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«ГОМЕЛЬСКИЙ ГОСУДАРСТВЕННЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ»**

Кафедра инфекционных болезней

В. М. МИЦУРА

ДЕТСКИЕ ИНФЕКЦИИ (курс лекций)

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

PEDIATRIC INFECTIONS (lectures abstracts)

**The educational-methodical manual
for 4th year students
of Faculty of general medicine for overseas students
of higher medical educational institutions**

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Представлен курс лекций по детским инфекционным болезням, предназначенный для студентов 4 курса факультета по подготовке специалистов для зарубежных стран. Рассмотрены вопросы этиологии, эпидемиологии, патогенеза, клинических проявлений, методов диагностики, лечения и профилактики инфекционных болезней у детей. Материал содержит самые современные сведения, соответствующие признанным зарубежным руководствам.

Пособие может быть использовано для подготовки к занятиям и для закрепления материала, изученного в курсе детских инфекционных болезней.

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LIST OF ABBREVIATIONS

Ab	— antibody
Bid	— bis in die (Lat.), 2 times daily
CD	— cluster of differentiation
CFT	— complement fixation test
CNS	— central nervous system
CSF	— cerebrospinal fluid
CRS	— congenital rubella syndrome
CTL	— cytotoxic T lymphocytes
DNA	— Deoxyribonucleic acid
EBV	— Epstein Barr virus
ECHO	— enteric cytopathic human orphan viruses
EIA	— enzyme immunoassay (syn. ELISA)
ELISA	— Enzyme Linked Immune Sorbent Assay
ESR	— erythrocyte sedimentation rate
EU	— European Union
HIV	— human immunodeficiency virus
HSV	— herpes simplex virus
IFA	— immune fluorescent assay
IFN	— interferon
Ig	— immunoglobulin
IL	— interleukins
IV	— intravenously
ORS	— oral rehydration solution
PCR	— polymerase chain reaction
PMN	— polymorphonuclear leukocytes
PO	— per os (orally)
qd	— quatro in die (Lat.), 4 times daily
RNA	— ribonucleic acid
RP	— reaction of precipitation
TB	— tuberculosis
Tid	— tres in die (Lat.), 3 times daily
TNF	— tumor necrosis factor
VZV	— varicella zoster virus
WHO	— World Health Organization

LECTURE 1. MEASLES

- Measles is an acute, highly contagious exanthematous respiratory viral disease capable of causing epidemics.
- The origin of the word «measles» likely stems from the Medieval Latin word miser, meaning miserable. Historically epidemics of measles have been huge killers of children and have been known to have changed the course of history.
- Immunization has dramatically reduced the incidence of measles in Europe but despite overall high immunization coverage, measles continues to cause frequent outbreaks; the 2010 European elimination target was not achieved.
- Globally, measles remains a leading cause of childhood deaths and an estimated 160 000 children die each year from complications of the disease.

Etiology

- The measles virus is a single-stranded RNA virus of the genus Morbillivirus and the family Paramyxoviridae.
- Humans are the only reservoir for the measles virus.
- The entire measles virus genome has been sequenced which has allowed for identification of distinct wild-virus lineages with different geographical distribution. This makes it possible to confirm or suggest the source of an outbreak.
- Measles is considered a monotypic virus despite the genetic variations. Vaccine induced immunity protects against all virus strains.

Epidemiology

- Measles is extremely communicable, 90 % of non-immune people exposed to an infective individual will catch the disease. One contagious individual can infect 12–18 susceptible persons.
- The virus is transmitted from person to person via respiratory droplets produced when sick people cough and sneeze. Virus-containing droplets can remain in the air for several hours and the virus remains infectious on contaminated surfaces for up to two hours.
- Infected people are considered contagious from about five days before the onset of rash to four days afterwards. Measles is maximally contagious during the prodromal phase which lasts for 2–4 days and is characterized by intense coughing.
- Individuals at increased risk of measles include infants who are too young to be immunized, people in whom the vaccine has failed to induce

immunity (primary vaccine failure), and individuals who have not been immunized.

- In the pre-vaccine era, measles was endemic in Europe and most people would be infected during childhood.
- Immunisation against measles started in the 1960s and has dramatically changed the epidemiology of the disease. Measles outbreaks in Europe now are the result of measles imported from other countries.
- Routine measles immunisation in childhood leads to widening intervals between epidemics during which the group of susceptible individuals builds up. This results in a shift towards older children and young adults in the age distribution of cases during epidemics.

Pathogenesis

- After invasion through the respiratory epithelium, measles virus replicates in the respiratory tract. The virus then spreads and multiplies in local lymphatic tissues, subsequently leading to viremia (2–3 days after exposure).
- Lymphoid tissue, skin, gastrointestinal tract, lungs, and liver are end-organs that may become infected.
- Acute measles infection may cause a suppression of the immune system, persisting for several months. This immunosuppression may contribute in part to the increased susceptibility of children with measles to secondary bacterial and viral infections such as pneumonia and gastroenteritis.
- Children with vitamin A deficiency are at particular risk for such complications and associated mortality.

Clinical features and sequelae

- The prodrome starts after a 10–12-day incubation period and is characterised by fever, conjunctivitis, coryza, cough and bronchiolitis. Nearly all infected susceptible individuals develop clinical disease.
- Koplik's spots, the enanthema believed to be pathognomic for measles, appear on the buccal mucosa 1–2 days before the onset of rash. These white spots were described initially by Russian scientists N. F. Filatov (1885) and A. P. Belsky (1890), then in 1896 — by American pediatrician Henry Koplik.
- The measles rash, an erythematous maculopapular exanthema, develops 2–4 days after the onset of fever and spreads from the head to the body over the next 3–4 days (Figure 1).
- The rash, which blanches on pressure early in the course, fades in the order of appearance during the next 3–4 days and assumes a non-blanching appearance. After this period, the rash may undergo fine desquamation or pigmentation («staining»).

- Mortality from measles is predominantly caused by complicating bacterial infections.
- Complications are likely to have developed if the fever does not drop within 1 or 2 days after the onset of the rash.

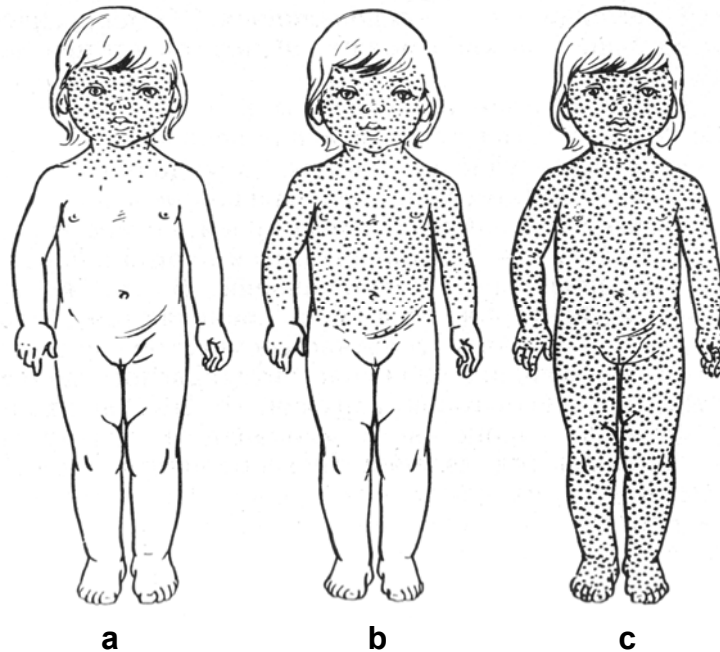


Figure 1 — Measles rash appearance:
a — 1st days; b — 2nd days; c — 3rd days

- The most common **complications** of measles are: otitis media (7–9 %), pneumonia (1–6 %), diarrhoea (8 %), post-infectious encephalitis (1 per 1000 to 2000 cases), and subacute sclerosing panencephalitis (SSPE), which affects 1 per 100 000 cases.
- Case fatality is 1–3 per 1000 cases and highest in those younger than five years of age and among immunocompromised individuals. Pneumonia accounts for 60% of measles associated deaths.
- Subacute sclerosing panencephalitis (SSPE) is a rare (1 per 100 000 cases) and fatal degenerative central nervous system disease caused by a persistent infection with a mutant measles virus. The onset is several years after the episode of measles (on average seven years) and most affected children had measles before two years of age.
- Infants are protected from birth against measles by maternal antibodies if the mother is immune to measles. This passive immunity gradually disappears over the second half of the first year of life. Infants with partial passive immunity may develop milder and shorter episodes of measles that still confers lasting immunity.

Measles case definition (CDC, 2012; www.cdc.gov/vaccines/pubs/surv-manual/chpt07-measles.html).

Probable case:

In the absence of a more likely diagnosis, an illness characterized by:

- Generalized rash lasting ≥ 3 days; AND
- Temperature ≥ 38.3 °C; AND
- Cough, coryza, or conjunctivitis; AND
- No epidemiologic linkage to a confirmed case of measles; AND
- Noncontributory or no serologic or virologic testing.

Confirmed case:

Laboratory confirmation by any of the following:

- Positive serologic test for measles immunoglobulin M antibody;
- Significant rise in measles antibody level by any standard serologic assay;
- Isolation of measles virus from a clinical specimen; OR
- Detection of measles-virus specific nucleic acid by polymerase chain reaction

Note: A laboratory-confirmed case does not have to have generalized rash lasting ≥ 3 days; temperature \geq or 38.3 °C; cough, coryza, or conjunctivitis.

OR

An illness characterized by:

- Generalized rash lasting ≥ 3 days; AND
- Temperature ≥ 38.3 °C; AND
- Cough, coryza, or conjunctivitis; AND
- Epidemiologic linkage to a confirmed case of measles.

Diagnosis

- Measles could be diagnosed on clinical grounds with reasonable accuracy. Koplik's spots are pathognomonic, and may be seen on the buccal mucosa in more than 80 % of cases.

- Virus isolation remains the «gold standard» for the laboratory confirmation of suspected measles cases, but performed only in specialized laboratories.

- A specific diagnosis of measles can be made quickly by immunofluorescent staining of a smear of respiratory secretions for measles antigen.

- Secretions can be examined microscopically for multinucleated giant cells.

- Measles virus RNA can be demonstrated by polymerase chain reaction in respiratory secretions or urine.

- A number of serologic tests are available. Antibody can be detected at rash onset and then peaks approximately 1 month after infection. A serologic diagnosis usually made by enzyme immunoassay (EIA). Immunoglobulin M (IgM) antibody testing is most commonly used in acute-

phase serum sample. Specific IgM antibodies are detectable within 1–2 days after rash onset, and the IgG titer rises significantly after 10 days. Immunoglobulin G (IgG) may be detected for years after infection.

Treatment

- There is no specific antiviral therapy for measles and most cases will recover with supportive treatment including hydration and antipyretics.
- Ribavirin is effective against measles virus *in vitro* and may be considered for use in immunocompromised individuals.
- Bacterial superinfections are common and should be treated with antibiotics but prophylactic treatment is not indicated. Continued fever beyond two days after the onset of rash is an indication of complications.
- Vitamin A treatment during measles can profoundly decrease the morbidity, the incidence of secondary complications, and mortality (two doses of 200 000 IU vitamin A reduce in mortality of 67 %). Controlled trials suggest clinical benefit from high doses of vitamin A in severe or potentially severe measles, especially in children <2 years old who are or may be malnourished. On the basis of limited data, a dose of 50,000 IU is used for infants 1–6 months old; 100,000 IU is recommended for infants 7–12 months old and 200,000 IU for children >1 year old. A single dose is administered on two consecutive days.

Prevention

- Immunization is the only effective preventive measure against acquiring measles.
- The live attenuated measles vaccine induces an immune response that is similar to naturally acquired immunity and can be boosted by challenge from wild or vaccine virus.
- Measles vaccine is at least 95 % effective and seroconversion rates are close 100%. Primary vaccine failure of the first dose at 12 months of age or older occurs in up to 5 % of people, but 95 % of first dose failures will seroconvert from a second dose.
- All European immunization programmes today promote a two-dose measles immunization schedule with the first dose given during the second year of life and the second dose at an older age that differs between countries.
- Measles vaccine is most commonly administered as part of a combination of live attenuated vaccines that includes measles, mumps, rubella (MMR) or measles, mumps, rubella and varicella (MMRV).
- Regarding post-exposure prophylaxis, administration of a measles-containing vaccine is the intervention of choice within 72 hours of exposure as the incubation period for vaccine virus is shorter than that for wild virus.

LECTURE 2. RUBELLA

- Rubella is an acute viral respiratory infection of children and adults that characteristically includes rash, fever, and lymphadenopathy.
- Rubella was formerly known as German measles because it was first distinguished clinically from rubeola (measles) in Germany.
- The rationale for immunizing against rubella is the high risk of congenital malformations associated with rubella infection during pregnancy.
- Congenital Rubella Syndrome (CRS) is characterized by a set of ophthalmologic, neurologic, cardiac and auditory anomalies.
- Immunization with the safe and highly effective attenuated live vaccine started in Europe in 1970s and has had a profound impact on the epidemiology of rubella and CRS.

Etiology

- The rubella virus is a RNA virus and belongs to the genus Rubivirus and the family Togaviridae. It is of a single serotype divided into two clades and within these two clades there are at least seven genotypes. The genetic variation does not translate into antigenic differences.
- The rubella virion is composed of an inner icosahedral capsid of RNA and protein that is surrounded by a lipid-containing envelope with glycoprotein spikes and a diameter of ≈ 60 nm. The structural proteins associated with rubella virus are E1 and E2 (transmembrane envelope glycoproteins) and C (the capsid protein that surrounds the viral RNA).
- Only one serotype has been identified.

Epidemiology

- Rubella is transmitted by direct contact or droplet spread similar to the transmission of measles. Humans are the only known hosts, children born with CRS also may be infectious for several years. The risk of transmission is 10–30 % but varies with the immunization rate of the population.
- Infectivity is high in those susceptible. The period of infectivity is seven days before to six days after the onset of rash.
- The transmission pattern of rubella is similar to that of measles and rubella was a childhood disease in the pre-vaccine era, with the highest incidence in the 4–9 years age group.
- Rubella was endemic in Europe before widespread immunization, and there were regular epidemics at 6–9 year intervals. Routine immunization has dramatically changed the epidemiology of rubella in Europe. The incidence of CRS in the pre-vaccine era has been estimated at 4–8 per 10 000 pregnancies in the United States and approximately 4.6 per 10 000

births in the UK between epidemics. A total of 111 cases of CRS were reported from EU member states in the 2000–2007 period.

- Elimination of rubella requires sustained overall immunization coverage of more than 95 % and maintenance of low levels of susceptibility across all subgroups of a population.

Pathogenesis

- Like that of measles, the rash of rubella is immunologically mediated; its onset coincides with the development of specific antibodies. Viremia can be demonstrated for \approx 1 week before and ends within a few days after the onset of rash.

- The cause of the damage to cells and organs in congenital rubella is not well understood. Proposed mechanisms of fetal damage include mitotic arrest of cells, tissue necrosis without inflammation, and chromosomal damage. The growth of the fetus may be retarded.

Clinical features

- The incubation period is 13–20 days.
- Rubella is typically a mild disease with few complications, and infections go unrecognised or are asymptomatic.
- Children usually have few or no constitutional symptoms but adults may experience a 1–5 days prodrome of fever, malaise, headache and arthralgia.
- The typical presentation of rubella is a transient, erythematous maculo-papular rash that starts in the face, becomes generalized over 24 hours and lasts for about three days. Enlarged post-auricular and sub-occipital lymph nodes, which precede the rash, are characteristic of rubella and last for 5–8 days.
- Clinically, rubella is indistinguishable from febrile rash illnesses caused by measles, parvovirus B19, human herpes virus 6 (HHV6), Coxsackie virus, ECHO virus, adenovirus and dengue virus, and laboratory confirmation is required for diagnosis unless there is an epidemiological link to a confirmed case.

Complications

- Complications of acute rubella are rare, with the exception of rubella infection during pregnancy which is discussed separately below:
 - Encephalitis occurs in 1 out of 5000–6000 cases of rubella. The presentation can be dramatic but fatalities are rare and most patients recover completely without sequelae.
 - Thrombocytopenia develops in 1 out of 3000 cases.

- Transient polyarthralgia and polyarthritis are common complications in adolescents and adults, but rare in children.

Case Definition (CDC, 2012; www.cdc.gov/vaccines/pubs/surv-manual/chpt14-rubella.html)

Probable case:

In the absence of a more likely diagnosis, an illness characterized by all of the following:

- acute onset of generalized maculopapular rash; AND
- temperature greater than or 37.2 °C, if measured; AND
- arthralgia, arthritis, lymphadenopathy, or conjunctivitis; AND
- lack of epidemiologic linkage to a laboratory-confirmed case of rubella; AND
- noncontributory or no serologic or virologic testing.

Confirmed case:

A case with or without symptoms who has laboratory evidence of rubella infection confirmed by one or more of the following:

- isolation of rubella virus; OR
- detection of rubella-virus specific nucleic acid by polymerase chain reaction; OR
- significant rise between acute-and convalescent-phase titers in serum rubella immunoglobulin G antibody level by any standard serologic assay; OR
- positive serologic test for rubella immunoglobulin M (IgM) antibody, not explained by MMR vaccination during the previous 6–45 days, not otherwise ruled out by more specific testing in a public health laboratory.

OR

An illness characterized by all of the following:

- acute onset of generalized maculopapular rash; AND
- temperature greater than 37.2° C; AND
- arthralgia, arthritis, lymphadenopathy, or conjunctivitis; AND
- epidemiologic linkage to a laboratory-confirmed case of rubella.

Congenital Rubella Syndrome (CRS)

- The clinical presentation of acute rubella in pregnancy is identical to that in non-pregnant women and adults, and asymptomatic and undiagnosed infections are common.

- The rubella virus is teratogenous and infection during pregnancy carries a considerable risk of Congenital Rubella Syndrome (CRS), foetal death and abortion.

- The risk of CRS and the extent and severity of the conditions are associated with gestation at the time of infection. The risk of CRS is

highest during the first 12 weeks of pregnancy when the overall risk has been estimated at 84 %. It declines after 12 weeks of pregnancy and the only reported complication from infections in the 16–20 week gestational period is deafness.

- The most frequent presentations of CRS are hearing impairment (60 %), heart defects (45 %), microcephaly (27 %), cataract (25 %), and hepatosplenomegaly (19 %).

- Women who plan to become pregnant should be tested for rubella and immunized if found to be susceptible.

- Pregnant women should have rubella immunity tested early in pregnancy.

Diagnosis

- There are three standard tests for laboratory confirmation of a suspect rubella case: (1) isolation of rubella virus from a clinical specimen; (2) detection of rubella virus nucleic acid in a clinical specimen by PCR test; or (3) rubella virus specific IgG antibody response in serum or saliva. A specific IgM antibody response indicates a probable acute infection.

- **Congenital rubella** is diagnosed by the isolation of the virus, a positive PCR assay, the detection of IgM antibodies in a serum sample, and/or the documentation of either the persistence of rubella antibodies in serum beyond 1 year of age or a rising antibody titer anytime during infancy in an unvaccinated child. Biopsied tissues and/or blood and cerebrospinal fluid have also been used for the demonstration of rubella antigens with monoclonal antibodies and for the detection of rubella RNA by in situ hybridization and PCR.

Treatment

- There is no specific treatment for rubella. Symptom-based treatment is given for manifestations such as fever, arthralgia, and arthritis.

- Suspected rubella infection among contacts of a pregnant woman should be laboratory confirmed as a matter of urgency wherever possible.

- Decisions on the management of a susceptible woman developing a non-vesicular rash or rubella in the first 20 weeks of pregnancy should be taken in partnership with a specialist foetal medicine unit and laboratory services.

Prevention

- Rubella immunisation was introduced in Europe in the 1970s. Many countries started by vaccinating prepubertal girls and non-immune women of childbearing age in order to prevent infection in pregnancy.

The vaccine is highly effective, with seroconversion rates of 95–100 % and the induced immunity is likely to be lifelong in most recipients.

- Elimination of rubella requires sustained vaccine coverage of > 95 %. Rubella could potentially be eradicated if all countries in the world achieved high immunization coverage.

- The rubella vaccine is a live attenuated vaccine. The most commonly used strain has a seroconversion rate of 98 % and induces secretory IgA antibodies, a quality that makes vaccination similar to natural infection and prevents reinfection with wild virus.

- All countries in Europe immunize against rubella with measles-mumps-rubella (MMR) vaccine, a combination vaccine with three live attenuated vaccines against measles, mumps and rubella respectively.

- Seronegative women of child-bearing age and healthcare workers who need to be protected against rubella should continue to be offered rubella vaccine, usually as combined MMR vaccine.

- In most of Europe, rubella antibody testing is offered to all pregnant women as part of their antenatal care. For practical reasons, the test is usually performed irrespective of immunisation history or previous laboratory reports of rubella specific IgG. If a pregnant woman is rubella antibody negative then MMR vaccine should be given post-delivery.

LECTURE 3. HERPETIC INFECTIONS (HSV)

Table 1 — Properties of herpes viruses (by R. Hunt, Microbiology and Immunology On-line, the University of South Carolina, 2010; modified)

Human herpes type	Name	Sub Family	Target cell type	Latency	Disease
1	Herpes simplex-1 (HSV-1)	Alphaherpesvirinae	Mucoepithelia	Neuron	HSV infection
2	Herpes simplex-2 (HSV-2)	Alphaherpesvirinae	Mucoepithelia	Neuron	
3	Varicella Zoster virus (VZV)	Alphaherpesvirinae	Mucoepithelia	Neuron	Varicella, shingles (herpes zoster)
4	Epstein-Barr virus (EBV)	Gammaherpesvirinae	B lymphocyte, epithelia	B lymphocyte	Infectious mononucleosis, tumors
5	Cytomegalovirus (CMV)	Betaherpesvirinae	Epithelia, monocytes, lymphocytes	Monocytes, lymphocytes, others?	CMV infection
6	Human herpes virus-6 (HHV-6, herpes lymphotropic virus)	Betaherpesvirinae	T lymphocytes and others	T lymphocytes and others	Sudden exanthema, Mononucleosis-like syndrome
7	Human herpes virus-7 (HHV-7)	Betaherpesvirinae	T lymphocytes and others	T lymphocytes and others	Chronic fatigue syndrome?
8	Human herpes virus-8 (HHV-8)	Gammaherpesvirinae	Endothelial cells	Unknown	Kaposi's sarcoma, lymphoma

Definition

- The 2 closely related herpes simplex viruses (HSVs), HSV type 1 (HSV-1) and HSV type 2 (HSV-2), cause a variety of illnesses depending on the anatomic site where the infection is initiated, the immune state of the host, and whether the symptoms reflect primary or recurrent infection.
 - Common infections involve the skin, eye, oral cavity, and genital tract.
 - Infections tend to be mild and self-limiting, except in the immune compromised patient and newborn infant, where the infection may be severe and life threatening.

HSV primary and recurrent infection

- **Primary infection** occurs in individuals who have not been infected previously with either HSV-1 or HSV-2. Because these individuals are HSV seronegative and have no pre-existing immunity to HSV, primary infections can be severe.
 - During initial infections HSV establishes latent infection in regional sensory ganglion neurons. Virus is maintained in this latent state for the life of the host but periodically can reactivate and cause **recurrent infection**. Symptomatic recurrent infections tend to be less severe and of shorter duration than first infections.

Etiology

- HSVs contain a double-stranded DNA genome that encodes at least 84 proteins. The DNA is contained within a capsid, which is surrounded by an outer envelope containing at least 12 viral glycoproteins. These glycoproteins are the major targets for humoral immunity, while other nonstructural proteins are important targets for cellular immunity. Two encoded proteins, viral DNA polymerase and thymidine kinase, are targets for antiviral drugs.

- HSV-1 and HSV-2 have a similar genetic composition with extensive DNA and protein homology. One important difference in the 2 viruses is their glycoprotein G genes.

Epidemiology

- HSV infections are ubiquitous and there are no seasonal variations in risk for infection. The only natural host is humans, and the mode of transmission is direct contact between mucocutaneous surfaces. Individuals with latent infection are periodically contagious, this explain the widespread prevalence of HSV.

- HSV-1 is usually spread mouth to mouth (kissing or the use of utensils contaminated with saliva) or by transfer of infectious virus to the hands after which the virus may enter the body via any wound or through the eyes. A large proportion of the population has evidence of HSV-1 infection as judged by antibodies, about 80–90 % of adults.

- HSV-2 is normally spread sexually and is found in the anus, rectum and upper alimentary tract as well as the genital area. An infant can be infected at birth by a genitally-infected mother. The infant can also be infected *in utero* if the mother's infection spreads. Because of the infant's underdeveloped immune system, the resulting infection can be very severe and sometimes lead to death.

- Despite the apparent *above the waist/below the waist rule*, both types of HSV can infect oral or genital mucosa depending on the regions of contact.

- **Neonatal herpes** is an uncommon but potentially fatal infection of the fetus or more likely the newborn. The estimated rate of neonatal herpes is 1 in 3,000–5,000 live births. Greater than 90 % of the cases are the result of maternal-fetal transmission. The risk for transmission is greatest during a primary infection (30–50 %) and much lower when the exposure is during a recurrent infection (<2 %). It is estimated that approximately 25 % of pregnant women are HSV-2 infected and that approximately 2 % of pregnant women acquire HSV-2 infection during pregnancy. Transmission generally occurs during delivery, although it is possible to occur even with cesarean delivery with intact membranes. The most common portals of entry are the conjunctiva, mucosal epithelium of the nose and mouth, and breaks or abra-

sions in the skin. Virus may also extend from the nose to the respiratory tract to cause pneumonia, move via intraneuronal transport to the central nervous system to cause encephalitis, or spread by hematogenous dissemination to visceral organs and the brain.

