins should be avoided as monotherapy, due to the selection of resistant organisms when these agents are used. The most reliable agent in this setting is a carbapenem (imipenem-cilastatin, ertapenem, meropenem, or doripenem).

No known MDR risk factors —intravenous antibiotic regimens for empiric coverage of HAP, VAP, and HCAP:

- Ceftriaxone (2 g intravenously daily).
- Ampicillin-sulbactam (3 g intravenously every six hours) or piperacillin-tazobactam (4.5 g intravenously every six hours) if there is concern based on prevailing pathogens within an institution for gram-negative bacilli not treated by ampicillin-sulbactam.
- Levofloxacin (750 mg intravenously daily) or moxifloxacin (400 mg intravenously daily). Both agents may be administered orally at the same doses when the patient is able to take oral medications.
- Ertapenem (1 g intravenously daily).

Choice of a specific agent for empiric therapy should be based on knowledge of the prevailing pathogens (and susceptibility patterns) within the healthcare setting.

Known MDR risk factors: host risk factors for infection with multidrug resistant (MDR) pathogens include receipt of antibiotics within the preceding 90 days, current hospi-

talization of ≥ 5 days, high frequency of antibiotic resistance in the community or in the specific hospital unit, immunosuppressive disease and/or therapy, and presence of risk factors for HCAP. For patients with known MDR risk factors, recommend empiric three-drug combination therapy including:

One of the following:

- Antipseudomonal cephalosporin such as cefepime (2 g intravenously every eight hours) or ceftazidime (2 g intravenously every 8 hours).
- Antipseudomonal carbapenem such as imipenem (500 mg intravenously every six hours) or meropenem (1 g intravenously every eight hours) or doripenem (500 mg intravenously every eight hours; administered over one hour for HAP or HCAP, administered over four hours for VAP).
- Piperacillin-tazobactam (4.5 g intravenously every six hours).
- For patients who are allergic to beta-lactam antibiotics: aztreonam (2 g intravenously every six to eight hours).

PLUS one of the following:

- Antipseudomonal fluoroquinolone, preferred regimen if Legionella is likely, such as ciprofloxacin (400 mg intravenously every eight hours) or levofloxacin (750 mg intravenously daily). These agents may be administered orally when the patient is able to take oral medications.The dose of levofloxacin is the same when given intravenously and orally, while the dose of ciprofloxacin is 750 mg orally twice daily.
- Aminoglycoside such as gentamicin or tobramycin (7 mg/kg intravenously per day adjusted to a trough level < 1 mcg/mL) or amikacin (20 mg/kg intravenously per day adjusted to a trough level < 4–5 mcg/mL). The aminoglycoside can be stopped after five to seven days in responding patients.

PLUS ONE of the following (if MRSA is suspected, there are MRSA risk factors, or there is a high incidence of MRSA locally):

- Linezolid (600 mg intravenously every 12 hours; may be administered orally when the patient is able to take oral medications).
- Vancomycin (15 to 20 mg/kg (based on actual body weight) intravenously every 8 to 12 hours for patients with normal renal function, with a target serum trough concentration of 15 to 20 mg/L). In seriously ill patients, a loading dose of 25 to 30 mg/kg can be used to facilitate rapid attainment of the target trough concentration.

If patients have recently received antibiotics, empiric therapy should generally be with a drug from a different class since earlier treatment may have selected pathogens resistant to the initial class. Because of increasing resistance of pathogens associated wth VAP, HAP, and HCAP, one potential strategy to enhance the antimicrobial potential of a given agent is to optimize the pharmacodynamic effect. Since the beta-lactams are associated with optimal outcomes when the level of the drug is above the minimum inhibitory concentration (MIC) for the pathogen for an appropriate percent of the dosing interval, this effect can potentially be improved with prolonged infusion of the antimicrobial. Colistin, polymyxin, or inhaled aminoglycosides may be considered as potential additional antibiotics in patients with MDR gram-negative bacilli. Aerosolization may increase antibiotic concentrations at the site of infection, and may be particularly useful for treatment of organisms that have high MICs to systemic antimicrobial agents.

Antibiotic regimens: when the etiology of HAP, VAP, or HAP has been identified based upon reliable microbiologic methods and there is no laboratory or epidemiologic evidence of coinfection, treatment regimens should be simplified and directed to that pathogen. Patients who are improving clinically, are hemodynamically stable, and able to take oral medications can be switched to oral therapy. If the pathogen has been identified, the choice of antibiotic for oral therapy is based upon the susceptibility profile for that organism. If a pathogen is not

identified, the choice of antibiotic for oral therapy is either the same antibiotic as the intravenous antibiotic, or an agent in the same drug class, which achieves adequate lung penetration when administered orally. Duration — The duration of therapy should be based upon the clinical response. The standard duration of therapy in the past was 14 to 21 days in part because of a concern for difficult to treat pathogens (eg, Pseudomonas spp). However, a shorter course could significantly reduce the amount of antimicrobial drugs used in hospitals where the emergence of resistant pathogens is a concern.

