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MANUAL FOR EDUCATION OF ENGLISH-SPEAKING STUDENTS "EBV INFECTION IN CHILDREN AND DIFFERENTIAL DIAGNOSIS OF DISEASES WITH PHARYNGITIS AND TONSILLITIS"

Навчальний посібник для англомовних студентів медичного факультету **"**ВЕБ-інфекція у дітей та диференційний діагноз захворювань з синдромом фарінготонзиліту**"**

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FOREWORD

"The needs of children should not be made to wait."

John F. Kennedy, 1963

In modern medicine, the discipline paediatric infectious diseases are an important medical specialty. The successful prevention of childhood diseases like diphtheria has made a major contribution to the improvement of public health. Understanding the biology of causative agents and the pathogenesis is an essential step in achieving control and elimination of disease. Today paediatric infectious diseases research is closely interconnected with other disciplines.

This manual addresses vaccination, historical, epidemiological and sociocultural issues as well as clinical and molecular biological aspects of tonsillitis. New insights into the pathogenesis of paediatric infectious diseases are presented and an update on diagnostics, prevention and treatment of diphtheria, infectious mononucleosis, is provided. The role of emerging new pathogens and antibiotics therapy is also pointed out. Finally, the future perspectives of paediatric infectious diseases are highlighted. Therefore, this book aims for students and interns as well as at an interdisciplinary audience of clinicians like paediatricians, infectious disease specialist etc.

1. EPSTEIN-BARR VIRUS

Infectious mononucleosis is the best-known clinical syndrome caused by Epstein-Barr virus (EBV). It is characterized by systemic somatic complaints consisting primarily of fatigue, malaise, fever, sore throat, and generalized lymphadenopathy. Originally described as glandular fever, it derives its name from the mononuclear lymphocytosis with atypical-appearing lymphocytes that accompany the illness. Other less common infections may cause infectious mononucleosis–like illnesses.

1.1. ETIOLOGY

EBV, a member of the Herpesviridae, causes more than 90% of infectious mononucleosis cases. Approximately 5–10% of infectious mononucleosis–like illnesses are caused by primary infection with cytomegalovirus, Toxoplasma gondii, adenovirus, viral hepatitis, human immunodeficiency virus (HIV), and possibly rubella virus. In the majority of EBV-negative infectious mononucleosis like illnesses, the exact cause remains unknown. (Box 1.1.)

Box 1.1.

Causes of infectious mononucleosis–like illnesses

Epstein-Barr virus

Cytomegalovirus

Toxoplasma gondii

Adenovirus

Viral hepatitis

Human immunodeficiency virus (HIV) and other

Epstein-Barr virus (EBV), or human herpes virus 4, is a gamma-1 herpes virus. Like the other members of the Herpesviridae family, EBV has a double stranded DNA genome encased in an icosahedral protein nucleocapsid surrounded by a lipid envelope embedded with viral glycoproteins. Herpes viruses also have an

amorphous protein layer, the tegument, which lies between the capsid and envelope. The B95-8 laboratory strain of EBV, the first herpes virus genome sequenced, was found to have a 12-kilobase (kb) deletion, and the wild-type EBV genome is now known to be approximately 184Â€ kb in size and to encode almost 100 proteins.

1.2. EPIDEMIOLOGY

The epidemiology of infectious mononucleosis is related to the epidemiology and age of acquisition of EBV infection. EBV infects up to 95% of the world's population. It is transmitted in oral secretions by close contact such as kissing or exchange of saliva from child to child, such as occurs between children in out-of-home child care. Nonintimate contact, environmental sources, or fomites do not contribute to spread of EBV.

EBV is shed in oral secretions for 6 month or longer after acute infection and then intermittently for life. Healthy individuals with serologic evidence of past EBV infection excrete virus 10–20% of the time. Immunosuppression may permit reactivation of latent EBV; approximately 60% of seropositive, immunosuppressed patients shed the virus. EBV is also found in the genital tract of women and may possibly be spread by sexual contact.

Infection with EBV in developing countries and among socioeconomically disadvantaged populations of developed countries usually occurs during infancy and early childhood. In central Africa, almost all children are infected by 3 year of age. Primary infection with EBV during childhood is usually inapparent or indistinguishable from other childhood infections; the clinical syndrome of infectious mononucleosis is practically unknown in undeveloped regions of the world. Among more affluent populations in industrialized countries, infection during childhood is still most common, but approximately one third of cases occur during adolescence and young adulthood. Primary EBV infection in adolescents and adults is manifest in 50% or more of cases by the classic triad of fatigue, pharyngitis, and generalized lymphadenopathy, which constitute the major clinical manifestations of infectious mononucleosis. This syndrome may be seen at all ages

but is rarely apparent in children younger than 4 year, when most EBV infections are asymptomatic, or in adults older than 40 year, when most individuals have already been infected by EBV. The true incidence of the syndrome of infectious mononucleosis is unknown but is estimated to occur in 20–70 of 100,000 persons per year; in young adults the incidence rises to about 1 in 1,000 persons per year. The prevalence of serologic evidence of past EBV infection increases with age; almost all adults in the United States are seropositive.

1.3. PATHOGENESIS

After acquisition in the oral cavity, EBV initially infects oral epithelial cells; this may contribute to the symptoms of pharyngitis. After intracellular viral replication and cell lysis with release of new virions, virus spreads to contiguous structures such as the salivary glands with eventual viremia and infection of B lymphocytes in the peripheral blood and the entire lymphoreticular system including the liver and spleen. The atypical lymphocytes that are characteristic of infectious mononucleosis are CD8+ T lymphocytes, which exhibit both suppressor and cytotoxic functions that develop in response to the infected B lymphocytes. This relative as well as absolute increase in CD8+ lymphocytes results in a transient reversal of the normal 2:1 CD4+/CD8+ (helper-suppressor) T-lymphocyte ratio. Many of the clinical manifestations of infectious mononucleosis may result, at least in part, from the host immune response, which is effective in reducing the number of EBV-infected B lymphocytes to less than one per 106 of circulating B lymphocytes.

Epithelial cells of the uterine cervix may become infected by sexual transmission of the virus, although neither local symptoms nor infectious mononucleosis have been described following sexual transmission.

EBV, like the other herpesviruses, establishes lifelong latent infection after the primary illness. The latent virus is carried in oropharyngeal epithelial cells and systemic B lymphocytes as multiple episomes in the nucleus. The viral episomes replicate with cell division and are distributed to both daughter cells. Viral integration into the cell genome is not typical. Only a few viral proteins, including

Box 1.2

Pathogenesis of primary EBV infection

Acquisition of EBV in the oral cavity

EBV initially infects oral epithelial cells

Virus spreads to contiguous structures such as the salivary glands

Viremia and infection of B lymphocytes in the peripheral blood and the entire lymphoreticular system including the liver and spleen

Atypical lymphocytes that are characteristic of infectious mononucleosis are CD8+ T lymphocytes, which exhibit both suppressor and cytotoxic functions that develop in response to the infected B lymphocytes

Absolute increase in CD8+ lymphocytes results in a transient reversal of the normal 2:1 CD4+/CD8+ (helper-suppressor) T-lymphocyte ratio

Pathogenesis of latent EBV infection after the primary illness

The latent virus is carried in oropharyngeal epithelial cells and systemic B lymphocytes as multiple episomes in the nucleus

The viral episomes replicate with cell division and are distributed to both daughter cells

Progression to viral replication begins with production of EBV early antigens (EA), proceeds to viral DNA replication, followed by production of viral capsid antigen (VCA), and culminates in cell death and release of mature virions.

the EBV-determined nuclear antigens (EBNA), are produced during latency. These proteins are important in maintaining the viral episome during the latent state. Progression to viral replication begins with production of EBV early antigens (EA), proceeds to viral DNA replication, followed by production of viral capsid antigen (VCA), and culminates in cell death and release of mature virions. Reactivation with viral replication occurs at a low rate in populations of latently infected cells and is responsible for intermittent viral shedding in oropharyngeal secretions of infected individuals. Reactivation is apparently asymptomatic and not recognized to be accompanied by distinctive clinical symptoms. (Box 1.2.)

Oncogenesis

EBV was the first human virus to be associated with malignancy and, therefore, was the first virus to be identified as a human tumor virus. EBV infection may result in a spectrum of proliferative disorders ranging from self-limited, usually benign disease such as infectious mononucleosis to aggressive, nonmalignant proliferations such as the virus-associated hemophagocytic syndrome to lymphoid and epithelial cell malignancies. Benign EBV-associated proliferations include oral, hairy leukoplakia, primarily in adults with the acquired immunodeficiency syndrome (AIDS), and lymphoid interstitial pneumonitis, primarily in children with AIDS. Malignant EBV-associated proliferations include nasopharyngeal carcinoma, Burkitt lymphoma, Hodgkin disease, and lymphoproliferative disorders and leiomyosarcoma in immunodeficient states including AIDS. (Box 1.3.)

Nasopharyngeal carcinoma occurs worldwide but is 10 times more common in persons in southern China, where it is the most common malignant tumor among adult men. It is also common among whites in North Africa and Inuits in North America. All malignant cells of undifferentiated nasopharyngeal carcinoma contain a high copy number of EBV episomes. Undifferentiated and partially differentiated, nonkeratinizing nasopharyngeal carcinomas have diagnostic and prognostic antibodies to EBV antigens. High levels of immunoglobulin (Ig) A antibody to EA and VCA may be detected in asymptomatic individuals and can be

used to follow response to tumor therapy. Cells of well-differentiated, keratinizing nasopharyngeal carcinoma contain a low or zero copy number of EBV genomes and have EBV serologic patterns similar to those of the general population.

Box 1.3.

Malignant EBV-associated proliferations

Nasopharyngeal carcinoma

Burkitt lymphoma

Hodgkin disease

Lymphoproliferative disorders

Eiomyosarcoma in immunodeficient states including AIDS

Endemic (African) Burkitt lymphoma, often found in the jaw, is the most common childhood cancer in equatorial East Africa and New Guinea. The median age of onset is 5 yr. These regions are holoendemic for Plasmodium falciparum malaria and have a high rate of EBV infection early in life. The constant malarial exposure acts as a B-lymphocyte mitogen that contributes to the polyclonal B-lymphocyte proliferation with EBV infection. It also impairs the T-lymphocyte control of EBV-infected B lymphocytes. Approximately 98% of cases of endemic Burkitt lymphoma contain the EBV genome compared with only 20% of nonendemic (sporadic or American) Burkitt lymphoma cases. Individuals with Burkitt lymphoma have unusually and characteristically high levels of antibody to VCA and EA that correlate with the risk of developing tumor).

All cases of Burkitt lymphoma, including those that are EBV negative, are monoclonal and demonstrate chromosomal translocation of the c-myc proto-oncogene to the constant region of the immunoglobulin heavy-chain locus, t(8;14), to the kappa constant light-chain locus, t(2;8), or to the lambda constant light-chain locus, t(8;22). This results in the deregulation and constitutive transcription of the

c-myc gene with overproduction of a normal c-myc product that autosuppresses c-myc production on the untranslocated chromosome.

The incidence of Hodgkin disease peaks in childhood in developing countries and in young adulthood in developed countries. Levels of EBV antibodies are consistently elevated preceding development of Hodgkin disease; only a small minority of patients are seronegative for EBV. Infection with EBV appears to increase the risk of Hodgkin disease by a factor of two to four. EBV is associated with more than one half of cases of mixed-cellularity Hodgkin disease and approximately one quarter of cases of the nodular sclerosing subtype and is rarely associated with lymphocyte-predominant Hodgkin disease. Immunohistochemical studies have localized EBV to the Reed-Sternberg cells and their variants, the pathognomonic malignant cells of Hodgkin disease.

Failure to control EBV infection may result from host immunologic deficits. The prototype is the X-linked lymphoproliferative syndrome (Duncan syndrome), an X chromosome–linked recessive disorder of the immune system associated with severe, persistent, and sometimes fatal EBV infection. Approximately two thirds of these male patients die of disseminated and fulminating lymphoproliferation involving multiple organs at the time of primary EBV infection. Surviving patients acquire hypogammaglobulinemia, B-cell lymphoma, or both. Most patients die by 10 year.

A number of other congenital and acquired immunodeficiency syndromes are associated with an increased incidence of EBV-associated B-lymphocyte lymphoma, particularly central nervous system lymphoma. The incidence of lymphoproliferative syndromes parallels the degree of immunosuppression. A decline in T-cell function evidently permits EBV to escape from immune surveillance. Congenital immunodeficiencies predisposing to EBV-associated lymphoproliferations include the X-linked lymphoproliferative syndrome, common-variable immunodeficiency, ataxia-telangiectasia, Wiskott-Aldrich syndrome, and Higashi syndrome. Individuals with acquired immunodeficiencies resulting from anticancer chemotherapy, immunosuppression after solid organ or

bone marrow transplantation, or HIV infection have a significantly increased risk of EBV-associated lymphoproliferations. The lymphomas may be focal or diffuse, and they are usually histologically polyclonal but may become monoclonal. Their growth is not reversed on cessation of immunosuppression.