Pathogenesis

- In the immunocompetent host the pathogenesis of HSV infection involves viral replication in skin and mucous membranes followed by replication and spread in neural tissue. Viral infection typically begins at a mucocutaneous **portal of entry** such as the oral cavity, genital mucosa, ocular conjunctiva, or breaks in keratinized epithelia. Virus penetrates the regional lymph nodes.

- Virus replicates locally, resulting in the death of the cell (necrosis) and sometimes produces clinically apparent inflammatory responses that facilitate the development of characteristic herpetic vesicles and ulcers. Virus also enters nerve endings and spreads beyond the portal of entry to sensory ganglia by intraneuronal transport.

- Virus persists and replicates in sensory neurons — phase of **latent infection**, a condition where the viral genome persists within the neuronal nucleus in a metabolically inactive state. During latent phase the virus can begin to replicate. This occurs despite the host having established a variety of humoral and cellular immune responses that successfully controlled the initial infection.

- With **reactivation** of the latent neuron, new virions are produced and transported within nerve fibers back to mucocutaneous sites somewhere in the area of the initial infection, where further replication occurs and causes recurrent infections. Virus is shed at the site where cutaneous replication occurs and can be transmitted to susceptible individuals.

- **Viremia** does not appear to play a role in HSV infections in the immunocompetent host but can occur in neonates, individuals with eczema, and severely malnourished children. Viremia can result in dissemination of the virus to visceral organs.

- In the skin — stratification and balloon degeneration of *stratum spinosum* cell layer of the epidermis, the formation of giant cells. It is used for morphological diagnosis (Tzanck test).

- In the central nervous system — colliquative necrosis of neurons and glial cells with perifocal vascular and proliferative reaction.

Clinical manifestations

- The hallmarks of common HSV infections are skin vesicles (blisters) and shallow ulcers.

- Classical infections present with small, 2–4 mm vesicles that may be surrounded by an erythematous base. These may persist for a few days before evolving into shallow, minimally erythematous ulcers. The vesicular phase tends to persist longer when keratinized epithelia is involved and be brief, when moist mucous membranes are the site of infection.

- The typical manifestations are seldom classical. Most infections are asymptomatic or unrecognized, and nonclassical presentations such as small skin fissures and small erythematous nonvesicular lesions are common.

Acute Oropharyngeal Infections

- In primary herpetic gingivostomatitis, the typical clear lesions first develop followed by ulcers that have a white appearance. The infection, often initially on the lips spreads to all parts of the mouth and pharynx.

- In older children, adolescents, and young adults the initial HSV oral infection may manifest as pharyngitis and tonsillitis rather than gingivostomatitis.

- The vesicular phase is often over by the time the patient presents to a health care provider, and signs and symptoms may be indistinguishable from streptococcal pharyngitis with fever, malaise, headache, sore throat, and white plaques on the tonsils.

Herpes labialis, Herpes nasalis (recurrent infection)

- Fever blisters, or cold sores, are the most common manifestation of recurrent HSV-1 infections. The most common site of herpes labialis is the vermilion border of the lip, although lesions sometimes occur on the nose, chin, cheek, or oral mucosa.

- Older patients report experiencing burning, tingling, itching, or pain 3–6 hr (rarely as long as 24–48 hr) before the development of the herpes lesion.

- The lesion generally begins as a small grouping of erythematous papules that over a few hours progress to create a small, thin-walled vesicle. The vesicles may form shallow ulcers or become pustular. The short-lived ulcer dries and develops a crusted scab.

- Complete healing without scarring occurs with re-epithelialization of the ulcerated skin, usually within 6–10 days. Some patients experience local lymphadenopathy but no constitutional symptoms.

Cutaneous HSV Infections

- In the healthy child or adolescent, cutaneous HSV infections are generally the result of skin trauma with macro- or micro-abrasions and exposure to infectious secretions. This situation most often occurs in play or contact sports such as wrestling (*herpes gladiatorum*) or rugby (scrumptox).

- **Herpes gladiatorum** usually appears in the head and neck region (which are frequently sites of contact in wrestling holds). Lesions begin as grouped, erythematous papules that progress to vesicles, pustules, ulcers, and crusts and then healing without scarring in 6–10 days.

- Cutaneous HSV infection results in multiple discrete lesions and involves a larger surface area. There can be regional lymphadenopathy, but seldom systemic symptoms. Recurrences are sometimes associated with local edema and lymphangitis or local neuralgia.

- Cutaneous HSV infections can be severe or life threatening in patients with disorders of the skin such as eczema (**eczema herpeticum**), pemphigus, burns, or following laser skin resurfacing. The lesions are frequently ulcerative and nonspecific in appearance, although typical vesicles may be seen in adjacent normal skin. If untreated, these can progress to disseminated infection and death. In primary infection case mortality rate is up to 40 %. Recurrent infections are common but generally less severe than the initial infection.

- **Herpes whitlow** is a term generally applied to HSV infection of fingers or toes, although strictly speaking it refers to HSV infection of the paronychia. The onset of the infection is heralded by itching, pain, and erythema 2–7 days after exposure. The cuticle becomes erythematous and tender and may appear to contain pus, although if incised, little fluid is present. Lesions and associated pain typically persist for about 10 days, followed by rapid improvement and complete recovery in 18–20 days.

Genital Herpes

- Genital HSV infection is common in sexually experienced adolescents and young adults, but up to 90 % of infected individuals are unaware they are infected. Symptomatically individuals and also those with asymptomatic or unrecognized infection periodically shed virus from anogenital sites and hence can transmit the infection to sexual partners or, in the case of the pregnant woman, to her newborn.

- Patients may develop urethritis and dysuria and bilateral, tender inguinal and pelvic lymphadenopathy. Women may experience a watery vaginal discharge and men a clear mucoid urethral discharge. Significant local pain and systemic symptoms including fever, headache, and myalgia are common. The course of classical primary genital herpes, from onset to complete healing, is 2–3 wk.

- Most patients with symptomatic primary genital herpes will experience at least 1 recurrent infection in the following year. Recurrent genital herpes is usually less severe and of shorter duration than the primary infection.

- Genital infections caused by HSV-1 and HSV-2 are indistinguishable. Genital HSV infection increases the risk for acquiring HIV infection.

Ocular Infections

- HSV ocular infections may involve the conjunctiva, cornea, or retina and may be primary or recurrent. Conjunctivitis or keratoconjunctivitis is usually unilateral and often associated with blepharitis and tender preauricular lymphadenopathy. Vesicular lesions may be seen on the lid margins and periorbital skin. Patients typically have fever. Untreated infection generally resolves in 2–3 weeks. Obvious corneal involvement is rare, but when it occurs it can produce ulcers that are described as appearing dendritic or geographic.

- Recurrent infections tend to involve the underlying stroma, and repeated recurrences can cause progressive corneal scarring and injury that can lead to blindness.

Central Nervous System Infections

- **HSV encephalitis** is the leading cause of sporadic, nonepidemic encephalitis in children and adults. It is an acute necrotizing infection generally involving the frontal and/or temporal cortex and the limbic system and, beyond the neonatal period, is almost always caused by HSV-1. The infection may present with nonspecific findings, including fever, headache, nuchal rigidity (neck stiffness), nausea, vomiting, generalized seizures, and alteration of consciousness. Injury to the frontal or temporal cortex or limbic system may produce anosmia, memory loss, peculiar behavior, expressive aphasia and other changes in speech, hallucinations, and focal seizures. The untreated infection progresses to coma and death in 75 % of cases.

- HSV is also a cause of **aseptic meningitis** and is the most common cause of recurrent aseptic meningitis (Mollaret meningitis).

Infections in Immunocompromised Persons

- Severe, life-threatening HSV infections can occur in patients with compromised immune functions, including neonates, the severely malnourished, those with primary and secondary immunodeficiencies diseases including AIDS, and those on some immunosuppressive regimens, particularly for cancer and organ transplantation.

- Mucocutaneous infections, including mucositis and esophagitis, are most common, although their presentations may be atypical and can result in lesions that slowly enlarge, ulcerate, become necrotic, and extend to deeper tissues.

- Other HSV infections include tracheobronchitis, pneumonitis, and anogenital infections. Disseminated infection can result in a sepsis-like presentation, with liver and adrenal involvement, disseminated intravascular coagulopathy, and shock.

Perinatal HSV Infections

- Neonatal HSV infection is almost never asymptomatic. Its clinical presentation reflects timing of infection, portal of entry, and extent of spread. Infants with intrauterine infection typically have skin vesicles or scarring, eye findings including chorioretinitis and keratoconjunctivitis, and microcephaly or hydranencephaly that are present at delivery. Few infants survive without therapy, and those that do generally have severe sequelae. Infants infected during delivery or postpartum present with 1 of 3 patterns of disease: (1) disease localized to the skin, eyes, or mouth; (2) encephalitis with or without skin, eye, or mouth (**SEM) disease**; or (3) disseminated infection involving multiple organs, including the brain, lungs, liver, heart, adrenals, and skin.

- Infants with SEM disease generally present at 5–11 days of life. If untreated, infants with SEM disease may progress to develop encephalitis or disseminated disease.

- Infants with encephalitis typically present at 8–17 days of life with clinical findings suggestive of bacterial meningitis, including irritability, lethargy, poor feeding, poor tone, and seizures. Fever is relatively uncommon, and only about 60% have skin vesicles. If untreated, 50 % will die and most survivors have severe neurologic sequelae.

- Infants with disseminated HSV infections generally become ill at 5–11 days of life. Their clinical picture is similar to bacterial sepsis with hyper- or hypothermia, irritability, poor feeding, and vomiting. They may also exhibit respiratory distress, cyanosis, apneic spells, jaundice, purpuric rash, and evidence of central nervous system infection; seizures are common. Skin vesicles are seen in about 75 % of cases. If untreated, the infection causes shock and disseminated intravascular coagulation; approximately 90 % of these infants die, and most survivors have severe neurologic sequelae.

Diagnosis

- The clinical diagnosis of an HSV infection is not always possible.
- Virus culture remains the gold standard for diagnosing HSV infections. The highest yield comes from rupturing a suspected herpetic vesicle and vigorously rubbing the base of the lesion to collect fluid and cells.

- The use of PCR for detection of HSV DNA is highly sensitive and specific and in some instances can be done rapidly. It is the test of choice in examining cerebrospinal fluid in cases of suspected HSV encephalitis.

- Direct detection of HSV antigens in clinical specimens (IFA, EIA and others) can be done rapidly and has very good specificity, although not as sensitive as viral culture.

- HSV immunoglobulin M (IgM) tests are unreliable, and the demonstration of a 4-fold or greater rise in HSV-specific IgG titers between acute and convalescent serum samples is only useful in retrospect.

- Histologic findings or imaging studies may support the diagnosis but should not substitute for virus-specific tests.

Treatment

- Three antiviral drugs — acyclovir, valacyclovir, and famciclovir — are available for the management of HSV infections. These are nucleoside analogues, inhibiting viral enzyme thymidine kinase and thus interrupting the DNA synthesis in replicating viruses. No effect on viruses in the latent state. Active against HSV-1, HSV-2 and VZV.

- Acyclovir has the poorest bioavailability and hence requires more frequent dosing. Valacyclovir, a prodrug of acyclovir (valin-acyclovir), and famciclovir, a prodrug of penciclovir, both have very good oral bioavailability and are dosed orally once or twice daily. Acyclovir and penciclovir are also available in a topical form but provide limited or no benefit to patients with recurrent mucocutaneous HSV infections. Only acyclovir has an intravenous formulation. Early initiation of therapy results in the maximal therapeutic benefit. All 3 drugs have an exceptional safety profile and are safe to use in pediatric patients. Doses should be modified in patients with renal impairment.

- Acyclovir and penciclovir resistance is rare in immunocompetent persons but does occur in immunocompromised persons. Foscarnet and cidofovir have been used in the treatment of HSV infections caused by acyclovir-resistant mutants. Topical trifluorothymidine, vidarabine, and idoxuridine are used in the treatment of herpes keratitis.

Acyclovir: doses

- **Acute Mucocutaneous Infections.** For gingivostomatitis, oral acyclovir (15 mg/kg/dose 5 times a day PO for 7 days, maximum 1 g/day) started within 72 hr of onset reduces the severity and duration of the illness.

- For **herpes labialis**, oral treatment is superior to topical antiviral therapy. For treatment of a recurrence in adolescents, oral valacyclovir (2,000 mg bid PO for 1 day), acyclovir (200–400 mg 5 times daily PO for 5 days) shortens the duration of the episode. Chronic daily use of oral acyclovir (400 mg bid PO) or valacyclovir (500 mg qd PO) has been used to prevent recurrences in individuals with frequent or severe recurrences.

- In the treatment of **eczema herpeticum** oral acyclovir (200 mg 5 times a day PO for 5 days) is effective.

- **Genital Herpes.** For adolescents: acyclovir (400 mg tid PO for 7–10 days), or valacyclovir (1000 mg bid PO for 7–10 days). The 1st episode of genital herpes can be extremely painful, and use of analgesics is generally indicated.

- There are 3 strategic options regarding the **management of recurrent infections**. Option 1 is no therapy; option 2 is episodic therapy; and option 3 is chronic suppressive therapy. For **episodic therapy**, treatment should be initiated at the 1st signs of an outbreak. Recommended choices for episodic therapy in adolescents include acyclovir (800 mg tid PO for 2 days), or valacyclovir (500 mg bid PO for 3 days). **Chronic suppressive therapy** offers the advantage that it prevents most outbreaks, improves patient quality of life pertaining to the psychosocial impact of genital herpes, and, with daily valacyclovir therapy, also reduces (but does not eliminate) the risk for sexual transmission to a susceptible sexual partner. Options for chronic suppressive therapy include acyclovir (400 mg bid PO), famciclovir (250 mg bid PO), and valacyclovir (500–1,000 mg qd PO) for 1 year and longer.

- **Central Nervous System Infections**. Patients beyond the neonatal period with herpes encephalitis should be promptly treated with intravenous acyclovir (10 mg/kg every 8 hr given over a 1 hr infusion for 14–21 days). Treatment for increased intracranial pressure, management of seizures, and respiratory compromise may be required.

- **Infections in Immunocompromised Persons**. Severe mucocutaneous and disseminated HSV infections in immunocompromised patients should be treated with intravenous acyclovir (5–10 mg/kg or 250 mg/m² every 8 hr) until there is evidence of resolution of the infection. Oral antiviral therapy with acyclovir, famciclovir, or valacyclovir has been used for treatment of less severe HSV infections and for suppression of recurrences during periods of significant immunosuppression.

- **Perinatal Infections**. All infants with proven or suspected neonatal HSV infection should be begun promptly on high-dose intravenous acyclovir (60 mg/kg/day divided every 8 hr). Treatment may be discontinued in those infants shown by laboratory testing to not be infected. Infants with HSV disease limited to skin, eyes, and mouth should be treated for 14 days, while those with disseminated or CNS disease should receive 21 days of therapy. Patients receiving high-dose therapy should be monitored for neutropenia.

Approach to HSV infections treatment in countries of former USSR

- **Immune modulators** can be given in combination with antiviral drugs in primary or symptomatic recurrent infection. These are interferons and their inducers, thymus hormones, recombinant cytokines (IL-2), and others. In latent phase of HSV infection immune modulators as monotherapy are indicated for persons with frequent recurrences.

- The use of **therapeutic herpetic vaccine** in latent phase of infection can stimulate immune response to HSV antigens and thus prolong the period between recurrences.

PROGNOSIS

- Most HSV infections are self-limiting, last from a few days (for recurrent infections) to 2–3 wk (for primary infections), and heal without scarring.
- Genital herpes, because it is a sexually transmitted infection, can be stigmatizing and may have psychologic consequences much greater than its physiologic effects.
- Some HSV infections can be severe and without prompt antiviral therapy may have serious consequences. Life-threatening conditions include neonatal herpes, herpes encephalitis, and HSV infections in immunocompromised patients, burn patients, and severely malnourished infants and children.
- Recurrent ocular herpes can lead to corneal scarring and blindness.

PREVENTION

- Patients should be advised about good hygienic practices, including handwashing and avoiding contact with lesions and secretions during active herpes outbreaks.
- The risk for acquiring genital herpes can be reduced but not eliminated through the correct and consistent use of condoms. The risk for transmitting genital HSV-2 infection to a susceptible sexual partner can be reduced but not eliminated by the daily use of oral valacyclovir by the infected partner.
- For pregnant women with active genital herpes at the time of delivery, the risk for mother-to-baby transmission can be reduced but not eliminated by delivering the baby via a cesarean section. The risk for recurrent genital herpes and therefore the need for cesarean delivery can be reduced in pregnant women with a history of genital herpes by the daily use of oral acyclovir or valacyclovir during the last 4 wk of gestation.
- Infants delivered vaginally to women with 1st episode genital herpes are at very high risk for acquiring HSV infection. The nasopharynx and umbilicus should be cultured at delivery and at day 2 of life; some recommend that these infants receive anticipatory acyclovir therapy for at least 2 wk. Others treat if signs develop or if the 48 hr cultures are positive. Infants delivered to women with a history of recurrent genital herpes are at low risk for developing neonatal herpes.
- Recurrent genital HSV infections can be prevented by the daily use of oral acyclovir, valacyclovir, or famciclovir, and these drugs have been used to prevent recurrences of oral-facial (labialis) and cutaneous (gladiatorum) herpes. Oral and intravenous acyclovir has also been used to prevent recurrent HSV infections in immunocompromised patients.

LECTURE 4. VARICELLA (Chickenpox)

Definition

- Varicella (Chickenpox) is an acute, extremely contagious respiratory viral disease, causes usually a benign illness of childhood characterized by vesicular rash.

Etiology

- Varicella is caused by varicella-zoster virus (VZV), which is a DNA virus that is a member of the herpesvirus group, subfamily Alphaherpesvirinae.
- After the primary infection, VZV stays in the body (in the sensory nerve ganglia) as a latent infection.
- Primary infection with VZV causes varicella. Reactivation of latent infection causes herpes zoster (shingles).

Transmission, Epidemiology

- Reservoir — Humans.
- Transmission occurs via the airborne route, environmental contamination, direct contact with vesicular zoster lesions or respiratory secretions and also, the hands of health care workers. In utero, infection also can occur as a result of transplacental passage of virus during maternal varicella infection.
- Varicella is highly contagious. The virus spreads by air droplets when an infected person coughs or sneezes. It can also be spread by touching or breathing in aerosolized virus from varicella lesions.
- A person with varicella is contagious from 1–2 days before rash onset until the lesions have crusted. It takes from 10–21 days after exposure to the virus for someone to develop varicella. Based on studies of transmission among household members, about 90 % of susceptible close contacts will get varicella after exposure to persons with disease.
- Varicella is less contagious than measles but more so than mumps and rubella.
- Susceptibility is universal among those who have not previously had disease or vaccine.
- Susceptible individuals should be considered infectious for 10 to 21 days following exposure.
- Infection usually confers lifelong immunity.

Incubation Period and Prodrome

- The incubation period is generally 14 to 16 days but may range from 10 to 21 days. This period may be prolonged in persons who have

had passive immunization (e. g., varicella-zoster immune globulin) against varicella or are immunocompromised.

- A mild prodrome of fever and malaise may occur 1 to 2 days before rash onset, particularly in adults. In children, the rash is often the first sign of disease.

Varicella in Unvaccinated Persons

- The rash is generalized and pruritic (itchy). It progresses rapidly from macules to papules to vesicular lesions before crusting. The rash usually appears first on the head, chest, and back then spreads to the rest of the body. The lesions are usually most concentrated on the chest and back.

- In healthy children, varicella is generally mild, with an itchy rash, malaise, and temperature up to 38.9 °C for 2 to 3 days. Adults are at risk for more severe disease and have a higher incidence of complications. Recovery from primary varicella infection usually provides immunity for life. In otherwise healthy people, a second occurrence of varicella is uncommon and usually occurs in people who are immunocompromised. As with other viral infections, re-exposure to natural (wild-type) varicella may lead to re-infection that boosts antibody titers without causing illness or detectable viremia.

Varicella in Vaccinated Persons (Breakthrough Varicella)

- Breakthrough varicella is infection with wild-type VZV occurring in a vaccinated person more than 42 days after varicella vaccination. Breakthrough varicella is usually mild. Patients typically are afebrile or have low fever and develop fewer than 50 skin lesions. They usually have a shorter illness compared to unvaccinated people who get varicella. The rash is more likely to be predominantly maculopapular rather than vesicular. However, 25–30 % of persons vaccinated with 1 dose with breakthrough varicella have clinical features typical of varicella in unvaccinated people.

- Since the clinical features of breakthrough varicella are often mild, it can be difficult to make a diagnosis on clinical presentation alone. Laboratory testing is increasingly important for confirming varicella and appropriately managing cases and their contacts. There is limited information about breakthrough varicella in persons who have received two doses of varicella vaccine, though it appears to occur less frequently among people vaccinated with two doses of varicella vaccine compared to persons who have received a single dose of vaccine.

Stages of the Chickenpox Rash

- Macule → Papule → Vesicle → Crust.
- «False» polymorphism of the rash — presence of different rash stages simultaneously due to their appearance in several consequent days.

Complications

The most common complications from varicella are:

- bacterial infections of the skin and soft tissues in children;
- pneumonia in adults;
- Severe complications include septicemia, toxic shock syndrome, necrotizing fasciitis, osteomyelitis, bacterial pneumonia, and septic arthritis;
- Other complications caused by varicella include cerebellar ataxia, encephalitis, viral pneumonia, and hemorrhagic conditions.

Diagnosis

- The diagnosis of varicella has been most often made clinically by history and physical examination.
- Confirmation of disease is done by taking a swab/scraping from the base of a fresh vesicular lesion.
- There are four testing approaches: direct detection of viral antigen by direct fluorescent antigen test (DFA); polymerase chain reaction (PCR); amplification and detection of virus; modified culture (shell vial) of material and testing a blood sample (serum separator tube) for VZV IgM and IgG tests. (Seroconversion for VZV IgG may indicate a recent acute VZV infection).

Treatment

- Supportive therapy as indicated.
- In persons under the age of 18 years, avoid the use of acetylsalicylic acid (ASA, Aspirin) because of the association with Reye's syndrome.
- Antivirals have a limited window of opportunity to affect the outcome of VZV infection and are usually reserved for:
 - any adult with varicella disease;
 - children with complicated varicella disease when presenting within 72 hours of the onset of the rash; or
 - an immunocompromised individual still getting new lesions.
- **Intravenous acyclovir** should be considered for persons at risk of severe complicated disease including: immunocompromised hosts, premature infants while still in hospital, and neonates of seronegative mothers with onset in the first month of life.
- Oral antivirals, when given to immunocompetent patients within 24 h of the rash's onset, slightly decrease symptom duration and severity. However, because the disease is generally benign in children, antiviral treatment is not routinely recommended.
- The dose is famciclovir 500 mg tid or valacyclovir 1 g tid. Acyclovir is a less desirable choice because it has poorer oral bioavailability, but it can be given at 20 mg/kg qid with a maximum daily dose of 3200 mg. Immunocompromised children > 1 yr should be given 500 mg/m² q 8 h.

Prevention

- Infection provides lifelong protection. Potentially susceptible people should take strict precautions to avoid people capable of transmitting the infection.

- **Vaccination:** All healthy children and susceptible adults should receive 2 doses of live-attenuated varicella vaccine. Vaccination is particularly important for women of child-bearing age and adults with underlying chronic medical conditions. Serologic testing to determine immune status before vaccination in adults is usually not required. Although the vaccine may cause chickenpox in immunocompetent patients, disease is usually mild (< 10 papules or vesicles) and brief and causes few systemic symptoms.

- **Vaccination is contraindicated in:**

- patients with moderate to severe concurrent illness;
- immunocompromised patients;
- pregnant women;
- patients taking high doses of systemic corticosteroids;
- children using salicylates.

LECTURE 5. INFECTIOUS MONONUCLEOSIS

Definition

- Infectious mononucleosis is the best-known clinical syndrome caused by Epstein-Barr virus (EBV). It is characterized by fatigue, malaise, fever, sore throat, and generalized lymphadenopathy. Originally described as glandular fever, it derives its name from the mononuclear lymphocytosis with atypical-appearing lymphocytes that accompany the illness. EBV is named for the English virologists professor Sir Anthony Epstein and Yvonne M. Barr.

Etiology

- EBV, a member of the γ -herpesviruses, causes >90 % of cases of infectious mononucleosis. Two distinct types of EBV, type 1 and type 2 (also called type A and type B), have been characterized and have 70–85 % sequence homology.

- EBV initially infects naïve B cells and then induces these to undergo a period of rapid proliferation leading eventually to differentiation into a pool of latently EBV-infected cells that resemble memory B cells.

- As many as 5–10 % of infectious mononucleosis-like illnesses are caused by primary infection with cytomegalovirus, HHV6, Toxoplasma gondii, adenovirus, viral hepatitis, HIV, and possibly rubella virus. In the majority of EBV-negative infectious mononucleosis-like illnesses, the exact cause remains unknown.

