ZOONOTIC AND PERCUTANEOUS INFECTIOUS DISEASES

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ZOONOTIC AND PERCUTANEOUS INFECTIOUS DISEASES

Textbook for Vth year medical student

ЗООНОЗНЫЕ И ПЕРКУТАННЫЕ ИНФЕКЦИОННЫЕ БОЛЕЗНИ

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Зоонозные и перкутанные инфекции: Учебное пособие для иностранных студентов медицинских вузов / В.Н. Козько, Д.В. Кацапов, А.В. Бондаренко и др. – Харьков: ФОП Воронюк В.В., 2016. – 188 с.

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

Материал, представленный в учебнике, посвящен фундаментальным вопросам зоонозных и перкутанных инфекционных болезней (этиологии, эпидемиологии, патогенеза, клиники, лечения). Учебник рекомендован для студентов медицинских ВУЗов и интернов.

INTRODUCTION

Over the past couple of decades the advent of relatively cheap air travel has meant that many millions of people travel every year for work or pleasure. Increasingly, many people from developed countries go to live and work for prolonged periods in less well-developed areas of the world. This increased movement around the globe has important health implications. Not only are individuals risking the acquisition of new diseases in endemic areas but physicians everywhere must be aware of the possibility of imported diseases with which they may be unfamiliar.

There are large numbers of zoonotic diseases that can potentially affect people which are caused by a wide variety of bacteria, parasites, viruses, and fungal organisms. People may become infected by a number of different routes.

Poor sanitary habits may lead to the ingestion of small amounts of animal waste products and transmission of zoonotic disease. Fecal waste is a source of many bacterial and parasitic infections. Ingestion of undercooked food products, skin contact with infectious agents, and bite wound or scratches are all potential modes of zoonotic transmission. Many zoonotic diseases are not directly transmitted from animals to people, but they require an intermediate host (a vector); such as, a flea or a tick, for transmission to occur.

Actuality of studies of zoonotic and percutaneous infectious diseases is conditioned the high level of their morbidity in the many countries, by an unfavorable situation in the world, by high migration of population, development of tourism, appearance of «emerging» infections, by wide international copulas, heavy course with possible complications and sometimes high lethality.

A textbook is intended for preparation of foreign students V year of studies with the English-language form of teaching of cycle «infectious diseases» on the department of infectious diseases. Edition of manual is designed taking into account the program of studies after ECTS.

In a textbook there is modern information of world science is systematized and generalized for most actual zoonotic and to percutaneous infections of human of viral and bacterial nature. Especially dangerous infections, which present the real threat of delivery in any country of the world, are examined in particular; plaque, tularemia and smallpox, an epidemiology situation in relation to which remains very tense in a number of countries of Torrid Zone.

TICK-BORNE ENCEPHALITIS

Tick-borne encephalitis (TBE) is a viral infectious disease of the central nervous system. The disease most often manifests itself as meningitis, encephalitis, or meningoencephalitis. Although tick-borne encephalitis is most commonly recognized as a neurological disorder, mild fever can also occur. Long-lasting or permanent neuropsychiatric sequelae are observed in 10-20% of infected patients.

ETIOLOGY

TBE is caused by tick-borne encephalitis virus of the genus Flavivirus in the family Flaviviridae. This is RNA-virus, covered by protein membrane. It was first discovered in 1937. This virus often develops in chickens' embryos and in the different cell cultures. Virus is infirm to high temperature and different physical and chemical agents.

EPIDEMIOLOGY

TBE is a typical seasonal natural-focal transmissive infection. Ticks are the main carriers of TBE virus. The tick becomes infected in 6-7 days after sucking on the blood of infected organisms (different types of mammals, such as squirrels, moles, porcupines, rats, field mice and also a man). This virus gets situated in the lymphatic system of a tick. Then they spread and concentrate in the sexual organs and salivary glands. Viruses are preserved during the entire life of a tick (up to 4 years).

The virus is maintained in nature by small mammals (such as mice and voles), domestic livestock (including sheep, goats and cattle) and certain species of birds. The infection of such ticks often happens through wild mammals. A simple way of an infection transmission of the TBE is use of unboiled goat or cow milk.

The morbidity has seasonal Character (May-June). Thousands of cases of TBE occur each year from late spring to early autumn. The number of reported cases has been increasing in most countries. Russia and Europe report about 5,000-7,000 human cases annually.

There are three subtypes of TBE:

- Western subtype, (or Central European encephalitis) transmitted by Ixodes ricinus ticks. This subtype is found in the forested areas of Central, Eastern and Northern Europe.
- Far Eastern subtype, (or Russian Spring/Summer encephalitis) transmitted by Ixodes persulcatus ticks. This subtype is found in former USSR, east of the Ural Mountains, and also in areas of China and Japan.
- Siberian subtype, transmitted by Ixodus persulcatus ticks, which is found in Siberia.

The risk of acquiring TBE infection is dependent on a number of factors including:

- destination
- duration of travel in a risk area
- time of travel
- activities undertaken
- tick activity in the endemic country
- vaccination status of traveller

Travellers to the endemic areas may be at risk when walking, camping or working in woodland terrain where they will be exposed to the tick carriers. Infection may also be acquired by consuming unpasteurized dairy products from infected animals.

PATHOGENESIS

Infection occurs mostly through the skin and intestinal mucous membrane. Virus enters into the lymphatic nodes, internal organs and central nervous system. Viruses multiply in the cells of the central nervous system. The virus causes the degeneration of the cells, multiplies in the mesenchymal cells and results in inflammation. The inflammatory process is mainly concentrated in the gray matter of the brain and spinal cord, especially the motile neurons of the brain and cervical part of the spinal cord. The middle brain, thalamus, hypothalamus and cerebellum are also infected during the process.

CLINICAL MANIFESTATIONS

The incubation period is 7-14 days, at times anywhere from 2 to 28 days. The onset of the disease is an rapid, with high temperature till 40,0-41,0°C. It is characterized by a non-specific flu-like illness with fatigue, headache, body ache, nausea, general malaise, pains in the loin and fever. The typical course of TBE is biphasic.

Also hyperemia of the face, neck, chest and conjunctivitis does happen, including the decreased arterial pressure, bradycardia, muffed heart tones.

There are 5 principal forms of the disease:

Feverish form of TBE is characterized by the development of general toxic syndrome.

Meningeal form is characterized by development of general toxic syndrome and signs of serous meningitis. The severe headache, fever, vomiting occur. The meningeal signs are revealed: rigidity of occipital muscles, Brudsyndsky's symptoms, Kernig's symptom. In cerebrospinal puncture the increased of pressure of cerebrospinal fluid is noted. Cerebrospinal fluid test indicate lymphocytic pleocytosis, an increase of protein, sugar and chlorides.

Meningoencephalitic form is accompanied by local diffusive disorder of the brain. The disruption of the consciousness is observed. The gravity of the state increases due to progress of edema of the brain: from light soporosic state till deep coma. The hallucinations, delirium, psychomotor excitement and cramps of skeletal muscles are marked. Thus, the damage of the white substance of the cerebral brain, spastic paralysis and pareses of the extremities may arise depending on the localization of the pathological processes and damages of the cranial nerves, also disorder of the speech. The violation of the eye's innervations (diplopia, ptosis, squint), bulbar syndrome (dysphonia, dysarthria, dysphagia) and damages of the nucleus of the cranial nerves may be observed.

Meningoencephalopolyomyelitic form is characterized by general toxic, meningeal symptoms and signs of diffusive local encephalitis and damage of gray matter of a spinal cord. The flabby paresis develops on 3rd or 4th day of the disease. Subsequently develops the atrophy of the muscles of the neck, shoulder belt and hands. The volume of the movement of the upper extremities is harshly limited, till full loss of the functions. In rare cases, the injuries of the lower extremities may also be, with disruption of the functions of the pelvic organs.

Polyradicyloneurotic form of TBE is manifested by general toxic, meningeal symptoms and signs of the damage of the peripheral nerves.

Depending on the severity of the disease the next types of TBE are differenced:

1. Light form
2. Moderate form
3. Severe form with high lethal rate.

The clinical course of TBE disease is largely determined by the virus subtype. The Far Eastern subtype is generally more virulent, tending to lead to paresis, and is associated with a higher mortality (approximately a 5 - 20% case fatality compared to 1 - 2% for the European subtype). There is currently little information on the virulence of the more recently described Siberian subtype.