Prognosis: variables associated with increased mortality include:

- Serious illness at the time of diagnosis (eg, high APACHE score, shock, coma, respiratory failure, ARDS).
- Bacteremia.
- Severe underlying comorbid disease.
- Infection caused by an organism associated with multidrug resistance (Pseudomonas aeruginosa, Acinetobacter spp).
- Multilobar, cavitating, or rapidly progressive infiltrates on lung imaging.
- Delay in the institution of effective antimicrobial therapy.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score has been considered the best system to predict mortality in patients with VAP.

Aspiration pneumonia. Aspiration is a common event even in healthy individuals and usually resolves without detectable sequelae. Markers placed in the stomach can often be detected in the lungs of healthy persons using scintigraphic methods. Aspiration pneumonia refers to the pulmonary consequences resulting from the abnormal entry of fluid, particulate exogenous substances, or endogenous secretions into the lower airways. There are usually two requirements to produce aspiration pneumonia:

- Compromise in the usual defenses that protect the lower airways including glottic closure, cough reflex, and other clearing mechanisms.
- An inoculum deleterious to the lower airways by a direct toxic effect, stimulation of an inflammatory process from a large enough bacterial inoculum, or obstruction due to a sufficient volume of material or particulate matter.

Most pneumonia arises following the aspiration of microorganisms from the oral cavity or nasopharynx. The term aspiration pneumonia should be reserved for pneumonitis resulting from the altered clearance defenses noted above. The pathogens that commonly produce pneumonia, such as Streptococcus pneumoniae, Haemophilus influenzae, gram-negative bacilli, and Staphylococcus aureus, are relatively virulent bacteria so that only a small inoculum is required and the aspiration is usually subtle. A true aspiration pneumonia, by convention, usually refers to an infection caused by less virulent bacteria, primarily anaerobes, which are common constituents of the normal flora in a susceptible host prone to aspiration.

Predisposing conditions: conditions that predispose to aspiration pneumonia include:

- Reduced consciousness, resulting in a compromise of the cough reflex and glottic closure.
- Dysphagia from neurologic deficits.
- Disorders of the upper gastrointestinal tract including esophageal disease, surgery involving the upper airways or esophagus, and gastric reflux.
- Mechanical disruption of the glottic closure or cardiac sphincter due to tracheostomy, endotracheal intubation, bronchoscopy, upper endoscopy, and nasogastric feeding.
- Pharyngeal anesthesia, and miscellaneous conditions such as protracted vomiting, large volume tube feedings, feeding gastrostomy, and the recumbent position.

The three syndromes that are most frequently seen clinically and best studied are chemical pneumonitis, bacterial infection, and airway obstruction.

Chemical pneumonitis: the term “chemical pneumonitis” refers to the aspiration of substances that are toxic to the lower airways, independent of bacterial infection. The prototype and best studied clinical example is chemical pneumonitis associated with the aspiration of gastric acid first described by Mendelson in 1946 and sometimes referred to as Mendelson's syndrome.Bile may also elicit an inflammatory response in the lungs and has been found frequently in endotracheal tubes of patients on ventilators.The following clinical features should raise the possibility of chemical pneumonitis:

- Abrupt onset of symptoms with prominent dyspnea.
- Fever, which is usually low-grade.
- Cyanosis and diffuse crackles on lung auscultation.

Severe hypoxemia and infiltrates on chest radiograph involving dependent pulmonary segments. The dependent lobes in the upright position are the lower lobes. However, aspiration that occurs while patients are in the recumbent position may result in infection in the superior segments of the lower lobes and the posterior segments of the upper lobes.

The diagnosis of acid pneumonitis is usually presumptive based upon the clinical features and course noted above. After a suspected aspiration, chest x-ray abnormalities typically appear within two hours. Bronchoscopy, if performed, demonstrates erythema of the bronchi, indicating acid injury.

Treatment: patients with an observed aspiration should have immediate tracheal suction to clear fluids and particulate matter that may cause obstruction. However, this maneuver will not protect the lungs from chemical injury, which occurs instantly in a manner that has been compared with a «flash burn»; the acid inoculum is rapidly neutralized by the physiologic response.The major therapeutic approach is to support pulmonary function.