EBV has been linked with a multitude of other tumors; the strongest association of EBV is to primary central nervous system lymphoma and carcinoma of the salivary glands. Other tumors include T-lymphocyte lymphoma, lethal midline granuloma (a T-cell lymphoma), angioimmunoblastic lymphadenopathy–like lymphoma, thymomas and thymic carcinomas derived from thymic epithelial cells, supraglottic laryngeal carcinomas, lymphoepithelial tumors of the respiratory tract and gastrointestinal tract, leiomyosarcoma, and gastric adenocarcinoma. The precise contribution of EBV to these various malignancies is not well defined.

1.4. CLINICAL MANIFESTATIONS (PRIMARY INFECTION)

Spectrum of Illness

Epstein-Barr virus induces a broad spectrum of illness in humans. Classic or typical infectious mononucleosis is an acute illness characterized clinically by sore throat, fever, and lymphadenopathy; serologically by the transient appearance of heterophile antibodies; andhematologically by a mononuclear leukocytosis that consists, in part, of atypical lymphocytes. An individual case may have most but not necessarily all the aforementioned characteristics. Specificserologic tests for EBV infection indicate that infection results in a spectrum of clinical manifestations. Attempts to exclude cases that fail to meet the classic criteria for infectious mononucleosis result in artificial and often misleading distinctions.

The age of the patient has a profound influence on the clinical expression of EBV infection. In children, primary EBV infection is often asymptomatic. Young children may be more likely to exhibit rashes, neutropenia, or pneumonia than individuals with primary EBV infection at an older age. Clinically apparent infections in very young children are heterophile negative in about one half of the cases. The proportions of clinically apparent disease and of heterophile-positive

cases increase with age. By 4 years of age, 80% of children with primary EBV infection are heterophile antibody positive. During the course of the illness, 90% of the adolescents with clinically apparent infectious mononucleosis should be heterophile positive.

Box 1.4.

Manifestations of Epstein-Barr Virus–Induced Infectious Mononucleosis

Clinical

Fever

Sore throat

Lymphadenopathy

Hematologic

More than 50% mononuclear cells

More than 10% atypical lymphocytes

Serologic

Transient appearance of heterophile antibodies

Permanent emergence of antibodies to EBV

In patients of college age, the ratio of clinically apparent to inapparent EBV infection ranges from 1:3 to 3:1. In military recruits, this ratio has been as low as 1:10. Because of previously existing immunity, the disease is less common in older patients. When it does occur, however, clinical and serologic manifestations are similar to those found in adolescents. In general, EBV infection is inapparent or is a self-limited illness that lasts 2 or 3 weeks. In rare cases, the disease can be devastating and can be accompanied by severe prostration, major complications, and even death, as discussed subsequently.

Symptoms

Most cases of infectious mononucleosis consist of the clinical triad o sore throat, fever, and lymphadenopathy. Epidemiologic studies suggest that the incubation period of acute infectious mononucleosis is 30 to 50 days, but this has not yet been confirmed with molecular epidemiologic techniques. Thus, the incubation period of the illness is somewhat speculative. The onset may be abrupt, but often several days of prodromal symptoms can be elicited, including, sweats, feverish sensations, anorexia, and malaise. Loss of taste for cigarettes is common early in the illness but is not specific for infectious mononucleosis. Retroorbital headaches, myalgias, and feelings of abdominal fullness are other common prodromal symptoms (Table 1.1). The most frequent symptom is sore throat, which may be the most severe the patient has experienced. Other patients seek medical attention because of prolonged fever or malaise and less frequently because of incidentally encountered lymphadenopathy. Rarely, the first manifestation of illness is one of the complications of infectious mononucleosis described subsequently.

Table 1.1.Symptoms of Infectious Mononucleosis

Symptom	***Percentage***
Sore throat	82
Malaise	57
Headache	52
Headache	21
Myalgias	20
Chills	16
Nausea	12
Abdominal discomfort	9
Cough	5
Vomiting	5
Arthralgias	2

Signs

The signs of infectious mononucleosis are summarized in Table 1.2. Fever is present in more than 90% of patients with infectious mononucleosis .The fever usually peaks in the afternoon with temperatures of 38°C to 39°C, although a temperature as high as 40°C is not uncommon. In most cases, fever resolves over a 10-day to 14-day period. A rash, which may be macular, petechial, scarlatiniform, urticarial, or erythema multiforme–like, is present in about 5% of patients. The administration of ampicillin or amoxicillin produces a pruritic, maculopapular eruption in 90% to 100% of the patients , and this rash may appear after cessation of treatment with the drug. The ampicillin-related rash does not necessarily predict future intoler manifestaance to ampicillin or amoxicillin. Periorbital edema has been reported in up to one third of cases in some series, but it has been observed less frequently in others. Tonsillar enlargement is usually present, occasionally with tonsils meeting at the midline. The pharynx is erythematous with an exudate in about one third of cases. Palatal petechiae may be seen in 25% to 60% of cases but are not diagnostic of infectious mononucleosis. The petechiae are usually multiple, are 1 to 2 mm in diameter, occur in crops that last 3 to 4 days, and are usually seen at the junction of the hard and soft palate. Cervical adenopathy, usually symmetrical, is present in 80% to 90% of patients. Posterior adenopathy is most common, but submandibular and anterior adenopathies are quite frequent as well, and axillary and inguinal adenopathies also occur. Individual nodes are freely movable, are not spontaneously painful, and are only mildly tender to palpation. The results of examination of the lungs and heart are usually normal. Abdominal examination may detect hepatomegaly in 10% to 15% of cases, although mild tenderness to fist percussion over the liver is present somewhat more frequently. Jaundice is present in approximately 5% of cases. Splenomegaly is present in about one half of cases if sought carefully over the course of the illness. The splenomegaly is usually maximal at the beginning of the second week of illness and regresses over the next 7 to 10 days. The results of neurologic examination are

generally normal, although occasional complications may occur (see subsequent discussion).

Table 1.2. Signs of Infectious Mononucleosis

Sign	Percentage
Lymphadenopathy	94
Pharyngitis	84
Fever	76
Splenomegaly	52
Hepatomegaly	12
Palatal enanthem	11
Jaundice	10
Rash	9

1.5. COMPLICATIONS

Most patients with infectious mononucleosis recover uneventfully. Complications that occasionally occur have been extensively reported in the literature. Even these complications have generally resolved fully, although rare fatalities have been reported. (BOX 1.5.)

Hematologic

Autoimmune hemolytic anemia occurs in 0.5% to 3% of the patients with infectious mononucleosis. Cold agglutinins, almost always of the IgM class, are present in 70% to 80% of cases. Anti-specificity has been reported in 20% to 70% of cases. Most but not all cases of autoimmune hemolytic anemia in infectious mononucleosis are mediated by antibodies of this specificity. The hemolysis usually becomes clinically apparent during the second or third week of illness and subsides over a 1-month to 2-month period. Corticosteroids may hasten recovery in some cases. Hemophagocytic syndrome, a rare complication of EBV infection, is discussed subsequently in a separate section. Mild thrombocytopenia is common in

infectious mononucleosis. Platelet counts less than 140,000/mm3 were noted in 50% of patients with uncomplicated infectious mononucleosis in one series.

BOX 1.5. COMPLICATIONS

Hematologic

Autoimmune hemolytic anemia

Hemophagocytic syndrome

Thrombocytopenia

Neutropenia

Splenic Rupture

Neurologic

Encephalitis

Meningitis

Guillain-Barré syndrome

Optic neuritis

Retrobulbar neuritis

Cranial nerve palsies

Brachial plexus neuropathy

Seizure

Subacute sclerosing panencephalitis

Transverse myelitis

Psychosis

Demyelination

Hemiplegia

Hepatic

Renal

Microscopic hematuria and proteinuria

Cardiac

Myocarditis

Profound thrombocytopenia with bleeding occurs rarely, but plateletbcounts less than 1000/mm3 and deaths from intracerebral bleeding have been reported. The mechanism for the thrombocytopenia is not known. The presence of normal or increased numbers of megakaryocytes in the marrow coupled with reports of antiplatelet antibodies suggests that peripheral destruction of platelets may occur, possibly on an autoimmune basis. Corticosteroids have been reported to be beneficial for the thrombocytopenia in some but not all cases. For refractory cases, splenectomy may be indicated. Neutropenia is seen rather frequently in uncomplicated infectious mononucleosis. The neutropenia is usually mild and self-limiting, although deaths associated with bacterial sepsis or pneumonia, or both, have been reported. Anaerobic sepsis without associated granulocytopenia, presumably of pharyngeal origin, has also been reported.

Splenic Rupture

Splenic rupture is a rare but dramatic complication of infectious mononucleosis. Lymphocytic infiltration of the capsule, trabeculae, and vascular walls coupled with rapid splenic enlargement predisposes the organ to rupture. The incidence of rupture is highest in the second or third week of illness but may be the first sign of infectious mononucleosis. Abdominal pain is uncommon in infectious mononucleosis, and splenic rupture must be strongly considered whenever abdominal pain occurs. The onset of this pain may be insidious or abrupt. Pathologic examination of some ruptured spleens has revealed subcapsular hematomas that suggest that rupture may be preceded by intermittent subcapsular bleeding. The pain, usually in the left upper quadrant, may radiate to the left scapular area. Left upper quadrant tenderness to palpation, with or without rebound tenderness, is usually present along with peritoneal signs or shifting dullness. In rare cases, splenic rupture is unaccompanied by pain and is manifested as shock. Laboratory findings include a falling hematocrit and, in some cases, an elevated left hemidiaphragm. The abdominal catastrophe may reverse the usual differential count of infectious mononucleosis and evoke a neutrophilia. Confirmatory findings should not be awaited if splenic rupture is suspected. Prompt splenectomy is the

treatment of choice, although nonoperative observation and splenorrhaphy have a role in the management of selected patients with subcapsular splenic hematoma. Because a history of trauma may be elicited in about one half the cases of splenic rupture, elimination of contact sports, attention to constipation, and caution in p lenic palpation are prudent measures for at least the first month after diagnosis (see Treatment section).

Neurologic

Neurologic complications, which occur in less than 1% of the cases, can dominate the clinical presentation (Box 3.) On occasion, these neurologic signs can be the first or only manifesta tion of infectious mononucleosis. In many cases, the heterophile antibody determination is negative, atypical lymphocytes may be low in number or delayed in appearance, and the diagnosis must be made by changes in EBV-specific antibodies. The encephalitis seen with infectious mononucleosis may be acute in onset and rapidly progressive and severe but is usually associated with complete recovery. The encephalitis is commonly manifested as a cerebellitis but may also be global. The clinical presentation may also resemble that of aseptic meningitis. In both encephalitis and meningitis, changes in the spinal fluid are mild. The opening pressure is normal or slightly elevated. A predominantly mononuclear pleocytosis may be present, with most cell counts much less than 200/mm3. Atypical lymphocytes have been seen in the cerebrospinal fluid (CSF) in a number of cases. The protein level is usually normal to mildly elevated, and the glucose concentration is usually normal. Low titers of EBV VCA can be found in the CSF. Cases of Guillain-Barré syndrome, Bell’s palsy, and transverse myelitis have been reported in primary EBV infection. Although neurologic complications are the most frequent cause of death in infectious mononucleosis, the benign outcome of most of these episodes should be emphasized. Eighty-five percent of the patients with neurologic complications recover completely.

Hepatic

Hepatic manifestations consist largely of self-limited elevations of hepatocellular enzyme levels, which are present in 80% to 90% of the cases of

infectious mononucleosis. Reported cases of infectious mononucleosis leading to cirrhosis or other chronic sequelae are poorly documented.

Renal

Abnormal urinary sediment is common in acute infectious mononucleosis. Microscopic hematuria and proteinuria are the most frequently noted abnormalities. Overt renal dysfunction is, however, extremely rare, although sporadic cases of acute renal failure in association with infectious mononucleosis have been reported. The renal manifestations of infectious mononucleosis have been hypothesized as usually attributable to interstitial nephritis from renal infiltration by activated T lymphocytes. Renal dysfunction in association with EBV-associated rhabdomyolysis has also been reported, although not all cases of rhabdomyolysis are accompanied by renal dysfunction.

Cardiac

Clinically significant cardiac disease is uncommon. Electrocardiographic abnormalities, usually confined to ST-T wave abnormalities, were reported in 6% of the cases in one series. Pericarditis and fatal myocarditis have also been observed.

Pulmonary

Pulmonary manifestations of infectious mononucleosis are rare. Early studies reported the presence of interstitial infiltrates in 3% to 5% of the cases. However, systematic examination for other causes of nonbacterial pneumonias, for example, Mycoplasma, was not carried out in these studies, and whether these infiltrates were related to EBV infection is not clear. Pneumonia has, however, been reported, and in at least one instance, EBERs were found in pulmonary tissue. The attribution of pulmonary lesions to EBV infection should be made only after other pathogens have been carefully excluded.

Death

Death from infectious mononucleosis is rare. Death may occur either as a result of overwhelming EBV infection or from complications of the disease. Neurologic complications of the illness, splenic rupture, and upper airway

obstruction are the most frequent causes of death from infectious mononucleosis in previously healthy persons. Deaths from complications associated with granulocytopenia, thrombocytopenia, hepatic failure, and myocarditis have also been reported.