Epidemiology

- The virus is not highly contagious. It is transmitted via penetrative sexual intercourse, and in oral secretions such as «deep kissing». Among children, transmission may occur by exchange of saliva from child to child, such as occurs between children in out-of-home child care. In addition to oropharyngeal spread, the virus can be transmitted by blood transfusion or through organ donation. Nonintimate contact, environmental sources, or fomites do not contribute to spread of EBV.

- EBV infects 90–95 % of the world's population. EBV is shed in oral secretions consistently for >6 mo after acute infection and then intermittently for life. As many as 20–30 % of healthy EBV-infected persons excrete virus at any particular time. Immunosuppression permits reactivation of latent EBV; 60–90 % of EBV-infected immunosuppressed patients shed the virus.

- Primary EBV infection in adolescents and adults manifests in >50 % of cases as the classic triad of fatigue, pharyngitis, and generalized lymphadenopathy. This syndrome may be seen at all ages but is rarely ap-

parent in children <4 yr of age, when most EBV infections are asymptomatic, or in adults >40 yr of age, when most individuals have already been infected by EBV. The incidence of infectious mononucleosis is highest in the 15- to 24-year-old age group.

Pathogenesis

- After acquisition in the oral cavity, EBV initially infects oral epithelial cells, which may contribute to the symptoms of pharyngitis. After intracellular viral replication and cell lysis with release of new virions, virus spreads to contiguous structures such as the salivary glands, with eventual viremia and infection of B lymphocytes in the peripheral blood and the entire lymphoreticular system, including the liver and spleen.

- The atypical lymphocytes that are characteristic of infectious mononucleosis are CD8+ T lymphocytes, which exhibit both suppressor and cytotoxic functions that develop in response to the infected B lymphocytes. This relative as well as absolute increase in CD8+ lymphocytes. Many of the clinical manifestations of infectious mononucleosis may result, at least in part, from cytokine release from the host immune response.

- EBV, like the other herpesviruses, establishes lifelong latent infection after the primary illness. The latent virus is carried in oropharyngeal epithelial cells and systemically in memory B lymphocytes. Only a few viral proteins, including the EBV-determined nuclear antigens (EBNAs), are produced during latency. Progression to viral replication begins with production of EBV early antigens (EAs), proceeds to viral DNA replication, is followed by production of viral capsid antigen (VCA), and culminates in cell death and release of mature virions. Reactivation with viral replication occurs at a low rate in populations of latently infected cells and is responsible for intermittent viral shedding in oropharyngeal secretions of infected individuals. Reactivation is apparently asymptomatic.

Oncogenesis

- EBV was the first human virus to be associated with malignancy. Benign EBV-associated proliferations include oral hairy leukoplakia, primarily in adults with AIDS, and lymphoid interstitial pneumonitis, primarily in children with AIDS. Malignant EBV-associated proliferations include nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, lymphoproliferative disorders, and leiomyosarcoma in immunodeficient states, including AIDS.

- About 15 % of cases of Burkitt's lymphoma in the US and ~90 % of those in Africa are associated with EBV. Malaria infection in Africa may impair cellular immunity to EBV and induce polyclonal B cell activation with an expansion of EBV-infected B cells. These changes may enhance

the proliferation of B cells, increasing the likelihood of a c-myc translocation — the hallmark of Burkitt's lymphoma.

- Nasopharyngeal carcinoma occurs worldwide but is 10 times more common in persons in southern China, where it is the most common malignant tumor among adult men.

Clinical Manifestations

- The incubation period of infectious mononucleosis in adolescents is 30–50 days. In children, it may be shorter. The majority of cases of primary EBV infection in infants and young children are clinically silent. Patients may complain of malaise, fatigue, acute or prolonged (>1 wk) fever, headache, sore throat, nausea, abdominal pain, and myalgia. This prodromal period may last 1–2 wk. The complaints of sore throat and fever gradually increase until patients seek medical care. Splenic enlargement may be rapid enough to cause left upper quadrant abdominal discomfort and tenderness, which may be the presenting complaint.

- The physical examination is characterized by generalized lymphadenopathy (90 % of cases), splenomegaly (50 % of cases), and hepatomegaly (10 % of cases). Symptomatic hepatitis or jaundice is uncommon, but elevated liver enzymes are frequent. Splenomegaly to 2–3 cm below the costal margin is typical; massive enlargement is uncommon.

- The sore throat is often accompanied by moderate to severe pharyngitis or tonsillitis with marked tonsillar enlargement, occasionally with exudates. Other clinical findings may include rashes and edema of the eyelids.

- Rashes are usually maculopapular and have been reported in 3–15 % of patients. Up to 80 % of patients with infectious mononucleosis experience «ampicillin rash» if treated with ampicillin or amoxicillin. This vasculitic rash is probably immune mediated and resolves without specific treatment.

Complications

- Very few patients with infectious mononucleosis experience complications. The most feared complication is subcapsular splenic hemorrhage or splenic rupture, which occurs most frequently during the 2nd week of the disease at a rate of <0.5 % of cases in adults; the rate in children is unknown but is probably much lower. Swelling of the tonsils and oropharyngeal lymphoid tissue may be substantial and may cause airway obstruction.

- Headache is present in about half of cases, with severe neurologic manifestations, such as seizures and ataxia, in 1–5 % of cases. There may be meningitis with nuchal rigidity and mononuclear cells in the cerebrospinal fluid, facial nerve palsy, transverse myelitis, and encephalitis.

- Guillain-Barré syndrome or Reye syndrome may follow acute illness. Hemolytic anemia occurs in 3 % of cases, the onset is typically in the 1st 2 wk of illness and lasts for <1 mo. Aplastic anemia is a rare complication that usually presents 3–4 wk after the onset of illness, usually with recovery in 4–8 days, but some cases do require bone marrow transplantation. Mild thrombocytopenia and neutropenia are common. Myocarditis or interstitial pneumonia may occur, both resolving in 3–4 wk. Other rare complications include pancreatitis, parotitis, and orchitis.

Diagnosis

- A presumptive diagnosis may be made by the presence of typical clinical symptoms with atypical lymphocytosis in the peripheral blood. The diagnosis is usually confirmed by serologic testing, either for heterophile antibody or specific EBV antibodies. PCR test for EBV DNA is also useful.

- The **culture method** is the transformation assay, which is performed by co-cultivating oropharyngeal or genital secretions, peripheral blood (10–30 mL), or tumor with human umbilical cord lymphocytes. The cultures are observed for 6 wk for signs of cell transformation: proliferation and rapid growth, mitotic figures, large vacuoles, granular morphology, and cell aggregation. EBV immortalizes the umbilical cord cells, resulting in cell lines that can be maintained in perpetuity that harbor EBV isolated from the patient.

- In >90 % of cases there is leukocytosis of 10,000–20,000 cells/mm³, of which at least 2/3 are lymphocytes; **atypical lymphocytes** usually account for 20–40 % of the total number (diagnostic threshold is 10 % and more).

- The atypical cells are mature T lymphocytes (predominantly CD8+ cells) that have been antigenically activated. Compared with regular lymphocytes microscopically, atypical lymphocytes are larger overall, with larger, eccentrically placed indented and folded nuclei with a lower nuclear-to-cytoplasm ratio. Although atypical lymphocytosis may be seen with many of the infections usually causing lymphocytosis, the highest degree of atypical lymphocytes is classically seen with EBV infection.

- Mild thrombocytopenia to 50,000–200,000 platelets/mm³ occurs in >50 % of patients. Mild elevation of hepatic transaminases occurs in approximately 50 % of uncomplicated cases but is usually asymptomatic without jaundice.

- **Heterophile antibody test.** Heterophile antibodies agglutinate cells from non-human species. The transient heterophile antibodies seen in infectious mononucleosis, also known as Paul-Bunnell antibodies, are IgM antibodies detected by the Paul-Bunnell-Davidsohn test for sheep red cell agglutination. The heterophile antibodies of infectious mononucleosis agglutinate sheep or, for greater sensitivity, horse red cells but not guinea pig kidney cells. Titers of >1:28 or >1:40, depending on the dilution system used, after absorption with guinea pig cells are

considered positive. Results of the test are often positive for several months after infectious mononucleosis. Children <4 yr of age typically develop a lower antibodies titer. The false-positive rate is <10 %. If the heterophile test result is negative and an EBV infection is suspected, EBV-specific antibody testing is indicated.

- **Specific EBV antibodies.** The EBNA, EA, and VCA antigen systems are most useful for diagnostic purposes. The detection of IgM antibody to VCA is the most valuable and specific serologic test for the diagnosis of acute EBV infection and is generally sufficient to confirm the diagnosis. The acute phase of infectious mononucleosis is characterized by rapid IgM and IgG antibody responses to VCA in all cases and an IgG response to EA in most cases. The IgM response to VCA is transient but can be detected for at least 4 wk and occasionally up to 3 mo. The laboratory must take steps to remove rheumatoid factor, which may cause a false-positive IgM VCA result. The IgG response to VCA usually peaks late in the acute phase, declines slightly over the next several weeks to months, and then persists at a relatively stable level for life. Anti-EA antibodies are usually detectable for several months but may persist or be detected intermittently at low levels for many years. Anti-EBNA antibodies are the last to develop in infectious mononucleosis and gradually appear 3–4 mo after the onset of illness and remain at low levels for life. Absence of anti-EBNA when other antibodies are present implies recent infection, whereas the presence of anti-EBNA implies infection occurring more than 3–4 mo previously (Table 2, Figure 2).

Differential Diagnosis

- Infectious mononucleosis-like illnesses may be caused by primary infection with cytomegalovirus, HHV-6, *T. gondii*, adenovirus, viral hepatitis, HIV, or possibly rubella virus. Cytomegalovirus infection is a particularly common cause in adults.

- Streptococcal pharyngitis may cause sore throat and cervical lymphadenopathy indistinguishable from that of infectious mononucleosis but is not associated with hepatosplenomegaly. Protracted onset, prolonged febrile period, enlargement of posterior cervical lymph nodes and ineffectiveness of penicillin group antibiotics are typical for EBV infection. Failure of a patient with streptococcal pharyngitis to improve within 48–72 hr should evoke suspicion of infectious mononucleosis.

The most serious problem in the diagnosis of acute illness arises in the occasional patient with extremely high or low white blood cell counts, moderate thrombocytopenia, and even hemolytic anemia. In these patients, bone marrow examination and hematologic consultation are warranted to exclude the possibility of leukemia.

Table 2 — Serum Epstein-Barr Virus (EBV) Antibodies in EBV Infection

Infection	VCA IgG	VCA IgM	EA(D)	EBNA
No previous infection	-	-	-	-
Acute infection	+	+	+/-	-
Recent infection	+	+/-	+/-	+/-
Past infection	+	-	+/-	+

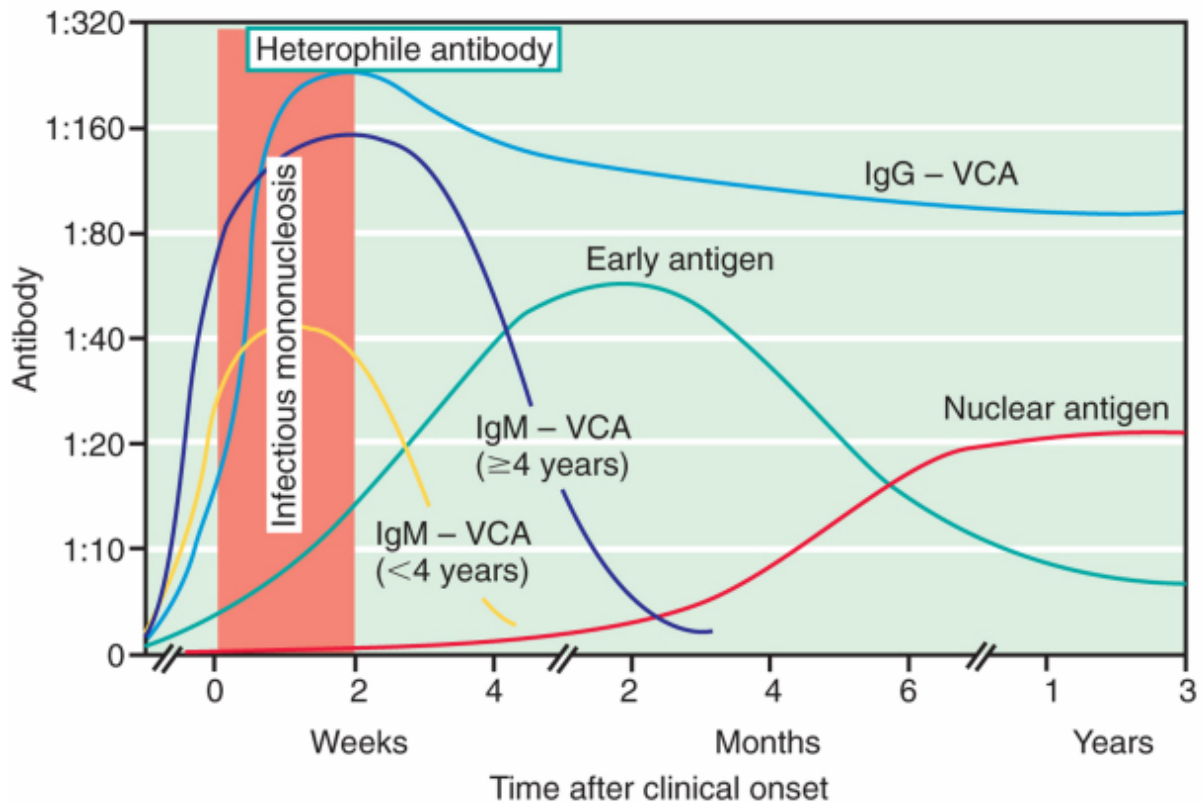


Figure 2 — Schematic representation of the development of antibodies to various Epstein-Barr virus antigens in patients with infectious mononucleosis

Treatment

- Rest and symptomatic treatments are the mainstays of management. Because blunt abdominal trauma may predispose patients to splenic rupture, it is reason to advise against participation in contact sports during the 1st 2–3 wk of illness or while splenomegaly is present.

- There is no specific treatment for infectious mononucleosis. Antiviral agents (acyclovir etc.) cannot accelerate the resolution of symptoms significantly or to prevent complications of the disease.

- Corticosteroids should not be used in uncomplicated cases of infectious mononucleosis. Short courses of corticosteroids (<2 wk) may be helpful for complications of infectious mononucleosis. Some appropriate in-

dications include incipient airway obstruction, thrombocytopenia with hemorrhaging, autoimmune hemolytic anemia, seizures, and meningitis. A recommended dosage is prednisone 0.5–1 mg/kg/day (maximum 60 mg/day) or equivalent for 7 days and tapered over another 7 days.

Prognosis. Prevention

- The **prognosis** for complete recovery is excellent if no complications ensue during the acute illness. The major symptoms typically last 2–4 wk, followed by gradual recovery. Second infections with a different type of EBV (type 1 or type 2) have been demonstrated in immunocompromised persons, but symptoms or 2nd attacks of infectious mononucleosis caused by EBV have not been documented. Prolonged and debilitating fatigue, malaise, and some disability that may wax and wane for several weeks to 6 mo are common complaints even in otherwise unremarkable cases.

- **Prevention.** The isolation of patients with IM is unnecessary. Vaccines directed against the major EBV glycoprotein have been effective in animal studies and are undergoing clinical trials.

LECTURE 6. EPIDEMIC PAROTITIS (MUMPS)

Definition

- Mumps is an acute respiratory viral infection, whose most distinctive feature is swelling of one or both parotid glands. Involvement of other salivary glands, the meninges, the pancreas, and the gonads also is common.

- While no longer common in countries with extensive vaccination programs, it remains endemic in the rest of the world, so continued vaccine protection is warranted.

Etiology

- Mumps virus is in the family Paramyxoviridae.
- It is a single-stranded pleomorphic RNA virus encapsulated in a lipoprotein envelope and possessing 7 structural proteins. Two surface glycoproteins, HN (hemagglutinin-neuraminidase) and F (fusion), mediate absorption of the virus to host cells and penetration into cells, respectively. Both stimulate production of protective antibodies. Mumps virus exists as a single immunotype, and humans are the only natural host.

Epidemiology

- Mumps is spread from person to person by respiratory droplets. Virus appears in the saliva from up to 7 days before to as long as 7 days after onset of parotid swelling. The period of maximum infectiousness is 1–2 days before to 5 days after parotid swelling. Viral shedding before onset of symptoms and in asymptomatic infected individuals impairs efforts to contain the infection in susceptible populations.

- In the prevaccine era, mumps occurred primarily in young children between the ages of 5 and 9 and in epidemics about every 4 years. Mumps infection occurred more often in the winter and spring months.

- Following introduction of the mumps vaccine, which was recommended for routine use, the incidence fell dramatically and shifted to older children, adolescents, and young adults. After implementation of the 2 dose measles-mumps-rubella (MMR) vaccine for measles control, the number of mumps cases declined further.

- The age group most affected (38 % of cases) was young adults 18–24 yr of age and included many college students. The outbreak subsequently spread to all age groups.

Pathology and pathogenesis

- Mumps virus targets the salivary glands, central nervous system (CNS), pancreas, testes, and, to a lesser extent, thyroid, ovaries, heart, kidneys, liver, and joint synovia.

- Following infection, initial viral replication occurs in the epithelium of the upper respiratory tract. Infection spreads to the adjacent lymph nodes by the lymphatic drainage, and viremia ensues, spreading the virus to targeted tissues.

- Mumps virus causes necrosis of infected cells and is associated with a lymphocytic inflammatory infiltrate. Salivary gland ducts are lined with necrotic epithelium, and the interstitium is infiltrated with lymphocytes. Swelling of tissue within the testes may result in focal ischemic infarcts. The cerebrospinal fluid (CSF) frequently contains mononuclear pleocytosis, even in individuals without clinical signs of meningitis.

Clinical manifestations

- The incubation period for mumps ranges from 12 to 25 days, but is usually 16 to 18 days.

- Mumps virus infection may result in clinical presentation ranging from asymptomatic or nonspecific symptoms to typical illness associated with parotitis with or without complications involving several body systems.

- The typical case presents with a prodrome lasting 1–2 days consisting of fever, malaise, myalgia and anorexia, sometimes also headache and vomiting.

- Parotitis then appears and may be unilateral initially but becomes bilateral in about 70 % of cases. The parotid gland is tender, and parotitis may be preceded or accompanied by ear pain on the ipsilateral side. Ingestion of sour or acidic foods or liquids may enhance pain in the parotid area. As swelling progresses, the angle of the jaw is obscured and the ear lobe may be lifted upward and outward. The opening of the Stensen duct may be red and edematous («Mourson's sign»). The parotid swelling peaks in approximately 3 days then gradually subsides over 7 days.

- Fever resolves in 3 to 5 days along with the other systemic symptoms. A morbilliform rash is rarely seen. Submandibular salivary glands may also be involved or may be enlarged without parotid swelling. Edema over the sternum due to lymphatic obstruction may also occur.

- Maternal infection with mumps during the 1st trimester of pregnancy results in increased fetal wastage. No fetal malformations have been associated with intrauterine mumps infection. However, perinatal mumps disease has been reported in infants born to mothers who acquired mumps late in gestation.

Diagnosis

- When mumps was highly prevalent, the diagnosis could be made based on history of exposure to mumps infection, an appropriate incubation period, and development of typical clinical findings.

- Confirmation of the presence of parotitis could be made with demonstration of an elevated amylase level.
- Leukopenia with a relative lymphocytosis is a common finding.
- Today, in patients with parotitis of >2 days of unknown cause, a specific diagnosis of mumps should be confirmed or ruled out by virologic or serologic means. This may be accomplished by isolation of the virus in cell culture, detection of viral antigen by direct immunofluorescence, or identification of nucleic acid by reverse transcriptase polymerase chain reaction. Virus can be isolated from upper respiratory tract secretions, CSF, or urine during the acute illness.
- Serologic testing is usually a more convenient and available mode of diagnosis. A significant increase in serum mumps immunoglobulin G (IgG) antibody between acute and convalescent serum specimens by complement fixation, neutralization hemagglutination, or enzyme immunoassay (EIA) tests establish the diagnosis. However, IgG antibody tests may cross react with antibodies to parainfluenza virus. More commonly, an EIA for mumps IgM antibody is used to identify recent infection.

Mumps Case Definition (CDC, 2011; <http://www.cdc.gov/vaccines/pubs/surv-manual/chpt09-mumps.html>).

Probable case:

- Acute parotitis or other salivary gland swelling lasting at least 2 days, or orchitis or oophoritis unexplained by another more likely diagnosis, in:
 - a person with a positive test for serum anti-mumps IgM antibody, or;
 - a person with epidemiologic linkage to another probable or confirmed case or linkage to a group/community defined by public health during an outbreak of mumps.

Confirmed case:

- A positive mumps laboratory confirmation for mumps virus with RT-PCR or culture in a patient with an acute illness characterized by any of the following:
 - Acute parotitis or other salivary gland swelling, lasting at least 2 days.
 - Aseptic meningitis.
 - Encephalitis.
 - Hearing loss.
 - Orchitis.
 - Oophoritis.
 - Mastitis.
 - Pancreatitis.

Differential Diagnosis

- Parotid swelling may be caused by many other infections and non-infectious conditions.
- Viruses that have been shown to cause parotitis include parainfluenza 1 and 3, influenza A, cytomegalovirus, Epstein-Barr virus, enteroviruses, lymphocytic choriomeningitis virus, and HIV.
- Purulent parotitis, usually caused by *Staphylococcus aureus*, is unilateral, extremely tender, and associated with an elevated white blood cell count, and may have purulent drainage from the Stensen duct.
- Submandibular or anterior cervical adenitis due to a variety of pathogens may also be confused with parotitis.
- Other noninfectious causes of parotid swelling include obstruction of the Stensen duct, collagen vascular diseases such as Sjögren syndrome, systemic lupus erythematosus, and tumor.

Complications

- The most common complications of mumps are meningitis, with or without encephalitis, and gonadal involvement. Uncommon complications include pancreatitis, conjunctivitis, optic neuritis, pneumonia, nephritis, and thrombocytopenia.
- **Meningitis and Meningoencephalitis.** Symptomatic CNS involvement occurs in 10–30 % of infected individuals, but CSF pleocytosis has been found in 40–60 % of patients with mumps parotitis. The meningoencephalitis may occur before, along with, or following the parotitis. It most commonly will present 5 days after the parotitis. Clinical findings vary with age. Infants and young children will have fever, malaise, and lethargy, while older children, adolescents, and adults will complain of headache and demonstrate meningeal signs. In 1 series in children with mumps with meningeal involvement, findings were fever in 94 %, vomiting in 84 %, headache in 47 %, parotitis in 47 %, neck stiffness in 71 %, lethargy in 69 %, and seizures in 18 %. In typical cases, symptoms resolve in 7–10 days. CSF in mumps meningitis has a white blood cell pleocytosis of 200–600/mm³ with a predominance of lymphocytes. The glucose is normal in most patients, but a moderate hypoglycorrhachia (20–40 mg/dL) may be seen in 10–20 % of patients. Protein is normal or mildly elevated. Less common CNS complications of mumps include transverse myelitis, aqueductal stenosis, and facial palsy. Sensorineural hearing loss is rare but has been estimated to occur in 0.5–5.0/100,000 cases of mumps. There is some evidence that it is more likely in patients with meningoencephalitis.
- **Orchitis and Oophoritis.** In adolescent and adult males, epidymo-orchitis is 2nd only to parotitis as a common finding in mumps.

Involvement in prepubescent male children is extremely rare, but following puberty it occurs in 30–40 % of males. It begins within days following onset of parotitis in the majority of cases and is associated with moderate to high fever, chills, and acute pain and swelling of the testes. In $\leq \frac{1}{3}$ of cases the orchitis is bilateral. Atrophy of the testes may occur, but sterility is rare even with bilateral involvement. Oophoritis is uncommon in postpubertal females but may cause severe pain and when on the right side it may be confused with appendicitis.

- **Pancreatitis.** Pancreatitis may occur in mumps with or without parotid involvement. Severe disease is rare, but fever, epigastric pain, and vomiting are suggestive. Epidemiologic studies have suggested that mumps may be associated with the subsequent development of diabetes mellitus, but a causal link has not been established.

Treatment

- No specific antiviral therapy is available for mumps. Management should be aimed at reducing the pain associated with meningitis or orchitis and maintenance of adequate hydration. Antipyretics may be given for fever. In a case of orchitis testicular pain may be minimized by the local application of cold compresses and gentle support for the scrotum; corticosteroids (prednisolone orally 1.5 mg/kg for 5–10 days) also may be used.

Prognosis

- The outcome of mumps is nearly always excellent, even when complicated by encephalitis, although fatal cases due to CNS involvement or myocarditis have been reported.

Prevention

- **Immunization** with the live mumps vaccine is the primary mode of prevention.

- In USA it is given as part of the **MMR 2** dose vaccine schedule, at 12–15 mo of age for the 1st dose and 4–6 yr of age for the 2nd dose. If not given at 4–6 yr, the 2nd dose should be given before children enter puberty. Antibody develops in 95 % of vaccinees after 1 dose. One study showed vaccine effectiveness of 88 % for 2 doses of MMR vaccine compared with 64% for a single dose. Immunity appears to be long lasting, with existing serologic and epidemiologic evidence indicating protection for >25 yr.