DIAGNOSIS

TBE should be suspected in travelers who develop a nonspecific febrile illness that progresses to neuroinvasive disease within 4 weeks of arriving from an endemic area. A history of tick bite may be a clue to this diagnosis; however, approximately 30% of TBE patients do not recall a tick bite.

In the clinical analysis of blood marked neutrophilic leukocytosis with shift of the formula to the left, increased ESR are observed. In cerebrospinal puncture the increased of pressure of cerebrospinal fluid is noted. Cerebrospinal fluid tests show the lymphocytic pleocytosis, increase of protein, sugar and chlorides ar.

The isolation from blood and cerebrospinal fluid and culture on chicken embryos and epithelial buds are used. Viral antigen can usually be found in brain

tissue. Serological testing can also be performed with a reaction complement fixation, indirect hemagglutination, neutralization and ELISA. IgM-capture ELISA performed on serum or cerebrospinal fluid is virtually always positive during the neuroinvasive phase of the illness.

TREATMENT

The specific treatment of TBE is performed with help of antiencephalitic donor's gammaglobulin, which is injected in a dose of 5-10ml intramuscularly during 3 days. There is no specific antiviral treatment for TBE; therapy consists of supportive care and treatment of aggravations.

The pathogenetic therapy plays important role. The desintoxication, dehydration, sedative remedies, hyperbaric oxygenation and artificial ventilation of the lungs are used. Symptomatic brain damage requires hospitalization and supportive care based on syndrome severity. Anti-inflammatory drugs, such as corticosteroids, may be considered under specific circumstances for symptomatic relief.

PREVENTION

Prevention includes non-specific (tick-bite prevention, tick checks) and specific prophylaxis (vaccine, TBE immunoglobulin). TBE vaccine is very effective and available in some disease endemic areas.

The risk of acquiring TBE can be reduced by insect bite avoidance methods. Travellers should be advised to:

- Wear clothing with long sleeves and long trousers (tucked into socks), which can be treated with insecticide sprays such as permethrin.
- Apply insect repellent to exposed skin.
- Check the body for ticks regularly. After a tick has attached itself to the host it may not start feeding for 12 hours. The larval form of Ixodes ticks are tiny and difficult to see. Adult ticks, once they have fed and become engorged, may be the size of a coffee bean. Common areas for ticks to attach are at the hair-line, behind the ears, elbows, backs of knees, groin and armpits.
- Remove ticks as soon as possible by using a pair of tweezers or tick remover. The tweezers should be placed as close as possible to the skin and then the tick pulled slowly, ensuring the mouth parts are removed completely. Evidence suggests that slow, straight method is best for removal without leaving the mouthparts. Care needs to be taken not to squeeze the stomach contents into the site of the bite.
- Travelers should also avoid consumption of un-pasteurized dairy products in areas of risk.

TBE vaccination is available for those travelers intending to visit rural endemic areas, or whose occupation may put them at higher risk. Vaccination against TBE is

considered to be the most effective means of preventing TBE for those living in endemic countries. The vaccine has been used in national vaccination campaigns in Austria since 1982 and has continued on an annual basis since. There is also widespread use of TBE vaccine in many other central European countries. Vaccine should be considered for travelers to endemic areas.

The vaccine is injected subcutaneously in a dose of 1,0 ml three times with interval 3-4 months. The revaccination is performed one time every year (1,0 ml vaccine, subcutaneously).

EHRLICHIOSIS and ANAPLASMOSIS

Ehrlichiosis and Anaplasmosis are groups of tick-borne bacterial infections in humans and mammals, caused by intracellular pathogens – bacteria of the family Anaplasmataceae, genera Ehrlichia and Anaplasma, and are characterized by the development of general infectious intoxication syndrome and a specific lesion of white blood cells.

ETIOLOGY

Ehrlichia and Anaplasma species, members of the family Rickettsiae, are gram-negative, obligate, intracellular coccobacilli that resemble Rickettsia species. All 3 are forms of Alphaproteobacteria.

Like Rickettsia, Ehrlichia organisms gain access to the blood via a bite from an infected tick. A. americanum is the principle tick carrier of E chaffeensis and is the primary a carrier of human monocytic ehrlichiosis. A phagocytophilum may be transmitted from Ixodes persulcatus ticks and possibly Dermacentor variabilis (dog tick/wood tick).

Five species have been shown to cause human infection:

- Anaplasma phagocytophilum (which causes human granulocytic anaplasmosis). A. phagocytophilium is endemic to New England and the north central and Pacific regions of the United States.
- Ehrlichia ewingii (which causes human ewingii ehrlichiosis). E. ewingii primarily infects deer and dogs.
- Ehrlichia chaffeensis (which causes human monocytic ehrlichiosis). E. chaffeensis is most common in the south central and southeastern states.
- Ehrlichia canis
- Neorickettsia sennetsu

The latter two infections are not well studied.

Ehrlichia/Anaplasma are tiny (0.2-2 μm) obligate, intracytoplasmic, gram-negative organisms that resemble Rickettsia; divide by binary fission; and multiply within the cytoplasm of infected white blood cells. Clusters of Ehrlichia multiply in host monocyte vacuoles (phagosomes) to form large, mulberry-shaped aggregates called morulae. Ehrlichia inclusion bodies, such as morulae, are visible in the cytoplasm of infected mononuclear phagocytic cells after 5-7 days. The type of ehrlichiosis that develops varies and depends on the infecting species and the type of leukocyte infected. Human granulocytic anaplasmosis, formerly known as human granulocytic ehrlichiosis, is caused by Anaplasma phagocytophilum, which infect granulocytes. In contrast, human monocytic ehrlichiosis is caused by Ehrlichia chaffeensis, which infects monocytes.

Characteristics of HME and HGA

	Human monocytic ehrlichiosis (HME)	Human granulocytic anaplasmosis (HGA)
Affected cells	Monocytes	Granulocytes
Organism	E chaffeensis	A phagocytophilum
Carrier	Amblyomma americanum (Lone Star tick)	Ixodes scapularis (black-legged tick), Ixodes pacificus (Western black-legged tick) in California, Ixodes ricinus in Europe, and probably Ixodes persulcatus in parts of Asia
Rash	30% of adults, 60% of children	Rare
Prognosis	~3% mortality	< 1% mortality

The primary target cell for HME is the macrophage, and the primary target for human granulocytic anaplasmosis is the granulocyte. Intracellular infection is established within phagosomes, most often found in macrophages of the liver, spleen, lymph nodes, bone marrow, lung, kidney, and central nervous system.

EPIDEMIOLOGY

Ehrlichiosis (anaplasmosis) occurs essentially worldwide, and the frequency parallels the distribution of the appropriate tick carriers for the transmission of Ehrlichia bacteria and the mammalian hosts. Ehrlichiosis is a seasonal disease observed mainly from April to September.

Ehrlichia sennetsu causes a mononucleosis-like illness in Japan and Malaysia. The distribution of ehrlichiosis in the United States mirrors the tick distribution and appropriate mammalian carriers (e.g., white-footed mouse, white-tailed deer). Ehrlichiosis occurs where mammalian hosts are in contact with the appropriate tick carrier (i.e., A americanum, D variabilis, Ixodes ticks).

The rates of HME and HGA are higher in males than in females, most likely due to a higher rate of participation in high-risk outdoor activities among males.

The incidence rates per 100,000 for males were 0.26 for HGA and 0.24 for HME. For females, the rates were 0.19 for HGA and 0.16 for HME.

Ehrlichiosis (anaplasmosis) is reported more frequently in adults than in children. The highest age range is between 40 and 64 years.

Ehrlichiosis (anaplasmosis) is an infection of white blood cells that affects various mammals, including mice, cattle, dogs, deer, horses, sheep, goats, and humans.

PATHOGENESIS

Infection occurs through the saliva of an infected tick. Gateway is a skin infection in a place of a tick bite, which may be a primary affect. Also known isolated cases of human infection due to transfusion of blood products and surgical interventions.

The major antigenic determinants of Ehrlichia are surface membrane proteins. These antigenic proteins are complex and consist of thermolabile and thermostable components. In terms of kilodalton (kd) molecular weight, the key protein bands associated with HME are the 27-, 29-, and 44-kd bands. The major antigenic determinants associated with HGA include the 40-, 44-, and 65-kd bands.

