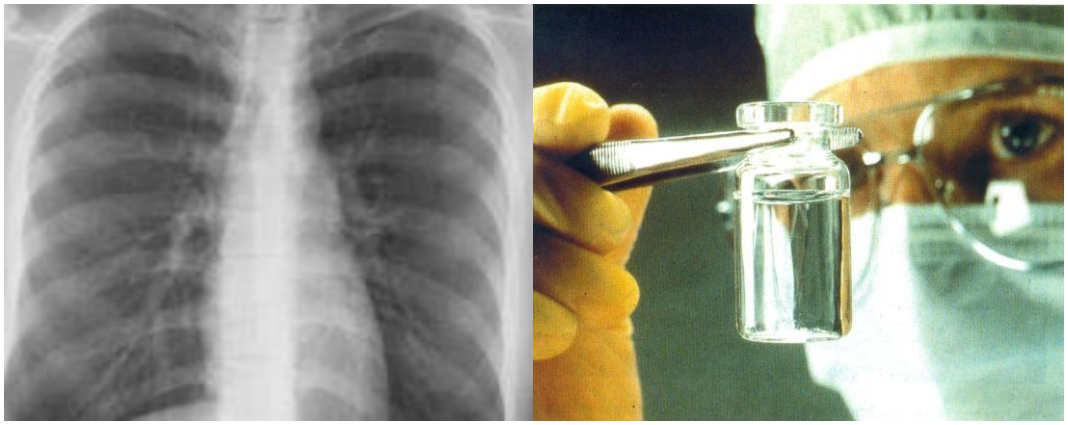
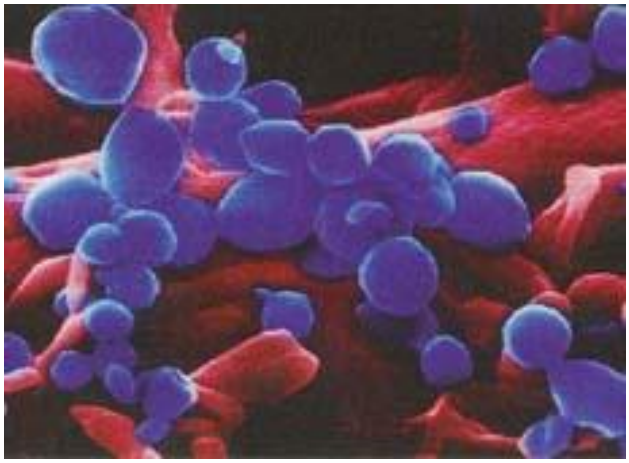
V.M. Kozko, D.V. Katsapov,
A.V. Bondarenko, M.I. Krasnov,
G.I. Gradil, N.O. Nikitina,
J.I. Kopeychenko



ACUTE RESPIRATORY INFECTIONS



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МИНИСТЕРСТВО ЗДРАВООХРАНЕНИЯ УКРАИНЫ
ХАРЬКОВСКИЙ НАЦИОНАЛЬНЫЙ МЕДИЦИНСКИЙ УНИВЕРСИТЕТ

ACUTE RESPIRATORY INFECTIONS

Textbook for Vth year medical students

ОСТРЫЕ РЕСПИРАТОРНЫЕ ИНФЕКЦИИ

Учебное пособие для студентов V курса медицинских ВУЗов

Утверждено
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Рецензенты:
Е. И. Бодня, профессор, д.мед.н., заведующая кафедрой медицинской паразитологии и тропических болезней ХМАПО;

А.К. Полукчи, д.мед.н., кафедра инфекционных болезней ХМАПО.

Авторы:

Козько В.Н., Кацапов Д.В., Бодаренко А.В., Краснов М.И., Градиль Г.И., Никитина Н.А., Копейченко Я.И.

О 072 Acute respiratory infections: Textbook for medical foreign students / V.N. Kozko, D.V. Katsapov, A.V. Bondarenko et al. – Kharkiv: FOP Segal' I.M., 2009. – 144 p.

Острые респираторные инфекции: Учебное пособие для иностранных студентов медицинских вузов / В.Н. Козько, Д.В. Кацапов, А.В. Бодаренко и др. – Харьков: ФОП Сегаль И.М., 2009. – 144 с.

The material contained in the textbook reviews to the fundamental questions of acute respiratory infections (etiology, epidemiology, pathogenesis, clinical manifestations, differential diagnosis and treatment). It would be helpful to medical students and interns.

Материал, представленный в учебнике, посвящен фундаментальным вопросам острых респираторных инфекций (этиологии, эпидемиологии, патогенеза, клиники, лечения). Учебник рекомендован для студентов медицинских ВУЗов и интернов.

INTRODUCTION

Infection of the respiratory tract is still a leading cause of diseases and death worldwide. Influenza pandemics have always been a great global threat. There have been 10 pandemics of influenza A in the last 300 years. Epidemics of influenza continue because of the difficulties in maintaining appropriate vaccines in the face of antigenic shift and drift of the virus and in implementating vaccination programs. The current widespread outbreaks of avian influenza, caused by emerging virus H5N1 among domestic fowl and wild aquatic birds, have reawakened concern that avian influenza viruses may again cross species barriers to infect the human population. Measles, the pneumococcus, and Haemophilus influenzae cause annually some 5 million deaths in young children in the developing countries where vaccination programs and the use of simple antimicrobials are not adequately provided for in poor, often rural, populations.

Clearly, no student or practitioner can own a library of monographs and journals that covers the whole of infectious diseases. One important function is to provide a sound basic account of the many disorders that comprise infections of respiratory tract and thus give the background to more recent advances that are best sought in specialist journals. Furthermore, as well as the greater complexity of the diseases of the richer countries, the increasing ease of international travel and the movements of massive refugee populations round the world mean that internal medicine today is truly global; diseases that once were restricted to tropical climates or particular countries can turn up in hospitals or consulting rooms anywhere in the world. With this background in mind we have proceeded with publishing the series of methodical recommendations and are presenting new one. We have expanded some of the background chapters of program, particularly with topics, which is not covered by lectures and consigned for out-class studies.

We are well aware that this methodical recommendation will rapidly date and hence it is important that students and practitioners continue to augment their reading with up-to-date journals, and refresh themselves by regular visits to student's scientific circle or postgraduate meetings. Information systems and related technology are rapidly changing the face of communication in medicine and readers should avail themselves of every opportunity of learning the complexities and potentials of this rapidly evolving branch of practice.

INFLUENZA

DEFINITION. *Influenza - it is the disease of viral origin with air-droplet route of transmission that is characterized with intoxication and signs of inflammation of respiratory tract, high level of complications and mortality and ability to epidemic and pandemic.*

ETIOLOGY

Influenza viruses are the members of Orthomyxoviridae. Influenza A and B viruses constitute the genus Influenza and influenza C virus make up the genus conditionally Influenza. Serotypes A, B and C are morphologically similar. The viruses are irregularly shaped spherical particles 80 to 120 nm in diameter and have a lipid envelop from the surface of which the H (haemagglutinin) and N (neuraminidase) glycoproteins project. The haemagglutinin is the site by which virus binds to cell receptors whereas the neuraminidase degrades receptors and probably plays a role in the release of virus from infected cells after replication had taken place.

Antibodies to the H antigen are the major determinants of immunity to influenza virus while those to the N antigen limit viral spread and contribute to reduction of the infection. The virion also contains M (matrix) protein of inner surface of lipid envelope, P or polymerize proteins that are essential for transcription and synthesis of viral RNA and nucleoproteid (NP) antigen, which is associated with the viral genome and contribute the type specify of A, B, C viruses. The genome of influenza viruses consists single-stranded RNA, which code structural and nonstructural proteins. Because of the segmented nature of the genome when two different viruses of a given type coinfect a cell mixtures of parental gene segments may be assembled into progeny virions. This phenomenon, called genetic reassortment, may result in sudden changes of viral surface antigens – a property that explain the epidemiological features of influenza and poses significant problem for vaccine development.

Influenza A viruses are subtyped on the basis of surface H and N antigens; individual strains are designated according to the site of origin, isolate number, year of isolation and subtypes (for example: influenza A/ Johanessburg/33/94 (H3N2). Influenza B and C viruses are designated similarly, but H and N antigens don't receive subtype designation since intratypic variations of these viruses are less extensive. Antigenic changes continually occur within the type A group of influenza and to a lesser degree in the type B grope, whereas type C appears to be antigenically stable.

EPIDEMIOLOGY

Influenza A is antropozoonotic infection. Both humans and animals – mammalian (horses, pigs, cows) and birds (ducks, hens and different transmigrational birds) can be the source of infection. Influenza B and C are exclusively human's infections. Influenza outbreaks are recorded virtually every year, although their extent and severity vary widely. Localized outbreaks take place at variable intervals,

usually every 1 to 3 years. Global epidemics or pandemics have occurred approximately every 19 to 15 years since the 1918-1919 pandemic. This pandemic named “Spanish flu” has taken away more than 20 millions (according to some reports up to 40 millions) of lives. As it has become known later the pandemic was caused with influenza A (H1N1) virus (Table 1).

Following supervision showed that the most extensive and severe outbreaks were caused by influenza A viruses. This predominance is a result of the remarkable propensity of the H and N antigens of influenza A to undergo periodic antigenic variations.

Table 1.

Emergence of antigenic subtypes of Influenza A virus associated with pandemic or epidemic disease

Year	Subtype	Extent of outbreak
1889-90	H2N8 ?	Severe pandemic
1099-03	H3N8 ?	Moderate epidemic ?
1918-19	H1N1 (formerly HswN1)	Severe pandemic
1933-35	H1N1 (formerly H0N1)	Mild epidemic
1946-47	H1N1	Mild epidemic
1957-58	H2N2	Severe pandemic
1968-69	H3N2	Moderate pandemic
1977-78	H1N1	Mild pandemic

Major antigenic variations are referred to an antigenic shift, which may be associated with pandemics. Minor variations result from point mutations of the H or the N antigens occurring during the spread of viruses from person to persons under action of human immunity. Such small changes in antigenic structure of viruses are named as antigenic drift and are associated with periodic epidemic outbreaks.

Antigenic shift may involve the H alone or both the H and the N antigens and three major antigenic subtypes of haemagglutinin (H1, H2 and H3) and two of neuraminidase (N1 and N2) have been recognized. An example of an antigenic shift involving both the H and the N antigens is that of 1957, when predominant influenza A virus subtype shifted from H1N1 to H2N2; this shift resulted in a severe pandemic, which has taken away about 1 million of lives. In 1968 an antigenic shift involving only the H antigen occurred (H2N2 to H3N2); the subsequent pandemic was less severe than that in 1957. In 1977 an H1N1 virus emerged and caused a pandemic that primarily affected younger individuals. As can be seen in Table 1, H1N1 viruses circulated from 1918 to 1956; thus individuals have been born prior to 1957 would be expected to have some degree of immunity to H1N1 viruses.

Since 1977 antigenic drifts have been reported nearly annually for H1N1 and since 1968 for H3N2 viruses, resulting in outbreaks of varying severity. H1N1 and H3N2 viruses often circulated simultaneously. In some outbreaks influenza B viruses have also circulated simultaneously with influenza A viruses.

The origin of pandemic strains is unknown. It seems unlikely that antigenic shifts result from spontaneous mutations in the haemagglutinin gene. Because the segmented genome of influenza A viruses may result in high rates of reassortments, it has been suggested that pandemic strains may emerge by reassortment of genes between human and animal viruses. The influenza A viruses have 15 haemagglutinin subtypes (H1-H15) and 9 neuraminidase subtypes (N1-N9) as is seen from Table 2.

All aquatic birds are considered to be at risk of being infected by all the subtypes of influenza A virus. But for humans, only H1, H2, H3 and N1, N2 subtypes have been established the linage in the population. From studying the viral genes scientists have discovered that aquatic birds are resistant to infection and thus are a natural reservoir from which the influenza viruses spread to other animal species. Whereas a transmission of avian influenza virus to pigs and horses is possible, there is usually no direct transmission of the avian influenza virus to humans (except the Avian H7N7 and H9N2) influenza that has been discovered to cause a typically mild, self-limited human infection.

Table 2.

Natural hosts of influenza A virus.

Antigens	**Hosts of influenza A virus**								
H	H1 Humans, pigs, ducks, turkey-cocks	H2 Humans, ducks, turkey-cocks	H3 Humans, pigs, horse, ducks, turkey-cocks	H4 Ducks, turkey-cocks	H5 Ducks, turkey-cocks	H6 Ducks, turkey-cocks	H7 Ducks, turkey-cocks, horses	H8 Ducks, turkey-cocks	H9 Ducks, turkey-cocks
H	H10 Ducks, turkey-cocks	H11 Ducks, turkey-cocks	H12 Ducks, turkey-cocks	H13 Ducks, turkey-cocks	H14 Ducks, turkey-cocks	H15 Ducks, turkey-cocks	-	-	-
N	N1 Humans, pigs, ducks, turkey-cocks	N2 Humans, pigs, ducks, turkey-cocks	N3 Ducks, turkey-cocks	N4 Ducks, turkey-cocks	N5 Ducks, turkey-cocks	N6 Ducks, turkey-cocks	N7 Ducks, turkey-cocks, horses	N8 Ducks, turkey-cocks, horses	N9 Ducks, turkey-cocks

However, in recent years, during the flu pandemic in poultry, H5N1 influenza virus, which was previously reported to cause the pandemic only in poultry, was first isolated from a boy who died of influenza pneumonia in Hong-Kong (1997). Surprisingly, the H5N1 isolates showed that all of the viral genes had directly originated from the avian influenza virus without any reassortments -– combinations between avian humans' viral genes – as had been the case in previous strains. That outbreak afflicted a total of 18 people, causing 6 deaths. Subsequent outbreaks were reported in some other Asian countries (2003-2005), with a mortality rate approaching 70%. The H5N1 transmission to humans is thus an ominous sign. It has

caused fear of a new influenza pandemic in humankind, causing widespread panic and economic loss due to quarantining of infected farms and large scale slaughtering of infected and potentially exposed poultry. The influenza virus that causes the epidemic in poultry is known as “highly pathogenic avian influenza” which is a virulent subtype. However, the “low’ pathogenic viruses can also genetically develop into the highly pathogenic ones after having circulated in the avian population for a while. This genetic lability is a distinct biological property of RNA viruses, including influenza virus. RNA viruses lack an efficient proofreading system that helps check errors during the replication process. This poor proofreading system helps RNA virus strains to evolve very rapidly compared other organisms.

During the course of infection, human flu viruses preferentially infect non-ciliated cells (mainly contained 2-6-linked sialic acids) in the human airway, whereas the avian viruses preferentially infect ciliated cells (mainly contained 2-3-linked sialic acids). This differential preference is due to the viral haemagglutinin specificities to receptors on different kinds of host cells. Recent studies suggest that although avian influenza viruses can infect human airway epithelial cells, their replication is limited. Influenza viruses that cause a pandemic in humans are presumed to also contain human-virus-like receptor specificity. The H5N1 virus, which is capable of infecting humans and causing many fatalities, originated directly from the avian virus and has avian-virus-like receptor specificity. Thus the disease directly transmits from birds to humans but fortunately is as yet unable to transmit efficiently from human to human. However, due to the rapid pace of influenza virus evolution, humankind is at risk of an H5N1 pandemic. Any alteration of receptor specificity of haemagglutinin gene in H5N1 that allow the viral transmission from human to human to occur will pose a worldwide threat.

Influenza B viruses do not have an animal reservoir and do not undergo antigenic shifts, although they do undergo antigenic drifts.

Influenza A epidemics begin abruptly over 2 to 3 week, generally last for 2 to 3 month. Attack rates have been highly variable, but most commonly are in the range of 10 to 20% of general population. During the pandemic of 1957 it was estimated as 50% of urban population and an additional 25% or more of individuals may have been subclinically infected. Epidemics of influenza occur almost exclusively during the winter months. Where and how influenza A virus persists between outbreaks is unknown. Influenza B epidemics occur each 3-5 years. Influenza C causes the sporadic infections.

Transmission of the infection occurs via aerosols generated by cough and sneezes. Although hand-to-hand contact, other personal contact transmission (through the tea-things, plates, towels and other fomites) may took place. Infection by aerosol (less than 10 nm) is more effective than the larger droplets, because the small particles can enter even into small bronchi and bronchioles.

Influenza viruses are relatively hardy and may be stored at 0-4˚C for weeks without loss of viability. The virus loses infectivity more rapidly at –20˚C than at +4˚C. Ether and protein denaturants destroy infectivity.

PATHOGENESIS

The initial event of influenza is *infection of the respiratory epithelium* with influenza virus. The life cycle of the flu viruses depends on its infecting host cells, replicating viral genetic material inside those cells, and than releasing the viral progenies to infect other cells. Essential to its life cycle is the ability of the virus to protrude into the host cells. The rod-shaped haemagglutinin spikes on the surface of the influenza virus help it infect host cells by allowing it to attach to sialic-receptors on the host cell membrane. The mushroom-shaped neuraminidase releases progeny virions from within infected cells. Viral infection involves *non-ciliated columnar epithelial cells (mainly contained 2-6 linked sialic acids)*, but it also may involve other respiratory tract cells, including alveolar cells, mucous gland cells and macrophages. In infected cells virus replicates within 4 to 6 h, after which infectious virus is released to infect adjacent or nearby cells. A few cells of respiratory epithelium are infected if deposited viral particles avoid removal by the cough reflex and escape neutralization by any preexisting specific IgA antibodies or inactivation by nonspecific inhibitors in the mucous secretion. Viral neuraminidase lowers the viscosity of the mucous film in the respiratory tract, laying bare the cellular surface receptors and promoting the spread of virus-containing fluid to lower portion of the tract. In this way infection spreads from a few foci to a large number of respiratory cells over several hours. The severity of illness is correlated with the quantity of virus shed in secretions; thus the degree of viral replication itself may be an important mechanism in the pathogenesis of illness. The columnar epithelial cells reveal degenerative changes, including granulation, vacuolization, swelling and pyknotic nuclei. The cells become necrotic and desquamate; in some areas previously columnar epithelium is replaced by flattened and metaplastic epithelial cells. Desquamation of columnar epithelial cells open the way for virus to enter into the bloodstream; subsequent *viraemia and systemic signs of toxicosis* develop. Despite of short duration of viraemia (2 to 4 days) its role in pathogenesis of disease is very significant. Circulating virus can damage endothelial cells, enter through the brain blood barrier and even damage the cells of brain. But at whole influenza virus has only rarely been detected in extrapulmonary sites. Influenza viruses are sensitive to the antiviral effects of interferon, and it is believed that the interferon response contributes to host recovery from infection. Specific antibody and cell-mediated responses cannot be detected for 1-2 weeks.

The mechanism of toxicosis in influenza is not enough known. Perhaps, the major role in this process belong to the massive destroying of the epithelial cells, that can be trigger factor for the *development of mechanisms of inflammation*, The

mechanisms of allergy and immunity which result in formation of antigen-antibody complexes and activation of macrophages and complement system may perform the similar role. As a result major cascade system, associated with inflammation (including the coagulation, complement, fibrinolisis, and kallikrein-kinin system) as well as production of histamine, numerous cytokines, interleukins and nitric oxide are all triggered. The most of the enumerated inflammatory mediators act as vasodilators and cause the increasing of microvessels permeability. The fluid part of blood may pass beyond the vessels bound into extracellular space. It results in *severe disorders of microcirculation*, edema of the tissue (edema of the brain, of the lung), as well as to hypovolemia and marked decreasing of general volume of blood, arterial hypotension and shock.. Progressive disseminated intravascular coagulation (DIC) syndrome and blockage of bloodstream is considered to be the main cause of the development of tissue hypoxia and respiratory distress syndrome of adult (RDSA). Thus a central role in the pathogenesis of influenza belongs to the circulatory disturbances in different organs and systems, especially in the central nervous system and lung, tissue hypoxia, metabolic acidosis.

The next important chain of influenza pathogenesis includes the *activation of bacterial flora and development of bacterial superinfection.* Several mechanisms play role in the development of bacterial complications and explain their frequency:

a) destruction of the columnar epithelial cells and suppressing of their function in mucociliar clearance;

b) activation of mucus production by cells of respiratory tract glands and difficulties in evacuation of this mucus creates the favorable conditions for the multiplication of bacterial flora;

c) immunosuppressive activity of influenza virus that able to reduce T-cell immunity, production of interferon and leucocytes and to suppress the phagocytic activity of neutrophils and macrophages;

d) influenza virus able to activate multiplication of bacterial flora and to increase its virulence.

Secondary bacterial flora invading the primary viral lesions can aggravate and prolong the primary viral disease and can be principal etiological factor in secondary pneumonia and other pathological processes.

The host immunity to influenza infection involves humoral antibodies, local antibodies, cell-mediated immunity, interferon and other defenses. Serum antibodies defenses can be detected by the second week after primary infection. Antibodies detected against haemagglutinin appear to be the most important mediator of immunity. Different classes of Ig are produced under way of disease. Primary immune response is connected with IgM and later IgG are produced. Serum antibodies IgM and IgG defend host against spread of infection (i.e. viraemia). Secretory antibodies IgA, produced in the respiratory tract defend humans against

contamination.

A variety of cell-mediated immune responses both antigen-specific and antigen-nonspecific can be detected early after infection, depending on the prior immunity of the host. These responses include T-cell proliferation, T-cell cytotoxic and natural killer cells activity. Interferon has been detected in respiratory secretions shortly after the shedding of virus has begun, and rises in interferon titers coincide with decreasing in virus shedding.

CLINICAL MANIFESTATIONS

Disease is characterized with the abrupt onset of symptoms, associated with toxemia, such as headache, feverishness, chills, myalgia, arthralgia and malaise. The temperature runs up to the highest level within the first 24 hours of illness as a rule. Myalgias may involve any part of the body but are the most common in the legs and lumbosacral area. These systemic symptoms depend on severity of disease. In severe cases adynamia, sleepiness, significant malaise and signs of intracranial syndrome may occur.

Intracranial syndrome is associated with the circulatory disturbances in the CNS and increasing of intracranial pressure. It is characterized by intensive frontal headache, hyperalgesia (photophobia, acusticophobia), vomiting of central origin and includes retroorbital pain, increased on side motion with eyes.

Signs of vascular disorders develop from the first days of disease. Skin of patient's face is hyperemic, hot and dry; the conjunctiva of eyelids and sclera and mucous membranes of soft palate, uvula and pharynx are hyperemic. In severe cases small hemorrhages are seen there (hemorrhagic syndrome). Epistaxis and presence of blood in sputum are not uncommon.

Respiratory syndrome is not constant in influenza; it is absent in 20 to 30% of cases. But in the majority of patients it is the most common syndrome and develops either to the end of the 1-st or on the 2-d day of disease. It often becomes more prominent as systemic symptoms subside. Rhinitis usually is not expressed; it is characterized with dryness in nose, sneezing, and moderate nasal secretions. Dryness and irritation in fauces arise. Many patients have a sore throat and persistent cough, which is accompanied by substernal discomfort (signs of tracheitis). Laryngitis manifests by hoarseness of the voice and hard barking cough. Sore throat in this case is localized at the level of cartilage and grows on swallowing and talk. Very often inflammation process spreads down with development of bronchitis. In these cases cough becomes more persistent; it is accompanied by substernal discomfort. Physical finding are usually minimal in cases of uncomplicated influenza. The results of chest examination are largely negative, although rhonchi, wheezes and not numerous scattered rales have been reported with variable frequency. Patients with apparently uncomplicated influenza have been reported to have a variety of mild ventilatory defects and decreased alveolar-capillary diffusion gradients; thus subclinical

pulmonary involvement may be more frequent that is appreciated. In some patients influenza provokes an obstructive bronchitis (or bronchiolitis) and an asthmatic syndrome expressed in marked expiratory dyspnea, copious whistling and moist non-resonant rales and emphysema. There are also marked symptoms of disturbed gaseous exchange.

Such signs as dyspnea, hyperpnea, cyanosis, diffuse rales, changing of sputum from mucous to purulent and signs of consolidation in lungs are indicative of pulmonary complications. Toxic signs in influenza also provoke marked changes of cardio-vascular system. A brief period of hypertension is followed by a fall of arterial pressure, tachycardia or bradycardia, diminished heart sounds and sometimes by cyanosis. Collapse occurs in severe cases.

Dynamic of illness. A rapid temperature rise is generally followed by a gradual defervescence over a 2-3 days period, although, on occasion, fever may last for a 4-5 days. Respiratory symptoms last longer (for 5-10 days and longer).

Clinical classification of Influenza

I. Typical forms
   1. Mild course;
   2. Moderate course;
   3. Severe course

II. Atypical forms
   1. Acatarrhal form;
   2. Afebrile form;
   3. Hypertoxic form:
      - cerebral form (edema of the brain);
      - pulmonary form (acute primary influenza hemorrhagic pneumonia or hemorrhagic edema of the lung or respiratory distress syndrome of adult – RDSA)

The spectrum of clinical presentations of influenza is wide, ranging from a mild, afebrile respiratory illness similar to the common cold (with either gradual or abrupt onset) to severe prostration with relatively few respiratory signs and symptoms.

Hypertoxic forms are the least common but most severe. *Cerebral form* of influenza usually develops abrupt onset with high temperature, which progresses to hyperthermia (higher than 39,5˚C), and signs of toxicosis. Adynamia, prostration, early intracranial syndrome with progressive frontal headache followed by vomiting of central origin is typical. Thereafter psychomotor excitation, disorders of consciousness (from stupor to comatose state) and convulsions, seizures appear. Slight neck rigidity, arterial hypertension, tachycardia and tachypnea and few respiratory signs are registered. Only immediate help may stop progressing of edema of the brain, in other cases jamming of brain steam by cerebellum in foramen occipital magnum results in breath and heart arrest. *Primary influenza viral*

pneumonia presents as acute influenza that does not resolve but instead progresses with persistent fever, dyspnea, and eventual cyanosis. Sputum production is generally scanty, but the sputum can contain blood. Few physical signs may be evident early in the illness. In more advanced cases, diffuse rales of different caliber may be noted, and chest x-ray finding consistent with diffuse interstitial infiltrates. In such cases, arterial blood-gas demonstrations show marked hypoxia; cyanosis, dyspnea progresses, sputum became more abundant and bloody; hemodynamic disorders also progress up to shock. All these clinical features demonstrate development of hemorrhagic edema of the lung. Such form of illness has a predilection for individuals with cardiac disease, particularly those with mitral stenosis, but also has been reported in otherwise healthy young adults as well as in older individuals with chronic pulmonary disorders. In some epidemics of influenza, pregnancy increased the risk of primary influenza pneumonia.

Criteria of influenza severity.

- Hyperthermia (temperature higher than 39.5˚C).
- Presence of hemorrhagic syndrome.
- Marked intracranial syndrome (intensive frontal headache, vomiting, convulsions, psycho-motor excitation, disorders of consciousness).
- Hemodynamic disorders (dizziness, faints, orthostatic hypotension, tachycardia).
- Presence of dyspnea.

Complications. Severe forms of disease may produce collapse and infectious toxic shock; development of DIC syndrome can cause severe bleedings (nasal, gastrointestinal, uterine, hemorrhages into adrenal glands).

The most common complication of influenza is secondary bacterial pneumonia. It usually follows acute period of influenza (on the 5-6 days of disease), but when the disease is severe, complications occur earlier. Improvement of the patient's condition over 2-3 days is followed by reappearance of fever along with clinical signs and symptoms of bacterial pneumonia, including cough, production of purulent sputum and physical and x-ray signs of consolidation. The most common bacterial pathogens in this setting are Streptococcus pneumoniae, Staphylococcus aureus, and Haemophylus influenzae organisms that can colonize nasopharynx and that cause infection in the bronchopulmonary system. Secondary bacterial pneumonia occurs most frequently in high-risk individuals with chronic bronchitis or pneumonia and cardiac diseases and in elderly individuals. It is the rule that when disease is more severe, complications occur earlier (even on the 2-3 day of disease).

Other pulmonary complications associated with influenza include acute purulent obstructive bronchitis or worsening of chronic obstructive pulmonary disease and exacerbation of chronic bronchitis and asthma. In children and in some adults influenza infection may present as croup.

Among other complications, sinusitis, tonsillitis, otitis as well as extrapulmonary complications such as toxic myocarditis, ganglionitis, arachnoiditis, encephalitis mono- and polyneuritis, transverse myelitis and Guillain-Barre syndrome have been reported during influenza.

DIAGNOSIS

Laboratory diagnosis is accomplished during acute influenza (the first 2-3 day of disease) by isolation of virus from throat swabs, nasopharyngeal washes or sputum. Virus usually is detected in tissue culture or is found in the amniotic cavity of chick embryos within 48 to 72 h after inoculation. Viral antigen may be detected somewhat earlier by immunofluorescent (IF) techniques in tissue culture or directly in exfoliated nasal cells obtained by washings (express-test). The type of influenza virus (A or B) may be determined by either IF or indirect hemagglutination (IHA) techniques, and the haemagglutinin subtype of influenza A virus (H1, H2, or H3) may be identified by IHA with use of subtype-specific antisera.

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

Other laboratory tests are generally not helpful in making a specific diagnosis of influenza virus infection. Leukocyte counts are variable, frequently being low early in illness and normal later. Lymphomonocytosis is common. Severe leukopenia has been detected in overwhelming viral infection, while leukocytosis with more than 15 000 cells per microliter raises the suspicion of secondary bacterial infection.

Differential diagnosis. On clinical grounds alone, an individual case of influenza may be difficult to differentiate from acute viral respiratory diseases caused by any of a variety of respiratory viruses or by *Mycoplasma pneumoniae*. Severe streptococcal pharyngitis or pneumonia may mimic influenza, although bacterial pneumonia generally does not run a self-limited course. Purulent sputum in which a bacterial pathogen can be detected by Gram’s staining is an important diagnostic feature in bacterial pneumonia. The fact that influenza occurs in characteristic outbreaks during the winter month’s nay facilitate a clinical diagnosis. When local health authorities indicate that influenza is present in community, an acute febrile respiratory illness can be attributed to influenza with a high degree of certainty, particularly if the typical features of abrupt onset and toxic symptoms are present.

TREATMENT

Up to 70-th years of XX century specific antiviral therapy was not elaborated. Amantadine and rimantadine were the first antiviral drugs to be used for treatment of influenza. These drugs are active only against influenza A viruses. If began within 48 h of the onset of illness, treatment with amantadine and rimantadine reduces the

duration of systemic and respiratory symptoms of influenza by approximately 50% percent. In adults the usual dose of these drugs is 150 (50 mg trice a day) or 200 mg/d for 3 to 7 days. In case of severe influenza rimantadine is given on the 1-st day of disease 300 mg/d, on the 2-d – 200 mg/d and from the 3-d day – 200 or 150 mg/d. Rimantadine has not been approved for treatment of influenza A in children.

Ribavirin, a nucleoside analogue with activity against a variety of viral agents has been reported to be effective against both influenza A and influenza B virus infections when administered as an aerosol or parenterally.

For today new drugs, effective against influenza infection caused with both viruses A and B, are known, but these drugs similar to rimantadine are effective if began within 48 h of the onset of disease. Zinamivir, an inhibitor of neuraminidase is effective when administered as an aerosol or parenterally. And only Oseltamivir carboxilate (Tamiflu) is used orally, in dose 75 to 150 mg/d for 3 to 5 days.

Beside of specific antiviral drugs interferons and different inductors of production of endogenous interferon are widely used for treatment of influenza. Interferon has nonspecific activity against a variety of viral agents, so both interferons and inductors of endogenous interferon production may be used for treatment of influenza A and B infections, numerous acute viral respiratory diseases and different other illnesses of viral origin. All these drugs also are effective when began within 48 h of the onset of disease. Leukocyte human interferon (consist 360 IU/ml), reaferone, realdirone, grippoferone (consist up to 10 000 IU/ml) usually are administered intranasally in droplets. Among inductors of endogenous interferon the most known are arbidole and amixin. Arbidole usually is used in dose 200 mg (2 tablets) trice a day for 3 to 7 days. Amixin is administered on the 1-st day of disease in dose 250 mg (2 tablets), on the 2-d day – 125 mg, and from the 3-d day of disease – 125 mg every other day.

Pathogenic treatment includes administration of antiphlogistic remedies, such as acetaminophen or salicylates, drugs, action of which is directed on decreasing of vessel's permeability (antihistamines, some vitamins and so on). A variant of compounds of such drugs is antigrippin which consist of 500 mg of acetylsalicylic acid, 25 mg of dimedrol, 200 mg of rutin, 300 mg of ascorbic acid and 500 mg of calcium gluconat. Later on similar compounds were synthesized. Among them Coldact (capsules, consisting of 8mg of chlorfeniramine maleate, 50 mg of phenilproramine hydrochloride; tablets of Coldrex**,** consisting of 500 mg of paracetamol, 5 mg of phenylephrine hydrochloride, 20 mg of terpine hydrate, 30 mg of ascorbic acid and 25 mg of codeine; Coldrex-Hotrem, consisting of 750 mg of paracetamol, 10 mg of phenylephrine hydrochloride and 60 mg of ascorbic acid; Rinza, each tablet of which consist of 500 mg of paracetamol, 30 mg of caffeine, 10 mg of phenylephrine hydrochloride and 2 mg of chlorfeniramine maleate and other of similar containing.

Symptomatic treatment includes intranasal droplets with vasoconstrictor effect (galasoline, sanorine, phormasoline, 1% naphthizine and others. Codeine containing compounds or tusuprex and glauvent may be employed if the cough is particularly troublesome. When cough become moist expectorators are administered. Patients should be advised to rest and maintain hydration during acute period of disease and should return to full activity only gradually after the illness has resolved, particularly if the illness has been severe. Antibiotics usually are not used for treatment of uncomplicated influenza of mild or moderate form of disease.

Treatment of hypertoxic forms of influenza includes detoxication with infusion of saline solutions, solutions of glucose and colloids. In case of cerebral forms of influenza steroids have to be administered (1 to 2 mg/kg and more of prednisolone), diuretics and antispasmodic drugs. Therapy for primary influenza pneumonia is directed at maintaining oxygenation and is most appropriately undertaken in an intensive care unit, with aggressive respiratory and hemodynamic support as needed. Glucocorticoids and antibiotics for prevention of secondary bacterial superinfection also are administered. Bypass membrane oxygenators have been employed in this setting with variable results. When respiratory distress syndrome progresses, fluid must be administered cautiously, with close monitoring of blood gases and hemodynamic function.

Antibacterial drugs should be reserved for the therapy of bacterial complications of influenza, such as secondary bacterial pneumonia. Gram's staining and culture of appropriate specimens of respiratory secretions, such as sputum or tracheal aspirates, should guide the choice of antibiotics. If the etiology of a case of bacterial pneumonia is unclear form an examination of respiratory secretions, empirical antibiotics effective against the most common bacterial pathogens in this setting (S. pneumoniae, S aureus, H. influenzae, M. pneumoniae) should be selected.

PREVENTION

The major public health measure for prevention of influenza has been the use of inactivated influenza vaccines derived from influenza A (H1N1 and H3N2) and B viruses that circulated during the previous influenza season. If the vaccine viruses and the currently circulating viruses are closely related, 50 to 80% protection against influenza would be expected. Presently available vaccines ("Influvac", "Fluorix", "Vaxigripp", "Inflexal" and others) have been highly purified and are associated with few reactions. An influenza virus can produce an epidemic only if the people exposed to it lack adequate immunity. Since the influenza viruses have many strains, including evolving new strains, infection with one type does not preclude infection with another not previously encountered. For this reason, a new flu vaccine is required every year. Even with this annually updated approach to prevention, there are practical problems that limit its effectiveness. Vaccine against many influenza variants can take as long as 6 months to produce, not including tests for safety, and

size of the population to be vaccinated also poses enormous problems of distribution and administration. These are among the factors limiting the effectiveness of a vaccine in prevention the outbreak and spread of pandemic influenza virus.

In the case of H5N1, there is no currently available vaccine for humans. While there is an H5N1 vaccine for poultry, some researchers' fear that industry-wide use of this vaccine might cause the fowl to become a reservoir for the virus, because vaccinated chickens will develop increased resistant and furthermore show no signs of sickness. The virus contained within a vaccinated chicken could also spread to other chickens, to other poultry, and even to humans, thus increasing the risk for an influenza epidemic. The study of avian H5N1 virus in vaccinated Mexican chickens demonstrated that the virus underwent antigenic drift away from the vaccine strain, thus underscoring the risk of vaccine use in the evolution of avian influenza virus. However, the World Health Organization has encouraged the use of the human flu vaccine (those that prevent H1-3, N1-2 subtypes), especially among those in close contact with poultry, in order to prevent a co-infection by H5N1 and normal human flu virus. This policy has aimed at preventing humans from providing a "mixing vessel" for H5N1 to evolve into a more virulent strain that can be transmitted from human to human.

For prevention of influenza may be used inductors of endogenous interferon.. High level of interferon, created in organism under effect of these drugs has nonspecific antiviral effect and prevents entering of any virus into susceptible cells preventing in such way viral infection. Inductors of Interferon have to be administered during all epidemic period. Arbidole is used in dose 100 mg/d and amixin is used in dose 125 mg 1 time a week. It is reported about prophylactic effect of rimantadine administered in dose 50 mg/d during all epidemic period.

Beside of vaccination and using of drug for prophylaxis common prophylactic measures also are effective.

PARAINFLUENZA

DEFINITION Parainfluenza viruses are ubiquitous and cause common respiratory illnesses in persons of all ages. They are major pathogens of severe respiratory tract diseases in infants and young children.

ETIOLOGY

R. Chanock firstly discovered parainfluenza viruses in 1956. These viruses belong to family Paramyxoviridae. The morphology of Paramixoviridae resembles that of influenza viruses, but paramyxoviruses are larger (150-300 nm in diameter). In contrast to genome of orthomyxoviruses, it is not segmented and this negates any opportunity for frequent reassortment. Parainfluenza virus has haemagglutinin (H) and fusion protein (F) antigens. All members of paramyxovirus grope are antigenically stable. There are 4 serotypes of Parainfluenza viruses: PI-1(includes 2

subtypes: Sendi and HA-2), PI-2 (CA - croup associated virus and monkey PI), PI-3 (includes human' and caw' subtypes), PI - 4 (subtypes A and B). Of the four serotypes of parainfluenza viruses able to infect humans, only the first three are associated with severe disease. Virus is susceptible to drying, may be kept in home temperature for 3 h.

EPIDEMIOLOGY

Disease is widespread and account about 10% of all cases of AVRD. The sources of infection are ill humans. Virus is discharged from patients for 3 to 10 days and is transmitted by direct person-to-person contact or by air-droplet way. Morbidity has seasonal character (autumn, winter for PI-1 and PI-2, spring for PI-3).

PATHOGENESIS

The common scheme of parainfluenza pathogenesis is similar to influenza one. Target cells appear to be ciliated columnar epithelial cells of respiratory tract. Viraemia is short and uncommon. The infection may involve only nose and throat, resulting in harmless "common cold" syndrome. Infection may be more extensive and, especially with types 1 and 2, involve the larynx and upper trachea, resulting in croup. Croup is characterized by respiratory obstruction due to swelling of larynx and related structures. The infection may spread deeper to the lower trachea and bronchi, culminating in pneumonia or bronchiolitis, especially with type 3.

Primarily infection tends to be severe and generally occur during the first 5 years of life. Reinfection is common but usually causes only mild, afebrile upper respiratory infection. Antibodies from previous infection do not confer absolute protection against reinfection but do modify the cause of ensuing illness.

CLINICAL MANIFESTATIONS

Incubation period is 3-6 days. The disease in adults is characterized with gradual onset, and development of rhinitis and pharyngitis; in most patients signs of laryngitis are noted. Other parts of respiratory tract may also be involved (rhino-laryngo-tracheitis, laryngo-tracheo-bronchitis). Temperature is normal or subfebrile and lasts for 1-8 (sometimes up to 14) days. Signs of intoxication are mild. Disease is severe in children and may range from laryngo-tracheitis and croup (serotypes 1 or 2) to bronchiolitis and pneumonia (serotype 3).

DIAGNOSIS

Total blood count usually is normal. Viral isolation from appropriate specimens by culturing of virus on kidney tissue of humans or monkeys may be used. For express diagnosis fluorescent antibody test is recommended. FAT (express test). Serological testing is retrospective and extremely difficult. Increasing of titer in IHAT or CFT in 4 and more times in second sera is confirmative for diagnosis.

TREATMENT

Inductors of endogenous interferon, pathogenic and symptomatic treatment may be administered. Ribavirin shows promise of being beneficial when delivered by

small-particle aerosol.

PREVENTION

Specific prevention has not been elaborated.

RESPIRATORY-SYNCYTIAL INFECTION

DEFINITION *Respiratory-syncytial (RS) virus is the most important cause of lower respiratory tract illness in infants and young children, usually, outranking all other microbial pathogens as the cause of bronchiolitis and pneumonia in infants less than 1 year of age. RS-virus accounts for about half of cases of bronchiolitis and one forth of pneumonia in infants.*

ETIOLOGY

RS-virus was first discovered n 1956 by Morris. It belongs to family Paramixoviridae, the genus Pneumovirus and has 1 type and 2 serotypes (Long and Randall). Virus contains RNA, has neither H nor N antigen. It's envelop contains 2 glycoproteins: F protein and GP protein; the last one help to bind virus to susceptible cells. Sizes of viruses are average 200-300 nm. Virus is cultivated on the lung tissue of young mammals or human embryos.

EPIDEMIOLOGY

Disease is widespread and accounts about 10-13% of all cases of ARVD. Season: cold time of the year. Severe disease predominates in newborns, young children and old patients. RS-infection is the problem in pediatric departments as nosocomial infection. The sources of infection are ill humans. Virus is discharged from the patients from the 3 to 8 days of disease and, rarely, up to 3 weeks. RS-virus is transmitted via large droplets, so spread can occur both air-droplets way and by contact with contaminated hands and surfaces. Virus is not stable, it may be kept on the skin nearly 20-25 min. Drying or heating up 55˚C kill virus for 5 min.

PATHOGENESIS

Viral replication occurs initially in epithelial cells of nasopharynx. F antigen (fusion protein) is responsible for cell-to-cell fusion, which permit direct viral spread to lower pars of respiratory tract. This phenomenon causes formation of large syncytia (giant cells), which are characteristic for RS-infection. Viral shedding may persist for 1-3 weeks. Viraemia has not been detected. In intact immune system seems to be important to clear an infection, as patients with impaired cell-mediated immunity may become persistently infected with RS-virus and shed virus for months. In the development of bronchiolitis immunopathologic processes and immediate hypersensitivity to virus-IgE interaction may be involved. At autopsy, the lung of children who have dead from RS-infection, show extensive bronchopneumonia, accompanied by sloughing of bronchiolar epithelium and infiltration with monocytes and other immunologic cells. There is abundant mucus secretion. These processes

result in obstruction of small bronchioles.