Clinical Course

Most cases of infectious mononucleosis resolve spontaneously over a 2-week to 3-week period. The sore throat is usually maximal for 3 to 5 days and then gradually resolves over the course of a week to 10 days. Patients remain febrile for 10 to 14 days, but in the last 5 to 7 days, the fever is usually low grade and associated with little morbidity. The prostration associated with infectious mononucleosis is generally more gradual in its resolution. As the illness resolves, patients often have days of relative well-being that alternate with recrudescence of symptoms.

1.6. DIAGNOSIS

The diagnosis of infectious mononucleosis implies primary EBV infection. A presumptive diagnosis may be made by the presence of typical clinical symptoms with atypical lymphocytosis in the peripheral blood. The diagnosis is confirmed by serologic testing.

Routine Laboratory Tests.

In more than 90% of cases, there is leukocytosis of 10,000–20,000 cells/mm3, of which at least two thirds are lymphocytes; atypical lymphocytes usually account for 20–40% of the total number. The atypical cells are mature T lymphocytes that have been antigenically activated. Compared with regular lymphocytes microscopically, atypical lymphocytes are larger overall, with larger, eccentrically placed indented and folded nuclei with a lower nuclear-cytoplasm ratio. Although atypical lymphocytosis may be seen with many of the infections usually causing lymphocytosis, the highest degree of atypical lymphocytes is classically seen with EBV infection. Other syndromes associated with atypical lymphocytosis include acquired cytomegalovirus infection (as contrasted to congenital cytomegalovirus infection), toxoplasmosis, viral hepatitis, rubella, roseola, mumps, tuberculosis,

typhoid, mycoplasma infection, malaria, as well as some drug reactions. Mild thrombocytopenia to 50,000–200,000 platelets/mm3 occurs in more than 50% of patients, but only rarely are values low enough to cause purpura. Mild elevation of hepatic transaminases occurs in approximately 50% of uncomplicated cases but is usually asymptomatic without jaundice.

Heterophile Antibody Test

Heterophile antibodies agglutinate cells from species different from those in the source serum (Table 1.3). The transient heterophile antibodies seen in infectious mononucleosis, also known as Paul-Bunnell antibodies, are IgM antibodies detected by the Paul-Bunnell–Davidsohn test for sheep red cell agglutination. The heterophile antibodies of infectious mononucleosis agglutinate sheep or, for greater sensitivity, horse red cells but not guinea pig kidney cells. This adsorption property differentiates this response from the heterophile response found in patients with serum sickness, rheumatic diseases, and some normal individuals. Titers greater than 1:28 or 1:40 (depending on the dilution system used) after absorption with guinea pig cells are considered positive.

Table 1.3. Heterophile Antibodies: Effect of Absorption

Source of Serum	Unabsorbed	Guinea Pig Kidney	Beef Red Cells
Infectious mononucleosis	++++	+++	0
Serum sickness	+++	0	0
Normal serum (Forssman antibody)	+	0	+

The sheep red cell agglutination test is likely to be positive for several months after infectious mononucleosis; the horse red cell agglutination test may be positive for as long as 2 yr. The most widely used method is the qualitative, rapid slide test using horse erythrocytes. It detects heterophile antibody in 90% of cases of EBV-

associated infectious mononucleosis in older children and adults but in only up to 50% of cases in children younger than 4 yr because they typically develop a lower titer. Approximately 5–10% of cases of infectious mononucleosis are not caused by EBV and are not uniformly associated with a heterophile antibody response. The false-positive rate is less than 10%, usually resulting from erroneous interpretation. If the heterophile test is negative and an EBV infection is suspected, EBV-specific antibody testing is indicated.

Specific EBV Antibodies

EBV-specific antibody testing is useful to confirm acute EBV infection, especially in heterophile-negative cases, or to confirm past infection and determine susceptibility to future infection. Several distinct EBV antigen systems have been characterized for diagnostic purposes. The EBNA, EA, and VCA antigen systems are most useful for diagnostic purposes (Table 1.4). The acute phase of infectious mononucleosis is characterized by rapid IgM and IgG antibody responses to VCA in all cases and an IgG response to EA in most cases. The IgM response to VCA is transient but can be detected for at least 4 wk and occasionally up to 3 mo. The laboratory must take steps to remove rheumatoid factor, which may cause a false-positive IgM VCA result. The IgG response to VCA usually peaks late in the acute phase, declines slightly over the next several weeks to months, and then persists at a relatively stable level for life.

Anti-EA antibodies are usually detectable for several months but may persist or be detected intermittently at low levels for many years. Antibodies to the diffuse-staining component of EA, EA-D, are found transiently in 80% of patients during the acute phase of infectious mononucleosis and reach high titers in patients with nasopharyngeal carcinoma. Antibodies to the cytoplasmic-restricted component of EA, EA-R, emerge transiently in the convalescence from infectious mononucleosis and often attain high titers in patients with EBV-associated Burkitt lymphoma, which in the terminal stage of the disease may be exceeded by antibodies to EA-D. High levels of antibodies to EA-D or EA-R may be found also in immunocompromised patients with persistent EBV infections and active EBV

replication. Anti-EBNA antibodies are the last to develop in infectious mononucleosis and gradually appear 3–4 monts after the onset of illness and remain at low levels for life. Absence of anti-EBNA when other antibodies are present implies recent infection, while the presence of anti-EBNA implies infection occurring more than 3–4 months previously. The wide range of individual antibody responses and the various laboratory methods used can occasionally make interpretation of an antibody profile difficult. The detection of IgM antibody to VCA is the most valuable and specific serologic test for the diagnosis of acute EBV infection and is generally sufficient to confirm the diagnosis.

Table 1.4. Antibodies to Epstein-Barr Virus (EBV)

Antibody Specificity	***Time of Appearance in Infectious Mononucleosis***	***Percentage of EBV-Induced Mononucleosis Cases with Antibody***	***Persistence***	***Comments***
Viral Capsid Antigens (VCAs)				
IgM VCA	At clinical presentation	100	4-8 wk	Highly sensitive and specific; major diagnostic utility
IgG VCA	At clinical presentation	100	Lifelong	High titer at presentation and lifelong persistence make IgG VCA more useful as epidemiologic tool than as diagnostic tool in individual cases
Early Antigens				
Anti-EA-D	Peaks at 3-4 wk after onset	70	3-6 mo	Correlated with severe disease; also seen in Nasopharyngeal carcinoma
Anti-EA-R	2 wk to several months after onset	Low	2 mo to >3 y	Occasionally seen with unusually severe or protracted illness; also seen in African Burkitt's lymphoma
EBV nuclear antigen	3-4 wk after onset	100	Lifelong	Late appearance helpful in diagnosis of heterophile-negative cases

1.7. DIFFERENTIAL DIAGNOSIS

In most cases, the diagnosis of infectious mononucleosis is straightforward. The clinical manifestations of sore throat, fever, lymphadenopathy, and malaise

coupled with atypical lymphocytosis and a positive heterophile test result establish the diagnosis of EBV-induced infectious mononucleosis. Difficulties arise, however, when the clinical manifestations are less striking, particularly when the heterophile test results are negative (Box 1.6).

Heterophile-negative infectious mononucleosis may be caused by several different agents. Attention to the clinical manifestations of the illness and proper use of the laboratory provide an etiologic diagnosis in 85% to 90% of all cases of infectious mononucleosis. The frequency with which heterophile-negative infectious mononucleosis is seen depends largely on three factors: (1) age of the population of patients (EBV-induced infectious mononucleosis tends to be a milder illness and is more often heterophile negative in pediatric populations than in young adults); sensitivity of the heterophile test (heterophile antibodies are more often demonstrable with horse red cell agglutination than with beef red-cell hemolysis or with sheep red-cell agglutination); and diligence with which heterophile antibodies are sought (typical cases of infectious mononucleosis may be heterophile negative on presentation but, if retested later in the course of the illness, may become heterophile positive).

The most frequent cause of heterophile-negative infectious mononucleosis in most populations is CMV. Although differentiation of individual cases of EBV-induced versus CMV-induced infectious mononucleosis may be difficult, certain features are more common in CMV infections. CMV more frequently follows transfusion and is more often manifested as a typhoid-like syndrome without sore throat and lymphadenopathy. Splenomegaly may be slightly more prominent with CMV-induced disease, whereas the atypical lymphocytosis is usually less intense in CMV-induced infectious mononucleosis. In age-matched control subjects, the results of liver function tests are less elevated when the agent is CMV. Cryoglobulins are seen in both EBVinduced and CMV-induced disease, but anti-i specificity is not seen in CMV-induced mononucleosis. The illness may be attributed to CMV with serologic evidence of acute CMV infection and no evidence of acute EBV infection.

Heterophile-negative infectious mononucleosis may also be caused by EBV. As previously noted, this is not uncommon in the pediatric age group. The diagnosis rests on the demonstration of appropriate changes in specific EBV serologic tests.

Viral hepatitis may result in fever, lymphadenopathy, malaise, and an atypical lymphocytosis. Generally, the atypical lymphocytosis is of lesser magnitude, and accounts for less than 10% of the leukocytes. In viral hepatitis, hepatocellular enzyme levels are usually markedly elevated at the initial visit, whereas in infectious mononucleosis, the results of liver function tests are only mildly elevated initially and rise gradually over a 1-week to 2-week period. In addition, specific serologic tests are currently available for the detection of infection with hepatitis A, B, and C viruses.

Acute toxoplasmosis may also give rise to an infectious mononucleosis– like illness. Usually the degree of the lymphocytosis is mild, and a diagnosis can be made with serologic tests for Toxoplasma. Rubella may also occasionally be manifested by fever, lymphadenopathy, and a mild atypical lymphocytosis, but the appearance of the exanthem and the clinical course of the illness are generally not confused with those of infectious mononucleosis. A serologic diagnosis of recent rubella infection can be obtained if the diagnosis remains in doubt. Infectious lymphocytosis of childhood is a disease of uncertain cause that is characterized by fever, lymphadenopathy, occasionally diarrhea, and a lymphocytosis that consists almost exclusively of small mature lymphocytes. The disease is most common in the pediatric age group, may occur in epidemics, and is not associated with EBV infection.

A streptococcal sore throat may also mimic infectious mononucleosis clinically. Adenopathy is generally submandibular and anterior cervical, and splenomegaly is absent in streptococcal sore throat. Culture of group A β-hemolytic streptococci from the throat is supportive but not conclusive evidence for this diagnosis because colonization with the organism is common in this population of patients. Serologic tests for recent infection with group A

streptococci may help to establish the cause. Patients with primary HIV infection may also present with fever, lymphadenopathy, and pharyngitis. Such patients may also have a maculopapular rash and signs of aseptic meningitis.

Patients with primary HIV infection are typically heterophile negative; however, rare cases of heterophile-positive primary HIV infection have been reported. Thus, serum or plasma should be sent for HIV RNA (viral load) as part of the evaluation of heterophile-negative infectious mononucleosis and may even be appropriate in heterophile-positive patients at high risk. Patients with primary HIV infection typically have negative or indeterminate HIV serology

Box 1.6.

The clinical manifestations of sore throat, fever, lymphadenopathy, and malaise coupled with atypical lymphocytosis and a positive heterophile test result establish the diagnosis of EBV-induced infectious mononucleosis.

Differential Diagnosis

Acute CMV infection

Viral hepatitis A,B,C

Acute toxoplasmosis

Streptococcal sore throat

Primary HIV infection

1.8. TREATMENT

There is no specific treatment for infectious mononucleosis. Therapy with high doses of intravenous acyclovir decreases viral replication and oropharyngeal shedding during the period of administration but does not affect the severity of

symptoms or the eventual clinical course. Rest and symptomatic therapy are the mainstays of management. Bed rest is necessary only when the patient has debilitating fatigue. As soon as there is definite symptomatic improvement, the patient should be allowed to begin resuming normal activities. Because blunt abdominal trauma may predispose patients to splenic rupture, it is customary and prudent to advise withdrawal from contact sports and strenuous athletic activities during the first 2–3 wk of illness or while splenomegaly is present.

Short courses of corticosteroids (less than 2 wk) may be helpful for complications of infectious mononucleosis, but their use has not been evaluated critically. Some appropriate indications include incipient airway obstruction, thrombocytopenia with hemorrhaging, autoimmune hemolytic anemia, and seizures and meningitis. A recommended dosage is prednisone 1 mg/kg/24 hr (maximum 60 mg/24 hr) or equivalent for 7 days and tapered over another 7 days. There are no controlled data to show efficacy of corticosteroids in any of these conditions. In view of the potential and unknown hazards of immunosuppression for a virus infection with oncogenic complications, corticosteroids should not be used in usual cases of infectious mononucleosis.

1.9. PROGNOSIS

The prognosis for complete recovery is excellent if no complications ensue during the acute illness. The major symptoms typically last 2–4 wk followed by gradual recovery. Second attacks of infectious mononucleosis caused by EBV have not been documented. Fatigue, malaise, and some disability that may wax and wane for several weeks to a few months are common complaints even in otherwise unremarkable cases. Occasional persistence of fatigue for a few years after infectious mononucleosis is well recognized. At present, there is no specific evidence linking EBV infection to chronic fatigue.