From the penetration agent lymphatic enters the bloodstream, affecting tropic cells: often - monocytes, granulocytes, macrophages, vascular endothelium, Kupfer cells. Pathogen affects the tissues and organs rich in phagocytic cells (spleen, lymph nodes, bone marrow, blood vessels and lungs).

Found profound cellular damage and the formation of an infectious granuloma. Depending on the type of infected blood cells rather arbitrarily distinguished two forms erlichial infections: human monocytic ehrlichiosis, with a characteristic lesion of monocytes and macrophages, and human granulocytic ehrlichiosis, reproduction of pathogens, mainly in granulocytes (neutrophils, eosinophils, etc.).

Clinically the disease manifests general infectious intoxication syndrome (fever, chills, headache, dizziness, myalgia, arthralgia, loss of appetite, nausea, vomiting, general weakness, etc.). In patients observed signs of violations rheological characteristics of blood (leykotsytopeniya, thrombocytopenia, lymphocytosis, monotsytopeniya, leukocyte shift to the left, rising ESR) and the influence on the liver (increasing its size, increased transaminases, alkaline phosphatase, etc.).

CLINICAL MANIFESTATIONS

Clinical manifestations of ehrlichiosis (anaplasmosis) usually begin 5-14 days after the tick bite. Approximately 68% of patients with human monocytic ehrlichiosis report a tick bite, and 83% of patients have a history of tick exposure in the 4-week period before onset of symptoms. Onset is abrupt or subacute.

The histories for HME, human granulocytic anaplasmosis, and human monocytic ehrlichiosis are similar and may include the following: tick bites or exposure (>90% in 1 series), fevers (>90%), headaches (>85%), malaise (>70%), myalgias (>70%), rigors (60%), nausea (40%), vomiting (40%), anorexia (40%), confusion (20%).

Rash is rare in patients with HME/HGA. However, if rash is present, it usually occurs on the chest, legs, arms, or face and may be macular, maculopapular, and/or petechial. Rash on the palms or the soles is very rare.

Physical findings due to ehrlichiosis (anaplasmosis) are minimal. Splenomegaly

is not uncommon, and some patients develop hepatomegaly. Lymphadenopathy is very uncommon. Patients with severe ehrlichiosis may develop thrombocytopenia or disseminated intravascular coagulation, which can result in purpura.

Complications of ehrlichiosis (anaplasmosis) include the following: renal failure, respiratory failure, coagulopathy, myocarditis, encephalopathy, and coma.

Ehrlichiosis carries an excellent prognosis in healthy hosts. A favorable outcome is associated with the early use of antibiotics. The mortality rate for human monocytic ehrlichiosis is reported to be 2-5%, while that for HGA is 7-10%.

Elderly patients (>60 y) are more likely than others to develop severe infections and account for most deaths due to ehrlichiosis (anaplasmosis). In addition, ehrlichiosis may be severe in immunocompromised hosts, manifesting as a Rocky Mountain spotted fever – like illness that may be fatal.

The great majority of cases of ehrlichiosis are asymptomatic. Most cases present as mild-to-moderate acute febrile illnesses, but some cases are severe/life threatening. HME has a reported hospitalization rate as high as 60%, while that for HGA is 28-54%.3% of human monocytic ehrlichiosis cases result in death, however these deaths occur "most commonly in immunosuppressed individuals who develop respiratory distress syndrome, hepatitis or opportunistic nosocomial infections.

DIAGNOSIS

The diagnosis of human monocytic ehrlichiosis or human granulocytic anaplasmosis rests on a single elevated immunoglobulin G (IgG) immunofluorescent antibody (IFA) Ehrlichia titer or demonstration of a 4-fold or greater increase between acute and convalescent IFA Ehrlichia titers.

Ehrlichiosis (anaplasmosis) may also be diagnosed by demonstrating characteristic morulae in the cytoplasm of leukocytes. Morulae are diagnostic of ehrlichiosis and occur more frequently in HGA than in HME. The microbiology laboratory should be alerted to look carefully in the blood smear for them.

The infecting organism is extremely difficult to culture from blood. Detection of the organism with polymerase chain reaction (PCR) assay is possible.

A complete blood cell (CBC) count should be obtained for possible neutropenia, relative lymphopenia, and/or thrombocytopenia. Anemia is not a feature of ehrlichiosis and, if present, is not a hemolytic anemia, as in babesiosis.

Atypical lymphocytes have been reported in patients with ehrlichiosis. The erythrocyte sedimentation rate is minimally/moderately elevated in ehrlichiosis.

Elevated C-reactive protein (CRP) levels are common in the first week of illness and typically resolve by the end of the second week.

Serum transaminases should be evaluated, because they are frequently mildly elevated in ehrlichiosis, as well as in other tick-borne infectious diseases. Abnormal liver enzymes are found in 86% of patients.

DIC may be diagnosed in patients with a cutaneous bleeding diathesis who have thrombocytopenia and in whom schistocytes are observed in the peripheral smear.

If other infectious diseases are suspected, appropriate tests should be obtained to rule out these diagnoses. If co-infection with Rocky Mountain spotted fever or babesiosis is suspected, appropriate serology should be obtained to diagnose each of these infectious diseases.

Microscopic examination (by an experienced microbiologist) of blood smears stained with eosin-azure type dyes, such as Wright-Giemsa stain, may reveal morulae in the cytoplasm of leukocytes. More than 20% of patients with HME and 20-80% of patients with HGA may demonstrate this in the first week of infection. A negative result should not be taken as proof of noninfection.

Hyponatremia (< 130 mEq/L) is found in 40% of patients.

DIFFERENTIAL DIAGNOSIS

Ehrlichiosis (anaplasmosis) is a difficult infectious disease to diagnose because it manifests as an acute, undifferentiated, febrile, Rocky Mountain spotted fever-like illness with few or no physical findings. Most patients who are diagnosed with Rocky Mountain spotted fever without rash probably have ehrlichiosis. Co-infections of various tick-borne pathogens transmitted by the same carrier are rare, but they do occur.

Ehrlichiosis has the same distribution as Rocky Mountain spotted fever and is transmitted by the same tick species (e.g., Amblyomma, Dermacentor). However, Rocky Mountain spotted fever causes physical findings that ehrlichiosis does not, including bilateral periorbital edema, edema of the dorsum of the hands and feet, and conjunctival suffusion. The petechial rash of Rocky Mountain spotted fever is absent in ehrlichiosis.

Laboratory findings associated with Rocky Mountain spotted fever and ehrlichiosis are similar (e.g., thrombocytopenia, relative lymphopenia, increased levels of serum transaminases, atypical lymphocytes). However, neutropenia is more common in ehrlichiosis than in Rocky Mountain spotted fever.

Most patients with ehrlichiosis (anaplasmosis) present with fever and a severe headache but do not have nuchal rigidity, as opposed to patients with aseptic or bacterial meningitis. The cerebrospinal fluid profile in patients with ehrlichiosis (anaplasmosis) is normal, in contrast to patients with viral or bacterial meningitis.

Other differential diagnostic possibilities include Lyme disease, typhoid fever, malaria, and babesiosis. All of these infectious diseases manifest as acute, undifferentiated, febrile illnesses with a paucity of physical signs. The diagnosis of typhoid fever and malaria are suggested by an appropriate epidemiologic profile and/or travel history. Exposure to large Dermacentor ticks would suggest Rocky Mountain spotted fever, whereas exposure to small Ixodes ticks would suggest the

possibility of babesiosis.

TREATMENT

Doxycycline is the drug of choice. For people allergic to drugs of the tetracycline class, rifampicin is an alternative. Early clinical experience suggested that chloramphenicol may also be effective, however in vitro susceptibility testing revealed resistance.

Scheme causal therapy in patients with ehrlichiosis

Antibiotic	Dose		Duration of therapy
	Adults	Children under 14 years	
Doxycycline	100 mg orally every 12 hours	2.5 mg / kg orally every 12 hours	5-14 days
Tetracycline hydrochloride	500 mg orally every 6 hours	6,25-12,5 mg / kg orally every 6 hours	5-14 days
Rifampicin (ryfampin)	300 mg orally or by injection every 12 hours	10 mg / kg orally or by injection every 12 hours	7-10 days

In carrying out antibiotic ehrlichiosis (anaplasmosis) usually the body temperature returns to normal after 1-2 days, but the causal treatment is recommended to continue for 3 days after lowering of the temperature.