CLINICAL MANIFESTATIONS

Incubation period of illness is 4-5 days. Temperature may be subfebrile in adults but is usually high in children, and lasts for 3-5 days. The spectrum of respiratory symptoms range from nasopharyngitis in adults to bronchitis, bronchiolitis and pneumonia in young children. Disease may be mild, moderate or severe. Progression of symptoms may be rapid, culminating in death. Reinfection is common in both children and adults and the infection in these cases is usually limited to the upper respiratory tract, resembling cold.

Criteria of diagnosis: cold time of the year, contact with ill children; rhinitis and involvement of lower parts of respiratory tract in patients with chronic diseases; severe bronchitis and bronchiolitis in young children; whistle rales over the lung; subfebrile temperature; X-ray examination show bronchitis, interstitial pneumonia, BC is normal.

Complications: bronchoobstructive respiratory insufficiency, pneumonia, purulent otitis, syndrome of sudden death in newborns, meningitis, encephalitis in children. Mortality rate – 0,5%, in immunocompromised children – 20-25%.

DIAGNOSIS

Tactic of laboratory investigation is similar to that in parainfluenza.

TREATMENT

Aerosols of ribavirin; inductors of endogenous interferon (lesser effective), pathogenic and symptomatic treatment are used. Treatment of severe forms of RS-infection depends primarily on supportive care (e.g. removal of secretions, inhalations of oxygen).

PREVENTION

To the date attempts to develop effective and harmless vaccine have not been successful.

ADENOVIRAL INFECTION

DEFINITION *Adenovirus infection is spread in all parts of the world. Adenoviruses may infect cells of different tissues and systems and the disease accordingly is characterized with wide spectrum of clinical manifestations.*

ETIOLOGY

Adenovirus was firstly isolated from tonsils and adenoids and described by W. Rowe in 1953. Adenoviruses belong to family Parvoviridae, genus Adenoviridae. Virus contains DNA, has 2 types – M (Mastadenovirus – viruses of mammals) and A (Aviadenoviruses – viruses of birds). Viruses of animals are not pathogenic for humans. There are about 44 humans' serotypes, among them the most pathogenic are the 3, 4, 7, 8, 14, 21 and 41. Size of viruses' average 70-90 nm. Virus has

ichosahedral shape appearance and 3 antigens: A, group - specific antigen; B – toxic one which suppresses production of interferon and increases the severity of disease; C – typospecific antigen. Virus has ability to long persisting in lymphatic tissue and to oncogenic transformation. Among the target cells there are ciliated columnar epithelium cells, cells of conjunctiva, intestinal epithelium, lymphatic tissue, and CNS.

EPIDEMIOLOGY

Disease is widespread and is present year-round. The sources of infection are ill persons. Virus is discharged from the patients with nasal, pharyngeal, conjunctival secretion, feces for a long time – up to 20-25 days of disease and more. The main routes of transmission are air-droplet and fecal-oral, but disease also may be transmitted by contaminated fomites. The disease may cause family outbreaks, predominantly enteric. Infection rates are highest among infants but siblings who introduce the infection into a household are more effective in spreading the disease than are infants. While adenoviruses cause only 2-5% of all respiratory illness in the general population, respiratory disease due to types 3, 4, 7, 14 and 21 is common among military recruits. Eye infection can be transmitted in several ways, but hand-to-eye transfer is particularly important. Outbreaks of swimming-pool conjunctivitis are presumably waterborne, usually occur in summer and are commonly caused by types 3, 7 and 8. Adenoviruses may be found in transplant patients. Types 34 and 35 are found most often in renal transplant recipients and in the urine of patients with AIDS.

Virus is stable; it may be kept at home temperature up to 14 days, at -40˚C up to 70 days.

PATHOGENESIS

Adenoviruses can replicate and produce disease in the eye and in the respiratory, gastrointestinal and urinary tract. They usually do not spread beyond the regional lymph nodes, but sometime viraemia is preset and it may be protracted. Many adenovirus infections are subclinical; and virus may persist in the host for months. In contrast to most respiratory agents, the adenoviruses induce effective and long lasting immunity against reinfection.

CLINICAL MANIFESTATIONS

Incubation period is 2-5 days. Temperature is usually febrile, lasts for 3-5 days, some times for 14 days and more. Other systemic symptoms (chills, headache, malaise and myalgia) also are present Different syndromes of respiratory infection have been linked to adenoviruses. Disease may be mild, moderate or severe.

Adenoviral AVRD: (rhinitis, pharyngitis, tonsillitis, tracheobronchitis). This syndrome usually includes cough, stuffy nose and sore throat. Mucosal membrane of oropharyngeal region is edematous and hyperemic. Regional lymph nodes are slightly enlarged and painful.

Adenoviral pneumonia is a complication of acute respiratory disease in military recruits. Children may also develop severe and sometimes fatal pneumonia following infection with common types, particularly with types 3 and 7. Adenoviral pneumonia has been reported to have an 8-10% mortality rate in the very young.

Pharyngoconjunctival fever. There are the symptoms of acute febrile pharyngitis and conjunctivitis also is present. This form of disease tends to occur in outbreaks, such as at children's summer camps and swimming-pool conjunctivitis. Complete recovery with no lasting sequelae is the common outcome.

Epidemic kerato-conjunctivitis is the more serious disease. It is highly contagious and characterized by acute conjunctivitis, with enlarged tender and painful preauricular nodes, followed by keratitis that leaves round subepithelial opacities in the cornea. It is caused by types 8, 19 and 37.

Adenoviral gastroenteritis. Repeated vomiting, watery diarrhea usually are present. Adenoviruses are abundantly present in diarrheic stool. This form may cause 5-15% of viral gastroenteritis in young children up to 2 years

Hemorrhagic cystitis. It is infrequent form of disease.

Other forms. Immunocompromised patients may suffer from adenoviral infection. The most common problem, caused with these infections in transplant patients is severe pneumonia which may be fatal (types 1-7). Patients, receiving liver transplants, may develop adenoviral hepatitis in the allograft.

Criteria of diagnosis: – polymorphous clinical signs; exudative component of local inflammation; long temperature; involvement of lymph nodes, tonsils; involvement of conjunctiva; diarrhea.

Complications: bacterial pneumonia, otitis, streptococcal tonsillitis, sinusitis.

DIAGNOSIS

Cultivating of virus from nasal, conjunctival, pharyngeal secretion, feces and blood. 2. FAT (express method). 3. Serological tests are also used.

TREATMENT

Inductors of endogenous interferon, pathogenic and symptomatic treatment may be used.

PREVENTION

Attempts to control adenoviral infection in military have focused on vaccines. Live attenuated virus, grown in human diploid cells, is encased in gelatin-coated capsules are given orally. Such live-virus vaccines against types 4 and 7 are licensed in USA but are recommended only for immunization of military population. In addition to vaccination, other methods of prevention and control are available. The risk of waterborne outbreaks of conjunctivitis can be minimized by chlorination of swimming pools and wastewater. Rigid asepsis during eye examination, coupled with adequate sterilization of equipment, is essential for control of epidemic kerato-conjunctivitis.

RHINOVIRAL INFECTION

DEFINITION *Rhinoviral infection is the main cause of common cold.*

ETIOLOGY

W. Price and W. Pelon firstly isolated and described virus in 1956-57 years. Rhinoviruses belong to family Picornaviridae, genus Rhinoviridae, which includes more than 110 serotypes and subtype 1 A. Some are cross-reacting. Antigenic drift is possible. There are 3 types of viruses: H-(human) which is cultured on the human tissue; M (monkey) – is cultured on the monkey tissue and O, which is cultured on tissue from ciliated epithelium cells.

EPIDEMIOLOGY

Rhinoviral infection is widespread disease, which account about 40% of all cases of ARVD. Infection more frequently is registered in spring and autumn. The sources of infection are ill persons. Virus is discharged from the patients mostly on the 2-3 days of disease and up to 2 weeks. The infection is transmitted through air-droplet way and close contact by large droplets. Members of isolated communities form highly susceptible groups. Cold in children spread more easily than do colds in adults. Virus is susceptible to drying, may be kept on the skin average 3 h.

PATHOGENESIS

The virus enters via the upper respiratory tract. Optimal temperature for replication of viruses is 33-35˚C; so maximal replication took place in nose. Viraemia is absent because temperature of 37˚C kills virus. Histopathologic changes are limited to submucosa and surface epithelium of nasal cavity. These include engorgement of blood vessels, edema, mild cellular infiltration and desquamation of surface epithelium. Nasal secretion increases in quantity and protein concentration.

CLINICAL MANIFESTATIONS

Incubation period is 1-6 days. Temperature is normal or subfebrile for 2-3 days. Signs of intoxication are mild. Respiratory signs: sneezing, difficulties in nasal breathing, intensive rhinorhea, and irritation of the nostrils, slight sore throat. Cough appears in patients with exacerbation of chronic pathologic process in bronchi or lung.

Complications: otitis, sinusitis, rarely bronchitis and pneumonia.

DIAGNOSIS

WBC is normal. Virus may be cultured on tissue media. Serological tests (NT, CFT) are retrospective. Four fold increasing of titer in second sera is confirmative for diagnosis. As express method IFT may be used.

TREATMENT

No specific treatment is available.

PREVENTION

The development of a potent rhinovirus vaccine is unlikely because of the many serotypes causing colds.

HERPES-VIRAL INFECTIONS

HERPES SIMPLEX VIRUSES

DEFINITION ***Herpes simplex virus infection (HSV-1, HSV-2) are viral diseases produces a variety of clinical forms involving mucocutaneous surfaces, the central nervous system, and in some cases – visceral organs.***

ETIOLOGY

The HSV has linear genome in double-stranded DNA molecule. It encodes more 90 transcription units with 84 identified proteins. The genomic structures of the two HSV subtypes are similar, and the overall sequence homology between HSV-1 and HSV-2 is 50%. Many type-specific regions unique to HSV-1 and HSV-2 proteins do exist, however, and a number of them appear to be important in host immunity. These type-specific regions have been used to develop serologic assays that distinguish between the two viral subtypes.

The variability of nucleotide sequences from clinical strains of HSV-1 and HSV-2 is such that HSV isolates obtained from two individuals can be differentiated by restriction enzyme patterns or genomic sequences unless the isolates are from epidemiologically related sources, such as sexual partners, mother-infant pairs, or persons involved in a common-source outbreak.

The viral genome is packaged in a regular icosahedral protein capsid composed of 162 capsomers. The outer covering of the virus is a lipid-containing membrane (envelope) derived from modified cell membrane and acquired as the DNA-containing capsid buds through the inner nuclear membrane of the host cell. Viral replication has both nuclear and cytoplasmic phases. Attachment and fusion between the viral envelope and the cell membrane involve several ubiquitous heparin-like surface receptors. After fusion and entry, the nucleocapsid enters the cytoplasm and several viral proteins are released from the virion. Some of these viral proteins shut off host protein synthesis (by increasing cellular RNA degradation), while others "turn on" the transcription of early genes of HSV replication.

HSV infection of some neuronal cells does not result in cell death. Instead, viral genomes are maintained by the cell in a repressed state compatible with survival and normal activities of the cell, a condition called latency. Latency is associated with transcription of only a limited number of virus-encoded proteins. Subsequently, the viral genome may become activated; its activation results in the normal pattern of regulated viral gene expression, replication, and release of HSV. The release of virus from the neuron and its subsequent entry into epithelial cells result in viral replication and reappearance of virus on mucosal surfaces. This process is termed reactivation.

EPIDEMIOLOGY

Seroepidemiologic studies have documented HSV infections worldwide. Serologic assays with whole-virus antigen preparations, such as complement fixation,

neutralization, indirect immunofluorescence, passive hemagglutination, radioimmunoassay, and enzyme-linked immunosorbent assay (ELISA), are useful for differentiating uninfected (seronegative) persons from those with past HSV-1 or HSV-2 infection, but they do not reliably distinguish between the two viral subtypes. Serologic assays that identify antibodies to type-specific surface proteins (epitopes) of the two viral subtypes have been developed and can distinguish reliably between the human antibody responses to HSV-1 and HSV-2.

Infection with HSV-1 is acquired more frequently and earlier than infection with HSV-2. More than 90% of adults have antibodies to HSV-1 by the fifth decade of life. In populations of low socioeconomic status, most persons acquire HSV-1 infection before the third decade of life.

Antibodies to HSV-2 are not detected routinely until puberty. Antibody prevalence rates correlate with past sexual activity and vary greatly among different population groups. Serosurveys indicate that nearly 20% of the population in developed countries has antibodies to HSV-2. In most routine obstetric and family planning clinics, 25% of women have HSV-2 antibodies, although only 10% report a history of genital lesions. As many as 50% of heterosexual adults are attending sexually transmitted disease clinics have antibodies to HSV-2. A wide variety of serologic surveys have indicated a similar or even higher seroprevalence of HSV-2 in most parts of Europe, Central and South America, and Africa. Antibody prevalence rates average 5% higher among women than among men.

HSV infections occur throughout the year. Transmission can result from contact with persons with active ulcerative lesions or with persons without clinical manifestations of infection who are shedding HSV or on whose mucosal surfaces the virus is replicating. Potential exposure to HSV from sexual or other close contact (kissing, sharing of glasses or silverware) is common, and these high rates of mucosal reactivation are consistent with the continuing spread and high seroprevalence of HSV infections worldwide.

PATHOGENESIS

Exposure to HSV at mucosal surfaces or abraded skin sites permits entry of the virus and initiation of its replication in cells of the epidermis and dermis. HSV infections are usually acquired subclinically. Both clinical acquisition and subclinical acquisition are associated with sufficient viral replication to permit infection of either sensory or autonomic nerve endings. On entry into the neuronal cell, the nucleocapsid – is transported intraaxonally to the nerve cell bodies in ganglia. The interval from inoculation of virus in peripheral tissue to spread to the ganglia is unknown.

During the initial phase of infection, viral replication occurs in ganglia and contiguous neural tissue. Virus then spreads to other mucosal skin surfaces through centrifugal migration of infectious virions via peripheral sensory nerves. This mode of spread helps explain the large surface area involved, the high frequency of new

lesions distant from the initial crop of vesicles that is characteristic in patients with primary genital or oral-labial HSV infection, and the recovery of virus from neural tissue distant from neurons innervating the inoculation site. Contiguous spread of locally inoculated virus also may take place and allow further mucosal extension of disease.

Host responses to infection with HSV influence the acquisition of disease, the severity of infection, resistance to the development of latency, the maintenance of latency, and the frequency of recurrences. Both antibody-mediated and cell-mediated reactions are clinically important. Immunocompromised patients with defects in cell-mediated immunity experience more severe and more extensive HSV infections than those with deficits in humoral immunity, such as agammaglobulinemia. Experimental ablation of lymphocytes indicates that T cells play a major role in preventing lethal disseminated disease, although antibodies help reduce virus titers in neural tissue.

The surface viral glycoproteins have been shown to be antigens recognized by antibodies mediating neutralization and immune-mediated cytolysis (antibody-dependent cell-mediated cytotoxicity). Monoclonal antibodies specific for each of the known viral glycoproteins have, in experimental infections, conferred protection against subsequent neurologic disease or ganglionic latency. However, the use of subunit glycoprotein vaccines in humans has been, up to the present, only partially successful in reducing acquisition of infection. Multiple cell populations, including natural killer cells, macrophages, and a variety of T lymphocytes, play a role in host defenses against HSV infections, as do lymphokines generated by T lymphocytes.

Maximum protection usually requires the activation of multiple T cell subpopulations, including cytotoxic T cells and T cells responsible for delayed hypersensitivity. The latter cells may confer protection by the antigen-stimulated release of lymphokines (e.g., interferons), which may have a direct antiviral effect and may activate and enhance a variety of specific and nonspecific effector cells. Increasing evidence suggests that HSV-specific CD8+ T cell responses are critical for clearance of virus from lesions. In addition, immunosuppressed patients with frequent and prolonged HSV lesions have fewer functional CD8+ T cells directed at HSV. The HSV virion contains a variety of genes that are directed at the inhibition of host responses. However, persons with prior HSV-1 infection who acquire HSV-2 appear to have a higher frequency of subclinical acquisition. These data suggest that type-specific immune responses are central to the control of HSV infection.

CLINICAL MANIFESTATIONS

The incubation period ranges from 1 to 26 days (median, 6 to 8 days). Both viral subtypes can cause genital and oral-facial infections, and the infections caused by the two subtypes are clinically indistinguishable. However, the frequency of reactivation of infection is influenced by anatomical site and virus type. Genital HSV-2 infection is twice as likely to reactivate and recurs 8 to 10 times more

frequently than genital HSV-1 infection. Conversely, oral-labial HSV-1 infection recurs more frequently than oral-labial HSV-2 infection. Asymptomatic shedding rates follow the same pattern.

Oral-Facial Infections

Gingivostomatitis and pharyngitis are the most frequent clinical manifestations of first-episode HSV-1 infection, while recurrent herpes labialis is the most frequent clinical manifestation of reactivation HSV infection. HSV pharyngitis and gingivostomatitis usually result from primary infection and are most commonly seen in children and young adults. Clinical symptoms and signs, which include fever, malaise, myalgias, inability to eat, irritability, and cervical adenopathy, may last from 3 to 14 days. Lesions may involve the hard and soft palate, gingiva, tongue, lip, and facial area. HSV-1 or HSV-2 infection of the pharynx usually results in exudative or ulcerative lesions of the posterior pharynx and/or tonsillar pillars. Lesions of the tongue, buccal mucosa, or gingiva may occur later in the course in one-third of cases. Fever lasting from 2 to 7 days and cervical adenopathy are common. It can be difficult to differentiate HSV pharyngitis clinically from bacterial pharyngitis, Mycoplasma pneumoniae infections, and pharyngeal ulcerations of noninfectious etiologies (e.g., Stevens-Johnson syndrome). No substantial evidence suggests that reactivation oral-labial HSV infection is associated with symptomatic recurrent pharyngitis.

Reactivation of HSV from the trigeminal ganglia may be associated with asymptomatic virus excretion in the saliva, development of intraoral mucosal ulcerations, or herpetic ulcerations on the vermilion border of the lip or external facial skin. About 50 to 70% of seropositive patients undergoing trigeminal nerve root decompression and 10 to 15% of those undergoing dental extraction develop oral-labial HSV infection a median of 3 days after these procedures.

In immunosuppressed patients, infection may extend into mucosal and deep cutaneous layers. Friability, necrosis, bleeding, severe pain, and inability to eat or drink may result. The lesions of HSV mucositis are clinically similar to mucosal lesions caused by cytotoxic drug therapy, trauma, or fungal or bacterial infections. Persistent ulcerative HSV infections are among the most common infections in patients with AIDS. HSV and Candida infections often occur concurrently. Systemic antiviral therapy speeds the rate of healing and relieves the pain of mucosal HSV infections in immunosuppressed patients.

The frequency of HSV reactivation during the early phases of transplantation or induction chemotherapy is high (50 to 90%), and prophylactic systemic antiviral agents such as intravenous acyclovir or penciclovir are used to reduce reactivation rates. Patients with atopic eczema may also develop severe oral-facial HSV infections (eczema herpeticum), which may rapidly involve extensive areas of skin and occasionally disseminate to visceral organs. Extensive eczema herpeticum has

resolved promptly with the administration of intravenous acyclovir. Erythema multiform may also be associated with HSV infections some evidence suggests that HSV infection is the precipitating event in nearly 75% of cases of cutaneous erythema multiform. HSV antigen has been demonstrated both in circulatory immune complexes and in skin lesion biopsy samples from these cases. Patients with severe HSV-associated erythema multiform are candidates for chronic suppressive oral antiviral therapy.

Genital infections

First-episode primary genital herpes is characterized by fever, headache, malaise, and myalgias. Pain, itching, dysuria, vaginal and urethral discharge, and tender inguinal lymphadenopathy are the predominant local symptoms. Widely spaced bilateral lesions of the external genitalia are characteristic. Lesions may be present in varying stages, including vesicles, pustules, or painful erythematous ulcers. The cervix and urethra are involved in more 80% of women with first-episode infections. First episodes of genital herpes in patients who have had prior HSV-1 infection are associated with less frequent systemic symptoms and faster healing than primary genital herpes. The clinical courses of acute first-episode genital herpes among patients with HSV-1 and HSV-2 infections are similar. However, the recurrence rates of genital disease differ with the viral subtype: the 12-month recurrence rates among patients with first-episode HSV-2 and HSV-1 infections are about 90% and nearly 55%, respectively (median number of recurrences, 4 and less 1, respectively). Recurrence rates for genital HSV-2 infections vary greatly among individuals and over time within the same individual. HSV has been isolated from the urethra and urine of men and women without external genital lesions. A clear mucoid discharge and dysuria are characteristics of symptomatic HSV urethritis. HSV has been isolated from the urethra of 5% of women with the dysuria-frequency syndrome. Occasionally, HSV genital tract disease is manifested by endometritis and salpingitis in women and by prostatitis in men. About 15% of cases of HSV-2 acquisition are associated with these nonlesional clinical syndromes, such as aseptic meningitis, cervicitis, or urethritis.

Herpetic whitlow

Herpetic whitlow – HSV infection of the finger – may occur as a complication of primary oral or genital herpes by inoculation of virus through a break in the epidermal surface or by direct introduction of virus into the hand through occupational or some other type of exposure. Clinical signs and symptoms include the abrupt onset of edema, erythema, and localized tenderness of the infected finger. Vesicular or pustular lesions of the fingertip that are indistinguishable from lesions of pyogenic bacterial infection are seen. Fever, lymphadenitis, and epitrochlear and axillary lymphadenopathy are common. The infection may recur. Prompt diagnosis (to avoid unnecessary and potentially exacerbating surgical therapy and/or

transmission) is essential. Antiviral chemotherapy (to speed the healing of the process) is usually recommended.

Herpes gladiatorum

HSV may infect almost any area of skin. Mucocutaneous HSV infections of the thorax, ears, face, and hands have been described among wrestlers. Transmission of these infections is facilitated by trauma to the skin sustained during wrestling. Several recent outbreaks of this infection have illustrated the importance of prompt diagnosis and therapy, which are required to contain the spread of this infection.

Eye infections

HSV infection of the eye is the most frequent cause of corneal blindness in the United States. HSV keratitis presents with an acute onset of pain, blurring of vision, chemosis, conjunctivitis, and characteristic dendritic lesions of the cornea. Use of topical glucocorticoids may exacerbate symptoms and lead to involvement of deep structures of the eye. Debridement, topical antiviral treatment, and/or interferon therapy hastens healing. However, recurrences are common, and the deeper structures of the eye may sustain immunopathologic injury. Stromal keratitis due to HSV appears to be related to T cell–dependent destruction of deep corneal tissue. An HSV-1 epitope that is autoreactive with T cell–targeting corneal antigens has been postulated to be a factor in this infection. Chorioretinitis, usually a manifestation of disseminated HSV infection, may occur in neonates or in patients with HIV infection. HSV and VZV can cause acute necrotizing.

Central and peripheral nervous system infections

HSV accounts for 10 to 20% of all cases of sporadic viral encephalitis. Cases are distributed throughout the year, and the age distribution appears to be biphasic, with peaks at 5 to 30 and more 50 years of age. Subtype 1 virus causes more 95% of cases of HSV encephalitis.

The pathogenesis of HSV encephalitis varies. In children and young adults, primary HSV infection may result in encephalitis; presumably, exogenously acquired virus enters the CNS by neurotropic spread from the periphery via the olfactory bulb. However, most adults with HSV encephalitis have clinical or serologic evidence of mucocutaneous HSV-1 infection before the onset of the CNS symptoms. In about 25% of the cases examined, the HSV-1 strains from the oropharynx and brain tissue of the same patient differ; thus some cases may result from reinfection with another strain of HSV-1 that reaches the CNS.

The clinical hallmark of HSV encephalitis has been the acute onset of fever and focal neurologic symptoms and signs, especially in the temporal lobe. Clinical differentiation of HSV encephalitis from other viral encephalitides, focal infections, or noninfectious processes is difficult. The most sensitive noninvasive method for early diagnosis of HSV encephalitis is the demonstration of HSV DNA in cerebrospinal fluid (CSF) by PCR. Although titers of CSF and serum antibodies to

HSV increase in most cases of HSV encephalitis, they rarely do so earlier than 10 days into the illness and therefore, while useful retrospectively, are generally not helpful in establishing an early clinical diagnosis. Demonstration of HSV antigen, HSV DNA, or HSV replication in brain tissue obtained by biopsy is highly sensitive and has a low complication rate; examination of such tissue also provides the best opportunity to identify alternative, potentially treatable causes of encephalitis. Antiviral chemotherapy reduces the rate of death from HSV encephalitis. Intravenous acyclovir is more effective than vidarabine. Even with therapy, however, neurologic sequelae are frequent, especially in persons more 50 years of age. Most authorities recommend the administration of intravenous acyclovir to patients with presumed HSV encephalitis until the diagnosis is confirmed or an alternative diagnosis is made. Among proven cases of HSV encephalitis, intravenous therapy is usually recommended until HSV DNA levels in CSF are substantially reduced or at nearly undetectable levels.

HSV DNA has been detected in CSF from 3 to 15% of persons presenting to the hospital with aseptic meningitis. HSV meningitis, which is usually seen in association with primary genital HSV infection, is an acute, self-limited disease manifested by headache, fever, and mild photophobia and lasting from 2 to 7 days. Lymphocytic pleocytosis in the CSF is characteristic. Neurologic sequelae of HSV meningitis are rare. HSV is the most commonly identified cause of recurrent lymphocytic meningitis (Mollaret's meningitis). Demonstration of HSV antibodies in CSF or persistence of HSV DNA in CSF can establish the diagnosis. For persons with frequent recurrences of HSV meningitis, antiviral therapy has been successful in reducing the frequency of such episodes.

Autonomic nervous system dysfunction, especially of the sacral region, has been reported in association with both HSV and VZV infections. Numbness, tingling of the buttocks or perineal areas, urinary retention, constipation, CSF pleocytosis, and (in males) impotence may occur. Symptoms appear to resolve slowly over days to weeks. Occasionally, hypoesthesia and/or weakness of the lower extremities may persist for many months. Rarely, transverse myelitis manifested by a rapidly progressive symmetric paralysis of the lower extremities or a Guillain-Barré syndrome may follow HSV infection. Similarly, peripheral nervous system involvement (Bell's palsy) or cranial polyneuritis may also be related to reactivation of HSV-1 infection. Transitory hypoesthesia of the area of skin innervated by the trigeminal nerve and vestibular system dysfunction as measured by electronystagmography are the predominant signs of disease. Studies to determine whether antiviral chemotherapy may abort these signs or reduce their frequency and severity are unavailable.

Visceral infections

HSV infection of visceral organs usually results from viraemia, and multiple-

organ involvement is common. Occasionally, however, the clinical manifestations of HSV infection involve only the esophagus, lung, or liver. HSV esophagitis may result from direct extension of oral-pharyngeal HSV infection into the esophagus or may occur de novo by reactivation and spread of HSV to the esophageal mucosa via the vagus nerve. The predominant symptoms of HSV esophagitis are odynophagia, dysphagia, substernal pain, and weight loss. There are multiple oval ulcerations on an erythematous base with or without a patchy white pseudomembrane. The distal esophagus is most commonly involved. With extensive disease, diffuse friability may spread to the entire esophagus. Neither endoscopic nor barium examination can reliably differentiate HSV esophagitis from Candida esophagitis or from esophageal ulcerations due to thermal injury, radiation, or corrosives. Endoscopically obtained secretions for cytologic examination and culture provide the most useful material for diagnosis. Systemic antiviral chemotherapy usually reduces symptoms and heals esophageal ulcerations.

HSV pneumonitis is uncommon except in severely immunosuppressed patients and may result from extension of herpetic tracheobronchitis into lung parenchyma. Focal necrotizing pneumonitis usually ensues. Hematogenous dissemination of virus from sites of oral or genital mucocutaneous disease may also occur and produce bilateral interstitial pneumonitis. Bacterial, fungal, and parasitic pathogens are commonly present in HSV pneumonitis. The mortality rate from untreated HSV pneumonia in immunosuppressed patients is high (more 80%). HSV has also been isolated from the lower respiratory tract of persons with adult respiratory distress syndrome. However, the relationship between the isolation of HSV and the pathogenesis of this syndrome is unclear.

HSV is an uncommon cause of hepatitis in immunocompetent patients. HSV infection of the liver is associated with fever, abrupt elevations of bilirubin and serum aminotransferase levels, and leukopenia (less 4000 white blood cells per microliter). Disseminated intravascular coagulation may also develop.

Other reported complications of HSV infection include monarticular arthritis, adrenal necrosis, idiopathic thrombocytopenia, and glomerulonephritis.

DIAGNOSIS

Both clinical and laboratory criteria are useful for establishing the diagnosis of HSV infections. A clinical diagnosis can be made accurately when characteristic multiple vesicular lesions on an erythematous base are present. However, it is increasingly being recognized that herpetic ulcerations may clinically resemble skin ulcerations of other etiologies. Mucosal HSV infections may also present as urethritis or pharyngitis without cutaneous lesions. Thus, laboratory studies to confirm the diagnosis and to guide therapy are recommended.

HSV infection is best confirmed in the laboratory by isolation of the virus in tissue culture or by demonstration of HSV antigens or DNA in scrapings from

lesions. HSV causes a discernible cytopathic effect in a variety of cell culture systems, and this effect can be identified within 48 to 96 h after inoculation. Spin-amplified culture with subsequent staining for HSV antigen has shortened the time needed to identify HSV to <24 h. Increasingly, PCR is being used for the detection of HSV DNA, and several studies have shown this assay to be more sensitive than culture for detection of HSV in CSF and at mucosal sites.

Acute- and convalescent-phase serum can be useful in demonstrating seroconversion during primary HSV-1 or HSV-2 infection. However, only 5% of patients with recurrent mucocutaneous HSV infections have a fourfold or greater rise in titer of antibody to HSV in the interval between the collection of the first and second samples. Serologic assays, especially type-specific assays, should be used to identify asymptomatic carriers of HSV-1 or HSV-2 infection.

TREATMENT

Many aspects of mucocutaneous and visceral HSV infections are amenable to antiviral chemotherapy. For mucocutaneous infections, acyclovir and its congeners famciclovir and valacyclovir have been the mainstay of therapy. Several antiviral agents are available for topical use in HSV eye infections: idoxuridine, trifluorothymidine, topical vidarabine, and cidofovir. For HSV encephalitis and neonatal herpes, intravenous acyclovir is the treatment of choice.

All licensed antiviral agents for use against HSV inhibit the viral DNA polymerase. One class of drugs, typified by the drug acyclovir, is made up of substrates for the HSV enzyme thymidine kinase. Acyclovir, ganciclovir, famciclovir, and valacyclovir are all selectively phosphorylated to the monophosphate form in virus-infected cells. Cellular enzymes convert the monophosphate form of the drug to the triphosphate, which is then incorporated into the viral DNA chain.

Acyclovir is the most frequently used agent for the treatment of HSV infections and is available in intravenous, oral, and topical formulations. Valacyclovir is the valyl ester of acyclovir and offers greater bioavailability than acyclovir. Famciclovir, the oral formulation of penciclovir, is clinically effective in the treatment of a variety of HSV-1 and HSV-2 infections. Ganciclovir is active against both HSV-1 and HSV-2; however, it is more toxic than acyclovir, valacyclovir, and famciclovir and generally is not recommended for the treatment of HSV infections.

All three recommended compounds – acyclovir, valacyclovir, and famciclovir – have proven effective in shortening the duration of symptoms and lesions of mucocutaneous HSV infections in both immunocompromised and immunocompetent patients. Intravenous and oral formulations prevent reactivation of HSV in seropositive immunocompromised patients during induction chemotherapy or in the period immediately after bone marrow or solid organ transplantation. Chronic daily suppressive therapy reduces the frequency of reactivation disease among patients with frequent genital or oral-labial herpes. Only valacyclovir has been shown to

reduce transmission of HSV-2 infection between sexual partners.

Mucocutaneous HSV infections, infections in immunosuppressed patients:

Acute symptomatic first or recurrent episodes: IV acyclovir (5 mg/kg q8h) or oral acyclovir (400 mg qid), famciclovir (500 mg tid), or valacyclovir (500 mg bid). Treatment duration may vary from 7 to 14 days.

Suppression of reactivation disease: IV acyclovir (5 mg/kg q8h) or oral valacyclovir (500 mg bid) or acyclovir (400–800 mg 3–5 times per day) prevents recurrences during the 30-day period immediately after transplantation. Longer-term HSV suppression is often used for persons with continued immunosuppression. In bone marrow and renal transplant recipients, oral valacyclovir (2 g/d) is also effective in preventing cytomegalovirus infection. Oral valacyclovir at a dose of 4 g/d has been associated with thrombotic thrombocytopenic purpura after extended use in HIV-positive persons. In HIV-infected persons, oral famciclovir (500 mg bid) is effective in reducing clinical and subclinical reactivations of HSV-1 and HSV-2.

Genital herpes

First episodes: Oral acyclovir (200 mg 5 times per day or 400 mg tid), valacyclovir (1 g bid), or famciclovir (250 mg bid) for 10–14 days is effective. IV acyclovir (5 mg/kg q8h for 5 days) is given for severe disease or neurologic complications such as aseptic meningitis.

Symptomatic recurrent genital herpes: Oral acyclovir (200 mg 5 times per day for 5 days, 800 mg tid for 2 days), valacyclovir (500 mg bid for 3 or 5 days), or famciclovir (125 mg bid for 5 days) is effective in shortening lesion duration.

Suppression of recurrent genital herpes: Oral acyclovir (200-mg capsules tid or qid, 400 mg bid, or 800 mg qd), famciclovir (250 mg bid), or valacyclovir (500 mg or 1 g qd or 500 mg bid) prevents symptomatic reactivation. Persons with frequent reactivation but <9 episodes per year can take valacyclovir (500 mg PO daily); those with >9 episodes per year should take 1 g PO daily or 500 mg PO bid.

Oral-labial HSV infections:

First episode: Oral acyclovir (200 mg) is given 4 or 5 times per day. Oral famciclovir (250 mg bid) or valacyclovir (1 g bid) has been used clinically.

Recurrent episodes: Oral valacyclovir (1 g bid for 1 day or 500 mg bid for 3 days) is effective in reducing pain and speeding healing. Self-initiated therapy with 6-times-daily topical penciclovir cream is effective in speeding the healing of oral-labial HSV. Topical acyclovir cream has also been shown to speed healing.

Suppression of reactivation of oral-labial HSV: Oral acyclovir (400 mg bid), if started before exposure and continued for the duration of exposure (usually 5–10 days), will prevent reactivation of recurrent oral-labial HSV infection associated with severe sun exposure.

Herpetic whitlow: Oral acyclovir (200 mg) is given 5 times daily for 7–10 days. **HSV proctitis:** Oral acyclovir (400 mg 5 times per day) is useful in shortening

the course of infection. In immunosuppressed patients or in patients with severe infection, IV acyclovir (5 mg/kg q8h) may be useful.

Herpetic eye infections: In acute keratitis, topical trifluorothymidine, vidarabine, idoxuridine, acyclovir, penciclovir, and interferon are all beneficial. Debridement may be required; topical steroids may worsen disease.

CNS HSV infections

HSV encephalitis: IV acyclovir (10 mg/kg q8h; 30 mg/kg per day) for at least 10 days.

HSV aseptic meningitis: No studies of systemic antiviral chemotherapy exist. If therapy is to be given, IV acyclovir (15–30 mg/kg per day) should be used.

Visceral HSV infections

HSV esophagitis: IV acyclovir (15 mg/kg per day). In some patients with milder forms of immunosuppression, oral therapy with valacyclovir or famciclovir is effective.

HSV pneumonitis: No controlled studies exist. IV acyclovir (15 mg/kg per day) should be considered.

Infections due to acyclovir-resistant HSV

IV foscarnet (40 mg/kg q8h) should be given until lesions heal. The optimal duration of therapy and the usefulness of its continuation to suppress lesions are unclear. Some patients may benefit from cutaneous application of trifluorothymidine or 5% cidofovir gel.

Intravenous acyclovir (30 mg/kg per day, given as a 10-mg/kg infusion over 1 h at 8-h intervals) is effective in reducing rates of death and morbidity from HSV encephalitis. Early initiation of therapy is a critical factor in outcome. The major side effect associated with intravenous acyclovir is transient renal insufficiency, usually due to crystallization of the compound in the renal parenchyma. This adverse reaction can be avoided if the medication is given slowly over 1 h and the patient is well hydrated. Because CSF levels of acyclovir average only 30 to 50% of plasma levels, the dosage of acyclovir used for treatment of CNS infection (30 mg/kg per day) is double that used for treatment of mucocutaneous or visceral disease (15 mg/kg per day). Even higher doses of intravenous acyclovir are used for neonatal HSV infection (60 mg/kg per day in 3 divided doses).

Among immunocompetent patients, recent studies have shown the effectiveness of short-course oral therapy to reduce the signs and symptoms of oral and genital HSV infection. These regimens include valacyclovir (1 or 3 days) for oral-labial HSV and acyclovir (2 days) or valacyclovir (3 days) for recurrent-episode genital herpes.

Suppression of Mucocutaneous Herpes

Recognition of the high frequency of subclinical reactivation has provided an ever-greater rationale for the use of daily antiviral therapy to suppress reactivations of

HSV, especially in persons with frequent clinical reactivations (e.g., those with recently acquired genital HSV infection). Immunosuppressed persons, including those with HIV infection, may also benefit from daily antiviral therapy. Of the various regimens used, famciclovir (500 mg twice daily) and valacyclovir (1 g twice daily) are two of the most common; valacyclovir at a dose of 4 g daily was associated with thrombotic thrombocytopenic purpura in one study of HIV-infected persons.

Reduction in Transmission of HSV to Sexual Partners

Once-daily valacyclovir (500 mg) has been shown to reduce transmission of HSV-2 between sexual partners. Transmission rates are higher from males to females and among persons with frequent HSV-2 reactivation. Serologic screening can be used to identify at-risk couples.

VARICELLA-ZOSTER VIRUS INFECTIONS

DEFINITION ***Varicella-zoster virus (VZV) causes two distinct clinical entities: varicella (chickenpox) and herpes zoster (shingles)***.

Chickenpox, a ubiquitous and extremely contagious infection, is usually a benign illness of childhood characterized by an exanthematous vesicular rash. With reactivation of latent VZV (which is most common after the sixth decade of life), herpes zoster presents as a dermatomal vesicular rash, usually associated with severe pain.

ETIOLOGY

A clinical association between varicella and herpes zoster has been recognized for nearly 100 years. Early in the twentieth century, similarities in the histopathologic features of skin lesions resulting from varicella and herpes zoster were demonstrated. VZV is a member of the family Herpesviridae, sharing with other members such structural characteristics as a lipid envelope surrounding a nucleocapsid with icosahedral symmetry, a total diameter of ~180 to 200 nm, and centrally located double-stranded DNA that is 125,000 bp in length.

EPIDEMIOLOGY

Humans are the only known reservoir for VZV. Chickenpox is highly contagious, with an attack rate of at least 90% among susceptible (seronegative) individuals. Persons of both sexes and all races are infected equally often. The virus is endemic in the population at large; however, it becomes epidemic among susceptible individuals during seasonal peaks - namely, late winter and early spring in the temperate zone. Historically, children between the ages of 5 and 9 are most commonly affected and account for 50% of all cases. Most other cases involve children aged 1 to 4 and those aged 10 to 14. Approximately 10% of the population of the United States over the age of 15 is susceptible to infection. VZV vaccination during the second year of life is dramatically changing the epidemiology of infection.

The incubation period of chickenpox ranges from 10 to 21 days but is usually between 14 and 17 days. Secondary attack rates in susceptible siblings within a household are between 70 and 90%. Patients are infectious ~48 h prior to the onset of the vesicular rash, during the period of vesicle formation (which generally lasts 4 to 5 days), and until all vesicles are crusted.

Herpes zoster, a sporadic disease, is the consequence of reactivation of latent VZV from the dorsal root ganglia. Patients with herpes zoster can transmit infection to seronegative individuals, with consequent chickenpox. Most patients have no history of recent exposure to other individuals with VZV infection. Herpes zoster occurs at all ages, but its incidence is highest (5 to 10 cases per 1000 persons) among individuals in the sixth decade of life and beyond. Recurrent herpes zoster is exceedingly rare except in immunocompromised hosts, especially those with AIDS.

Herpes zoster, also called shingles, is characterized by a unilateral vesicular eruption within a dermatome, often associated with severe pain. The dermatomes from T3 to L3 are most frequently involved. If the ophthalmic branch of the trigeminal nerve is involved, zoster ophthalmic results. The factors responsible for the reactivation of VZV are not known. In children reactivation is usually benign, whereas in adults it can be debilitating.

PATHOGENESIS

Transmission is most likely to take place by the respiratory route; the subsequent localized replication of the virus at an undefined site (presumably the nasopharynx) leads to seeding of the reticuloendothelial system and ultimately to the development of viraemia. Viraemia in patients with chickenpox is reflected in the diffuse and scattered nature of the skin lesions and can be verified in selected cases by the recovery of VZV from the blood or routinely by polymerase chain reaction (PCR). Vesicles involve the corium and dermis, with degenerative changes characterized by ballooning, the presence of multinucleated giant cells, and eosinophilic intranuclear inclusions. Infection may involve localized blood vessels of the skin, resulting in necrosis and epidermal hemorrhage. With the evolution of disease, the vesicular fluid becomes cloudy because of the recruitment of polymorphonuclear leukocytes and the presence of degenerated cells and fibrin. Ultimately, the vesicles either rupture and release their fluid (which includes infectious virus) or are gradually reabsorbed.

The mechanism of reactivation of VZV that results in herpes zoster is unknown. Presumably, the virus infects the dorsal root ganglia during chickenpox, where it remains latent until reactivated. Histopathologic examination of representative dorsal root ganglia during active herpes zoster demonstrates hemorrhage, edema, and lymphocytic infiltration.

Active replication of VZV in other organs, such as the lung or the brain, can occur during either chickenpox or herpes zoster but is uncommon in the

immunocompetent host. Pulmonary involvement is characterized by interstitial pneumonitis, multinucleated giant cell formation, intranuclear inclusions, and pulmonary hemorrhage. Central nervous system (CNS) infection leads to histopathologic evidence of perivascular cuffing similar to that encountered in measles and other viral encephalitides. Focal hemorrhagic necrosis of the brain, characteristic of herpes simplex virus encephalitis, is uncommon in VZV infection.