Bacterial infection: the most common form of aspiration pneumonia is caused by bacteria that normally reside in the upper airways or stomach. A true aspiration pneumonia usually refers to an infection caused by less virulent bacteria, primarily anaerobes and streptococci, which are common constituents of the normal flora in a susceptible host prone to aspiration. The presenting findings in aspiration pneumonia due to bacterial infection are highly variable depending upon the time the patient is seen during course of the infection, the bacteria involved, and the status of the host. As noted, most cases involve anaerobic bacteria and aerobic or microaerophilic streptococci that normally reside in the gingival crevices. Compared with most cases of community-acquired pneumonia, the tempo of the disease in this type of aspiration pneumonia often evolves slowly and chills are uncommon. There is an association with periodontal disease, and this complication is less common in patients with good dental hygiene and those who are edentulous. Most patients present with the common manifestations of pneumonia including cough, fever, purulent, sputum and dyspnea, but the process evolves over a period of several days or weeks instead of hours. Many patients have accompanying weight loss and anemia as common features of a more chronic process.Although the majority of patients have an indolent course, some patients have a relatively abrupt onset suggestive of a pyogenic pneumonia due to common bacterial pathogens, including Streptococcus pneumoniae. One symptom, which assists in distinguishing these entities, is rigors since patients with aspiration pneumonia almost never have shaking chills. Many patients with aspiration pneumonia do not present with the acute infection but present later with complications characterized by suppuration and necrosis. Lung abscess, necrotizing pneumonia, or empyema secondary to a bronchopleural fistula all represent later stages of untreated aspiration pneumonia. Clinical features, which are characteristic of aspiration pneumonia involving anaerobic bacteria, include:

- Indolent symptoms.
- A predisposing condition for aspiration, usually compromised consciousness due to drug abuse, alcoholism, or anesthesia; or dysphagia.

- Absence of rigors.
- Failure to recover likely pulmonary pathogens with cultures of expectorated sputum.
- Sputum that often has a putrid odor.
- Concurrent evidence of periodontal disease.
- X-ray or computed tomography (CT) scans showing evidence of pulmonary necrosis with lung abscess and/or an empyema.

The presence of putrid discharge in sputum or pleural fluid is regarded as diagnostic of anaerobic infection. Chest radiographs show involvement of dependent pulmonary segments, which are favored in aspiration: the lower lobes when aspiration occurs in the upright position; or the superior segments of the lower lobes or posterior segment of the upper lobes when aspiration occurs in the recumbent position.

Microbiology: anaerobic bacteria are the dominant organisms in the upper airways. The critical role of these microbes in aspiration pneumonia, lung abscess, and empyema was established in the 1970s in studies employing careful techniques for the isolation of anaerobes and transtracheal aspiration as a method to obtain uncontaminated specimens from the lower airways. Expectorated sputum is unsuitable for anaerobic culture because of inevitable contamination by the normal flora of the mouth. There is a limited experience with quantitative cultures of specimens obtained at bronchoscopy by a protected brush or bronchoalveolar lavage, but available data suggest these may be suitable when combined with high quality anaerobic cultures. Another problem is that anaerobic bacteria are extremely difficult to cultivate when specimens are collected after the inception of antibiotic treatment. In current practice, anaerobic bacteria are virtually never detected in pulmonary infections due to lack of access to specimens that are uncontaminated with the normal flora of the upper airways. Specimens with well established validity for anaerobic culture include transthoracic needle aspirate, transtracheal aspirates, and pleural fluid. The major isolates that have been isolated are Peptostreptococcus, Fusobacterium nucleatum, Prevotella, and Bacteroides spp.

Most patients with aspiration pneumonia acquired in the community have a mixed infection that includes anaerobic and aerobic bacteria, especially cases involving aerobic and microaerophilic streptococci which are thought to be important pathogens and necessary to treat.

Treatment: in contrast to chemical pneumonitis, antibiotics are the most important component of treatment of aspiration pneumonia due to bacterial infection. Historically, the antibiotic of choice for the treatment of aspiration pneumonia and lung abscess involving anaerobic bacteria was penicillin, usually given intravenously or orally in high doses. Alternative regimens that appear effective include amoxicillin-clavulanate and penicillin combined with metronidazole. Metronidazole should NOT be used alone since monotherapy is associated with a failure rate of about 50 percent in the treatment of anaerobic pleuropulmonary infections. The presumed reason for the high failure rates with metronidazole is its lack of activity against microaerophilic and aerobic streptococci, which can be cultured in approximately 40 to 70 percent of cases. Among the fluoroquinolones, moxifloxacin is preferred because early studies showed good in vitro activity against anaerobes and a small trial has shown benefit for aspiration pneumonia and primary lung abscess. However, moxifloxacin has not been studied adequately to recommend it as a first-line agent for aspiration pneumonia, and the rate of resistance of anaerobes to this drug is increasing.Otherdrugfor anaerobic lung infections is clindamycin. Drugs that show poor in vitro activity include trimethoprim-sulfamethoxazole, ciprofloxacin, ceftazidime, and aminoglycosides. The utility of ceftriaxone, cefotaxime, and macrolides is not well enough established to recommend.