PREVENTION

Educate patients in endemic ehrlichiosis (anaplasmosis) areas to take proper precautions when traveling through wooded and/or tick-infested areas.

Prevention of ehrlichiosis (anaplasmosis) includes the following: wear light-colored clothes, tuck pants into socks, use insect repellent, regularly examine the body for ticks.

After returning from wooded and/or tick-infested areas, individuals should check themselves carefully for ticks. If found, ticks should be removed carefully and a physician should be consulted.

After removal, the skin should be disinfected. Check to make sure that the tick head is not still embedded.

Some have recommended keeping the tick in a jar along with a damp paper towel in the refrigerator for a month or so, in case symptoms develop, as it may help to identify what (if any) infection has been transmitted.

BORRELIOSIS

Borreliosis (Lyme disease) is an emerging tick-transmitted spirochetal disease, caused by bacteria belonging to the genus Borrelia, characterized in early stage by symptoms of intoxication and a characteristic skin rash – erythema migrans (EM), in disseminated stage by secondary annular skin lesions, meningitis, cranial or peripheral neuritis, carditis, atrioventricular nodal block, or migratory musculoskeletal pain and in a later stage by intermittent or chronic arthritis, chronic encephalopathy or polyneuropathy, acrodermatitis.

ETIOLOGY

Borrelia species, the causative agents of the disease, are fastidious, microaerophilic bacteria. The structure of borrelia species, including B. burgdorferi, is similar to that of all spirochetes: distinct bacteria that have a unique mode of motility by means of axial filaments (endoflagella). The spirochetes have a unique cell surface which accompanies their unique type of motility. The endoflagella are contained within the periplasmic space between a semi rigid peptidoglycan helix and a multi-layer, flexible outer membrane sheath. When the filaments rotate within this space, the spirochetes move in cork-screw fashion. This type of movement is thought to be an adaptation to viscous environments, such as aquatic sediments, biofilms, mucosal tissues and the intestinal tracts of animals. For pathogens, this allows the spirochetes to hide their flagella, which are normally antigenic, from the host immune defenses.

The genome of B. burgdorferi (strain B31) is quite small (approximately 1.5 megabases) and consists of a highly unusual linear chromosome of 950 kilobases as well as 9 linear and 12 circular plasmids. The remarkable aspect of the B. burgdorferi genome is its large number of sequences for predicted or known lipoproteins, including the plasmid-encoded outer-surface proteins (Osp) A through F. These and other differentially expressed Osp presumably help the spirochete adapt to and survive in markedly different arthropod and mammalian environments. In addition, during early, disseminated infection, a surface-exposed lipoprotein, called VlsE, has been reported to undergo extensive antigenic variation. The organism has few proteins with biosynthetic activity and apparently depends on the host for most of its nutritional requirements. The genome contains no homologues for systems that specialize in the secretion of toxins or other virulence factors. The only known virulence factors of B. burgdorferi are surface proteins that allow the spirochete to attach to mammalian cells.

The spirochetes are not classified as either Gram-positive or Gram-negative. When Borrelia burgdorferi is Gram-stained, the cells stain a weak Gram-negative by default, as safranin is the last dye used. Borrelia, like most spirochetes, does have an

outer membrane that contains a lipopolysaccharide-like substance, an inner membrane, and a periplasmic space which contains a layer of peptidoglycan. Therefore, it has a Gram-negative bacterial type cell wall, despite its staining characteristics.

EPIDEMIOLOGY

Borreliosis is classified as a zoonosis, as it is transmitted to humans from a natural reservoir among rodents by ticks that feed on both sets of hosts. Hard-bodied ticks of the genus Ixodes are the main vectors of Lyme borreliosis. And the distribution of Borreliosis correlates closely with the geographic ranges of certain ixodid ticks Ixodes dammini (also called I. scapularis, the black-legged tick or deer tick), I. pacificus, I. ricinus, (also called the sheep tick or castor bean tick) and I. persulcatus (the taiga tick). I. dammini is the principal vector in the northeastern states and I. pacificus is the vector in the western United States. In Europe the vector is Ixodes ricinus. The highest reported frequencies of the disease are in middle Europe and Scandinavia, particularly in Germany, Austria, Slovenia, and Sweden. The infection is also found in Russia and Ukraine.

These ticks have larval, nymphal, and adult stages; they require a blood meal at each stage. The risk of infection in a given area depends largely on the density of these ticks. The Ixodes tick has a two-year life cycle, first progressing from larva to nymph, and then from nymph to adult. During the spring, the ticks lay their eggs. The Ixodes tick is born as a larval tick in the summer and feeds only once. In the fall, large acorn forests attract tick as well as mice, chipmunks and other small rodents infected with B. burgdorferi, thus the larvae acquire infection from the rodents. At this stage, tick infestation may be controlled using acaricides (miticides). Its preferred host is the common field mouse, but other animals apparently suffice. The following spring, it becomes a nymph and again feeds only once, with its preferred host again being the field mouse. In the fall, the nymph becomes an adult and feeds a single time.

After feeding, female adult ticks lay their eggs on the ground, and the cycle is complete. Thus, unless the tick feeds on an infected host before feeding on a person, infection cannot result from that tick bite. Even if a tick feeds on an infected animal, it may not acquire the infection. Mice do not appear to develop Borreliosis, but they do carry the bacteria. They may be considered infested rather than infected.

Not all strains of mice continue to carry the bacteria after exposure to B. burgdorferi. As mice mature, they may be less able to sustain a B. burgdorferi bacteremia. Even when they are exposed to the bacteria, they do not remain carriers for extended periods. Other animals are even poorer hosts for B. burgdorferi.

Most infections are caused by ticks in the nymphal stage (85%) of the time (spring to summer) and the adult stage 15% of the time (fall). Thus, for many

reasons, only approximately 1% of all tick bites occurring in an endemic area result in Borreliosis. Larval ticks are very rarely infected. Tick bites often go unnoticed because of the small size of the tick in its nymphal stage, as well as tick secretions that prevent the host from feeling any itch or pain from the bite.

Lyme spirochetes have been found in semen and breast milk, however transmission of the spirochete by these routes is not known to occur. Congenital transmission of Borreliosis can occur from an infected mother to fetus through the placenta during pregnancy. The risk for fetal harm is much higher in the first three months of pregnancy than later. Prompt antibiotic treatment almost always prevents fetal harm. Persons of all ages and both sexes are affected.

Cases have occurred in association with hiking, camping, or hunting trips and with residence in wooded or rural areas. Urbanization and other anthropogenic factors can be implicated in the spread of Borreliosis to humans. In many areas, expansion of suburban neighborhoods has led to the gradual deforestation of surrounding wooded areas and increasing border contact between humans and tick-dense areas. Human expansion has also resulted in a gradual reduction of the predators that normally hunt deer as well as mice, chipmunks and other small rodents – the primary reservoirs for Borreliosis. As a consequence of increased human contact with host and vector, the likelihood of transmission to Lyme residents has greatly increased. Researchers are also investigating possible links between global warming and the spread of vector-borne diseases including Borreliosis.

PATHOGENESIS

B. burgdorferi is injected into the skin by the bite of an infected Ixodes tick. Once feeding begins, the bacteria then multiply in the gut of the tick. The bacteria then migrate to the salivary glands of the tick after 2-3 days. There, they are injected into the animal or human by the tick as it ends its feeding. Until this multiplication occurs, ticks are rarely able to pass on the infection.

Tick saliva, which accompanies the spirochete into the skin during the feeding process, contains substances that disrupt the immune response at the site of the bite. This provides a protective environment where the spirochete can establish infection. The spirochetes multiply and migrate outward within the dermis.