CLINICAL MANIFESTATIONS

Chickenpox presents as a rash, low-grade fever, and malaise, although a few patients develop a prodrome 1 to 2 days before onset of the exanthem. In the immunocompetent patient, this is usually a benign illness that is associated with lassitude and with body temperatures of 37.8° to 39.4°C of 3 to 5 days' duration. The skin lesions – the hallmark of the infection – include maculopapules, vesicles, and scabs in various stages of evolution. These lesions, which evolve from maculopapules to vesicles over hours to days, appear on the trunk and face and rapidly spread to involve other areas of the body. Most are small and have an erythematous base with a diameter of 5 to 10 mm. Successive crops appear over a 2- to 4-day period. Lesions can also be found on the mucosa of the pharynx and/or the vagina. Their severity varies from one person to another. Some individuals have very few lesions, while others have as many as 2000. Younger children tend to have fewer vesicles than older individuals. Secondary and tertiary cases within families are associated with a relatively large number of vesicles.

Immunocompromised patients – both children and adults, particularly those with leukaemia – have lesions (often with a hemorrhagic base) that are more numerous and take longer to heal than those of immunocompetent patients. Immunocompromised individuals are also at greater risk for visceral complications, which occur in 30 to 50% of cases and are fatal 15% of the time in the absence of antiviral therapy.

The most common infectious complication of varicella is secondary bacterial superinfection of the skin, which is usually caused by Streptococcus pyogenes or Staphylococcus aureus. This complication may result from excoriation of skin lesions after scratching. Gram's staining of skin lesions should help clarify the etiology of unusually erythematous and pustulated lesions.

The most common extracutaneous site of involvement in children is the CNS. The syndrome of acute cerebellar ataxia and meningeal irritation generally appears ~21 days after the onset of the rash and rarely develops in the preeruptive phase. The cerebrospinal fluid (CSF) contains lymphocytes and elevated levels of protein. CNS involvement is a benign complication of VZV infection in children and generally does not require hospitalization. Aseptic meningitis, encephalitis, transverse myelitis, Guillain-Barré syndrome, and Reye's syndrome can also occur. Encephalitis is reported in 0.1 to 0.2% of children with chickenpox. Other than supportive care, no

specific therapy is available for patients with CNS involvement.

Varicella pneumonia is the most serious complication following chickenpox, developing more commonly in adults (up to 20% of cases) than in children. It usually has its onset 3 to 5 days into the illness and is associated with tachypnea, cough, dyspnea, and fever. Cyanosis, pleural chest pain, and hemoptysis are frequent. Roentgenographic evidence of disease consists of nodular infiltrates and interstitial pneumonitis. Resolution of pneumonitis parallels improvement of the skin rash; however, patients may have persistent fever and compromised pulmonary function for weeks.

Other complications of chickenpox include myocarditis, corneal lesions, nephritis, arthritis, bleeding diatheses, acute glomerulonephritis, and hepatitis. Hepatic involvement, distinct from Reye's syndrome and usually asymptomatic, is common in chickenpox and is generally characterized by elevated levels of liver enzymes, particularly aspartate and alanine aminotransferases.

The continuum of pain from onset to resolution is known as zoster-associated pain. The onset of disease is heralded by pain within the dermatome that may precede lesions by 48 to 72 h; an erythematous maculopapular rash evolves rapidly into vesicular lesions. In the normal host, these lesions may remain few in number and continue to form only for a period of 3 to 5 days. The total duration of disease is generally between 7 and 10 days; however, it may take as long as 2 to 4 weeks for the skin to return to normal.

In a few patients, characteristic localization of pain to a dermatome with serologic evidence of herpes zoster has been reported in the absence of skin lesions. When branches of the trigeminal nerve are involved, lesions may appear on the face, in the mouth, in the eye, or on the tongue. Zoster ophthalmicus is usually a debilitating condition that can result in blindness in the absence of antiviral therapy. In the Ramsay Hunt syndrome, pain and vesicles appear in the external auditory canal, and patients lose their sense of taste in the anterior two-thirds of the tongue while developing ipsilateral facial palsy. The geniculate ganglion of the sensory branch of the facial nerve is involved.

The most debilitating complication of herpes zoster, in both the normal and the immunocompromised host, is pain associated with acute neuritis and postherpetic neuralgia. Postherpetic neuralgia is uncommon in young individuals; however, at least 50% of patients over age 50 with zoster report some degree of pain in the involved dermatome months after the resolution of cutaneous disease. Changes in sensation in the dermatome, resulting in either hypo- or hyperesthesia, are common.

CNS involvement may follow localized herpes zoster. Many patients without signs of meningeal irritation have CSF pleocytosis and moderately elevated levels of CSF protein. Symptomatic meningoencephalitis is characterized by headache, fever, photophobia, meningitis, and vomiting. A rare manifestation of CNS involvement is

granulomatous angiitis with contralateral hemiplegia, which can be diagnosed by cerebral arteriography. Other neurologic manifestations include transverse myelitis with or without motor paralysis.

Like chickenpox, herpes zoster is more severe in the immunocompromised host than in the normal individual. Lesions continue to form for over a week, and scabbing is not complete in most cases until 3 weeks into the illness. Patients with Hodgkin's disease and non-Hodgkin's lymphoma are at greatest risk for progressive herpes zoster. Cutaneous dissemination develops in nearly 40% of these patients. Among patients with cutaneous dissemination, the risk of pneumonitis, meningoencephalitis, hepatitis, and other serious complications is increased by 5 to 10%. However, even in immunocompromised patients, disseminated zoster is rarely fatal.

DIAGNOSIS

Unequivocal confirmation of the diagnosis is possible only through the isolation of VZV in susceptible tissue-culture cell lines, the demonstration of either seroconversion or a fourfold or greater rise in antibody titer between convalescent- and acute-phase serum specimens, or the detection of VZV DNA by PCR. A rapid impression can be obtained by a Tzanck smear, with scraping of the base of the lesions in an attempt to demonstrate multinucleated giant cells, although the sensitivity of this method is low (~60%). PCR technology for the detection of viral DNA in vesicular fluid is available in a limited number of diagnostic laboratories. Direct immunofluorescent staining of cells from the lesion base or detection of viral antigens by other assays (such as the immunoperoxidase assay) is also useful, although these tests are not commercially available. The most frequently employed serologic tools for assessing host response are the immunofluorescent detection of antibodies to VZV membrane antigens, the FAMA test, immune adherence hemagglutination, and ELISA. The FAMA test and the ELISA appear to be the most sensitive.

TREATMENT

Medical management of chickenpox in the immunologically normal host is directed toward the prevention of avoidable complications. Obviously, good hygiene includes daily bathing and soaks. Secondary bacterial infection of the skin can be avoided by meticulous skin care, particularly with close cropping of fingernails. Pruritus can be decreased with topical dressings or the administration of antipruritic drugs. Tepid water baths and wet compresses are better than drying lotions for the relief of itching. Aluminum acetate soaks for the management of herpes zoster can be both soothing and cleansing. Administration of aspirin to children with chickenpox should be avoided because of the association of aspirin derivatives with the development of Reye's syndrome. Acyclovir therapy (800 mg by mouth five times daily for 5 to 7 days) is recommended for adolescents and adults with chickenpox of

less 24 h duration. Likewise, acyclovir therapy may be of benefit to children less 12 years of age if initiated early in the disease (less 24 h) at a dose of 20 mg/kg every 6h.

Patients with herpes zoster benefit from oral antiviral therapy, as evidenced by accelerated healing of lesions and resolution of zoster-associated pain with acyclovir, valacyclovir, or famciclovir. Acyclovir, now off patent, is administered at a dosage of 800 mg five times daily for 7 to 10 days. Famciclovir, the prodrug of penciclovir, is at least as effective as acyclovir and perhaps more so. One study showed twofold faster resolution of postherpetic neuralgia in famciclovir-treated patients with zoster than in recipients of placebo. The dose is 500 mg by mouth three times daily for 7 days. Valacyclovir, the prodrug of acyclovir, accelerates healing and resolution of zoster-associated pain more promptly than acyclovir. The dose is 1 g by mouth three times daily for 5 to 7 days. Both famciclovir and valacyclovir offer the advantage of a lower dosing frequency than acyclovir.

In the immunocompromised host, both chickenpox and herpes zoster (including disseminated disease) should be treated with intravenous acyclovir, which reduces the occurrence of visceral complications but has no effect on healing of skin lesions or pain. The dose is 10 to 12.5 mg/kg every 8 h for 7 days. Oral acyclovir therapy is not recommended for the treatment of VZV infections in immunocompromised patients. Concomitant with the administration of intravenous acyclovir, it is desirable to attempt to wean these patients from immunosuppressive treatment.

Patients with varicella pneumonia may require removal of bronchial secretions and ventilatory support. Persons with zoster ophthalmicus should be referred immediately to an ophthalmologist. Therapy for this condition consists of the administration of analgesics for severe pain and the use of atropine. Acyclovir accelerates healing.

The management of acute neuritis and/or postherpetic neuralgia can be particularly difficult. In addition to the judicious use of analgesics, ranging from nonnarcotics to narcotic derivatives, drugs such as gabapentin, amitriptyline hydrochloride, lidocaine patches, and fluphenazine hydrochloride have been reported to be beneficial for pain relief. In one study, glucocorticoid therapy administered early in the course of localized herpes zoster significantly accelerated such quality-of-life improvements as a return to usual activity and termination of analgesia. The dose of prednisone administered orally was 60 mg/d on days 1 through 7, 30 mg/d on days 8 through 14, and 15 mg/d on days 15 through 21. This regimen is appropriate only for relatively healthy elderly persons who have moderate or severe pain at presentation. Patients with osteoporosis, diabetes mellitus, glycosuria, or hypertension may not be appropriate candidates. Glucocorticoids should not be used without concomitant antiviral therapy.

EPSTEIN-BARR VIRUS INFECTIONS, INFECTIOUS MONONUCLEOSIS

DEFINITION ***Epstein-Barr virus (EBV) is the cause of heterophile-positive infectious mononucleosis (IM), which is characterized by fever, sore throat, lymphadenopathy, and atypical lymphocytosis. EBV is also associated with several human tumors, including nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's disease, and (in patients with immunodeficiency) B cell lymphoma.***

ETIOLOGY

The EBV was discovered 36 years ago by electron microscopy of cells cultured from Burkitt's lymphoma tissue by Epstein, Achong, and Barr. Four years later, in 1968, EBV was shown to be the etiologic agent of heterophile-positive infectious mononucleosis. EBV DNA was detected in tissues from patients with nasopharyngeal carcinoma in 1970. In the 1980s, EBV was found to be associated with non-Hodgkin's lymphoma and oral hairy leukoplakia in patients with the AIDS. Since then, EBV DNA has been found in tissues from other cancers, including T-cell lymphomas and Hodgkin's disease.

EBV is a member of the herpesvirus family. The viral genome is encased within a nucleocapsid, which is, in turn, surrounded by the viral envelope. Before the virus enters the B cell, the major envelope glycoprotein, gp350, binds to the viral receptor, the CD21 molecule (the C3d complement receptor), on the surface of the B cell. Other factors in addition to CD21 are important for infection. The MHC class II molecule serves as a cofactor for the infection of B cells. Patients with X-linked agammaglobulinemia lack mature B cells and their B cells cannot be infected with the virus either in vitro or in vivo.

The EBV genome consists of a linear DNA molecule that encodes nearly 100 viral proteins. During viral replication, these proteins are important for regulating the expression of viral genes, replicating viral DNA, forming structural components of the virion, and modulating the host immune response.

EPIDEMIOLOGY

EBV infections occur worldwide. These infections are most common in early childhood, with a second peak during late adolescence. By adulthood, more than 90% of individuals have been infected and have antibodies to the virus. IM is usually a disease of young adults. In lower socioeconomic groups and in areas of the world with lower standards of hygiene (e.g., developing countries), EBV tends to infect children at an early age, and symptomatic IM is uncommon. In areas with higher standards of hygiene, infection with EBV is often delayed until adulthood, and IM is more prevalent.

EBV is spread by contact with oral secretions. The virus is frequently transmitted from asymptomatic adults to infants and among young adults by transfer of saliva during kissing. Transmission by less intimate contact is rare. EBV has been transmitted by blood transfusion and by bone marrow transplantation. More than 90%

of asymptomatic seropositive individuals shed the virus in oropharyngeal secretions.

PATHOGENESIS

EBV is one of the most successful viruses, infecting over 90% of humans and persisting for the lifetime of the person. EBV is closely related to viruses present in Old World nonhuman primates, including EBV-like viruses of chimpanzees and rhesus monkeys. For example, the rhesus monkey virus and EBV share similar sequences and genetic organization, and they maintain persistent infection in the oropharynx and in B cells. Thus, EBV probably evolved from a nonhuman-primate virus.

Infection of humans with EBV usually occurs by contact with oral secretions. The virus replicates in cells in the oropharynx, and nearly all seropositive persons actively shed virus in the saliva. Studies suggest that B cells in the oropharynx may be the primary site of infection.

Resting memory B cells are thought to be the site of persistence of EBV within the body. Shedding of EBV from the oropharynx is abolished in patients treated with acyclovir, whereas the number of EBV-infected B cells in the circulation remains the same as before treatment. In addition, the observation that EBV can be eradicated in bone marrow–transplant recipients who have received therapy that ablates their hematopoietic cells, but not their oropharyngeal cells, provides further evidence that B cells are the site of EBV persistence. In normal adults, from 1 to 50 B cells per million in the circulation are infected with EBV, and the number of latently infected cells within a person remains stable over years.

Of the nearly 100 viral genes that are expressed during replication, only 10 are expressed in latently infected B cells in vitro. Two types of nontranslated RNA, six nuclear proteins, and two membrane proteins are expressed in these latently infected B cells. By markedly limiting viral gene expression during latency, EBV reduces the number of viral proteins that permit the recognition of infected cells by cytotoxic T cells.

The EBV nuclear antigen (EBNA) 1 protein binds to viral DNA and allows the EBV genome to be maintained in the B cell as a circular DNA episome. EBNA-2 up-regulates the expression of EBV latent membrane protein (LMP) 1 and LMP-2, as well as cellular proteins that contribute to the growth and transformation of B cells. The EBNA-3 proteins also regulate the expression of cellular genes, whereas EBNA leader protein augments the ability of EBNA-2 to up-regulate LMP-1.

LMP-1 acts as an oncogene, and expression of this protein in transgenic mice results in B-cell lymphomas. LMP-1 induces a signaling response in cells that mimics a constitutively active form of the B-cell–surface molecule CD40. LMP-1 binds to several of the tumor necrosis factor receptor–associated factors both in vitro and, in EBV-positive lymphomas, in vivo. These activities result in activation of the nuclear factor-κB (NF-κB) transcription factor in vitro and in vivo, activation of c-*jun*, up-

regulation of cellular adhesion molecules, cytokine production, and B-cell proliferation.

EBV LMP-2 prevents reactivation of EBV from latently infected cells by blocking tyrosine kinase phosphorylation. Expression of LMP-2 in transgenic mice allows nontransformed B cells to survive even in the absence of normal B-cell–receptor signaling. The nontranslated types of EBV-encoded RNA (EBER) do not encode proteins, but they may be important for oncogenesis and resistance to programmed cell death, or apoptosis. Another viral RNA, BARF0, has been detected in latently infected B cells. EBV-associated diseases generally show viral gene expression limited to one of three patterns of latency.

In the first form, only EBNA-1 and EBER are expressed, whereas in the second form, EBNA-1, LMP-1, LMP-2, and EBER are expressed. In the third pattern, all the latency genes are expressed. A fourth pattern of latency is seen in B cells obtained from the peripheral blood of healthy persons infected with EBV in the past, in which only EBER and LMP-2, and in some studies, EBNA-1 RNA have been detected.

Infection of humans with EBV results in both humoral and cellular immunity to the virus. Although the finding of antibodies directed against viral structural proteins and the EBNAs is important for the diagnosis of infection, the cellular immune response is more important for the control of EBV infection. Natural killer cells and CD4+ and CD8+ cytotoxic T cells control proliferating EBV-infected B cells during primary infection. In infectious mononucleosis, up to 40 percent of CD8+ T cells are targeted to one replicative EBV protein sequence, whereas 2 percent are targeted to one latent EBV protein sequence. After recovery from acute infection, HLA-restricted cytotoxic T cells are important in controlling EBV, and CD8+ T cells are targeted to similar percentages of replicative and latent antigens. Many of the cytotoxic-T-cell responses directed against latent proteins are targeted to the EBNA-3 proteins.

The ability of EBV to persist, despite potent immune effector responses against it, indicates that the virus has evolved strategies to elude the immune system. EBV encodes a cytokine and a cytokine receptor that may be important for modulating the immune system to allow persistent infection. The EBV BCRF1 protein shares 70 percent of its amino acid sequence with interleukin-10. The BCRF1 protein mimics the activity of interleukin-10 by inhibiting interferon-γ synthesis by human peripheral-blood mononuclear cells in vitro. The EBV BARF1 protein functions as a soluble receptor for colony-stimulating factor 1. Since colony-stimulating factor 1 normally enhances the expression of interferon-α by monocytes, BARF1 protein may function as a decoy receptor to block the action of the cytokine. Because interferon-γ and interferon-α inhibit the outgrowth of EBV-infected cells in vitro, the BCRF1 and BARF1 proteins may help the virus to evade the host's immune system during acute EBV infection or reactivation of virus from latently infected cells.

EBNA-1 has been shown to block its own degradation by proteosomes in the

cell. Since viral proteins are normally broken down by proteasomes to peptides for presentation to cytotoxic T cells, the ability of EBNA-1 to inhibit its degradation may allow the protein to avoid triggering the activation of cytotoxic T cells.

EBV encodes at least two proteins that inhibit apoptosis. The EBV BHFR1 protein is a homologue of the human bcl-2 protein, which also blocks apoptosis, whereas EBV LMP-1 up-regulates the expression of several cellular proteins that inhibit apoptosis, including bcl-2 and A20.

EBV-infected Burkitt's lymphoma cells down-regulate the expression of several proteins that are important for killing by cytotoxic T cells. These include the transporter proteins associated with antigen processing that convey viral peptides from the cytoplasm to the endoplasmic reticulum for antigen presentation, cellular adhesion molecules that allow cells to contact each other, and MHC class I (but not class II) molecules that allow cytotoxic T cells to recognize virus-infected cells.

Cellular immunity is more important than humoral immunity in controlling EBV infection. In the initial phase of infection, suppressor T cells, natural killer cells, and nonspecific cytotoxic T cells are important in controlling the proliferation of EBV-infected B cells. Levels of markers of T cell activation and serum interferon γ are elevated. Later in infection, HLA-restricted cytotoxic T cells that recognize EBNAs and LMPs and destroy EBV-infected cells are generated. Studies have shown that one of the late genes expressed during EBV replication, BCRF1, is a homologue of interleukin 10 and can inhibit the production of interferon γ by mononuclear cells in vitro.

If T cell immunity is compromised, EBV-infected B cells may begin to proliferate. When EBV is associated with lymphoma, virus-induced proliferation is but one step in a multistep process of neoplastic transformation. In many EBV-containing tumors, LMP-1 mimics members of the tumor necrosis factor receptor family (e.g., CD40), transmitting growth-proliferating signals.

CLINICAL MANIFISTATIONS

Acute infection (Infectious mononucleosis)

Most EBV infections in infants and young children either are asymptomatic or present as mild pharyngitis with or without tonsillitis. In contrast, up to 75% of infections in adolescents present as IM.

The incubation period for IM in young adults is about 4 to 6 weeks. A prodrome of fatigue, malaise, and myalgia may last for 1 to 2 weeks before the onset of fever, sore throat, and lymphadenopathy. Fever is usually low-grade and is most common in the first 2 weeks of the illness; however, it may persist for more than one month.

Lymphadenopathy and pharyngitis are most prominent during the first 2 weeks of the illness, while splenomegaly is more prominent during the second and third weeks. Lymphadenopathy most often affects the posterior cervical nodes but may be

generalized. Enlarged lymph nodes are frequently tender and symmetric but are not fixed in place. Pharyngitis, often the most prominent sign, can be accompanied by enlargement of the tonsils with an exudate resembling that of streptococcal pharyngitis. A morbilliform or papular rash, usually on the arms or trunk, develops in ~5% of cases. Most patients treated with ampicillin develop a macular rash; this rash is not predictive of future adverse reactions to penicillins. Most patients have symptoms for 2 to 4 weeks, but malaise and difficulty concentrating can persist for months.

Symptomatic IM is uncommon in infants and young children. IM in the elderly presents relatively often as nonspecific symptoms, including prolonged fever, fatigue, myalgia, and malaise; in contrast, pharyngitis, lymphadenopathy, splenomegaly, and atypical lymphocytes are relatively rare in elderly patients.

The white blood cell count is usually elevated and peaks at 10,000 to 20,000/μL during the second or third week of illness. Lymphocytosis is usually demonstrable, with >10% atypical lymphocytes. The latter cells are enlarged lymphocytes that have abundant cytoplasm, vacuoles, and indentations of the cell membrane. CD8+ cells predominate among the atypical lymphocytes. Low-grade neutropenia and thrombocytopenia are common during the first month of illness. Liver function is abnormal in more than 90% of cases. Serum levels of aminotransferases and alkaline phosphatase are usually mildly elevated; the serum concentration of bilirubin is elevated in ~40% of cases.

Most cases of IM are self-limited. Deaths are very rare and most often are due to CNS complications, splenic rupture, upper airway obstruction, or bacterial superinfection.

When CNS complications develop, they usually do so during the first 2 weeks of EBV infection; in some patients, especially children, they are the only clinical manifestations of IM. Heterophile antibodies and atypical lymphocytes may be absent. Meningitis and encephalitis are the most common neurologic abnormalities, and patients may present with headache, meningism, or cerebellar ataxia; acute hemiplegia and psychosis have also been described. The CSF contains mainly lymphocytes, with occasional atypical lymphocytes. Most cases resolve without neurologic sequelae. Acute EBV infection has also been associated with cranial nerve palsies (especially ones involving cranial nerve VII), Guillain-Barré syndrome, acute transverse myelitis, and peripheral neuritis.

Autoimmune hemolytic anemia occurs in ~2% of cases during the first 2 weeks. In most cases the anemia is Coombs'-test positive, with cold agglutinins directed against the red blood cell antigen. Most patients with hemolysis have mild anemia that lasts for 1 or 2 months, but some patients have severe disease with hemoglobinuria and jaundice. Nonspecific antibody responses may also include rheumatoid factor, antinuclear antibodies, anti–smooth muscle antibodies, antiplatelet

antibodies, and cryoglobulins. IM has been associated with red-cell aplasia, severe granulocytopenia, thrombocytopenia, pancytopenia, and hemophagocytic syndrome. The spleen ruptures in less than 0.5% of cases.

Splenic rupture is more common among males than among females and may be manifest as abdominal pain, referred shoulder pain, or hemodynamic compromise.

Hypertrophy of lymphoid tissue in the tonsils or adenoids can result in upper airway obstruction, as can inflammation and edema of the epiglottis, pharynx, or uvula. About 10% of patients with IM develop streptococcal pharyngitis after their initial sore throat resolves.

Other rare complications associated with acute EBV infection include hepatitis (which can be fulminant), myocarditis or pericarditis with electrocardiographic changes, pneumonia with pleural effusion, interstitial nephritis, genital ulcerations, and vasculitis.

Chronic Active EBV Infection

Chronic active EBV infection is a very rare disorder that has been defined by the presence of the following three features: severe illness of more than six months' duration that begins as a primary EBV infection or that is associated with abnormal EBV antibody titers; histologic evidence of organ disease, such as pneumonitis, hepatitis, bone marrow hypoplasia, or uveitis; and demonstration of EBV antigens or EBV DNA in tissue. There are often extreme elevations of virus-specific antibody titers. In contrast, chronic fatigue syndrome is a different disorder in which patients can have slightly elevated antibody titers to EBV and other viruses.

EBV-associated lymphoproliferative disease

EBV-associated lymphoproliferative disease has been described in patients with congenital or acquired immunodeficiency, including those with severe combined immunodeficiency, AIDS, and recipients of bone marrow or organ transplants who are receiving immunosuppressive drugs (especially cyclosporine). Proliferating EBV-infected B cells infiltrate lymph nodes and multiple organs, and patients present with fever and lymphadenopathy or gastrointestinal symptoms. Pathologic studies show B cell hyperplasia or poly- or monoclonal lymphoma. The X-linked lymphoproliferative syndrome (Duncan's disease) is a recessive disorder of young boys who have a normal response to childhood infections but develop fatal lymphoproliferative disorders after infection with EBV. The gene mutated in this syndrome, SAP or SH2D1A, has been identified; its product binds to a protein that mediates interactions of B and T cells. Most patients with this syndrome die of acute IM; others develop hypogammaglobulinemia, malignant B cell lymphomas, aplastic anemia, or agranulocytosis. IM has also proved fatal to some patients with no obvious preexisting immune abnormality.

Burkitt's lymphoma

Burkitt's lymphoma is a high-grade malignant lymphoma of small, noncleaved

B cells. In equatorial Africa, Burkitt's lymphoma is associated with *Plasmodium falciparum* malaria, and tumors usually present in the jaw; over 90 percent of these cases are associated with EBV. Infection with malaria is thought to diminish the T-cell control of proliferating EBV-infected B cells and enhance their proliferation. EBV is associated with several malignancies. About 15% of cases of Burkitt's lymphoma in US and nearly 90% of those in Africa are associated with EBV. African patients with Burkitt's lymphoma have high levels of antibody to EBV, and their tumor tissue usually contains viral DNA.

Burkitt's lymphoma cells contain a chromosomal translocation involving chromosomes 8 and 14, 22, or 2. These translocations result in the positioning of the c-*myc* oncogene (chromosome 8) near the immunoglobulin heavy-chain (chromosome 14) or light-chain (chromosome 2 or 22) constant region, leading to abnormal regulation of the c-*myc* gene. Expression of c-*myc* in EBV-immortalized B cells results in increased tumorigenicity of the cells.

Epidemiologic studies suggest that EBV may have a causal role in the development of Burkitt's lymphoma in Africa. Children in Uganda who have elevated titers of antibody to EBV structural proteins are at high risk for Burkitt's lymphoma. Tissue from patients with Burkitt's lymphoma in Africa usually contains EBV DNA and expresses only one EBV protein, EBNA-1. As in nasopharyngeal carcinoma, clonal EBV genomes are found in Burkitt's lymphoma tissues, indicating that the tumor arises from a single EBV-infected cell

Hodgkin's disease

EBV DNA has been detected in tumors from about 40 to 60 percent of patients with Hodgkin's disease in the United States. The EBV genome is present in the Hodgkin's and Reed–Sternberg cells, and the viral genomes are monoclonal.[7] EBV is present in Hodgkin's disease tumors of the mixed-cellularity or lymphocyte-depletion subtypes more often than in tumors of other subtypes, in tumors from children from underdeveloped countries more often than in tumors from children from developed countries, in tumors from Hispanic patients more often than in tumors from whites, in tumors from young men more often than in tumors from young women, and in tumors from patients with immunodeficiency (including those with human immunodeficiency virus (HIV) infection) more often than in tumors from healthy persons. Patients with Hodgkin's disease often have higher titers of antibody to EBV structural proteins before the onset of lymphoma or with the development of lymphoma than the general population

Lymphoproliferative disease

EBV is associated with lymphoproliferative disease in patients with congenital or acquired immunodeficiency. These include patients with severe combined immunodeficiency, recipients of organ or bone marrow transplants, and patients with AIDS. These patients have impaired T-cell immunity and are unable to control the

proliferation of EBV-infected B cells. They present with symptoms of infectious mononucleosis or with fever and localized or disseminated lymphoproliferation involving the lymph nodes, liver, lung, kidney, bone marrow, central nervous system, or small intestine. Patients who receive T-cell–depleted or HLA-mismatched bone marrow, receive antilymphocyte antibodies, have cytomegalovirus disease, or acquire primary EBV infection after receiving a transplant are at higher risk for lymphoproliferative disease. Increases in EBV viral load in peripheral blood have been detected in patients before the development of disease, and these levels decrease with effective therapy. Similarly, EBV RNA was detected in liver-biopsy specimens from 71 percent of patients before the development of lymphoproliferative disease, but in only 10 percent of those in whom the disease did not develop. Patients with EBV lymphoproliferative disease often have elevated serum levels of interleukin-6, a B-cell growth factor that may increase the proliferation of EBV-infected B cells.

Tissues from patients with EBV lymphoproliferative disease show plasmacytic hyperplasia, B-cell hyperplasia, B-cell lymphoma, or immunoblastic lymphoma. The lesions may be monoclonal, oligoclonal, or polyclonal; patients with polyclonal lesions have the best prognosis. Lymphoproliferative lesions usually do not have the chromosomal translocations typical of Burkitt's lymphoma. The diagnosis of EBV lymphoproliferative disease requires the demonstration of EBV DNA, RNA, or protein in biopsy tissue.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma is prevalent in southern China, in northern Africa, and among Alaskan Eskimos. In southern China the incidence of nasopharyngeal carcinoma approaches 50 per 100,000 persons per year. Nasopharyngeal carcinoma occurs sporadically in the United States and Western Europe. Nearly 100 percent of anaplastic or poorly differentiated nasopharyngeal carcinomas contain EBV genomes and express EBV proteins. The EBV genome is present in the transformed epithelial cells but not in the lymphocytes of the tumor. Clonal EBV genomes are found in the early preinvasive dysplastic lesions or carcinoma in situ, indicating that EBV infection precedes the development of malignant invasive tumors.

Patients with nasopharyngeal carcinoma often have elevated titers of IgA antibody to EBV structural proteins. Measurement of EBV-specific IgA antibodies is useful in screening patients for early detection of nasopharyngeal carcinoma in southern China. An increase in EBV-specific antibody titers after therapy for nasopharyngeal carcinoma is associated with a poor prognosis, whereas a declining or constant level of antibody is associated with a better prognosis.

EBV DNA or proteins may have a pathogenic role in several other tumors in which they have been detected, including nasal T-cell/natural-killer-cell lymphomas, lymphomatoid granulomatosis, angioimmunoblastic lymphadenopathy, central nervous system lymphomas in nonimmunocompromised patients, smooth-muscle

tumors in transplant recipients, and gastric carcinomas. Viral DNA or proteins have also been found in peripheral T-cell lymphomas, which can be accompanied by virus-associated hemophagocytic syndrome.

Chronic fatigue syndrome

Patients with the chronic fatigue syndrome may have titers of antibody to EBV that are elevated but are not significantly different from those in healthy EBV-seropositive adults. While some patients have malaise and fatigue that persist for weeks or months after IM, persistent EBV infection is not a cause of the chronic fatigue syndrome. Chronic active EBV infection is very rare and is distinct from the chronic fatigue syndrome. The affected patients have an illness lasting >6 months with markedly elevated titers of antibody to EBV and evidence of organ involvement, including hepatosplenomegaly, lymphadenopathy, and pneumonitis, uveitis, or neurologic disease.

EBV-infection as AIDS defining disease

Patients with AIDS have 10 to 20 times as many circulating EBV-infected B cells as healthy persons. T cells from patients with AIDS suppress EBV-infected B cells less effectively than do cells from normal controls. Patients with HIV have increased amounts of EBV in their oropharyngeal secretions and have higher EBV antibody titers than HIV-seronegative persons. A decline in EBV-specific cytotoxic T cells and an elevated and increasing EBV viral load preceded the development of EBV-associated non-Hodgkin's lymphomas in patients with HIV infection; however, these changes were not seen in patients with HIV before the development of opportunistic infections. HIV viral load and the progression of HIV disease were not affected by primary infection with EBV.

Oral Hairy Leukoplakia

Oral hairy leukoplakia occurs in HIV-infected patients as well as in some immunosuppressed transplant recipients. It presents as raised, white, corrugated lesions of the oral mucosa, especially on the lateral aspect of the tongue. It is a non-malignant hyperplastic lesion of epithelial cells. EBV DNA and herpesvirus particles are present in the upper, keratinized epithelial cells of the lesions. Multiple EBV strains are often present in the same lesion. Unlike EBV-associated cancers, oral hairy leukoplakia lesions show active viral replication and expression of lytic viral proteins.

Lymphoid interstitial pneumonitis

Lymphoid interstitial pneumonitis occurs primarily in children, but it also occurs in adults infected with HIV. It is characterized by diffuse interstitial pulmonary infiltrates. The pathological changes in the lesions include infiltration of the alveolar septa by lymphocytes, plasma cells, and immunoblasts. EBV DNA and proteins have been detected in pulmonary lesions from children with HIV and lymphoid interstitial pneumonitis.

Non-Hodgkin's Lymphoma in AIDS

EBV was detected more frequently in biopsy specimens from benign-appearing lymph nodes of HIV-infected patients who subsequently or concurrently had non-Hodgkin's lymphoma than in specimens from patients without lymphoma. About 50 to 60 percent of these tumors contain EBV DNA or proteins. Most of the tumors are classified as either immunoblastic lymphomas or Burkitt-type lymphomas, and a smaller number are large-cell lymphomas; most are monoclonal. Burkitt-type lymphomas in patients with AIDS often present before the development of severe immunodeficiency and usually have c-*myc* rearrangements. In contrast, immunoblastic lymphomas develop in the later stages of AIDS, lack c-*myc* rearrangements, and are more frequently EBV-positive.

Unlike other cancers in patients with AIDS, virtually all central nervous system lymphomas contain EBV DNA. These tumors are usually immunoblastic lymphomas and occur in patients with very low CD4+ cell counts. A positive polymerase-chain-reaction test for EBV DNA in the cerebrospinal fluid is a useful predictor of lymphoma in patients with AIDS and focal brain lesions

Primary effusion lymphomas in patients with AIDS often contain genomes from both EBV and Kaposi's sarcoma–associated herpesvirus (human herpesvirus 8). EBV has also been detected in leiomyosarcomas from patients with AIDS.

DIAGNOSIS

The heterophile test is used for the diagnosis of IM in children and adults. In the test for this antibody, human serum is absorbed with guinea pig kidney, and the heterophile titer is defined as the greatest serum dilution that agglutinates sheep, horse, or cow erythrocytes. Although heterophile antibody binds to certain animal erythrocytes, it does not interact with EBV proteins. A titer of 40-fold or greater is diagnostic of acute EBV infection in a patient who has symptoms compatible with IM and atypical lymphocytes. Tests for heterophile antibodies are positive in 40% of patients with IM during the first week of illness and in 80 to 90% during the third week. Therefore, repeated testing may be necessary, especially if the initial test is performed early. Tests usually remain positive for 3 months after the onset of illness, but heterophile antibodies can persist for up to 1 year. These antibodies usually are not detectable in children <5 years of age, in the elderly, or in patients presenting with symptoms not typical of IM. The commercially available monospot test for heterophile antibodies is somewhat more sensitive than the classic heterophile test. The monospot test is about 75% sensitive and nearly 90% specific compared with EBV-specific serologies (Table 3). False-positive monospot results are more common in persons with connective tissue disease, lymphoma, viral hepatitis, and malaria.

EBV-specific antibody testing is used for patients with suspected acute EBV infection who lack heterophile antibodies and for patients with atypical infections. Serologic tests are particularly useful in young children, who often do not develop

heterophile antibodies. Titers of IgM and IgG antibodies to viral capsid antigen (VCA) are elevated in the serum of more than 90% of patients at the onset of disease. IgM antibody to VCA is most useful for the diagnosis of acute IM because it is present at elevated titers only during the first 2 to 3 months of the disease; in contrast, IgG antibody to VCA is usually not useful for diagnosis of IM but is often used to assess exposure to EBV in the past because it persists for life. Seroconversion to EBNA positivity is also useful for the diagnosis of acute infection with EBV.

Table 3.

Serologic diagnosis EBV-infection (J.Cohen 2000)

Disease	Heterophile	Anti-VCA		Anti-EA		Anti-EBNA
		IgM	IgG	EA-D	EA-R	
Acute infectious mononucleosis	+	+	++	+	-	-
Convalescence	±	-	+	-	±	+
Past infection	-	-	+	-	-	+
Reactivation with immunodeficiency	-	-	++	+	+	±
Burkitt's lymphoma	-	-	+++	±	++	+
Acute infectious mononucleosis	-	-	+++	++	±	+

VCA, viral capsid antigen; EA, early antigen; EA-D antibody, antibody to early antigen in diffuse pattern in nucleus and cytoplasm of infected cells; EA-R antibody, antibody to early antigen restricted to the cytoplasm; and EBNA, Epstein-Barr nuclear antigen.

Antibodies to EBNA are detectable relatively late (3 to 6 weeks after the onset of symptoms) in nearly all cases of acute EBV infection and persist for the lifetime of the patient. These antibodies may be lacking in immunodeficient patients and in those with chronic active EBV infection.

Titers of other antibodies may also be elevated in IM; however, these elevations are less useful for diagnosis. Antibodies to early antigens (EAs) are found either in a diffuse pattern in the nucleus and cytoplasm of infected cells (EA-D antibody) or restricted to the cytoplasm (EA-R antibody). These antibodies are detectable 3 to 4 weeks after the onset of symptoms in patients with IM. About 70% of individuals with IM have EA-D antibodies during the course of illness; the presence of EA-D antibodies is especially likely in those with relatively severe disease. These antibodies usually persist for only 3 to 6 months. Levels of EA-D antibodies are also elevated in patients with nasopharyngeal carcinoma or chronic active EBV infection. EA-R antibodies are only occasionally detected in patients with IM but are often found at elevated titers in patients with African Burkitt's lymphoma or chronic active EBV infection. IgA antibodies to EBV antigens have proved useful

for the identification of patients with nasopharyngeal carcinoma and of persons at high risk for the disease.

Detection of EBV DNA, RNA, or proteins has been valuable in demonstrating the association of the virus with various malignancies. The polymerase chain reaction has been used to detect EBV DNA in the CSF of some AIDS patients with lymphomas and to monitor the amount of EBV DNA in the blood of patients with lymphoproliferative disease. Culture of EBV from throat washings or blood is not helpful in the diagnosis of acute infection, since EBV commonly persists in the oropharynx and in B cells for the lifetime of the infected individual.

TREATMENT

Therapy for IM consists of supportive measures, with rest and analgesia. No specific therapy is indicated for most patients with infectious mononucleosis. Although acyclovir inhibits EBV replication and reduces viral shedding, it has no significant effect on the symptoms of infectious mononucleosis (which are primarily due to the immune response to the virus) and is therefore not recommended.

Acyclovir is effective in the treatment of oral hairy leukoplakia, in which lesions appear to be driven directly by the replication of linear viral genomes, but recurrences are frequent after therapy is stopped. Corticosteroids shorten the duration of fever and oropharyngeal symptoms associated with infectious mononucleosis; however, they are generally not recommended for the treatment of uncomplicated disease and have been associated with increases in certain complications. Corticosteroid therapy should be considered for patients with severe complications of infectious mononucleosis, such as impending upper-airway obstruction, acute hemolytic anemia, severe cardiac involvement, or neurologic disease. Prednisone (40 to 60 mg/d for 2 to 3 days, with subsequent tapering of the dose over 1 to 2 weeks) has been used for the prevention of airway obstruction in patients with severe tonsillar hypertrophy, for autoimmune hemolytic anemia, and for severe thrombocytopenia. Glucocorticoids have also been used in a few selected patients with severe malaise and fever and in patients with severe CNS or cardiac disease.

A double-blind, placebo-controlled study of combined therapy with acyclovir and prednisolone in uncomplicated infectious mononucleosis showed that this treatment did not affect the duration of illness or of absence from work.

Excessive physical activity during the first month should be avoided to reduce the possibility of splenic rupture. If splenic rupture occurs, splenectomy is required. Glucocorticoid therapy is not indicated for uncomplicated IM and in fact may predispose to bacterial superinfection.

Acyclovir, at a dosage of 400 to 800 mg five times daily, has been effective for the treatment of oral hairy leukoplakia (despite common relapses) and some cases of chronic active EBV disease.

Therapy for EBV lymphoproliferative disease should include reduction in the

dose of immunosuppressive medication when possible. Reducing the dose may result in complete resolution of some lesions. Surgical removal or irradiation of localized lymphoproliferative lesions, especially in the gastrointestinal tract, has been effective in selected patients. Acyclovir, which inhibits the replication of linear EBV DNA but does not affect EBV episomes in latently infected cells, is generally not effective. Interferon alfa has been effective in some patients. In one study, 8 of 14 patients had total regression of lesions after therapy with interferon alfa.

Monoclonal-antibody therapy has also been used in patients with EBV lymphoproliferative disease. Treatment of 58 patients with murine monoclonal antibodies to both CD21 (the EBV receptor) and CD24 (a pan-B-cell antibody) resulted in complete remission in 61 percent of patients. Although these monoclonal antibodies are not approved for clinical use, rituximab, a monoclonal antibody directed against the CD20 B-cell antigen, was recently approved by the Food and Drug Administration for the treatment of low-grade B-cell non-Hodgkin's lymphoma. Two of three patients in whom EBV lymphoproliferative disease developed after lung transplantation had complete remissions after treatment with rituximab. A preliminary study of 26 patients with lymphoproliferative disease found that 54 percent had a complete remission with rituximab therapy. Cytotoxic chemotherapy has been effective for some patients who have had no response to a reduction in the dose of immunosuppressive drugs or to other therapies.

Infusion of unirradiated donor leukocytes into 18 patients with EBV lymphoproliferative disease after bone marrow transplantation resulted in the resolution of lymphomas in about 90 percent of them. At follow-up 3 to 42 months later, 56 percent were still in remission; 11 patients had acute or chronic graft-versus-host disease.

EBV-specific cytotoxic T cells have been used in an effort to reduce the frequency of graft-versus-host disease associated with infusions of donor leukocytes. Two of three patients with lymphoproliferative disease at one center had complete regression of disease after treatment with EBV-specific cytotoxic T cells. The patient for whom the therapy was unsuccessful had a tumor with a deletion in the EBV genome that allowed the malignant cells to escape killing by cytotoxic T cells. EBV-specific cytotoxic T cells have also been used to prevent lymphoproliferative disease in recipients of T-cell–depleted bone marrow. None of 42 patients receiving prophylactic cytotoxic T cells had lymphoproliferative disease, and only 1 had graft-versus-host disease, whereas 15 percent of patients who did not receive prophylaxis had lymphoproliferative disease. Studies using gene-marked EBV-specific T cells have shown that they persist for up to three years in some patients.

Whereas EBV lymphoproliferative lesions in bone marrow–transplant recipients are nearly always derived from donor cells, lesions in patients who receive solid-organ transplants are usually from recipient cells, and therefore donor-derived T

cells are not an option for therapy. Infusions of HLA-matched allogeneic cells from a sibling, autologous lymphokine-activated killer cells, or autologous EBV-specific cytotoxic T cells have resulted in regression of lymphoproliferative disease in organ-transplant recipients.

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 small-scale clinical trials. Vaccination against EBV might be useful for several groups of people who are seronegative for EBV. These include patients undergoing organ or bone marrow transplantation, persons with X-linked lymphoproliferative disease, people in areas of the world with a high incidence of Burkitt's lymphoma (equatorial Africa) or nasopharyngeal carcinoma (southern China), and adolescents and adults at risk for infectious mononucleosis. Vaccination with purified EBV gp350 or vaccinia virus expressing gp350 protected cotton-top tamarin monkeys from the development of EBV-positive lymphomas after challenge with the virus.