- As a live-virus vaccine, MMR should not be administered to pregnant women or severely immunodeficient or immunosuppressed individuals. HIV-infected patients not severely immunocompromised may receive the vaccine. Individuals with anaphylactoid reactions to egg or neomycin may be at risk for immediate-type hypersensitivity reactions to the vaccine. Adverse reactions to mumps virus vaccine are rare.

LECTURE 7. ENTEROVIRAL INFECTION

- The genus Enterovirus contains a large number of viral agents that produce a broad range of important illnesses.
- The genus name reflects the importance of the gastrointestinal tract as the primary site of viral invasion and replication and source for transmission.
- Viremic spread to distant sites accounts for the majority of clinical manifestations.

Etiology

- Enteroviruses are nonenveloped, single-stranded RNA viruses in the Picornaviridae («small RNA virus») family.
- The original human enterovirus subgroups — polioviruses, coxsackieviruses, and echoviruses — were differentiated by their replication patterns in tissue culture and animals.
- Coxsackieviruses derive their name from Coxsackie, New York, where they were discovered. The name for echoviruses reflects an acronym applied to a group of viruses originally without disease associations (enteric cytopathic human orphan viruses).
- The human enteroviruses have been recently reclassified based on nucleotide and amino acid sequences into 5 species, polioviruses and human enteroviruses A–D.
- Enterovirus serotypes are distinguished by antigenic and genetic sequence differences; newer enteroviruses are classified by numbering. Although >70 serotypes have been identified, 10–15 account for the majority of disease. No enterovirus disease is uniquely associated with any specific serotype, although certain manifestations are preferentially associated with specific serotypes.

Classification of Human Enteroviruses

- Family Picornaviridae.
- Genus Enterovirus.
- Subgroups:
 - Poliovirus serotypes 1–3.
 - Coxsackie A virus serotypes A1–A22, A24 (A23 reclassified as echovirus 9).
 - Coxsackie B virus serotypes B1–B6.
 - Echovirus serotypes 1–9, 11–27, 29–33 (echoviruses 10 and 28 reclassified as non-enteroviruses; echovirus 34 reclassified as coxsackievirus A24; echoviruses 22 and 23 have been reclassified within the genus *Parechovirus*).

— Numbered enterovirus serotypes (enterovirus 72 reclassified as hepatitis A virus).

Epidemiology

- Humans are the only known reservoir for human enteroviruses.
- Virus is primarily spread person to person, by the fecal-oral and respiratory routes, and vertically, from mother to neonate, either prenatally or in the peripartum period.
 - Enteroviruses can survive on environmental surfaces, permitting transmission via fomites.
 - Enteroviruses also can frequently be isolated from water sources and sewage and can survive for months in wet soil.
 - Transmission occurs within families with young children (>50 % spread to susceptible household contacts), daycare centers, playgrounds, summer camps, orphanages, and hospital nurseries; severe secondary infections may occur in nursery outbreaks.
 - Enterovirus infections are very common and have a worldwide distribution.
 - In temperate climates there is an annual epidemic peak in summer and fall, although some transmission occurs year-round.
 - In tropical and semitropical areas, enteroviruses frequently circulate year-round.
 - Enteroviruses are responsible for 33–65 % of acute febrile illnesses and 25% of hospitalizations for suspected sepsis in infants.
 - Infections by different serotypes in the same child can occur within the same season.
 - Factors associated with increased incidence and/or severity include young age, male sex, poor hygiene, overcrowding, and low socioeconomic status; more than 25 % of symptomatic infections occur in children <1 yr of age.
 - **Incubation period and infectivity.** The incubation period of enterovirus infections is typically 3–6 days, for acute hemorrhagic conjunctivitis: 1–3 days.
 - Infected children, both symptomatic and asymptomatic, frequently shed enteroviruses from the respiratory tract for <1–3 wk, whereas fecal shedding continues up to 7–11 wk postinfection.

Pathogenesis

- Enterovirus infections are acquired by the ingestion of virus.
- Virus replication occurs initially in the upper respiratory tract and distal small-bowel lymphoid tissue.
 - A transient «minor» viremia, that distributes virus to reticuloendothelial tissue in distant lymph nodes, liver, spleen, and bone marrow, follows.

- Further replication in these organs leads to a sustained “major” viremia with dissemination of virus to target organs such as the central nervous system (CNS) and heart.

- Most infected persons experience asymptomatic infections when virus replication is controlled by host defense mechanisms before the onset of major viremia.

- The onset of symptomatic disease coincides with major viremia, and organ-specific disease (i.e., meningitis, myocarditis) results from the inflammatory response to virus replication.

Immunity

- Immunity to enterovirus infection is serotype-specific. Antibodies that recognize specific epitopes on capsid proteins, neutralize enteroviruses, probably by interfering with viral attachment to the cell membrane.

- Immunoglobulin M (IgM) antibodies, followed by long-lasting IgA and IgG antibodies, and secretory IgA, mediating mucosal immunity, are produced. Secretory immunoglobulin A (IgA) antibodies appear in nasal and duodenal secretions 2 weeks after primary infection and persist for at least 15 years.

- Heterotypic antibody may enhance disease caused by a different serotype.

- Passive immunity conferred by immune globulin or transplacental maternal antibody may prevent enterovirus disease.

- Cellular defenses (especially macrophage function) may play an important role in recovery from infection.

Clinical manifestations

- Clinical manifestations are variable, ranging from asymptomatic infection or undifferentiated febrile or respiratory illnesses in the majority, to, less frequently, severe diseases such as meningoencephalitis, myocarditis, and neonatal generalized disease.

- A majority of individuals shedding virus are asymptomatic or have very mild illness, yet may serve as a significant source for spread of infection. Symptomatic disease is generally more frequent in young children.

Spectrum of Illness Caused by Enteroviruses

- Asymptomatic infection.
- Nonspecific febrile illness («summer grippé») with or without respiratory symptoms and rash.

- **Exanthems/Enanthems:**

- Herpangina.

- Hand-foot-and-mouth disease.

- Nonspecific rash.

- **Central nervous system infections:**
 - Aseptic meningitis (often associated with an exanthem).
 - Encephalitis.
 - Paralytic disease (poliomyelitis-like).
- **Diseases of muscles:**
 - Pleurodynia.
 - Myositis.
 - Myopericarditis.
- **Ophthalmic Infections:**
 - Acute hemorrhagic conjunctivitis.
- **Respiratory Tract Syndromes:**
 - Common cold.
 - Lower respiratory tract infections (bronchiolitis, pneumonia).
- **Generalized disease of the newborn.**

Nonspecific Febrile Illness (Summer Grippe)

- Most common symptomatic manifestation, especially frequent in infants and young children.
 - Illness usually begins with abrupt onset of fever, usually 38.5–40 °C, malaise, and irritability. Other symptoms may include lethargy, anorexia, diarrhea, nausea, vomiting, abdominal discomfort, rash, sore throat, and respiratory symptoms. In older children, headache and myalgia frequently occur.
 - Findings are generally nonspecific and may include mild conjunctivitis, mild pharyngeal injection, and cervical lymphadenopathy. Fever lasts a mean of 3 days. Occasionally, fever is biphasic. Duration of illness is usually 4–7 days but can range from 1 day to >1 wk. White blood cell (WBC) count and results of other routine laboratory tests are generally normal.
 - Enterovirus illnesses may be associated with a wide variety of skin manifestations including macular, maculopapular, urticarial, vesicular, and petechial rash.

Herpangina

- Herpangina is characterized by sudden onset of fever, sore throat, dysphagia, and lesions in the posterior pharynx. The term «herpangina» reflects vesicular enanthem in oral cavity similar to that in HSV infection.
 - Temperatures can range from normal to 41 °C; fever tends to be greater in younger patients. Headache and backache may occur in older children, and vomiting and abdominal pain occur in 25 %.
 - Characteristic lesions, present on the anterior tonsillar pillars, soft palate, uvula, tonsils, posterior pharyngeal wall, and, occasionally, the posterior buccal surfaces, are discrete 1–2 mm vesicles and ulcers that

enlarge over 2–3 days to 3–4 mm and are surrounded by erythematous rings that vary in size up to 10 mm. Typically about 5 lesions are present, with a range of 1 to >15. The remainder of the pharynx appears normal or minimally erythematous.

- Most cases are mild and have no complications; however, some are associated with aseptic meningitis or other more severe illness. Fever generally lasts 1–4 days, and resolution of symptoms occurs in 3–7 days.

Hand-Foot-and-Mouth Disease

- It is usually a mild illness, with or without low-grade fever. The oropharynx is inflamed and contains scattered vesicles on the tongue, buccal mucosa, posterior pharynx, palate, gingiva, and/or lips. These may ulcerate, leaving 4–8 mm shallow lesions with surrounding erythema. Maculopapular, vesicular, and/or pustular lesions may also occur on the hands and fingers, feet, and buttocks and groin; hands are more commonly involved than the feet. Lesions on the hands and feet are usually tender vesicles varying in size from 3 to 7 mm and are more common on dorsal surfaces but frequently also occur on palms and soles. Vesicles resolve in about 1 wk.

Neurologic Manifestations:

- **Aseptic meningitis** Enteroviruses are the most common cause of viral meningitis in mumps-immunized populations, accounting for >90 % of cases in which a causative agent is identified. Meningitis is particularly common in infants, especially those <3 mo of age. Most cases in infants and young children are mild and lack specific signs and symptoms. Fever is present in 50–100 %; other findings may include irritability, malaise, headache, photophobia, nausea, emesis, anorexia, lethargy, rash, cough, rhinorrhea, pharyngitis, diarrhea, and myalgia. Nuchal rigidity («neck stiffness») is apparent in more than half of children >1–2 yr of age. Some cases are biphasic, with fever and nonspecific symptoms for a few days, followed by absence of symptoms for several days, then return of fever with meningeal signs. Fever usually resolves in 3–5 days, and other symptoms in infants and young children usually resolve within 1 wk. Symptoms tend to be more severe and longer lasting in adults. CSF findings include pleocytosis that generally is <500 WBC/mm³, mostly lymphocytes; normal or slightly low glucose; and normal or mildly increased protein, generally <100 mg/dL. CSF occasionally has normal parameters, particularly in the 1st few months of life. Complications occur in approximately 10 % of young children, including simple and complex seizures, increased intracranial pressure, syndrome of inappropriate antidiuretic hormone secretion, ventriculitis, transient cerebral arteriopathy, and coma. The prognosis for most children with meningitis is good.

- **Encephalitis.** Enteroviruses are also responsible for 10–20 % of cases of encephalitis with an identified cause. After initial nonspecific symptoms, encephalitis becomes apparent by progression to marked confusion, weakness, lethargy, and/or irritability. Depression is usually generalized, although focal findings such as focal motor seizures, hemichorea, acute cerebellar ataxia, aphasia, extrapyramidal symptoms, and/or focal imaging abnormalities occur. Encephalitis includes a spectrum from altered mental status to coma to decerebrate status; long-term neurologic sequelae or death may follow severe disease.

- **Poliomyelitis-Like Illness.** Enterovirus 71 and coxsackievirus A7 have been associated with outbreaks of acute motor neuron disease clinically indistinguishable from poliomyelitis. Motor neuron disease caused by the nonpoliovirus enteroviruses generally has a better outcome than poliomyelitis. Transient muscle weakness is more common than flaccid paralysis, and the paresis is not usually permanent.

Diseases of muscles:

- **Pleurodynia (Bornholm disease)** is an epidemic or sporadic illness characterized by paroxysmal thoracic pain, due to myositis involving chest and abdominal wall muscles. Prodromal symptoms such as malaise, myalgias, and headache are followed by sudden onset of fever and spasmodic, pleuritic pain, typically located in the chest or upper abdomen and aggravated by coughing, sneezing, deep breathing, or other movement. During spasms, which last from a few minutes to several hours, pain may be severe and respirations are usually rapid and shallow, suggesting pneumonia or pleural inflammation. Chest radiographs are generally normal. Illness usually lasts 3–6 days, but can last up to a couple of weeks. Pleurodynia may be associated with meningitis, orchitis, myocarditis, or pericarditis.

Myocarditis and Pericarditis

- Enteroviruses account for approximately 25–35 % of cases of myocarditis and pericarditis with proven cause. Adolescents and young adults, especially males, are disproportionately affected by enterovirus myocarditis.

- Myopericarditis may be the dominant feature of illness or it may be part of disseminated disease, as in neonates. Disease ranges from relatively mild to severe. Presentations may mimic myocardial infarction; in other cases, patients present with sudden death (including apparent sudden infant death syndrome).

- The acute mortality of enterovirus myocarditis is 0–4 %. Recovery is complete without residual disability in the majority. Occasionally, chronic cardiomyopathy, inflammatory ventricular microaneurysms, or constrictive pericarditis may result.

Ocular Manifestations

- Enterovirus 70 and coxsackievirus A24 are the primary causes of **acute hemorrhagic conjunctivitis**. Epidemics are explosive, spread mainly via eye-hand-fomite-eye transmission. Sudden onset of severe eye pain is associated with photophobia, blurred vision, lacrimation, conjunctival erythema and congestion, lid edema, preauricular lymphadenopathy, and, in some cases, subconjunctival hemorrhages and superficial punctate keratitis. Eye discharge is initially serous but becomes mucopurulent with secondary bacterial infection. Systemic symptoms including fever are rare, although clinical manifestations suggestive of **pharyngoconjunctival fever** occasionally occur. Recovery is usually complete within 1–2 weeks. Enteroviruses have been implicated in cases of keratoconjunctivitis, chorioretinitis, uveoretinitis, optic neuritis, and unilateral acute idiopathic maculopathy.

Generalized Disease of the Newborn

- Most serious enterovirus infections in infants develop during the first week of life, although severe disease can occur up to 3 months of age. Neonates often present with an illness resembling bacterial sepsis, with fever, irritability, and lethargy. Laboratory abnormalities include leukocytosis with a left shift, thrombocytopenia, elevated values in liver function tests, and CSF pleocytosis.

- The illness can be complicated by myocarditis and hypotension, fulminant hepatitis and disseminated intravascular coagulation, meningitis or meningoencephalitis, or pneumonia.

LABORATORY DIAGNOSIS

- **Cell Culture.** Enteroviruses produce characteristic cytopathic effect (CPE) in susceptible cultured cells permitting their isolation and identification. Development of visible CPE requires 2 to 6 days. Stool and rectal swabs are most likely to produce an isolate. Often, CSF (in cases of CNS disease), oropharyngeal secretions, urine, and serum are sampled. «False-positive» results can occur because children excrete enteroviruses for up to 8 weeks in stool from a previous infection. Cell culture for enteroviruses is generally labor-intensive, expensive, and less sensitive than PCR.

- **Polymerase Chain Reaction (PCR)** detects enterovirus RNA in 66 to 86 % of patients with acute viral meningitis, compared with cell culture isolation rates of approximately 30 %. PCR in blood, feces, and CSF samples has also been used to diagnose enteroviral infection.

- **Serology.** Serologic assays are mainly used for determination of prior immunity for epidemiologic or research purposes. They are not very useful for diagnosis of acute disease except when infection with a spe-

cific serotype or one of a small number of serotypes is suspected. The microneutralization test is the standard method for determination of antibodies to enteroviruses. This test is serotype-specific, and has limited usefulness in the routine diagnosis. Immunoassays (e.g., enzyme immunoassay and indirect fluorescent antibody tests) to test antibodies against several serotypes are easier to perform, but show some degree of cross-reactivity among different serotypes and are difficult to interpret. These assays require both acute and convalescent sera. Serum IgM antibody to the group B coxsackieviruses can often be detected in a single serum specimen early in the course of illness, but positive test results are not serotype-specific (Table 3).

Table 3 — Differential diagnosis of enteroviral diseases

CLINICAL MANIFESTATION	BACTERIAL PATHOGENS	VIRAL PATHOGENS
Nonspecific febrile illness	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> type b, <i>Neisseria meningitidis</i>	Influenza viruses, HHV-6, HHV-7
Exanthems/enanthems	Group A streptococcus, <i>Staphylococcus aureus</i> , <i>Neisseria meningitidis</i>	HSV, adenoviruses, VZV, EBV, measles virus, rubella virus, HHV-6, HHV-7
Respiratory illness/ conjunctivitis	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> (nontypable and type b), <i>Neisseria meningitidis</i> , <i>Mycoplasma pneumoniae</i> , <i>Chlamydia pneumoniae</i>	Adenoviruses, influenza viruses, respiratory syncytial virus, parainfluenza viruses, rhinovirus
Myocarditis/pericarditis	<i>Staphylococcus aureus</i> , <i>Haemophilus influenzae</i> type b, <i>Mycoplasma pneumoniae</i>	Adenoviruses, influenza virus, parvovirus
Meningitis/encephalitis	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> type b, <i>Neisseria meningitidis</i> , <i>Mycobacterium tuberculosis</i> , <i>Borrelia burgdorferi</i> , <i>Mycoplasma pneumoniae</i> , <i>Bartonella henselae</i> , <i>Listeria monocytogenes</i>	HSV, West Nile virus, Influenza viruses, adenovirus, EBV, mumps virus, lymphocytic choriomeningitis virus, arboviruses
Neonatal infections	Group B streptococcus, gram-negative enteric bacilli, <i>Listeria monocytogenes</i> , <i>Enterococcus</i>	HSV, adenoviruses, CMV, rubella virus

Complications and prognosis

- The prognosis in the vast majority of infections is excellent.
- Mortality is primarily associated with myocarditis, neurologic disease, severe neonatal infections, and infections in immune compromised hosts.

Treatment

- Most enterovirus infections are mild and resolve spontaneously with no specific treatment. IV immunoglobulin can be given in some cases of life-threatening infection in neonates and have clear benefit in those with hypo- or aglobulinemia.

- The antiviral compounds now in clinical development are more promising than immune-based therapy. The oxazolines are a class of antiviral agents that exhibit potent in vitro activity against many HEVs by binding avidly to a pocket in the viral capsid, thereby preventing virus attachment and uncoating. One compound, pleconaril, is an orally administered drug with a favorable pharmacokinetic and toxicity profile. Pleconaril reduces the duration and severity of headache and shortened the period of viral shedding. This drug is used in some countries.

Prevention

- Simple hygienic measures such as handwashing and careful disposal of soiled diapers should reduce transmission. It is prudent to advise pregnant women and children who are immunocompromised to avoid contact, whenever possible, with persons suspected of having enterovirus infection.

- Because pre-exposure administration of immune serum globulin reduces the risk of paralytic poliomyelitis, it is possible that nonpoliovirus enterovirus infections could be prevented in the same manner.

- Active immunization against the nonpoliovirus enteroviruses is not practical because of the large number of serotypes.

LECTURE 8. INFLUENZA

Definition

- Influenza is an acute respiratory illness caused by infection with influenza viruses.
- The illness affects the upper and/or lower respiratory tract and is often accompanied by systemic signs and symptoms such as fever, headache, myalgia, and weakness.
- Outbreaks of illness of variable extent and severity occur nearly every winter.

Etiology

- Orthomyxoviridae family, separate genera: influenza A, B, and C viruses. These are large (80–120 nm in diameter), single-stranded RNA viruses with a segmented genome encased in a lipid-containing spherical envelope.
- The designation of influenza viruses as type A, B, or C is based on antigenic characteristics of the nucleoprotein (NP) and matrix (M) protein antigens.
- Whereas influenza B and C viruses are principally human pathogens, influenza A viruses primarily infect aquatic birds and sometimes other animal hosts, including mammals.
- Influenza A viruses are further subdivided (subtyped) on the basis of the surface hemagglutinin (HA) and neuraminidase (NA) antigens, which project as spikes through the envelope. Individual strains are designated according to the site of origin, isolate number, year of isolation, and subtype — for example, influenza A/Hiroshima/52/2005 (H3N2).
- Influenza A viruses are further classified into subtypes on the basis of their HA and NA glycoproteins. Sixteen HA and nine NA subtypes are currently recognized in nature, but only three HAs (H1, H2, and H3) and two NAs (N1 and N2) have been associated with epidemics of disease in humans.
- The genomes of influenza A and B viruses consist of eight single-stranded RNA segments, which code for the structural and nonstructural proteins. Because the genome is segmented, the opportunity for gene reassortment during infection is high; reassortment often occurs during infection of cells with more than one influenza A virus.
- Influenza viruses are inactivated by temperatures above 50 °C, and by lipid solvents, acid, formaldehyde, ionizing radiation, and ultraviolet (UV) light.

Antigenic Variation and Influenza Outbreaks

- The most extensive and severe outbreaks are caused by influenza A viruses, in part because of the remarkable propensity of the H and N antigens of these viruses to undergo periodic antigenic variation. Occa-

sionally drastic alterations in structure appear, probably by recombination of two subtypes in a single cell. This is called **antigenic shift**, e.g. H1N1 → H2N1. It may be associated with pandemics and are restricted to influenza A viruses. Sequence variants in the genes for hemagglutinin and neuraminidase appear regularly. This is called **antigenic drift** (minor variations).

Epidemiology

- Influenza is a disease of the colder months of the year in temperate climates; spread appears to occur by small-particle aerosol.
- Source of infection is only a sick person on 1–7 day of illness. Infection occurs by air-droplet mechanism during conversation, cough, sneezing. Hand-to-hand contact, other personal contact, and even fomite transmission may take place.
- Typically, 1 or 2 predominant strains spread to create the annual epidemic. At present, influenza type A strains with the H1N1 and H3N2 serotypes and type B strains are co-circulating, and either type may be predominant in any 1 year, making predictions about the serotype and severity of the upcoming influenza season difficult.
- Postinfectious immunity of flu A remains from 1–3 years, of B, 3–6 years.

Pathogenesis

- In humans, the influenza viruses replicative cycle is confined to the respiratory epithelium. Viral replication in the upper respiratory tract generally peaks within 1 or 2 days of symptom onset and, depending on age and prior immunity, continues for about 3–8 days.
- The virus infects the respiratory mucosa causing lysis and desquamation of respiratory epithelium, mononuclear cell infiltrates, and altered muco-ciliary clearance. Tracheobronchitis is a typical feature, often associated with prolonged abnormalities in small airways pulmonary function and airway hyperreactivity. These changes permit secondary bacterial invasion directly through the epithelium.
- Primary influenza viral pneumonia results in diffuse alveolar damage, alveolar hemorrhage and exudate, hyaline membranes, and reactive fibrosis. Fatal cases of 2009 pandemic influenza A (H1N1) showed pathological changes of multiorgan dysfunction syndrome, such as brain congestion and swelling, myocardial inflammation, fibrinoid changes in arterioles, thrombosis in branches of pulmonary and splenic arteries, leading to splenic infarcts.
- The exact immune mechanisms involved in termination of primary infection and protection against reinfection may correspond to the induction of cytokines that inhibit viral replication, such as interferon and tumor necrosis factor.

- Serum and secretory antibodies directed to HA and NA appear 10 days post infection and correlate with durable protection against reinfection by homologous strain. Infection also induces cell-mediated immunity detectable 3–6 days later, which seems to be important for recovery. Because of strain variation, symptomatic reinfection with influenza can be seen at intervals of 3–4 yr. Vaccine-induced protection may last for up to 2–3 years against homotypic virus.

- The incubation period of influenza can be as short as 48–72 hr.

Clinical Manifestations

- Typical influenza: 2 syndromes: 1) general intoxication + 2) respiratory, or catarrhal, syndrome. Atypical influenza: afebrile, acatarrhal, fulminant.

- Abrupt onset of systemic symptoms, such as headache (typically frontal), feverishness, chills, myalgia, or malaise, and accompanying respiratory tract signs, particularly cough and sore throat. In many cases, the onset is so abrupt that patients can recall the precise time they became ill.

- The spectrum of clinical presentations is wide, ranging from a mild, afebrile respiratory illness similar to the common cold to severe prostration with relatively few respiratory signs and symptoms. In most of the cases the patient has a fever, with temperatures of 38–41 °C. A rapid temperature rise within the first 24 h of illness is generally followed by gradual defervescence over 2–3 days, although, on occasion, fever may last as long as 1 week. Patients report a feverish feeling and chilliness. Headache, either frontal or generalized, is often particularly troublesome. Myalgias and arthralgias may also develop.

- Respiratory symptoms often become more prominent as systemic symptoms subside. Many patients have a sore throat or persistent cough, which may last for ≥1 week and which is often accompanied by substernal discomfort. Tracheitis is typical. Ocular signs and symptoms include pain on motion of the eyes, photophobia, and burning of the eyes.

Complications

- One of severe and common complication of flu is **pneumonia**, which can be observed in any stage of disease and can have both primary viral, and secondary bacterial origin. Primary influenza viral pneumonia develops early in disease (first 1–4 days of illness), has few physical signs, and chest X-ray findings consistent with diffuse interstitial infiltrates and/or acute respiratory distress syndrome with marked hypoxia. Secondary bacterial pneumonia (the most common pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae*) follows acute influenza.

- **Other Pulmonary Complications** associated with influenza include worsening of chronic obstructive pulmonary disease and exacerbation of

chronic bronchitis and asthma. In children, influenza infection may present as croup.

- The affection of ENT organs. Purulent, hemorrhagic otitis, eustachitis, neuritis of acoustical nerve, sinusitis, ethmoiditis are observed.

- Reye's syndrome, a serious complication in children that is associated with influenza B and to a lesser extent with influenza A virus infection as well as with varicella-zoster virus infection. An epidemiologic association between Reye's syndrome and aspirin therapy has been proven.