2. PHARYNGITIS AND TONSILLITIS

Pharyngitis is an inflammatory illness of the mucous membranesand underlying structures of the throat; it is invariably associated with the symptom of sore throat. Most cases of pharyngitis in children are caused by viruses and are benign self-limiting illnesses. Group A β-hemolytic streptococcus (*S. pyogenes*) is the most important etiologic agent because of its potential to cause rheumatic fever. The prevention of rheumatic fever defines the management of pharyngitis.

Pharyngitis includes tonsillitis, tonsillopharyngitis, and nasopharyngitis. The inflammation frequently also involves the nasopharynx, uvula, and soft palate. Pharyngitis with nasal symptoms (sometimes called nasopharyngitis) is usually caused by a virus, whereas pharyngitis without nasal symptoms can be caused by a wide variety of infectious agents.

When an infectious agent is inoculated onto the pharyngeal or tonsillar tissue, localized inflammation occurs. This may occur de novo or as a complication of the common cold, when the etiologic agent is more likely to be viral. A list of etiologic agents is presented in Boxes 2.1 and 2.2. S. pyogenes causes 15% to 30% of acute pharyngitis in children.

Pharyngitis occurs more frequently during the colder months of the year. In temperate climates, pharyngitis due to S. pyogenes infection usually occurs in the winter and early spring. Pharyngitis due to S. pyogenes is primarily a disease of children 5 to 15 years old. Group C streptococci are a common cause of pharyngitis in college students. Group C streptococci are also described as the etiologic organism in epidemic pharyngitis spread by contaminated food.

The inflammation causes erythema of the pharynx, the tonsils, or both structures. Exudate typically occurs with only some organisms, including adenovirus, herpes simplex virus, β hemolytic streptococci, Corynebacterium

diphtheriae, Arcanobacterium haemolyticum, Epstein-Barr virus, and Candida species. Ulceration is usually seen only with herpes simplex virus and enterovirus.

The pharyngeal involvement may be overshadowed by other symptoms, such as cough and coryza, when, for example, the infecting organism is the parainfl uenza virus, and fever, exanthem, and meningitis when the infecting organism is an enterovirus.

The tonsillopharyngeal involvement with marked exudate caused by Epstein-Barr virus looks similar to that caused by *S. pyogenes.* It appears that bacterial adhesion is the cause of the exudate that occurs with this Epstein-Barr virus infection.

Primary and recurrent herpes simplex virus infection occasionally has associated pharyngitis. In almost all instances, there are herpes lesions in the anterior mouth, externally around the mouth, and at the mucocutaneous border.

BOX 2.1

Viral Agents in

Pharyngitis and Tonsillitis

Common Viral Causes

Adenovirus types 1 to 7, 7a, 9, 14 to 16

Coronavirus

Enteroviruses: coxsackievirus types A and B, echovirus type A

Epstein-Barr virus

Influenza virus types A and B

Parainfluenza virus types 1 to 4

Respiratory syncytial virus

Less Common Viral Causes

Cytomegalovirus

Herpes simplex virus

Measles virus

Poliovirus

Reovirus

Rhinoviruses

Rotaviruses

Rubella virus

BOX 2.2

Other Agents in

Pharyngitis and Tonsillitis

Common Bacterial Causes

Streptococcus pyogenes

Less Common Bacterial Causes

Actinomyces spp.

Bacteroides melaninogenicus

Bacteroides spp.

Borrelia spp.

Corynebacterium diphtheriae

Corynebacterium pyogenes

Corynebacterium ulcerans

Francisella tularensis

Fusobacterium spp.

Haemophilus infl uenzae

β-Hemolytic streptococci B, C, and G

Legionella pneumophila

Leptospira spp.

Neisseria gonorrhoeae

Neisseria meningitidis

Peptostreptococcus spp.

Salmonella typhi

Streptobacillus moniliformis

Streptococcus pneumoniae

Treponema pallidum

Yersinia enterocolitica

Other Organisms

Candida spp.

Chlamydia pneumoniae

Coxiella burnetii

Mycoplasma hominis

Mycoplasma pneumoniae

Toxoplasma gondii

2.1. Clinical Features

Children of any age can develop pharyngitis and tonsillitis. The onset is usually sudden with fever, sore throat, and anorexia. There may be headache, nausea, vomiting, lassitude, and sometimes abdominal pain. With viral infection, there are often other signs of respiratory tract infection, with more or less systemic involvement. The cervical lymph nodes are enlarged and tender. There is moderate to severe pharyngeal erythema, and there may be follicles, ulcers, petechiae, and generalized exudate. Petechial lesions on the soft palate may occur with pharyngitis due to *S. pyogenes,* Epstein-Barr virus, measles virus, and rubella virus.

In all cases of acute pharyngitis, streptococcal disease must be considered. Various clinical factors (exposure, season, incubation period, age of patient, and associated clinical findings) may distinguish among causative organisms in large epidemiologic studies, but in the individual child, the clinical distinction of streptococcal pharyngitis from viral pharyngitis is unreliable. If there is an obvious nasal infection, ulceration, or conjunctivitis, the etiology is most likely viral. In a child under the age of 4 years, pharyngitis with no exudate is almost always viral. In a child older than 4 years of age, pharyngitis with exudate or fever is most likely caused by *S. pyogenes,* but other bacteria may mimic this condition. The clinical features of pharyngitis due to group A, C, and G β-hemolytic streptococci are similar. The clinical and epidemiologic features that differ in pharyngitis due to *S. pyogenes* versus a viral cause are shown in Boxes 2.3 and 2.4.

BOX 2.3

Clinical and Epidemiologic Features Suggesting Streptococcus pyogenes Pharyngitis

Sudden onset

Sore throat

Fever

Scarlet fever rash

Headache

Nausea, vomiting, and abdominal pain

Infl ammation of pharynx and tonsils and uvula

Patchy discrete exudates

Palatal petechiae

Excoriated nares (especially in infants)

Tender, enlarged anterior cervical nodes

Patient age 5 to 15 years

Presentation in winter or early spring

History of exposure

Modifi ed from Gerber MA: Diagnosis and treatment of pharyngitis in children. Pediatr Clin North Am 52:729-747, 2005; and Bisno AL, Gerber MA, Gwaltney JM, et al: Practice guidelinesfor the diagnosis and management of A streptococcal pharyngitis. Clin Infect Dis 35:113-125, 2002.

BOX 2.4

Clinical and Epidemiologic Features Suggesting Viral Pharyngitis

Conjunctivitis

Coryza

Cough

Hoarseness

Anterior stomatitis

Discrete oral ulcers

Diarrhea

Characteristic exanthems

Modifi ed from Gerber MA: Diagnosis and treatment of pharyngitis in children. Pediatr Clin North Am 52:729-747, 2005; and Bisno AL, Gerber MA, Gwaltney JM, et al: Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 35:113-125, 2002.

2.2. Diagnosis

A throat swab is necessary to determine the presence of *S. pyogenes.* Identification can be with either culture or a rapid antigen detection test. For both, an adequate swab of the inflamed tonsillar area is required and the manner in which the swab is obtained is the main determinant of diagnostic accuracy. The surfaces of both tonsils and the pharyngeal wall should be swabbed. Other areas of the mouth and pharynx should not be swabbed. If collected in this manner, a single swab has a sensitivity of 90% to 95% for the detection of *S. pyogenes* in the pharynx.

The throat swab should be incubated for 18 to 24 hours on a sheep blood agar plate. Agar plates that are negative at 24 hours should be reexamined at 48 hours. Rapid antigen detection tests have been developed because of this 24- to 48-hour delay before a throat swab can inform clinical management. The results may be obtained in about 10 minutes. Most available rapid antigen detection tests have specificities of 95% or greater, and thus a positive result is a very good indicator of the need to treat. Sensitivities range from 80% to 90%, so a negative antigen test does not exclude *S. pyogenes* infection. When *S. pyogenes* pharyngitis is suspected clinically but the rapid diagnostic test is negative, a throat swab for culture should be obtained. A large proportion of false-negative rapid antigen tests are true infections rather than *S. pyogenes* carriage. Because of the limited number of direct test-to-test comparisons that have been performed, the relative sensitivities of different rapid antigen test have not been established.

A positive culture or rapid antigen test for *S pyogenes* cannot differentiate a child with a true infection from another with a symptomatic viral pharyngitis who is a *S. pyogenes* carrier.

2.3. Treatment

Symptomatic relief may be obtained from drinking warm fluids or, in the older child, saltwater gargles. An analgesic such as acetaminophen is appropriate. Simple lemon-based throat lozenges may be soothing, but ones that contain potentially toxic substances should be avoided. Decongestants and antihistamines have no place in the treatment of pharyngitis and tonsillitis.

Antibiotics are used to treat symptomatic pharyngitis caused by infection with *S. pyogenes.* The aim is to prevent the development of rheumatic fever. If the rapid antigen test and culture are both negative, then antibiotics should be withheld or, if already started, discontinued.

In addition to preventing rheumatic fever, treatment of *S. pyogenes* pharyngitis reduces the duration of symptoms and the risk of spread and enables quicker return to school and work.

Several different antibiotics are effective, including penicillin, ampicillin and amoxicillin, many cephalosporins, macrolides, and clindamycin. Antimicrobial therapy options for *S. pyogenes* pharyngitis are summarized in Table 1. Penicillin remains the recommended treatment because of its proved efficacy, narrow antimicrobial spectrum, low cost, and excellent safety profile. *S. pyogenes* has never developed resistance to penicillins or cephalosporins. The minimum inhibitory concentration of penicillin has not increased over the past 50 years.

Penicillin can be effective in preventing rheumatic fever even when therapy is started up to 9 days after the onset of the acute illness. Although the conventional oral dosage regimen is penicillin V, 250 mg 3 to 4 times a day, a twice daily dose of 250 mg, if reliably given, is as effective. In children over 12 years of age, a higher dose of 500 mg twice a day is recommended. Intramuscular benzathine

penicillin is very effective and should be considered for children who are particularly unlikely to complete a course of oral treatment.

Although the efficacy of penicillin in eliminating *S. pyogenes* from the tonsils and pharynx has not diminished after 40 years of use, the failure rate in practice may be at least as high as 18% in certain communities. Ampicillin and amoxicillin are associated with a 95% risk of skin rash in infectious mononucleosis; therefore, they are not recommended in the treatment of pharyngitis.

The course of oral antibiotic must be 10 days; courses of shorter duration are associated with lack of effective treatment. A child must complete a full 24 hours of therapy before returning to school or day care; otherwise, he or she remains infectious to other children.

Both suppurative and nonsuppurative (acute rheumatic fever, acute post streptococcal glomerulonephritis, and post streptococcal reactive arthritis) complications can develop from pharyngitis.

Scarlet fever is a streptococcal pharyngitis with a characteristic rash. The rash occurs if the *S. pyogenes* causing the infection produces a pyrogenic (erythrogenic) toxin and infects an individual who does not have antitoxin antibodies. The rash is either the first sign of the illness or occurs within 24 to 48 hours of illness onset. It begins around the neck and chest, spreads downward and is often more intense in the skin creases of the neck, axillae, elbows, groins, and knees (Pastia’s lines). The palms and soles are spared as is the face, where there is characteristic circumoral pallor and flushed cheeks. The rash is diffuse, bright red, papular, and rough to the touch. The sandpaper texture is caused by occlusion of sweat glands. The rash fades over a week and is followed by desquamation for several weeks. In addition to palatal petechiae, the tongue has a white strawberry (yellowish white coating through which the red papillae are seen) and then, when the coating disappears, a red strawberry appearance (red swollen papillae).

2.4. Clinical Course and Prognosis

Pharyngitis is self-limited, lasting 4 to 10 days, and it has an excellent prognosis. However, in 0.3% to 3.0% of untreated *S. pyogenes* throat infections, the serious complication of rheumatic fever results.

Table 2.1

Antimicrobial Therapy for Streptococcus pyogenes Pharyngitis

Route of Administration, Antimicrobial Agent	Dosage	Duration
Oral	Children: 250 mg	10 days
Penicillin*	Adolescents and adults: 250 mg	10 days
	Adolescents and adults: 500 mg	10 days
Intramuscular		
Benzathine penicillin G	1.2 × 106 U (for patients ≥27 kg)	1 dose
Mixtures of benzathine and procaine penicillin G	6.0 × 105 U (for patients <27 kg)	1 dose
	Varies with formulation†	1 dose
Oral, for Patients Allergic to Penicillin		
Erythromycin		10 days
First-generation cephalosporin‡	Varies with formulation	10 days
	Varies with agent	

**Amoxicillin is often used in place of oral penicillin V in young children because of the acceptance of the taste of the suspension, not because of any microbiologic advantage.*

†Dose should be determined on basis of benzathine component.