Preliminary studies in which nine EBV-seronegative children were vaccinated with vaccinia virus expressing gp350 found that neutralizing antibody responses to EBV developed in all nine and that six remained uninfected by EBV after 16 months, whereas all the unvaccinated controls became infected. A phase 1 clinical trial using purified recombinant gp350 protein was recently completed. In addition, immunization with EBV peptides corresponding to latent EBV antigens, which might boost cellular immunity and reduce morbidity from EBV-associated malignant diseases, is currently being tested in humans.

Since most cases of EBV lymphoproliferative disease associated with bone marrow transplantation are due to the proliferation of donor B cells, the frequency of disease may be reduced by the infusion of B-cell–depleted marrow. Removal of donor B cells along with T cells from bone marrow resulted in a lower incidence of lymphoproliferative disease in transplant recipients than did T-cell depletion alone. Preemptive treatment with acyclovir or ganciclovir during therapy with antilymphocyte antibodies or beginning at the time of transplantation reduced the rate of lymphoproliferative disease in organ-transplant recipients relative to that in historical controls. However, another study found no difference in the development of EBV lymphoproliferative disease between patients receiving two weeks and those receiving one year of antiviral therapy after transplantation.

CYTOMEGALOVIRAL INFECTION

DEFINITION: *cytomegalovirus (CMV) infection characterizes by severe birth defects, CMV causes a wide spectrum of disorders in older children and adults, ranging from an asymptomatic, subclinical infection to a mononucleosis syndrome in*

healthy individuals to disseminated disease in immunocompromised patients.

ETIOLOGY

Human CMV is one of several related species-specific viruses that cause similar diseases in various animals. All are associated with the production of characteristic enlarged cells – hence the name cytomegalovirus.

CMV is a member of the β-herpesvirus group and has double-strand DNA, four species of mRNA, a protein capsid, and a lipoprotein envelope. Like other herpesviruses, CMV demonstrates icosahedral symmetry, replicates in the cell nucleus, and can cause either a lytic and productive or a latent infection. CMV can be distinguished from other herpesviruses by certain biologic properties, such as host range and type of cytopathology induced. Viral replication is associated with the production of large intranuclear inclusions and smaller cytoplasmic inclusions. The virus appears to replicate in a variety of cell types in vivo; in tissue culture it grows preferentially in fibroblasts. Although there is little evidence that CMV is oncogenic in vivo, the virus does transform fibroblasts in rare instances, and genomic transforming fragments have been identified.

EPIDEMIOLOGY

CMV has a worldwide distribution. Approximately 1% of newborns in the United States are infected with CMV, and the percentage is higher in many less-developed countries. Communal living and poor personal hygiene facilitate early spread. Perinatal and early childhood infections are common. Virus may be present in breast milk, saliva, feces, and urine. Transmission of CMV has been identified among young children in day-care centers and has been traced from infected toddler to pregnant mother to developing fetus. When an infected child introduces CMV into a household, 50% of susceptible family members seroconvert within 6 months.

The virus is not readily spread by casual contact but requires repeated or prolonged intimate exposure for transmission. In late adolescence and young adulthood, CMV is often transmitted sexually, and asymptomatic viral carriage in semen or cervical secretions is common. CMV antibody is present at detectable levels in nearly 100% of female prostitutes and sexually active homosexual men. Sexually active adults may harbor several strains of CMV simultaneously. Transfusion of whole blood or certain blood products containing viable leukocytes may also transmit CMV, with a frequency of 0.14 to 10% per unit transfused.

Once infected, an individual probably carries CMV for life. The infection usually remains latent. However, CMV reactivation syndromes develop frequently when T lymphocyte–mediated immunity is compromised – for example, after organ transplantation or in association with lymphoid neoplasms and certain acquired immunodeficiencies (in particular, infection with HIV). Most primary CMV infections in organ transplant recipients result from transmission of the virus in the graft itself. In CMV-seropositive transplant recipients, infection results from

reactivation of latent virus or, less commonly, from reinfection by a new strain of CMV. CMV infection may be associated with coronary artery stenosis following heart transplantation or coronary angioplasty, but this association requires further validation.

PATHOGENESIS

Congenital CMV infection can result from either primary or reactivation infection of the mother. However, clinical disease in the fetus or newborn is almost exclusively related to primary maternal infection. The factors determining the severity of congenital infection are unknown; a deficient capacity to produce precipitating antibodies and to mount T cell responses to CMV is associated with relatively severe disease.

Primary infection in late childhood or adulthood is often associated with a vigorous T - lymphocyte response that may contribute to the development of a mononucleosis syndrome similar to that observed following Epstein-Barr virus (EBV) infection. The hallmark of such infection is the appearance of atypical lymphocytes in the peripheral blood; these cells are predominantly activated CD8+ T lymphocytes. Polyclonal activation of B cells by the virus contributes to the development of rheumatoid factors and other autoantibodies during CMV mononucleosis.

Once acquired by symptomatic or asymptomatic primary infection, CMV persists indefinitely in tissues of the host. The sites of persistent or latent infection probably include multiple cell types and various organs. Transmission following blood transfusion or organ transplantation is due to silent infections in these tissues. Autopsy studies suggest that salivary glands and bowel may be areas of latent infection.

If the host's T cell responses become compromised by disease or by iatrogenic immunosuppression, latent virus can be reactivated to cause a variety of syndromes. Chronic antigenic stimulation in the presence of immunosuppression (for example, following tissue transplantation) appears to be an ideal setting for CMV activation and CMV-induced disease. Certain particularly potent suppressants of T cell immunity, such as antithymocyte globulin, are associated with a high rate of clinical CMV syndromes, which may follow either primary or reactivation infection. CMV may itself contribute to further T lymphocyte hyporesponsiveness, which often precedes superinfection with other opportunistic pathogens, such as Pneumocystis. CMV and Pneumocystis are frequently found together in immunosuppressed patients with severe interstitial pneumonia.

Cytomegalic cells in vivo (presumed to be infected epithelial cells) are two to four times larger than surrounding cells and often contain an 8- to 10-μm intranuclear inclusion that is eccentrically placed and is surrounded by a clear halo, producing an “owl's eye” appearance. Smaller granular cytoplasmic inclusions are demonstrated

occasionally. Cytomegalic cells are found in a wide variety of organs, including salivary gland, lung, liver, kidney, intestine, pancreas, adrenal gland, and the central nervous system.

The cellular inflammatory response to infection consists of plasma cells, lymphocytes, and monocyte-macrophages. Granulomatous reactions occasionally develop, particularly in the liver. Immunopathologic reactions may contribute to CMV disease. Immune complexes have been detected in infected infants, sometimes in association with CMV-related glomerulopathies. Immune-complex glomerulopathy has been observed in some CMV-infected patients after renal transplantation.

CLINICAL MANIFESTATIONS

Congenital CMV Infection

Fetal infections range from inapparent to severe and disseminated. Cytomegalic inclusion disease develops in ~5% of infected fetuses and is seen almost exclusively in infants born to mothers who develop primary infections during pregnancy. Petechiae, hepatosplenomegaly, and jaundice are the most common presenting features (60 to 80% of cases). Microcephaly with or without cerebral calcifications, intrauterine growth retardation, and prematurity are reported in 30 to 50% of cases. Inguinal hernias and chorioretinitis are less common.

Laboratory abnormalities include elevated alanine aminotransferase levels, thrombocytopenia, conjugated hyperbilirubinemia, hemolysis, and elevated cerebrospinal fluid protein levels. The prognosis for severely infected infants is poor; the mortality rate is 20 to 30%, and few of the patients who survive escape intellectual or hearing difficulties later in childhood. The differential diagnosis of cytomegalic inclusion disease in infants includes syphilis, rubella, and toxoplasmosis, infection with herpes simplex virus or enterovirus, and bacterial sepsis.

Most congenital CMV infections are clinically inapparent at birth. Between 5 and 25% of asymptomatically infected infants develop significant psychomotor, hearing, ocular, or dental abnormalities over the next several years.

Perinatal CMV Infection

The newborn may acquire CMV at the time of delivery by passage through an infected birth canal or by postnatal contact with breast milk or other maternal secretions. Approximately 40 to 60% of infants who are breast-fed for more 1 month by seropositive mothers become infected. Iatrogenic transmission can also result from neonatal blood transfusion. Screening of blood products before they are transfused into low-birth-weight seronegative infants or into seronegative pregnant women decreases the risk of infection.

The great majority of infants infected at or after delivery remain asymptomatic. However, protracted interstitial pneumonitis has been associated with perinatally acquired CMV infection, particularly in premature infants, and occasionally has been

accompanied by infection with Chlamydia trachomatis, Pneumocystis, or Ureaplasma urealyticum. Poor weight gain, adenopathy, rash, hepatitis, anemia, and atypical lymphocytosis may also be found, and CMV excretion often persists for years.

CMV Mononucleosis

The most common clinical manifestation of CMV infection in normal hosts beyond the neonatal period is a heterophile antibody–negative mononucleosis syndrome. This manifestation may develop spontaneously or may follow the transfusion of leukocyte-containing blood products. Although the syndrome occurs at all ages, it most often involves sexually active young adults. Incubation periods range from 20 to 60 days, and the illness generally lasts for 2 to 6 weeks.

Prolonged high fevers, sometimes accompanied by chills, profound fatigue, and malaise, characterize this disorder. Myalgias, headache, and splenomegaly are frequent, but in CMV mononucleosis (as opposed to infectious mononucleosis caused by EBV), exudative pharyngitis and cervical lymphadenopathy are rare. Occasional patients develop rubelliform rashes, often after exposure to ampicillin. Less commonly observed are interstitial or segmental pneumonia, myocarditis, pleuritis, arthritis, and encephalitis. In rare cases, Guillain-Barré syndrome complicates CMV mononucleosis.

The characteristic laboratory abnormality is relative lymphocytosis in peripheral blood, with more than 10% atypical lymphocytes. Total leukocyte counts may be low, normal, or markedly elevated. Although significant jaundice is uncommon, serum aminotransferase and alkaline phosphatase levels are often moderately elevated. Heterophil antibodies are absent; however, transient immunologic abnormalities are common and may include the presence of cryoglobulins, rheumatoid factors, cold agglutinins, and antinuclear antibodies. Hemolytic anemia, thrombocytopenia, and granulocytopenia complicate recovery in rare instances.

Most patients recover without sequelae, although postviral asthenia may persist for months. The excretion of CMV in urine, genital secretions, and/or saliva often continues for months or years. Rarely, CMV infection is fatal in immunocompetent hosts; even when such patients survive, they can have recurrent episodes of fever and malaise that are sometimes associated with autonomic nervous system dysfunction (e.g., attacks of sweating or flushing).

CMV Infection in the Immunocompromised Host

CMV appears to be the most common and important viral pathogen complicating organ transplantation. In recipients of kidney, heart, lung, and liver transplants, CMV induces a variety of syndromes, including fever and leukopenia, hepatitis, pneumonitis, esophagitis, gastritis, colitis, and retinitis. CMV disease may be an independent risk factor for both graft loss and death. The period of maximal risk is between 1 and 4 months after transplantation, although retinitis may be a later

complication. Disease likelihood and levels of viral replication generally are greater after primary infection than after reactivation. In addition, molecular studies indicate that seropositive transplant recipients are susceptible to reinfection with donor-derived, genotypically variant CMV, and such infection often results in disease. Reactivation infection, although frequent, is less likely than primary infection to be important clinically.

The risk of clinical disease is related to various factors, such as the degree of immunosuppression; the use of antibodies to T cell receptors; and co-infection with other pathogens, such as human herpesvirus type 6. The transplanted organ is particularly vulnerable as a target for CMV infection; thus, there is a tendency for CMV hepatitis to follow liver transplantation and for CMV pneumonitis to follow lung transplantation (Table 4).

CMV pneumonia occurs in 15 to 20% of bone marrow transplant recipients, with a case-fatality rate of 84 to 88%. The risk is greatest between 5 and 13 weeks after transplantation, and the several risk factors identified include certain types of immunosuppressive therapy, acute graft-versus-host disease, older age, viraemia, and seropositivity before transplantation.

Table 4.

CMV in the Immunocompromised Host

Population	***Risk Factors***	***Principal Syndromes***	***Treatment***	***Prevention***
Fetus	Primary maternal infection/early pregnancy	Cytomegalic inclusion disease	None (ganciclovir)	Avoidance of exposure
Organ transplant recipient	Seropositive donor, seronegative recipient; intensive immunosuppression, particularly with antilymphocyte globulins, cyclosporine	Febrile leukopenia; pneumonia; gastrointestinal disease	Ganciclovir	Donor matching; CMV immunoglobulin; ganciclovir or high-dose acyclovir
Bone marrow transplant recipient	Graft-vs.-host disease; older age; seropositive recipient; viraemia	Pneumonia; gastrointestinal disease	Ganciclovir plus CMV immunoglobulin	Ganciclovir or high-dose acyclovir
Person with AIDS	<100 CD4+ cells per microliter; CMV seropositivity	Retinitis; gastrointestinal disease; neurologic disease	Foscarnet, ganciclovir, valganciclovir, or cidofovir	Oral ganciclovir

CMV is recognized as an important pathogen in patients with advanced HIV infection, in whom it often causes retinitis or disseminated disease, particularly when peripheral-blood CD4+ cell counts fall below 50 to 100/μL. As treatment for underlying HIV infection has improved, the incidence of serious CMV infections (e.g., retinitis) has decreased. However, institution of highly active antiretroviral regimens sometimes leads to acute flare-ups of CMV retinitis during the first few weeks of therapy.

Syndromes produced by CMV in the immunocompromised host often begin with prolonged fever, malaise, anorexia, fatigue, night sweats, and arthralgia or

myalgias. Liver function abnormalities, leukopenia, thrombocytopenia, and atypical lymphocytosis may be observed during these episodes. The development of tachypnea, hypoxia, and unproductive cough signals respiratory involvement.

Radiologic examination of the lung often reveals bilateral interstitial or reticulonodular infiltrates, which begin in the periphery of the lower lobes and spread centrally and superiorly; localized segmental, nodular, or alveolar patterns are less common. The differential diagnosis includes infection with Pneumocystis; infections due to other viral, bacterial, or fungal pathogens; pulmonary hemorrhage; and injury secondary to irradiation or to treatment with cytotoxic drugs.

Gastrointestinal CMV involvement may be localized or extensive and almost exclusively affects compromised hosts. Ulcers of the esophagus, stomach, small intestine, or colon may result in bleeding or perforation. CMV infection may lead to exacerbations of underlying ulcerative colitis. Hepatitis occurs frequently, particularly following liver transplantation, and CMV-associated acalculous cholecystitis and adrenalitis have been described.

CMV rarely causes meningoencephalitis in otherwise-healthy individuals. Two forms of CMV encephalitis are seen in patients with AIDS. One resembles HIV encephalitis and presents as progressive dementia; the other is a ventriculoencephalitis characterized by cranial-nerve deficits, nystagmus, disorientation, lethargy, and ventriculomegaly. In immunocompromised patients, CMV can also cause subacute progressive polyradiculopathy, which is often reversible if recognized and treated promptly.

CMV retinitis is an important cause of blindness in immunocompromised patients, particularly patients with advanced AIDS. Early lesions consist of small, opaque, white areas of granular retinal necrosis that spread in a centrifugal manner and are later accompanied by hemorrhages, vessel sheathing, and retinal edema. CMV retinopathy must be distinguished from that due to other conditions, including toxoplasmosis, candidiasis, and herpes simplex virus infection.

Fatal CMV infections are often associated with persistent viraemia and the involvement of multiple organ systems. Progressive pulmonary infiltrates, pancytopenia, hyperamylasemia, and hypotension are characteristic features that are frequently found in conjunction with a terminal bacterial, fungal, or protozoan superinfection. Extensive adrenal necrosis with CMV inclusions is often documented at autopsy, as is CMV involvement of many other organs.

DIAGNOSIS

The diagnosis of CMV infection usually cannot be made reliably on clinical grounds alone. Isolation of the virus or detection of CMV antigens or DNA from appropriate clinical specimens is the preferred diagnostic approach. Virus excretion or viraemia is readily detected by culture of appropriate specimens on human fibroblast monolayers. If viral titers are high, as is frequently the case in congenital

disseminated infection or in patients with AIDS, characteristic cytopathic effects may be detected within a few days. However, in some situations – such as CMV mononucleosis – viral titers are low, and cytopathic effects may take several weeks to appear.

Many laboratories expedite diagnosis with an overnight tissue-culture method (shell vial assay) involving centrifugation and an immunocytochemical detection technique employing monoclonal antibodies to an immediate-early CMV antigen. Isolation of virus from urine or saliva does not, by itself, constitute proof of acute infection, since excretion from these sites may continue for months or years after illness. Detection of CMV viraemia is a better predictor of acute infection.

Detection of CMV antigens (pp65) in peripheral-blood leukocytes or of CMV DNA in blood or tissues may hasten the diagnosis of CMV disease in certain populations, including organ transplant recipients and persons with AIDS. Such assays may yield a positive result several days earlier than culture methods. The most sensitive way to detect CMV in blood or other fluids may be by amplifying CMV DNA by polymerase chain reaction (PCR) assays. PCR detection of CMV DNA in blood may predict the risk for disease progression, and PCR detection of CMV DNA in cerebrospinal fluid is useful in the diagnosis of CMV encephalitis or polyradiculopathy.

A variety of serologic assays are available to detect increases in titers of antibody to CMV antigens. An increased antibody level may not be detectable for up to 4 weeks after primary infection, and titers often remain high for years after infection. For this reason, single-sample antibody determinations are of no value in assessing the acuteness of infection. Detection of CMV-specific IgM is sometimes useful in the diagnosis of recent or active infection; circulating rheumatoid factors may result in occasional false-positive IgM tests.

TREATMENT

Several prophylactic measures are useful for the prevention of CMV infection in patients at high risk. The use of blood from seronegative donors or of blood that has been frozen, thawed, and deglycerolized greatly decreases the rate of transfusion-associated transmission of CMV. Similarly, matching of organ or bone marrow transplants by CMV serology, with exclusive use of organs from seronegative donors in seronegative recipients, reduces rates of primary infection following transplantation. Both live attenuated and CMV subunit vaccines have been evaluated, but neither is close to approval for general use.

CMV immune globulin has been reported to reduce rates of CMV-associated syndromes and of fungal or parasitic superinfections among seronegative renal transplant recipients. Studies in bone marrow transplant recipients have produced conflicting results. Prophylactic acyclovir or valacyclovir may reduce rates of CMV infection and disease in certain seronegative renal transplant recipients, although

neither drug is effective in the treatment of active CMV disease.

Ganciclovir is a guanosine derivative that has considerably more activity against CMV than its congener acyclovir. After intracellular conversion by a viral phosphotransferase encoded by CMV gene region UL97, ganciclovir triphosphate is a selective inhibitor of CMV DNA polymerase. Several clinical studies have indicated response rates of 70 to 90% among patients with AIDS given ganciclovir for the treatment of CMV retinitis or colitis. In bone marrow transplant recipients with CMV pneumonia, ganciclovir is less effective when given alone, but it elicits a favorable clinical response 50 to 70% of the time when it is combined with CMV immune globulin.

Prophylactic or suppressive ganciclovir may be useful in high-risk bone marrow or organ transplant recipients (e.g., those who are CMV-seropositive before transplantation or who are CMV culture–positive afterward). In many patients with AIDS, persistently low CD4+ cell counts, and CMV disease, clinical and virologic relapses occur promptly if treatment with ganciclovir is discontinued. Therefore, prolonged maintenance regimens are recommended for such patients. Resistance to ganciclovir is common among patients treated for >3 months and is usually related to mutations in the CMV UL97 gene.

Ganciclovir therapy for CMV retinitis consists of a 14- to 21-day induction course (5 mg/kg intravenously twice daily for ganciclovir) followed by a prolonged maintenance regimen. For parenteral maintenance, the ganciclovir dose is 5 mg/kg daily or 6 mg/kg 5 days per week. Peripheral-blood neutropenia develops in 16 to 29% of treated patients but may be ameliorated by granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor. Discontinuation of maintenance therapy should be considered in patients with AIDS who, while receiving antiretroviral therapy, have a sustained (more 6-month) increase in CD4 cell counts to more 100–150/μL.

Foscarnet (sodium phosphonoformate) also acts against CMV infection by inhibiting viral DNA polymerase. Because this agent does not require phosphorylation to be active, it is also effective against most ganciclovir-resistant CMV isolates. Foscarnet is less well tolerated than ganciclovir and causes considerable toxicity, including renal dysfunction, hypomagnesemia, hypokalemia, hypocalcemia, genital ulcers, dysuria, nausea, and paresthesia. Moreover, foscarnet administration requires the use of an infusion pump and close clinical monitoring. With aggressive hydration and dose adjustments for renal dysfunction, the toxicity of foscarnet can be reduced. The use of foscarnet should be avoided when a saline load cannot be tolerated (e.g., in cardiomyopathy). The approved induction regimen is 60 mg/kg every 8 h for 2 weeks, although 90 mg/kg every 12 h is equally effective and no more toxic. Maintenance infusions should deliver 90 to 120 mg/kg once daily; no oral preparation is available. Foscarnet-resistant viruses may emerge during extended

therapy.

Ganciclovir may also be administered via a slow-release pellet sutured into the eye. Although this intraocular device provides good local protection, contralateral eye disease and disseminated disease are not affected, and early retinal detachment is possible. A combination of intraocular and systemic therapy may be better than the intraocular implant alone.

Cidofovir is a nucleotide analogue with a long intracellular half-life that allows intermittent intravenous administration. Induction regimens of 5 mg/kg weekly for 2 weeks are followed by maintenance regimens of 3 to 5 mg/kg every 2 weeks. Cidofovir can cause severe nephrotoxicity through dose-dependent proximal tubular cell injury; however, this adverse effect can be ameliorated somewhat by saline hydration and probenecid.

It is still not clear whether universal prophylaxis or preemptive therapy in immunocompromised hosts with CMV seropositivity is the preferable approach. For patients with advanced HIV infection (CD4 cell counts of less 50/μL), some authorities have advocated prophylaxis with oral ganciclovir or valganciclovir. However, side effects, lack of proven benefit, possible induction of viral resistance, and cost have precluded the wide acceptance of this practice. Similar questions have arisen concerning prophylaxis in organ transplant recipients. As techniques for identifying individuals at risk improve (e.g., quantification of CMV DNA by PCR), it may become possible to preemptively treat those at highest risk to prevent end-organ disease.

HUMAN HERPESVIRUS TYPES 6, 7, 8 (HHV6, 7, 8)

Human herpesvirus (HHV) type 6 was first isolated in 1986 from peripheral-blood leukocytes of six persons with various lymphoproliferative disorders. The virus has a worldwide distribution, and two genetically distinct variants (HHV-6A and HHV-6B) are now recognized.

Human herpesvirus 6 (HHV-6) infects over 90% of people within the first two years of life. Studies of febrile children in the emergency department indicate that primary HHV-6 infection accounts for a large proportion of visits and febrile seizures. Despite the interest in HHV-6 as an important pathogen, no prospective, population-based study has evaluated the acquisition of HHV-6 outside the acute care setting. Thus, the full spectrum of illness and virologic aspects of primary HHV-6 infection remain unknown. We developed a noninvasive method of testing serially collected saliva specimens for HHV-6 and used it prospectively in children from birth to two years of age to determine the pattern of acquisition and natural history of HHV-6 infection.

Infection with HHV-6 frequently develops during infancy as maternal antibody

wanes. The incidence of infection was highest between 9 and 21 months of age, with a cumulative incidence of 40% by 12 months of age and 77% by 24 months of age. Primary HHV-6 infection is defined by the onset of persistent salivary secretion.

Congenital infections have also been described. Of the 81 children with a well-defined time of acquisition of HHV-6, percent had symptoms. Fever, fussiness, and rhinorrhea were present in most children at the time of HHV-6 acquisition, whereas cough, diarrhea, and rash occurred less frequently. This virus is also a major cause of febrile seizures without rash during infancy.

Roseola, a clinical syndrome that is relatively specific for HHV-6 infection. HHV-6 (mostly variant B) can cause exanthem subitum (roseola infantum), a common illness characterized by fever with subsequent rash.

The onset of roseola followed the initial detection of salivary HHV-6 by less than one week.

In older age groups, HHV-6 has been associated with mononucleosis syndromes, focal encephalitis, and (in immunocompromised hosts) pneumonitis and disseminated disease. In transplant recipients, HHV-6 infection may be associated with graft dysfunction. As many as 80% of adults are seropositive for HHV-6. The virus may be transmitted by saliva and possibly by genital secretions. Like many other viruses, HHV-6 has been implicated in the pathogenesis of multiple sclerosis, although further study is needed to distinguish between association and etiology.

HHV-7 was isolated in 1990 from T lymphocytes from the peripheral blood of a healthy 26-year-old man. Other isolates have since been obtained. It appears that the virus is frequently acquired during childhood and is commonly present in the saliva of healthy adults. No human disease has yet been definitively linked to HHV-7, although some cases of exanthem subitum, other childhood febrile illnesses, and neurologic syndromes (encephalitis, flaccid paralysis) have been associated with HHV-7 infection. An association has been made between HHV-7 and pityriasis rosea, but further studies must confirm this relationship.

HHV-6, HHV-7, and CMV infections may cluster in transplant recipients, making it difficult to sort out the roles of the various agents in individual clinical syndromes. HHV-6 and HHV-7 appear to be susceptible to ganciclovir and foscarnet, although definitive evidence of clinical responses is lacking.

Compelling epidemiologic evidence, including the peculiar geographic distribution of Kaposi's sarcoma, prompted speculation about an infectious cause as well as the possibility of sexual transmission. In 1994 Chang and colleagues identified DNA fragments of a previously unrecognized herpesvirus, which has been called Kaposi's sarcoma-associated herpesvirus (KSHV, also known as human herpesvirus 8), in a Kaposi's sarcoma skin lesion from a patient with AIDS. Over 95% of Kaposi's sarcoma lesions, regardless of their source or clinical subtype, have been found to be infected with KSHV. Although studies have been published on the

contribution of cytokines as well as HIV tat protein to the pathogenesis of Kaposi's sarcoma lesions, it is clear that the presence of KSHV is the primary and necessary factor in the development of this tumor. In addition, immunosuppression in the host appears to be an important cofactor in the clinical expression of Kaposi's sarcoma in some KSHV-infected patients. The relation between clinical lesions and immunosuppression underscores the unusual pathology and clinical course of this proliferative disease and suggests that Kaposi's sarcoma may not be a conventional neoplasm.

KSHV is the eighth human herpesvirus to be identified. Most human herpesviruses are associated with disease in immunocompromised hosts, as a result of either the reactivation of latent virus or the proliferation of growth-transformed cells. Herpesviruses are divided into three subfamilies, and both KSHV and Epstein–Barr virus (EBV) are members of the gammaherpesvirus subfamily. Gamma-herpesviruses are notable for causing tumors, particularly lymphoproliferative disorders and lymphomas in humans and animals. Molecular epidemiologic data suggest that KSHV may be an ancient pathogen of humans that has spread very slowly in the population. Alternatively, the virus may have become pathogenic to humans more recently (within the past several thousand years), originating from a nonhuman primate host in Africa and slowly spreading to Mediterranean populations. In either case, any attempt to trace the origin and distribution of KSHV must take into consideration the more recent rapid intercontinental dissemination of the virus before and during the AIDS epidemic.

KSHV appears to have spread from epicenters of AIDS in US to homosexual communities in Canada and Europe, suggesting that its appearance early in the AIDS epidemic actually represents an independent epidemic.

KSHV DNA can be detected in peripheral-blood cells from only about half of infected persons with the use of standard polymerase-chain-reaction (PCR) assays, indicating that viraemia is not prominent. However, this technique as well as the less sensitive Southern blot hybridization assay can detect viral DNA in virtually all lesions of Kaposi's sarcoma. The identification of a small percentage of lesions as negative for KSHV almost always results from misdiagnosis or suboptimal preparation of specimens. KSHV is clearly associated with Kaposi's sarcoma, body-cavity-related B-cell lymphoma (primary effusion lymphoma), and some plasma-cell forms of multicentric Castleman's disease. Reports of the involvement of KSHV in other diseases, such as multiple myeloma, sarcoidosis, and post-transplantation skin tumors, have not been confirmed.

Serologic assays to detect KSHV-specific antibodies have high sensitivity, and such methods are preferable to PCR, particularly for detecting previous exposure to the virus. Antibody responses to KSHV antigens appear to be lifelong in most persons, but they may be lost in patients at the end stage of AIDS. The results of

serologic studies support the notion that infection with KSHV is nearly universal in patients with Kaposi's sarcoma, since specific antibodies are detectable in 70-90% of all patients with Kaposi's sarcoma and almost 100% of immunocompetent patients with the disease. The results of an indirect immunofluorescence assay for LANA and of an enzyme-linked immunosorbent assay that uses recombinant antigens made from KSHV open-reading-frame (ORF) proteins 65 and K8.1A are highly concordant. When properly performed in standardized formats, these assays can be used in combination for diagnostic purposes.

Results of serologic studies show that, unlike other human herpesviruses, KSHV is not ubiquitous. The infection rates instead parallel the incidence of Kaposi's sarcoma, with low rates in US, many parts of Europe, and Asia; intermediate rates in Mediterranean countries; and the highest rates in Central Africa (Uganda, Zambia, and South Africa). The seroprevalence of KSHV among blood donors ranges from 0.2% in Japan, where Kaposi's sarcoma is rare, to up to 10% in the United States, and to more than 50% in many African populations, with rates in Italy and other Mediterranean countries falling between these extremes. Within this range, there are at-risk populations with particularly high seroprevalence rates. Regardless of their HIV serostatus, homosexual men have a higher rate of Kaposi's sarcoma than the general male population and can have rates of asymptomatic infection that approach 40%.

KSHV can be transmitted sexually and by other means. Sexual transmission predominates in developed countries with a low prevalence of the virus, and it is thought to be more readily transmissible through homosexual than through heterosexual activities. The prevalence of KSHV infection increases with the number of male sexual partners, and receptive anal intercourse has been identified as a risk factor for infection in some studies. In contrast, other modes of transmission predominate in African countries, where infection can occur during childhood. Maternal-infant transmission, whether during labor and delivery or transplacentally, accounts for a portion of KSHV infections in areas where infection is highly endemic. However, KSHV infection also occurs later in childhood and during adolescence in such areas, a point that suggests transmission of the virus through some form of nonsexual contact. The exact routes of transmission are not known, although KSHV has been detected in both saliva and semen from infected persons.

Kaposi's sarcoma develops in 0.1-1% of transplant recipients in areas with a low prevalence of the disease and in up to 5% of such patients in areas with a high prevalence. Clinical disease results predominantly from reactivation of the virus, but it may also represent a primary infection transmitted by the transplanted organs. In contrast to the established risk of infection posed by organ transplantation, the risk of transmission of KSHV through blood products is unknown, although it is clearly lower than that for HIV.

Most primary KSHV infections appear to be asymptomatic. Clinical and epidemiologic studies have shown that, in healthy adults, there is immunologic control of KSHV infection. In HIV-seropositive patients, the incubation period for diseases caused by KSHV infection largely depends on the host's immune status rather than on the duration of KSHV infection. In some patients with AIDS who are infected with KSHV, the ability of HLA class I-restricted cytotoxic T lymphocytes to respond to KSHV proteins is lost as immunodeficiency worsens and Kaposi's sarcoma develops. Underscoring the importance of the immune status of the host is the finding that both Kaposi's sarcoma and body-cavity-related B-cell lymphoma have dramatically responded to highly active antiretroviral therapy in patients with AIDS. Post-transplantation Kaposi's sarcoma has also resolved when immunosuppressive regimens were discontinued.

In 1872, Moritz Kaposi, a Hungarian dermatologist, described five men with aggressive "idiopathic multiple pigmented sarcomas of the skin." One patient died of gastrointestinal bleeding 15 months after the initial appearance of the skin lesions, and an autopsy showed visceral lesions in the lungs and the gastrointestinal tract. Subsequently, other investigators described four clinical variants of Kaposi's sarcoma that had identical histologic features but developed in specific populations and had different sites of involvement and rates of progression. In the light of recent discoveries regarding the viral pathogenesis of Kaposi's sarcoma, these variants most likely represent different manifestations of the same pathologic process.

The classic variant primarily affects elderly men of Eastern European and Mediterranean origin. Classic Kaposi's sarcoma is much more common in men than in women, with a ratio as high as 15 to 1. Multiple firms, purple-blue or reddish-brown plaques and nodules typically appear initially on the hands and feet and progress up the arms and legs over a period of years or decades, eventually involving the viscera or mucosa in about 10% of patients. Untreated lesions evolve from flat discolorations or patches to plaques and then to raised nodules that become confluent. Lymphedema may precede or follow the appearance of visible lesions. Characteristic histologic features include spindle-shaped tumor cells surrounding hyperemic vascular slits, often in association with extravasated erythrocytes, hemosiderin, and fibrosis.

An increased risk of lymphoma has been observed in association with Kaposi's sarcoma in some studies but not others. Homosexual men may be at increased risk for classic Kaposi's sarcoma, even in the absence of clinically detectable immunosuppression.

DIPHTHERIA

DEFINITION. *Diphtheria is a contagious acute localized infection of mucous membranes or skin caused by Corynebacterium diphtheriae. Respiratory diphtheria characterized by sore throat, fever, an adherent membrane (a pseudomembrane) and exudation thrown out on the mucous of tonsils, pharynx, nasal cavity and sometimes in trachea and bronchial tubes.*

Some strains of C. diphtheriae produce diphtheria toxin, a protein that can cause myocarditis, polyneuritis, and other systemic toxic effects. Respiratory diphtheria is usually caused by toxinogenic (tox^+) C. diphtheriae, but cutaneous diphtheria is frequently caused by nontoxinogenic (tox^-) strains.

History. The disease was described in the 5th century BCE by Hippocrates, and epidemics were described in the 6th century AD by Aetius. The bacterium was first observed in diphtheritic membranes by Klebs in 1883 and cultivated by Löffler in 1884. Antitoxin was invented in the late 19th century, and toxoid was developed in the 1920s.

ETIOLOGY

C. diphtheriae (Greek διφθερα (diphthera) – "pair of leather scrolls") is a facultatively aerobic, nonmotile, nonsporulating, irregularly staining, gram-positive rod. The bacteria are 2 to 6 um long, 0.5 to 1 um wide, club-shaped, and often arranged in clusters (Chinese letters) or parallel arrays (palisades). C. diphtheriae forms gray to black colonies on selective media containing tellurite within 18-20 hours. Three biotypes, designated gravis, mitis, and intermedius, are distinguished on the basis of colonial morphology and laboratory tests. Both tox^+ and tox^- strains cause infections, and tox^+ strains of all three biotypes can cause severe disease.

The gene for diphtheria toxin is present in specific corynephages. Nontoxinogenic C. diphtheriae acquires the ability to produce diphtheria toxin by infection with tox^+ phages, a process termed phage conversion. Growth of C. diphtheriae under low-iron conditions mimicking the environment of host tissues induces the synthesis of diphtheria toxin and the expression of a siderophore-dependent, high-affinity iron uptake system.

EPIDEMIOLOGY

Diphtheria occurs worldwide, but clinical cases are more prevalent in temperate zones. Disease has been epidemic, endemic, and sporadic. Humans are the only known reservoir of C. diphtheriae. Diphtheria is a highly contagious disease spread by direct physical contact or breathing the aerosolized secretions of infected individuals. The risk of transmission from patients appears to be substantially greater than that of transmission from asymptomatic carriers. Transmission involving fomites and indirect routes is less common, although C. diphtheriae can survive for weeks to months in the environment.

In populations in temperate climates, diphtheria primarily involves the

respiratory tract; occurs throughout the year, with a peak incidence in colder months; and is usually caused by tox^+ strains. Before the introduction of active immunization, diphtheria was generally a disease of children; it affected up to 10% of individuals in this group and sometimes occurred in devastating epidemics. Most infants were immune because of transplacental transfer of maternal IgG antitoxin, but children became susceptible by 6 to 12 months of age. Approximately 75% of individuals became immune by age 10 as a result of clinical or subclinical infection with C. diphtheriae. Significant risk factors include crowded environments, poor hygiene, alcoholism, and lack of immunization.

In the tropics, cutaneous diphtheria is more common than respiratory diphtheria, occurs throughout the year, and often develops as a secondary infection complicating other dermatoses (impetiginous scabies, impetiginous eczema or impetigo). Isolates of C. diphtheriae from skin lesions are more often tox^- than tox^+.

PATHOGENESIS

C. diphtheriae infects mucous membranes, most commonly in the respiratory tract, and also invades open skin lesions resulting from insect bites or trauma. In infections caused by tox^+ C. diphtheriae, initial edema and hyperemia are often followed by epithelial necrosis and acute inflammation as a result of inhibition by toxin of cellular protein synthesis. Coagulation of the dense fibrinopurulent exudate produces a pseudomembrane, and the inflammatory reaction accompanied by vascular congestion extends into the underlying tissues. The pseudomembrane contains large numbers of C. diphtheriae, but the bacterium is rarely isolated from the blood or internal organs.

Diphtheria toxin acts both locally and systemically. Very small amounts cause dermonecrosis, and toxin presumably contributes to pseudomembrane formation. The lethal dose of diphtheria toxin for nonimmune humans and highly susceptible animals is about 0.1 ug/kg of body weight. Absorbed toxin can cause thrombocytopenia, myocarditis, neuritis, and focal necrosis in various organs, including the kidneys, liver, and adrenal glands. Early changes in diphtheritic myocarditis include cloudy swelling of muscle fibers and interstitial edema. These changes are followed within weeks by hyaline and granular degeneration of muscle fibers (sometimes with fatty degeneration of the myocardium) progressing to myolysis and finally to the replacement of lost muscle by fibrosis. Thus, diphtheria can cause permanent cardiac damage. In diphtheritic polyneuritis, pathologic changes include patchy breakdown of myelin sheaths in peripheral and autonomic nerves, but recovery of nerve damage is the rule if the patient survives.

Diphtheria toxin is produced by C. diphtheriae as an extracellular polypeptide. It is cleaved by proteases to form nicked toxin consisting of fragments A and B. Fragment B binds to a plasma-membrane receptor (a precursor of a heparin-binding growth factor resembling epidermal growth factor) on cells from humans or

susceptible animals, and the bound toxin is internalized by receptor-mediated endocytosis. Fragment A is translocated across the endosomal membrane and released into the cytoplasm, where it catalyzes the transfer of the adenosine diphosphate ribose moiety from nicotinamide adenine dinucleotide (NAD) to a modified histidine residue (diphthamide) on elongation factor 2 (EF-2), thereby inactivating EF-2 and inhibiting protein synthesis. One molecule of fragment A in the cytoplasm can kill a cell. Other metabolic alterations in intoxicated cells are secondary to inhibition of protein synthesis.

CLINICAL MANIFESTATIONS

Classification of respiratory diphtheria

By form:	***By localization:***
Subclinical	Tonsillopharyngeal
Mild	Nasal
Moderate	Laryngeal
Severe	Tracheal and bronchial
Hypertoxic	
Bacteriocarrier	***By character of process:***
By spread:	Catarrhal
Localized	Islet
Diffused (in one anatomical region)	Membranous
Combined (in different regions)	

The disease affects the mucous membranes of the respiratory tract (respiratory diphtheria), the skin (cutaneous diphtheria), and occasionally mucous membranes at other sites (eyes, ears, or vagina). The incubation period for respiratory diphtheria is typically 2 to 5 days (range 1-10 days). Cutaneous diphtheria is usually a secondary infection whose signs develop an average of 7 days (range, 1 to 21 days) after the appearance of primary skin lesions.

Patients with C. diphtheriae in the respiratory tract are classified as diphtheria cases if they have symptoms consistent with local infection (tonsillopharyngeal, laryngeal, nasal, and tracheobronchial) and as diphtheria carriers or subclinical if they are asymptomatic. Signs and symptoms vary with the site and severity of the local infection, the patient's age, and the patient's status with regard to preexisting nasopharyngeal disease and concomitant systemic disease. Patients without toxicity exhibit discomfort and malaise associated with local infection, whereas severely toxic patients may develop listlessness, pallor, and tachycardia, hypotonia that can progress rapidly to vascular collapse.

Multiple sites are frequently involved and secondary spread of pharyngeal infection upward to the nasal mucosa or downward to the larynx and tracheobronchial tree is much more common than primary infection at those sites.

Anterior Nasal Diphtheria. The onset of anterior nasal diphtheria is

indistinguishable from that of the common cold and is usually characterized by a mucopurulent nasal discharge which may become blood-tinged. A white membrane usually forms on the nasal septum. The disease is usually fairly mild because of apparent poor systemic absorption of toxin in this location, and it can be terminated rapidly by antitoxin and antibiotic therapy.

Pharyngeal and Tonsillar Diphtheria. Infection at these sites is the most common (one-half to two-thirds of cases) and is usually associated with substantial systemic absorption of toxin. The onset is often gradual. Early symptoms include malaise, difficulty in swallowing, loss of appetite, and a low-grade fever. Sore throat is the most common symptom, but children are less likely than adults to complain of sore throat and are more likely to have nausea and vomiting.

In tonsillopharyngeal diphtheria, only erythema (catarrhal diphtheria) may be noted initially, but isolated spots of gray or white exudate are common (islet diphtheria). These spots often extend and coalesce within a day to form a confluent, sharply demarcated bluish-white or greyish-green pseudomembrane varying in size from covering a small patch on the tonsils to covering most of the soft palate, pharynx that becomes progressively thicker, more tightly adherent to the underlying tissue, and darker gray (membranous diphtheria). Unlike the exudate in streptococcal pharyngitis, the diphtheritic pseudomembrane often extends beyond the margin of the tonsils onto the tonsillar pillars, palate, or uvula. The membrane is adherent to the tissue, and forcible attempts to remove it cause bleeding.

Patients with severe disease may develop extensive pseudomembrane formation, marked edema of the tonsils and uvula, submandibular areas and the anterior neck along with cervical lymphadenopathy, giving a characteristic "bullneck" appearance. In severe cases patients develop prostration, striking pallor, rapid pulse, stupor, and coma, and may even die within 6 to 10 days.

Laryngeal Diphtheria. Laryngeal diphtheria can be either an extension of the pharyngeal form or can only involve this site. Symptoms include fever, hoarseness, and a barking cough. The throat infection causes a gray-to-black, tough, fiber-like membrane, which can lead to airway obstruction, coma, and death. Demonstration of laryngeal pseudomembrane by laryngoscopy is helpful for distinguishing diphtheria from other infectious forms of laryngitis.