Choice of regimen: when anaerobic bacteria are probable pathogens in aspiration pneumonia, suggest clindamycin (600 mg IV twice daily followed by 300 mg orally four times daily) as first-line therapy. Alternative agents with activity based upon clinical trials are amoxicillin-

clavulanate (875 mg orally twice daily); or the combination of metronidazole (500 mg orally or IV three times daily) PLUS amoxicillin (500 mg orally three times daily) or penicillin G (1 to 2 million units IV every four to six hours). Drugs that are probably effective, but should not be used preferentially, are moxifloxacin, macrolides, and selected cephalosporins.

Duration: the duration of antibiotics for aspiration pneumonia is arbitrary and not well studied. The usual duration of therapy for cases that are not complicated by cavitation or empyema is 7 to 10 days; shorter therapy may be effective but has not been adequately studied. Patients with associated pleural effusions should have a thoracentesis to exclude empyema, which often complicates pneumonia involving anaerobes. Patients with lung abscess need a longer course of antibiotics, usually until there is radiographic clearance or significant improvement, such as a small stable residual lesion.

Mechanical obstruction: aspiration pneumonia may involve fluid or particulate matter, which are not inherently toxic to the lung, but can cause airway obstruction or reflux airway closure.

Typical fluids that are aspirated and are not toxic to the lungs include:

- Saline.
- Barium.
- Most ingested fluids including water.
- Gastric contents with a pH exceeding 2.5.

The most frequently observed form of aspiration of fluids is simple mechanical obstruction that is noted in victims of drowning. Patients at risk for mechanical obstruction are those who cannot clear the inoculum due to a profound neurologic deficit such as absence of a cough reflex or impaired consciousness.The obvious critical clinical intervention is tracheal suctioning. If a subsequent chest x-ray does not show a pulmonary infiltrate, no further therapy is required except for measures intended to prevent subsequent episodes of aspiration. In hospitalized patients, the most important preventative measure is the semi-upright or upright position.

The severity of respiratory obstruction depends upon the relative size of the object that is aspirated and the caliber of the lower airways. Foreign body aspiration is most common in children from one to three years of age. The usual objects recovered from the lower airways are peanuts, other vegetable particles, inorganic materials, and teeth. Vegetable materials, including peanuts, are problematic because they are not visualized on plain chest radiographs.The clinical consequences depend upon the level of obstruction. Large objects that lodge in the larynx or trachea cause sudden respiratory distress, cyanosis, and aphonia that lead quickly to death if the obstruction is not immediately reversed. This is sometimes referred to as the «café coronary syndrome» because the symptoms simulate those of myocardial infarction and are often seen with aspiration of meat during restaurant dining. The suggested treatment is the Heimlich maneuver consisting of firm and rapid pressure applied to the upper abdomen in an effort to force the diaphragm up to dislodge the particle.

Aspiration of smaller particles cause less severe obstruction. These patients often present with an irritative cough, and chest radiograph shows atelectasis or obstructive emphysema with a cardiac shift and elevated diaphragm. When the obstruction is partial, unilateral wheezing may be appreciated. Bacterial superinfection is a frequent complication when the obstruction or partial obstruction persists for more than one week; the usual pathogens are anaerobic bacteria from the upper airways as described above. The primary therapeutic modality is removal of the foreign object, usually with fiberoptic or rigid bronchoscopy.

Mycoplasma pneumonia

The term «mycoplasma» is widely used to refer to any organism within the class Mollicutes that is composed of five genera (Mycoplasma, Ureaplasma, Acholeplasma, Anaeroplasma, and Asteroloplasma). Over 120 named Mycoplasma species exist and 13 Mycoplasma

species, two Acholeplasma species, and one Ureaplasma species have been isolated from humans. However, only four species are well-established human pathogens:

- Mycoplasma pneumoniae.
- Mycoplasma hominis.
- Mycoplasma genitalium.
- Ureaplasma urealyticum.

Pathogenesis: the mechanisms by which mycoplasma produces infection are becoming better understood. Pathogenic organisms for humans and animals possess specialized tip organelles that mediate their interactions with host cells. This host-adapted survival is achieved by surface parasitism of target cells, the acquisition of essential biosynthetic precursors, and in some cases cell entry and intracellular survival. Toll-like receptor 2 is believed to be important for binding of Mycoplasma and activation of inflammatory mediators, including cytokines. M. pneumoniae grows under both aerobic and anaerobic conditions and can be isolated on media supplemented with serum. The organism most commonly exists in a filamentous form and has adherence proteins that attach to epithelial membranes with particular affinity for respiratory tract epithelium. Once attached, M. pneumoniae produces hydrogen peroxide and superoxide, causing injury to epithelial cells and their associated cilia. However, many of the pathogenic features of infection with M. pneumoniae are believed to be immune-mediated rather than induced directly by the bacteria. An immune-mediated mechanism is supported by the finding that infants and young children infrequently develop pneumonia despite evidence of infection. In addition, the antibodies produced against the glycolipid antigens of M. pneumoniae may act as autoantibodies, since they crossreact with human red cells and brain cells.