- **Central nervous system (CNS) diseases**, including encephalitis, transverse myelitis, and Guillain-Barré syndrome, have been reported during influenza. Meningismus syndrome can occur.

- Influenza outbreaks include a number of cases in which elderly and other high-risk individuals develop influenza and subsequently experience a gradual deterioration of underlying cardiovascular, pulmonary, or renal function.

- **Complications of Avian Influenza**. Cases of influenza caused by avian A/H5N1 virus are reportedly associated with high rates of pneumonia (>50 %) and extrapulmonary manifestations such as diarrhea and CNS involvement. Deaths have been associated with multisystem dysfunction, including cardiac and renal failure. Mortality rate is 60–100 % in different outbreaks.

Diagnosis

- Leukocyte counts are variable, frequently being low early in illness and normal or slightly elevated later.

- Virus may be detected in throat swabs, nasopharyngeal washes, or sputum. The virus can be isolated by use of tissue culture — or chick embryos — within 48–72 h after inoculation.

- Rapid viral tests detect viral nucleoprotein or neuraminidase by means of immunologic or enzymatic techniques that are highly sensitive and 60–90 % as specific as tissue culture.

- Viral nucleic acids can also be detected in clinical samples by reverse transcriptase polymerase chain reaction (RT-PCR).

- The type of the infecting influenza virus (A or B) may be determined by either immunofluorescence or HI (Haemagglutination Inhibition) techniques.

- Serologic methods for diagnosis require comparison of antibody titers in sera obtained during the acute illness with those in sera obtained 10–14 days after the onset of illness and are useful primarily in retrospect. Fourfold or greater titer rises as detected by HI or CF (Complement fixation) or significant rises as measured by ELISA are diagnostic of acute infection.

Differential Diagnosis

- During a community-wide outbreak, a clinical diagnosis of influenza can be made with a high degree of certainty in patients who present to a physician's office with the typical febrile respiratory illness described above.
- In the absence of an outbreak (i.e., in sporadic or isolated cases), influenza may be difficult to differentiate on clinical grounds alone from an acute respiratory illness caused by any of a variety of respiratory viruses (parainfluenza, adenovirus, RS virus etc.) or by *Mycoplasma pneumoniae*.
- Other infections with high intoxication and/or respiratory syndrome: measles, leptospirosis, ornithosis (psittacosis), legionellosis, typhoid fever, malaria, dengue fever etc.

Treatment

- In uncomplicated cases of influenza, symptom-based therapy with acetaminophen (paracetamol) for the relief of headache, myalgia, and fever may be considered, but the use of salicylates should be avoided in children <18 years of age because of the possible association of salicylates with Reye's syndrome.
- Patients should be advised to rest and maintain hydration during acute illness and to return to full activity only gradually after illness has resolved, especially if it has been severe.
- Pathogenetically, the use of vitamins C and PP, calcium supplements and antihistamine medications also reasonable.

Specific antiviral therapy for influenza

- The neuraminidase inhibitors zanamivir and oseltamivir for both influenza A and influenza B and the adamantane agents amantadine and rimantadine for influenza A.
- In 2005–2006, resistance to amantadine was reported in >90 % of A/H3N2 viral isolates; thus amantadine and rimantadine are no longer recommended, but their use may be reconsidered if sensitivity becomes reestablished.
- Oseltamivir (administered orally at a dose of 75 mg twice a day for 5 days) or zanamivir (which must be given by an oral inhalation device; 10 mg twice a day for 5 days) reduces the duration of signs and symptoms of influenza by 1–1.5 days if treatment is started within 2 days of the onset of illness (Table 4).

Table 4 — Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Prophylaxis

Antiviral agent	Route	Treatment	Prophylaxis	Age group		
				1–6 yr	7–9 yr	>10 yr
Zanamivir	Inhaled	Yes	Not indicated	Not indicated	10 mg bid	10 mg bid
Oseltamivir	Oral	Yes	Yes		Dose varies, 30–75 mg bid	
Amantadine	Oral	Yes	Yes	5 mg/kg/day (maximum dose, 150 mg)		100 mg bid
Rimantadine	Oral	Yes	No	5 mg/kg/day (maximum dose, 150 mg)		100 mg bid

Prevention: vaccination

- Inactivated and live attenuated vaccines against influenza are available, and their use represents the major public health measure for prevention of influenza.

- The vast majority of currently used vaccines are inactivated («killed») preparations derived from influenza A and B viruses that circulated during the previous influenza season. If the vaccine virus and the currently circulating viruses are closely related, 50–80 % protection against influenza would be expected from inactivated vaccines.

- The available inactivated vaccines have been highly purified and are associated with few reactions. Up to 5 % of individuals experience low-grade fever and mild systemic symptoms 8–24 h after vaccination, and up to one-third develop mild redness or tenderness at the vaccination site. Since the vaccine is produced in eggs, individuals with true hypersensitivity to egg products either should be desensitized or should not be vaccinated.

- Vaccine should be administered early in the autumn before influenza outbreaks occur and should then be given annually to maintain immunity against the most current influenza virus strains. A live attenuated influenza vaccine that is administered by intranasal spray is also available.

Persons for whom annual influenza vaccination is recommended

- Children 6–59 months old.
- Women who will be pregnant during the influenza season.
- Persons ≥ 50 years old.
- Children and adolescents (6 months to 18 years old) who are receiving long-term aspirin therapy and therefore may be at risk for developing Reye's syndrome after influenza.
- Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma.
- Adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunodeficiency (including immunodeficiency caused by medications or by HIV).
- Adults and children who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or can increase the risk of aspiration.

- Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions.
- Persons who live with or care for persons at high risk for influenza-related complications, including healthy household contacts of and caregivers for children from birth through 59 months of age.
- Health care workers.

Chemoprophylaxis with antiviral drugs

- Chemoprophylaxis with oseltamivir (75 mg/d by mouth) or zanamivir (10 mg/d inhaled) has been 84–89 % efficacious against influenza A and B.
- Chemoprophylaxis with amantadine or rimantadine is no longer recommended because of reports of widespread resistance to these drugs. In earlier studies with sensitive viruses, prophylaxis with amantadine or rimantadine (100–200 mg/d) was 70–100 % effective against illness associated with influenza A.
- Chemoprophylaxis is most likely to be used for high-risk individuals who have not received influenza vaccine or in a situation where the vaccines previously administered are relatively ineffective because of antigenic changes in the circulating virus. During an outbreak, antiviral chemoprophylaxis can be administered simultaneously with inactivated vaccine, since the drugs do not interfere with an immune response to the vaccine. In fact, there is evidence that the protective effects of chemoprophylaxis and inactivated vaccine may be additive.

LECTURE 9. ACUTE RESPIRATORY INFECTIONS OF NON-INFLUENZA ETIOLOGY IN CHILDREN

General considerations

- Acute viral respiratory illnesses are among the most common of human diseases, accounting for one-half or more of all acute illnesses.
 - Morbidity from acute respiratory illnesses accounts for 30–50 % of time lost from work by adults and for 60–80 % of time lost from school by children.
 - It has been estimated that two-thirds to three-fourths of cases of acute respiratory illnesses are caused by viruses.
 - More than 200 antigenically distinct viruses from 10 genera have been reported to cause acute respiratory illness.
 - The illnesses caused by respiratory viruses traditionally have been divided into multiple distinct syndromes, such as the «common cold», pharyngitis, croup (laryngotracheobronchitis), tracheitis, bronchiolitis, bronchitis, and pneumonia.
 - Some types of respiratory illness are more likely to be associated with certain viruses (e.g., the common cold with rhinoviruses), whereas others occupy characteristic epidemiologic niches (e.g., adenovirus infections in military recruits) — see Table 5.

Table 5 — The syndromes most commonly associated with infections with the major respiratory virus groups

Virus	Frequency of respiratory syndromes		
	Most frequent	Occasional	Infrequent
Rhinoviruses	Common cold	Exacerbation of chronic bronchitis and asthma	Pneumonia in children
Human respiratory syncytial virus	Pneumonia and bronchiolitis	Common cold in adults	Pneumonia in elderly and in young children immunosuppressed patients
Parainfluenza viruses	Croup and lower respiratory tract disease in young children	Pharyngitis and common cold	Tracheobronchitis in adults; lower respiratory tract disease in immunosuppressed patients
Adenoviruses	Common cold and pharyngitis in children	Outbreaks of acute respiratory disease in military recruits	Pneumonia in children; lower respiratory tract and disseminated disease in immunosuppressed patients

Epidemiology

- Respiratory viruses are spread from the respiratory tract by aerosolized secretions or direct hand contact with secretions. The viruses can survive in hands and fomites (inanimate objects, such as toys, utensils, table tops, etc.) for a considerable period of time (several hours, even

days when contained in biological material, such as sputum and saliva). These contaminated objects can be an important source of indirect transmission.

- Source of infection — sick persons. The infectious period following the onset of illness varies with age. Young children with primary infection shed a higher titer of viruses, and for a longer period of around 10 days.

- Large or small (< 5 μ m median diameter) droplets: — Large droplets in close person-to-person contact, incl. mucous membrane contact; — Small droplets in coughs, sneezes, talking.

PARAINFLUENZA

- Viruses in the parainfluenza family are common causes of respiratory illness in infants and young children. They cause a spectrum of upper and lower respiratory tract illnesses, but are particularly associated with laryngotracheitis, bronchitis, and croup.

- ETIOLOGY. The parainfluenza viruses are members of the Paramyxoviridae family. There are 4 viruses in the parainfluenza group that cause illness in humans; they are designated types 1–4. The viruses have a nonsegmented, single-stranded RNA genome with a lipid-containing envelope. The major antigenic structures are envelope spike proteins that exhibit hemagglutinating (HN protein) and cell fusion (F protein) properties.

- PATHOGENESIS. Parainfluenza viruses replicate in the respiratory epithelium without evidence of systemic spread. The propensity to cause illness is presumably related to enhanced replication in the larynx, trachea, and bronchi compared with other viruses. Illness caused by parainfluenza occurs within 4–5 days after inoculation with the virus. The most severe illness coincides with the time of maximal viral shedding. The level of immunoglobulin A antibody is the best predictor of susceptibility to infection. Reinfection is seen, particularly with parainfluenza type 3, as mucosal immunity wanes.

- CLINICAL MANIFESTATIONS. Most parainfluenza virus infections are confined to the upper respiratory tract. Compared with influenza, catarhal syndrome is predominant over general intoxication. The parainfluenza viruses account for 50 % of hospitalizations for croup and 15 % of cases of bronchiolitis and pneumonia. Parainfluenza virus infections are not usually associated with high fever. Aside from low-grade fever, systemic complaints are rare. The illness usually lasts 4–5 days; however, virus may be recovered in low titers for 2–3 wk.

- COMPLICATIONS. Croup syndrome; bacterial tracheitis; otitis media, parotitis.

ADENOVIRUSES

- Adenoviruses cause 5–11 % of acute respiratory disease in infants plus a wide array of other syndromes, including pharyngoconjunctival fever, follicular conjunctivitis, epidemic keratoconjunctivitis, myocarditis, hemorrhagic cystitis, acute diarrhea, intussusception, and encephalomyelitis. Only $\frac{1}{3}$ of the 51 human serotypes have been associated with disease. Fatal disease is rare and is associated with infection by certain serotypes (particularly type 7) and infection in immunocompromised hosts.

- **ETIOLOGY.** The Adenoviridae are DNA viruses of intermediate size, which are classified into subgenera A to F. The virion has an icosahedral capsid made up of 252 subunits, or capsomers. Adenoviruses can also be classified by their characteristic DNA fingerprints on gels, which generally conforms to the antigenic types. The common adenovirus types, including types 1, 2, and 5, are shed for prolonged periods, particularly from the gastrointestinal tract. These types also establish low-level and chronic infection of the tonsils and adenoids.

- **PATHOGENESIS.** Adenoviruses are among the few “respiratory” viruses that grow well in the epithelium of the small intestine. Although mucosal surfaces are the primary target early in infection and typically the site of the most common pathology, viremia can be demonstrated by polymerase chain reaction (PCR) of serum or plasma and occurs relatively frequently, even in immunologically normal children.

- **CLINICAL MANIFESTATIONS.** Acute respiratory disease in infants and children are not clinically distinctive. Primary infections in infants are frequently associated with fever and respiratory symptoms and are complicated by otitis media in more than half of cases. Adenovirus respiratory infections are associated with a significant incidence of diarrhea. Pharyngitis caused by adenovirus typically includes symptoms of coryza, sore throat, and fever. Adenoviruses can be identified in 15–20 % of children with isolated pharyngitis, mostly in preschoolers and infants. About 7–9 % of hospitalized children with acute pneumonia have adenovirus infection. These infections have a mortality rate as high as 10 %, and survivors may have residual airway damage, manifested by bronchiectasis, bronchiolitis obliterans, or, rarely, pulmonary fibrosis. Neonatal adenovirus pneumonia occurs rarely, but may be severe or fatal.

- A pertussis-like syndrome has been described in association with adenovirus infections. In these cases, adenoviruses frequently accompany Bordetella pertussis as co-infecting agents, but occasionally they may also be causative on their own.

- Pharyngoconjunctival fever is a clinically distinct syndrome with a high temperature that lasts 4–5 days, pharyngitis, conjunctivitis, preauricular and cervical lymphadenopathy, and rhinitis. Nonpurulent conjunctivitis occurs in

75 % of patients and is manifested by inflammation of both the bulbar and palpebral conjunctivae of one or both eyes, which often persists after the fever and other symptoms have resolved. Headache, malaise, and weakness are common, and there is considerable lethargy after the acute stage.

- Conjunctivitis and Keratoconjunctivitis. Follicular conjunctivitis is a relatively mild illness and is highly contagious. Keratitis begins as the conjunctivitis wanes, and may cause corneal opacities that last several years.

- Myocarditis.

- Gastrointestinal Infections. Adenoviruses can be found in the stools of 5–9 % of children with acute diarrhea. Mesadenitis (inflammation of mesenteric lymph nodes) needs to be differentiated with acute appendicitis and enteric intussusception.

- Hemorrhagic Cystitis. This syndrome has a sudden onset of bacteriologically sterile hematuria, dysuria, lasting 1–2 wk.

- Reye Syndrome and Reye-like syndromes.

RESPIRATORY SYNCYTIAL VIRUS (RSV)

- Respiratory syncytial virus (RSV) is the major cause of bronchiolitis and pneumonia in children <1 yr of age and is the most important respiratory tract pathogen of early childhood.

- **ETIOLOGY**. RSV is a medium-sized, RNA virus that develops in the cytoplasm of infected cells and matures by budding from the cell membrane. It belongs to the family Paramyxoviridae, along with parainfluenza and measles viruses, and is in the subfamily Pneumovirinae, which also contains the human metapneumovirus. It is the only member of the genus Pneumovirus that infects humans. There are 2 antigenic subtypes of RSV. Virus grows in many cell cultures and produces characteristic syncytial cytopathology, from which it derives its name.

- **PATHOGENESIS**. Bronchiolitis is characterized by virus-induced necrosis of the bronchiolar epithelium, hypersecretion of mucus, and round cell infiltration and edema of the surrounding submucosa. These changes result in formation of mucous plugs obstructing bronchioles, with consequent hyperinflation or collapse of the distal lung tissue. In interstitial pneumonia the infiltration is more generalized and epithelial necrosis may extend to both the bronchi and the alveoli. Infants have particular tendency to experience small airway obstruction because of the small size of the normal bronchioles. Several facts suggest immunologic injury as a major factor in the pathogenesis of bronchiolitis caused by RSV. Severe disease requiring hospitalization, including intensive care, occurs primarily in children with underlying risk factors such as prematurity, chronic pulmonary disease (most often bronchopulmonary dysplasia), congenital heart disease, or immune deficiency.

- **CLINICAL MANIFESTATIONS.** The 1st signs of infection of the infant with RSV are rhinorrhea and pharyngitis. Cough may appear simultaneously but more often after an interval of 1–3 days, at which time there may also be sneezing and a low-grade fever. Soon after the cough develops, the child begins to wheeze audibly. If the disease is mild, the symptoms may not progress beyond this stage. Auscultation often reveals diffuse rhonchi, fine rales or crackles, and wheezes. Clear rhinorrhea usually persists throughout the illness, with intermittent fever. Chest X-rays at this stage are frequently normal.

- If the illness progresses, cough and wheezing increase and air hunger ensues, with increased respiratory rate, intercostal and subcostal retractions, hyperexpansion of the chest, restlessness, and peripheral cyanosis. Signs of severe, life-threatening illness are central cyanosis, tachypnea of >70 breaths/min, apathy, and apneic spells. At this stage, the chest may be greatly hyperexpanded and almost silent to auscultation because of poor air movement.

- Fever is an inconstant sign in RSV infection. Rash and conjunctivitis each occur in a few cases. In young infants, periodic breathing and apneic spells have been distressingly frequent signs, even with relatively mild bronchiolitis. It is likely that a small portion of deaths included in the category of sudden infant death syndrome are due to RSV infection.

- Chest X-rays of infants hospitalized with RSV bronchiolitis are normal in 10–30 % of cases, and show hyperexpansion of the chest in 20–40 %, peribronchial thickening or central pneumonia in 35–50 %, and segmental or lobar consolidation in 8–20 %.

RESPIRATORY VIRUSES: DIAGNOSIS PRINCIPLES

- The clinical diagnosis of respiratory viral infections is very rarely possible.

- Isolation of the virus in cell culture (poor sensitivity, retrospective diagnosis).

- Immune fluorescent tests: to detect viral antigens in nasopharyngeal aspirates (early diagnosis).

- Detection of viral RNA or DNA using PCR: early diagnosis. Nasopharyngeal aspirates, plasma or serum, and stool are the preferred samples, although other body fluids and tissues may also contain the virus.

- Serologic testing: detection of IgM antibody, or seroconversion from negative to positive, or a 4-fold or greater rise in IgG titer is indicative of recent infection. The disadvantage of serology is that antibody is not detectable until 6–10 days after the onset of symptoms, and IgG seroconversion may be delayed for up to 4 wk — retrospective diagnosis.

RESPIRATORY VIRUSES: TREATMENT PRINCIPLES

- Patients should be advised to rest and maintain hydration during acute illness and to return to full activity only gradually after illness has resolved.
- As antipyretics in pediatric practice, if fever >38.5 °C paracetamol and ibuprofen are usually recommended. The use of salicylates should be avoided in children <18 years of age because of the possible association with Reye's syndrome.
- All other therapy is pathogenetic and symptomatic.
- Ribavirin has some antiviral activity against parainfluenza virus and RSV, it should be considered in the immunocompromised child with persistent viral pneumonia. Cidofovir is a nucleoside analog with demonstrable antiviral activity against adenovirus and can be used sometimes in immunocompromised patients. Palivizumab is directed against a protective epitope of the RSV fusion (F) protein. Currently, palivizumab is recommended for selected children who are younger than 2 years and are considered to have a high risk for developing severe RSV disease.
- The indications for antibiotics are limited to well-documented secondary bacterial infections of the middle ears or lower respiratory tract.

RESPIRATORY VIRUSES: PREVENTION

- Vaccine is available only for influenza virus.
- In some risk groups intravenous immune globulin can be given.
- Other (non-specific) measures include wearing masks plus eye protection, good hand hygiene, use of hand-rub antiseptic products, and care of contaminated tissues, toys, and other objects likely to be contaminated with secretions.

MYCOPLASMA PNEUMONIAE INFECTION

- *Mycoplasma pneumoniae* is a major cause of respiratory infections in school-aged children and young adults.
- ETIOLOGY. *Mycoplasmas* are small self-replicating intracellular organisms. *M. pneumoniae* is fastidious, and growth in commercially available culture systems is too slow to be of practical clinical use.
- CLINICAL MANIFESTATIONS. *M. pneumoniae* is perhaps best known as the cause of community-acquired walking or atypical pneumonia, but the most frequent clinical syndrome caused by this organism is actually tracheobronchitis or bronchiolitis, often accompanied by upper respiratory tract manifestations. Pneumonia develops in only 5–10 % of persons who are infected. Acute pharyngitis may also occur. Less than 10 % of cases of *M. pneumoniae* infections are associated with nonrespiratory illnesses. Complications, including bacterial superinfection, are unusual. Extrapulmonary manifestations may include meningoencephalitis, ascending paralysis, myopericarditis, hemolytic anemia etc.

- **DIAGNOSIS.** Positive immunoglobulin M (IgM) *M. pneumoniae* antibody identified by indirect fluorescence or enzyme-linked immune assay (EIA) more specifically supports the diagnosis. A 4-fold increase in IgG *M. pneumoniae* antibody titer, by complement fixation or EIA, between acute and convalescent sera is diagnostic. PCR of a nasopharyngeal or throat swab (doing both may increase sensitivity) for *M. pneumoniae* DNA is very specific (>97 %).

- **TREATMENT.** The recommended treatment is macrolide antibiotics clarithromycin (15 mg/kg/day divided bid PO for 10 days) or azithromycin (10 mg/kg once PO on day 1 and 5 mg/kg once daily PO on days 2–5). *M. pneumoniae* is also sensitive to erythromycin, and tetracyclines.

CHLAMYDIA PNEUMONIAE INFECTION

- *Chlamydomphila* (*Chlamydia*) *pneumoniae* is a common cause of lower respiratory tract diseases, including pneumonia in children and bronchitis and pneumonia in adults.

- **ETIOLOGY.** *Chlamydiae* are obligate intracellular pathogens, having gram-negative envelope. *Chlamydiae* are characterized by a unique developmental cycle with morphologically distinct infectious and reproductive forms: the elementary body and reticulate body.

- **CLINICAL MANIFESTATIONS.** Infections caused by *C. pneumoniae* cannot be readily differentiated from those caused by other respiratory pathogens, especially *M. pneumoniae*. The pneumonia usually presents as a classic atypical (or nonbacterial) pneumonia characterized by mild to moderate constitutional symptoms including fever, malaise, headache, cough, and frequently pharyngitis. *C. pneumoniae* may serve as an infectious trigger for asthma and can cause pulmonary exacerbations in patients with cystic fibrosis. Asymptomatic respiratory infection has been documented in 2–5 % of adults and children and may persist for a year or more.

- **DIAGNOSIS.** Specific diagnosis of *C. pneumoniae* infection is based on isolation of the organism in tissue culture. The organism can be isolated from sputum, throat cultures, bronchoalveolar lavage fluid, and pleural fluid, but few laboratories perform such cultures because of technical difficulties. Polymerase chain reaction (PCR) testing is the most promising technology in the development of a rapid, nonculture method for detection of *C. pneumoniae*. Serologic diagnosis can be accomplished using the microimmunofluorescence (MIF) or the complement fixation (CF) tests. Acute infection, using the MIF test, was defined by a 4-fold increase in immunoglobulin G (IgG) titer or an IgM titer of 16 or greater.

- **TREATMENT.** The optimum dose and duration of antimicrobial therapy for *C. pneumoniae* infections remain uncertain. The use of erythromycin (40 mg/kg/day divided bid PO for 10 days), clarithromycin (15 mg/kg/day divided bid PO for 10 days), and azithromycin (10 mg/kg PO on day 1, then 5 mg/kg/day PO on days 2–5) are effective in approximately 80 % of cases. Coughing often persists for several weeks even after therapy.

LECTURE 10. SCARLET FEVER

Definition

- Scarlet fever (scarlatina) is an infectious disease caused by an infection with group A Streptococcus, characterized by fever, sore throat (tonsillopharyngitis), and a characteristic rash.
- Scarlet fever is predominantly a childhood disease occurring in children 2–10 years of age, though it can less commonly occur in older children and adults.
- The incidence and mortality rates have significantly decreased due to the introduction and widespread use of antibiotics.

History

- Scarlet fever has been responsible for devastating epidemics, particularly in the 19th century. In 1923, the husband and wife team of George and Gladys Dick identified the streptococcal bacterium responsible for causing scarlet fever, and shortly thereafter they isolated the toxin responsible for causing the characteristic rash of scarlet fever.

Etiology

- Group A streptococcus (GAS), also known as Streptococcus pyogenes, is a common cause of infections of the upper respiratory tract (pharyngitis) and the skin (impetigo, pyoderma) in children and is a less common cause of perianal cellulitis, vaginitis, septicemia, pneumonia, endocarditis, pericarditis, osteomyelitis, suppurative arthritis, myositis, cellulitis, and omphalitis. These microorganisms also cause distinct clinical entities (scarlet fever and erysipelas), as well as a toxic shock syndrome and necrotizing fasciitis.
- GAS is also the cause of 2 potentially serious nonsuppurative complications: rheumatic fever and acute glomerulonephritis.
- Group A streptococci are gram-positive coccoid-shaped bacteria that tend to grow in chains. They are broadly classified by their reactions on mammalian red blood cells. The zone of complete hemolysis that surrounds colonies grown on blood agar distinguishes β -hemolytic (complete hemolysis) from α -hemolytic (green or partial hemolysis) and γ (nonhemolytic) species. More than 20 serologic groups are identified, designated by the letters A through V. GAS can be subdivided into >100 serotypes on the basis of the M protein antigen.
- Exotoxin-producing group A beta-hemolytic streptococci (GABHS). The release of a particular toxin is responsible for the characteristic scarlet-colored rash seen with scarlet fever (giving the disease its name). In the majority of cases, scarlet fever occurs as a result of a pharyngeal streptococcal

infection («strep throat»). It is estimated that scarlet fever develops in up to 10 % of individuals who develop streptococcal pharyngitis.