Cutaneous Diphtheria. Cutaneous diphtheria usually presents as an infection by C. diphtheriae of preexisting dermatoses involving, in decreasing order of frequency, the lower extremities, upper extremities, head, or trunk. Skin infections may be manifested by a scaling rash or by ulcers with clearly demarcated edges and membrane. Other sites of involvement include the mucous membranes of the conjunctiva genitourinary and gastrointestinal tracts, as well as the external auditory canal. The clinical features are similar to those of other secondary cutaneous bacterial infections. A wound infected diphtheria-causing bacteria is typically red, painful and

swollen and also may have patches of a sticky, gray material. In the tropics, the presentation of cutaneous diphtheria occasionally includes morphologically distinct "punched-out" ulcers that are covered by necrotic slough or membrane and have well-demarcated edges.

C. diphtheriae is an occasional cause of invasive infections, including endocarditis and septic arthritis. Risk factors for such infections include preexisting cardiac abnormalities, abuse of intravenous drugs, and alcoholic cirrhosis.

Complications. Obstruction of the respiratory tract, presenting as tachypnea, dyspnea, stridor, cyanosis, and use of accessory muscles of respiration, can be caused by extensive pseudomembrane formation and swelling during the first few days of the disease or by sloughed pseudomembrane that becomes lodged in the airways at a later stage in the disease. The risk of respiratory obstruction is greater when infection involves the larynx or the tracheobronchial tree and is higher in children because of the small size of the airways.

Table 5.

Diphtheritic croup

Clinical forms	Description
a) Localized croup (I – III stage)	- Larynx is affected (membranes, edema) - Severity is determined by the stage of croup
b) Diffuse croup (I – III stage)	- Other parts are involved besides the larynx (trachea, bronchus) - Severity is determined by the stage of croup
The croup passes 3 stages	
I stage catarrhal	- Edema and hyperemia of laryngeal mucous under laryngoscopy - Mild pyrexia - Productive cough → barking cough → hoarse voice
II stage stenotic	- Grey membranes on the laryngeal mucous - Intoxication, hypoxemia - Aphonia → soundless cough → noisy heavy respiration, breath is extended - Anxiety
III stage asphyctic	- Hypoxemia, cyanosis - Somnolence, adynamia - Thready pulse, arrhythmia - Forced position - Stop of breathing

Diphtheria toxin can cause serious systemic complications, including myocarditis, polyneuritis and neuropathies, if it is absorbed from the site of infection. The risk of developing these manifestations is proportional to the severity of local disease, and the two can occur together in the same patient. Myocarditis may present during the acute phase of illness (primary), develop as local disease is resolving, or begin insidiously after several weeks (secondary). One-half to two-thirds of patients with typical diphtheria have subtle evidence of cardiac dysfunction, including electrocardiographic abnormalities, but clinically apparent myocarditis develops in 10 to 25% of patients and is usually more severe when the onset is early. Electrocardiographic abnormalities include ST-T-wave changes, varying degrees of heart block, and arrhythmias, including atrial fibrillation, ventricular premature beats, ventricular tachycardia, and ventricular fibrillation. Clinical signs include diminished heart sounds, gallop rhythm, systolic murmurs, and (less commonly) acute or insidiously progressive congestive heart failure. Serum levels of aspartate aminotransferase reflect the intensity of myocardial damage and can be used to monitor its course.

Polyneuritis is uncommon in mild diphtheria but occurs in approximately 10% of cases of average severity and in up to 75% of severe cases. Bulbar dysfunction typically develops during the first 2 weeks. Palatal and pharyngeal paralyses usually develop first. Swallowing is difficult, the voice sounds nasal, and ingested fluids may be regurgitated through the nose. With unilateral pharyngeal infection, ipsilateral palatal paralysis is more common than contralateral or bilateral paralysis. Additional bulbar signs may develop over several weeks, with oculomotor and ciliary paralysis occurring more often than facial or laryngeal paralysis. Peripheral polyneuritis typically begins from 1 to 3 months after the onset of diphtheria with proximal weakness of the extremities that spreads distally. The severity of this condition varies from mild weakness of the pelvic muscles with unsteady gait to total paralysis, including failure of respiration. Paresthesias may develop and most often have a glove-and-stocking distribution. Approximately half of patients with diphtheritic neuropathy have evidence of cardiac vagal denervation, and fewer have abnormal baroreceptor function. Polyneuritis usually resolves completely, with the time needed for improvement approximately equal to that elapsing from exposure to the development of symptoms. Since severe muscular weakness may develop 1 to 2 weeks before maximal abnormalities in peripheral-nerve conduction velocity are demonstrated, there may be a striking dissociation between clinical and electrophysiologic findings. CSF most often contains moderately increased levels of albumin, occasionally with pleocytosis, but the abnormalities in CSF do not determine prognosis.

Secondary pneumonia may result from diaphragmatic paralysis and occurs in more than half of fatal cases of diphtheria. Other complications include otitis media,

respiratory insufficiency due to airway obstruction, especially in infants, renal failure, encephalitis, cerebral infarction, pulmonary embolism, and bacteremia or endocarditis due to invasive infection by C. diphtheriae. Serum sickness may result from antitoxin therapy.

Most cases of diphtheria develop in nonimmunized patients. The attack rate, severity of disease, and risk of complications are much lower in immunized patients. The pseudomembrane may continue to increase in size during the first day after administration of antitoxin. During the next several days to a week, it becomes softer, less adherent, and nonconfluent and eventually disappears. In the preantibiotic era, C. diphtheriae persisted in the throat for about 2 weeks in one-half of patients and for 1 month or more in about one-fifth. Mortality increases with the severity of local disease, the extent of pseudomembrane formation, and the interval between onset of local disease and administration of antitoxin. The death rate is highest during the first week of illness; among patients with bull-neck diphtheria; among patients with myocarditis who develops ventricular tachycardia, atrial fibrillation, or complete heart block; among patients with laryngeal or tracheobronchial involvement; among infants and patients over 60 years of age; and among alcoholics. Both mortality and the risk of myocarditis or peripheral neuropathy are significantly lower in cutaneous diphtheria than in respiratory diphtheria. Mortality rates of 30 to 40% were common in untreated disease and sometimes exceeded 50% in epidemics. Treatment with antitoxin reduced the case-fatality rate to 5 to 10%.

DIAGNOSIS

Diagnosis of respiratory diphtheria is usually made on the basis of clinical presentation since it is imperative to begin presumptive therapy quickly. A characteristic pseudomembrane on the mucosa of the oropharynx, palate, nasopharynx, nose, or larynx suggests diphtheria but is not uniformly present. Diphtheritic pseudomembrane must be distinguished from other pharyngeal exudates, including those of group A beta-hemolytic streptococcal infections, infectious mononucleosis, viral pharyngitides, fusospirochetal infection, and candidiasis. A diagnosis of diphtheria should be considered in patients with sore throat, cervical adenopathy or swelling, and low-grade fever, especially when these manifestations are accompanied by systemic toxicity, hoarseness, stridor, palatal paralysis, or serosanguineous nasal discharge with or without demonstrable pseudomembrane.

The definitive diagnosis of diphtheria depends on the isolation of C. diphtheriae from local lesions. It is critical to take a swab of the pharyngeal area, especially any discolored areas, ulcerations, and tonsillar crypts. Culture medium containing tellurite is preferred because it provides a selective advantage for the growth of this organism. A blood agar plate is also inoculated for detection of hemolytic streptococcus. If diphtheria bacilli are isolated, they must be tested for toxin production. Primary isolates can be screened rapidly for toxinogenicity by the

polymerase chain reaction, although occasional strains of C. diphtheriae that carry an inactive toxin gene give false-positive results.

Gram stain of material from the membrane itself can be helpful when trying to confirm the clinical diagnosis. The Gram stain may show multiple club-shaped forms that look like Chinese characters. Other Corynebacterium species (diphtheroids) that can normally inhabit the throat may confuse the interpretation of direct stain. The biochemical tests needed to differentiate C. diphtheriae from diphtheroids require several days. Group A beta-hemolytic streptococci and Staphylococcus aureus are also isolated frequently from patients with diphtheria. However, treatment should be started if clinical diphtheria is suggested, even in the absence of a diagnostic Gram stain. In the event that prior antibiotic therapy may have impeded a positive culture in a suspect diphtheria case, two sources of evidence can aid in presumptive diagnosis: 1) isolation of C. diphtheriae from cultures of specimens from close contacts, or 2) a low nonprotective diphtheria antibody titer (less than 0.1 IU) in serum obtained prior to antitoxin administration. This is done by commercial laboratories and requires several days. To isolate C. diphtheriae from carriers, it is best to inoculate a Löffler or Pai slant with the throat swab. After an incubation period of 18-24 hours, growth from the slant is used to inoculate a medium containing tellurite.

Cutaneous diphtheria may present as a characteristic punched-out ulcer with a membrane, but it is more often indistinguishable from other inflammatory dermatoses. Its diagnosis depends on a high degree of suspicion and on culture of cutaneous lesions on laboratory media appropriate for the isolation of C. diphtheriae. Throat samples from all patients with cutaneous diphtheria should be cultured for C. diphtheriae.

TREATMENT

Patients with respiratory or cutaneous diphtheria caused by tox+ strains or by strains of unknown toxinogenicity should be hospitalized, kept in bed initially, handled with isolation procedures appropriate for the site of infection, and given supportive care as needed. Respiratory and cardiac function must be monitored closely. Early intubation or tracheostomy is recommended when the larynx is involved or signs of impending airway obstruction are detected. Tracheobronchial membrane can sometimes be removed mechanically via the endotracheal tube or tracheostomy.

The decision to administer diphtheria antitoxin must be based on the clinical diagnosis of diphtheria without definitive laboratory confirmation, since each day of delay in treatment is associated with increased mortality. Antitoxin will not neutralize toxin that is already fixed to tissues, but it will neutralize circulating (unbound) toxin and will prevent progression of disease. Because diphtheria antitoxin is produced in horses, it is necessary to inquire about possible allergy to horse serum and to perform a conjunctival or intracutaneous test with diluted antitoxin for immediate

hypersensitivity. Epinephrine must be available for immediate administration to patients with severe allergic reactions. Patients with immediate hypersensitivity should be desensitized before a full therapeutic dose of antitoxin is given. The dose of diphtheria antitoxin currently recommended is based on the form of infection. Antitoxin is administered intramuscularly or intravenously by infusion in saline over 60 min to neutralize unbound toxin rapidly. The approximately 10% risk of serum sickness is acceptable because of the established therapeutic value of antitoxin in decreasing mortality from respiratory diphtheria. The potential systemic complications of cutaneous diphtheria must be weighed against the potential adverse effects of antitoxin treatment; authorities are not unanimous in recommending antitoxin therapy for cutaneous diphtheria. Antitoxin neither prevents colonization by C. diphtheriae nor eradicates the carrier state.

Table 6.

Diphtheria antitoxin treatment doses in adults

Clinical form	1st dose (IU)	Dosing regimen	Course dose (IU)	Comment
Subclinical	-	-	-	-
Mild	30.000-40.000	1	30.000-40.000	In bacteriocarriers with catarrhal process – 20.000 IU
Moderate	50.000-70.000	1-2	50.000-90.000	Repeatedly injected in the absence of the 1st dose effect
Severe	100.000-120.000	2-3 (every 12-24 hours)	250.000-300.000	During the first 2 days of treatment all dose is injected. 2 and 3 doses make up ¾ of the 1st dose.
Hypertoxic	130.000-150.000	2-3 (every 12 hours)	300.000-400.000	All doses are injected during first two days. 2 and 3 doses make up ¾ of the 1st dose.

Antibiotics have little demonstrated effect on the healing of local infection in diphtheria patients treated with antitoxin. The primary goal of antibiotic therapy for patients or carriers is therefore to eradicate C. diphtheriae and prevent its transmission from the patient to susceptible contacts. Erythromycin, penicillin G, rifampin, or clindamycin is recommended. The commonly recommended regimen for the treatment of adults with respiratory diphtheria is erythromycin (500 mg four times daily, given parenterally or orally) or intramuscular procaine penicillin G (600,000 units at 12-h intervals, given intramuscularly) for 14 days. Patients with cutaneous diphtheria and carriers can be treated orally with erythromycin (500 mg four times daily) or rifampin (600 mg once daily) for 7 days. If compliance is in question, a

single dose of benzathine penicillin G (1.2 to 2.4 million units intramuscularly) can be substituted. Eradication of C. diphtheriae should be documented by negative cultures of samples taken on two or three successive days, beginning at least 24 h after the completion of antibiotic therapy. It is also recommended to repeat throat culture 2 weeks later. The small percentage of patients who continue to be infected with C. diphtheriae after treatment should receive an additional 10-day course of oral erythromycin or rifampin.

Primary or secondary pneumonia should be diagnosed and treated promptly. Sedative or hypnotic drugs that may mask respiratory symptoms are contraindicated. Close electrocardiographic monitoring, treatment of arrhythmias, and electrical pacing for heart block is essential. Glucocorticoids do not reduce the risk of diphtheritic myocarditis or polyneuritis. Oral therapy with DL-carnitine (100 mg/kg per day, given in twice-daily doses for 4 days) may have a beneficial effect in diphtheritic myocarditis. Ulcerative or ecthymatous cutaneous lesions should be treated with Burow's solution applied on wet compresses after debridement of necrotic areas, and treatment for associated conditions such as pediculosis, scabies, or underlying dermatoses should be instituted.

PREVENTION

Close contacts of patients with diphtheria should be cultured for C. diphtheriae, kept under surveillance for 1 week, and treated with appropriate antibiotics if cultures are positive (benzathine penicillin G – 600,000 units for persons younger than 6 years old and l,200,000 units for those 6 years old and older or a 7- to 10-day course of oral erythromycin – 40 mg/kg/day for children and 1 g/day for adults). Identified carriers in the community should also receive antibiotics. Previously immunized close contacts should receive an appropriate booster injection including diphtheria toxoid if their last booster dose was given more than 5 years previously. If their immunization status is uncertain, close contacts should receive a primary immunization series appropriate for their age.

Vaccines for immunization against diphtheria include diphtheria and tetanus toxoids (nontoxic products which converts from toxins by treating with formaldehyde) and pertussis vaccine adsorbed (DTP), diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DTaP), diphtheria and tetanus toxoids adsorbed (DT; for pediatric use), and tetanus and diphtheria toxoids adsorbed (Td; for adult use). The adsorbent is alum, which functions as an adjuvant and enhances the immunogenicity of the vaccines. Immunization with toxoid elicits antibody (antitoxin) that neutralizes the toxin and prevents infection.

DTaP is the vaccine of choice for children 6 weeks through 6 years of age. The usual schedule is a primary series of 4 doses at ages 3, 4, 5 and 18 months (2, 4, 6 and between 15-18 months in USA) administered as 0.5 ml intramuscularly. The first, second, and third doses of DTaP should be separated by a minimum of 4 weeks. The

fourth (booster) dose should follow the third dose by no less than 6 months, and should not be administered before 12 months of age. If a child has a valid contraindication to pertussis vaccine, pediatric DT should be used to complete the vaccination series. If the child was younger than 12 months old when the first dose of DT was administered (as DTP, DTaP, or DT), the child should receive a total of four primary DT doses. If the child was 12 months of age or older at the time the first dose of DT was administered, three doses (third dose 6-12 months after the second) complete the primary DT series. If the fourth dose of DT, DTP or DTaP is administered before the fourth birthday, a fifth (booster) dose is recommended at 6 years of age (between 4-6 years in USA) before entry into elementary school. The fifth dose is not required if the fourth dose was given on or after the fourth birthday.

Because of waning antitoxin titers, most persons have antitoxin levels below the optimal level 10 years after the last dose. Tetanus toxoid should be given with diphtheria toxoid as Td every 10 years. Td is the vaccine of choice for children 7 years and older and for adults. Td contains less diphtheria toxoid than DTP, DTaP, or DT and causes fewer adverse reactions in adults. The booster dose may be given at 14 years of age (11-12 years in USA) and at 18 years (through 10 years after previous booster in USA). If a dose is given sooner as part of wound management, the next booster is not needed for 10 years thereafter. More frequent boosters are not indicated and have been reported to result in an increased incidence and severity of local adverse reactions.

For unvaccinated persons 7 years and older (including persons who cannot document prior vaccination), the primary series is three doses. The first two doses should be separated by at least 4 weeks, and the third dose given 6 months after the second. Booster dose follows the third dose after 6 months.

Interruption of the recommended schedule or delay of subsequent doses does not reduce the response to the vaccine when the series is finally completed. There is no need to restart a series regardless of the time elapsed between doses. Diphtheria disease might not confer immunity. Persons recovering from diphtheria should begin or complete active immunization with diphtheria toxoid during convalescence.

No specific amount of antitoxin provides absolute protection against diphtheria, but the attack rate and the mortality rate for diphtheria are much lower in individuals with 0.01 unit of antitoxin per milliliter. If most individuals in a population have antitoxic immunity, however, the carriage of tox^+ strains of C. diphtheriae decreases to a low level. Thus, herd immunity reduces the risk that nonimmune individuals in the population will be exposed to tox^+ C. diphtheriae. Nonimmune individuals may contract diphtheria if they travel to regions where the disease is present or if tox^+ strains of C. diphtheriae are introduced into their community.

ANGINA

DEFINITION *Angina – acute infection disease caused by streptococci and/or staphylococci, characterized by intoxication, fever, inflammatory process in lymphatic tissues of oropharynx (pharyngeal cycle of Pirogov-Valdeer).*

ETIOLOGY

Streptococci are gram-positive bacteria of spherical to ovoid shape that characteristically form chains when grown in liquid media. Most streptococci that cause human infections are facultative anaerobes, although some are strict anaerobes. Streptococci are relatively fastidious organisms, requiring enriched media for growth in the laboratory. Many of the streptococci associated with human infection produce a zone of complete hemolysis around the bacterial colony when cultured on blood agar, a pattern known as beta hemolysis. The β-hemolytic streptococci can be classified by the Lancefield system, a serologic grouping based on the reaction of specific antisera with cell-wall carbohydrate antigens of the bacteria. With rare exceptions, organisms belonging to Lancefield groups A, B, C, and G are all β-hemolytic streptococci, and each is associated with characteristic patterns of human infection. The most important bacterial cause of angina is group A Streptococcus (Streptococcus pyogenes). The cell wall contains a carbohydrate antigen that may be released by treatment with acid. The reaction of such acid extracts with group A-specific antiserum is the basis for the definitive identification of a streptococcal strain as S. pyogenes. This organism is responsible for about 15% of all cases of exudative pharyngitis (20-40% in children) and uniquely associated with postinfectious syndromes of acute rheumatic fever and poststreptococcal glomerulonephritis. Group C and group G streptococci occasionally cause human infections similar to those caused by group A streptococci.

Other streptococci produce a zone of partial, or alpha, hemolysis, often imparting a greenish appearance to the agar. These α-hemolytic streptococci are identified more specifically by biochemical testing and include S. pneumoniae and several species of streptococci referred to collectively as the viridans streptococci. Several species of viridans streptococci, including S. salivarius, S. mutans, S. sanguis, and S. mitis, are part of the normal flora of the mouth, where they live in close association with the teeth and gingiva. Finally, some streptococci are nonhemolytic, a pattern sometimes called gamma hemolysis. Anaerobic streptococci, or peptostreptococci, are part of the normal flora of the oral cavity, bowel, and vagina. They are involved, usually along with other organisms, in odontogenic infections (Ludwig's angina, abscesses of the retropharyngeal or lateral pharyngeal space).

Staphylococci are nonmotile, nonsporulating gram-positive cocci, 0.5 to 1.5 um in diameter, that occur singly and in pairs, short chains, and the irregular three-dimensional clusters. Staphylococci can grow over a wide range of environmental conditions, but they grow best at temperatures between 30°C and 37°C and at a pH

around neutrality. They are resistant to desiccation and to chemical disinfectants, and they tolerate NaCl concentrations up to 12%. With rare exceptions, the staphylococci are facultatively anaerobic and catalase-positive. The more virulent staphylococci can clot plasma (coagulase-positive), while the less virulent cannot (coagulase-negative). Of the five recognized coagulase-positive staphylococcal species, the only important human pathogen is Staphylococcus aureus, whose colonies are larger than those of S. epidermidis, are often pigmented (golden yellow), and are usually α-hemolytic on sheep blood agar. Twenty-seven species of coagulase-negative staphylococci are recognized. Of these, S. epidermidis is by far the most common nonurinary human isolate. Strains of S. epidermidis are typically white and nonhemolytic and may be tenaciously adherent as a result of their production of polysaccharide adhesin.

EPIDEMIOLOGY

Angina are usually caused by endogenous flora i.e., strains of Streptococci or Staphylococci that are hardy and ubiquitous colonizers of human skin and mucous membranes. Colonization may be intermittent or persistent and is probably influenced by both microbial and host factors. Carriage is more common among persons with habitual or chronic disruption of cutaneous epithelial integrity. Thus, health care workers, dialysis patients, diabetic patients, injection drug users, and persons with chronic dermatologic conditions are often colonized. Colonization of mucocutaneous sites is an important risk factor for infection. Angina is acquired through contact with another individual carrying the organism in nasopharynx, on the skin, or in the vagina, anus etc. The risk of transmitting infection to others is substantially lower among asymptomatic carriers than among individuals with symptomatic pharyngitis. Airborne droplets are the usual mechanism of spread, although other routes, including food-borne outbreaks, have been well described. The risk of person-to-person transmission is greatest at the onset of symptoms, when the numbers of organisms colonizing the throat and nose is highest. Streptococcal angina occurs most commonly in winter and early spring.

PATHOGENESIS

Pathogenesis involves bacterial colonization and proliferation, evasion or neutralization of host defenses, production and absorption of toxins, intoxication, invasion or destruction of host tissues, local and systemic responses by the host to these events.

Group A ***streptococci*** elaborate a number of cell-surface components and extracellular products important both in the pathogenesis of infection and in the immune response of the human host. The major surface protein is M protein, which occurs in more than 80 antigenically distinct types and is the basis for the serotyping of strains with specific antisera. The M protein molecules are fibrillar structures anchored in the cell wall of the organism and extending as hair - like projections away from the cell surface. The amino acid sequence of the distal or amino-terminal

portion of the M protein molecule is quite variable, accounting for the antigenic variation of the different M types, while more proximal regions of the protein are relatively conserved. The presence of M protein correlates with the capacity of a strain to resist phagocytic killing in fresh human blood; this phenomenon appears to be due, at least in part, to the binding of plasma fibrinogen to M protein molecules on the streptococcal surface, which interferes with complement activation and deposition of opsonic complement fragments on the bacterial cell. This resistance to phagocytosis may be overcome by M protein-specific antibodies, and thus individuals with antibodies to a given M type acquired as a result of prior infection are protected against subsequent infection with organisms of the same M type but not against that with different M types.

Group A streptococci also elaborate (to varying degrees) a polysaccharide capsule composed of hyaluronic acid. The production of large amounts of hyaluronic acid capsule by certain strains results in a characteristic mucoid appearance of the bacterial colonies. The capsular polysaccharide also plays an important role in protecting the organisms from ingestion and killing by phagocytes. In contrast to M protein, the hyaluronic acid capsule is a weak immunogen, presumably because of the apparent structural identity between streptococcal hyaluronic acid and the hyaluronic acid of mammalian connective tissues. Antibodies to hyaluronate have not been shown to be important in protective immunity.

Group A streptococci produce a large number of extracellular products that may be important in local and systemic toxicity and in the spread of infection through tissues. These products include streptolysins S and O, toxins that damage cell membranes and account for the hemolysis produced by the organisms; streptokinase; DNases; protease; and pyrogenic exotoxins A, B, and C (cause the rash of scarlet fever, necrotizing fasciitis and a systemic syndrome termed toxic shock-like syndrome). Several extracellular products stimulate specific antibody responses useful in the serodiagnosis of recent streptococcal infection.

Rheumatic fever is a sequel to streptococcal angina, although poststreptococcal glomerulonephritis may follow either skin or throat infection. The reason for this difference is not known. One hypothesis is that the immune response necessary for the development of rheumatic fever occurs only after infection of the pharyngeal mucosa. In addition, the strains of group A streptococci that cause pharyngitis generally have a different type of M protein than those associated with skin infections; thus, the strains that cause pharyngitis may have rheumatogenic potential, while the skin-infecting strains may not.

Staphylococcal adherence to the nasal mucosa is mediated by cell wall and cell membrane ribitol teichoic acid. After colonization, the production of certain staphylococcal toxins (toxic shock syndrome toxin-1, enterotoxins) can ensue if the appropriate environmental signals are present. Toxin absorption leads to systemic

intoxication. Alternatively, colonization may persist for a while before the organism is cleared. If in the meantime the organism gains access to deeper tissues, the process of infection may begin.

S. aureus can adhere to any of several molecules present either on cell surfaces or in the extracellular matrix. These molecules include fibrinogen, fibronectin, laminin, thrombospondin, collagen, elastin, vitronectin, and bone sialoprotein. A number of products of S. aureus alter the host environment in a way that benefits the bacterium. Coagulase is a secreted enzyme that binds prothrombin and thereby causes the conversion of fibrinogen to fibrin; it may aid in the establishment of an environment within host tissues that is protected from cells of the immune system or from antibiotics. Hyaluronidase hydrolyzes hyaluronic acid, a mucopolysaccharide present in extracellular ground substance; its action may ease the spread of the organism through the extracellular matrix. Fatty acid-modifying enzyme inactivates mammalian staphylocidal lipids, which accumulate during development of the staphylococcal abscess and which are thought to be a component of the body's nonspecific antistaphylococcal defense. Staphylokinase, thermonuclease, and serine protease are other extracellular enzymatic products that may play roles in pathogenesis.

S. aureus also produces a number of membrane-active toxins that probably contribute to pathogenesis by damaging host cells. These toxins include α-, β-, and γ-hemolysins and the synergohymenotropic toxins (α-hemolysin and Panton-Valentine leukocidin). α-Hemolysin is the prototypic pore-forming toxin; it inserts into the cell membrane, creating ion-conductive channels that destroy membrane integrity. β-Hemolysin is a sphyngomyelinase that exhibits species-specific hemolytic activity dependent on the sphyngomyelin content of the target cell membrane. Little is known about γ-hemolysin, although it appears to exert a detergent-like effect on cell membranes. The synergohymenotropic toxins are a newly described family of bicomponent toxins. Their name derives from the fact that their two components, which are secreted separately, are tropic for cell membranes and are synergistically active against them. The synergohymenotropic toxins are pore-forming toxins. Panton-Valentine leukocidin is most active against polymorphonuclear cells, monocytes, and macrophages. α-Hemolysin is active against a wide range of mammalian erythrocytes.

Once staphylococci have breached mucosal barrier, the host's immune response is directed at containing and eliminating them, principally by polymorphonuclear recruitment and phagocytic killing. The bacteria fight back by cloaking antigenic determinants on their surface, by interfering with the function of opsonins, by directly killing the phagocytes, and by developing strategies to survive within them. The pyogenic abscess represents the battlefield for this encounter and in some sense benefits both the microorganism and the host. The microorganism by providing an

environment in which leukocyte function is impaired and into which antibiotics penetrate poorly, and the host by containing the spread of the bacteria.

Certain staphylococcal components and products are direct chemoattractants for polymorphonuclear leukocytes; others provoke the release of chemoattractant cytokines that recruit phagocytic cells to the infected area. The toxic action of staphylococcal leukocidin may in part explain the zone of necrosis. After several days, fibroblasts populate the margin of the abscess and there elaborate collagen, which creates a true capsule around the abscess.

Staphylococcal cell wall peptidoglycan activates complement, which is an important opsonin in persons lacking antibody to staphylococcal surface components. Peptidoglycan also acts as a general stimulator of inflammatory cytokine release but is much weaker in this regard than gram-negative lipopolysaccharide.

Opsonic antibodies specific for peptidoglycan or capsule also mediate phagocytosis. There is considerable interstrain variation in susceptibility to opsonization, and acquired protective immunity to staphylococcal infection is generally thought not to develop. At least two staphylococcal products mitigate against opsonization. Polysaccharide capsule is produced by about 80 percent of clinical isolates and lies external to the cell wall; it physically interferes with opsonization by complement. Protein A, an important cell surface component, binds the Fc portion of IgG subclasses 1, 2, and 4 and thereby interferes with antibody-mediated opsonization. Acquired antibody-mediated immunity to systemic staphylococcal intoxications (as opposed to infections) does occur.

Opsonized organisms are efficiently ingested by polymorphonuclear leukocytes and macrophages. Most are then killed rapidly by the oxidative burst within the phagosome. Staphylococcal catalase, which converts hydrogen peroxide to oxygen and water, detoxifies oxygen radicals and potentiates intracellular bacterial survival. Staphylococci are also taken up by nondedicated phagocytes, such as endothelial cells and osteoblasts, and may survive within them. Yet another staphylococcal strategy for intracellular survival is the genesis of so-called small-colony variants. These slow-growing cells exhibit alterations in electron transport and generally produce reduced amounts of virulence determinants such as α-toxin. They are relatively resistant to antibiotics and appear capable of persisting intracellularly for extended periods. Their existence may in part explain the startling capacity of certain S. aureus infections (e.g., chronic osteomyelitis) to recrudesce after years of dormancy.

The superantigens are Vα-restricted T cell mitogens: they bind directly and without prior processing to major histocompatibility class II molecules on the surface of antigen-presenting cells, thereby stimulating T cells on the basis of the sequence of the variable region of the α-chain of the T cell receptor rather than on the basis of the epitope specified by this receptor. Accordingly, a superantigen may be able to

stimulate up to about 10 % of the T cells in a given individual a percentage much higher than the approximately 1 in 106 cells stimulated by conventional antigens. This massive T cell stimulation provokes an exuberant and dysregulated immune response characterized by the release of the cytokines interleukins 1 and 2, tumor necrosis factor, and interferon. S. aureus produces a number of superantigens, including the staphylococcal enterotoxins (SEs), TSST-1, and possibly the exfoliative toxins (ETs). Eight SEs are currently known (enterotoxins A, B, C1-3, D, E, and H) and are the causative agents of staphylococcal food poisoning. The mechanism by which the SEs cause vomiting is uncertain but may involve direct neural stimulation of the autonomic nervous system rather than a local effect on the gastrointestinal mucosa. The superantigenic properties of TSST-1 are thought to explain its ability to cause TSS, although the exact mechanism by which it crafts the various clinical manifestations of TSS is uncertain. There is conflicting evidence as to whether the ETs, which cause scalded skin syndrome, are superantigens; structural data suggest that they may instead be related to the serine proteases.

CLINICAL MANIFESTATIONS

Clinical classification of angina

By etiology:

a) Streptococcus
b) Strepto-staphylococcus
c) Staphylococcus
d) Fusospirochetal

By localization of pathological process:

a) palatine tonsils (*tonsilla palatina*)
b) pharyngeal tonsil (*tonsilla pharyngealis*)
c) lingual tonsil (*tonsilla lingualis*)
d) tonsils of torus tubaris (*tonsilla tubaris*)
e) tororum levatorium
f) lymphoid formations of pharynx posterior wall
g) lymphoid formations of larynx

By character of inflammatory process:

a) catarrhal
b) lacunar
c) follicular
d) necrotic

By severity:

a) mild
b) moderate
c) severe

By rate:

a) primary
b) recurrent

By complications:

a) uncomplicated
b) complicated

After incubation period of 1 to 4 days sudden onset of sore throat, headache, fever, chills, malaise, and sometimes abdominal complaints and vomiting (particularly in children) occur. Both symptoms and signs are quite variable, ranging from scratchy or mild throat discomfort with minimal physical findings (mimic the pharyngitis of the common cold but without significant coryza or cough) to high fever and severe pain in the tonsil area, painful/difficult swallowing, associated with intense erythema and swelling of the tonsillar or pharyngeal mucosa and the presence

of purulent exudate over the posterior pharyngeal wall and tonsillar pillars. Enlarged, tender anterior cervical lymph nodes commonly accompany exudative pharyngitis. In the usual course of uncomplicated angina, symptoms resolve after 3 to 5 days. The course is shortened little by treatment, which is given primarily to prevent suppurative complications and rheumatic fever.

Complications of angina result from the spread of infection from the pharyngeal mucosa, either by direct extension or by the hematogenous or lymphatic route, and may include suppurative cervical lymphadenitis, sinusitis, otitis media, endocarditis, meningitis, pneumonia, septic arthritis, osteomyelitis, peritonitis, and visceral abscesses. Rarely, the infection may spread beyond the tonsil resulting in inflammation and infection of the internal jugular vein giving rise to a spreading septicaemia infection (Lemierre's syndrome). In very rare cases, diseases like rheumatic fever or glomerulonephritis can occur. These complications are extremely rare in developed nations but remain a significant problem in poorer nations.

Local complications, such as abscess formation in the peritonsillar or parapharyngeal space, should be considered in a patient with unusually severe or prolonged symptoms or localized pain associated with high fever and a toxic appearance. In quinsy patients speak with a "hot-potato" voice. Examination reveals pronounced unilateral peritonsillar swelling and erythema causing deviation of the uvula.

Clinical manifestation of angina

Course of angina:

1. Incubation period (1-2 days)
2. Initial period (few hours - to 1 day)
3. Climax period
4. Convalescence (early and late)

Criteria of angina severity:

1. Degree and duration of fever
2. Level of intoxication
3. Character of inflammatory process
4. Functional disorders of nervous, cardiovascular and other systems and organs.
5. Presence of early or late complications.

Complications of angina:

1. tonsillar abscess
2. paratonsillar abscess
3. parapharyngeal phlegmon
4. meningitis
5. mediastinitis
6. cervical lymphadenitis
7. retropharyngeal abscess
8. tonsillar sepsis
9. chronic tonsillitis
10. myocarditis
11. tonsillocardial syndrome
12. rheumatism
13. glomerulonephritis
14. cholangiocholecystitis

DIAGNOSIS

The throat swab (agar plate culture) remains the gold standard for diagnosis. Culture of a throat specimen that is properly collected (i.e., by vigorous rubbing of a sterile swab over both tonsillar pillars) and properly processed is the most sensitive and specific means available by which to make a definitive diagnosis. But the throat swab has its limitations as there are no agreed criteria for differentiating between infection and carriage. Errors can arise when the swab is positive because of carriage rather than streptococcal/staphylococcal infection, the symptoms being due to concurrent viral infection.

Follow-up culture after treatment is no longer routinely recommended but may be warranted in selected cases, such as those involving patients or families with frequent streptococcal infections or those occurring in situations in which the risk of rheumatic fever is thought to be high (for example, when cases of rheumatic fever have recently been reported in the community).

Plasma levels of C-reactive protein increase rapidly in response to infection, the rise being significantly greater with bacterial sore throat than with a viral upper respiratory infection. Titers of anti-streptolysin O (ASO) rises too late to help in the immediate management of angina but can confirm recent streptococcal infection retrospectively in patients who remain unwell or develop complications.

Rapid antigen detection tests using latex agglutination or enzyme immunoassay of swab specimens are now widely available and can serve as a useful adjunct to the throat culture. These tests are specific but not very sensitive (relative sensitivity ranging from 55 to 90%): a positive test may be considered equivalent to a positive culture, but a negative test requires culture confirmation.

Differential diagnosis. Other causes of acute exudative pharyngitis include infectious mononucleosis and adenovirus infection, especially in young adults. Diphtheria may give a similar appearance. Occasionally infection with Arcanobacterium haemolyticum, which mainly affects 10-20 year olds and responds best to erythromycin, produces pharyngitis, often in association with a scarlet fever-like rash. Other causes of pharyngitis, usually without a purulent exudate, include infections with rhinovirus, coronavirus, coxsackievirus, parainfluenza or influenza viruses, Mycoplasma pneumoniae and Chlamidia pneumoniae, Neisseria gonorrhoeae and Yersinia enterocolitica. Fever and nonexudative pharyngitis are common symptoms of the acute retroviral syndrome that develops several weeks after infection with HIV. Because of the large number of other agents that can produce the same clinical picture, the diagnosis of angina on clinical grounds alone is not reliable. Although some patients may in fact have viral pharyngitis and may simply be colonized with group A streptococci, these individuals must nevertheless be treated for presumed streptococcal pharyngitis.

TREATMENT

Therapy is intended to relieve symptoms, prevent complications and limit spread of the illness by eradicating the infecting strains from the pharynx. Antibiotic treatment should be started immediately without waiting for the result of a throat swab. Eradication of streptococci and staphylococci from the tonsillopharynx by use of antibiotics is the essential outcome to prevent suppurative and nonsuppurative sequelae, abate symptoms, prevent contagion and requires a single 10-day course of oral penicillin treatment. Shorter treatment eradicates pathogen less effectively and clinical recurrence is more common, so patients should be told to complete the course even if they feel better. Without treatment eradication of pathogenic microorganisms takes up to 4 months. Erythromycin may be substituted for penicillin in the treatment of individuals allergic to penicillin. 10 days' treatment is effective given in four times daily or twice daily dosage, but unwanted gastrointestinal effects are common. Newer macrolides such as clarithromycin cause fewer unwanted effects but are expensive and no more effective against resistant strains.

Broad-spectrum antibiotics that are active against beta-lactamase-producing organisms may be used (e.g., cephalexin, amoxicillin, cefuroxime, or cefprozil), although studies of the prevention of rheumatic fever are available only for penicillin. Because of the poor clinical response of some patients treated with penicillin alone, the addition of gentamicin (1 mg/kg every 8 h for patients with normal renal function) is recommended for the treatment of complicated angina (endocarditis, septic arthritis etc.).

In peritonsillar abscess immediate aspiration by an otolaryngologist is required in conjunction with antibiotic therapy with penicillin plus metronidazole, clindamycin, or ampicillin/sulbactam.

In many cases of tonsillitis, the pain caused by the inflamed tonsils warrants the prescription of topical anesthetics for temporary relief. Viscous lidocaine solutions are often prescribed for this purpose. Ibuprofen, paracetamol or other analgesic can help to decrease the edema and inflammation which will ease the pain and allow the patient to swallow liquids sooner. Also using warm water and salt solution, and gargling contrary to common belief will not kill the infection, however may reduce pain and swelling.

PREVENTION

Aggressive attempts to eradicate carriage are the situation in which an asymptomatic carrier is a potential source of infection to others. The combination of penicillin and rifampin has been used to eliminate pharyngeal carriage, and the addition of oral vancomycin has led to success in eradicating rectal colonization.

PLAUT-VINCENT ANGINA

DEFINITION *Plaut-Vincent angina (trench mouth, acute necrotizing ulcerative gingivitis) is a polymicrobial progressive infection of the fauces characterized by ulcerations, necrosis of the mucous membranes, bleeding, and foul breath.*

ETIOLOGY

Causative organisms include anaerobes residing in the mouth, especially gram-positive Peptostreptococcus spp. (P. magnus, P. asaccharolyticus, P. anaerobius, P. prevotii, etc.), gram-negative bacilli from Bacteroidales order (Bacteroides fragilis group, Fusobacterium spp., Prevotella spp., Porphyromonas spp.), Bacillus spp. (B. fusiformis) and as well as spirochetes (Borrelia spp. and Treponema spp.).

Bacteroides spp. are anaerobic bacteria that are predominant components of the bacterial florae of mucous membranes and are therefore a common cause of endogenous infections. The B. fragilis group contains the pathogens most frequently isolated from clinical infections (B. fragilis, B. thetaiotaomicron, B. distasonis, B. vulgatus, B. uniformis, and B. ovatus). Of this group, B. fragilis is the most important clinical isolate. However, B. fragilis is isolated from the normal fecal flora at a lower frequency than other Bacteroides species. Pigmented Prevotella, such as Prevotella melaninogenica and Prevotella intermedia (which were previously called the Bacteroides melaninogenicus group), Porphyromonas (e.g., Porphyromonas asaccharolytica), and nonpigmented Prevotella (eg, Prevotella oralis, Prevotella oris) are part of the normal oral and vaginal florae. Because of Bacteroidaceae fastidiousness, they are difficult to isolate and are often overlooked. Their isolation requires appropriate methods of collection, transportation, and cultivation of specimens.

EPIDEMIOLOGY

The condition is caused by an overpopulation of established mouth bacteria due to a number of interacting factors and predisposing conditions such as poor hygiene, poor diet, smoking, previous surgery, immunodeficiency, malignancy, trauma, diabetes, steroid therapy, presence of a foreign body, reduced blood supply, vascular disease, genetic deficiency of catalase, sickle cell anemia, etc.).

PATHOGENESIS

Anaerobic bacteria isolated from infected sites have survived changes in oxidation-reduction potential and exposure to host defenses. Because of the specific growth requirements of anaerobic organisms and their presence as commensals on mucosal surfaces, conditions must arise that allow these organisms to penetrate mucosal barriers and enter tissue with a lowered oxidation-reduction potential. Therefore, tissue ischemia, trauma, surgery, shock provide environments conducive to the proliferation of anaerobes. Some highly fastidious anaerobes lack the enzyme superoxide dismutase, which in other organisms reduces toxic superoxide radicals

and thereby lessens the potentially lethal effects of superoxide.

The ability of an organism to adhere to host tissues is important to the establishment of infection. These organisms have fimbriae or pili that facilitate attachment. The most extensively studied virulence factor of the nonsporulating anaerobes is the polysaccharide capsule of B. fragilis. This polysaccharide possesses distinct biologic properties, such as the ability (owing to a unique motif of charged sugars) to promote abscess formation in a rodent model of intraabdominal sepsis. Abscess induction is a T cell-dependent phenomenon. Immunization with the capsule confers protection against abscess induction following challenge with B. fragilis or other intestinal microorganisms capable of inducing abscesses. This protection is mediated by a T cell circuit that blocks the tissue response of abscess formation.

Anaerobic bacteria produce a number of exoproteins that are capable of enhancing the organisms' virulence. These enzymes include a heparinase elaborated by B. fragilis that may contribute to intravascular clotting and necessitate increased doses of heparin for patients receiving heparin therapy. Collagenase, produced by P. gingivalis, may enhance tissue destruction. Alteration of the secretory cytoskeleton of epithelial cells by an enterotoxin from B. fragilis has been described. Both B. fragilis and P. melaninogenica possess lipopolysaccharides (endotoxins) that lack the biologic potency characteristic of endotoxins associated with aerobic gram-negative bacteria.

CLINICAL MANIFESTATIONS

The onset of disease is usually sudden and is associated with sore throat, sensation of choking, foul breath and a bad taste. Symptoms may be accompanied by fever. Examination of the pharynx demonstrates that the tonsillar pillars are swollen, red, ulcerated, and covered with a grayish membrane which is removable with gentle pressure. Acute necrotizing infection of the tonsils and pharynx usually occur in association with ulcerative gingivitis. The gingival mucosa, especially the papillae between the teeth, becomes ulcerated and may be covered by a gray exudate, associated with tender bleeding gums.