The host inflammatory response to the bacteria in the skin causes the characteristic circular EM lesion. However neutrophils, which are necessary to eliminate the spirochetes from the skin, fail to appear in the developing EM lesion. This allows the bacteria to survive and eventually spread throughout the body. The spirochete can adhere to many types of mammalian cells. If untreated, the bacteria may persist in the body for months or even years, despite the production of anti-B. burgdorferi antibodies by the immune system. Spirochetal lipoproteins, which bind the CD14 molecule and toll-like receptor 2 on macrophages, are potent activators of

the innate immune response, leading to the production of macrophage-derived inflammatory cytokines. In humans, infiltrates of macrophages and T-cells in EM lesions express messenger RNA for both inflammatory and anti-inflammatory cytokines. Particularly in disseminated infection, adaptive T-cell and B-cell responses in lymph nodes lead to the production of antibody against many components of the organism. Despite the innate and adaptive immune responses, B. burgdorferi may sometimes survive in certain sites. The infiltrates of T-cells and macrophages in these lesions had a restricted cytokine profile, with little or no production of interferon, which may explain in part why the immune response is ineffective in eradicating the spirochete.

Days to weeks following the tick bite, the spirochetes spread via the bloodstream to joints, heart, nervous system, and distant skin sites. A number of mechanisms may aid in the dissemination of B. burgdorferi. For example, the sequences of OspC vary considerably among strains, and only a few of the groups of sequences are associated with disseminated disease. Spread within the host is probably facilitated through binding to the spirochete's surface by human plasminogen and urokinase-type plasminogen activator, which activates plasmin, a potent protease. Borrelia decorin-binding proteins A and B bind decorin, a glycosaminoglycan on collagen fibrils, which may explain why the organism is commonly aligned with collagen fibrils in the extracellular matrix in the heart, nervous system, or joints.

Inflammatory innate immune responses are critical in the control of early, disseminated infection. The immune response in Borreliosis develops gradually. After the first several weeks of infection, mononuclear cells generally exhibit heightened responsiveness to B. burgdorferi antigens, and evidence of B-cell hyperactivity is found, including elevated total serum IgM levels, cryoprecipitates, and circulating immune complexes. Titers of specific IgM antibody to B. burgdorferi peak between the third and sixth week after disease onset. The specific IgG response develops gradually over months, with response to an increasing array of 12 or more spirochetal polypeptides and maximal expansion during the period of arthritis. The spirochete is a potent inducer of proinflammatory cytokines, including tumor necrosis factor and interleukin 1.

Autoimmunity may develop within the inflammatory milieu of affected joints in these patients because of molecular mimicry between an immunodominant T-cell epitope of OspA of B. burgdorferi and human-lymphocyte-function-associated antigen 1 (hLFA-1), an adhesion molecule that is highly expressed on T-cells in synovium. T-cells that react to OspA are concentrated in the joints of these patients. When hLFA-1 is processed and presented by the HLA-DRB1*0401 molecule, this self-peptide may behave as a partial agonist for such cells. However, it may not be the only relevant autoantigen in treatment-resistant Lyme arthritis. Lyme arthritis is

associated with certain immunological factors, including the production of proinflammatory cytokines and the formation of immune complexes, and also genetic factors, such as human leukocyte antigen (HLA)–DR4 and HLA-DR2.

B. burgdorferi may induce astrocytes to undergo astrogliosis (proliferation followed by apoptosis), which may contribute to neurodysfunction. The spirochetes may also induce host cells to secrete products toxic to nerve cells, including quinolinic acid and the cytokines IL-6 and TNF-alpha, which can produce fatigue and malaise. Both microglia and astrocytes secrete IL-6 and TNF-alpha in the presence of the spirochete. This cytokine response may contribute to cognitive impairment.

A developing hypothesis is that the chronic secretion of stress hormones as a result of Borrelia infection may reduce the effect of neurotransmitters, or other receptors in the brain by cell-mediated pro-inflammatory pathways, thereby leading to the dysregulation of neurohormones, specifically glucocorticoids and catecholamines, the major stress hormones. This process is mediated via the hypothalamic-pituitary-adrenal axis. Additionally tryptophan, a precursor to serotonin appears to be reduced within the CNS in a number of infectious diseases that affect the brain, including Lyme Researchers are investigating if this neurohormone secretion is the cause of neuropsychiatric disorders developing in some patients with borreliosis.

Histologic examination of all affected tissues reveals an infiltration of lymphocytes and plasma cells with some degree of vascular damage (including mild vasculitis or hypervascular occlusion), suggesting that the spirochete may have been present in or around blood vessels

CLINICAL MANIFESTATIONS

Once B. burgdorferi is injected into the host, 1 of 3 events occurs, as follows:

1. In the first event, patients may clear the infection without developing any manifestations, as demonstrated by patients who are asymptomatic but seropositive.
2. In the second event, B. burgdorferi spreads throughout the body and produces symptoms by direct invasion, particularly in the early stages of the disease. Because growing B. burgdorferi is difficult, confirming that the organism is actually present in a specific organ that may be involved in Borreliosis is also difficult..
3. In the third event, B. burgdorferi induces an immune response that may lead to symptoms in various organs, with little evidence of bacterial invasion.

Borreliosis can affect multiple body systems and produce a range of symptoms. Not all patients with borreliosis will have all symptoms, and many of the symptoms are not specific to borreliosis but can occur with other diseases as well.

The incubation period from infection to the onset of symptoms is usually one

to two weeks, but can be much shorter (days), or much longer (months to years). Symptoms most often occur from May through September, because the nymphal stage of the tick is responsible for most cases.

The manifestations of Borreliosis have been divided into 3 stages: localized, disseminated, and persistent. The first 2 stages are part of the early infection, while persistent disease is considered late infection. Unlike syphilis, stage 3 disease may occur within 1 year of infection, not many years later.

The primary symptoms of stage 1 are EM and some associated symptoms. The primary symptoms of stage 2 include intermittent arthritis, cranial nerve palsies and radicular symptoms, atrioventricular nodal block, and severe malaise and fatigue. The primary symptoms of stage 3 include prolonged arthritis; chronic encephalitis, myelitis, and parapareses; and symptoms consistent with fibromyalgia.

Early Infection: Stage 1 (Localized Infection). The classic sign of early local infection with Borreliosis is a circular, outwardly expanding rash called EM, which occurs at the site of the tick bite 3 to 32 days after being bitten, usually begins as a red macule or papule that expands slowly to form a large annular lesion, most often with a bright red outer border and partial central clearing. The rash may be warm, but is generally painless. Classically, the innermost portion remains dark red and becomes indurated; the outer edge remains red; and the portion in between clears, giving the appearance of a bull's-eye. However, partial clearing is uncommon, and the bullseye pattern more often involves central redness. The center of the lesion sometimes becomes intensely erythematous and vesicular, or necrotic. In other instances, the expanding lesion remains an even, intense red; several red rings are found within an outside ring; or the central area turns blue before the lesion clears. Although EM can be located anywhere, the thigh, groin, and axilla are particularly common sites. EM is thought to occur in about 80% of infected patients. The skin lesion is frequently accompanied by influenza-like symptoms, such as malaise and fatigue, headache, arthralgias, myalgias, fever, or regional lymphadenopathy, and these symptoms may be the presenting manifestation of the illness.

Borreliosis can progress to later stages even in patients who do not develop a rash. Perhaps as many as 25% of patients do not exhibit this characteristic skin manifestation. Except for fatigue and lethargy, which are often constant, the early signs and symptoms of Borreliosis are typically intermittent and changing. Even in untreated patients, the early symptoms usually become less severe or disappear within several weeks.

Early Infection: Stage 2 (Disseminated Infection). Within days or weeks after the onset of EM, the organism often spreads hematogenously to many sites. In these cases patients frequently develop secondary annular skin lesions similar in appearance to the initial lesion. Another skin condition, which is apparently is borrelial lymphocytoma, a purplish lump that develops on the ear lobe, nipple, or

scrotum. Other discrete symptoms include migrating pain in muscles, joint, and tendons, and heart palpitations and dizziness caused by changes in heartbeat. Skin involvement is frequently accompanied by severe headache, mild stiffness of the neck, fever, chills, migratory musculoskeletal pain, arthralgias, and profound malaise and fatigue. Less common manifestations include generalized lymphadenopathy or splenomegaly, hepatitis, sore throat, nonproductive cough, conjunctivitis, iritis, or testicular swelling.