Epidemiology

Mycoplasma pneumoniae is one of the most common causes of atypical pneumonia. M. pneumoniae is transmitted from person-to-person by infected respiratory droplets during close contact. The incubation period after exposure averages three weeks. Infection occurs most frequently during the fall and winter but may develop year-round. The cumulative attack rate in families approaches 90 percent, and immunity is not long-lasting. Recognized outbreaks of Mycoplasma infection have been described in military recruits, institutions for developmentally disabled individuals, hospitals, and in the community including periodic epidemics over a number of years. However, the incidence may be higher in patients with milder disease that can be managed without hospitalization. Incidence estimates vary depending upon the techniques used for diagnosis, the age of the patients, and whether the series include outpatients, hospitalized patients, or both. Mycoplasma pneumoniae infection may worsen asthma symptoms and can produce wheezing in children who do not have asthma.

Clinical features: many infections due to M. pneumoniae are asymptomatic. When present, the signs and symptoms vary according to the stage of illness. The onset of the illness is gradual and is usually heralded by headache, malaise, and low grade fever. Chills are frequent but rigors are rare. Patient complaints usually exceed objective findings since abnormalities on physical examination are often minimal. Symptoms and signs due to M. pneumoniae infection may be divided into those due to respiratory tract or extrapulmonary disease. Most patients with respiratory infection due to M. pneumoniae do not develop pneumonia. The cough due to M. pneumoniae infection ranges from nonproductive to mildly productive, with sputum discoloration occurring late in the disease. Wheezing and dyspnea may occur, although dyspnea is not a common complaint. Chills are common but rigors very rare. Additional respiratory symptoms include pharyngitis, rhinorrhea, and ear pain. Clinically inapparent sinusitis may coexist with pneumonia.

There may be no findings on chest auscultation even if pneumonia is present early in the course of disease. However, scattered rales, wheezes, or both may be present later. Other respira-

tory tract findings may include sinus tenderness, mild erythema of the posterior pharynx, erythema or occasionally bullae of the tympanic membrane, and nonprominent cervical adenopathy.

Extrapulmonary abnormalities are an important part of mycoplasma disease and may suggest the diagnosis. These manifestations include hemolysis; skin rash; joint involvement; and symptoms and signs indicative of gastrointestinal tract, central nervous system, and heart disease. It is not clear whether the pathogenesis of some or all of these entities is due to immune mechanisms or to the direct action of the organisms. Antibodies (IgM) to the I antigen on erythrocyte membranes appear during the course of infection and produce a cold agglutinin response in about 60 percent of patients. Although hemolysis may be severe, it is usually not clinically significant. Dermatologic manifestations may range from a mild erythematous maculopapular or vesicular rash (which is most commonly seen accompanying respiratory tract infections) to the Stevens-Johnson syndrome. Antibiotics may intensify the dermatosensitive potential of M. pneumoniae. Central nervous system (CNS) involvement occurs most frequently in children, with encephalitis as the most frequent manifestation. Other manifestations include aseptic meningitis, peripheral neuropathy, transverse myelitis, cranial nerve palsies, and cerebellar ataxia. Acute transverse myelitis (ATM) and acute disseminated encephalomyelitis (ADEM) can lead to some of the most severe complications associated with mycoplasma infection. Although uncommon, CNS involvement is associated with significant morbidity and mortality. Gastrointestinal symptoms are most often nonspecific but may include hepatitis and, rarely, pancreatitis which may be due in part to antibodies to M. pneumoniae. Rheumatologic symptoms can occur, including tender joints and muscles and a polyarthritis. While arthralgias are common, actual arthritis is rare. Arthritis is believed to result from immune-mediated mechanisms; however, M. pneumoniae has been isolated from synovial fluid in some patients with polyarthritis, suggesting a possible role for direct infection. Cardiac or renal involvement is unusual. Clinically significant glomerulonephritis is a rare complication that is presumed to be secondary to immune complex deposition. Another rare finding is uveitis. Anterior uveitis has been described in case reports of children, adolescents, and adults, and has been found in association with pneumonia as well as meningitis.

Chest radiography: M. pneumoniae involving the lung results in four frequently described chest x-ray patterns:

- Bronchopneumonia.
- Plate-like atelectasis.
- Nodular infiltration.
- Hilar adenopathy.