The disease may last for only a few days or, if not treated, may persist for weeks. Patients may become systemically ill, developing fever, cervical lymphadenopathy, and leukocytosis. Lesions begin unilaterally but may spread to the other side of the pharynx or the larynx, to the buccal mucosa, the teeth, and the mandible or maxilla, resulting in widespread destruction of bone and soft tissue. This infection is termed acute necrotizing ulcerative mucositis (cancrum oris, noma). It destroys tissue rapidly, causing the teeth to fall out and large areas of bone or even the whole mandible to be sloughed. A strong putrid odor is frequently detected, although the lesions are not painful. The gangrenous lesions eventually heal, leaving large disfiguring defects. This infection is seen most commonly following a debilitating illness or in severely malnourished children.

DIAGNOSIS

Because of the time and difficulty involved in the isolation of anaerobic bacteria, diagnosis of this infection must frequently be based on presumptive evidence. A foul odor is often indicative of anaerobes, which produce certain organic acids as they proliferate in necrotic tissue. Although the presence of these odors is nearly pathognomonic for anaerobic infection, the absence of odor does not exclude these organisms as etiologic agents. Because anaerobes often coexist with other bacteria to cause mixed or synergistic infection, Gram's staining of exudate frequently reveals numerous pleomorphic cocci and bacilli suggestive of anaerobes. Sometimes these organisms will have morphologic characteristics associated with specific species.

In general, swabs should not be used. If a swab must be used, it should be placed in a reduced semisolid carrying medium before transport to the laboratory. Delays in transport may lead to a failure to isolate anaerobes due to exposure to oxygen or overgrowth of facultative organisms, which may eliminate or obscure the anaerobes that are present. When cultures of obviously infected sites yield no growth, streptococci only, or a single aerobic species such as Escherichia coli, and Gram's staining reveals a mixed flora, the implication is that the anaerobic microorganisms failed to grow because of inadequate transport and/or culture techniques. Failure of a patient to respond to antibiotics that are not active against anaerobes for example, aminoglycosides and in some circumstances penicillin, cephalosporins, or tetracyclines suggests the possibility of anaerobic infection.

TREATMENT

Patients with Plaut-Vincent angina require treatment with appropriate antibiotics. Because culture results are often not available, many patients are treated empirically. Treatment is complicated by increasing resistance of microorganisms to antimicrobial agents and the polymicrobial synergistic nature of the infection. Because anaerobic bacteria are generally recovered mixed with aerobic organisms, the appropriate choice for antimicrobial agents should provide adequate treatment of both groups of pathogens.

The efficacy of macrolides (e.g., erythromycin) and imidazoles (e.g., metronidazole) is variable and unpredictable. Imidazoles are ineffective against some anaerobic gram-positive cocci and all aerotolerant strains. They cannot be administered as a single agent in mixed infections.

Ciprofloxacin should not be used as primary agents against B. fragilis. 40-60% of the clinical isolates classified as Prevotella or Porphyromonas, Bacteroides, or Fusobacterium species have been reported as producing β-lactamase. The newer quinolones (trovafloxacin, moxifloxacin, and gatifloxacin) are effective against more than 90% of anaerobic cocci; ciprofloxacin is less effective. The use of the quinolones is restricted in growing children and pregnancy because of their possible

adverse effects on the cartilage. Penicillin G is still the drug of choice against most non-beta-lactamase-producing anaerobic bacteria. However, in addition to the B. fragilis group, which is resistant to penicillin, pigmented Prevotella and Porphyromonas species, P. bivia, P. disiens, Bilophila wadsworthia, and Bacteroides splanchnicus show increased resistance. The combination of beta-lactamase inhibitors (eg, clavulanic acid, sulbactam, tazobactam) with a beta-lactam antibiotic (eg, ampicillin, amoxicillin, ticarcillin, piperacillin) can overcome these beta-lactamase-producing microorganisms.

The B. fragilis group, Prevotella species, and Porphyromonas species are resistant to first-generation cephalosporins by virtue of cephalosporinase production. Cefoxitin is the most effective cephalosporin against the B. fragilis group, although 5-15% may be resistant. Other second-generation cephalosporins, such as cefotetan and cefmetazole, have a longer half-life than cefoxitin and are as effective as cefoxitin against B. fragilis; however, they are less efficacious against other members of the B. fragilis group.

Chloramphenicol shows excellent in vitro activity against most anaerobic bacteria, and resistance is rare; however, the development of less-toxic newer agents has limited their use.

Clindamycin is effective against anaerobes and has good activity against aerobic gram-positive cocci. Resistance of the B. fragilis group is 5-25%. Antibiotic-associated colitis due to Clostridium difficile, although associated with most antimicrobials, was first described following clindamycin therapy.

Glycylcyclines (tigecycline) has effective in vitro activity against both gram-positive and gram-negative anaerobes, as well as against gram-positive aerobic strains such as methicillin-resistant staphylococci, streptococci, and enterococci. Other effective agents include carbapenems (imipenem, meropenem, doripenem, and ertapenem), glycopeptides (vancomycin, teicoplanin), ketolides (telithromycin), oxazolidinones (linezolid), and streptogramins (quinupristin/dalfopristin).

Additional treatment is the simple reduction of the bacteria through improved oral cleaning and salt water or hydrogen peroxide-based rinses. Chlorhexidine can also be used in addition.

MENINGOCOCCAL INFECTION

DEFINITION *Meningococcal infection – acute infectious disease caused by Neisseria meningitidis, with airborne route of transmission and characterizes by nasopharyngitis or generalized infection (meningococcemia and meningitis).*

Invasion of the bloodstream by *Neisseria meningitidis* causes a spectrum of diseases ranging from an overwhelming infection that is rapidly fatal to a transient bacteremia that is relatively benign. Meningitis commonly occurs during the course

of meningococcemia. However, spread to other sites, such as the pericardium, the joints, and the eyes, are uncommon but possible. *Neisseria meningitidis* can cause a variety of infections; bacteremia and meningitis are by far the most common. Meningococcal disease remains a worldwide problem and occurs sporadically, as localized outbreaks, or as widespread epidemics. The clinical manifestations are varied and range from transient bacteremia to fulminant disease culminating in death within hours of the onset of symptoms. Few, if any, infectious diseases rival severe meningococcemia in fulminance.

ETIOLOGY

Reports of illness resembling meningococcal disease date back to the 16th century. The first description reported by Vieusseux in 1805 is generally thought to be the first definitive and identification of the disease. The causative organism, *Neisseria meningitidis*, was first isolated by Weichselbaum in 1887. It is likely that epidemic meningococcal disease is a relatively new condition. Outbreaks were first recorded in Geneva in 1805 and in New England the following year. Because of the characteristic features of meningococcal disease it seems unlikely that epidemics would have remained unreported had they occurred at an earlier time. Meningococcal disease was reported for the first time in North Africa in 1840 and in sub-Saharan Africa during the first years of the twentieth century.

N. meningitidis is a gram-negative diplococcici whose adjacent sides are flattened to produce its characteristic biscuit shape. The microorganism grows best on enriched media such as Mueller-Hinton or chocolate agar and at 37°C in an atmosphere of 5 to 10% CC>2. *Neisseria* spp. are differentiated by their ability to use sugars as sources of energy. Typically, meningococci use glucose and maltose and not sucrose or lactose. In contrast to other Neisseriae, meningococci are surrounded by a polysaccharide capsule. On the basis of antigenic differences among their capsular polysaccharides, the microorganisms are divided into at least 13 serogroups. Although encapsulated meningococci from all serogroups frequently colonize the nasopharynx and have the potential to cause systemic disease, more than 99 % of meningococcal infections are caused by strains of serogroups A, B, C, 29E, W-135, and Y.

EPIDEMIOLOGY

Reservoir is human. Route of transmission - respiratory droplets shed from the upper respiratory tract transmit meningococci from one person to another. Humans are the only natural hosts for meningococci and the organism dies quickly outside the human host. It is not able to be isolated from environmental surfaces or samples. Salivary contact has in the past been regarded as a means of transmission of meningococci. There is little evidence to support this view. Available evidence indicates that neither saliva nor salivary contact is important in the transmission of meningococci. Saliva has been shown to inhibit the growth of meningococci. Carriage of meningococci has not been convincingly shown to be associated with

saliva contact. A case-control study of United Kingdom university students found no association between carriage of meningococci and sharing of drinks or cigarettes and a weak association with ‘intimate kissing’ (OR = 1.4 & 95% CI, 1.0–1.8%). It is unclear whether carriage in these circumstances is due to saliva contact rather than to droplets shed during household-like (close and prolonged) contact. Period of communicability. It is communicable until the organisms are no longer present in discharges from the nose and mouth. Masks are effective protection contra meningococcal infection for doctor and nurse only 20 minute.

Meningococci are confined entirely to humans; the natural habitat of these bacteria is the nasopharynx. The organisms are presumably transmitted from person to person through the inhalation of droplets of infected nasopharyngeal secretions and by direct or indirect oral contact. As usually patients with generalized form of meningococal infection and nasopharyngitis are exerting in environmental medium more meningococci than carriers, thereby they are more dangerous for non infected person. In nonepidemic periods, the overall rate of nasopharyngeal carriage is about 10 percent but may approach 60 to 80 percent in closed populations, such as those at military recruit camps or schools. Rates of carriage are also high among family members and other close contacts of patients with meningococcal disease. Carriage usually persists for a few months; chronic carriage is not uncommon. Observations during epidemics suggest that invasive meningococcal disease is most likely to occur within a few days of acquisition of a new strain, i.e., before the development of specific serum antibodies. Most infections occur among children 6 months to 3 years of age. Meningococcal disease occurs throughout the world, from the Arctic to the edge of the Sahara. In areas with a temperate climate the infection is usually endemic, with an attack rate of around 2 cases/100 000 population per year. In epidemics, the age distribution of the patients is shifted to older individuals, and more cases develop among individuals 3 to 20 years of age. When sporadic cases occur in families, the attack rate among household contacts may increase dramatically to 1 in 1000. Major outbreaks of meningococcal disease are regularly reported from Africa, China, and South America. These epidemics may involve thousands of individuals and cause many deaths. Serogroup A meningococci are the primary cause of the epidemics. In the "meningitis belt" of sub-Saharan Africa, the incidence of meningococcal disease rises sharply towards the end of the dry and dusty season and falls with the onset of rains. It has been postulated that the presence of dust interferes with local IgA secretion in the nasopharynx, reducing host defenses against meningococci. Serogroup A strains caused most outbreaks of meningococcal disease in Europe and the United States in the first half of the twentieth century. Since World War II, meningococci of serogroups B and C have become predominant. Currently, group B strains account for 50 percent of sporadic cases. Serogroup C strains have caused more infections in older age groups, and serogroup B strains have been especially common in very young

children. Outbreaks occur more frequently among the poorest segments of the population, where overcrowding and poor sanitation are common.

PATHOGENESIS

Meningococcal infection begins in the nasopharynx. Shortly after adherence to the nasopharyngeal mucosa, encapsulated meningococci are transported through nonciliated epithelial cells in large, membrane-bound phagocytic vacuoles. Within 24 h the microorganisms are observed in the submucosa in close proximity to local immune cells and blood vessels. In most instances, this nasopharyngeal infection is subclinical, but mild symptoms occasionally develop. After mucosal penetration and presumably a phase of adaptation, the bacteria may gain access to the circulation. In the vascular compartment, the invading meningococci either may be killed by the combined actions of serum bactericidal antibodies, complement, and phagocytic cells or may multiply, initiating the bacteremic stage. After that meningococci damage envelop of brain. There is purulent inflammatory process. The total volume of cerebrospinal fluid is 150 ml. All contain their change 7 times in a day. Thus, intracranial pressure increases due to hypersecretion of cerebrospinal fluid, distention of vessels, and edema substance of brain. The symptoms and signs of systemic disease appear concurrently with meningococcemia and usually precede symptoms of meningitis by 24 to 48 h. Meningococci are capable of replicating at an astonishing rate; within hours, a patient may deteriorate from good health to irreversible shock, marked hemorrhagic diathesis, and death. Lipopolisaccharides (LPS) or endotoxin play important role in pathogenesis. LPS is released into the circulation during multiplication and autolysis of meningococci, and a fair correlation has been established between LPS levels in plasma and disease severity: patients with minor symptoms have low or undetectable levels of LPS, while patients with fulminant meningococcemia have among the highest LPS levels detected in human plasma. In fulminant disease, major cascade systems associated with inflammation (including the coagulation, complement, fibrinolysis, and kallikrein-kinin systems) as well as the production of cytokines [tumor necrosis factor a (TNFa), interleukin (IL) 1, M-6, IL-8, and IL-10] and nitric oxide are all triggered and upregulated simultaneously by native LPS. This dose-dependent inflammatory response results in marked vasodilation, reduced cardiac performance, platelet aggregation, disseminated intravascular coagulation (DIC), and capillary leak. The end results of these complicated processes are septic shock, adult respiratory distress syndrome, and multiple-organ failure. Although systemic meningococcal infection is primarily a bacteremic disease, *N. meningitidis* exhibits marked tropism for the meninges and skin and to a lesser degree for synovia, serosal surfaces, and adrenal glands. The most common clinical presentation is a composite of bacteremia and meningitis. Infection of the central nervous system may begin in the vicinity of the ependyma that lines the cerebral ventricles, subsequently spreading to the subarachnoid space. Meningococci appear to

adhere readily to the cerebrovascular endothelium and (by yet poorly defined mechanisms) to penetrate the vessel walls. Later, the permeability of the blood-brain barrier may be further increased by locally produced inflammatory mediators such as TNFa, IL-1, and IL-6 induced by increasing levels of LPS in the cerebrospinal fluid (CSF). In patients with meningococcal meningitis, LPS levels in CSF are 100 to 1000 times higher than those in simultaneously collected plasma. This compartmentalized bacterial growth is also reflected in the higher CSF levels of bioactive TNFa, IL-1, IL-6, and IL-10 in patients with meningitis than in patients with septic shock or mild bacteremia. The development of invasive disease is most dependent on host factors. Invasive meningococcal disease occurs almost exclusively in individuals who lack protective bactericidal antibodies to the infecting strain. The complement system plays a critical role in host defenses against invasive meningococcal disease, and activated complement brings about bacterial cell death by direct lysis or opsonophagocytosis. Occasional individuals who experience recurrent attacks of meningococcal disease have a high prevalence of a familial deficiency in a terminal complement component. This deficiency results in an inability to assemble the membrane attack complex (C5 to C9). The population prevalence of terminal complement-component deficiency is very low (about 0.03 %), but approximately 50 % of affected individuals experience an attack of meningococcal disease at some time. An association between respiratory virus infections and meningococcal infection has been postulated. While infection with influenza A virus seems to predispose to meningococcal disease, this association appears to be less likely for other viral infections. Reasons for epidemics of meningococcal disease are poorly understood. Overcrowding is clearly a prominent risk factor. Moreover, it has been suggested that epidemic meningococcal strains are clonal and that important surface structures vary cyclically, providing a new bacterial surface that allows evasion of host defense systems.

Pathology. The predominant pathological finding in patients who have died from acute meningococcemia is vascular damage associated with thrombosis and haemorrhage. There may also be signs of encephalitis. Haemorrhage into the adrenals is frequently found at autopsy (the Waterhouse-Friderichsen syndrome) and this lesion has been associated with the pathogenesis of meningococcal shock. The meninges of patients with meningococcal meningitis show classical acute inflammatory changes, with edema, vascular dilatation, fibrin deposition and infiltration with polymorphoneutrophil leucocytes. A vasculitis may be present.

CLINICAL MANIFESTATIONS

The incubation period is commonly three to four days, but can vary from two to seven days. People who do not develop the disease in the seven days after colonisation may become asymptomatic carriers.

Classification of meningococcal infection

(by clinical course):

1. Primarily - localized forms

- meningococcal carriers;
- nasopharyngitis (nasopharyngeal infections);
- pneumonia due to meningococci;

2. Hematogenous – generalized forms:

a) Meningococcemia;
- Typical,
- Fulminant (Waterhouse – Friderichsen syndrome),
- Chronic,

b)Meningitis;

c) Meningoencephalitis;

d) Mixed form (meningococcemia + meningitis, etc.);

By degree of severity of clinical course:

Mild, moderate, severe, very severe.

There are acute carriers, patients with nasopharyngitis, patients with meningitis, patients with meningitis and meningococcemia or only meningococcemia. *N. meningitidis* typically causes an acute infective illness, and more than 90 % of the patients who become ill have meningococcemia and/or meningitis. As usually more often are meningococcal meningitis to appearance. A sequential development of clinical manifestations can be discerned, the usual sequence consisting of initial infection of the upper respiratory tract followed by meningococcemia, meningitis, and less common focal manifestations. ***Nasopharyngeal infection.*** Most nasopharyngeal infections with meningococci are asymptomatic but some subjects develop a mild sore throat at the initial stage of the infection. The portal of entry of meningococci is the nasopharynx. Most patients are asymptomatic or report fever alone before the onset of systemic manifestations. Some patients with invasive meningococcal disease describe mild prodrome symptoms of sore throat, rhinorrhea, cough, headache, and conjunctivitis in the week before hospital admission. Whether these manifestations are due to infection with the meningococcus or with other microorganisms that may facilitate meningococcal invasion is not known. ***Meningitis.*** The onset of meningococcal meningitis is generally more gradual than that of acute meningococcemia. Headache, fever, and general malaise are the usual presenting symptoms. Headache is severe and is usually generalized. Patients may complain also of backache, photophobia, nausea, and vomiting. There is clinical triad of meningitis that includes temperature, headache and vomiting. The onset for estimation clinical situation we are recommended from the looking-for of clinical triad of meningitis. It is doesn’t meet levels degree this

symptoms. This triad play role for suspicion of meningitis in patients and triad point to that examination of meningeal sign are necessary. After looking-for triad doctor must be examination rigid neck, symptoms of Kerning and Brudsinsky. They may be negative. But if they are positive next step is lumbar puncture. In cases of meningism (irritation of envelop brain but there is notinflammation) as usually only rigidity neck present, other meningeal sign are absent. Estimation of level or degree of headache is very important. Mostly headache very strong, there is not effect after analgin, sometime patient take several tablet's of analgin without effect. As usually headache intensify in night, after changing position of body, in evening and don't disappearance until lumbar puncture or loss of consciousness. Many patients clench to head by hand. Patients usually cry due to headache. These symptoms be used for estimation headache, is "visit card" of meningitis. Meningitis is frequently associated with meningococcemia; in patients with systemic disease, the onset of meningitis may be inapparent. However, most patients with meningitis soon develop symptoms of meningeal inflammation, including severe headache, confusion, lethargy, and vomiting. Signs of meningeal irritation are present in most but not all cases. The symptoms and signs associated with meningococcal meningitis cannot be differentiated from those associated with meningitis due to other organisms. Meningitis may also occur without specific signs in elderly patients or in those with fulminant meningococcemia. As the infection advances, lethargy may progress to coma, and seizures, cranial nerve palsies, and hemiparesis or other focal neurologic signs may appear. As usually, in average, 50% patients with meningococcal meningitis were admitted in intensive care ward unconsciousness. They lost consciousness it home cause by edema of brain. Most typical complication of meningitis is edema of brain. ***Meningococcemia.*** The proportion of patients with meningococcal disease who develop acute meningococcaemia varies from place to place and from outbreak to outbreak, but it is usually less than 10 per cent. Between 30 and 40 % of patients with meningococcal disease have meningococcemia without clinical signs of meningitis. The clinical manifestations vary from minor symptoms of transient bacteremia to fulminating disease of a few hours' duration. The onset is usually sudden, with fever, chills, nausea, vomiting, rash, myalgia, and arthralgia. Fever, usually between 39 and 41 °C, is almost universal, although occasional patients with fulminant disease may be afebrile or even hypothermic. Most patients suffer from nausea and vomiting and are distressed. One-third of patients have myalgias and/or arthralgias. The most striking feature is rash, which develops in three-fourths of patients and may be maculopapular, petechial, or ecchymotic. The term for these elements appearance is from 8 to 16 hours after onset of disease. During many ears we can meet tetrad of meningococcemia – are temperature rash, arthritis and eyes injury (iridocyclitis, panophthalmitis). But now, only two sign from this tetrad are present temperature and rash. The maculopapular rash appears soon after the onset of disease;

the lesions are pink, 2 to 10 mm in diameter, and sparsely distributed on the trunk and extremities and quickly disappearance. As usually doctor, if examination of patient in several hours after onset of disease, can see most typical hemorrhagic rash. These elements are localization in surrounding of joints, like belts of watch, over the bigger muscles. Often petechial appear in the center of the macules. As has beensed, the rash may progress within hours to become hemorrhagic as the general condition of the patient deteriorates. The petechial lesions are 1 to 2 mm in diameter and are distributed mainly on the trunk and lower extremities but also on the face, palate, and conjunctivae. In relatively severe cases, petechiae may become confluent and develop into hemorrhagic bullae, with extensive ulcerations.As usuallyshaped of haemorrhagia like stars ("ink blotch"). Widespread petechial eruption, hypotension, reduced peripheral circulation, and lack of meningism are all indicators of poor prognosis. Ecchymoses and fulminant purpuric rash are common among patients with fulminant meningococcemia. If we can't cover a place of purpuric rash with help of palm – there is bed prognosis for recovery of patients. Most typical complication of meningococcemia is septic shock. ***Fulminant meningococcemia,*** previously called Waterhouse-Friderichsen syndrome, differs from the milder form in its rapid progression and overwhelming character. It occurs in 10 to 20 % of patients with meningococcal disease and is characterized by the development of shock, DIC syndrome, and multiple-organ failure. The onset is abrupt; purpuric lesions, hypotension, and peripheral vasoconstriction with cold cyanotic extremities frequently develop within hours. The state of consciousness is variable, but many patients remain alert despite hypotension. The purpuric lesions enlarge rapidly and involve skin, mucous membranes, and internal organs such as skeletal muscle, adrenal glands, and occasionally the pituitary gland. Myocardial depression contributing to shock is evidenced by impaired myocardial contractility, lowered cardiac index, increased wedge pressure, and elevated serum levels of creatinine phosphokinase. Metabolic acidosis, serum electrolyte derangement, oliguria, leukopenia, and low levels of coagulation factors are common. Despite advanced intensive care management, 50 to 60 % of patients die, usually from cardiac and/or respiratory failure. Patients who recover may have severe skin lesions necessitating plastic surgery or loss of parts of limbs due to gangrene. ***Chronic meningococcemia*** makes up only 1 to 2 percent of all cases of meningococcal disease. This syndrome of recourse fever, maculopapular rash, and arthralgia may last for weeks to months. The rash may also be petechial. During afebrile periods, patients appear remarkably well. Failure to diagnose and treat chronic meningococcemia may result in the development of systemic disease. A number of ***less common manifestations*** of meningococcal infections have been reported. These include arthritis, pneumonia, sinusitis, otitis media, conjunctivitis, endophthalmitis, endocarditis, pericarditis, urethritis, and endometritis. Arthritis occurs in 5 to 10 percent of patients and may develop at any stage of the acute illness. Large joints are

most commonly affected, particularly the knee. Meningococci are infrequently isolated from the synovial fluid, and the majority of cases, especially when arthritis develops after the initiation of therapy, are immunologically mediated. Sequelae are rare. Primary meningococcal pneumonia is well recognized, particularly in association with serogroup Y strains. The clinical syndrome is similar to that of other bacterial pneumonias. Since the introduction of antibiotics, endocarditis and pericarditis have become very unusual features of acute meningococcal disease. ***Complications.*** The complications of meningococcal infections include intercourse infections and damage to the central nervous system. Most pyogenic complications have become uncommon. However, superinfection of the respiratory tract with microorganisms other than meningococci may develop, particularly during assisted ventilation of seriously ill patients. Neurologic complications may result from direct infection of brain parenchyma (cerebritis or brain abscess), injury to cranial nerves as they pass through the inflamed meninges, venous or arterial infarction (seizures, focal deficits), cerebral edema (raised intracranial pressure), interruption of CSF pathways (hydrocephalus), or effusions into the subdural space producing mass effects. Nonetheless, permanent neurologic sequelae are infrequent, occurring in fewer than 5 percent of survivors of acute meningococcal meningitis. As in other severe infections, herpes labialis is prevalent in the acute stage of meningococcal disease.

DIAGNOSIS

Diagnosis is usually made on clinical grounds confirmed by laboratory tests. Laboratory tests include:

- gram stain of cerebrospinal fluid, skin lesion smear or joint fluid;
- culture of blood, CSF or other sterile site;
- polymerase chain reaction.

The CBA – as usually there is higher leucocytosis, shift to the left and increase RSE. It is obligate, that CSF we don't take more 10 ml, due to dislocation of the trunk brain and impaction oblong in foramen magnum. In IS normal digits for CSF is< 0,03 g/L of protein, 0 to 3 cells per microliter (cytosis), test Pandi (about albumin's) one +, test Nonne- Apelt (about globulin's) are negative. Glucos -2,2-3,3 mmol/ L, Chlorides – 120-130 mmol/ L. In cases of meningococcal meningitides CSF is no transparent, whitish color, like water with milk. Increase of pressure of CSF, sometime outlet like stream. There is increase of protein, higher cytosis (sometime several thousand per microliter). There are predomination of neutrophils in compared with lymphocytes. Mostly there are cells – protein dissociation. We may medications with antibiotic cancel, if cytosis there is no more 150 cells per microliter and all cells must be lymphocytes. CSF findings in meningitis include increased pressure, increased protein content, low glucose concentrations, and (in most cases) 100 to 20,000 polymorphonuclear leukocytes per microliter. Meningococci usually can be isolated from blood and CSF of patients with meningococcal disease and occasionally are

found in petechial aspirate and synovial, pleural, or pericardial fluid. The growth of meningococci in blood culture bottles can be inhibited by sodium polyanetholesulfonate, a frequent additive to media. Gram-negative diplococci may be demonstrated in CSF, petechiae, or buffy coat smears from at least half of patients. Group-specific capsular polysaccharides can be detected in CSF, synovial fluid, serum, or urine by counter immunoelectrophoresis or latex agglutination assays. However, these tests give false-negative results in 50 percent of culture-proven cases. The combined use of cultures, gram-stained smears, and immunoassays will provide a diagnosis in more than 95 percent of cases. The immunoassays may be particularly useful in situations where cultures are of limited value because of prior antibiotic administration. The polymerase chain reaction may also be a valuable tool in these situations. CSF examinations indicate that the specificity and sensitivity of PCR for the diagnosis of meningococcal meningitis are at least 90 percent. A specific antibody response during convalescence may also be diagnostic. Other laboratory data offer limited support in the diagnosis of meningococcal disease. Elevated counts of polymorphonuclear leukocytes with a left shift are common, but normal counts are not unusual. Patients with fulminant meningococcemia usually have neutropenia and markedly reduced platelet counts; prothrombin and partial thromboplastin times are prolonged, plasma fibrinogen levels are diminished, and fibrinogen degradation product titers are elevated as a result of DIC.

Meningococcal infection in its early stage may resemble any acute systemic infection, including influenza or another common viral infection, and the distinction between the latter infections and early meningococcemia may be most difficult. In contrast to the prevalence of neurologic symptoms in meningococcal meningitis, the lack of such symptoms in meningococcemia may prevent early recognition of this severe form of meningococcal disease. However, early in meningococcal disease there is often a generalized, mottled erythema or a light pink maculopapular rash resembling the rose spots of typhoid fever. By careful examination of the patient, the physician can detect these lesions and establish a presumptive diagnosis. As the disease progresses, a petechial or purpuric rash usually develops, and the diagnosis becomes more obvious. The rash seen in some common viral exanthems, Mycoplasma infection, Rocky Mountain spotted fever, endemic typhus, and vascular purpura may be confused with that of meningococcemia. In the absence of rash or other manifestations of bacteremia, meningococcal meningitis is indistinguishable from meningitis caused by other pathogens. The ultimate diagnosis of meningococcal disease depends on the recovery of N. meningitidis or the detection of its antigens in various body fluids or petechial aspirates. Isolation of meningococci from the nasopharynx only confirms the carrier state and cannot be used alone to establish the diagnosis of systemic infection.

TREATMENT

Any febrile patient with a petechial or haemorrhagic rash should be considered to have meningococcal infection. Blood for cultures should be taken immediately and treatment begun without awaiting confirmation. *Empiric antibiotic therapy.* If doctor haven't idea about meningococcal ***meningitis*** by clinically - as usually start of antibiotic medication from cephalosporin's third generation. But in many cases we may recognize of meningococcal infection (abrupt start of disease, in previously healthy person, there is not focal infections). In these cases like start from penicillin or penicillin G. Despite the availability of potent antibiotics and advances in intensive care management, overall mortality from meningococcal disease is about 10 percent, rising to as high as 50 to 60 percent among patients with meningococcemia and shock. To improve the prognosis, early diagnosis and treatment are of utmost importance, particularly in patients with meningococcemia. If the patient is not initially seen in the hospital, intravenous penicillin G (60,000 to 100,000 units per kilogram) should be given and the patient immediately admitted. In the outpatient setting, if vascular access is problematic, antibiotics can be given intramuscularly (at several injection sites in light of the large volume). If the patient is first seen in the hospital, intravenous access should be established immediately, blood obtained for cultures, and antibiotics administered as soon as possible. Initiation of therapy in patients with signs of circulatory insufficiency or rapid deterioration in cerebral condition should not await lumbar puncture. Penicillin G remains the drug of choice for meningococcal disease. ***E.g.*** *If mass of body in patient with meningococcal meningitis is 70 kg and choose of drug – penicillin, it is necessary the dose on kg/mass 500.000 U . Daily dose may be – 35 million units. Prescription - 6 million 6 times a day IM.*

Prior to the identification of the etiologic agent, the choice of antibiotics depends upon the age of the patient, the status of the patient's underlying host-defense system, and the prevalence of antimicrobial resistance in the community. *Streptococcus pneumoniae* as well as *Haemophilus influenzae* and other gram-negative bacteria may cause a clinical picture similar to that of meningococcal infection. The third-generation cephalosporins cefotaxime and ceftriaxone are recommended as empiric therapy. Although mortality and long-term morbidity among patients given cephalosporins for the treatment of meningococcal disease are similar to those among patients treated with penicillin, the cephalosporins are preferred because of their high level of activity against other common meningeal pathogens, including most penicillin-resistant pneumococci; their excellent penetration into the CSF; their lack of toxicity; and the convenience of using a single agent that can be administered three times daily (cefotaxime) or once or twice daily (ceftriaxone). As part of their empiric regimen, patients undergoing immunosuppressive therapy, newborns, and the elderly should receive high-dose penicillin to cover *Listeria monocytogenes.* The cephalosporins are also highly active

against *N. meningitidis* strains with reduced sensitivity to penicillin. Such strains have been reported from several countries and have been described especially often in reports from South Africa and Spain. The usual daily dosage of cefotaxime is 150 to 200 mg/kg intravenously up to a maximum daily dosage of 12 g; that of ceftriaxone is 75 to 100 mg/kg intravenously up to a maximum daily dosage of 5 g. Once meningococci have been isolated and shown to be sensitive to penicillin G, the therapeutic regimen can be changed to penicillin G. Chloramphenicol is as effective as penicillin G for the treatment of meningococcal disease and can be used in patients allergic to penicillins or cephalosporins. The usual daily dosage of penicillin G is 200,000 to 300,000 units per kilogram intravenously in divided doses every 6 h up to a maximum daily dosage of 24 million units; that of chloramphenicol is 75 to 100 mg/kg intravenously in divided doses every 6 h up to a maximum daily dosage of 4 g. A 7-day course of high-dose parenteral therapy is adequate for both meningococcal meningitis and meningococcemia. The dose should not be tapered over the course of therapy.

***Acute meningococcemia*.** Chloramphenicol is an alternative treatment for patients who are known to be sensitive to penicillin or who are at risk of infection with a penicillin-insensitive strain, as most such strains are sensitive to this antibiotic. Because other bacteria that may not respond well to penicillin can cause clinical syndromes identical to acute meningococcemia, a case can be made for starting treatment initially with a broader-spectrum antibiotic such as a third-generation cephalosporin. Maxipim/Amoxyclav 50–100 mg\kg, Levofloxacin (tavanik) 500 mg ^{x} 1 IV a day. Penicillin remains the antibiotic of choice for the treatment of acute meningococcemia. Given in high doses by a parenteral route, for example 4 mega units of crystalline penicillin 6-hourly by intravenous injection in adults, it is effective even in infections caused by meningococci which are relatively insensitive to penicillin.

Supportive Care. The course of meningococcal disease is highly unpredictable. All patients with invasive meningococcal infection, whatever their clinical condition on admission, should be considered to have potentially life-threatening infection and should be carefully observed during the first 48 h in the hospital, with monitoring of arterial blood pressure, pulse, perfusion, urine output, and core and peripheral temperature. Many patients who do not appear acutely ill on admission may deteriorate suddenly in the following hours, with the development of severe shock and profound DIC. Patients with a rapidly progressive purpuric rash, a low peripheral white cell count, and no evidence of meningeal involvement are likely to deteriorate very soon after admission. The most important manifestation requiring urgent intervention is severe meningococcemia with shock. Patients with this form of meningococcal disease have a severe capillary leak syndrome and myocardial dysfunction. Strategies to reverse circulatory failure include optimizing preload,

decreasing after load, and improving myocardial contractility. Intravenous fluid administration together with ionotropic support with dobutamine (1 to 10 ug/kg per minute) or dopamine (2 to 10 ug/kg per minute) should be started immediately and tailored to the needs of each patient on the basis of clinical assessment and of monitoring of systemic arterial pressure and central venous or pulmonary wedge pressure . Vasodilators should be administered with extreme caution to patients with severe shock. In marked tissue edema in adults, the administration of as much as 8 to 10 L of intravenous fluid may be necessary during the first 24 h. Because the risk of pulmonary edema is considerable, patients in severe shock should be electively ventilated, even if they are ventilating adequately. Several controlled studies of patients with septic shock have demonstrated no beneficial effect of high-dose glucocorticoid treatment. Although these studies have included only small numbers of patients with meningococcemia, a beneficial effect of glucocorticoids in fulminant meningococcemia seems unlikely. A wide variety of supportive measures has been tried in patients with fulminating acute meningococcemia but none has been particularly successful. Whenever possible, patients with acute meningococcemia should be nursed in an intensive-care unit. Fluid balance, acid-base status, central venous pressure, and the electrocardiogram should be monitored carefully. Assisted ventilation may be required. Most such patients have a reduced circulatory volume and require infusion with a plasma expander such as plasma or dextran to maintain their circulation. The central venous pressure should be maintained at between 10 and 15mmHg if possible. A careful watch must be kept for the development of pulmonary edema; if pulmonary crepitations appear an intravenous diuretic, such as furosemide, should be given. If the blood pressure cannot be maintained by colloid infusion, it can be increased transitorily by administration of a sympathomimetic amine such as noradrenaline, but giving such a drug increases peripheral vascular constriction and may enhance peripheral tissue damage. A better approach is to use an inotropic agent, such as an infusion of dopamine, which increases tissue perfusion and reduces the after load on the heart. If a vasodilator is used, then further colloid infusion may be required to maintain the circulation. Dophamine 5,0 in 5% glucose IV by method of titration under control of blood pressure. The value of corticosteroids in the management of shocked patients with acute meningococcemia has never been established by a controlled trial.

Empiric antibiotic therapy. In patients with bacterial brain abscess, once a diagnosis is made either presumptively by radiologic studies or by CT-guided aspiration of the lesion, antimicrobial therapy should be initiated. If an aspiration cannot be performed or if Gram staining is unrevealing, empiric therapy should be initiated based on the presumed pathogenic mechanism of abscess formation.

PREVENTION

Note that most strains of meningococci do not cause disease, but instead provide protection. Other protective bacteria such as Lactamicas (Neisseria lactamica spp.) also colonise the nasopharynx. By giving chemoprophylaxis when it is not needed these bacteria, which are protective, are also eradicated. People can carry meningococci with no ill effects for many months. Carriage produces protection. There is no evidence to suggest carriers will suddenly become cases after weeks or months of carriage. Conjugate vaccines are available that can give long lasting protection against meningococcal serogroup C disease. There is no vaccine for meningococcal serogroup B disease. There is polysaccharide quadrivalent vaccine available in Australia against groups A, C, Y and W135 however it cannot be given under two years of age and only protects for one to five years. This vaccine is considered a 'travel' vaccine for travellers to epidemic and highly endemic areas such as Brazil, Mongolia, Vietnam, India, Nepal and sub-Saharan Africa and is a requirement for visits to Mecca. There are different brands of (conjugate) meningococcal serogroup C vaccine available. The vaccines contain meningococcal serogroup C 'sugars' joined with an inactive protein of either diphtheria or tetanus toxoid and additives aluminium phosphate or hydroxide. Under the National Immunisation Program, a single dose of meningococcal serogroup C vaccine is given at 12 months of age. If parents wish to purchase vaccine to immunise their child prior to 12 months of age, infants from six weeks to four months of age at the commencement of vaccination receive three doses one to two months apart. Babies from four months to 11 months at the commencement of vaccination receive two doses one to two months apart. The National Meningococcal C Vaccination Program is a four year program from 2003–2006 in which all persons aged 1–19 years in 2003 are eligible for a dose of meningococcal C vaccine. Attack rates are approximately 100-fold higher among household contacts of patients with meningococcal disease than in the general population. The risk is highest in the first week after the index case has presented with infection. Chemoprophylaxis helps avert secondary cases of infection and should be administered to intimate contacts in the household, day-care center, and nursery school and also to anyone who has had oral contact with the index case (kissing, mouth-to-mouth resuscitation). The recommended regimen for prophylaxis consists of rifampin at a dosage of 10 mg/kg (up to 600 mg) every 12 h for 2 days for adults and children over 1 year of age and 5 mg/kg every 12 h for 2 days for children less than 1 year old. Ciprofloxacin or ofloxacin (a single oral dose of 500 or 400 mg, respectively) is a suitable alternative for adults but is not recommended for children or pregnant women. A single 250-mg intramuscular dose of ceftriaxone is recommended for pregnant contacts; for children less than 12 years of age, 125 mg of ceftriaxone can be given. Vaccines are available against four serogroups of meningococci: A, C, W-135, and Y. No effective serogroup B vaccine is presently

available. The efficacy rate of a single dose of serogroup A or serogroup C vaccine is at least 90 percent in adults and children over 2 years of age, and routine immunization of recruits has eliminated nearly all disease among military personnel. To prevent late secondary cases, close contacts of patients with sporadic disease caused by strains of serogroup A or C should receive a single dose of polysaccharide vaccine. Travelers to areas where disease is epidemic as well as individuals with splenic dysfunction or deficiencies in complement or properdin should be immunized. Conjugate serogroup A and serogroup C vaccines have been developed and are now undergoing clinical trials. If these vaccines provide young infants with long-lasting protection, they may be used in outbreak management as well as in routine infant-immunization programs. Serogroup B vaccines are also being developed. Clearance antibiotic for contacts of meningococcal disease:

Rifampicin can be dispensed for meningococcal prophylaxis as syrup for children or in capsules for older children and adults. The product information should be consulted for the adverse events and side effects of rifampicin, although it should be noted that the product information recommends a once-daily four-day regimen of rifampicin for the chemoprophylaxis of meningococcal disease. Ciprofloxacin: Adults 500 mg orally, single dose (minimum age 12 years and weight >40 kg). This is preferred in women taking the oral contraceptive pill. Although ciprofloxacin is not registered for chemoprophylaxis of meningococcal disease in Australia the Communicable Diseases Network Australia recommends it for that purpose. Ceftriaxone: Adults 250 mg IM (recommended for pregnant contacts). This may be dissolved in lignocaine 1% solution to reduce pain at the injection site. Dosage for children (<12yrs) is 125 mg IM. Not for infants under 1 month of age.

LEGIONELLOSIS

DEFINITION: *legionellosis is acute infectious disease with an air-droplet mechanism of transmission, caused Legionellae and characterized by a wide spectrum of clinical manifestations - from subclinical or mild respiratory diseases up to a severe pathology of lungs, nervous, digestive system, etc.*

The Legionnaire’s disease for the first time is described during investigation of outbreak of pneumonia among the delegates of a congress of organization "American Legion" and members of their families, in hotel "Belue Stratford" in Philadelphia in period from July 21 till July 28, 1976. In total 221 cases was registered, 34 with lethal outcome. The etiology remained unknown 5 more months, until I. McDade (1977) had revealed an unknown Gram-negative microorganism from pulmonary tissue of the man, who died during the outbreak. The retrospective study of serums, stored in Center of control of infectious diseases (Atlanta), also has proved a role L. pneumophilia in the not deciphered earlier outbreaks of acute respiratory diseases and

pneumoniae, which had place in 1965 in Washington in st. Elisabeth hospital; in 1968 in Pontiac. Later, also retrospectively, the etiological role of L. Micdadei in outbreak of an unusual fever among 40 soldiers on military base in a Fort - Brag (USA) in 1942 is proved.

Since the reservoirs of legionellae were detected, it is considered as widespreaded pathogen of community acquired and nosocomial pneumonia. In 1982, according to the WHO guidelines, term "the legionnaire's disease" is decided to hold on epidemic disease called L. pneumophilia, others to name a legionell-infection. The term legionellosis includes all forms of diseases stipulated by microorganisms of a Legionellaceae family. The role of legionella as the pathogen in outbreaks of a pneumonia varies from 2 to 15% of pneumonias subject to hospitalization. Legionella pneumophilia is the etiological factor in approximately 3/4 cases of an infectious pneumonia of legionella etiology.

ETIOLOGY

Legionellae - DNA - containing aerobic gramme - negative microorganisms, size 0.5 - 0.7 microns, having two diametrically posed ropes, associated with toxigenity, show catalase and weak oxidase activity. It is stained by Gimens, hematoxylin and eosin, impregnation by silver by Diterle. In tissues for the pathogen is characteristic outside of - and intracellular replication in vacuoles and cytoplasm.

In the laboratory, legionellae are fastidious in their growth requirements and will not grow on standard bacteriological media. Aces buffered charcoal yeast-extract (BCYE) agar, pH 6.9, supplemented with L-cysteine, α-ketoglutarate and iron, is a very satisfactory medium and is made semiselective by the addition of antibacterial and antifungal agents that suppress other microflora in specimens from contaminated sites. On BCYE agar, incubated at 35 to 37°C, typical colonies usually appear in 3 to 5 days; occasional slow-growing strains require the plates to be incubated for 10 days. Some legionella species, grown on BCYE agar, auto fluoresces when exposed to long-wave ultraviolet light (approx. 365 nm). The family Legionellaceae can be divided into three groups by this observation. It is known about 30 species of legionella; the etiological role in pathology of the human is reliably proved for 12 of them. The greatest spread for taxonomic classification of legionella is one by D. Brenner (Table 7).

On antigenic properties legionella are divided on 7 serologic groups, from which most numerous is 1, which enters L. pneumophilia (Philadelphia 1).