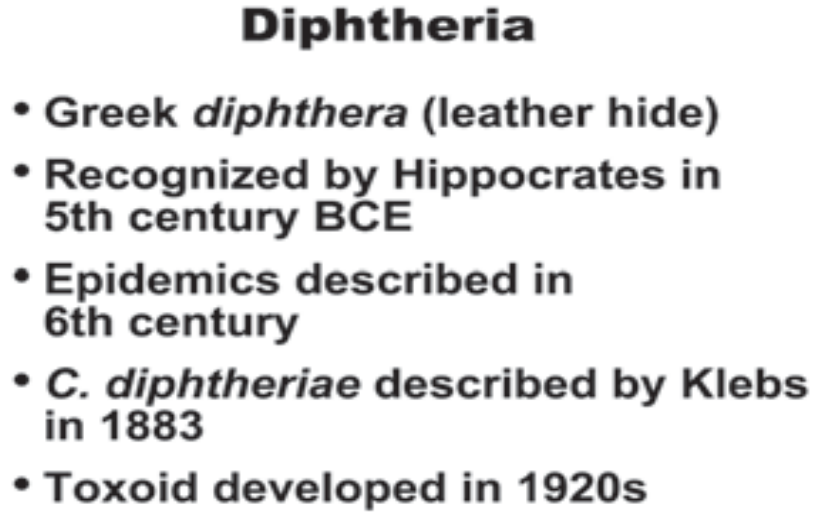
‡These agents should not be used to treat patients with immediate-type hypersensitivity to β-lactam antibiotics.

Modifi ed from Gerber MA: Diagnosis and treatment of pharyngitis in children. Pediatr Clin North Am

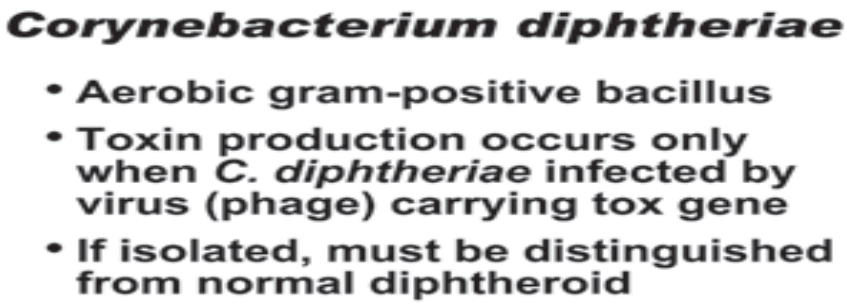
52:729-747, 2005; and Bisno AL, Gerber MA, Gwaltney JM, et al: Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Clin Infect Dis 35:113-125, 2002.

3. DIPHTHERIA

Diphtheria is an acute toxicoinfection caused by Corynebacterium diphtheriae. Diphtheria was the first infectious disease to be conquered on the basis of principles of microbiology and public health. Reduced from a major cause of childhood death in the West in the early 20th century to a medical rarity, modern reminders of the fragility of such success underscore the need to assiduously apply those same principles in an era of vaccine dependency and a single global community.



3.1. ETIOLOGY (Box 3.1)



Corynebacterium species are aerobic, nonencapsulated, non–spore-forming, mostly non-motile, pleomorphic, gram-positive bacilli. Not fastidious in growth requirements, their isolation is enhanced by selective media (i.e., cystine-tellurite blood agar) that inhibits growth of competing organisms and, when reduced by C. diphtheriae, renders colonies gray-black. Three biotypes (i.e., mitis, gravis, and intermedius), each capable of causing diphtheria, are differentiated by colonial morphology, hemolysis, and fermentation reactions. A lysogenic bacteriophage carrying the gene that encodes for production of exotoxin confers diphtheria-producing potential to strains of C. diphtheriae, but it provides no essential protein to the bacterium. Investigation of outbreaks of diphtheria in England and the United States using a molecular technique suggested that indigenous nontoxigenic C. diphtheriae had been rendered toxigenic and disease producing after the importation of toxigenic C. diphtheriae. Diphtheritic toxin can be demonstrated in vitro by the agar immunoprecipitin technique (Elek test), an investigational polymerase chain reaction test, or by the in vivo toxin neutralization test in guinea pigs (lethality test). Toxigenic strains are indistinguishable by colony type, microscopy, or biochemical tests.

Box 3.1

Etiology of Diphtheria

- Three biotypes of C. diphtheriae exist (mitis, intermedius, and gravis)
- Only toxinogenic isolates produce exotoxin
- Nontoxinogenic isolates may produce symptomatic diphtheria, but

3.2. EPIDEMIOLOGY

Unlike other diphtheroids (coryneform bacteria), which are ubiquitous in nature, C. diphtheria is an exclusive inhabitant of human mucous membranes and skin. Spread is primarily by airborne respiratory droplets or direct contact with respiratory secretions of symptomatic individuals or exudate from infected skin lesions. Asymptomatic respiratory carriers are important in transmission. Where diphtheria is endemic, 3–5% of healthy individuals may harbour toxigenic organisms, but carriage is exceedingly rare if diphtheria is rare. Skin infection and skin carriage are silent reservoirs of diphtheria. Viability in dust and on fomites for up to 6 months has less epidemiologic significance. Transmission through contaminated milk and an infected food handler have been proved or suspected.

In the 1920s, more than 125,000 cases and 10,000 deaths due to diphtheria were reported annually in the United States, with highest fatality rate among very young and elderly patients. From 1921–1924, diphtheria was the leading cause of death among Canadian children 2–14 year of age. The incidence began to fall, and with the widespread use of diphtheria toxoid in the United States after World War II, it declined steadily, with dramatic reductions in the latter 1970s. Since then, there have been zero to five cases per year and no epidemics of respiratory tract diphtheria. Similar decreases have been seen in Europe. Although disease incidence has fallen worldwide, diphtheria remains endemic in many developing countries. The sustained low incidence of diphtheria and high level of childhood vaccination have led authorities to set a goal to eliminate diphtheria among persons 25 year of age or younger in the United States by the year 2000.

When diphtheria was endemic, it primarily affected children younger than 15 year of age, but recent epidemiology has shifted to adults who lack natural

exposure to toxigenic C. diphtheriae in the vaccine era and have low rates of boosting injections. In the 27 sporadic cases of respiratory tract diphtheria reported in the United States in the 1980s, 70% occurred in persons older than 25 year of age. The largest outbreak of diphtheria in the developed world since the 1960s occurred from 1990–1995 throughout the New Independent States of the former Soviet Union, where more than 47,000 cases and 1,700 deaths occurred in 1994 alone. This outbreak is due to lack of immunization for diphtheria. Most affected individuals were older than 14 year of age. Smaller epidemiologically similar outbreaks have occurred in Denmark and Sweden.

A survey of antitoxin levels in Sweden is particularly noteworthy, because the childhood immunization rate exceeds 95%, but 19% of persons younger than 20 year of age and 81% of women and 56% of men older than 60 year of age lacked the protective antibody. Other broad serosurveys have identified large subgroups of underimmunized individuals in the United States and elsewhere where immunization is "universal" that would be at perilous risk if the organism were introduced. Only 40–60% of 2-yr-old urban and rural poor children are appropriately immunized. Twenty per cent of 396 children younger than 5 year of age in a Dade County, Florida, serosurvey lacked protective immunity to diphtheria (antitoxin level >0.01 IU/mL). State laws requiring vaccination for school entry have ensured protective immunity for more than 97% of children 5–14 year of age. In serosurveys in the United States and other developed countries with almost universal immunization during childhood, such as Sweden, Italy, and Denmark, 25% to more than 60% of adults lacked protective antitoxin levels, with particularly low levels found in the elderly.

Cutaneous diphtheria, a curiosity when diphtheria was common, accounted for more than 50% of C. diphtheriae isolates reported in the United States by 1975 and features prominently in the changing epidemiology of diphtheria in the 1990s. An indolent local infection with infrequent toxic complications, cutaneous infection, compared with mucosal infection, is associated with more prolonged bacterial shedding, increased contamination of the environment, and increased

transmission to pharynx and skin of close contacts. Outbreaks are associated with homelessness, crowding, poverty, alcoholism, poor hygiene, contaminated fomites, underlying dermatosis, and introduction of new strains from exogenous sources. No longer a tropical or subtropical disease, 1,100 C. diphtheriae infections were documented in the Skid Row neighbourhood in Seattle, Washington, from 1971–1982; 86% were cutaneous, and 40% involved toxigenic strains. Cutaneous diphtheria is the important reservoir for toxigenic C. diphtheriae in the United States and a frequent mode of importation of source cases for subsequent sporadic respiratory tract diphtheria. In an attempt to focus attention on respiratory tract diphtheria, which is much more likely to cause acute obstructive complications and toxic manifestations, skin isolates of C. diphtheriae were removed from annual diphtheria statistics reported by the Centers for Disease Control (CDC) after 1979.

3.3. PATHOGENESIS (Box 3.2)

Box 3.2. Pathogenesis of Diphtheria

- Toxigenic C. diphtheriae remains in the superficial layers of skin lesions or respiratory mucosa, inducing local inflammatory reaction
- Exotoxin inhibits protein synthesis and causes local tissue necrosis
- A dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes forms, advances, and becomes a gray-brown adherent pseudomembrane
- Paralysis of palate and hypopharynx are early local effects of the toxin
- Toxin absorption can lead to necrosis of kidney tubules, thrombocytopenia, mycocardiopathy, and demyelination of nerves
- The pathophysiologic mechanism in cases of mycocardiopathy, and demyelination of nerve - immunologically mediated

Toxigenic and nontoxigenic C. diphtheriae organisms cause skin and mucosal infection and some cases of distant infection after bacteremia. The organism usually remains in the superficial layers of skin lesions or respiratory mucosa, inducing local inflammatory reaction. The major virulence of the organism lies in

its ability to produce the potent polypeptide exotoxin, which inhibits protein synthesis and causes local tissue necrosis. Within the first few days of respiratory tract infection, a dense necrotic coagulum of organisms, epithelial cells, fibrin, leukocytes, and erythrocytes forms, advances, and becomes a gray-brown adherent pseudomembrane. Removal is difficult and reveals a bleeding edematous submucosa. Paralysis of palate and hypopharynx are early local effects of the toxin. Toxin absorption can lead to necrosis of kidney tubules, thrombocytopenia, mycocardiopathy, and demyelination of nerves. Because the latter two complications can occur 2–10 wk after mucocutaneous infection, the pathophysiologic mechanism in some cases may be immunologically mediated.

3.4. CLINICAL MANIFESTATIONS

Tonsillopharyngeal Diphtheria (Box 3.3)

This usually has an insidious onset of symptoms, in contrast to streptococcal sore throat. There is mild sore throat with slight redness and low-grade fever. Systemic signs of illness are absent in the early stages. Within 1 or 2 days, areas of yellow or “dirty” white exudate appear, most frequently on or adjacent to the tonsils; these areas subsequently coalesce to form a light reflective, sharply outlined pseudomembrane on the mucous membranes of the pharynx, tonsils, and uvula. Pseudomembranes consist of necrotic epithelium embedded in an inflammatory, organized exudate at the surface. Less frequently, such lesions are found in the nose, larynx, and lower respiratory tract. Rarely, pseudomembranous lesions extend to the middle ear, the esophagus or the stomach, or involve the skin or mucosa of the genitalia.

Inflammatory changes in underlying epithelium may extend into the submucosa, where hemorrhage may be present. The bacilli remain in these surface lesions and rarely invade deeper structures or cause bacteremia. Diphtheria toxin is absorbed from the local lesion, causing damage in distant organs and tissues.

Persons with partial antitoxic immunity may not progress beyond the exudative stage. In those lacking immunity, the pseudomembrane may spread to the soft palate and to the posterior pharynx, but not anteriorly. There is bleeding with attempts to remove the pseudomembrane. Cervical lymph nodes may be mildly enlarged, but the single large, tender nodes characteristic of streptococcal infection are not found. With extensive membrane formation, there may be dysphagia and drooling. After approximately 5 days, the pseudomembrane changes to a grayish color secondary to hemorrhage as it loosens and sloughs. Occasionally (approximately 10% of patients) the illness has a hyperacute presentation with high fever, systemic toxicity, cerebral obtundation, and rapid proliferation of the pseudomembrane associated with marked edema of the face and neck. This phenomenon is referred to as “bull neck” diphtheria, which has a grave prognosis.

Box 3.3.

Clinical manifestation of tonsillopharyngeal Diphtheria

- Mild sore throat with slight redness and low-grade fever
- Light reflective, sharply outlined pseudomembrane on the mucous membranes of the pharynx, tonsils, and uvula
- Less frequently, such lesions are found in the nose, larynx, and lower respiratory tract
- Hemorrhage into the submucosa
- Cervical lymph node mildly enlarged
- Dysphagia and drooling
- Hyperacute presentation of diphtheria - high fever, systemic toxicity, cerebral obtundation, and rapid proliferation of the pseudomembrane associated with marked edema of the face and neck - “bull neck” diphtheria

Laryngotracheobronchial Diphtheria (Box 3.4.)

Box 3.4.

Clinical manifestation of laryngotracheobronchial Diphtheria

- Varying degrees of hoarseness
- Stridor
- Respiratory embarrassment, depending on the extent and thickness of the membrane in relation to the caliber of the airway
- Rarely, the membrane extends into the bronchi, which is invariably fatal

In fewer than 5% of patients, diphtheria of the laryngotracheal area occurs in the absence of tonsillopharyngeal involvement, but in about 10% of patients, there is secondary downward spread from the pharynx. Varying degrees of hoarseness, stridor, and respiratory embarrassment occur, depending on the extent and thickness of the membrane in relation to the caliber of the airway. Young children are at higher risk of compromise because of small airways. Rarely, the membrane extends into the bronchi, resulting in a virtual cast of the airway, which is invariably fatal.