The most common radiographic finding is the peribronchial pneumonia pattern, which consists of a thickened bronchial shadow, streaks of interstitial infiltration, and areas of atelectasis; these changes have a predilection for the lower lobes. Nodular infiltrates and hilar adenopathy are less common, and result in a broader differential diagnosis, including tuberculosis, mycotic infections, and sarcoidosis. Pleural effusions can be seen in up to 20 percent of patients when lateral decubitus films are performed. Empyema is a rare complication of M. pneumoniae pneumonia.

Laboratory abnormalities: subclinical evidence of hemolytic anemia is present in the majority of patients with pneumonia as suggested by a positive Coombs' test and an elevated reticulocyte count. Cold agglutinin titers are elevated in 50 percent of patients with mycoplasma disease, and the titer usually exceeds 1:128 in patients with pneumonia. With overt hemolysis, titers may be as high as 1:50,000. Elevated cold agglutinin titers can also be seen in a number of other disorders including mononucleosis secondary to Epstein Barr virus or cytomegalovirus, adenovirus pneumonia, other viral illnesses, and in some patients with lymphoma and collagen vascular disorders. The white blood cell count (WBC) may be normal. Thrombocytosis can occur and probably represents an acute phase response, while thrombo-

cytopenia is unusual. In patients with neurologic involvement, the cerebrospinal fluid (CSF) typically reveals a lymphocytic pleocytosis, elevated protein, and normal glucose. Isolation of M. pneumoniae in CSF is possible but rare. A culture is more likely to be positive in encephalitis rather than myelitis. PCR testing for Mycoplasma in the CSF can also be performed, and has been positive in two cases of ATM.

Differential diagnosis: мycoplasma can be difficult to diagnose given both the variety of clinical presentations and the severity of symptoms. Respiratory symptoms can be consistent with a viral-like illness, ranging from rhinovirus to influenza; pharyngitis and cough may be attributed to other bacterial pathogens. Mycoplasma and other atypical pneumonia pathogens are associated with extrapulmonary manifestations more frequently than are more typical bacterial pathogens. However, it is frequently difficult to differentiate among the «atypical pathogens», including Chlamydia pneumoniae, Legionella spp, Chlamydia psittaci, Coxiella burnetii (causing Q fever), and Francisella tularensis (the agent causing tularemia). In some instances, exposure history and the pattern of extrapulmonary manifestations can assist in distinguishing among these organisms. However, the protean manifestations and varying severity of mycoplasma infection can cause confusion in distinguishing mycoplasma from both typical bacterial pathogens causing pneumonia and other atypical pathogens.

Diagnosis: there are no distinguishing clinical or radiologic manifestations that allow a secure diagnosis of Mycoplasma pneumoniae versus other causes of atypical pneumonia such as Chlamydia or Legionella spp. Compared to those with pyogenic pneumonia, however, patients with atypical pneumonia tend to have a more gradual onset of symptoms, more multisystem involvement (ie, abnormal renal or liver function tests, or mild central nervous system findings), and usually have a normal white blood cell count. These findings are neither sufficiently sensitive nor specific to exclude other etiologies. A positive Gram stain and sputum culture can establish the diagnosis of bacterial pneumonia, but some patients cannot produce sputum and others have a false negative result because they have already been treated with antibiotics. Furthermore, sputum Gram stain and culture is not recommended on a routine basis for outpatients with community-acquired pneumonia. Although the isolation of M. pneumoniae on SP-4 medium is possible, culture requires two to three weeks and the organism is fastidious. As a result, the specific diagnosis of M. pneumoniae infection relies upon nonculture techniques. The formation of cold agglutinins is a nonspecific early IgM reaction against the red cell «I» antigen. Cold agglutinins develop in approximately 50 to 75 percent of all patients, one to two weeks after infection. The incidence of cold agglutinins is highest in children and decreases with age. Other bacterial, rickettsial and viral (in particular, influenza) infections can also result in the production of cold agglutinins. Since it is neither sensitive nor specific, the utility of this test has been questioned; it may have a place in the right clinical setting, although do not suggest ordering it routinely. Antibody titers rise seven to nine days after infection and peak at three to four weeks. In the past, the most widely used approach for serodiagnosis was the complement fixation (CF) test, which measured «early» IgM (predominantly) and IgG antibody (to a lesser extent) to M. pneumoniae. More recently, EIA techniques have been used with higf sensitivity and specificity. EIAs are more sensitive for detecting acute infection than culture, and can be comparable in sensitivity to PCR, assuming enough time has elapsed. A positive EIA result is best determined by comparing acute and convalescent phase sera two to three weeks apart. In general, a fourfold or greater increase in titer in paired sera is indicative of infection. A single titer is not felt to be definitive for diagnosis. Antigen detection tests have been developed, and are best used for detection of mycoplasma in respiratory secretions. They have been largely replaced by PCR testing. The antigen capture-enzyme immunoassay (Ag-EIA) is most often positive within seven days of onset. The utility of this technique is reduced by its time-sensitivity, overall low test sensitivity, and cross-reactivity

with other mycoplasmas. Direct polymerase chain reaction (PCR) detects genomic DNA and may be highly sensitive and specific for Mycoplasma pneumoniae in patients with respiratory tract infections. The yield with real-time PCR may be even higher. PCR is not in widespread use for the diagnosis of individual patients due to a lack of standardization of the probe and assay. Unfortunately, there are no diagnostic tests that allow for the reliable, rapid diagnosis of M. pneumoniae. As such, a high clinical suspicion is essential for early treatment of mycoplasma. The diagnosis is usually made in retrospect.