Epidemiology

- The streptococcal bacterium is typically spread via airborne respiratory droplets transmitted by infected individuals or by asymptomatic pharyngeal carriers.

- Streptococcal infections can also be transmitted by coming in direct contact with infected secretions and rarely by food-borne outbreaks. Transmission is enhanced in crowded environments in which individuals come in close contact with each other (for example, schools or day-care centers).

- Scarlet fever can occur at any time of the year, though it is more common during the winter and spring.

Pathogenesis

- Virulence of GAS depends primarily on the M protein, and strains rich in M protein resist phagocytosis in fresh human blood, whereas M-negative strains do not. GAS isolated from chronic pharyngeal carriers contain little or no M protein and are relatively avirulent. The M protein antigen stimulates the production of protective type specific antibodies. They protect against infection with a homologous M type but confer no immunity against other M types. Therefore, multiple GAS infections attributable to different M types are common during childhood and adolescence. By adult life, individuals are probably immune to many of the common M types in the environment, but because of the large number of serotypes it is doubtful that total immunity is ever achieved.

- GAS produces a large variety of enzymes and toxins, including erythrogenic toxins (known as streptococcal pyrogenic exotoxins, or Dick toxin). Streptococcal pyrogenic exotoxins A, B, and C are responsible for the rash of scarlet fever. These exotoxins stimulate the formation of specific anti-toxin antibodies that provide immunity against the scarlatiniform rash but not against other streptococcal infections. Because GAS can produce three different rash-producing pyrogenic exotoxins (A, B, or C), a second attack of scarlet fever may sometimes occur.

Clinical Manifestations

- Incubation period: one to four days.
- Scarlet fever typically occurs in association with a pharyngeal streptococcal infection, therefore many of the symptoms and signs initially will be similar to that of «strep throat» (streptococcal tonsillitis) and may include the following:

1) Signs of general intoxication (fever, headache, chills, malaise, nausea, vomiting, abdominal pain);

2) Sore throat. The throat may appear reddened and swollen, and there may be white patches on the tonsils or on the back of the throat (tonsillar exudate);

3) Swollen and tender lymph nodes on the sides of the neck (cervical lymphadenopathy).

• **Skin rash.** Approximately one to four days after the onset of illness, a characteristic skin rash will appear with the following properties. The rash typically begins on the chest, neck, and armpit area and then spreads to other areas of the body. The rash is often more pronounced and reddened in areas of skin creases, such as the axilla, the neck, the inguinal area, and in the creases of the elbow (antecubital fossa) and the knee (popliteal fossa). Ruptured capillaries in these areas may cause the resultant rash to appear as lines (termed Pastia lines). The rash is described as fine and rough-textured (like sandpaper), consisting of multiple red punctate lesions. The rash blanches when pressed upon. The face may appear flushed, and the area around the mouth may appear pale (circumoral pallor, or Filatov's sign). The rash may last anywhere between two to seven days. After the rash has faded, the skin begins to peel (desquamation), and this may last up to several weeks. The extent and duration of skin peeling is directly related to the initial severity of the rash. Areas commonly affected include the fingers, toes, palms, axilla, and the groin.

• During the first one to two days of illness, the tongue may have a white-colored coating with protruding, swollen, and red papillae on the surface («white strawberry tongue»). After about four to five days, the white coating sloughs off revealing a red-colored tongue with prominent papillae («red strawberry tongue»).

Prognosis. Complications

• The prognosis for individuals diagnosed with scarlet fever is excellent when properly treated. There are typically no long-term sequelae in uncomplicated cases of scarlet fever. Individuals will generally begin to improve after a few days. Historically, scarlet fever resulted in mortality rates of 15–20 %, however, with the advent of antibiotics, mortality rates are now less than 1 %.

• Rarely, several serious complications can occur as a result of scarlet fever as streptococcal infection. Potential septic complication may include the following: otitis media, peritonsillar abscess, cervical lymphadenitis, sinusitis, pneumonia, meningitis, septicemia, hepatitis. Allergic complications: acute rheumatic fever, poststreptococcal glomerulonephritis, myocarditis.

Diagnosis

- The diagnosis of scarlet fever can be made based on medical history, physical exam, and laboratory testing. Neutrophilic leukocytosis and increased ESR in routine blood analysis is also helpful.

- **Culture** of a throat swab on a sheep blood agar plate remains the standard for the documentation of the presence of GAS in the upper respiratory tract and for the confirmation of the clinical diagnosis of acute streptococcal pharyngitis. If performed correctly, a single throat swab cultured on a blood-agar plate has a sensitivity of 90–95 % for detecting the presence of GAS in the pharynx. A disadvantage of culturing a throat swab on a blood-agar plate is the delay (overnight or longer) in obtaining the culture result.

- **Rapid antigen detection** tests have been developed for the identification of GAS directly from throat swabs. The results are ready in 5–10 minutes. The great majority of the rapid antigen detection tests have an excellent specificity of >95 % when compared with blood-agar plate cultures.

- **Serological Diagnosis.** GAS infection can also be diagnosed retrospectively on the basis of an elevated or increasing streptococcal antibody titer. The antistreptolysin O assay is the streptococcal antibody test most commonly used. Because streptolysin O also is produced by group C and G streptococcus, the test is not specific for group A infection. In contrast, the anti-DNase B responses are present after both skin and throat infections. A significant antibody increase is usually defined as an increase in titer of 2 or more dilution increments between the acute phase and convalescent phase specimens, regardless of the actual height of the antibody titer. Interpretation of a single antibody titer for clinical purposes may be difficult and must take several factors into consideration. Antibody titers reported by different clinical laboratories may vary. In addition, the upper limits of normal are higher for children than for adults, and these values, even for the same age groups, are higher in some populations than in others. Frequently, values given by laboratories for upper limits of normal have been determined on adult sera; these values are often much too low to be used in a pediatric population.

- Typical scarlet fever is not difficult to diagnose; however, the milder forms with equivocal pharyngeal findings can be confused with viral exanthems, Kawasaki disease, and drug eruptions. Staphylococcal and Yersinia infections are occasionally associated with a scarlatiniform rash.

Treatment

Antibiotics

- **Penicillin** is the drug of choice for pharyngeal infections as well as for suppurative complications. Treatment with oral **penicillin V** (250 mg/dose

bid–tid for ≤60 lb and 500 mg/dose bid–tid for >60 lb PO) for 10 days is recommended but it must be taken for a full 10 days even though there is symptomatic improvement in 3–4 days. Penicillin V (phenoxymethylpenicillin) is preferred over penicillin G because it may be given without regard to mealtime. The major problem with all forms of oral therapy is the risk that the drug will be discontinued before the 10-day course has been completed. Therefore, when oral treatment is prescribed, the necessity of completing a full course of therapy must be emphasized. If oral therapy is not possible, parenteral therapy with a single intramuscular injection of **benzathine penicillin G** (600,000 IU for ≤60 lb, 1.2 million IU for >60 lb, IM) is the most efficacious and often the most practical method of treatment.

- Antibiotics not only prevent the potential complications associated with streptococcal infection (for example, acute rheumatic fever), but they also shorten the duration of symptoms (by up to one day) and decrease contagiousness. In general, individuals with scarlet fever are not contagious after taking antibiotics for at least 24 hours.

- Alternative antibiotics include the first-generation **cephalosporin** drug class. For those individuals allergic to penicillin, **erythromycin** is recommended. Erythromycin (erythromycin estolate 20–40 mg/kg/day divided bid–qid PO, or erythromycin ethylsuccinate 40 mg/kg/day divided bid–qid PO) for 10 days.

Other Treatment

- The vast majority of cases of scarlet fever can be managed at home unless the rare serious complications of the disease develop.

- Individuals with scarlet fever can take over-the-counter medications such as acetaminophen (Paracetamol) or ibuprofen for pain control and fever reduction.

- Adequate rest and increased fluid intake are also important for promoting a more rapid recovery.

- If pharyngitis is present, various throat lozenges can provide temporary relief for a minor sore throat. Gargling with warm saltwater may also be helpful.

Prevention

- The best preventative measure against scarlet fever is early and appropriate treatment with antibiotics. This will significantly decrease or eliminate an individual's chances of developing scarlet fever. The introduction and widespread use of antibiotics has been the most important factor in diminishing the cases of scarlet fever.

- Minimizing the risk of transmitting group A streptococcal infection is also important. Try to avoid close contact with individuals who have

been diagnosed with strep throat, and avoid sending children to school or day care until they have been treated with antibiotics for at least 24 hours. Those individuals diagnosed with strep throat should try to avoid spreading the disease to others by maintaining good hygiene practices (wash hands frequently, use separate utensils and cups, and cover the mouth and nose when coughing or sneezing).

- A streptococcal vaccine was produced using a recombinant fusion protein containing N-terminal fragments from 6 GAS M types of clinical and epidemiologic importance. A phase I trial of this vaccine demonstrated that parenteral vaccine was well tolerated, did not induce cross-reactive antibodies to human tissue, and stimulated bactericidal activity when given as a 3-dose regimen to healthy adults. A similar vaccine containing N-terminal peptides of 26 M types was constructed and is currently undergoing clinical evaluation in adults.

LECTURE 11. ERTUSSIS

Definition

- Pertussis (whooping cough), an acute respiratory illness with a potentially protracted clinical course, is caused by infection with *Bordetella pertussis*. Pertussis-like illness can be caused by *Bordetella parapertussis*. The infection is highly contagious and can have both endemic and epidemic features in a population.

- Pertussis was well described initially in the 1500s. Synonym: «hundred days cough». Sydenham first used the term pertussis, meaning intense cough, in 1670; it is preferable to *whooping cough* because most infected individuals do not «whoop».

- Pertussis is not solely a pediatric illness, and the greatest increases in incidence in recent years have been in adolescents and adults.

- Seroepidemiologic data suggest that 25 % of adolescents and adults with a cough lasting more than 1 week have pertussis.

Etiology

- There are now eight species in the genus *Bordetella*: *B. pertussis*, *B. parapertussis* and *B. bronchiseptica* (primarily a veterinary pathogen) are all closely related.

- *Bordetella pertussis* and *B. parapertussis* cause whooping cough, *B. bronchiseptica* (a canine pathogen) may cause chronic respiratory illnesses in human.

- Fastidious Gram negative coccobacilli with a capsule.

- *B. pertussis* was first isolated by Bordet and Gengou in 1906, and the medium used for culture (Bordet-Gengou agar) still bears their names.

- *B. pertussis* does not survive for prolonged periods in the environment.

- *B. pertussis* antigenic and biologically active components: pertussis toxin (PT), filamentous hemagglutinin (FHA), agglutinogens, adenylate cyclase, pertactin, tracheal cytotoxin.

Epidemiology

- There are 60 million cases of pertussis each year worldwide, resulting in >500,000 deaths. Before vaccination was available, pertussis was the leading cause of death due to communicable disease among children <14 yr of age in developed countries. Widespread use of pertussis vaccine led to a >99 % decline in cases.

- Pertussis is extremely contagious, with attack rates as high as 100 % in susceptible individuals exposed to aerosol droplets at close range. *B. pertussis* is believed to be spread primarily by large droplets. Cough-

ing adolescents and adults (usually not recognized as having pertussis) currently are the major reservoir for *B. pertussis*. Chronic carriage by humans is not documented.

- Neither natural disease nor vaccination provides complete or life-long immunity against reinfection or disease. Protection against typical disease begins to wane 3–5 yr after vaccination and is unmeasurable after 12 yr. Despite history of disease or complete immunization, outbreaks of pertussis have occurred in the elderly, in nursing homes, in residential facilities with limited exposures, and in adolescents and adults with lapsing time since immunization.

Pathogenesis

- *Bordetella* organisms only colonize ciliated epithelium. Exact mechanism of disease symptomatology remains unknown.

- *B. pertussis* expresses **pertussis toxin (PT)**, the major virulence protein. PT has numerous proven biologic activities (e.g., histamine sensitivity, insulin secretion, leukocyte dysfunction), some of which may account for systemic manifestations of disease. PT causes lymphocytosis by rerouting lymphocytes to remain in the circulating blood pool. PT appears to have a central but not a singular role in pathogenesis.

- *B. pertussis* produces an array of other biologically active substances, many of which are postulated to have a role in disease and immunity. After aerosol acquisition, **filamentous hemagglutinin (FHA)**, some **agglutinogens** (especially fimbriae [Fim] types 2 and 3), and a 69 kd nonfimbrial surface protein called **pertactin (Pn)** are important for attachment to ciliated respiratory epithelial cells. **Tracheal cytotoxin**, adenylate cyclase, and PT appear to inhibit clearance of organisms. Tracheal cytotoxin, dermonecrotic factor, and adenylate cyclase are postulated to be predominantly responsible for the local epithelial damage that produces respiratory symptoms and facilitates absorption of PT.

Pathogenesis

- Attachment to cilia of ciliated epithelial cells in respiratory tract.
- Pertussis antigens allow evasion of host defenses (lymphocytosis promoted but impaired chemotaxis).
 - Local tissue damage and necrosis in respiratory tract.
 - Systemic disease may be toxin mediated.
 - No bacteremic phase.
 - Prolonged cough is maintained by neuro-reflectory mechanism (sustained irritation of coughing center, «dominant» mechanism by Ukhtomsky).

Clinical Features

- Incubation period 4–21 days.
- 3 Stages:
 - 1st Stage — Catarrhal Stage 1–2 weeks;
 - 2nd Stage — Paroxysmal Stage 1–6 weeks;
 - 3rd Stage — Convalescent Stage weeks-months.
- The **catarrhal stage** (1–2 wk) begins insidiously after an incubation period ranging from 3–12 days with nondistinctive symptoms of congestion and rhinorrhea variably accompanied by low-grade fever, sneezing, lacrimation, and conjunctival suffusion.
 - As initial symptoms wane, coughing marks the onset of the **paroxysmal stage**. The cough begins as a dry, intermittent, irritative hack and evolves into the inexorable paroxysms that are the hallmark of pertussis. A well-appearing, playful toddler with insignificant provocation suddenly expresses an anxious aura and may clutch a parent or comforting adult before beginning a machine-gun burst of uninterrupted coughs, chin and chest held forward, tongue protruding maximally, eyes bulging and watering, face purple, until coughing ceases and a loud whoop follows as inspired air traverses the still partially closed airway. Post-tussive emesis is common, and exhaustion is universal. The number and severity of paroxysms escalate over days to a week and remain at that plateau for days to weeks. At the peak of the paroxysmal stage, patients may have more than 1 episode hourly.
 - As the paroxysmal stage fades into the **convalescent stage** (≥ 2 wk), the number, severity, and duration of episodes diminish.

Clinical manifestation: age groups

- Infants < 3 mo of age do not display classical stages. The catarrhal phase lasts only a few days or is unnoticed. Cough may not be prominent. Whoop infrequently occurs in infants < 3 mo of age. Cyanosis can follow a coughing paroxysm, or apnea can occur without a cough. Apnea may be the only symptom. The paroxysmal and convalescent stages in young infants are lengthy.
 - Paradoxically, in infants, cough and whooping may become louder and more classic in convalescence. Convalescence includes intermittent paroxysmal coughing throughout the 1st year of life, including «exacerbations» with subsequent respiratory illnesses.
 - Immunized children have foreshortening of all stages of pertussis.
 - Adults have no distinct stages. Classically, adults describe a sudden feeling of strangulation followed by uninterrupted coughs, feeling of suffocation, headache, and then a gasping breath, usually without a whoop. Post-tussive emesis and intermittency of paroxysms separated

by hours of well-being are specific clues to the diagnosis in adolescents and adults. Findings on physical examination generally are uninformative. Signs of lower respiratory tract disease are not expected unless complicating secondary bacterial pneumonia is present. Conjunctival hemorrhages and petechiae on the upper body are common.

Complications

- Infants <6 mo of age have excessive mortality and morbidity, with infants <2 mo of age having the highest reported rates of pertussis-associated hospitalization (82 %), pneumonia (25 %), seizures (4 %), and encephalopathy (1 %). Mortality is about 1 %. Infants <4 mo of age account for 90 % of cases of fatal pertussis. Preterm birth and young maternal age are significantly associated with fatal pertussis.

- The principal complications of pertussis are apnea, secondary infections (such as otitis media and pneumonia), and physical sequelae of forceful coughing. Increased intrathoracic and intra-abdominal pressure during coughing can result in conjunctival and scleral hemorrhages, petechiae on the upper body, epistaxis, hemorrhage in the central nervous system (CNS) and retina, pneumothorax and subcutaneous emphysema, and umbilical and inguinal hernias. Laceration of the lingual frenulum is also common.

- *B. pertussis* is an occasional cause of sudden infant death.

Pertussis Case Definition (CDC, 2010)

▶ **Probable case:** In the absence of a more likely diagnosis, a cough illness lasting ≥ 2 weeks, with at least one of the following symptoms:

- ▶ paroxysms of coughing;
- ▶ inspiratory «whoop»; or
- ▶ post-tussive vomiting;

AND

- ▶ absence of laboratory confirmation; and
- ▶ no epidemiologic linkage to a laboratory-confirmed case of pertussis.

Confirmed case: Acute cough illness of any duration, with isolation of *B. pertussis* from a clinical specimen;

OR cough illness lasting ≥ 2 weeks, with at least one of the following symptoms:

- ▶ paroxysms of coughing;
- ▶ inspiratory «whoop»; or
- ▶ post-tussive vomiting

AND

- ▶ polymerase chain reaction (PCR) positive for pertussis;

OR illness lasting ≥ 2 weeks, with at least one of the following symptoms:

- ▶ paroxysms of coughing;
- ▶ inspiratory «whoop»; or
- ▶ post-tussive vomiting;

AND, contact with a laboratory-confirmed case of pertussis.

Diagnosis

- Pertussis should be suspected in any individual who has pure or predominant complaint of cough, especially if the following are absent: fever, malaise or myalgia, exanthem or enanthem, sore throat, hoarseness, tachypnea, wheezes, and rales.

- **Culture** is «gold standard» (when done well). Careful attention must be directed to specimen collection, transport, and isolation technique. Cultures are incubated at 35–37 °C in a humid environment and examined daily for 7 days for slow-growing, tiny, glistening colonies. Specimen — aspirate or nasopharyngeal swab, Bordet-Gengou or Regan Lowe media. Dacron or calcium alginate swabs are recommended to obtain culture specimens. Dacron swabs are appropriate if polymerase chain reaction testing will be performed.

- **Polymerase chain reaction (PCR)** — results can be positive after a week of antibiotic therapy. PCR to test nasopharyngeal wash specimens has a sensitivity similar to that of culture, averts difficulties of isolation, but is not standardized or available universally.

- **Direct fluorescent antibody test (DFA)** — used for identify *B. pertussis* after culture on solid media. Direct testing of nasopharyngeal secretions by DFA is a rapid test, but is reliable only in laboratories with continuous experience.

- Results of DFA, culture, and PCR are all expected to be positive in unimmunized, untreated children during the catarrhal and early paroxysmal stage of disease.

- **Serologic tests** for detection of antibodies to *B. pertussis* antigens in acute and convalescent samples are the most sensitive tests in immunized individuals and are useful epidemiologically. A single serum sample showing immunoglobulin G (IgG) antibody to pertussis toxin elevated >2 standard deviations above the mean of the immunized population indicates recent infection. IgA and IgM pertussis antibody tests are not reliable methods for diagnosis.

- **Leukocytosis** (15,000–100,000 cells/mm³) due to absolute **lymphocytosis** is characteristic in the catarrhal stage. Lymphocytes are of T- and B-cell origin and are normal small cells, rather than the large atypical lymphocytes seen with viral infections. Adults, partially immune

children, and occasionally young infants have less impressive lymphocytosis. A severe course and death are correlated with extreme leukocytosis (median peak white blood cell count fatal vs nonfatal cases, 94 vs 18×10^9 cells/L) and thrombocytosis (median peak platelet count fatal vs nonfatal cases, 782 vs 556×10^9 /L).

- The **chest X-ray** is only mildly abnormal in the majority of hospitalized infants, showing perihilar infiltrate or edema (sometimes with a butterfly appearance) and variable atelectasis. Pneumothorax, pneumomediastinum, and air in soft tissues can be seen occasionally.

Differential Diagnosis

- Adenoviral infections are usually distinguishable by associated features, such as fever, sore throat, and conjunctivitis.

- Mycoplasma causes protracted episodic coughing, but patients usually have a history of fever, headache, and systemic symptoms at the onset of disease as well as more continuous cough and frequent finding of rales on auscultation of the chest. Although pertussis is often included in the laboratory evaluation of young infants with afebrile pneumonia, B. pertussis is not associated with staccato cough (breath with every cough), purulent conjunctivitis, tachypnea, rales or wheezes that typify infection due to Chlamydia trachomatis, or predominant lower respiratory tract signs that typify infection due to respiratory syncytial virus.

Treatment

- Goals of therapy are to limit the number of paroxysms, to observe the severity of the cough, to provide assistance when necessary, and to maximize nutrition, rest, and recovery without sequelae.

- Infants <3 mo of age are admitted to hospital almost without exception, as are those between 3–6 mo unless witnessed paroxysms are not severe, and those of any age if significant complications occur.

- Prematurely born young infants and children with underlying cardiac, pulmonary, muscular, or neurologic disorders have a high risk for severe disease, and should be hospitalized.

Antibiotics

- An antimicrobial agent is always given when pertussis is suspected or confirmed primarily to limit the spread of infection and secondarily for possible clinical benefit. **Macrolides** are preferred agents, resistance has been reported rarely. Azithromycin is the preferred agent for use in neonates. All infants <1 mo of age treated with any macrolide should be monitored for symptoms of hypertrophic pyloric stenosis possible side ef-

fect of macrolides. **Trimethoprim-sulfamethoxazole** (TMP-SMZ) can be used as an alternative agent to macrolides in patients aged ≥ 2 mo who are allergic to macrolides, who cannot tolerate macrolides, or who are infected with a rare macrolide-resistant strain of *Bordetella pertussis*.

Recommended Antimicrobial Treatment and Postexposure Prophylaxis for Pertussis, by Age Group (from Recommended antimicrobial agents for treatment and postexposure prophylaxis of pertussis, CDC Guidelines, 2005):

- **<1 month:** Azithromycin 10 mg/kg/day in a single dose for 5 days, OR Erythromycin 40–50 mg/kg/day in 4 divided doses for 14 days if azithromycin is unavailable.

- **1–5 months:** Azithromycin 10 mg/kg/day in a single dose for 5 days, OR Erythromycin 40–50 mg/kg/day in 4 divided doses for 14 days OR Clarithromycin 15 mg/kg/day in 2 divided doses for 7 days.

- **Infants (aged ≥ 6 mo) and children:** Azithromycin 10 mg/kg in a single dose on day 1 then 5 mg/kg/day (maximum 500 mg) on days 2–5 OR Erythromycin 40–50 mg/kg/day (maximum 2 g/day) in 4 divided doses for 14 days OR Clarithromycin 15 mg/kg/day in 2 divided doses (maximum 1 g/day) for 7 days. Alternative agent: Trimethoprim-sulfamethoxazole (TMP-SMZ) TMP 8 mg/kg/day, SMZ 40 mg/kg/day in 2 divided doses for 14 days.

- **Adults:** Azithromycin 500 mg in a single dose on day 1 then 250 mg/day on days 2–5 OR Erythromycin 2 g/day in 4 divided doses for 14 days OR Clarithromycin 1 g/day in 2 divided doses for 7 days. Alternative agent: Trimethoprim-sulfamethoxazole (TMP-SMZ) TMP 320 mg/day, SMZ 1,600 mg/day in 2 divided doses for 14 days.

Adjunct Therapies

- Isolation.
- Patients with suspected pertussis are placed in respiratory isolation with use of masks by all health care personnel. Children and staff with pertussis in child-care facilities or schools should be excluded until macrolide prophylaxis has been taken for 5 days.

- No beneficial effect of $\beta 2$ -adrenergic stimulants such as salbutamol or albuterol.

- The clinical use of corticosteroids in the management of pertussis is not recommended.

Prevention

- Universal immunization of children with pertussis vaccine, beginning in infancy with periodic reinforcing doses, is central to the control of pertussis.

- Three diphtheria and tetanus toxoids combined with acellular pertussis (DTaP) vaccines currently are licensed in the USA for children <7 yr of age. DTaP vaccines have fewer adverse effects than the vaccines containing whole-cell pertussis (DTP), which continues to be given to infants and children in many other countries. Acellular pertussis vaccines all contain inactivated PT and contain 2 or more other bacterial components (FHA, Pn, and Fim 2 and 3). Clinical efficacy against severe pertussis is 80–85 %. Mild local and systemic adverse events occur significantly less frequently among infants who receive DTaP compared with DTP vaccine. DTaP-containing vaccines can be administered simultaneously with any other vaccines used in standard schedules for children.

- Three (primary) doses of DTaP should be administered during the 1st year of life, generally at ages 2, 4, and 6 mo of age. A 4th dose (1st booster) is recommended for children at 15–18 mo of age, at least 6 mo after the 3rd dose, to maintain adequate immunity during the preschool years. The 4th dose may be administered as early as 12 mo of age, provided 6 mo have elapsed since the 3rd dose. The 5th dose (2nd booster) is recommended for children at 4–6 yr of age to confer continued protection against disease during the early years of schooling.