Nasal Diphtheria

Primary nasal diphtheria is more common in infants and young children. The discharge is mucoid, profuse, and grayish in color. After a few days when the membrane begins sloughing there is often blood in the discharge. This is the mildest form of diphtheria and seldom has toxic manifestations.

Other Mucous Membranes and Skin

Rarely, the primary site of infection is the mucous membrane of the eye, vagina, or ear. An ulcerating lesion with exudate or pseudomembrane forms, but these are self-limited lesions uncommonly associated with toxicity. Skin lesions are most often superficial, have no characteristic appearance, and are not associated with pseudomembranes. Occasionally, ulcerating or ecthymatous

lesions develop. They occur in persons with preexisting antitoxic immunity or they induce immunity because they are not associated with toxic manifestations. Individual lesions heal, but new ones may form at the sites of breaks in the integrity of skin from insect bites or trauma over a period of weeks.

Effects of Toxin (Box 3.5)

The heart, kidneys, and neural system are susceptible to damage by diphtheria toxin. The degree of toxic damage is determined by two factors: (a) the extent of disease at the primary site and, hence, the amount of toxin produced and disseminated hematogenously; and (b) the amount of circulating antitoxin. The latter is determined by both the preexisting antitoxin resulting from prior subclinical infection or immunization and by the therapeutic amounts of antitoxin administered. Because immunity wanes with the passing years, previously immunized persons can eventually become susceptible to toxin.

Electrocardiographic evidence of myocardial toxicity is present in many patients with diphtheria, but clinically manifest myocarditis develops in about 10% of patients. Myocarditis generally develops during the first week of illness, but can be delayed for 1 month or longer. Dysrhythmias are common. Death occurs more often from severe dysrhythmia (including complete heart block) than from heart failure. On histology, myocarditis is characterized by degenerative or “toxic” damage, rather than by inflammation. Minute hemorrhages may be present, or, in some areas, an accompanying round-cell infiltration may be seen. The conducting system frequently is involved.

Box 3.5. *Effects of Toxin*

- The degree of toxic damage is determined by two factors
  - The extent of disease at the primary site and, hence, the amount of toxin produced and disseminated hematogenously;
  - The amount of circulating antitoxin.
- Myocarditis generally develops during the first week of illness
  - Dysrhythmias are common
  - Electrocardiographic evidence
- Renal failure changes in the urinalysis

Renal failure is rare, but minor injury as reflected by changes in the urinalysis (proteinuria, cylindruria, increased cells) is common. If toxic nephropathy develops, it is almost uniformly fatal. Hemolytic uremic syndrome has been reported in diphtheria. The kidneys may exhibit cloudy swelling, with swollen granular epithelial cells of the convoluted tubules. Interstitial nephritis may occur. Lesions in the adrenal cortex, similar to those present in meningococcemia, often are found in fatal infections. Hepatic function may be mildly impaired; liver cells show degenerative changes at autopsy, with scattered areas of focal necrosis.

Neural involvement is common, occurring in 5 to 10% of patients, and can be manifested as isolated peripheral nerve palsies or as a symptom complex mimicking Guillain-Barré syndrome. Contiguous muscles in the palate, pharynx, or larynx are most commonly involved and tend to be affected earlier in the disease course than the extraocular muscles, diaphragm, or muscles supplied by peripheral nerves. Paralysis can occur as early as the first week of illness, but more often develops between the second and sixth week. If the patient does not succumb to respiratory complications of paralysis, full recovery can be expected within a few weeks. Degenerative changes in the nervous system occur in nearly all fatal infections. In the spinal cord, changes are seen in the ganglion cells of the anterior horns and in the posterior root ganglia. The cranial nerves and their centers can be affected, but the cortex is spared. Other lesions encountered are degenerative

changes in the spleen and lymph nodes; occasionally, subcapsular hemorrhages in these organs are seen. Subcutaneous hemorrhages are frequent.

3.5. DIAGNOSIS

Many bacterial and viral pathogens can cause pseudomembranous tonsillitis, the most common being S. pyogenes, adenoviruses, and Epstein-Barr virus. Although there is sometimes exudate on the part of the uvula touching the enlarged tonsil in these conditions, the pseudomembrane does not otherwise extend away from the tonsil. In rare instances of laryngeal diphtheria without oropharyngeal involvement, the diagnosis is suspected if there is a history of exposure to diphtheria or when a pseudomembrane is seen at the time of laryngoscopy or bronchoscopy. Otherwise, the differential diagnosis from viral causes of croup is exceedingly difficult. (Box 3.6.)

Box 3.6.

Clinical clues for diagnosis of diphtheria

- mildly painful tonsillitis or pharyngitis with associated membrane, especially if the membrane extends to the uvula and soft palate;
- adenopathy and cervical swelling, especially if associated with membranous pharyngitis and signs of systemic toxicity;
- hoarseness and stridor;
- palatal paralysis;
- serosanguineous nasal discharge with associated mucosal membrane;
- temperature elevation rarely in excess of 39^{o}C;
- history of recent travel to a country where diphtheria is endemic.

When diphtheria is suspected, attempts should be made to isolate the organism from the local lesion. It is advisable to take specimens for culture from the nasopharynx as well as the throat because the yield of positive results is 20% greater with two cultures as opposed to one culture. If transport time to the

laboratory is longer than 24 hours, the swabs should be placed in laboratory-recommended commercial transport medium. Specimens should be inoculated onto recommended media (usually a Loeffler or Paislant, a cystine-tellurite agar plate, and a 5% sheep's blood agar plate) and incubated overnight at 35°C (95°F). Growth from slants may be stained with Neisser or Loeffler methylene blue and examined for the characteristic morphologic appearance of C. diphtheriae (eg, metachromatic granules). Toxigenicity is usually determined using the modified Elek immunodiffusion test in reference laboratories. (Box 3.7.)

Box 3.7

Plan of investigation for patients when diphtheria is suspected

1. Common blood test
2. Common urine test
3. Bacterioscopy from the nasopharynx and the throat
4. Bacteriological test from the nasopharynx and the throat for Loeffler bacteria №3
5. Serological test with diphtheria diagnostics
6. Proteinogram
7. Coagulation test
8. ALaT, ASaT
9. ECG
10. Examination of otorhinolaryngologist, ophthalmologist, neurologist

The degree of leukocytosis in the peripheral blood generally reflects the severity of disease. In mild to moderate disease, the leukocyte count is between 10,000 and 20,000/µL. The likelihood of a fatal outcome rises sharply in patients with leukocyte counts higher than 25,000/µL. Thrombocytopenia and disseminated intravascular coagulation (DIC) are rare. Some patients develop mild anemia.

In postdiphtheritic paralysis, protein concentrations increase in the cerebrospinal fluid (CSF), but there is no increase in the number of cells and the glucose content is normal, as occurs in idiopathic Guillain-Barré syndrome. The protein content continues to increase during the initial weeks of neurologic symptoms and slowly returns to normal after clinical recovery.

Albuminuria is common, and in severe disease there may be cells and casts in the urine.

3.6. DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes infectious mononucleosis, streptococcal or viral pharyngitis and tonsillitis, Vincent angina, and acute epiglottitis. The membrane of mononucleosis characteristically remains on the tonsils, rarely loses its creamy white appearance, and does not cause bleeding when removed. Streptococcal infection usually produces a more intense local pharyngitis, higher fever, and more pronounced dysphagia. Vincent's angina often involves the gums, and Gram stain of the exudate from the necrotic ulcerative pharyngeal lesions shows characteristic fusobacteria and spirochetes. Bacterial epiglottitis secondary to Haemophilus influenzae often develops more acutely, and indirect laryngoscopy shows a bright red epiglottis without associated membrane. Finally, toxin-producing C. ulcerans can cause typical respiratory diphtheria, requiring the same treatment.

3.7. ANTITOXIN(Box 3.8.)

Diphtheria Antitoxin

- Produced in horses
- First used in the U.S. in 1891
- Used only for treatment of diphtheria
- Neutralizes only unbound toxin

Diphtheria antitoxin (DAT), hyperimmune antiserum produced in horses, has been the cornerstone of therapy for diphtheria since it was first shown to reduce mortality from 7% to 2.5% in a controlled trial published in 1898. The antibodies only neutralize toxin before its entry into cells, so it is critical that DAT be administered as soon as a presumptive clinical diagnosis has been made, before

laboratory confirmation. The degree of protection is inversely related to the duration of clinical illness preceding its administration. Although the minimal therapeutic dose has never been determined, traditional (empirical) dosage recommendations assume that the duration of disease and extent of membrane formation roughly indicate the patient's toxin burden. The Committee on Infectious Diseases of the American Academy of Paediatrics recommends 20,000 to 40,000 units of antitoxin for pharyngeal or laryngeal disease of 48 hours' duration or less; 40,000 to 60,000 units for nasopharyngeal lesions; and 80,000 to 120,000 units for extensive disease of 3 or more days' duration and for anyone with brawny swelling of the neck. It recommends administration by intravenous infusion over 60 minutes to inactivate toxin as rapidly as possible, but other experts suggest intramuscular injection of antitoxin for moderate disease and combined intramuscular and intravenous administration for severe disease. Repeated injections are of no additional benefit.

Box 3.8.

Diphtheria antitoxin must be given early, since the antitoxin neutralizes only toxin not yet bound to cells!

- Caution: diphtheria antitoxin is derived from horses; hence, a skin test to rule out sensitivity should always precede administration
- The first doze must be given 0,1 ml intra skin in solution 1:100
- After 20 minutes, you must meter erythema and papule
- If it smaller than 10 mm in diameter you must to give 0,1 ml antitoxin subdermaly

Doses of diphtheria antitoxin

Mild form of diphtheria - 20,000 to 40,000 units of antitoxin

Moderate form of diphtheria 50,000 to 60,000 units

Sevier form of diphtheria 80,000 to 120,000 units

Hypertoxic form of diphtheria 120,000 to 150,000 units

Because 5% to 20% of individuals may show some hypersensitivity to horse protein, even very sick patients must be questioned first concerning known allergy and evaluated first with a scratch test (a drop of 0.0mL of a 1:1000 dilution of serum applied to a superficial scratch on the forearm), followed in 15 minutes if no wheal develops with 0.02 mL of a 1:1000 dilution injected intracutaneously, with epinephrine available for immediate administration.65 If an immediate reaction occurs, the patient should be desensitized with progressively higher doses of antiserum. The incidence of serum sickness of about 10% is acceptable in light of the pronounced reduction in mortality resulting from antitoxin administration. Diphtheria antitoxin is no longer licensed in the United States, but a foreign-licensed product is available from the CDC Director's Emergency Operations Center by calling 770-488-7100.

3.8. ANTIMICROBIAL THERAPY (Box 2.9.)

Box 3.9.

Three benefits of antibiotic therapy, by killing the organism

- termination of toxin production;
- amelioration of the local infection;
- prevention of spread of the organism to uninfected contacts.

Antimicrobial therapy is indicated to halt toxin production, treat localized infection, and prevent transmission of the organism to contacts. C. diphtheriae is usually susceptible to a variety of agents in vitro, including penicillins, erythromycin, clindamycin, rifampin, and tetracycline. Resistance to erythromycin is common in closed populations if the drug has been used broadly. Only penicillin or erythromycin are recommended; erythromycin is marginally superior to penicillin for eradication of nasopharyngeal carriage. Appropriate therapy is erythromycin given orally or parenterally (40–50 mg/kg/24 hr; maximum, 2 g/24

hr), aqueous crystalline penicillin G given intramuscularly or intravenously (100,000–150,000 U/kg/24 hr divided in four doses), or procaine penicillin (50,000–100,000 U/kg/24 hr divided in two doses) given intramuscularly. Antibiotic therapy is not a substitute for antitoxin therapy. Therapy is given for 14 days. Some patients with cutaneous diphtheria have been treated 7–10 days. Elimination of the organism should be documented by at least two successive cultures from the nose and throat (or skin) taken 24 hr apart after completion of therapy. Treatment with erythromycin is repeated if the culture result is positive.

OTHER MEASURES

Patients with pharyngeal diphtheria are placed in strict isolation, and patients with cutaneous diphtheria are placed in contact isolation until the cultures taken after cessation of therapy are negative. Cutaneous wounds are cleaned thoroughly with soap and water. Bed rest is essential during the acute phase of disease, with a return to physical activity guided by the degree of toxicity and cardiac involvement. The complications of airway obstruction and aspiration should be aggressively avoided in patients with oropharyngeal and laryngeal diphtheria, with an artificial airway established pre-emptively. Congestive heart failure and malnutrition should be anticipated and prevented, if possible. For 66 children with respiratory tract diphtheria alternately treated with prednisone or no steroid therapy for 14 days at the time of diagnosis, toxic myocarditis occurred in 26%, neuritis in 17% and bull-neck diphtheria in 10%, with no difference in occurrence or death among those who received steroids. Steroid therapy is not recommended. The use of digitalis for treatment of myocarditis is associated with an excess occurrence of dysrhythmia and must be individualized.

The prognosis for a patient with diphtheria depends on the virulence of the organism (subspecies gravis has the highest fatality), age, immunization status, site of infection, and speed of administration of the antitoxin. Mechanical obstruction from laryngeal diphtheria or bull-neck diphtheria and the complications of myocarditis account for most diphtheria-related deaths. The case-fatality rate of

almost 10% for respiratory tract diphtheria has not changed in 50 year; the rate was 18% in the Swedish outbreak. At recovery, administration of diphtheria toxoid is indicated to complete the primary series or booster doses of immunization, because not all patients develop antibodies after infection.