Neurologic manifestations. Acute neurological problems, which appear in 15% of untreated patients, encompass a spectrum of disorders. Possible manifestations include lymphocytic meningitis with episodic headache and mild neck stiffness, subtle encephalitis with difficulty with mentation, cranial neuropathy (particularly unilateral or bilateral facial palsy), motor or sensory radiculoneuritis, causes shooting pains that may interfere with sleep as well as abnormal skin sensations mononeuritis multiplex, cerebellar ataxia, or myelitis, facial or Bell's palsy, which is the loss of muscle tone on one or both sides of the face. In children, the optic nerve may also be affected because of inflammation or increased intracranial pressure, which may lead to blindness. Mild encephalitis may lead to memory loss, sleep disturbances, or mood changes. In addition, some case reports have described altered mental status as the only symptom seen in a few cases of early neuroborreliosis the first neurologic sign is characteristically radicular pain, which is followed by the development of CSF pleocytosis (called Bannwarth's syndrome), but meningeal or encephalitic signs are frequently absent. Even in untreated patients, acute neurologic abnormalities typically improve or resolve within weeks or months.

In up to 5% of untreated patients, B. burgdorferi may cause chronic neuroborreliosis, sometimes after long periods of latent infection. A chronic axonal polyneuropathy may develop, manifested primarily as spinal radicular pain or distal paresthesias. Electromyograms typically show diffuse involvement of both proximal and distal nerve segments. B. garinii may cause chronic encephalomyelitis, characterized by spastic paraparesis, cranial neuropathy, or cognitive impairment with marked intrathecal production of antibodies against the spirochete.

Cardiac manifestations. Within several weeks after the onset of disease, about 7% of untreated patients have acute cardiac involvement – most commonly fluctuating degrees of atrioventricular block (first-degree, Wenckebach, or complete heart block), occasionally acute myopericarditis or mild left ventricular dysfunction, and rarely cardiomegaly or fatal pancarditis. Cardiac involvement usually lasts for only a few weeks but may recur. One case of chronic cardiomyopathy caused by B. burgdorferi has been reported. During this stage, musculoskeletal pain is common. The typical pattern consists of migratory pain in joints, tendons, bursae, muscles, or bones (usually without joint swelling) lasting for hours or days and affecting one or two locations at a time.

Late Infection: Stage 3 (Persistent Infection). Joint manifestations. Months after the onset of illness, about 60% of untreated patients begin to have intermittent attacks of joint (oligoarticular arthritis) swelling and pain, primarily in large joints, especially the knee. Small joints and periarticular sites also may be affected, primarily during early attacks. The number of patients who continue to have recurrent attacks decreases each year. However, in a small percentage of cases, involvement of large joints usually one or both knees becomes chronic and may lead to erosion of cartilage and bone.

Synovial tissue from affected patients shows synovial hypertrophy, vascular proliferation, and a marked infiltration of mononuclear cells, sometimes with pseudolymphoid follicles that are reminiscent of a peripheral lymph node. White cell counts in joint fluid range from 500 to 110,000/uL (average, 25,000/uL); most of these cells are polymorphonuclear leukocytes. Tests for rheumatoid factor or antinuclear antibodies usually give negative results. Examination of synovial biopsy samples reveals fibrin deposits, villous hypertrophy, vascular proliferation, microangiopathic lesions, and a heavy infiltration of lymphocytes and plasma cells. During attacks of arthritis, innate immune responses to B. burgdorferi lipoproteins are found, and T-cells in joint fluid may aid in this response. In addition, there are marked adaptive immune responses to many spirochetal proteins. A borrelia-specific, inflammatory Th1 response is concentrated in joint fluid, but anti-inflammatory (Th2) cytokines are also present. Furthermore, patients with Lyme arthritis usually have higher borrelia-specific antibody titers than patients with any other manifestation of the illness, including late neuroborreliosis.

Neurologic manifestations. Although less common, chronic neurologic involvement may also become apparent months or years after the onset of infection, sometimes following long periods of latent infection. The most common form of chronic CNS involvement is subtle encephalopathy affecting memory, mood, or sleep and often accompanied by axonal polyneuropathy manifested as either distal paresthesias or spinal radicular pain. Patients with encephalopathy frequently have evidence of memory impairment in neuropsychological tests and abnormal results in CSF analyses. In cases with polyneuropathy, electromyography generally shows extensive abnormalities of proximal and distal nerve segments. Encephalomyelitis or leukoencephalitis, a rare manifestation of Lyme borreliosis, is a severe neurologic disorder that may include spastic parapareses, upper motor-neuron bladder dysfunction, and lesions in the periventricular white matter. The prolonged course of chronic neuroborreliosis following periods of latent infection is reminiscent of tertiary neurosyphilis.

Skin manifestations. Acrodermatitis chronica atrophicans, the late skin manifestation of the disorder, has been associated primarily with B. afzelii infection in Europe and Asia. It has been observed primarily in elderly women. The skin

lesions, which are usually found on the sacral surface of an arm or leg, begin insidiously with reddish-violaceous discoloration; they become sclerotic or atrophic over a period of years.

DIFFERENTIAL DIAGNOSIS

The most common problem in diagnosis is to distinguish late Borreliosis from chronic fatigue syndrome or fibromyalgia. This difficulty is compounded by the fact that a small percentage of patients develop these chronic pain or fatigue syndromes in association with or soon after Borreliosis. Compared with Borreliosis, chronic fatigue syndrome or fibromyalgia tends to produce more generalized and disabling symptoms, including marked fatigue, severe headache, diffuse musculoskeletal pain, multiple symmetric tender points in characteristic locations, pain and stiffness in many joints, diffuse dysesthesias, difficulty with concentration, and sleep disturbances. Patients with chronic fatigue syndrome or fibromyalgia lack evidence of joint inflammation; they have normal results in neurologic tests; and they usually have a greater degree of anxiety and depression than patients with chronic neuroborreliosis.

Diagnosis of late-stage Borreliosis is often difficult because of the multi-faceted appearance which can mimic symptoms of many other diseases. Borreliosis may be misdiagnosed as multiple sclerosis, rheumatoid arthritis, fibromyalgia, chronic fatigue syndrome, lupus, or other autoimmune and neurodegenerative diseases.

DIAGNOSIS

Borrelia burgdorferi can be cultivated in vitro. However, the bacterium is fastidious and requires a very complex growth medium – Barbour-Stoenner-Kelly (BSK) medium. It contains over thirteen ingredients in a rabbit serum base. Borrelia burgdorferi has an optimal temperature for growth of 32^{o}C, in a microaerobic environment. Even under optimal conditions, the generation time is slow, about 12-24 hours. Borreliae from ticks and from the blood, skin, and CSF of Borreliosis patients have been successfully cultivated in BSK medium. BSK solidified with 1.3% agarose allows the production of colonies from single organisms. Because of the difficulty in culturing Borrelia bacteria in the laboratory, diagnosis of Borreliosis is typically based on the clinical exam findings and a history of exposure to endemic Lyme areas.

Serological testing can be used to support a clinically suspected case but is not diagnostic by itself. These tests may be negative in early infection, before the body has produced significant quantities of antibody, but they are considered a reliable aid in the diagnosis of later stages of Borreliosis. The EM rash, which does not occur in all cases, is considered sufficient to establish a diagnosis of Borreliosis even when

serologic blood tests are negative. Most widely available and employed are the Western blot and ELISA. The sensitive ELISA test is performed first, and if it is positive or equivocal then the more specific Western blot is run. The reliability of testing in diagnosis remains controversial; however studies show the Western blot IgM has a specificity of 94-96% for patients with clinical symptoms of early Borreliosis.

During the first month of infection, both IgM and IgG responses to the spirochete should be determined, preferably in both acute- and convalescent-phase serum samples. Approximately 20% to 30% of patients have a positive response detectable in acute-phase samples, whereas about 70% to 80% have a positive response during convalescence (2 to 4 weeks later even after antibiotic treatment). After that time, the great majority of patients continue to have a positive IgG antibody response, and a single test (that for IgG) is usually sufficient. In persons who have been ill for longer than one month, a positive IgM test alone is likely to represent a false positive result; therefore, such a response should not be used to support the diagnosis after the first month of infection. In patients with acute neuroborreliosis, especially those with meningitis, the intrathecal production of IgM, IgG, or IgA antibody against B. burgdorferi may often be demonstrated by antibody-capture enzyme immunoassay, but this test is less often positive in those with chronic neuroborreliosis.