LECTURE 12. DIPHTHERIA

Definition

- Diphtheria is an acute infectious disease caused by toxigenic strains of *Corynebacterium diphtheriae*, a gram-positive bacillus. The organism infects primarily the respiratory tract, where it causes tonsillopharyngitis, laryngitis, or both (typically with a pseudomembrane), as well as the skin, where it is responsible for a variety of indolent lesions. If the infecting strain produces exotoxin, myocarditis and neuritis may ensue.

- Greek *korynee* (meaning «club»), which describes the shape of the organism on stained smears — with one end usually being wider — and *diphtheria* (meaning «leather»), for the characteristic adherent membrane.

- Recognized by Hippocrates in 5th century B.C.

Etiology

- The genus *Corynebacterium* is characterized by bacilli that line up in parallel groups and bend when dividing to create «Chinese character» arrangements. It is a group of aerobic, nonmotile, unencapsulated, nonsporulating, pleomorphic gram-positive bacilli.

- Both nontoxigenic and toxigenic *C. diphtheriae* strains exist. Toxigenicity is conferred when a nontoxigenic organism is infected with a bacteriophage carrying the gene for the toxin (tox).

- *C. diphtheriae* has three biotypes — *gravis*, *mitis*, and *intermedius* — that are distinguished by colonial morphology and varying biochemical and hemolytic reactions.

- *C. diphtheriae* reduces tellurite to tellurium and produces characteristic black colored colonies when grown on tellurite containing media.

- **Virulence: diphtheria toxin.** For *C. diphtheriae* to produce disease it needs to colonize the upper respiratory tract and produce toxin. The diphtheria toxin is the main virulence determinant of *C. diphtheriae*. Chemically modified toxin (toxoid) is used for immunization.

- Toxin production is dependent on two important factors: (1) the presence of low extracellular concentrations of iron and (2) infection by a virus, also called a bacteriophage. Only those strains of *C. diphtheriae* that are lysogenized by a specific bacteriophage produce diphtheria toxin.

Epidemiology

- Humans are the only natural reservoir of *C. diphtheriae*.

- Spread occurs in close-contact settings through respiratory droplets or by direct contact with respiratory secretions or skin lesions.

- The organism survives for weeks and possibly months on environmental surfaces and in dust, and fomite transmission may occur.

- The majority of nasopharyngeal *C. diphtheriae* infections result in asymptomatic carriage, with clinical disease developing in only about one in seven individuals. However, asymptomatic carriers are important in maintaining transmission.

- Diphtheria immunization protects against disease but does not prevent carriage.

- In the prevaccine era, respiratory disease dominated in temperate climates, with a fall/winter peak in incidence. Most individuals acquired natural immunity by the midteen years. Cutaneous disease was the predominant form of the disease in tropical countries, but the current contribution of cutaneous diphtheria in inducing or maintaining diphtheria immunity in tropical countries is not known.

- Over the past 3 decades, outbreaks of diphtheria have occurred in the United States and Europe, typically in homeless and alcoholic inner-city adults.

- By 1990, the vaccination coverage in Soviet Union decreased. Diphtheria again became an urgent problem for many countries in Eastern Europe, including Belarus. For the period 1990 to 1996 in Belarus had registered 965 diphtheria cases and 28 deaths.

Pathogenesis

- Both toxigenic and nontoxigenic *C. diphtheriae* cause skin and mucosal infection, and rarely can cause focal infection after bacteremia. The organism usually remains in the superficial layers of skin lesions or respiratory tract mucosa, inducing local inflammatory reaction.

- The major virulence of the organism lies in its ability to produce the potent 62-kd polypeptide exotoxin, which inhibits protein synthesis and causes local tissue necrosis.

- Within the 1st few days of respiratory tract infection (usually in the pharynx), a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes forms, advances, and becomes a gray-brown, leather-like adherent pseudomembrane. Removal is difficult and reveals a bleeding edematous submucosa. Paralysis of the palate and hypopharynx is an early local effect of diphtheritic toxin. Toxin absorption can lead to systemic manifestations: kidney tubule necrosis, thrombocytopenia, cardiomyopathy, and/or demyelination of nerves. Because the latter 2 complications can occur 2–10 wk after mucocutaneous infection, the pathophysiology in some cases is suspected to be immunologically mediated.

Clinical Manifestations

- The manifestations of *C. diphtheriae* infection are influenced by the anatomic site of infection, the immune status of the host, and the production and systemic distribution of toxin.

CLASSIFICATION BY THE ANATOMIC SITE OF INFECTION

- Respiratory tract diphtheria:
 - Anterior Nasal;
 - Faucial;
 - Laryngeal and Tracheobronchial.
- Cutaneous diphtheria.
- Other sites diphtheria (ear, conjunctivae, vagina).
- Invasive disease (endocarditis, osteomyelitis, septic arthritis — caused by non-toxigenic *C.diphtheriae*, rarely occurs in immune compromised people).

Anterior Nasal diphtheria

- Infection limited to the anterior nares presents with a serosanguineous or seropurulent nasal discharge often associated with a subtle whitish mucosal membrane, particularly on the septum. The discharge can excite an erosive reaction on the external nares and upper lip, but symptoms of general intoxication are mild, and signs indicating toxin effects are rare.

Faucial diphtheria

- The faucial (pharyngeal) form is most common. Incubation period of 1 to 7 days.

- Including the posterior structures of the mouth and the proximal pharynx, this area is the most common site for clinical diphtheria. Onset is usually subacute over several days, with low-grade fever (rarely >39 °C), malaise, sore throat, mild pharyngeal injection.

- Initially there is mild pharyngeal erythema, usually followed by progressive formation of a whitish tonsillar exudate; over 24 to 48 hours, this exudate changes into a grayish membrane that is tightly adherent and bleeds on attempted removal. Membrane is typically located on one or both tonsils, with extension variously to involve the tonsillar pillars, uvula, soft palate, oropharynx, and nasopharynx. The membrane initially appears white and glossy but evolves into a dirty gray color, with patches of green or black necrosis.

- The extent of the membrane correlates with the severity of symptoms: localized tonsillar disease is often mild, but involvement of the posterior pharynx, soft palate, and periglottal areas is associated with profound malaise, weakness, prostration, cervical adenopathy, and swelling. The latter can distort the normal contour of the submental and cervical area, creating a «bull-neck» appearance and causing respiratory stridor.

Laryngeal and tracheobronchial diphtheria (True Croup)

- Pharyngeal infection may spread downward into the larynx, or occasionally the disease may begin there. Symptoms then include hoarse-

ness, dyspnea, respiratory stridor, and a brassy cough. Edema and membrane involving the trachea and bronchi can embarrass respiration further, and a child so afflicted will appear anxious and cyanotic, use accessory muscles of respiration, and demonstrate inspiratory retractions of intercostal, supraclavicular, and substernal tissues. If this state is not relieved promptly by intubation and mechanical removal of membrane, patients become exhausted and die.

- Systemic complications are due to diphtheria toxin, which, although toxic to all tissues, has its most striking effects on the heart and nervous system.

Cutaneous diphtheria

- This is a variable dermatosis most often characterized by punched-out ulcerative lesions with necrotic sloughing or pseudomembrane formation.

- The diagnosis requires cultivation of *C. diphtheriae* from lesions, which most commonly occur on the extremities.

- Patients usually seek medical attention because of nonhealing or enlarging skin ulcers, which may be associated with a preexisting wound or dermatoses such as eczema, psoriasis, and venous stasis disease. The lesions rarely exceed 5 cm.

CDC 2010 Diphtheria Case Definition

Probable case:

- In the absence of a more likely diagnosis, an upper respiratory tract illness with;
 - an adherent membrane of the nose, pharynx, tonsils, or larynx; AND
 - absence of laboratory confirmation; AND
 - lack of epidemiologic linkage to a laboratory-confirmed case of diphtheria.

Confirmed case:

- An upper respiratory tract illness with an adherent membrane of the nose, pharynx, tonsils, or larynx; AND any of the following:
 - isolation of *Corynebacterium diphtheriae* from the nose or throat; OR
 - histopathologic diagnosis of diphtheria; OR
 - epidemiologic linkage to a laboratory-confirmed case of diphtheria.

Complications

- **Airway obstruction** due to pseudomembranes may slough and obstruct the airway or may advance to the larynx or into the tracheobronchial tree. Children are particularly prone to obstruction because of their small airways.

- **Myocarditis** typically occurs 7–14 days after onset of disease. The most common electrocardiographic complications are flattening and inversion of T waves, ST-segment changes, and conduction abnormalities, including complete heart block. The prognosis appears to be worse in cases of diphtheria myocarditis with conduction disturbances or ventricular ectopy.

- **Neuropathy** may be seen either early or late in the course of illness. Palatal neuropathy and other cranial nerve palsies are often seen early in the course — as early as the first week of illness — while ocular palsies, diaphragmatic paralysis, and paralysis of limbs are generally seen later in the course of illness. Diaphragmatic paralysis may necessitate ventilatory support. If the patient survives, ultimately complete recovery is expected.

- **Other complications** include renal failure, thrombocytopenia, and coagulation abnormalities. Disseminated intravascular coagulation may occur in severe cases.

Diagnosis

- The decision to initiate therapy should be based on clinical grounds because delayed treatment, especially delay in the administration of antitoxin, is associated with worse outcomes. A high index of suspicion is required.

- Specimens for culture should be taken from beneath the membrane, from the nasopharynx, and from any suspicious skin lesions. Because special media are required, the laboratory should be alerted to the possibility of diphtheria. *C. diphtheriae* is best isolated on selective media that inhibit the growth of other nasopharyngeal organisms; one containing potassium tellurite is generally used. Based on colonial morphology and Gram stain appearance, a presumptive diagnosis may be possible within 18 to 24 hours. Cultures may be negative if the patient previously received antibiotics.

- Toxigenicity testing should be performed on all *C. diphtheriae* isolates. Because both nontoxic and toxic strains may be isolated from the same patient, more than one colony should be tested. Traditional methods include guinea pig inoculation and the Elek test, in which the isolate and appropriate controls are streaked on a culture plate in which a filter strip soaked with antitoxin has been embedded; toxin production is confirmed by an immunoprecipitation line in the agar.

- Identification of the diphtheria tox gene has allowed the development of rapid and accurate polymerase chain reaction-based methods for identifying toxic strains.

Differential Diagnosis

- Streptococcal and viral tonsillopharyngitis.
- Infectious mononucleosis.
- Vincent's angina.

- Candidiasis.
- Acute epiglottitis.
- A history of travel to a region with endemic diphtheria or a history of contact with a recent immigrant from such an area increases the possibility of diphtheria, as does a serum antitoxin level of less than 0.01 IU/mL before antitoxin treatment.

Treatment

The goals of treatment: 1) to neutralize the toxin rapidly, 2) to eliminate the infecting organism, 3) to provide supportive care, 4) to prevent further transmission.

- The mainstay of therapy is equine **diphtheria antitoxin**. Because only unbound toxin can be neutralized, treatment should commence as soon as the diagnosis is suspected because each day of delay in administration increases the likelihood of a fatal outcome. A single dose is given, ranging from 20,000 units for localized tonsillar diphtheria to 100,000 units for extensive disease with severe toxicity. Antitoxin can be administered intramuscularly or intravenously; particularly for more severe cases, the intravenous route is preferred. Tests for sensitivity to antitoxin should be performed according to package insert instructions before administering it, and desensitization should be carried out if necessary.

- **Antibiotic therapy**, by eliminating the organism, halts toxin production, limits local infection, and prevents transmission. Parenteral penicillin (4 to 6 million U/day) and erythromycin (40 mg/kg/day in four divided doses to a maximum of 2 g/day, usually orally if the patient can swallow) are the drugs of choice.

- **General supportive care** includes ensuring a secure airway (with tracheotomy, if necessary), monitoring the electrocardiogram for evidence of myocarditis, treating heart failure and arrhythmias, and preventing secondary complications of neurologic impairment such as aspiration pneumonia. The patient should be in strict isolation until follow-up cultures are negative. Convalescing patients should receive diphtheria toxoid.

Prognosis

- The prognosis for patients with diphtheria depends on the virulence of the organism (subspecies *gravis* has the highest fatality rate), patient age, immunization status, site of infection, and speed of administration of the antitoxin.

- Mechanical obstruction from laryngeal diphtheria or bull-neck diphtheria and the complications of myocarditis account for most diphtheria-related deaths.

- The case fatality rate of almost 10 % for respiratory tract diphtheria has not changed in 50 years.

- Without antitoxin treatment, respiratory diphtheria is frequently fatal, with case-fatality rates of 30–50 % reported. With the introduction of diphtheria antitoxin for treatment of diphtheria, mortality has decreased to 5–10 %. In diphtheria, receipt of antitoxin within the first 2–3 days of illness is clearly associated with reduced mortality. Disease in vaccinated persons is usually mild.

- At recovery, administration of diphtheria toxoid is indicated to complete the primary series or booster doses of immunization, because not all patients develop antibodies to diphtheritic toxin after infection.

Prevention

- The local health department must be notified. Close contacts should have cultures performed and should be given prophylactic antibiotics. A positive culture in a contact may confirm the diagnosis if the patient is culture negative. All contacts without full primary immunization and a booster within the preceding 5 years should receive diphtheria toxoid.

- **Immunization with diphtheria toxoid** is the only effective means of primary prevention. The primary series is four doses of diphtheria toxoid (given with tetanus toxoid and pertussis vaccine) at 2, 4, 6, and 15 to 18 months of age; a preschool booster dose is given at 4 to 6 years of age. Thereafter, a booster should be given as part of the adolescent immunization schedule (i.e., between 11 and 13 years of age), followed by doses administered every 10 years. Since 2005, the CDC recommends the routine use of tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis vaccine, adsorbed (Tdap), in adolescents aged 11 to 18 years in place of tetanus and diphtheria toxoid (Td) vaccines. In addition, the CDC recommends the routine use of a single dose of Tdap for adults 19 to 64 years of age to replace the next booster dose of Td.

- Genetically altered, fully immunogenic mutants of diphtheria toxin have been created (e.g., CRM197) and could be used as potentially less reactogenic alternatives to immunization with the toxoid. CRM197 is used as a protein carrier in several polysaccharide-protein conjugate vaccines.

LECTURE 13. CROUP SYNDROME IN CHILDREN

Definition and epidemiology

- Croup (acute laryngotracheobronchitis) is a respiratory illness of childhood and one of the most common causes of upper airway obstruction in children.

- Croup was once a deadly disease caused by diphtheria bacteria — laryngeal diphtheria («true croup»). Nowadays the term «croup» usually referred to acute laryngotracheitis caused by viruses (previously «false croup»).

- In the United States, it is estimated to affect around 3 % of the population and is most common in children aged 6 months to 6 years with the largest number of cases seen in those between 1 and 2 years of age. Reinfection and recurrence of croup is common. The ratio of males to females with croup is 1.43:1.

The most common infectious and noninfectious causes of croup:

Infectious:

- ▶ Parainfluenza virus.
- ▶ Respiratory syncytial virus (RSV).
- ▶ Influenza type A and B.
- ▶ *Mycoplasma pneumoniae*.
- ▶ Human metapneumovirus.

Noninfectious:

- ▶ Gastroesophageal reflux disease.
- ▶ Postintubation.
- ▶ Foreign body aspiration.

Pathogenesis

- Localized inflammation of the upper airway caused by an upper respiratory tract infection leads to varying degrees of airway obstruction and the range of symptoms seen in croup.

- Specifically, the infection causes the mucosa of the vocal folds and subglottis become erythematous and swollen.

- The subglottic area is the narrowest part of the airway and any edema affects the lumen negatively. This narrowing disrupts airflow resulting in the barking cough, stridor and increased work of breathing (indrawing).

Clinical Presentation

- Clinical symptoms of croup include a hoarse voice, a seal-like barking cough and stridor. As croup symptoms worsen, respiratory distress

and occasionally cyanosis can appear. Symptoms typically worsen when the child is agitated and at nighttime.

- Fortunately croup symptoms are short-lived with the majority (60 %) having resolution within 48 hours, and only a small portion having symptoms lasting up to 1 week.

- The majority of children with croup can be managed as outpatients with less than 5 % requiring admission. For those children requiring hospitalization, the need for endotracheal intubation is rare (1–5 %) and mortality is extremely rare.

- Croup symptoms are usually classified into mild, moderate, and severe and are based upon the Westley croup score (Table 6). Symptoms of croup (barky seal-like cough and stridor) almost always begin in the night time.

- If the child develops severe respiratory distress, they may appear agitated but do not drool or appear toxic. Respiratory failure is often preceded by a change in mental status such as fatigue, pallor or cyanosis, and decreasing stridor, breath sounds, and chest wall retractions.

Table 6 — Westley Croup Score

Symptom	Score	
Stridor	None	0
	When agitated	1
	At rest	2
Retractions	None	0
	Mild	1
	Moderate	2
	Severe	3
Air entry	Normal	0
	Decreased	1
	Markedly decreased	2
Cyanosis in room air	None	0
	With agitation	4
	At rest	5
Level of consciousness	Normal	0
	Disorientated	5
Total score		0–17

Note: Mild croup, 1–2; Moderate croup, 3–8; Severe croup, >8.

Diagnosis

- The diagnosis of croup is a clinical one.
- Radiological studies are useful to help exclude other diagnoses but are rarely helpful in diagnosing croup. If radiographs are performed after initial management, the lateral and anteroposterior neck X-rays will show the classic «steep sign» which is caused by subglottic narrowing.

A membrane in the trachea as well as a ragged tracheal contour suggests bacterial tracheitis.

- Findings of thickened aryepiglottic folds and epiglottis suggest epiglottitis. A widened soft tissue space of the posterior pharynx is suspicious for retropharyngeal abscess.

- The use of routine bronchoscopy in croup is not recommended; bronchoscopy should only be used when the diagnosis is severely in question, when the case is prolonged, or nonresolving in spite of optimal medical management.

- If endoscopy is used, caution should be taken to avoid further damage to the vocal chords and subglottic area.

Differential Diagnosis (Table 7.)

Table 7 — Differential Diagnoses of Croup and Associated Symptoms

Diseases	Differential signs
Bacterial Tracheitis	Prolonged symptoms of croup Toxic appearing Poor response to standard treatment or requires repeated doses of racemic epinephrine
Epiglottitis	Short history Very sore throat, drooling, and dysphagia Toxic appearing Cough absent
Peritonsillar abscess	Sore throat Muffled voice with drooling and dysphagia
Retropharyngeal abscess	Fever Sore neck with lateral movement or extension
Foreign Body Aspiration	Coughing spell prior to symptoms Stridor is often biphasic

Treatment

- **Cold Air** soothes the airway and helps to decrease the swelling of the subglottic area.

- **Mist Therapy.** In 2007, a Cochrane review by Moore and Little concluded that the croup score of children that are managed in the emergency department will not improve greatly with the inhalation of humidified air.

- **Corticosteroids.** The onset of action of corticosteroids to decrease symptoms in croup is as early as 2 hours after corticosteroid administration. One dose of dexamethasone (0.6 mg/kg) is usually all that is needed because of its long half-life and bioavailability (up to 82 h). May be repeated if symptoms still persistent >24h for an additional dose. Most children will have resolution of symptoms approximately 72 hours after medical assessment and administration of corticosteroids. This is most frequently

given orally but may be given intramuscularly if needed. The oral route is preferred because it is less traumatic to the patient, has excellent absorption and serum concentrations peak as fast as with intramuscular injection. If the patient is vomiting, the inhaled or intramuscular routes may be used as an alternative. Budesonid 2 mg (2 mL) solution may be given via nebulizer.

- **Racemic Epinephrine.** A dose of 0.5 mL of a solution of 2.25 % of racemic epinephrine is given via nebulizer over 5–10 minutes. If racemic epinephrine is not available, a dose of 5 mL of L-epinephrine (1:1000) may be given to achieve the same effect. The clinical effect of racemic epinephrine is present for at least 1 hour and essentially nonexistent after 2 hours. With the addition of oral dexamethasone or inhaled budesonide, the child, who has been treated with racemic epinephrine and observed for a period of 2–4 hours if symptom free, may be safely discharged home from the emergency department.

- **Heliox** (a helium-oxygen mixture at a ratio of 80:20 or 70:30) administered by a non-rebreather mask for the alleviation of croup symptoms. Heliox is thought to provide increased laminar airflow through the narrowed airway, thereby decreasing the mechanical work of breathing. Heliox cannot be used to treat children who require supplemental oxygen >30 %. Most authors concluded that although heliox may improve symptoms of croup, it is not superior to other conventional treatments (i.e., racemic epinephrine).

Course and prognosis

- Only 2 % of children with croup require hospitalization; of these, less than 1.5 % require endotracheal intubation.

- Factors that should prompt hospitalization include a history of severe obstructive symptoms prior to presentation, a congenital or acquired airway anomaly (e.g., subglottic stenosis), age younger than 6 months, stridor at rest, inadequate oral intake, extreme parental anxiety, or worsening symptoms.

LECTURE 14. MENINGITIS IN CHILDREN

Definitions

- **Meningitis:** inflammation of the leptomeninges (the tissues surrounding the brain and spinal cord). Usually caused by bacteria or viruses.
- **Encephalitis** — inflammation of brain tissue.
- **Meningoencephalitis** — inflammation of brain with meningeal involvement.
- **Meningism (meningsmus)** — the brain membranes irritation with appearing positive meningeal signs without inflammatory changes in cerebrospinal fluid (CSF).

Meningitis Etiology:

1. Bacterial Meningitis (3 types of bacteria cause >70 % of all reported cases): 1) Haemophilus influenzae; 2) Neisseria meningitidis (meningococcal meningitis); 3) Streptococcus pneumoniae (pneumococcal meningitis).

2. Bacterial pathogens, less common: group B Streptococci, gramnegative enteric bacilli (Klebsiella, Enterobacter, and Serratia species), Escherichia coli, Listeria monocytogenes, Mycobacterium tuberculosis, Leptospira interrogans, Borrelia burgdorferi (Lyme disease), Staphylococcus aureus.

3. Viral meningitis:

- Enteroviruses: Echoviruses, Coxsackie viruses A and B, poliovirus;
- Mumps virus;
- Herpes viruses: Herpes simplex virus 1 and 2 (meningoencephalitis), Varicella zoster virus; rarely Epstein-Barr virus and cytomegalovirus;
- Lymphocytic choriomeningitis virus;
- Arboviruses;
- HIV (can be the initial presentation of infection).

4. Others pathogens (rare):

- Fungi (Cryptococcus neoformans);
- Protozoa (Amebae, Naegleria, Acanthameba).

Syndromes typical for meningitis

• Meningeal syndrome:

- Cerebral general symptoms (pain, vomiting, seizures).
- The actual meningeal signs (symptoms of hyperesthesia, reactive pain signs, tonic contraction signs — neck stiffness etc).

• Syndrome of infectious disease (intoxication, fever);

• The syndrome of inflammatory changes in cerebrospinal fluid.

The classic symptoms of meningitis:

- fever + headache + vomiting (so called «meningeal triad»);
- photophobia (extreme sensitivity to light);
- Stiff neck, meningeal pose;

- positive meningeal signs (Kernig’s sign, Brudzinski’s upper, medial and lower signs etc.)
- irritability or lethargy;
- consciousness is confused or lost; coma; hallucination;
- seizures.

Clinical Manifestation in infants under 1 month of age

- tend to exhibit irritability, lethargy, unusual cry, seizure, poor feeding, and vomiting;
- high fever and signs of meningeal irritation may be absent;
- Lessage’s symptom (hanging, or suspension) positive.

Clinical Manifestation in infants older than 4 months

- typically produces fever;
- stiff neck;
- irritability and seizures;
- signs of increased intracranial pressure (including and bulging anterior fontanel, vomiting);
- Lessage’s symptome positive;
- funduscopic changes are usually absent at the time of diagnosis.

Plan of examination

- Funduscopy (to reveal papilledema);
- Lumbar puncture and examination of cerebrospinal fluid (Table 8);
- Blood cultures; Cultures of the nose and throat;
- CT or MRI scan.

Table 8 — Cerebrospinal fluid parameters normally and in meningitis

Indicator	Normal (N)	Bacterial meningitis	Aseptic meningitis
Pressure (mm H ₂ O)	100–200 (60–70 drops/min)	>300	N or ↑
Cells/μL	0–10	100–10,000	10–1000
Predominant cell type	Lymphocytes	Neutrophils	Lymphocytes
Glucose (mg/dL)	50–100	<40 (<50 % of serum glucose)	N
Protein (mg/dL)	20–45	> 100	N or ↑ (<100 mg/dL)

Diagnosis of Meningitis

- If meningitis is a consideration, a lumbar puncture must be performed.
- If focal neurologic deficits and papilledema are absent, a lumbar puncture can be performed before computed tomography scan.
- Gram stain of CSF is positive in more than 75 % of bacterial meningitis cases (negative in aseptic meningitis).
- Blood and CSF cultures with antibiotic sensitivity testing — for bacterial meningitis.

- Serological testing and PCR test for aseptic meningitis etiological agents. If tuberculosis not excluded, perform TB culture because CSF in tuberculosis meningitis is similar to viral meningitis.

Treatment of Meningitis

- If bacterial meningitis is suspected, antibiotics should be given within 30 minutes. Empiric therapy with ceftriaxone or cefotaxime. If severely ill, add vancomycin. Maximal doses of antibiotics must be given because of limited passage through the blood-brain barrier. Blood samples for culture should be drawn and antibiotics given before a computed tomography scan is done.