3.9. EXPOSED PERSONS (BOX 3.10.)

Box 3.10.

Management of an Outbreak

- All symptomatic patients should be isolated
- Contact precautions (private room, use of gloves at all times, hand washing with an antibacterial agent, gowns worn at all times) are also recommended
- Nasopharyngeal and throat cultures for C. diphtheriae should be obtained for all close contacts
- Asymptomatic contacts with positive throat cultures for C. diphtheriae (Carriers) should be hospitalization for the duration of therapy, and given erythromycin or rifampicin 6 days
- Cultures should be rechecked at a minimum of 2 wk after completion of antimicrobial therapy

Local public health officials should be notified promptly when a diagnosis of diphtheria is suspected or proved. Investigation is aimed at preventing secondary cases in exposed individuals and at determining the source and carriers to halt spread to unexposed individuals. Reported rates of carriage in household contacts of case patients have been 0–25%. The risk of developing diphtheria after household exposure to a case is approximately 2%, and the risk is 0.3% after similar exposure to a carrier

ASYMPTOMATIC CASE CONTACTS

Prompt identification and investigation of close contacts (i.e., all household contacts and those others who have had intimate respiratory or habitual physical contact with the patient) are the highest priorities. Several steps are taken. First, these individuals are closely monitored for illness through the 7-day incubation period. Second, cultures of the nose, throat, and any cutaneous lesions are performed. Third, antimicrobial prophylaxis is given, regardless of immunization status, using oral erythromycin (40–50 mg/kg/24 hr for 7–10 days; maximum, 2 g/24 hr) or, if intolerant of erythromycin or if complete compliance is not assured, using intramuscular benzathine penicillin (600,000 U for those <30 kg or 1,200,000 U for those who greater than or equal 30 kg). The efficacy of antimicrobial prophylaxis is presumed but not proved. Fourth, diphtheria toxoid vaccine, in age-appropriate concentration, is given to immunized individuals who have not received a booster dose within 5 yr. Some experts suggest that the longevity of protective antibody is variable enough that a booster should be given to close contacts if 1 year has elapsed since immunization. Children who have not received their fourth dose should be vaccinated. Those who have received fewer than three doses of diphtheria toxoid or who lack knowledge of immunization status are immunized with age-appropriate preparation on a primary schedule.

ASYMPTOMATIC CARRIERS

When an asymptomatic carrier is identified, several steps are taken. First, antimicrobial prophylaxis is given for 7–10 days. Second, age-appropriate preparation of diphtheria toxoid is administered immediately if there has not been a booster within 1 yr. Third, individuals are placed in strict isolation (respiratory tract colonization) or contact isolation (cutaneous colonization only) until at least two subsequent cultures taken 24 hr apart after cessation of therapy are negative. Fourth, repeat cultures are performed at a minimum of 2 wks after completion of therapy for cases and carriers, and if positive, an additional 10-day course of oral erythromycin should be given and follow-up cultures performed. Neither antimicrobial agent eradicates carriage in 100% of individuals. In one report, 21% of carriers had failure of eradication after a single course of therapy. Antitoxin is

not recommended for asymptomatic close contacts or carriers, even if inadequately immunized. Transmission of diphtheria in modern hospitals is rare. Only those with an unusual contact with respiratory or oral secretions should be managed as contacts. Investigation of the casual contacts of patients and carriers or persons in the community without known exposure has yielded extremely low carriage rates and is not routinely recommended.

3.10. PREVENTION

Universal immunization with diphtheria toxoid throughout life to provide constant protective antitoxin levels and to reduce indigenous C. diphtheriae is the only effective control measure. Although immunization does not preclude subsequent respiratory or cutaneous carriage of toxigenic C. diphtheriae, it decreases local tissue spread, prevents toxic complications, diminishes transmission of the organism, and provides herd immunity when at least 70–80% of a population is immunized. Serum antitoxin concentration of 0.01 IU/mL is conventionally accepted as the minimum protective level, and 0.1 IU/mL provides the certain protective level.

Preparations.

DTaP, DT, Td and Tdap

	Diphtheria	Tetanus
DTaP, DT	7-8 Lf units	5-12.5 Lf units
Td, Tdap (adult)	2-2.5 Lf units	5 Lf units

DTaP and pediatric DT used through age 6 years. Adult Td for persons 7 years and older. Tdap for persons 10-18 years (Boostrix) or 11-64 years (Adacel)

Diphtheria toxoid is prepared by formaldehyde treatment of toxin, standardized for potency, and adsorbed to aluminum salts, which enhance immunogenicity. Two preparations of diphtheria toxoids are formulated according

to the limit of flocculation (Lf) content, a measure of the quantity of toxoid. The pediatric preparation (i.e., DTP, DT, DTaP) contains 6.7–12.5 Lf units of diphtheria toxoid per 0.5-mL dose; the adult preparation (i.e., Td) contains no more than 2 Lf units of toxoid per 0.5-mL dose. The higher-potency (i.e., D) formulation of toxoid is used for primary series and booster doses for children through 6 year of age because of superior immunogenicity and minimal reactogenicity. For individuals 7 year of age and older, Td is recommended for the primary series and booster doses, because the lower concentration of diphtheria toxoid is adequately immunogenic and because increasing the content of diphtheria toxoid heightens reactogenicity with increasing age.

Schedules

Diphtheria Toxoid

- Formalin-inactivated diphtheria toxin
- Schedule — Three or four doses + booster
Booster every 10 years
- Efficacy — Approximately 95%
- Duration — Approximately 10 years
- Should be administered with tetanus toxoid as DTaP, DT, Td, or Tdap

For children from 6 wk to the seventh birthday, give five 0.5-mL doses of diphtheria-containing (D) vaccine. The primary series includes doses at approximately 2, 4, and 6 months of age. The fourth dose is an integral part of the primary series and is given approximately 6–12 months after the third dose. A booster dose is given at 4–6 year (unless the fourth primary dose was administered after the fourth birthday). For persons 7 year of age or older, use three 0.5-mL doses of diphtheria-containing (D) vaccine. The primary series includes two doses 4–8 wk apart and a third dose 6–12 months after the second dose. The only contraindication to tetanus and diphtheria toxoid is a history of neurologic or severe hypersensitivity reaction after a previous dose. For children in whom pertussis immunization is contraindicated, DT or Td is used. Those begun with

DTP or DT at before 1 year of age should have a total of five 0.5-mL doses of diphtheria-containing (D) vaccines by 6 yr. For those beginning at or after 1 year of age, the primary series is three 0.5-mL doses of diphtheria-containing (D) vaccine, with a booster given at 4–6 year, unless the third dose was given after the fourth birthday.

Routine DTaP Primary Vaccination Schedule

Dose	Age	Interval
Primary 1	2 months	---
Primary 2	4 months	4 weeks
Primary 3	6 months	4 weeks
Primary 4	15-18 months	6 months

Further reduction in the number of cases of diphtheria in industrialized countries will require universal booster immunization throughout life.

Children Who Receive DT

- The number of doses of DT needed to complete the series depends on the child's age at the first dose:
  - —if first dose given at <12 months of age, 4 doses are recommended
  - —if first dose given at ≥12 months, 3 doses complete the primary series

Booster doses of 0.5 mL of Td should be given every 10 year after the last dose (conveniently given to most starting at 15 year, of age).

Routine DTaP Schedule Children Younger Than 7 years of age

Booster Doses
- 4-6 years of age, before entering school
- 11-12 years of age if 5 years since last dose (Tdap)
- Every 10 years thereafter (Td)

Vaccination with diphtheria toxoid should be used whenever tetanus toxoid is indicated to ensure continuing diphtheria immunity.

There is no known association of DT or Td with increased risk of convulsions. Local side effects alone do not preclude continued use. Persons who experience Arthus-type hypersensitivity reactions or a temperature of 39.4^{o} C after a dose of Td (rare in childhood) usually have high serum tetanus antitoxin levels and should not be given Td more frequently than every 10 year, even if a significant tetanus-prone injury is sustained. DT preparations and Td can be given concurrently with other vaccines.

Diphtheria and Tetanus Toxoids Adverse Reactions

- Local reactions (erythema, induration)
- Fever and systemic symptoms not common
- Exaggerated local reactions (Arthus-type)
- Severe systemic reactions rare

Haemophilus influenzae conjugate vaccines containing diphtheria toxoid (PRP-D) or the variant of diphtheria toxin, CRM197 protein (HbOC) are not substitutes for diphtheria toxoid immunization and do not affect reactogenicity.

Diphtheria and Tetanus Toxoids Contraindications and Precautions

- Severe allergic reaction to vaccine component or following a prior dose
- Moderate or severe acute illness

4. ANTIBACTERIAL THERAPY

The first antibiotic to be discovered was penicillin, a natural product of Penicillium mold. Innumerable microbial products have been investigated since then, and much work has been done in chemically modifying these natural products in an attempt to enhance the beneficial effects, while minimizing the undesirable effects. These modified products, termed semisynthetic antibiotics, increased stability and solubility, improved pharmacokinetics (ie, wider distribution and longer half-life), and increased antimicrobial activity. Minimizing the undesirable effects creates antibiotics with decreased toxicity and increased efficacy.

Unfortunately, overuse of this vast array of antibiotics now is one of our most pressing problems. Antibiotics are the most commonly prescribed drugs with sales that exceed $5 billion per year. In children antibiotics represent about 30% of all prescribed drugs. During a recent 10-year period, antibiotic production and use increased 300%, whereas the population increased by only 11%.

Misuse of antibiotics is common. Thirty to 65% of antibiotic prescriptions in hospitals are found to be irrational, inappropriate, or of questionable value. In community practice, market research data have determined that 50% of physicians prescribe antibiotics for the common cold. The reasons for this antibiotic are multifactorial, but the desire to help patients, fear of missing a bacterial infection that might respond to antibiotics, and the ease of treating a possible bacterial infection versus considering and investigating an alternative diagnosis all contribute.

One prevalent attitude is that the risk of not treating an infection is greater than the risk of side effects from antibiotic treatment. In fact, approximately 5% of patients taking antibiotics experience side effects, and the indiscriminant use of antibiotics alters the drug-resistance patterns of isolates from the individual being

treated and from the environment in general. Furthermore, a potentially more serious infection such as meningitis can be masked by incidental antibiotic therapy.

4.1. GENERAL PRINCIPLES OF ANTIBIOTIC THERAPY

Antibiotic Selection

The decision to prescribe an antibiotic is based upon proof or strong suspicion that the patient has a bacterial infection. Probable viral infectious or noninfectious processes should not be treated with antibiotics. However, in the critically ill patient in whom there is some chance that a bacterial infection may be a contributing factor, it is prudent to administer antibiotics effective against the most likely pathogens.

Whenever possible the antibiotic selection should be based upon the isolation of a pathogen, but most patients who require antibiotic therapy present with an acute problem that mandates initial empiric therapy. The specific antibiotic chosen is based upon knowledge of the pathogens likely to cause a specific infection and the likely antibiotic sensitivities in a specific host. If more than one antibiotic is active against the likely pathogens at the site of infection, the specific agent should be chosen on the basis of relative toxicity, convenience of administration, and cost.

Administration, the drug levels required for therapy, and questions of assuring compliance. Outpatient therapy is usually given orally except when a single intramuscular injection may suffice or if long-term intravenous therapy is required. In the sick hospitalized patient the intravenous route is commonly used, because it assures direct delivery of the antibiotic, and, in general, the blood concentration of antibiotic attained is higher. Patients who do not have established intravenous access can have antibiotics administered intramuscularly, unless they have a bleeding disorder or are in shock or have certain infections such as meningitis and endocarditis. If treatment is likely to be prolonged, frequent intramuscular injections are uncomfortable for the patient, and the intravenous route is preferable.

Increasingly, antibiotics are initially given by the parenteral route until the patient is stable, when the oral route is used to complete the course of therapy. This innovative treatment protocol is most common in treating osteomyelitis and septic arthritis. Compliance must be assured, the adequacy of antibiotic absorption must be assessed frequently, and the patient must have frequent clinical examinations. The advantages are self-evident: technical demands related to prolonged maintenance of an intravenous access route are reduced, as are risks of thrombophlebitis, catheter-associated infections, and the duration of hospitalization.

Duration of Therapy

The duration of antibiotic administration recommended for specific infections is often based on uncontrolled experience, not on controlled trials. Guidelines concerning the duration of therapy for most infections are outlined in this text. However, clinicians should not commit patients to a rigid duration of therapy when the infection is first diagnosed; therapy should be guided by clinical response rather than by an arbitrary number of days.

Clinical monitoring usually involves sequential physical examinations with special reference to the site originally infected and body temperature. Signs of inflammation and fever should resolve within several days after appropriate antibiotics are initiated. Laboratory monitoring may include repeat bacterial cultures to assure sterilization, and for severe infections, it may be useful to monitor the peripheral white blood cell count and acute phase reactants [eg, erythrocyte sedimentation rate (ESR) or C-reactive protein]. A lack of clinical or laboratory response to therapy may mandate a change of antibiotics.