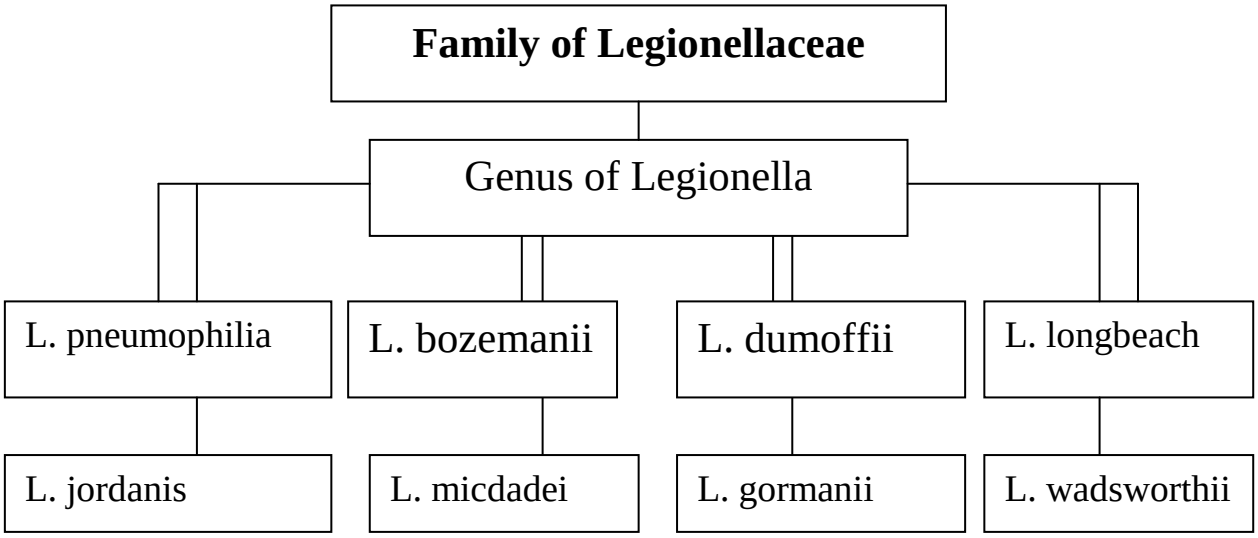
Legionella contain thermostable lypopolysacharid endotoxin, and also thermolabile, bound with a cell wall typospesific citotoxin. Almost all legionella evolve β - lactamase, inactivating Penicillins.

The pathogen is inconvertible in exterior medium, especially in water. L. pneumophilia survives 69 - 139 days in distilled water and 364 - 369 days - in undistilled. The pathogen is sensitive to action of acids, Iodine, Phenol, 70 % of

ethanol.

Table 7

CLASSIFICATION OF LEGIONELLACEAE (BY D. BRENNER)



EPIDEMIOLOGY

Legionellosis is considered as sapronosis. The reservoir of the pathogen and factors of transmission are warm reservoirs with growing blue-green algas and soil waters in endemic areas. A route of transmission is aerogenic. The Legionnaires' disease can be received by an aerosol inhalation, or microaspiration of particles of water containing the pathogen. Cases of infection through inhalation of dust are also known. An aerosol - generating systems, bound with transmission of disease, include air conditioners, whirlpool baths, respiratory medical equipment, headings of shower installations.

The disease is characterized with summer and autumn seasonal prevalence. The men are more susceptible to the disease. People of medial and elderly age more tend to the Legionnaires' disease. On the contrary, ARI of legionella etiology more often are observed at the young persons. As risk factors it is concerned smoking (about 59.4 %), chronic lung diseases, and immunosupression (especially stipulated with corticosteroids therapy).

Hospital-acquired legionellosis has been a particular problem. This is because of the size and complexity of the buildings and the difficulty of maintaining the hot water hot (storage at 60°C and 50°C at the taps), either because of the length of pipework or for fear of scalding patients. Hospital patients, too, are a highly susceptible population and species other than L. pneumophila more frequently cause infections in these circumstances.

PATHOGENESIS

Legionella species are obligate or facultative intracellular parasites. Entering gates for the pathogen is mucosa of the upper respiratory tract, tissue of lungs, wounds or other. Inoculation directly into a blood or tissue fluid is also possible during operative measures, manipulations.

The most serious course of Legionnaires ' disease is observed in persons, who have undergone to action of high infecting dose, when the diameter of particles of an aerosol no more than 2.0 - 2.5 microns, that allows microorganisms to reach alveoles. Having overcome a barrier of ciliary epithelium, legionella are brought to the alveoles in bronchioles, and can immediately be implanted in alveolocites. During development of inflammation legionella are taped in macrophages, monocytes and polymorphonuclear neutrophils. The affection of lungs is accompanied by involving of vessels in process that causes damaging of microcirculation up to respiratory distress-syndrome.

In cases of acute respiratory infections, connected with legionellosis, the major number of microorganisms does not pass a barrier of a ciliar system and is impeded in a system of bronchi and mucosa of a trachea.

Legionella species infect human macrophages and monocytes, and intracellular replication of the bacterium is observed within these cells in the alveoli.

Activated T cells produce lymphokines that stimulate increased antimicrobial activity of macrophages. This cell-mediated activation is the key to halting the intracellular growth of legionellae. The significant role of cellular immunity explains why legionellae are observed more frequently in immunocompromised patients. Humoral immunity is thought to play a secondary role in the host response to legionellae infection.

Legionella causes a toxic action on a CNS, causing development of toxic encephalopathy. The renal epithelial cells of canals are most sensitive to a toxic action of legionella that results in their necrosis. The development of acute renal failure is possible. The defeat of a canalicular epithelium of kidneys promotes drop of reabsorbtion of sodium that is one of reasons of a hyponatraemia, characteristic for legionnaires' disease. After the transferred disease is long-term the antibodies of IgG class are maintained.

Typically, legionellae histopathological lesions are found in interstitial lining and alveoli with polymorphonuclear cells and macrophages.

The pathological changes in the people died from Legionnaires ' disease are characterized by diffuse, focal and total infiltrates, with filling of alveoles by eosinophilic, albuminous and fibrinous detritus and a very small exudation. As characteristic indications frequent necrosis of alveolar septums with a weak interstitial inflammatory response are considered also. The bronchioles are involved in inflammatory process.

CLINICAL SYMPTOMS

Clinical classification of legionellosis.

- legionnaires' disease with syndrome of lung affection;
- Pontiac fever – respiratory infection without pneumonia;
- Fort-Brag fever (fever, respiratory signs and rush);
- Pittsburgh pneumonia in patients with immunodeficiency;

By clinical course:

- subclinical;
- mild;
- moderate;
- severe;
- extremely severe.

Carriage of legionellae is possible.

The Pontiac fever is cased by L. pneumophilia, L. feeleii.

The incubation period varies from 6 to 66 hr, on average 36 hr. The onset is acute with malaise, diffuse muscle pain, nausea and anorexia. Chill, rising of temperature till 38-40°C are typical. In 50% of patients' signs of upper respiratory tract affection - rhinitis, dry cough, pain and dryness in a pharynx, pain in the breast bone projection are observed. In cases of severe course toxic affection of CNS is typical: a giddiness, sleeplessness, hallucination, vomiting, and violation of consciousness and coordination of motions, disturbances of memory; 30 % of the patients have an abdominal pain, frequent watery stool, and nasal bleedings. The disease lasts for 2-5 days. In phase of reconvalescence irritability, weakness, disturbances of memory are possible; 14 % of the patients have relapses.

The Fort – Brag fever by clinical signs is quite similar to Pontiac fever. Principal difference is presents of polymorphic rash, which occur from the first days of the disease, and regress without modifications.

Pittsburgh pneumonia was named by locality, where the first outbreak of the disease took place, caused L. micdadei. Frequently occurs in immunodeficient persons, on ground of immunosuppressive therapy, after graft transplantation. The disease more often is recorded as nosocomial infection. In immunodeficient patients course is characterized by an acute beginning, high temperature expressed signs of intoxication (headache, myalgias), abdominal pain and diarrhea. Cough, dyspnea even in bed, chest pain, connected with respiration, pleuritis frequently arises.

Legionnaires' disease. Pneumonia - dominating clinical syndrome. The incubation period varies from 2 about 11 days, on average 7 days. On a beginning of disease nonspecific signs are observed: malaise, muscular pain, anorexia and headache. Temperature frequently reaches 40°C. The cough is nonproductive in 50% of patients – with little sputum sometimes with a blood, frequently is combined with a dyspnea in rest and at a minimal exertion. Pleural pain can be observed. Diarrhea

and vomiting can be met in 20- 40 % of cases, begins on 4- 5 day of disease.

On physical examination the indications of pneumonia are frequently are less expressed, than radiographic findings.

In peripheral blood the neutrophil leukocytosis up to 10- 15*109 1/l (45- 78 % of the patients), thrombocytopenia and lymphopenia, increasing ESR to 80 mm/hr are possible. The hyponatraemia (concentration of Sodium in serum less then 130 Mmol/l) more often, than during other types of pneumonias (54- 68 % of cases). Rising a lactate dehydrogenase in 45% of the patients, alkaline phosphatase at 62 %, and bilirubin at 15 % of patients also is observed.

Complications of legionellosis

- Edema, abscess, infarct of lung;
- Empyema of pleura;
- Toxic shock;
- Disseminated blood coagulation;
- Acute renal failure;

A. Miller (1980) successfully differentiated 17 cases of legionnaire's disease, using following diagnostic criterions.

During first 24 hours of disease:

1) preceding disease with toxicosis and a hyperthermia not less 39°C, during 4- 5 days;

2) cough, diarrhea, disturbance of consciousness or combination of these signs;

3) lymphocytopenia less $10*10^9$/l in a combination with leukocytosis not less $15*10^9$/l;

4) hyponatraemia less than 130 Mmol/l.

Next 2- 4 days:

- X-ray acknowledgement of pneumonia, despite of usual therapy by antibiotics; - disturbance of liver tests (the level of a bilirubin or transaminases more than twice exceeds a normal);
- hypoalbuminaemia less than 25 mg/l.

DIAGNOSIS

Pneumonias caused by numerous pathogens share similar laboratory findings, hyponatraemia (sodium <130 mEq/L) secondary to the syndrome of inappropriate antidiuretic hormone is more common in legionnaires disease than in pneumonias secondary to other pathogens; however, this is not specific for legionellosis.

Additional laboratory findings in legionellosis include:

- elevated liver enzyme levels;
- increased creatine phosphokinase levels;
- increased CPK levels
- increased C - reactive protein levels (>30 mg/L).
- hypophosphatemia (specific to legionellosis excluding other causes of

hypophosphatemia);

- microscopic hematuria;
- proteinuria (40%);

On stain by Gram typically, many leukocytes and a paucity of organisms are observed. If visible, the organisms are small, faintly staining, gram-negative bacilli.

The definitive method for diagnosing legionellosis is isolation of the organism in the respiratory secretions (sputum, lung fluid, pleural fluid). However, Legionella species do not grow on standard microbiologic media. Legionella requires BCYE agar and cysteine for growth. Optimal growth occurs at 35-37°C.

Legionella is a slow-growing organism and can take 3-5 days to produce visible colonies. The organisms typically have a ground-glass appearance.

Routine sputum cultures have a sensitivity and specificity of 80% and 100%, respectively. Transtracheal aspiration of secretions or bronchoscopy specimen increases the sensitivity. Bronchoalveolar lavage (BAL) fluid provides a higher yield than bronchial wash specimens.

Blood cultures: Legionella can be isolated from blood, but it shows a much lower sensitivity.

DFA is a rapid test that yields results in 2-4 hours but has a lower sensitivity. The specificity of DFA is 96-99% using monoclonal antibody instead of polyclonal antibody. A positive result depends on finding large numbers of organisms in the specimen; therefore, the sensitivity is increased when samples from the lower respiratory tract are used. DFA results rapidly become negative (in 4-6 days).

The most widely used serological tests include the IFA and ELISA. A single increased antibody titer confirms legionellosis if the IFA titer is greater than or equal to 1:256.

While legionellosis serologic tests are the most readily available, they require a 4-fold increase in antibody titer to 1:128 or greater, which takes 4-8 weeks. Paired measurements from both the acute and convalescent periods should be obtained, since an antibody response may not be apparent for up to 3 months. Of note, antibody levels do not increase in approximately one third of patients with legionnaires' disease.

The Legionella lipopolysaccharide antigen in urine can be detected with ELISA, radioimmunoassay, and the latex agglutination test. The Legionella lipopolysaccharide antigen becomes detectable in 80% of patients on days 1-3 of clinical illness. The urinary antigen assay can be used to detect only L pneumophila (serogroup 1). The advantages of this test include rapidity and simplicity. In addition, the relative ease of obtaining a urine sample compared with obtaining sputum specimens and the persistence of antigen secretion in patients who are on antibiotic therapy increase the usefulness of the urine antigen detection method. The urinary antigen result can remain positive for months after the acute episode has resolved.

PCR of urine, serum, and bronchiolar lavage fluid is very specific for the detection of legionellae, but the sensitivity is not greater than that of culture. The primary benefit of this procedure, like IFA titers, is that it can be used to detect infections caused by legionellae other than L pneumophila serogroup 1.

TREATMENT

A delay in treatment significantly increases the risk of mortality. Therefore, include empiric anti-Legionella therapy in the regimen for severe CAP and in specific cases of nosocomial pneumonia.

Although Legionella pneumonia can present as a mild illness, most patients require hospitalization with parenteral antibiotics.

Historically, erythromycin was used for L. pneumophila infection, but doxycycline, azithromycin, macrolides, and quinolones are more active against legionnaire's disease than erythromycin.

Fluoroquinolones, telithromycin, and azithromycin have greater in vitro activity and better intracellular penetration than erythromycin.8 In addition; animal studies of L. pneumophila infection have shown these agents to have superior activity.

The fluoroquinolones doxycycline, telithromycin, and azithromycin are superior because of their activity and pharmacokinetic properties (eg, better bioavailability, better penetration into macrophages, longer half-life).

For severe disease, a fluoroquinolones is recommended. Severe disease is defined by respiratory failure, bilateral pneumonia, rapidly worsening pulmonary infiltrates, or the presence of at least 2 of the following 3 characteristics:

- Blood urea nitrogen greater than or equal to 30 mg/dL;
- Diastolic blood pressure lower than 60 mm Hg;
- Respiratory rate greater than 30/min.

With doxycycline or fluoroquinolones, rifampin does not need to be added in severely ill patients.

Most healthy hosts exhibit clinical response to treatment within 3-5 days. But the common duration of therapy of 10- 14 days, however for the patients with immunodeficiency, and also at extensive affection in lungs on X-radiographies is recommended 21- day course.

Disintoxication therapy, which character depends on a degree of an intoxication, violation mineral balance (hyponatraemia), acid – alkaline level, level of a glucose in a blood, function of kidneys. It is more preferable to realize Disintoxication per orally. The monitoring behind liquid balance is binding.

Development of ARI, TSH, DBC, edema of brain requires the relevant measures. Developing on a background of respiratory failure the hypoxia requires assigning inhalations of humidified Oxygenium, and in serious cases - intubation and translation on artificial respiration. Glucocorticosteroids are contraindicative. If the

patient before the disease taken them, it is necessary to cancel. Only in case of development TSH glucocorticosteroids can be prescribed in high doses with a short course (2 - 3 days).

PREVENTION

Legionellosis is acquired from environmental water sources by the inhalation of water droplets. At first all the cases were attributed to exposure to the drift escaping from cooling towers of recirculating cooling systems. Now it is known that domestic and industrial piped water is the source of many cases. As legionellae are ubiquitous in natural waters there are three aspects to consider in reducing the risk of legionellosis:

- measures to minimize colonization, growth, and release of legionellae into the atmosphere;
- physical or chemical treatment of water to kill the bacteria;
- the protection of maintenance personnel who work on contaminated systems.

In Britain, particularly following the Stafford Hospital outbreak, a large number of publications aimed at minimizing the risk of legionellosis have appeared. In 1991 in Britain an Approved Code of Practice, The Prevention or Control of Legionellosis (including Legionnaires' Disease), sets out statutory requirements for dealing with this risk. Together with the Health and Safety guidance booklet HS(G)70, which was published with it and should be consulted for more details, the Code applies wherever water is stored or used in a way that may create a reasonably foreseeable risk of legionellosis. Examples are:

- recirculating water systems incorporating a cooling tower or evaporative condenser;
- hot-water systems with a volume greater than 300 l;
- hot- and cold-water systems of any size, serving a particularly susceptible population;
- water systems that create a spray and are likely to exceed a water temperature of 20°C;

In any building or environment, systems that could be colonized by legionellae must be identified and their potential risks assessed. Then a scheme is prepared for prevention or control. The most important principle to follow is to avoid holding water at temperatures between 20 and 45°C, which is the range in which legionella multiplication occurs. Other general precautions include:

- prevention of water stagnation;
- avoidance of plumbing and engineering materials that can provide nutrients for bacterial growth;
- preventing the concentration of sediments in the water by cleaning and good maintenance;
- the use of chemical or other water treatment, where appropriate and safe, to

prevent bacterial growth;

- reduction or prevention of aerosol dispersion.

The implementation of the control scheme and maintenance program must be monitored and records kept of all procedures, treatments, and test results. Above all, a senior manager must be appointed to have overall responsibility.

The Second Report of the Committee of Inquiry into the outbreak of Legionnaires' disease in Stafford in April 1985 recommended dry cooling equipment for air-conditioning plants. Recent improvements in wet cooling-system designs have made them easier to clean. Improved drift eliminators have reduced water droplets discharged into the atmosphere from cooling towers from 2 to 0.001 % of the circulating water. The number of bacteria released has consequently fallen. Biocidal treatment of the recirculating water in cooling systems is also essential.

Water sampling specifically for legionella is necessary to monitor the efficacy of maintenance and precautionary measures and in the event of an associated human infection, to trace the source.

RESPIRATORY CHLAMIDIOSIS

DEFINITION: *respiratory chlamididosis – is a group of infectious diseases with multiple ways of transmission and affection of acute onset, fever and affection of respiratory tract.*

Three chlamydial organisms are pathogenic to humans: Chlamydophila (formerly Chlamydia) pneumoniae, Chlamydophila psittaci, and Chlamydia trachomatis. These are small, gram-negative, obligate intracellular organisms. All 3 species can cause pneumonia in humans.

C pneumoniae causes mild pneumonia or bronchitis in adolescents and young adults. Older adults may experience more severe disease and repeated infections.

C psittaci causes psittacosis or ornithosis after exposure to infected birds. Ornithosis is the preferred term, because almost any bird can transmit the organism. The clinical spectrum of C psittaci infection ranges from an asymptomatic infection to a fulminant toxic syndrome. Patients with ornithosis most commonly present with pneumonia or fever of unknown origin.

C trachomatis is an important cause of sexually transmitted diseases, including trachoma, pelvic inflammatory disease, and cervicitis. C trachomatis can also cause pneumonia, primarily in infants and young children. Reports document cases of pneumonia due to C trachomatis in immunocompromised adults and laboratory workers.

ETIOLOGY

Chlamydia pneumoniae was described in 1965 Taiwan. It was extracted from conjunctival swab, and first named TW 183. Later in USA (1983) from pharyngeal

smear from patient with acute respiratory infection was isolated pathogen, named as agent AR 39. After identification of identity of both microorganisms it was renamed to TWAR. Later the strain TWAR was rated to chlamidia. New species was classified as Chlamydia pneumoniae. It is intracellular parasite, containing specific DNA, only on 10% similar with another species of Chlamydia. It gives cross-reactions of agglutination with antigens of Ch. psittaci, Ch. Trachomatis. Mainly Ch. pneumonia is connected with affection of respiratory tract, taking part in general etiology of respiratory infections from 6 до 17%. It is not stable in environment, in transport medium by 4°C it survives about 24 hours. Ch. pneumoniae is sensitive to tetracycline and erythromycin and resistant to penicillins. It is cultivated in chicken embryos and cellular cultures. There is only one serological variant.

Ch. psittaci has common properties with other types of the genus. The pathogen has two types of antigens – thermostable and thermolabile. First are group - specific, reacting with antibodies to all species of Chlamydia in reaction of agglutination and reaction of inhibition of agglutination. Latter are species – specific and reacting with homologous antigens.

EPIDEMIOLOGY

Infection, caused by C psittaci is connected with exposure to birds, especially sick ones, is a clue to the diagnosis in a patient with pneumonia and splenomegaly. Pet shop employees and poultry industry workers are also at risk. Obtain an occupational and a vocational history in all patients with community-acquired pneumonia.

C. pneumonia is anthroponosal infection with air-droplet route of transmission. Increasing of morbidity is usual for cold season. Epidemic outbreaks, especially in closed communities are possible. Young persons are most prone to infection.

PATHOGENESIS

Chlamydiae initiate infection by attaching to the outer membrane of susceptible host cells. The organism subsequently produces cytoplasmic inclusions in the infected cells. The cells release the matured inclusions to infect adjacent cells.

The mode of transmission is different between the 3 species, but all can cause systemic disease by hematogenous spread. Respiratory secretions transmit C pneumoniae from human to human, whereas infected birds transmit C psittaci to humans via the respiratory route through direct contact or aerosolization.1 Birds known to cause ornithosis include cockatiels, parrots, parakeets, macaws, chickens, ducks, turkeys, pigeons, and sparrows, among others.

When pregnant women have a C trachomatis infection of the cervix, the organism is transmitted when the infant passes through the infected birth canal. C trachomatis infection may cause neonatal conjunctivitis, nasopharyngitis, otitis media, and pneumonitis. The tendency to chronic inflammation is typical, and chronic persistent infection may occur if neonatal infections remain untreated.

Hystologically intra-alveolar inflammation with a milder degree of interstitial reaction is a characteristic pathologic finding in the lungs are quite typical for the infection. Alveolar-lining cells contain intracytoplasmic inclusions.

CLINICAL MANIFESTATIONS

Psittacosis (ornithosis).

The incubation period is 5-14 days or longer. Abrupt onset of constitutional symptoms is a common presentation in symptomatic patients.

The severity of disease ranges from asymptomatic to severe pneumonia with systemic illness.

A nonproductive cough has been observed in 50-80% of patients; however, this symptom is often absent initially. Chest pain is common, but pleuritic pain is rare.

Fever is the most common symptom and may reach 39 - 40° C. Some patients may present with culture-negative endocarditis or fever of unknown origin.

Signs of meningitis or encephalitis, including focal neurological deficits and seizures, may develop. Photophobia, epistaxis, tinnitus, deafness, gastrointestinal symptoms, and arthralgia have been reported in less than 50%f of patients.

On examination one can observe a pulse-temperature dissociation (fever without elevated pulse), which is also seen in typhoid fever and Legionnaires' disease; somnolence; splenomegaly; and an erythematous, blanching, maculopapular rash in the presence of pneumonia suggest ornithosis. Auscultatory findings may be sparse and may underestimate the extent of pneumonia. Defervescence is usually slow. Signs of hepatitis, hemolytic anemia, disseminated intravascular coagulation, meningoencephalitis, or reactive arthritis may be observed.

Cutaneous manifestations, including Horder spots (rare), splinter hemorrhages, superficial venous thromboses, acrocyanosis, and erythema nodosum, may be observed. On X-ray examination, consolidation in a single lower lobe is the most common finding. However, various findings have been observed, including patchy reticular infiltrates radiating from the hilum, a diffuse ground-glass appearance, and a miliary pattern. Pleural effusions are evident in as many as 50% of cases; however, the effusions are usually small and do not cause symptoms.

In case of chlamydiosis, caused by C pneumoniae, incubation period is approximately 3-4 weeks. The onset is usually gradual and may be biphasic. Symptoms of bronchitis or pneumonia follow upper respiratory tract symptoms (rhinitis, laryngitis, pharyngitis and sinusitis) in 1-4 weeks. Most persons with C pneumoniae infections are asymptomatic, and most have relatively mild respiratory illnesses. Sputum is usually scant, but cough is prominent. A history of hoarseness is more common in C. pneumoniae infection than in mycoplasmal infection or other pneumonias. Headache occurs in as many as 58% of cases and may be important as a nonclassic pneumonia finding. Patients with C pneumoniae infection are less likely to report fever. Symptoms may be prolonged, with persistent cough and malaise for

weeks to months despite appropriate use of antibiotics.

Fever is more often present in the first few days than in a week or later. Fever is often absent by the time of examination. Pharyngeal hyperemia without exudate occurs in various atypical pneumonias. Rhonchi and rales are present even in mild cases of disease.

Chest radiographs most commonly show a single subsegmental infiltrate that is mainly located in the lower lobes. Extensive consolidation is rare, although acute respiratory distress syndrome has been reported. No radiographic findings are characteristic. Residual changes can be observed even after 3 months. Pleural effusion occurs in 20-25% of cases.

The white blood cell count is usually not elevated in C pneumoniae infection. Alkaline phosphate levels may be elevated.

In case of pneumonia, caused by C. trachomatis, chest radiographs show bilateral interstitial infiltrates with hyperinflation.

Complications.

Complications of C psittaci infections include endocarditis, thrombophlebitis, myocarditis, thyroiditis, pancreatitis, hepatitis, renal failure, disseminated intravascular coagulation, and fetal death in infected pregnant women.

Complications of C pneumoniae infection include otitis, erythema nodosum, exacerbations of asthma, endocarditis, Guillain-Barré syndrome, and encephalitis. New-onset asthma also has been observed after C pneumoniae infection.

While some studies clearly associate C pneumoniae organisms with atheromatous plaques or sarcoidosis, the role of C pneumoniae in the pathogenesis of these syndromes remains to be established. Antibiotic trials for coronary artery disease are not supportive of their role.

DIAGNOSIS

Single serum titers to C. psittaci are insensitive and nonspecific. Confirmation with paired acute and convalescent sera is advised. A confirmed case involves isolation of the organism by culture or compatible clinical illness with a 4-fold rise in complement-fixing (CF) or microimmunofluorescence (MIF) antibodies against C. psittaci (to a reciprocal titer of 32 or greater by paired sera at least 2 wk apart) or detection of IgM titer of 16 or greater against C psittaci by MIF. Serologic tests are preferred because culture is difficult. CF tests can cross-react with C pneumoniae and C trachomatis. MIF and polymerase chain reaction assays can be used to distinguish C psittaci infection from infection with other chlamydial species. A third serum sample may be necessary to confirm the diagnosis because antibiotic treatment can delay or diminish the antibody response. All serologic tests should be performed simultaneously at the same laboratory.

The commonly used serologic criteria for detection of C pneumoniae infection are an IgM titer exceeding 1:16 or a 4-fold increase in the IgG titer by MIF. Serologic

testing is poorly standardized and studies have shown poor reproducibility. In addition, the presence of a single elevated IgG titer may not be reliable because elderly patients can have persistently elevated IgG titers due to repeated infections.

The absence of detectable antibodies several weeks after the onset of infection does not exclude a diagnosis of acute C. pneumoniae pneumonia because the IgM antibody response may take as long as 6 weeks and the IgG antibody response may take as long as 8 weeks to appear in primary infections.

In some laboratories, a polymerase chain reaction with pharyngeal swab, bronchoalveolar lavage, sputum, or tissue can be used to seek C pneumoniae – specific DNA. It is the most promising rapid test but still not totally available.

Cell culture with oropharyngeal swabs is probably the best test, but it requires specialized culture techniques. It is performed only in research laboratories.

Clinical findings suggest the diagnosis of C trachomatis pneumonia. The presence of chlamydial inclusions or elementary bodies on Giemsa-stained smears of the conjunctivae or nasopharynx confirms the diagnosis. Testing may show findings of elevated antichlamydial IgM titer. Peripheral eosinophilia and elevated serum immunoglobulin levels are characteristic.

TREATMENT

For infections, caused by C psittaci tetracycline or doxycycline is the treatment of choice. Continue treatment for 10-21 days. Neseccity of longer course to prevent relapse is controversial. Erythromycin is the alternative treatment, but this drug may be less efficacious in severe cases.

C. pneumoniae infection must be treated empirically, because rapid testing is not readily available and antibiotic therapy is usually completed before the results of serology testing become available. Doxycycline is the treatment of choice except in children younger than 9 years and in pregnant women. Treatment should be continued for at least 10-14 days after defervescence. If symptoms persist, a second course with a different class of antibiotics is usually effective.

In outpatient settings doxycycline (100 mg PO bid) or tetracycline hydrochloride (500 mg PO qid) can be used. In inpatient settings, use doxycycline hyclate (100 mg IV bid). Alternatives include erythromycin (500 mg PO/IV qid) and newer macrolides such as azithromycin (500 mg PO/IV qd for 7-10 d) and clarithromycin (1 g PO qd or 500 mg PO bid for 10 days). Newer macrolides are better tolerated than erythromycin. Shorter courses of the newer macrolides appear to be effective. Hepatotoxicity has been reported.

Fluoroquinolones, including levofloxacin (500 mg PO/IV qd for 10-14 d or 750 mg PO/IV qd for 5 days) and moxifloxacin (400 mg PO/IV qd for 10-14 days), also have some activity, although less than that of tetracyclines or macrolides.

MYCOPLASMA INFECTIONS

DEFINITION *Mycoplasmosis is a group of acute infectious diseases, caused by Mycoplasma spp. and characterized with affection of respiratory tract, joints, urogenital system and affection of a fetus.*

ETIOLOGY

Although there was isolated at least 17 species of Mycoplasma from humans, 4 types of organisms are responsible for most clinically significant infections. These species are Mycoplasma pneumoniae, Mycoplasma hominis, Mycoplasma genitalium, and Ureaplasma species. The main role in infection of respiratory tract belongs to M. pneumoniae.

Mycoplasmae – polymorphic microorganisms, but M. pneumonia is mainly filamentary microorganisms 2-5 mkm long. They have three-layered cellular wall and contain DNA.

EPIDEMIOLOGY

The most typical is air-droplet route of transmission. Spread of infection throughout households is also common, but person-to-person transmission is slower than for many other common bacterial respiratory tract infections; close contact appears necessary. The organism may persist in the respiratory tract for several months, and sometimes for years in patients who are immunosuppressed, after initial infection.

M pneumoniae infections occur both endemically and in cyclic epidemics worldwide. Less information is available for tropical or polar countries; however, based on seroprevalence studies, the disease also occurs in these regions, suggesting that climate and geography are not important determinants in the epidemiology of M pneumoniae infections.

PATHOGENESIS

M pneumoniae is best known as the cause of “atypical” pneumonia, but the most frequent clinical syndrome caused by this organism actually is tracheobronchitis or bronchiolitis, often accompanied by upper respiratory tract manifestations. Pneumonia develops in only 5-10% of persons who are infected. Acute pharyngitis and myringitis are less common.

After inhalation of respiratory aerosols, the organism attaches to host cells in the respiratory tract. The P1 adhesin and other accessory proteins mediate attachment, followed by induction of ciliostasis, local inflammation that consists primarily of perivascular and peribronchial infiltration of mononuclear leukocytes, and tissue destruction that may be mediated by liberation of peroxides. The organism also has the ability to exist intracellularly.

The development of a cell-mediated immune response to M. pneumoniae has been shown further by positive lymphocyte transformation, macrophage migration inhibition and delayed-hypersensitivity skin tests. A polysaccharide-protein fraction

of the organisms is involved in this response rather than the glycolipid that is the main antigenic determinant in complement fixation and other serological reactions. The initial lymphocyte response is followed by a change in the character of the bronchiolar exudate, with polymorphonuclear leucocytes and macrophages predominating. The rather slow development of these events on primary infection contrasts with an accelerated and often more intense host response seen on reinfection. To at least some extent, therefore, the pneumonia caused by M. pneumoniae is an immunopathological process. Children of 2 to 5 years of age often possess mycoplasmacidal antibody, suggesting infection at an early age, although it is not clear whether the antibody is induced entirely by M. pneumoniae infection. Nevertheless, it is tempting to suggest that the pneumonia which occurs in older persons is an immunological over-response to reinfection, the lung being infiltrated by previously sensitized lymphocytes.

Additionally, acute mycoplasmal respiratory tract infection may be associated with exacerbations of chronic bronchitis and asthma.

CLINICAL MANIFESTATIONS

The great majority of M. pneumoniae respiratory tract infections are mild and self-limited. Hospitalization is sometimes necessary, but recovery is almost always complete and without sequelae. Recent studies have indicated that M. pneumoniae is second only to Streptococcus pneumoniae as a cause of bacterial pneumonia that requires hospitalization in elderly adults. Subclinical infections may occur in 20% of adults infected with M pneumoniae, suggesting that some degree of immunity may contribute to the failure of clinical symptoms in some instances.

But recent studies suggests that M pneumoniae disease is sometimes much more severe than appreciated, even in otherwise healthy children and adults. Severe disease is more common in persons with underlying disease or immunosuppression. While reports describe fatal cases of mycoplasmal pneumonia, the overall mortality rate is extremely low, probably less than 0.1%.

Generally, the incubation period of respiratory mycoplasmosis is 2-3 weeks. Onset is usually acute. Typical symptoms can develop and persist over weeks to months and include flulike manifestations. Patients have complaints on generalized aches and pains, fever up to 39° C, cough - usually nonproductive, sometimes fit-like. Quite typical symptoms of throat affection – pharyngeal pain, hyperemia of mucosal layer, hypertrophy of lymph patches of throat (nonexudative pharyngitis). Most patients have complaints on headache, myalgias, chills but not rigors. Nasal congestion with coryza, earache, general malaise is also observed.

Physical findings can be quite variable. Examination typically does not reveal severe intoxication, but some abnormalities may be apparent in a significant proportion of cases. Oropharyngeal inflammation is typical. In some cases there are enlarged lymph nodes, usually cervical chains. Conjunctivitis is also one of clinical

symptoms. Maculopapular or urticarial rash may appear in one third cases.

Chest auscultation in patients with pneumonia may demonstrate localized wheezes and scattered moist rales, generally involving multiple lobes of the lung and sometimes accompanied by wheezes, with no signs of consolidation, egophony, or bronchial breathing. In many persons, chest auscultative and percussive abnormalities are minimal to absent, in contrast to radiographic changes that makes diagnosis of pneumonia more difficult. Abnormalities on chest radiographs often appear more severe than predicted based on the clinical condition of the patient. Although lobar consolidation is unusual, diffuse or interstitial infiltrates that involve the lower lobes are the most common radiographic abnormalities. Small pleural effusions may develop in approximately 20% of cases. Lung involvement tends to be unilateral but can be bilateral.

Extrapulmonary manifestations may occur quite rare.

There are no specific changes for mycoplasmal pneumonia. About 25% of patients develop leukocytosis; the rest have leukocyte counts within the reference range. 30% of patients have an elevated erythrocyte sedimentation rate. Cellular response of sputum is mononuclear, with no bacteria visible with Gram staining. No specific abnormalities of hepatic or renal function are likely to occur.

Extrapulmonary complications quite rare (less than 10% of cases of M pneumoniae infections) may include meningoencephalitis, ascending (Guillain-Barré) paralysis, transverse myelitis, myopericarditis, cardiac arrhythmia, hemolytic anemia, disseminated intravascular coagulation, renal failure, arthritis, erythema multiform (Stevens-Johnson syndrome), erythema nodosum, ulcerative stomatitis and other less common conditions.

DIAGNOSIS

Laboratory investigation should focus on both the clinical illness (e.g., tracheobronchitis and pneumonia) and the many possible infectious etiologies that can cause clinically similar manifestations. The extent of laboratory investigation also should reflect the severity of the illness and whether the illness warrants hospitalization.

In as many as half of all cases of community-acquired pneumonias, the microbiological etiology is never determined, despite appropriate laboratory testing. The typical mild illness caused by M. pneumoniae in otherwise healthy persons may not warrant a comprehensive microbiological investigation because empiric treatment with oral antimicrobials can cover M. pneumoniae and most other bacterial agents that produce similar illnesses.

About 75% of patients have a cold agglutinin titer of at least 1:32 by the second week of illness, disappearing by 6-8 weeks. This is not a specific test for M pneumoniae infection but the greater the cold agglutinin titer is (>1:64) in a patient with CAP, the more likely the cold agglutinins are due to M. pneumoniae. To confirm

mycoplasmal respiratory tract infection, culture, molecular-based tests, and serological tests are necessary.

Respiratory tract specimens suitable for culture include throat swabs, sputum, tracheal aspirates, bronchial lavage fluid, pleural fluid, or lung biopsy tissue, depending on the patient's clinical condition.

Mycoplasmal organisms have fastidious growth requirements and are often difficult to grow in a cell-free medium. Take care during specimen collection to inoculate into a suitable transport medium. Clinicians advise freezing at -70°C if specimens cannot be transported to the diagnostic laboratory immediately after collection.

Growth in culture is slow, requiring 3 weeks in some cases, and the culture is not extremely sensitive for detecting M. pneumoniae infection. The culture medium is often unavailable except from specialized reference laboratories. If culture is attempted, alternative procedures including serology and molecular-based nucleic acid amplification tests should also be performed.

Serological testing is most frequently used to confirm M. pneumoniae infection. Most used are enzyme-linked immunosorbent assay to the older, less sensitive complement fixation assays and nonspecific cold agglutinin titers. These types of tests are widely available through commercial reference laboratories.

Because primary infection does not guarantee protective immunity against future infections and residual IgG may remain from earlier encounters with the organism, experts have launched a great impetus to develop sensitive and specific tests that can differentiate between acute and remote infection.

Definitive diagnosis requires seroconversion documented by paired specimens obtained 2-4 weeks apart. Although researchers purport that single-titer IgM or IgA assays reveal course infection, data regarding how long IgM persists after acute infection are not clear, and as many as 50% of adults may not mount a detectable IgM response. So, relying on a single serological test can be clinically misleading, and experts recommend basing diagnosis of acute infection on seroconversion measured simultaneously in assays for both IgM and IgG. Use of serology for diagnosis of mycoplasmal infection is valid only if the patient has a satisfactory capacity of the humoral immune system to mount an antibody response.

There are molecular-based systems for detection of M. pneumoniae using the polymerase chain reaction evaluable. However, only limited information describing the application of this methodology in a clinical setting is known. Some reference laboratories offer these types of tests for patient care purposes using reagents developed internally. Carriage of mycoplasmas in the upper respiratory tract for variable periods following prior infection may confound the interpretation of a single positive polymerase chain reaction assay result. Furthermore, a polymerase chain reaction assay may reveal very small numbers of organisms that may not be of

etiologic significance.

A specific threshold of quantity of mycoplasmas in the respiratory tract that can differentiate colonization from infection has not been established, so a highly sensitive detection method such as the polymerase chain reaction performed in a nonquantitative manner may overestimate the clinical importance of M pneumoniae as a pathogen since it often co circulates with other bacterial and viral respiratory pathogens. For these reasons, molecular-based assays should be accompanied by serological assays for maximum diagnostic accuracy unless testing a normally sterile body fluid in which the presence of any number of mycoplasmas would be considered evidence of disease.

TREATMENT

The choice of outpatient management or hospitalization for persons with community-acquired pneumonia depends on the clinical syndrome and not the organism, largely because the microbiologic diagnosis is often unavailable. The decision to hospitalize a patient depends on an assessment of the person's ability to tolerate and comply with oral medication, possibility of immunosuppression, age and other factors. Relatively few patients with M pneumoniae pneumonia require hospitalization based on these criteria.

Appropriate antimicrobial therapy shortens the symptomatic period and hastens radiological resolution of pneumonia and recovery, even though patients may shed organisms for several weeks. When treating community-acquired pneumonia, physicians usually must provide empiric coverage for several different bacterial agents that may be responsible because the microbiologic diagnosis is seldom available at the initiation of treatment. M pneumoniae remains predictably susceptible to macrolides and tetracyclines; therefore, in vitro susceptibility testing to guide therapy is not indicated. Oral erythromycin has long been the standart for mycoplasmal respiratory tract infections. Tetracycline and its analogues are also active. Clindamycin is effective in vitro, but limited reports suggest it may not be active in vivo and thus is not considered a first-line treatment. Several of the newer fluoroquinolones exhibit bactericidal antimycoplasmal activity but are generally less potent in vitro than macrolides against M pneumoniae. Their advantage lies in the fact that they are active against all classes of bacteria that produce clinically similar respiratory tract infections, including macrolide-resistant Streptococcus pneumoniae. As would be predicted by the lack of a cell wall, none of the beta-lactams is effective in vitro or in vivo against M pneumoniae, and neither are the sulphonamides or trimethoprim.

Mycoplasma species are slow-growing organisms that have the capacity to reside intracellularly; thus, respiratory tract infections are expected to respond better to longer treatment courses than might be offered for other types of infections. A 14- to 21-day course of oral therapy with most agents is also appropriate. A 5-day course

of oral azithromycin is approved for the treatment of community-acquired M pneumoniae pneumonia. Clinical data indicate that this duration of treatment is of comparable efficacy to a 10-day course of erythromycin.

In addition to the administration of antimicrobials for the management of M pneumoniae infections, other measures (e.g., cough suppressants, antipyretics, analgesics) should be administered as needed to relieve headaches and other systemic symptoms.

PREVENTION

Resistance to disease

One of the best ways of assessing the relative importance of cell-mediated and humoral immune mechanisms in resistance is to determine the ability of lymphocytes and of serum from immune animals to confer immunity when they are transferred to recipient, non-immune animals. However, serum antibody to M. pneumoniae does not confer complete protection against infection or disease, as they may occur despite high titres of, for example, serum mycoplasmacidal antibody. Furthermore, mycoplasmal infection of the respiratory tract of laboratory animals may stimulate only a weak antibody response and yet induce greater resistance to reinfection and disease than parenteral inoculation with organisms that stimulate much higher titres of serum antibodies. Such observations have led to the belief that local immune factors are crucial in resistance. The correlation between the resistance of adult volunteers to M. pneumoniae disease and the presence of IgA antibody in respiratory secretions is consistent with this contention. This antibody could provide the first line of defence by preventing attachment of the organisms to respiratory epithelial cells.

Vaccination

The efficacy of formalin-inactivated M. pneumoniae vaccines in preventing pneumonia caused by this mycoplasma has ranged from 28 to 67 % in field trials. The failure of some killed M. pneumoniae vaccines to protect fully may have been due to poor antigenicity, but others induced serum antibody levels similar to those that develop after natural infection. This suggests that the relatively poor protection afforded by the killed vaccines may have been due to their inability to stimulate cell-mediated immunity and/or local antibody and they are no longer produced commercially. With local antibodies in mind, live attenuated vaccines, particularly those based on temperature-sensitive mutants of M. pneumoniae, were developed. But they were considered unacceptable for general human use and this approach to vaccination was abandoned. Finally, recombinant DNA vaccines involving P1 and other proteins, and a live adenovirus recombinant vaccine developed by cloning a component of the M. pneumoniae P1 gene into an adenovirus vector, are being explored.