The limitation of serologic tests is that they do not clearly distinguish between active and inactive infection Patients with previous Borreliosis particularly in cases progressing to late stages often remain seropositive for years, even after adequate antibiotic treatment. In addition, some patients are seropositive because of asymptomatic infection. If these individuals subsequently develop another illness, the positive serologic test for Borreliosis may cause diagnostic confusion. On the other hand, a few patients who receive inadequate antibiotic therapy during the first several weeks of infection develop subtle joint or neurologic symptoms but are seronegative. The important point is that seronegative Borreliosis is usually a mild, attenuated illness.

Erroneous test results have been widely reported in both early and late stages of the disease. These errors can be caused by several factors, including antibody cross-reactions from other infections including Epstein-Barr virus and cytomegalovirus, as well as herpes simplex virus.

After antibiotic treatment, antibody titers fall slowly, but IgG and even IgM responses may persist for many years after treatment. Thus, even an IgM response cannot be interpreted as a demonstration of recent infection or reinfection unless the appropriate clinical characteristics are present. In addition, B. burgdorferi may cause asymptomatic infection. IgG seroconversion was demonstrated on Western blotting in about 10% of subjects who had no symptoms of the infection. More than half the

subjects who were seropositive by ELISA did not remember having symptoms of Lyme borreliosis. If patients with past or asymptomatic infection have symptoms caused by another illness, there is a danger that the symptoms will be attributed incorrectly to Borreliosis. Several second-generation tests that use recombinant spirochetal proteins or synthetic peptides have shown promising results.

Polymerase chain reaction (PCR) tests for Borreliosis have also been developed to detect the genetic material (DNA) of the Borreliosis spirochete. PCR tests are susceptible to false-positive results from poor laboratory technique. Even when properly performed, PCR often shows false-negative results with blood and CSF specimens. Hence PCR is not widely performed for diagnosis of Borreliosis. However PCR may have a role in diagnosis of Lyme arthritis because it is highly sensitive in detecting DNA in synovial fluid. With the exception of PCR, there is no currently practical means for detection of the presence of the organism, as serologic studies only test for antibodies of Borrelia.

Western blot, ELISA and PCR can be performed by either blood test via venipuncture or CSF via lumbar puncture. Though lumbar puncture is more definitive of diagnosis, antigen capture in the CSF is much more elusive; reportedly CSF yields positive results in only 10–30% of patients cultured. The diagnosis of neurologic infection by Borrelia should not be excluded solely on the basis of normal routine CSF or negative CSF antibody analyses.

New techniques for clinical testing of Borrelia infection have been developed, such as Lymphocyte Transformation Test - Memory Lymphocyte Immunostimulation Assay (LTT-MELISA), which is capable of identifying the active form of Borrelia infection. Others, such as focus floating microscopy, are under investigation. New research indicates chemokine CXCL13 may also be a possible marker for neuroborreliosis.

Single photon emission computed tomography (SPECT) imaging has been used to look for cerebral hypoperfusion indicative of Lyme encephalitis in the patient. Although SPECT is not a diagnostic tool itself, it may be a useful method of determining brain function. In Borreliosis patients, cerebral hypoperfusion of frontal subcortical and cortical structures has been reported. In about 70% of chronic Borreliosis patients with cognitive symptoms, brain SPECT scans typically reveal a pattern of global hypoperfusion in a heterogeneous distribution through the white matter. This pattern is not specific for Borreliosis, since it can also be seen in other CNS syndromes such as HIV encephalopathy, viral encephalopathy, chronic cocaine use, and vasculitides. However, most of these syndromes can be ruled out easily through standard serologic testing and careful patient history taking. The presence of global cerebral hypoperfusion deficits on SPECT in the presence of characteristic neuropsychiatric features should dramatically raise suspicion for Lyme encephalopathy among patients who inhabit or have traveled to endemic areas,

regardless of patient recall of tick bites. Late disease can occur many years after initial infection. The average time from symptom onset to diagnosis in these patients is about 4 years. Because seronegative disease can occur, and because CSF testing is often normal, Lyme encephalopathy often becomes a diagnosis of exclusion: once all other possibilities are ruled out, Lyme encephalopathy becomes ruled in. Although the aberrant SPECT patterns are caused by cerebral vasculitis, a vasculitide, brain biopsy is not commonly performed for these cases as opposed to other types of cerebral vasculitis.

Abnormal magnetic resonance imaging (MRI) findings are often seen in both early and late Borreliosis. MRI scans of patients with neurologic Borreliosis may demonstrate punctuated white matter lesions on T2-weighted images, similar to those seen in demyelinating or inflammatory disorders such as multiple sclerosis, systemic lupus erythematosus, or cerebrovascular disease. Cerebral atrophy and brainstem neoplasm has been indicated with Lyme infection as well. Diffuse white matter pathology can disrupt these ubiquitous gray matter connections and could account for deficits in attention, memory, visuospatial ability, complex cognition, and emotional status. White matter disease may have a greater potential for recovery than gray matter disease, perhaps because neuronal loss is less common. Spontaneous remission can occur in multiple sclerosis, and resolution of MRI white matter hyper-intensities, after antibiotic treatment, has been observed in Borreliosis.

TREATMENT

Antibiotics are the primary treatment for Borreliosis; the most appropriate antibiotic treatment depends upon the patient and the stage of the disease.

For early localized or disseminated infection, treatment with doxycycline (100 mg twice a day) for 14 to 21 days is recommended in persons older than eight years of age, except for pregnant women. An advantage of doxycycline is its efficacy against the agent of human granulocytic ehrlichiosis, which is transmitted by the same tick that transmits the Borreliosis agent.

Amoxicillin (500 mg three times a day in adult and in children- 50 mg/kg per day, but not more than 2 g/d), the second-choice alternative, should be used in children and pregnant women. In patients who are allergic to either of these drugs, cefuroxime axetil (500 mg twice a day), is a third-choice alternative. Erythromycin (250 mg four times a day) or its congeners, which are fourth-choice alternatives, are recommended only for patients who are unable to take doxycycline, amoxicillin, or cefuroxime axetil.

For patients with infection localized to the skin, a 10-day course of therapy is generally sufficient; in contrast, for patients with disseminated infection, a 20- to 30-day course is recommended. Approximately 15% of patients experience a Jarisch-Herxheimer-like reaction during the first 24 h of therapy.

These oral antibiotic regimens, when given for 30 to 60 days, are effective for the treatment of Lyme arthritis. However, the response to therapy may be slow. A small percentage of patients with arthritis, particularly those with the HLA-DR4 allele and an immune response to the OspA or OspB protein of the spirochete, do not respond to antimicrobial therapy. Treatment with anti-inflammatory agents or synovectomy may be successful in such cases.

For patients with objective evidence of neurologic abnormalities, a two-to-four-week course of intravenous ceftriaxone is most commonly given. Parenteral therapy with cefotaxime (2 g three times a day) or penicillin (20 million units per day in divided doses) for the same duration may a satisfactory alternative.

The signs and symptoms of acute neuroborreliosis usually resolve within weeks, but those of chronic neuroborreliosis improve slowly over a period of months. Objective evidence of relapse is rare after a four-week course of therapy. Doxycycline is not effective for the treatment of chronic neuroborreliosis.

In patients with atrioventricular nodal block with a PR interval greater than 0.3 second, therapy with one of the intravenous regimens for at least part of the course and cardiac monitoring are recommended, but the insertion of a permanent pacemaker is not necessary. In patients with complete heart block or congestive heart failure, glucocorticoids may be of benefit if antimicrobial therapy alone does not result in improvement within 24 h.

The oral or intravenous regimens, most often oral doxycycline or intravenous ceftriaxone, are usually effective for the treatment of Lyme arthritis. Oral therapy is easier to administer, is associated with fewer side effects, and is considerably less expensive. Its disadvantage is that some patients treated with oral agents have subsequently had overt neuroborreliosis, which may require intravenous therapy for successful treatment. Despite treatment with either oral or intravenous antibiotic therapy, about 10% of patients have persistent joint inflammation for months or even several years after two months or more of oral antibiotic therapy or one month or more of intravenous antibiotic therapy. If patients have persistent arthritis despite this treatment and if the results of PCR testing of joint fluid are negative, they may be treated with anti-inflammatory agents or arthroscopic synovectomy.