4.2. CLASSIFICATION OF ANTIBIOTICS

Antibiotics target unique bacterial synthetic processes that differ from those in human cells. This directed attack is referred to as selective toxicity. Only four

general categories of sites of antibacterial action have been commercially developed: inhibition of cell wall synthesis, nucleic acid synthesis, protein synthesis, and folate synthesis. Antibiotics can be classified by mechanism of action or may be classified as either bacteriostatic or bactericidal. Bacteriostatic agents inhibit bacterial cell replication but require the host's immune factors to clear the infection, whereas bactericidal agents kill the bacteria. If host immunity is suppressed or the infection is in an area of poor immunologic surveillance (eg, CSF), bacteriostatic agents may not be as effective as bactericidal agents.

Chloramphenicol and erythromycin are bacteriostatic against most bacteria, although chloramphenicol is bactericidal against

Haemophilus influenzae type b, Streptococcus pneumoniae, and Neisseria meningitidis. Bactericidal antibiotics include penicillins, cephalosporins, vancomycin, and aminoglycosides. They cause microbial death by cell lysis. Some antibiotics, such as the sulfonamides and tetracyclines, may be either bacteriostatic or bactericidal, depending on the concentration of drug, the nature of the environment, and the specific bacteria against which they are being used.

4.3. ANTIBIOTIC RESISTANCE

The development of microbial drug resistance inescapably results from the widespread utilization of a growing array of antimicrobial agents, coupled with the ability of bacteria to acquire and spread resistance and the capacity of humans to spread bacteria. Antimicrobial drug resistance represents the greatest threat to successful antibiotic therapy and is a major driving force behind the search for newer drugs. Infections caused by S. aureus can no longer be treated with penicillin, and an increasing number of strains are not sensitive to methicillin or related drugs (eg, oxacillin and nafcillin). The rate of ampicillin resistance among strains of H. influenzaetype b has risen from 0% to more than 30% in the United States, and the rate of penicillin resistance among clinical isolates of S. pneumoniae is steadily increasing. The potential consequences of antibiotic

resistance for the individual patient are an increased likelihood of hospitalization, a longer hospital stay, and about a two-fold increased death rate. Furthermore, the treatment of drug-resistant bacteria often demands the use of more toxic and expensive drugs.

Developing countries and hospitals have become the common breeding grounds and reservoirs for antimicrobial-resistant pathogens. Clinical isolates commonly are resistant to a number of antimicrobial agents. usually arises when the same mechanism confers resistance to several agents or when individual resistance genes cluster on either the bacterial chromosome or on extrachromosomal resistance plasmids (R-plasmids).

There are a limited number of mechanisms by which bacteria develop resistance to antibiotics. In very general terms, these mechanisms include (a) the production of enzymes that inactivate or modify the antibiotic; (b) decreased antibiotic uptake or an active efflux system; and (c) alteration in antibiotic target). β-Lactamases probably are the best known inactivating enzymes produced by resistant bacteria. Bacterial resistance to penicillins and cephalosporins is often mediated by these enzymes. Alterations in outer-membrane proteins can decrease penetration of antibiotics into the bacteria. An example of an alteration of the antibiotic target may also result in resistance. Strains of penicillin-resistent S. pneumoniae have a markedly reduced affinity of the penicillin protein. Bacteria may develop resistance mediated by more than one mechanism.

4.4. USE OF ANTIBIOTICS IN COMBINATION

Usually a single antibiotic can be prescribed to treat an uncomplicated infection caused by a single pathogen. The most common reason for combining two or more antibiotics is to assure adequate therapy until the infecting pathogen has been identified. Combination therapy is also advisable when the infection is presumed or proved to be caused by more than one bacterium that cannot be

adequately treated with a single agent. Pelvic and intraabdominal infections, usually caused by a mixture of aerobes and anaerobes, are examples.

Combining two agents may theoretically prevent or delay emergence of resistance, which justifies the use of two drugs to treat Pseudomonas aeruginosa or mycobacterial infections. Antibiotics are also prescribed in combination in the hope that there will be greater inhibition or killing of the pathogenic bacteria than would occur with single-drug therapy. An example is treatment of enterococcal infections with a penicillin plus an aminoglycoside. Disadvantages of combination antibiotic therapy include an increased incidence of superinfection and toxicity, increased cost, and potential adverse drug interactions.

4.5. GUIDANCE IN ANTIBIOTIC USE

The rational use of antibiotics requires knowledge of their spectrum of activity, certain aspects of their pharmacokinetics, their most common side effects, and their cost as compared to agents of equal safety and efficacy. The formulations available and the palatability of each are also particularly relevant in children. The seasoned clinician will depend on a small number of antibiotics that have established reliability. The newest antibiotics are not necessarily the best, although they are often among the most expensive.

The minimum kinetic knowledge required for frequently prescribed antibiotics includes the following:

- The expected concentration of the antibiotic at the site of infection that will be attained after the selected dose. This implies knowledge of the serum concentrations attained and the diffusion characteristics of the antibiotic into infected tissue. The adequacy of the anticipated concentration of drug at the site of infection is determined by the antibiotic sensitivity pattern of the infecting bacterium.

- The half-life (t1/2) of the antibiotic. In general, antibiotics should be administered every third half-life.

- The sources of pharmacokinetic variation, knowledge of which necessitates some understanding of excretion and metabolism. If an agent is excreted primarily by the kidneys or by the liver, and the patient has compromised renal or hepatic function, the dose may have to be adjusted. Some host variables that influence the kinetics of different antibiotics are outlined in Table 13-4. The use of antibiotics in infants whose organ maturity is evolving presents a special challenge to clinicians.

5. AIM. CONCRETE TASKS. CONTROL QUESTIONS. TEST CONTROL.

AIM

To study the information about etiology, epidemiology, pathogenesis, pathophysiology, clinical manifestations, diagnosis, differential diagnosis, complications, prognosis, treatment, prevention of Tonsillitis, Diphtheria, Infectious mononucleosis.

CONCRETE TASKS

1. To study information about etiology, epidemiology, pathogenesis, pathophysiology of Diphtheria.

2. To discuss questions of clinical manifestations, diagnosis, differential diagnosis of the Diphtheria.

3. To discuss questions of complications, prognosis of the Diphtheria in children.

4. To study information about modern diagnostics of the Diphtheria in children.

5. To teach students to prescribe treatment of the Diphtheria in children.

6. To teach students to administered of antidiphtheritic serum to children with Diphtheria

7. To discuss questions of prevention of the Diphtheria in children.

8. To study information about etiology, epidemiology, pathogenesis of Infectious mononucleosis.

9. To discuss questions of clinical manifestations, diagnosis, differential diagnosis of the Infectious mononucleosis.

10. To teach students clinical peculiarities of the Infectious mononucleosis in children of the 1 st year of life.

11. To discuss questions of complications, prognosis of the Infectious mononucleosis in children.

12. To study information about modern diagnostics of the Infectious mononucleosis in children.

13. To teach students to prescribe treatment of the Infectious mononucleosis in children.

CONTROL QUESTIONS

1. Comment the terms “Diphtheria”. Ground the actuality of this problem concerning the children of the 1st year of life.

2. What is etiology of Diphtheria?

3. What do you know about epidemiology of Diphtheria?

4. What do you know about pathogenesis of Diphtheria?

5. Describe the clinical picture of Diphtheria in children.

6. What do you know about clinical and laboratory methods of investigation in diagnostics of Diphtheria?

7. Make differential diagnosis of Diphtheria and other infection diseases.

8. What do you know about complications and prognosis of Diphtheria?

9. Prescribe an adequate therapy of the Diphtheria to children.

10. Prescribe an adequate serum therapy of the Diphtheria to children.

11. What do you know about prophylaxis of the Diphtheria?

12. Comment the terms “Infectious mononucleosis”. Ground the actuality of this problem concerning the children of the 1st year of life.

13. What is etiology of Infectious mononucleosis?

14. What do you know about epidemiology of Infectious mononucleosis?

15. What do you know about pathogenesis of Infectious mononucleosis?

16. Describe the clinical picture of Infectious mononucleosis in children.

17. What do you know about clinical and laboratory methods of investigation in diagnostics of Infectious mononucleosis?

18. Make differential diagnosis of Infectious mononucleosis and other infection diseases.

19. What do you know about complications and prognosis of Infectious mononucleosis?

20. Prescribe an adequate therapy of the Infectious mononucleosis to children.

21. What do you know about prophylaxis of Infectious mononucleosis?

TEST CONTROL

Question № 1

The diphtheria carrier complained of elevating of the temperature up to $38^{O}C$, pain in a throat.

What result of a laboratory test will indicate not diphtheria carrier, but diphtheria?

A. Normal contents of specific antibodies.

B. Increase subtitle of specific antibodies in dynamics.

C. Low subtitle of specific antibodies.

D. Positive bacteriological test on BL.

E. Negative bacteriological test on BL.

Question № 2

At the child of the 8 years old, who was vaccinated against diphtheria, the diseases has an acute onset with fever up to 39-40^{o}C, weakness, headache, pain in throat. A doctor has exhibited the diagnosis quinsy.

What antibiotic is not applied for treatment of this disease?

A. Ampicillin.

B. Cephasolin.

C. Azitromicin.

D. Gentamicin.

E. Penicillin.

Question № 3

At the child of the 5 years old with clinical picture of quinsy for the 3-rd day of illness an assistant laboratory have defined 42 % atypical mononuclear cells in the general analysis of blood. A doctor diagnosed infectious mononucleosis.

Which antibiotic is contra-indicated to the patient?

A. Ampicillin.

B. Cephasolin.

C. Azitromicin.

D. Cephtriaxon.

E. Penicillin.

Question № 4

At the child of three years in the two weeks is marked fever up to 38,5-39^{o}C, congested nose, weakness. Objectively: lacunar quinsy, enlarged lymph nodes, a liver + 5sm, a lien+ 8 sm.

What disease is most probably?

A. Acute lycemia.

B. Infectious mononucleosis.

C. Acute lympholycemia.

D. Diphtheria.

E. Adenoviral infection.

Question № 5

In a kindergarten at the child a doctor diagnosed epidemic parotitis.

What from the transferred measures are necessary for conducting after isolation of the patient?

A. To impose quarantine in group of a children's garden for 21 days.

B. To conduct final disinfection.

C. To impose quarantine for all children's garden for 21 days

D. To give gammaglobulin to contact persons.

E. To immunized contact persons by a vaccine.

Question № 6

The child of the 6 years sick in 3 days. An intoxication is considerable, the fibrinosis membranes are grayish-white, located on the tonsils, an edema of the neck.

The diagnosis "Diphtheria of the tonsils. Widespread several form.” What doze of antidiphtheritic serum is requisite to the patient?

A. 50 thousand units

B. 80 thousand units

C. 120 thousand units

D. 250 thousand units

E. 300 thousand units

Question № 7

The child up to 10 months wasn’t vaccinated of the APDT. From 10 months he was vaccinated three times (in 10, 11, 12 months).

When is it necessary to conduct revaccination?

A. At the age of 1,5 years.

B. At the age of 2 years.

C. At the age of 2,5 years.

D. Revaccination is not conducted.

E. At the age of 5 years

Question № 8

The child of the 12 years was ill acutely with increase of temperature up to 40^{o}C, pain in a throat, weakness, edema of neck. Objectively: several intoxication, congestive hyperemia, grayish-white, wide-spread, cannot be removed membranes on tonsils, enlarged and painful cervical lymph nodes, edema of neck to the clavicles. It has been suspected diphtheria.

What laboratory investigation will confirm the diagnosis?

A. Bacteriological test on BL.

B. Hemoculture.

C. Bacterioscopy of mucous.

D. Blood test.

E. Response of Paul-Bunuel.

Question № 9

At the child of the 6 years within a week: temperature 37,5-38,0^{o}C, weakness, pain in a throat. Objectively: moderately toxicosis, lacunar tonsillitis, hepatosplenomegalia, polyadenopatia. Is suspected infectious mononucleosis.

What minimum quantity of the atypical mononuclear in blood test will confirm this diagnosis?

A. More than 5%.

B. More than 10%.

C. More than 20%.

D. More than 30%.

E. More than 40%.

Question № 10

The child of the 4 years has been admitted to the hospital for 4 day from a beginning of disease. He was treated of the erythromycin concerning quinsy. He was vaccination with APDT vaccine. Bacteriological test: is selected C. diphtheria gravis, toxigen culture. Objectively: a common state is satisfactory. In oropharigeas - moderate hyperemia of mucous membrane, membranes are not present.

What doze of the ADS is necessary to prescribe to the patient?

A. 50 thousand unitis.

B. 80 thousand unitis.

C.ADS is not introduced.

D. 120 thousand unitis

E. 250 thousand unitis

Question № 11

At the child of the 11 years: the temperature is 38-39^{o}C, weakness, pain in a throat. Objectively: bright hyperemia of mucous membrane, hypertrophia of the tonsils, yellowish-white liquid pus in lacunas are removed easily, enlarged of cervical lymph nodes.

Your preliminary diagnosis is:

A. Tonsillar diphtheria.

B. Necrotic tonsillitis.

C. Lacunar tonsillitis.

D. Infectious mononucleosis.

E. Simanosky-Vincent’s diseases.

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