MEASLES

DEFINITION *Measles is an acute anthroponosis highly contagious viral infection disease characterized by intoxication, fever, upper airways affection, and conjunctivitis, enanthema (Koplik spots) on the buccal and pharyngeal mucosa and maculopapular rash.*

ETIOLOGY

Causative agent of measles is an RNA virus of the family Paramyxoviridae, genus Morbillivirus. Only one antigenic type is known. Measles virions are pleomorphic spherical structures having a diameter of 120 to 250 nm and consisting of six proteins. Virus has hemagglutination, complement-fixing and hemolytic abilities, can have a mutagenic effect on chromosomes. During the prodrome period and for a short time after the rash appears, it is found in nasopharyngeal secretions, blood, and urine.

EPIDEMIOLOGY

Ill person is a source of infection. Presence of the healthy carriage is not established. Measles virus is transmitted by respiratory secretions. Patients are contagious from 2 or 3 days before the onset of symptoms until 4 days after the appearance of the rash. Infectivity peaks during the prodrome phase. Isolation precautions should be maintained from the 7th day after exposure until 5 days after the rash has appeared. Measles is very contagious; about 90 % of susceptible family contacts acquire the disease. Morbidity peak happens in cold season (predominantly from February to April).

Persistent and prolonged immunity is formed after illness. Infants transplacentally acquire immunity from mothers who have had measles or measles immunization.

PATHOGENESIS

Measles virus invades the respiratory epithelium and spreads via the bloodstream to the reticuloendothelial system (tonsils, glands, liver, spleen, myeloid tissue of marrow). Multiplication and accumulation of viruses are happed in these organs. Multinucleated giant cells with inclusion bodies in the nucleus and cytoplasm (Warthin-Finkeldey cells) are found in respiratory and lymphoid tissues and are pathognomonic for measles.

The essential lesion of measles is found in the skin; in the mucous membranes of the nasopharynx, bronchi, and intestinal tract; and in the conjunctivae. Serous exudate and proliferation of mononuclear cells and a few polymorphonuclear cells occur around the capillaries. In the skin, the reaction is particularly notable about the sebaceous glands and hair follicles. Koplik spots consist of serous exudate and proliferation of endothelial cells similar to those in the skin lesions. A general inflammatory reaction of the buccal and pharyngeal mucosa extends into the lymphoid tissue and the tracheobronchial mucous membrane. Interstitial pneumonitis

resulting from measles virus takes the form of Hecht giant cell pneumonia. Bronchopneumonia may be due to secondary bacterial infection.

Sometimes viruses are discovered in CNS where they cause development of hemorrhages, perivascular infiltration and demyelinization. Both the spinal cord and the brain may be affected.

CLINICAL MANIFESTATIONS

Clinical classification of measles.

Course:

- typical;
- atypical, with variants: abortive, mitigated, subclinical, measles with a toxic.

The severe form has marked symptoms of toxaemia (hyperthermia, affection of the nervous system with disturbances of consciousness, adynamia, and acute cardiovascular failure). In the hemorrhagic type of measles (black measles), bleeding may occur from the mouth, nose, or bowel.

An abortive or rudimentary form of measles is encountered quite rarely among the unimmunized. Measles sometimes runs an atypical (but not mitigated) course in people treated with antibiotics.

In people subjected to serum prophylactic immunization mitigated (attenuated) measles is noted, in which the incubation period is protracted to a maximum of 21 days, but the initial and eruptive periods are shortened. Catarrhal symptoms in the mucous membrane are usually mild or absent; and the enanthema and Belsky-Filatov-Koplik spots may also not appear. Rash is usually sparse or even represented by a few elements. Temperature is sometimes only subfebrile and lasts for two or three days. The patient's general condition is usually not disturbed, or only slightly affected. In mild cases the rash may be less macular and more nearly pinpoint, somewhat resembling that of scarlet fever or rubella.

The incubation period is 9 – 11 days (sometimes 2–3 weeks). The prodrome (catarrhal) phase typically lasts 3–5 days, and is characterized by fatigability, mild pyrexia and throat tickle, conjunctivitis with lacrimation, slight cough, and nasal discharge. Usually the coryza, fever, and cough are increasingly severe up to the time the rash has covered the body. An enanthema or red mottling is usually present on the hard and soft palates. Koplik's spots appear on 2-3 days of prodrome phase, and are the pathognomonic sign of measles. Spots are little white dots usually as small as grains of sand, with slight, reddish areoles. Without adequate illumination for examination, they may be overlooked. Koplik's spots are typically located on the buccal mucosa alongside the second molars and may be extensive; they are not associated with any other infectious disease. The spots wane after the onset of rash and soon disappear. The entire buccal and inner labial mucosa may be inflamed, and the lips may be reddened.

Phase of eruptions usually lasts 3 days. Accurate consecution of rash appearance

is characteristic. The rash usually starts as faint macula on the upper lateral parts of the neck, behind the ears, along the hairline, and on the posterior parts of the cheek. The individual lesions become increasingly maculopapular as the rash spreads rapidly over the entire face, neck, upper arms, and upper part of the chest within approximately the first 24 hr. During the succeeding 24 hr it spreads over the back, abdomen, entire arms, and thighs. As it finally reaches the feet on the 2nd–3rd day, it begins to fade on the face. At this time, the patient is at the most severe point of the illness. The fading of the rash proceeds downward in the same sequences in which it appeared (convalescence phase is beginning). Brownish discoloration of the skin and desquamation may occur later. Sometimes the rash is slightly hemorrhagic; in severe cases with a confluent rash, petechiae may be present in large numbers, and there may be extensive ecchymoses. In the hemorrhagic type of measles (black measles), bleeding may occur from the mouth, nose, uterus or bowel.

During the phase of eruptions intoxication and catarrhal syndromes remain. Lymph nodes at the angle of the jaw and in the posterior cervical region are usually enlarged, and slight splenomegaly may be noted. Mesenteric lymphadenopathy may cause abdominal pain. In patients with severe course of measles the hyperthermia (40°C and more), respiratory failure, secondary infection addition and nervous system affection (convulsions, loss of consciousness, pareses, and pelvic organs dysfunction) may be occurred.

The severity of the disease depends on intoxication and catarrhal syndromes, extent and confluence of the rash, presence and nature of complications. The disease tends to be more severe in adults than in children, with higher fever, more prominent rash, and a higher incidence of complications. Usually measles runs very severe in patients with HIV-infection.

Complications of measles may be sorted into two groups.

1. Complications, which caused by virus action: interstitial pneumonia, diarrheal syndrome, keratitis, uveitis, spontaneous abortion, premature birth, measles encephalitis and subacute sclerosing panencephalitis, encephalomyelopolyradiculoneuritis, interstitial nephritis, postinfectious thrombocytopenic purpura (rarely).

2. Bacterial complications: otitis media, otogenic meningitis, arthritis, frontitis, laryngitis, tracheitis, bronchitis and pneumonia, mediastinitis, pleurisy, myocarditis, skin abscess, noma (water canker; the deep lesion of mouth tunica mucosa), and cutaneous gangrene of genitals in babies. Gastrointestinal complications of measles include gastroenteritis, hepatitis, appendicitis, ileocolitis, and mesenteric adenitis. It is not uncommon to detect high levels of alanine and aspartate aminotransferases in the absence of gastrointestinal signs such as jaundice.

DIAGNOSIS

This is usually made from the typical clinical picture; laboratory confirmation is rarely needed. During the prodrome stage multinucleated giant cells can be demonstrated in smears of the nasal mucosa. Virus can be isolated in tissue culture, and diagnostic rises in antibody titer can be detected between acute and convalescent sera. The white blood cell count tends to be low with a relative lymphocytosis. Lumbar puncture in patients with measles encephalitis usually shows an increase in protein and a small increase in lymphocytes. The glucose level is normal.

TREATMENT

Sedatives, antipyretics for high fever, bed rest, and an adequate fluid intake may be indicated. Humidification of the room may be necessary for laryngitis or an excessively irritating cough, and it is best to keep the room comfortably warm rather than cool. The patient should be protected from being exposed to strong light during the period of photophobia. The complications of otitis media and pneumonia require appropriate antimicrobial therapy.

With complications such as encephalitis, subacute sclerosing panencephalitis, giant cell pneumonia, and disseminated intravascular coagulation, each case must be assessed individually. Good supportive care is essential. Gamma globulin, hyperimmune gamma globulin, and steroids are of limited value.

PREVENTION

Common prophylaxis includes the exposure and isolation of patient, observation for contact people and quarantine (in child's collectives). Quarantine is of little value because of the contagiousness during its prodrome stage, when measles may not be suspected.

Urgent prophylaxis preventive is human measles immunoglobulin. Younger children (under 3 year), pregnant women and people with immunodeficiency are subjected to urgent prophylaxis.

Specific planned prophylaxis. The initial measles immunization may be given at 12 to 15 mo. Because the seroconversion rate following immunization is not 100% and there may be some waning of immunity with time, a second immunization against measles, usually given as measles-mumps-rubella (MMR), is indicated. This dose can be given when the child enters school or later on entry to middle school. Adolescents entering college should also have received a second measles immunization. Expressed immunity after vaccination is created for a term of 10-15 years. Use of live measles vaccine is not recommended for pregnant women, people with immunodeficiency, and patients with oncological or acute infectious diseases.

SCARLET FEVER

DEFINITION *Scarlet fever is form of streptococcal infection accompanied by fever, quinsy tonsillitis, characteristic rash, which creates streptococcal and infection-allergic complications.*

ETIOLOGY

Scarlet fever is caused by group A β {beta}-hemolytic streptococci. They are gram-positive bacteria of spherical to ovoid shape that characteristically form chains when grown in liquid media. B-hemolytic streptococci are facultative anaerobes cocci that are classified on the basis of their ability to hemolyze red blood cells. Group A β -hemolytic streptococci can be divided into more than 80 immunologically distinct types that are based on differences in the M protein.

EPIDEMIOLOGY

Scarlet fever patient is a primary source of infection. Contagious period lasts from first hours to 7-8 days of disease. Patients with other streptococci diseases are also infectious.

Scarlet fever more often spreads by oral droplet. Infection also may be spread by contact with skin lesions or transmitted by food, milk, and water.

Scarlet fever is most common in children between 2 and 7 yr of age. Streptococcal disease, including scarlet fever, is uncommon in children less than 3 year of age, but in families with known streptococcal infection, it may present as nonspecific upper respiratory tract infection, pharyngitis, and otitis media, with or without impetigo. Scarlet fever is unusual in teenagers and adults since they have antitoxic immunity after previous meetings with streptococcus.

Persistent antitoxic immunity is formed after illness.

PATHOGENESIS

Tonsils mucous membranes (more often), defective skin, endometrium, lungs (rarely) are localities of infection penetration. Here streptococcus gives inflammatory and necrotic changes. Then pathogens go on in blood and spread round the organism. Some of them get into regional glands. Scarlet fever–producing streptococci lead to clinical manifestations that are similar to those produced by nonpyogenic exotoxin - containing strains except for the scarlatiniform rash. Rash production is dependent in part on a host hypersensitivity reaction and is decreased by host synthesis of specific antitoxins.

According to A. Koltypin, three principal components can be schematically distinguished in the pathogenesis of scarlet fever: toxic, infectious (septic), and allergic. They are closely interrelated, their distinction is, of course, rather artificial, and they are manifested in a different degree. In some cases toxic phenomena, and in others septic, predominate; in some cases there may be allergic waves and in others none. A complex of characteristic symptoms (central and vegetative disorders, hyperthermia, exanthema, and cardiovascular disturbances) expresses the toxaemia

caused by the Scarlet fever toxin. Given preliminary sensitization of the organism, signs of allergy begin to develop from the very onset of the disease. Moreover, sensitization during the first stage resulting from the action of various allergens (streptococci and their breakdown products) creates favorable conditions for the development of late complications if there is re-infection.

CLINICAL MANIFESTATIONS

Clinical classification of Scarlet fever (according to A. Koltypin) includes:

I. typical forms.

II. atypical forms:

- obliterated;
- form with malignant symptoms (hypertoxic, hemorrhagic);
- extrabuccal Scarlet fever.

The incubation period lasts 2–7 days (may be prolonged to 12 days). The onset is acute and is characterized by fever, vomiting, headache, pharyngitis, tonsillitis, and chills. The rash typically begins on the first or second day of illness over the face, neck, upper trunk, spreading to involve the extremities but sparing the palms and soles. The rash is made up of minute papules, giving a characteristic "sandpaper" texture to the skin. It settles on hyperemic background. The forehead and cheeks appear flushed, and the area around the mouth is pale. The rash is most intense in the axillae and groin and at pressure sites. Petechiae may occur owing to capillary fragility. Areas of hyperpigmentation that do not blanch with pressure may appear in the deep creases, particularly in the antecubital fossae. In severe disease, small vesicular lesions (miliary sudamina) may appear over the abdomen, hands, and feet. White dermographism shows distinctly. Skin dryness is typical for Scarlet fever. Rash usually lasts out 3-7 days, don’t leave the pigmentation. Desquamation begins on the face in fine flakes toward the end of the 1st wk and proceeds over the trunk and finally to the hands and feet. The duration and extent of desquamation vary with the intensity of the rash; it may continue for as long as 6 wk.

Tonsillitis is permanent symptom of Scarlet fever. Bright fauces hyperemia (“ablaze throat”) is typical for it. Hyperemia is neatly localized and don’t spread for mucous membrane of hard palate. Scarlet tonsillitis may be catarrhal, follicular and necrotic. During the early days of illness the dorsum of the tongue has a white coat through which the red and edematous papillae project. After several days the white coat desquamates; the red tongue studded with prominent papillae persists ("strawberry tongue"). The palate and uvula may be edematous, reddened, and covered with petechial rash. Regional nodes are also involved in pathologic process.

Intensity of intoxication and high temperature correspond to disease severity. In mild scarlet fever the toxaemia is weak. The temperature is within the range of 38-38.5°C. The patients' general condition is little disturbed.

Moderately severe scarlet fever has an acute onset, with a complete set of

symptoms. Toxaemia is marked; the temperature rises to 39°C, and even to 40°C on individual cases. There are headache, lassitude, malaise, and sometimes delirium at night.

The onset of the severe toxic form is abrupt. It is characterized by repeated vomiting, which may continue during the second and third day. Diarrhoea is not infrequent. Fever is high, up to 40-41°C. The patient is in a state of strong excitation or, on the contrary, of depression. Consciousness is clouded, and there is delirium; there may be convulsions and meningeal symptoms.

Severe toxicoseptic scarlet fever has a combination of the symptoms of the two forms described above. It usually begins as a toxic form, but on the third to fifth day signs of a septic character aggravate it.

In the hypertoxic or fulminant form the symptoms of severe toxaemia described above progress with extreme rapidity; the patient lapses into a comatose state and dies in the first days sometimes even during the first 24 hours. A rare variety of toxic form - haemorrhagic scarlet fever - has been described, in which severe nervous and cardiovascular phenomena are accompanied with extensive haemorrhages into the skin and mucous membranes. This form is usually fatal. The rudimentary form is the mildest form of scarlet fever with very weakly expressed symptoms.

In extrabuccal or extrapharyngeal forms of scarlet fever the portal of entry of infection is not the fauces, but damaged skin or mucosa in various regions. The following variants can be distinguished according to the portal of entry and the mechanism of infection: (a) burn; (b) wound, or traumatic; (c) surgical; (d) puerperal; (e) complicating various exposed purulent foci on the skin.

COMPLICATIONS**.** Early complications of scarlet fever are lymphadenitis, sinusitis, otitis, mastoiditis, nephritis, arthritis. They are the result of the allergy and secondary infection. Late complications are generally encountered during the third or fourth week, and are apparently allergic in origin; streptococci play an important role in most of them (nephritis, myocarditis, and synovitis, rheumatism rheumatic polyarthritis, and endocarditis).

DIAGNOSIS

Streptococcal pharyngitis is suggested by age greater than 5 yr, high fever, exudates, tender anterior cervical lymphadenopathy, scarlatiniform rash, and a history of exposure. The immunologic response of the host after exposure to streptococcal antigen can be assessed by measuring antistreptolysin O (ASO) titers. ASO titers may be very high in patients with rheumatic fever; in contrast, they are weakly positive or not elevated at all in patients with streptococcal pyoderma; responses in patients with glomerulonephritis are variable.

The differential diagnosis of scarlet fever includes other causes of fever and generalized rash, such as pseudotuberculosis, yersiniosis, infectious mononucleosis,

measles, and rubella and other viral exanthems, Kawasaki disease, toxic shock syndrome, and systemic allergic reactions (e.g., drug eruptions).

TREATMENT

- Confinement to bed (during acute period).
- Antibiotic therapy. Penicillin or macrolide may be used in patients with mild or moderately severe course of disease. Patients with severe scarlet fever should be treated parenterally with cephalosporin, vancomycin, clindamycin, preferably intravenously.
- Disintoxication therapy (abundant drinking, glucose-saline solution).
- Antihistamine.
- Medication, which strengthens vessels wall (ascorutinum).
- Febrifuge (paracetamol, ibuprofen).
- Remedy for local treatment (throat rinsing and other).

RUBELLA

DEFINITION *Rubella is an acute viral infection disease characterized a rash similar to that of mild rubella, enlargement and tenderness of the postoccipital, retroauricular, and posterior cervical lymph nodes, fever, and mild intoxication, and has a wide spectrum of other possible symptoms.*

A high rate of rubella is subclinical. In adults, especially adult women, the infection may occasionally be severe, with manifestations such as arthritis and purpura. Rubella in early pregnancy can lead to fetal infection (congenital rubella syndrome) and severe congenital anomalies.

ETIOLOGY

Rubella virus listed in the family Togaviridae, genus Rubivirus. The rubella virion is composed of an inner helical capsid of RNA and protein that is surrounded by a lipid-containing envelope with a diameter of about 60 nm. This envelope has glycoproteins thorns (E1 and E2).

EPIDEMIOLOGY

Rubella is anthroponosis. Ill persons or virus carriers are a source of infection. Patients with subclinical disease are also infectious. During clinical illness the virus is present in nasopharyngeal secretions, blood, feces, and urine. Virus has been recovered from the nasopharynx 7 days before exanthem and 7–8 days after its disappearance. Rubella virus is spread by oral droplet or transplacentally through congenital infection.

PATHOGENESIS

There is little known about the microscopic pathology of postnatally acquired rubella since the disease is invariably self-limited. Viruses get into mucous membranes of upper airways with droplets of saliva and mucus. Then they go on in

blood and spread round the organism. Some of viruses get into glands and produce lymphadenopathy, lymphopenia. Rash is result of immediate virus action. Also the rash of rubella is immunologically mediated; its onset coincides with the development of specific antibodies. Circulating immune complexes play a vital part in development of arthritis.

Viraemia can be demonstrated for about a week before and ends within 2-3 weeks 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. Other findings may include decreased numbers of megakaryocytes in the bone marrow, extramedullary hematopoesis, and interstitial pneumonia.

CLINICAL MANIFESTATIONS

The incubation period is 11–24 days. A prodrome phase is uncommon in children; adults may have more severe disease, with a brief prodrome of malaise, fever, and anorexia. The foremost characteristic sign is retroauricular, posterior cervical and postoccipital adenopathy, fever and rash. No other disease causes the tender enlargement of these nodes to the extent that rubella does. Lymphadenopathy may remain for 1 wk or more. An enanthema may appear just before the onset of the skin rash. The rash begins on the face and quickly spreads down the body, usually within 24 hr. It is maculopapular. The elements of rash may be confluent, particularly on the face. The rash is the richest on the unbending surfaces of extremity, back and fundament. Palms and soles are free from eruption. The elements of rash usually clear by the 3rd day. Desquamation is minimal. Rubella without a rash has been described. Eruption is sometimes accompanied by mild coryza and conjunctivitis, there is no photophobia. Fever may be absent entirely or may be present for only several days in the early phase of the illness. The temperature seldom exceeds 38.40C. Mild itching may occur. Anorexia, headache, and malaise are not common. The spleen is often slightly enlarged. Arthritis develops as the rash is appearing and may take several weeks to resolve, most frequently involving the fingers, wrists, and/or knees. Paresthesia also has been reported. Chronic arthritis resulting from rubella is extremely rare.

Congenital Rubella Maternal infection in early pregnancy can lead to fetal infection, with resultant congenital rubella. The classic signs of congenital rubella are cataract, heart disease, and deafness, but a myriad of other defects have been reported. These abnormalities include signs and symptoms that are transient, such as low birth weight, thrombocytopenia, hepatosplenomegaly, jaundice, and pneumonia; those that are permanent, such as deafness, pulmonic stenosis, patent ductus arteriosus, glaucoma, and cataract; and those that are developmental, such as mental

retardation, diabetes mellitus, and behavioral disorders. The most important factor in the pathogenicity of rubella virus for the fetus is gestational age at the time of infection. While a fetus was infected in the 4-6-th weeks of gestation pathology of eyes develops, 5-10-th – heart, 3-11-th – brain, 7-10-th – organs of hearing.

Complications of postnatally acquired rubella are acute and chronic arthritis, hemorrhage due to both thrombocytopenia and vascular damage, which occurs in 1 of every 3000 patients. Thrombocytopenia may last for weeks or months. Encephalitis, meningitis, polyneuritis may develop after rubella. Adults are more likely than children to develop encephalitis; the mortality rate from this complication is 20 to 50 percent. Mild hepatitis is a rare complication.

DIAGNOSIS

The leucocyte count is normal or slightly reduced, the lymphocytes count is increased; thrombocytopenia is rare, with or without purpura.

Specific diagnostic tests include isolation rubella-specific immunoglobulin M antibodies (immune-enzyme analysis), and RNA of rubella virus (PCR).

A woman presenting with suspected rubella infection during the first 4 months of pregnancy must be offered investigation. Any asymptomatic woman who has been exposed to rubella during this period also requires investigation; because of the possibility of laboratory error and of reinfection, most virologists now recommend that even women previously reported to be immune should be investigated. A blood sample should be tested for the presence of IgG and IgM antibodies, with a repeat sample being tested after 2 weeks if the results are equivocal. A rise in IgG or the presence of IgM antibody is diagnostic of recent infection.

TREATMENT

Unless bacterial complications occur, treatment is symptomatic.

The use of immunoglobulin in women who have been exposed to rubella in early pregnancy is of no proven value. Although large doses of immunoglobulin may attenuate the course of the infection, there is no evidence that this reduces the likelihood of transmission to the fetus. Treatment should therefore be restricted to seronegative women in recent contact with rubella who definitely intend to continue with the pregnancy. As viraemia is present up to a week before the onset of symptoms, immunoglobulin should be given as soon as possible after contact, once susceptibility is confirmed.

PREVENTION

Active specific prevention include in vaccination with vaccine RA 27/3. Vaccination is conducted in childhood. Vaccine is administered as a single subcutaneous injection. Antibody develops in about 98% of those vaccinated. Although virus may persist, especially in the nasopharynx, and shedding occurs from 18–25 days after vaccination, communicability does not appear to be a problem.

The duration of persistence of rubella antibody following vaccination with RA

27/3 is uncertain but is probably lifelong. Preventive measures are of the greatest importance for the protection of the fetus. It is especially important that girls have immunity to rubella before reaching child-bearing age, either by contracting the natural disease or by active immunization. The immune status can be evaluated by appropriate serologic tests.

EPIDEMIC PAROTIDITIS (MUMPS)

DEFINITION *epidemic parotiditis is an acute, generalized communicable viral disease whose most distinctive features are lesions of glands (salivary glands, pancreas, gonads and other) and nervous system.*

ETIOLOGY

Epidemic parotiditis virus listed in the family Paramyxoviridae, genus Paramyxovirus.

Virus is pleomorphic and has a diameter ranging from 100 to 300 nm. It contains ribonucleic acid (RNA) and five proteins. The RNA is surrounded by an envelope with glycoprotein projections. There are two envelope glycoproteins a haemagglutinin-neuraminidase (HN) and a hemolysis cell fusion antigen (F) as well as a matrix envelope protein (M). There are two internal components: a nucleocapsid protein (NP) and an RNA polymerase protein. Only one serotype is known. The virus is of low stability and is rapidly inactivated by high temperatures, ultra-violet rays, weak formalin solutions, lyzol, and alcohol. It is grown on developing chick embryos.

Virus has been isolated from saliva, cerebrospinal fluid, blood, urine, brain, and other infected tissues.

EPIDEMIOLOGY

Ill person is a source of infection. The virus is discharged only during the last days of incubation and the first days after onset of the illness. Patients cease to be contagious by the ninth day. The virus is spread by direct contact, airborne droplets, fomites contaminated by saliva, and possibly by urine.

Susceptibility to mumps is very high, practically ubiquitous. It is the greatest between the ages of one and twenty.

The disease is not uncommon in adults, and there are many reports of epidemic outbreaks in military units.

Now disease often occurs in young adults, producing epidemics in colleges or in the work place. Epidemics appear to be primarily related to lack of immunization rather than to waning of immunity. Epidemics occur at all seasons but are slightly more frequent in late winter and spring.

Persistent immunity is formed after illness.

PATHOGENESIS

Little is known of the pathogenesis and pathological anatomy of mumps. It is a general infection in which the virus develops not only in the salivary glands, but also in the blood and other organs. The possibility of primary infection in the pia mater of brain or testes has been established. Apparently the virus invades the parotid glands not through Stensen's duct, but by way of the blood circulation. The portal of entry is apparently the mucous membrane of the mouth, nose, and pharynx from which the virus penetrates into the blood and is carried secondarily to the salivary glands and other organs where it predominantly affects the interstitial tissue. The affected glands contain perivascular and interstitial mononuclear cell infiltrates with prominent edema. Necrosis of acinar and epithelial duct cells is evident in the salivary glands and in the germinal epithelium of the seminiferous tubules.

The antibodies appear during the first days of the disease. The titer attains its maximum in 2-4 weeks.

CLINICAL MANIFESTATIONS

The incubation period is 2 – 4 weeks (more often 15–19 days). The mumps may begin acute.

Clinical classification of mumps:

A. Clinical form (including abortive and atypical): salivary glands affection, mumps orchitis, mumps pancreatitis, mumps thyroiditis, mumps encephalitis, mumps meningitis (meningoencephalitis), mixed affection.

B. Subclinical (inapparent).

Sometimes there are prodrome period during 1 – 2 days. The prodrome manifestations of mumps consist of fever, chill, headache, malaise, myalgia, and anorexia. The height of the disease is usually characterized by elevation of temperature (up to 38° or 40° C) and swelling of the parotid gland. It is generally bilateral, although the onset on the two sides may not be synchronous and at times only one side is affected. The swelling obliterates the fossa retromaxil laris and may spread downwards anteriorly and posteriorly to the neck. The centre of the swelling is elastic-solid and painful on palpation. The skin over the inflamed gland is tense and lustrous, but remains usually of normal color. The patient frequently reports an earache and finds it difficult to eat, swallow, or talk. Palpation in Filatov points (in front of ear lobe, behind of ear lobe, in the areas of mastoid bone and angle of the mandible) is very painful. On mucous membrane of cheek the orifice of Stensen's duct is commonly red and swollen (Myrsus symptom). The swelling of the affected gland increases for the first three to five days. In one or two days the parotid gland on the opposite side may become involved; and in about half the cases the submaxillary, and sometimes the sublingual, glands are affected. In submaxillitis palpation directly inward from the margin of the lower jaw displays a swollen, solid, and painful

submaxillary gland, oval or round in shape. Submaxillitis is sometimes accompanied with extensive edema of the cervical cellular tissue; cases of isolated inflammation of the submaxillary gland and of its primary affection with subsequent supervention of parotitis have been observed.

The swelling of the affected gland usually subsides by the eighth to tenth day. Sometimes it may be prolonged to several weeks. When the inflammation calms down, the temperature falls, the pain declines, and the patient's general condition improves.

Mumps is sometimes attended with bradycardia and enlargement of the spleen.

Affection of the nervous system and of various glandular organs is a typical feature of mumps.

Orchitis – is the most prevalent manifestations of mumps among young men and boys at puberty, developing in about 30% of cases. More often develops on the sixth to eighth day of the disease. Addition of orchitis is accompanied by high fever, chill, malaise, nausea, vomiting, pain in inguinal and lumbar regions, adynamia, and sometimes with delirium, excitation, and symptoms of circulatory failure. The testis enlarges, becomes tender and painful; the scrotum is enlarged and its skin is often tense and hyperemic. A bilateral process is rare. The symptoms begin to subside in four or six days. Atrophy of testicle develops in part of patients. Bilateral mumps orchitis may lead to sterility. Primary orchitis without previous affection of the salivary glands has been reported.

Oophoritis, mastitis and bartholinitis are rare manifestations of mumps in older girls and young women. Oophoritis may cause lower abdominal pain but does not lead to sterility.

Mumps pancreatitis more often develops in adults on the fourth to sixth day of the disease. It usually manifests by strong girdle epigastric pains and pains in the region of the left hypochondrium. Positive Voskresenskiy symptom and symptoms of peritoneum irritation may be noted. Pancreatitis may be accompanied by fever, anorexia, nausea, vomiting and diarrhea. In most cases the course is favorable.

Mumps thyroiditis, parathyroiditis, dacryocystitis have been described.

Meningitis and encephalitis develop often. It usually appears at the height of the disease, and is characterized by symptoms of meningeal irritation (headache, frequent vomiting, rigidity of the occipital muscles, Kernig's and Brudzinsky's signs). Clinical manifestations may be moderate (rise of temperature, weakness, drowse, headache, meningeal signs) and severe (hyperthermia, loss of consciousness, convulsions, paresises, paralysises, coma and others).

Duration of course is depending on process heaviness. Sometimes period of reconstruction lasts for weeks.

Complications to be related with autoimmune, toxic, mechanical and others factors. Meningoencephalomyelitis, heart defeats (myocarditis, breach of heart

rhythm), arthralgia, arthritises, and atrophy of the optic nerve, deafness, pancreatic (insular) diabetes, nephritis, and priapism may be developed.

Mumps embryopathy. There are no firm confirmations that maternal infection is damaging to the fetus; a possible relationship to endocardial fibroelastosis has not been established. Mumps in early pregnancy does increase the chance of abortion.

DIAGNOSIS

The routine laboratory tests are nonspecific; there is usually leukopenia with relative lymphocytosis, but complications often result in polymorphonuclear leukocytosis of moderate degree. The ESR usually normal or deviates a little from the normal.

At the height of the disease insignificant quantities of protein and glucose may be noted in urine.

The transparent or opalescent cerebrospinal fluid flowing in lumbar puncture is at normal or elevated pressure. Its protein content is normal or slightly increased; the cytosis is increased at the expense of lymphocytes (500-2000 cells per mm3). The sugar and chloride content is normal. The mumps virus is often discovered in the cerebrospinal fluid.

In patients with pancreatitis the diastase of the blood and urine increases highly.

Isolation of virus is the most reliable diagnostics method. Virus is found out from the saliva, urine, faeces, spinal fluid, milk or blood. Also specific diagnostic tests include isolation mumps-specific immunoglobulin M antibodies (immune-enzyme analysis), and RNA of mumps virus (PCR).

Differential diagnostics of epidemic parotitis is made with cytomegalovirus and purulent parotitises, cervical lymphadenitis, ductal obstruction due to stones or strictures, lymphosarcoma or other rare tumors of the parotid.

Mumps orchitis should be differentiate with gonococcal and syphilitic orchitises.

Primary meningitis of mumps etiology can be confused with tuberculous meningitis, acute serous meningitis caused, for instance, by an enterovira.

Prognosis is favorable. Mortality of mumps is remarkably low. Affection of the internal ear may lead to permanent deafness. Atrophy of the testes with subsequent aspermia can follow bilateral orchitis.

TREATMENT

Treatment of parotitis is entirely symptomatic. Diet is restricted to fluids or semi-fluids to spare the affected glands. Heat is applied to the glands by means of cotton or wool bandages, Sollux lamp, etc. Ultra-high frequency therapy and ultra-violet irradiation are also recommended.

The mouth should be rinsed with weak disinfecting solutions. In severe mumps some investigators recommend gamma-globulin (3-6 ml). Strict confinement to bed is

called for in orchitis; the testis should be supported and cold applied. Corticosteroid preparations produce considerable alleviation of pain and subjective improvement. To relieve the severe headache and other meningeal symptoms in concomitant meningitis lumbar puncture, this is also recommended when complications develop in the inner ear. Dehydration therapy is carried out.

Mumps arthritis may respond to a 2-wk course of corticosteroids or a nonsteroidal anti-inflammatory agent. Salicylates do not appear to be effective.

PREVENTION

Hyperimmune mumps gamma globulin is not effective in preventing mumps or decreasing complications.

Vaccinated children usually do not experience fever or other detectable clinical reactions, do not excrete virus, and are not contagious to susceptible contacts. Rarely, parotitis can develop 7–10 days after vaccination. The vaccine induces antibody in about 96% of seronegative recipients and has a protective efficacy of about 97% against natural mumps infection. The protection appears to be long lasting. In one outbreak of mumps, several children who had been immunized with mumps vaccine in the past experienced an illness characterized by fever, malaise, nausea, and a red papular rash involving the trunk and extremities but sparing the palms and soles. The rash lasted about 24 hr. No virus was isolated from these children, but increases in the titer of mumps antibody were demonstrated.

Appendix

Diphtheria Antitoxin (Equine)

Indications and clinical uses: For the treatment of suspected or confirmed cases of diphtheria.

Precautions: Before administering any serum or antitoxin to a patient, physicians are well advised to ascertain whether the patient has a history of asthma, or hay fever, and particularly, whether the patient suffers distress when in proximity to horses. Patients with such a history may develop serious reactions of an anaphylactic character upon the administration of serum of equine origin either s.c., i.m. or i.v. It should be borne in mind, also, that a patient who has been given a previous injection of serum of equine origin may develop a marked reaction when given a second injection, especially if the previous injection was i.v.

At the time of administering any serum or antitoxin to a patient, it is desirable to have 1 mL of epinephrine HCl solution (1:1000) immediately available.

Tests for sensitivity to serum or antitoxin: A test for sensitivity to serum or antitoxin should be carried out each time a serum or antitoxin is administered, unless it is being given daily. Sensitivity to any particular serum or antitoxin may be gauged by one of the following methods:

Skin or eye tests for sensitivity should be done before any injection, regardless of whether or not the patient has had the serum previously. The skin test dose is 0.1 mL of a 1:100 saline dilution of the serum to be given intracutaneously. In persons with a history of allergy, the dose is reduced to 0.05 mL of a 1:1000 dilution, intracutaneously. The reaction is read in 5 to 30 minutes and is positive if a wheal with a hyperemic areola appears. (In a marked reaction the wheal is likely to have irregular projections.) The extent of the wheal and of its projections and the dimensions of the hyperemic area provide a rough index of the degree of the patient's sensitivity, and of the resultant likelihood of his reacting unfavorably to the injection of the particular serum or antitoxin concerned. A negative skin test does not entirely preclude the possibility of the occurrence of serum reactions.

Except in small children, an eye test often is simpler and is less likely to show nonspecific reactions. A drop of a 1:10 dilution of serum in physiologic saline is instilled in one eye, controlled by a drop of physiologic saline solution in the other eye; a positive reaction consists of lacrimation and conjunctivitis appearing in 10 to 30 minutes. Eye tests have not been known to be fatal, but skin tests have resulted in fatalities. Therefore, a serum should never be injected, nor a skin test performed unless a syringe containing 1 mL of epinephrine HCl solution (1:1000) is within immediate reach.

Serum reactions: 1. Anaphylactic Reaction: In the event of a reaction of an anaphylactic character, 0.5 mL of epinephrine HCl solution (1:1000) should be administered by the s.c. or i.m. route.

2. Thermal reaction: When this reaction occurs, it usually develops from 20 minutes to 1 hour after the injection of serum or antitoxin. It is characterized by a chilly sensation, slight dyspnea and a rapid rise in temperature.

3. Serum sickness: The symptoms of serum sickness are fever, skin rashes, edema of the skin, glandular enlargement and pains in the joints. These symptoms may appear individually, or in combination, within 14 days after the administration of a serum or antitoxin. Urticarial reaction is usually relieved by a s.c. or i.m. injection of 0.5 mL of epinephrine HCl solution (1:1000). In severe cases of serum sickness ACTH or cortisone may be required.

It has been recommended that 0.3 mL of epinephrine HCl solution (1:1000) be administered not only to every patient who gives a positive reaction to a sensitivity test, or has received serum or antitoxin before, or has a history of allergy, but to every patient before receiving serum irrespective of these factors.

Dosage and administration: Since diphtheria antitoxin injected i.m. is absorbed much more rapidly than when injected s.c., i.m. injections are greatly superior to s.c. injections in the treatment of diphtheria. In the treatment of diphtheria, results are best when very large doses of antitoxin are administered. In an uncomplicated pharyngeal case, the dose should not be less than 20000 IU for a child or 40000 IU for an adult. In laryngeal or severe cases or in cases left untreated for several days much larger doses amounting to 100000 or even 150000 units are recommended. Such circumstances call for a combination of i.m. and i.v. injections, and the use of from 10000 to 20000 units i.v. is recommended. Diphtheria antitoxin may be quite satisfactorily used i.v., at a 1:10 dilution. It should be at ambient temperature before being injected.

Administration of antitoxin to sensitive persons: Whenever there is a history of allergy, sensitivity to horse serum or manifestations of sensitivity when in proximity to horses, or if the reaction to the skin or eye test is positive, great care must be exercised in the administration of serum (or antitoxin).

No one method can be advised for the administration of serum or antitoxin for sensitive persons as each presents an individual problem. Desensitization of the patient should be carried out by serial injections of diluted antitoxin as indicated below at intervals of 20 minutes, provided no reaction occurs.

Schedule for desensitization: (a) 0.05 mL of 1:20 dilution s.c., (b) 0.1 mL of 1:10 dilution s.c., (c) 0.3 mL of 1:10 dilution s.c., (d) 0.1 mL undiluted serum s.c., (e) 0.2 mL undiluted serum s.c., (f) 0.5 mL undiluted serum s.c., (g) inject remaining therapeutic doses i.m.

After the patient can properly withstand these doses of serum or antitoxin, it is usually safe to inject larger doses (i.m.) at 20-minute intervals.

If a reaction occurs after a desensitizing dose, injections should be stopped for 1 hour, recommencing the schedule at 20-minute intervals by repeating the last dose

which failed to cause a reaction.

If deemed imperative on clinical grounds, i.v. administration of a serum or antitoxin may be commenced after the purpose of the desensitization has been satisfactorily served. The first i.v. dose should be small, however, i.e., 0.1 mL diluted with 10 mL of sterile physiological saline, and it should be injected very slowly, 1 mL/minute. Increasingly larger doses may then be similarly given at half-hourly intervals.

A separate sterilized syringe and needle should be used for each individual patient to prevent transmission of homologous serum hepatitis and other infectious agents from one person to another.

Note: Following the administration of serum (or antitoxin), and particularly in those cases showing a positive skin or eye test, the patient should be kept under close observation for 1 to 2 hours and under reasonably close surveillance for a period of 24 hours.

The site of injection should be prepared with a suitable antiseptic.

If sterile disposable syringes and needles are not used, syringes and needles should be sterilized in an autoclave 121°C for 30 minutes. If this method of sterilization is not available syringes and needles should be boiled for at least 20 minutes. Care should be taken to maintain sterility until used.

Withdrawing the preparation from a rubber-stopped vial. Do not remove the rubber stopper from the vial.

Apply a sterile pledget of cotton moistened with a suitable antiseptic to the surface of the rubber stopper and allow it to act for at least 5 minutes. Draw into the sterile syringe a volume of air equal to the amount of the preparation to be withdrawn from the vial. Pierce the centre of the rubber stopper with the sterile needle of the syringe; invert the vial; slowly inject into it the air contained in the syringe; and, keeping the point of the needle immersed, withdraw into the syringe the required amount of the preparation. Then hold the syringe-plunger steady and withdraw the needle from the vial.

The person giving the immunization should record the dose, route of administration, date of immunization and the antitoxin lot number on the patient's immunization card or medical record.

Availability and storage: Each vial contains: 20000 IU of a refined and concentrated preparation of globulins obtained from horse serum modified by enzymatic digestion. Also contains phenol 0.22% as a preservative. Note: The volume of antitoxin in a vial will vary from lot to lot. This is because the potency of the bulk antitoxin varies from lot to lot and it is therefore necessary to adjust the filling volume of each lot so that each vial contains 20000 IU. As a result, vials from one lot may appear half full while vials from a different lot may appear three-quarters full. Store in a refrigerator between 2 and 8°C.

ABBREVIATION

ADP – adenosine diphosphate;
AIDS – acquired immunodeficiency syndrome;
AMP – adenosine monophosphate;
ARI – acute respiratory infection;
ARVD – acute respiratory viral diseases;
ASO – anti-streptolysin O;
BAL – bronchoalveolar lavage;
BC – blood count;
BCYE – buffered charcoal yeast-extract agar;
CAP – community acquired pneumonia;
CF – complement-fixing;
CFT – compliment fixation test
CMV – cytomegalovirus;
CNS – central nervous system;
CPK – creatine phosphokinase;
CSF – cerebrospinal fluid;
DFA – direct fluorescent antibody staining;
DIC – disseminated intravascular coagulation;
DOC – drug of choice;
DTaP – acellular pertussis vaccine adsorbed;
DTP – pertussis vaccine adsorbed;
EBER – EBV-encoded RNA;
EBNA – EBV nuclear antigen;
EF-2 – elongation factor 2;
ELISA – enzyme-linked immunoassays;
FAMA – fluorescent antibody to membrane antigen;
FAT – fluorescent antibody test;
GBS – Guillain-Barre syndrome;
GI – gastrointestinal;
GMP – guanosine monophosphate;
H – haemagglutinin;
HHV – human herpesvirus
HIV – human immunodeficiency virus;
HSV – herpes virus;
IF – immunofluorescent;
IFA – immunofluorescent antibody assay;
IFAT – indirect fluorescent antibody test;
IFN – interferon;
Ig – immunoglobulin;
IHA – indirect hemagglutination;
IHAT – indirect hemagglutination test;
IM – infectious mononucleosis;
IM – intramuscular;
IU – international unit;
IV – intravenous;
KSHV – Kaposi's sarcoma-associated herpesvirus;
LA – latex agglutination;
LMP – latent membrane protein;
LT – heat-labile enterotoxin;
MHC – major-histocompatibility-complex;
MIF – microimmunofluorescence;
MMR – measles-mumps-rubella vaccine;
N – neuraminidaze;
NAD – nicotinamide adenine dinucleotide;
NP – nucleoprotein;
O – orally;
PCR – polymerase chain reaction;
PEG-INF – pegylated interferon;
PHA – passive hemagglutination;
RDSA – respiratory distress syndrome of adults;
RIA – radioimmunoassay;
RIA – radioimmunoassay;
RIAG – reaction of indirect agglutination;
RNA – ribonucleic acid;
RS – Respiratory-syncytial;
ST – heat-stable enterotoxin.
VZV – varicella zoster virus

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Кацапов Дмитрий Владимирович
Бодаренко Андрей Владимирович
Краснов Максим Игоревич
Градиль Григорий Иванович
Никитина Нонна Алексеевна
Копейченко Ярослава Игоревна

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