- For aseptic meningitis — Acyclovir 10 mg/kg 3 times per day during 7–10 days; in case of encephalitis — 15–30 mg/kg 3 times per day during 10–14 days, after that 200–400 mg 5 times (per os) during 14 days.

- Give dexamethasone 30 minutes before antibiotics.
- Maintain ventilation, prevent increase in PaCO₂ or decrease in PaO₂.
- Avoid hypotonic solutions, consider mannitol or glycerol for increased cerebrospinal fluid pressure.
- Anti-seizure medications after first seizure.

Outcome and Prevention of Bacterial Meningitis

1. **Mortality** is high: 26 % for *Listeria*, 19 % for *Streptococcus pneumoniae*, 13 % for *Neisseria meningitidis*, and 3 % for *Haemophilus influenzae*.

2. **Permanent sequelae** are common:

a) In children: mental retardation, hearing loss, seizure disorders, cerebral palsy;

b) In adults: hydrocephalus, cerebellar dysfunction, paresis, seizure disorder, hearing loss.

3. Efficacious **vaccines** are available:

a) *S. pneumoniae*: 23-valent vaccine; safe, inexpensive. Recommended in individuals more than 65 years of age; those with chronic cardiovascular, pulmonary, or liver disease, diabetes mellitus, sickle cell disease, and asplenia; heptavalent conjugated vaccine for all children under 2 years of age.

b) *H. influenzae*: PedvaxHIB vaccine at age 2 and 4 months; safe, inexpensive.

c) *N. meningitidis*: quadrivalent meningococcal vaccine for serogroups A, C, Y, and W135; misses group B. Recommended in military recruits, college students, and individuals with asplenia and terminal complement defects.

4. **Chemoprophylaxis** use:

a) *H. influenzae*: Rifampin within 6 days for household contacts with unvaccinated child under 2 years of age, and for children under 2 years of age exposed in a daycare center.

b) *N. meningitidis*: Single-dose ciprofloxacin within 5 days for household and daycare contacts, and for those exposed to oral secretions from the index case.

LECTURE 15. ACUTE INTESTINAL INFECTIONS IN CHILDREN

General considerations

- According to the WHO, 1.8 million people (mostly children) die every year from diarrheal diseases (including cholera).
- Globally infectious diarrhea remains one of the most common diseases afflicting children under five years of age and accounts for 15–30 % of deaths in children under five years of age.
- Clinically, in intestinal infection both general intoxication and gastrointestinal syndromes are present. The most dangerous consequence is dehydration syndrome.
- Gastritis is stomach inflammation with nausea, vomiting, epigastric pain. Enteritis is small intestine lesion, with diarrhea (loose, or even watery stool) and central or diffuse abdominal pain. Colitis is large intestine involvement with lower lateral abdominal pain, tenesmus, stools contain mucus and blood, increased neutrophil count in coprogram. These syndromes usually are combined to make a syndromal diagnosis (e.g. acute gastroenteritis, or enterocolitis).

Etiology

- **Bacterial infections:** The three most common bacterial causes of acute infectious diarrhea are Salmonella, Shigella, and Campylobacter. Other important bacterial pathogens include Escherichia coli, Vibrio cholerae, Vibrio parahaemolyticus, Yersinia enterocolitica. Food-borne toxico-infections in children can be caused by Bacillus cereus, Staphylococcus aureus, and Clostridium perfringens. The various causes of acute bacterial diarrhea are usually not distinguishable clinically, and diagnosis requires isolation of the organism on stool culture.
- **Viral infections:** Rotavirus, Noroviruses, Human caliciviruses, Enteric adenoviruses, Astroviruses.
- **Protozoal infections:** Giardia lamblia, Cryptosporidium spp., Entamoeba histolytica, Cyclospora, Isospora belli, Balantidium coli.

Epidemiology of intestinal infections

- Transmission mechanism — fecal-oral. Enteric infections enter the body through the mouth and intestinal tract and are usually spread through contaminated food and water or by contact with vomit or feces. For young children aerogenic transmission (nosocomial salmonellosis, viral infections) is also possible.

SALMONELLOSIS

- **ETIOLOGY.** Salmonella is an aerobic gram-negative bacillus that can grow readily on simple culture media. It is motile, and most strains

do not ferment lactose. Salmonellae are classified by their antigenic structure (somatic O antigen, flagellar H antigen, capsule K antigen etc) into several groups (Kauffman–White scheme), having more than 2200 serovariants. *Salmonella enteritidis* and *S.typhimurium* are most common. *Salmonella typhi* and paratyphi A and B cause typhoid (or enteric fever) and paratyphoid, respectively.

- **EPIDEMIOLOGY.** Salmonellosis is usually a zoonotic disease which infects both wild and domestic animals. Pet turtles, iguanas, rodents, and birds can carry large numbers of organisms, and can infect humans, particularly young children. Contamination of the water supply with sewage also can lead to gastrointestinal infection. *Salmonella* infections are more common in the summer months, when the warmer temperatures allow the organism to multiply more rapidly on contaminated foods. Because chickens often excrete *Salmonella* in their stools, eggs, egg products, and undercooked chicken are the foods most commonly associated with disease. Contamination of processed foods (ice cream, unpasteurized goat cheese, and whitefish) as well as fruits and vegetables contaminated with human or animal feces, has resulted in large outbreaks of salmonellosis.

- **PATHOGENESIS.** *Salmonella* attach to epithelial cells in the small intestine and colon and injects proteins that stimulate internalization. *Salmonella* destroys these cells and spread to mesenteric lymph nodes eventually causing bacteremia. The organism is acid-sensitive, with 10^4 to 10^8 organisms required for infection. Risk factors for disease include antacid use, prior antibiotics (reduces competition by normal flora), and depressed immune function (AIDS and transplant patients, sickle cell disease). The incubation period is usually 8 to 24 hours.

- **CLINICAL CLASSIFICATION.**

1. **Gastrointestinal form** with gastritic, enterocolitic, gastroenterocolitic variants. These diseases are self-limited with fever lasting up to 6 days. Depending on fever maximum and frequency of diarrheal episodes, mild, moderate and severe forms are established.

2. **Generalized form:** typhoid-like and septic forms.

3. **Bacillicarrier state:** acute, chronic, transitory.

SHIGELLOSIS (DYSENTERY)

- **ETIOLOGY.** The gram-negative *Shigella* bacillus (Enterobacteriaceae family) is nonmotile and does not ferment lactose. It grows readily on standard media. The four major pathogens exist: 1) *Shigella dysenteriae* and 2) *S. boydii* are seldom found in the world, but 3) *S. flexneri* and 4) *S. sonnei* are most commonly seen.

- **EPIDEMIOLOGY.** The primary mode of spread is person-to-person by fecal-oral transmission. Foodborne and waterborne outbreaks may

also occur as a consequence of fecal contamination. Children in daycare centers have a high incidence of infection, as do institutionalized individuals, particularly mentally challenged children. Can be spread by flies.

- **PATHOGENESIS.** Induces ruffling of host cells; once internalized, escapes to the cytoplasm. Moves through the cytoplasm and spreads from cell to cell by polymerizing actin. Accelerates cell death, forming plaques of necrotic cells. Induces marked inflammation and rarely invades the bloodstream. Shigella produces a cytotoxic Shiga toxin and induces premature cell death. This combination of efficient cell-to-cell spread and host-cell destruction produces superficial ulcers in the bowel mucosa and induces an extensive acute inflammatory response that usually prevents entry of Shigella into the bloodstream. Resistance to gastric acid means that a small numbers of organisms (200 bacteria) can cause disease. The organism first takes up residence in the small intestine. After several days, it is cleared by the small intestine, but then invades the colon, where it causes an intense inflammatory response, forming microabscesses and mucosal ulcerations. Because such a low inoculum is required to cause disease, the epidemiology of Shigella is different from that of Salmonella. Shigella has no intermediate animal hosts; the bacteria reside only in the intestinal tract of humans. The incubation period after ingestion of Shigella 36 to 72 hours.

- **CLINICAL MANIFESTATIONS.** Initial signs are high fever and general intoxication symptoms and gastroenteritis with severe abdominal pain. Then appears distal colitis with anal pain, painful defecation, tenesmus and false urge to defecate. The diarrhea may be watery and of large volume initially, evolving into frequent small-volume, bloody mucoid stools (with mucus, high neutrophils and RBC count in microscopy); most children (>50 %) never progress to the stage of bloody diarrhea. Untreated diarrhea may last 1–2 wk; only about 10 % of patients have diarrhea persisting for more than 10 days. Complications: significant dehydration, hemolytic-uremic syndrome, rectal prolapse, toxic megacolon or pseudomembranous colitis (usually associated with *S. dysenteriae*), conjunctivitis, iritis, arthritis (usually 2–5 wk after enteritis), reactive arthritis with uveitis, urethritis and rash, cystitis, myocarditis, and vaginitis are uncommon events.

ESCHERICHIA COLI INFECTION

- Multiple strains of *E. coli* can cause diarrheal illness. These strains cannot easily be distinguished from the nonpathogenic strains of *E. coli* that normally colonize the bowel. Serotyping methods are available that can identify specific lipopolysaccharide antigens (O antigens) and flagellar antigens (H antigens) associated with specific pathogenic characteristics. The diarrhea-causing *E. coli* (EC) strains are generally divided into five major classes based on their mechanisms of virulence:

1. **Enteropathogenic (EPEC)** strains. Adhere to the small bowel and induce the polymerization of actin filaments to form a pedestal directly beneath the site of bacterial attachment. This process is associated with mild inflammation and usually causes watery diarrhea. These strains are transmitted by contaminated food or water and by person-to-person spread in nurseries. This disease primarily affects children under the age of 3 years, and it is more common in developing countries.

2. **Enterotoxigenic (ETEC)** strains. Colonize the small bowel and produce a cholera-like or heat-stable toxin that stimulates secretion of chloride, causing watery diarrhea. These organisms are most commonly encountered in developing countries and are contracted from water contaminated with human sewage. These strains are a major cause of travelers' diarrhea.

3. **Enteroinvasive (EIEC)** strains. Invade colonic epithelial cells by the same mechanisms that *Shigella* uses. The EIEC strains do not produce toxins, but rather cause an inflammatory colitis that is indistinguishable from that caused by *Shigella*. These strains require ingestion of a large inoculum (10^8 organisms) to cause disease. Outbreaks are rare and are usually associated with contaminated foods in developing countries.

4. **Enterohemorrhagic (EHEC)** strains. Produce verotoxins or Shiga-like cytotoxins that inhibit protein synthesis and cause cell death. In certain strains, the toxin damages vascular endothelium in the bowel and glomeruli, causing hemorrhagic inflammatory colitis and hemolytic uremic syndrome. The strain most commonly associated with this syndrome is O157:H7; however, other toxin-producing serotypes are being identified with increasing frequency. Cattle appear to be the primary reservoir, and the disease is most commonly associated with ingestion of undercooked contaminated ground beef. Less commonly, cases have developed after consumption of unpasteurized milk or contaminated apple cider, spinach, lettuce, or commercial mayonnaise. Person-to-person spread can occur in daycare centers and nursing homes. This infection is found primarily in industrialized nations and usually occurs during the summer months.

5. **Enteraggregative (EAggEC)** strains. Adhere in large aggregates to human colonic mucosa and produce a low-molecular-weight enterotoxin that causes watery diarrhea. The diarrhea is often prolonged. These strains are contracted by ingesting contaminated water or food. Enteraggregative *E. coli* are reported in developing countries and are an important cause of travelers' diarrhea.

DIAGNOSIS OF BACTERIAL INTESTINAL INFECTIONS

- Stool cultures using both standard media and Campylobacter-selective media. The bacterial culture is positive in approximately 5 % of cases of acute diarrhea.

- Direct examination of the stool using methylene blue stain assesses polymorphonuclear leukocyte (PMN) response. That is typical for «invasive» diarrhoeas such as Shigella, Campylobacter, enteroinvasive Escherichia coli and Salmonella infections, but the same result may also be seen in amoebic dysentery and in antibiotic-associated pseudomembranous colitis.

- Gram stain can also be performed, mainly for identification of Vibrio cholerae and Campylobacter. The members of Enterobacteriaceae family cannot be distinguished by microscopy.

- Pathogenic strains of E. coli cannot be readily identified by culture; immunologic and molecular biologic methods are required. Slide agglutination using specific antiserum against O antigens has been performed in several epidemics.

- Routine blood analysis usually is not informative.

- Sometimes serological test (e.g. for Shigella, Salmonella) or PCR diagnostics can be used.

TREATMENT OF BACTERIAL DIARRHEA

- Most cases of bacterial enterocolitis are self-limiting, usually lasting 3 to 7 days. They may not require antibiotic therapy.

- Fluid and electrolyte replacement is generally the most important supportive measure.

- Agents that slow peristalsis are contraindicated in patients with bacterial enterocolitis who have fever or bloody stools. These drugs may prolong fever, increase the risk of bacteremia, lead to toxic megacolon, and prolong fecal excretion of the pathogen.

- Antibiotic therapy for Salmonella enterocolitis prolongs carriage in the stool and has not been shown to shorten the duration of gastroenteritis. Antibiotics are specifically contraindicated in patients with EHEC, because they may exacerbate the hemolytic uremic syndrome.

- To prevent potential complications associated with bacteremia, nontyphoidal salmonella should also be treated with antibiotics when this disease develops in neonates, people over age of 50 years, immunocompromised patients, and patients with prosthetic valves or vascular grafts. Antibiotic therapy should be continued only for 48 to 72 hours, or until the patient no longer has a fever.

- If needed, treat bacterial diarrhea with antibiotics approved in your region because of major geographic variations in antibiotic susceptibility.

- **Antibiotic Treatment of Acute Bacterial Diarrhea:**

- **Salmonella:** Ciprofloxacin 500 mg PO q12h OR levofloxacin 400 mg PO q24h for 5–7 days. Treatment prolongs the carrier state, avoid in most cases.

- **Shigella:** Ciprofloxacin 500 mg PO q12h, OR levofloxacin 400 mg PO q24h OR.

— TMX-sulfa 1 double-strength tablet q12h for 3 days. Sterilizes the stool and reduces secondary cases.

— **Escherichia coli**: Enterotoxigenic, Enteroaggregative, Enteropathogenic, Enteroinvasive:

— Ciprofloxacin 500 mg PO q12h OR levofloxacin 400 mg PO q24h for 3 days. Shortens the course of illness. Not recommended in mild cases.

— Enterohemorrhagic E.coli: No treatment. Also avoid anti-motility drugs; both increase toxin release and worsen hemolytic uremic syndrome; supportive care only.

VIRAL DIARRHEA

- Viral diarrhea is the most common form of infectious diarrhea. Viruses spread easily and are often called stomach flu.

- The disease is caused primarily by four viral groups:

- a) Norovirus («Norwalk»); b) Rotavirus; c) Enteric adenovirus 40, 41; d) Astrovirus.

- Self-limiting diseases; use supportive care with hydration.

Norovirus

The single-stranded RNA Norovirus belongs to the calicivirus family. Histopathology has revealed that the virus causes blunting of villi and PMN infiltration of the lamina propria in the jejunum. Patients present with the acute onset of nausea, vomiting, and watery diarrhea. The virus is shed in the stool for 24 to 48 hours after the onset of illness, and it also is present in high concentrations in vomitus. Ingestion of 100 viral particles can cause disease. Infection is transmitted by contaminated water and food and by person-to-person spread. In addition to contaminated drinking water, swimming pools and lakes can transmit the disease. Norovirus is relatively resistant to chlorine. Shellfish are a leading food source, and because the virus is relatively heat-resistant, cooking contaminated shellfish does not completely eliminate the risk of infection. Infected food handlers can contaminate food, resulting in large outbreaks. Large outbreaks have also been reported in closed environments such as ships, military installations, hospitals, and nursing homes. Norovirus is more commonly associated with outbreaks in adults, but infants and children may also be infected.

Rotavirus

The name Rotavirus (from the Latin *rota*, meaning wheel) for this double-stranded RNA virus is derived from the wheel-like appearance of the viral capsid on electron micrographs. It is a member of the reovirus family. Rotaviruses are able to replicate in mature villous epithelial cells in the small intestine. The viral capsid attaches to and penetrates the pe-

ripheral membrane of the host cell and enters the cytoplasm. Diarrhea is thought to be caused by loss of absorption by epithelial villi, lactase deficiency, and a decrease in the intestinal concentrations of other disaccharidases. The virus may also increase chloride secretion. Rotavirus is the most common cause of infant diarrhea, and by age 3 years, more than 90 % of children have acquired antibodies. Repeated infections may occur, indicating minimal cross-protection between strains. Adults may also contract the infection, most commonly from infected children as a consequence of fecal-oral transmission. The virus is resistant to hand washing and to many commonly used disinfectants, but it is inactivated by chlorine. It is able to survive on surfaces, in water, and on the hands for prolonged periods. In developed countries, infections most commonly occur during the winter months.

The clinical manifestations of viral diarrhea

- Viral diarrhea is the most common form of the disease, usually causing mild self-limiting watery diarrhea (gastroenteritis). These diseases are self-limiting and last 2 to 6 days depending on the agent.
- At one end of the clinical spectrum, the patient may experience mild watery diarrhea with minimal symptoms; at the other extreme, the patient may develop severe nausea, vomiting, abdominal cramps, headache, myalgias, and fevers to 39 °C. Stool smear reveals no leukocytes, and cultures are negative for bacterial pathogens.
- **Diagnosis.** Identification of the specific viral agent is usually not possible. The infecting agents are most readily identified by their appearance on electron microscopy. The PCR technique shows promise for identifying Norovirus in stool and in the environment. Commercial ELISA assays for Rotavirus are available and provide satisfactory results. Maintaining hydration is the primary goal of therapy.

PREVENTION OF INTESTINAL INFECTIONS

- Public health measures are the most efficient and cost-effective way of reducing diarrheal diseases. By understanding the epidemiology of each pathogen, the public health investigator can track down the source of contamination and prevent additional cases.
- After symptomatic disease, Salmonella fecal carriage may continue for an extended period, particularly if the patient received antibiotics. This carriage represents a potential health hazard for food handlers. The carrier state can usually be eradicated by prolonged therapy with amoxicillin (standard dose for 4 to 6 weeks) or a fluoroquinolone (ciprofloxacin: standard dose for 4 to 6 weeks). In patients with gallstones, the carrier state often cannot be eliminated.
- For individuals visiting areas endemic for travelers' diarrhea, a nonabsorbable rifamycin derivative, rifaximin, 200 mg orally, once or twice daily is protective.

LECTURE 16. REHYDRATION PRINCIPLES

- Treatment of a child with diarrhea is based on presence or absence of dehydration and severity of dehydration.
- Watery diarrhea requires replacement of fluid and electrolytes irrespective of etiology.
- Feeding should be continued to the greatest extent possible and should be increased during convalescence.

Types of diarrhea

- Acute watery diarrhea (including cholera).
- Acute bloody diarrhea (dysentery).
- Persistent diarrhea (lasts 14 days or longer).
- Diarrhea with severe malnutrition (Marasmus or Kwashiorkor).

Assessment of dehydration severity (Table 9).

Table 9 — Assessment of dehydration severity

Sign	No dehydration	Some dehydration	Severe dehydration
Condition	Well, alert	Restless, irritable	Lethargic or unconscious
Eyes	Normal	Sunken	Sunken
Thirst	Drinks normally, not thirsty	Thirsty, drinks eagerly	Drinks poorly, or not able to drink
Skin pinch	Goes back quickly	Goes back slowly	Goes back very slowly
Fluid deficit	< 5 % of body wt or < 50 ml/kg body wt	5–10 % of body wt or 50–100 ml/kg of body wt	> 10% of body wt or > 100 ml/kg of body wt
Treatment	Plan A	Plan B	Plan C

Management of Acute Diarrhea (without blood)

The objectives of treatment are to:

- Prevent dehydration.
- Treat dehydration when present.
- Prevent malnutrition (feed the child).
- Reduce duration and severity of diarrhea and occurrence of future episodes by giving supplemental zinc.

Oral rehydration therapy (ORT) is as effective as intravenous therapy in rehydrating and replacing electrolytes in children with some dehydration and should be the therapy of choice.

Constituents of WHO oral rehydration solution (ORS) are:

- Sodium chloride: 3.5 g;
- Sodium bicarbonate: 2.5 g;
- Potassium chloride: 1.5 g; and
- Glucose: 20 g in one liter of water.

Plan A:

- Home therapy to prevent dehydration and malnutrition: Children with no signs of dehydration need extra fluid and salt to replace their losses of water and electrolytes due to diarrhea.

- **Fluids to be given:** ORS; salted drinks (eg. salted rice water or salted yoghurt drink); vegetable or chicken soup with salt; home based ORS: 3 gm of table salt and 18 gm of common sugar in one liter of water. Plain water should also be given. Commercial carbonated beverages, fruit juices, sweetened tea, coffee, medicinal tea should be avoided.

- **How much to give.** Give as much fluid as the child wants until diarrhea stops. Children < 2 years of age: 50–100 mL of fluid; Children 2–10 years: 100–200 mL; older children and adults: As much as they want.

- The infant's usual diet should be continued during diarrhea and increased afterwards. Breastfeeding should always be continued.

- Zinc supplement (10–20 mg) every day for 10 to 14 days should be given.

Plan B:

- Oral rehydration therapy for children with some dehydration: ORS + Zinc supplementation. Amount of ORS to be given in first 4 hours see Table 10.

Table 10 — Amount of ORS to be given in 1st 4 hours

Age*	< 4 mths	4–11 mths	12–23 mths	2–4 years	5–15 years	15 years or older
Weight	< 5 kg	5–7.9 kg	8–10.9 kg	11–15.9 kg	16–29.9 kg	30 kg or more
ml	200–400	400–600	600–800	800–1200	1200–2200	2200–4000

*Age should be used only if weight is not known.

- Approximate amount of ORS required (in mL) can also be calculated by multiplying the patient's weight in kg by 75.

- If more ORS is required, give more.

- Except for breast milk, food should not be given during the initial 4 hour rehydration period.

- However children continued on treatment Plan B longer than 4 hours should be given some food every 3–4 hours as in Plan A.

- After 4 hours, reassess the child and decide what treatment to be given next as per Grade of dehydration.

- Children who continue to have some dehydration even after 4 hours should receive ORS by nasogastric tube or Lactated Ringer's solution (RL) intravenously (75 mL/kg in 4 hours).

- If abdominal distension then oral rehydration should be withheld and only IV rehydration should be given.

Plan C: For patients with severe dehydration

- Preferred treatment is rapid intravenous rehydration. Give 100 ml/kg RL or normal saline solution as follows (Table 11).

Table 11 — Amount of intravenous rehydration

Age	First give 30 mL/kg in	Then give 70 mL/kg in
Infants	1 hour*	5 hours
Older children	30 min*	2½ hours

*Repeat once if pulses are weak or not detectable.

- Reassess patient every 1–2 hours. If hydration is not improving, give the IV drip more rapidly.
- After completion of IV fluids, reassess the patient and choose the appropriate treatment Plan (A, B or C).
- If IV therapy is not available, then ORS by nasogastric tube or orally at 20 ml/kg/hour for 6 hours (total of 120/kg) should be given.
- If abdomen becomes swollen or the child vomits repeatedly, then ORS should be given more slowly.

Management of suspected cholera

- With cholera, unusually large amounts of ORS solution may be required to replace large continuing losses of watery stool after dehydration is corrected (Rice based ORS is superior to standard ORS for cholera and used whenever its preparation is convenient. It does not have benefit in children with acute non-cholera diarrhea).
- After being rehydrated, patients should be reassessed every 1–2 hours for signs of dehydration.
- Antimicrobial in form of doxycycline (in children more than 8 years) or erythromycin for 3 days is recommended.

Management of Acute bloody diarrhea (dysentery)

- Any child with bloody diarrhea and severe malnutrition should be referred immediately to hospital. All other children should be assessed, given appropriate fluids to prevent or treat dehydration and feeding should be continued as described earlier. In addition, antibiotic such as Ciprofloxacin (15 mg/kg/dose bd for 3 days or alternately Ceftriaxone (50–100 mg/kg once daily intramuscularly or IV for 2 to 5 days). Should be given to treat shigellosis as shigella causes most episodes of bloody diarrhea in children. Antimicrobials that are ineffective for treatment of shigellosis are Metronidazole, aminoglycosides, tetracycline, chloramphenicol, sulphonamides, amoxycillin, nitrofurans and 1st and

2nd generation cephalosporins. If there is no improvement after two days, antimicrobial should be changed to another recommended for Shigella in the area to be given for 5 days. If there is no improvement, then hospitalize. Treatment for amoebiasis should be given if stool shows trophozoites of E.histolytica or treatment for Shigella fails inspite of 2 different antimicrobials.

Rational use of antimicrobials in the treatment of diarrhea:

- Antimicrobials and anti parasitic agents should not be routinely used as most episodes of diarrhea are self-limiting and do not benefit from such treatment.

- Antimicrobials are indicated in: 1) Dysentery; 2) Suspected cholera with severe dehydration; 3) Persistent diarrhea, when trophozoites/cysts or Giardia or trophozoites of E.histolytica are detected in feces.

- Empiric antibiotic therapy may even lead to development of Clostridium difficile associated enterocolitis and worsening of symptoms.

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