Treatment: since there is no rapid way to confirm the diagnosis of M. pneumoniae pneumonia, treatment begins with empiric therapy for atypical pneumonia. Patients with community-acquired pneumonia require empiric treatment with a regimen that would cover atypical pneumonias. As noted above, indolent onset, extrapulmonary involvement, and normal white blood cell count are findings that favor the presence of atypical pneumonia. Treatment options for outpatient community-acquired pneumonia are presented in the consensus IDSA/ATS guideline: macrolide antibiotics (azithromycin, clarithromycin or erythromycin) are advised as first line treatment. Azithromycin (500 mg orally once daily, initially followed by 250 mg orally for 4 days) has become the most commonly used drug regimen. Erythromycin (333 mg orally three times daily) is less expensive but commonly associated with gastrointestinal side effects. Although the majority of isolates worldwide remain sensitive to macrolides, alternative therapy should be considered if patients do not respond to macrolide therapy, particularly in those who reside in areas where there is a substantial rate of macrolide resistance. Other antibiotic classes, tetracyclines (doxycycline 100 mg orally twice daily) and fluoroquinolones (in particular, levofloxacin and moxifloxacin), may be used as well. Many of these drugs also cover Legionella spp.

Specific mycoplasma therapy: the present mainstays of therapy for possible M. pneumoniae infection are azithromycin, doxycycline, erythromycin, or a fluoroquinolone, such as levofloxacin or moxifloxacin. In several in vitro studies, azithromycin was the most active drug and resistance to this agent did not develop despite multiple passages in the presence of the drug. Trials that evaluated the treatment of community-acquired pneumonia in which cases caused by M. pneumoniae were identified have shown excellent efficacy of azithromycin, levofloxacin, and moxifloxacin, although the numbers of patients with a diagnosis of M. pneumoniae were small. The duration of treatment for atypical pathogens is a minimum of five days, with the total duration depending upon clinical response to treatment and patient comorbidities.

Adjunctive therapies: no studies have been performed which evaluate the effectiveness of adjunctive therapies in patients with hemolytic anemia or CNS involvement. These disorders are thought to arise from immune-mediated mechanisms, presumably at a time when antibodies to the organism have already been made by the host, so antibiotics would not be expected to have significant therapeutic impact. For hemolytic anemia, some patients respond to warming, steroid therapy, or possibly plasmapheresis. For CNS disease, therapy with steroids, antiinflammatory drugs, diuretics, and plasma exchange have been used in addition to antibiotics.

Pneumonia caused by Chlamydophila (Chlamydia) species. The Chlamydia and Chlamydophila species are obligate, intracellular bacteria. Chlamydia trachomatis is a major cause of genital tract and ocular infections worldwide. The role of Chlamydophila (formerly Chlamydia) pneumoniae and less often Chlamydophila (formerly Chlamydia) psittaci in causing atypical pneumonia has become more appreciated in recent years. Chlamydophila species are unusual bacteria in a number of ways. The genome of the organisms is only 660 million daltons, smaller than any other prokaryote except mycoplasma. They do not contain a peptidoglycan in the cell wall. The growth cycle of the organism is complex and biphasic, consisting of two distinct entities: elementary (EB) and reticulate bodies (RB). The form in which the bacterium multiplies is the RB, which is intracellular. Replication occurs within a membrane-

bound inclusion. RB are unstable and revert to EB within the inclusion, which then ruptures causing release of EB, the form that survives in the extracellular environment; EB are the infectious particles. EB attach to epithelial cells and enter cells via a phagosome. Once inside, EB reorganize to RB, which then replicate. There are two known species of Chlamydophila that are associated with human disease:

- C. pneumoniae, which has only the single strain TWAR and causes respiratory infection.
- C. psittaci for which man is an incidental host.

Pathogenic mechanisms — One critical feature of chlamydophila organisms is that immunity to infection is not long-lived. As a result, reinfection or persistent infection and its associated inflammatory response are common, particularly with ocular and genital infections in which an ongoing immune reaction can lead to scarring and blindness or infertility, respectively. For pulmonary infections, an association with chlamydophila and acute airway hyperreactivity has been noted. In some cases of new wheezing, for example, serologic evidence for chlamydophila infection (which may be acute or chronic) has been found. However, the absence of clear documentation of acute infection (by culture or polymerase chain reaction) makes it difficult to ascertain if there is a true etiologic role for the organism.

Chlamydophila pneumoniae infection: the estimated incidence of C. pneumoniae lower respiratory tract infection among adults and children is 100 cases per 100,000 population; the infection is most common in those aged 65 to 79 years. Atypical pneumonia by convention is used to refer to infection by Mycoplasma pneumoniae, Legionella sp, and C. pneumoniae. A pathogen could not be identified in about 50 percent of cases, while the remaining patients were infected with typical organisms. C. pneumoniae is the most common chlamydophila species to cause human infection. Pneumonia due to C. pneumoniae has a higher incidence in elderly adults; this is in contrast to M. pneumoniae infection, which occurs most commonly in younger age groups. Transmission of the organism is felt to be person-to-person and has been implicated in outbreaks of nursing-home-acquired pneumonia. The true incidence of C. pneumoniae infection is not entirely known because of difficulties in confirming the diagnosis However, there were some patients who were culture-positive without serologic evidence of acute infection and others who were culture-negative with antibody titers indicative of acute infection. In addition, several patients were culture-positive repeatedly for 12 months. A reasonable conclusion is that C. pneumoniae infection is common, especially in outpatients, but that serologic methods of establishing the incidence of infection are fraught with hazard since repeated and persistent infection can occur.

Clinical manifestations: no distinguishing clinical characteristics identify cases of C. pneumoniae infection. Some common features, however, include gradual onset of symptoms, associated pharyngitis, and often hoarseness. Sinusitis frequently accompanies or develops as a complication of C. pneumoniae pneumonia. Infection with mycoplasma, legionella, and respiratory viruses also can present in a similar fashion. Asymptomatic or mildly symptomatic infection is frequently seen; however, life-threatening infection can occur. As with other atypical pneumonias, infection with C. pneumoniae usually presents with a normal white blood cell count and the chest x-ray typically shows one patchy area of subsegmental infiltration. Extrapulmonary manifestations have been described with C. pneumoniae infections including:

- Meningoencephalitis.
- Guillain-Barré syndrome.
- Reactive arthritis.
- Myocarditis.

The diagnosis of C. pneumoniae pneumonia cannot be reliably distinguished from pneumococcal pneumonia by clinical presentation or radiographic findings, although lobar pneumonia is seen more often with S. pneumoniae. Clinical laboratory methods for identifica-

tion of C. pneumoniae are suboptimal, due to problems related to availability, technical expertise, reproducibility, and result turnaround times. Thus, it is rare to definitively establish a diagnosis of C. pneumoniae in the clinical setting, and treatment is most often on an empirical basis. Other diagnostic modalities for chlamydophila include:

- Antibody tests (complement fixation and microimmunofluorescence).
- Direct antigen detection (direct immunofluorescence (DFA) and enzyme immunoassay — EIA).
- Polymerase chain reaction (PCR).

Treatment recommendations: since there is no rapid way to make the diagnosis of C. pneumoniae pneumonia, treatment begins with empiric therapy for atypical pneumonia. In the absence of a test such as PCR or a positive Gram's stain for a pyogenic organism, patients with CAP are treated empirically with a regimen that would cover atypical pneumonias. As noted above, indolent onset, extrapulmonary involvement, and normal white blood cell count are findings that favor the presence of atypical pneumonia. For patients who are treated as outpatients, recommend azithromycin (500 mg on day one followed by four days of 250 mg a day or 500 mg a day for three days). For more severely ill patients, begin therapy with azithromycin (500 mg IV daily) to treat legionella infection as well as mycoplasma and chlamydophila. If the patient fails to respond, add doxycycline (100 mg IV twice daily) since this is the superior agent for chlamydophila. If legionella infection is documented, recommend azithromycin or fluoroquinolone. The treatment of choice for C. pneumoniae infection is doxycycline (100 mg PO twice daily for 10 to 14 days). For the rare patient who is hospitalized with this infection, the drug may be administered intravenously at the same dose. Newer macrolides, including azithromycin and clarithromycin, have in vitro activity against C. pneumoniae, and azithromycin has become the treatment of choice for atypical pneumonia of any etiology. Recommend empiric treatment with azithromycin. However, if a patient with atypical pneumonia is not responding to azithromycin, or if C. pneumoniae is documented, a change to doxycycline should be considered. Quinolones have some activity against C. pneumoniae, but they are less active than tetracyclines or macrolides. The response to antibiotics is slow in C. pneumoniae pneumonia. It is not uncommon to require a second course of therapy, usually with doxycycline.

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