It is unclear how and whether asymptomatic infection should be treated, but patients with such infection are often given a course of oral antibiotics. The appropriate treatment for Borreliosis during pregnancy is also unclear. Because the risk of maternal-fetal transmission seems to be very low, standard therapy for the documented stage and manifestation of the illness may be sufficient. Relapse may follow the use of any of the antibiotic regimens for Borreliosis, and a second course of therapy may be necessary. On the other hand, in patients who develop chronic fatigue syndrome or fibromyalgia after Borreliosis, further antibiotic therapy does not seem to be of benefit.

In later stages, the bacteria disseminate throughout the body and may cross the blood-brain barrier, making the infection more difficult to treat. Late diagnosed Lyme is treated with oral or IV antibiotics, frequently ceftriaxone for a minimum of four weeks. Minocycline is also indicated for neuroborreliosis for its ability to cross the blood-brain barrier. After appropriately treated Borreliosis, a small percentage of patients continue to have subjective symptoms – primarily musculoskeletal pain, neurocognitive difficulties, or fatigue – that may last for years. This disabling syndrome, which is sometimes called "chronic Borreliosis" or "post-Borreliosis syndrome", is similar to chronic fatigue syndrome or fibromyalgia. This postinfectious syndrome occurs more frequently in patients whose symptoms are suggestive of early dissemination of the spirochete to the nervous system, particularly if treatment is delayed. However, in a large study, the frequency of symptoms of pain and fatigue was no greater in patients who had had Borreliosis than in age-matched subjects who had not had this infection.

In a study of patients with post-Borreliosis syndrome who received either intravenous ceftriaxone for 30 days followed by oral doxycycline for 60 days or intravenous and oral placebo preparations for the same duration, there were no significant differences between the groups in the percentage of patients who said that their symptoms had improved, gotten worse, or stayed the same. Such patients are best treated symptomatically rather than with prolonged courses of antibiotic therapy. Prolonged ceftriaxone therapy for unsubstantiated Borreliosis has resulted in biliary complications; and in one reported case, the prolonged administration of cefotaxime resulted in death.

PREVENTION

Protective measures for the prevention of Borreliosis may include:

1. Personal prevention tips. Avoid sitting directly on the ground, stonewalls, woodpiles or fallen logs; use an impervious ground cover, walk in the center of trails, check yourself for ticks periodically while in tick-infested areas.
2. Clothing. Wear light-colored long pants, long sleeved shirts and closely knitted socks. Tuck shirt into pants and tuck pants into your socks. This will help prevent a tick from crawling under clothing and getting to your skin. Wear a hat to protect your head. Rynoskin protective underwear is made of a closely knitted but breathable stretch fabric that ticks have difficulty penetrating. It is especially helpful for hunters and anyone outdoors when the weather is cooler. It is available in long sleeved tops, long bottoms, socks, hoods, and gloves.
3. Skin protection**.** Insect repellents can be used on skin or clothing. Repellents should be applied to the skin carefully. Follow label instructions and avoid getting the repellant in the eyes or mouth. Higher concentrations provide longer protection. A number of plant oils are reported to be tick repellants.

4. After returning indoors**.** Perform a careful tick check after returning indoors. Deer ticks are tiny and difficult to see. If possible, have someone else inspect you. Be sure to check your hairline and waistline. Parents should check children whenever they have been outdoors. Shower using a washcloth immediately to remove any unattached ticks. Remove attached ticks as soon as detected using fine pointed tweezers or tick removal tool. Grasp the tick as close to the skin as possible. Pull gently straight out. Do not put petroleum jelly, alcohol, soap, lit match or cigarette, etc. on the tick. Any irritation might cause the tick to regurgitate the Lyme bacteria into you. Save the tick in a plastic bag or vial with a moistened cotton ball for identification and testing. After removing the tick, call your doctor promptly and consider requesting immediate antibiotic treatment. If the tick is infected early diagnosis and appropriate treatment is key to recovery. Delay will allow the infection to disseminate into tissue in the body where treatment is often less effective. Keep outdoor clothes in the garage or shed as ticks can migrate from clothing brought indoors and invade the home. You can also wash and dry your clothes immediately
5. Antibiotic prophylaxis. The risk of infection with B. burgdorferi after a recognized tick bite is so low that antibiotic prophylaxis is not routinely indicated. However, if the tick is engorged, if follow-up is difficult, or if the patient is quite anxious, therapy with amoxicillin or doxycycline for 10 days is likely to prevent Borreliosis.
6. Modifications of landscapes in or near residential areas. Clear brush and leaves, where ticks live. Keep woodpiles in sunny areas.
7. Vaccine. A vaccine consisting of recombinant OspA in adjuvant was developed for use in high-risk areas, but it is no longer available. It was removed from the market because of uncertainty over its effectiveness and lack of demand. A vaccine for Borreliosis is currently being tested.

PROGNOSIS

The response to treatment is best early in the disease. Later treatment of Lyme borreliosis is still effective, but convalescence may be longer. However, the severity and treatment of Borreliosis may be complicated due to late diagnosis, failure of antibiotic treatment, and simultaneous infection with other tick-borne diseases (co-infections) including ehrlichiosis, babesiosis, and bartonella, and immune suppression in the patient. Eventually, most patients recover with minimal or no residual deficit. But some patients with Borreliosis have fatigue, joint or muscle pain, and neurocognitive symptoms persisting for years despite antibiotic treatment. Patients with late stage Borreliosis have been shown to experience a level of physical disability equivalent to that seen in congestive heart failure. In rare cases, Borreliosis can be fatal.

LOUSE-BORNE TYPHUS

Louse-borne typhus is an acute anthroponotic infectious disease caused by Rickettsia Prowazeki. Louse-borne typhus is characterized by development of generalized thrombovasculitis, meningoencephalitis, severe intoxication, by appearance of rash, hepatosplenomegaly.

ETIOLOGY

Louse-borne typhus is caused by rickettsial organisms. The causative agent is ***Rickettsia Prowazekii***. Rickettsia are pleomorphic bacteria that may appear as cocci or bacilli and are obligate intracellular parasites. The rickettsiae make up a family of gram-negative coccobacilli and short bacilli that grow strictly in eukaryotic cells. Characteristics of these organisms include their intracellular localization and persistence. Reproduction is by binary fission and diplobacilli are produced that are frequently seen in tissue sections. Special staining (Giemsa) provides good visualization of the organisms in the cytoplasm of the cells.

EPIDEMIOLOGY

The rickettsiae move through mammalian reservoirs; they are transmitted by insect vectors. The vector is the body louse which lives in clothes and is found in conditions of poor hygiene. P corporis is the most common louse vector; however, Pediculus capitis and Phthirus pubis also transmit epidemic typhus. The infected louse defecates during its blood meal and the patient autoinoculates the organisms by scratching. Since the louse does not pass the organism to its offspring, the disease usually is spread from person to person by the louse-borne route. This epidemic form of typhus is associated with poverty, cold weather, war, and disasters. Humans are the host in epidemic typhus, but the flying squirrel has also been linked with the disease in several cases in the United States.

In epidemic the susuptibility is high for all age groups.

Epidemic typhus occurs in Central and South America (Mexico, Peru), Africa (Burundi, Ethiopia), northern China, and certain regions of the Himalayas. Outbreaks may occur when conditions arise that favor the propagation and transmission of lice. Brill-Zinsser disease develops in approximately 15% of people with a history of primary epidemic typhus.

The typhus group of infections has no sexual and age predilection.

PATHOGENESIS

The louse becomes infected with R. Prowazekii after feeding on a rickettsemic person with a primary case of typhus or during a recrudescent case (Brill-Zinsser disease).

Of all the typhus vectors, the louse is the only arthropod that dies of this infection. Rickettsia lives in the alimentary tract and cause obstruction and subsequent death of the louse after 2-3 weeks of infection. After local proliferation at the site of the louse bite, the Rickettsia travel to the bloodstream and rickettsemia develops. Rickettsia parasitize the endothelial cells of the small venous, arterial, and capillary vessels. The organisms proliferate and cause endothelial cellular enlargement with resultant multiorgan vasculitis. This process may cause thrombosis, and the deposition of leukocytes, macrophages, and platelets may result in small nodules. Thrombosis of supplying blood vessels may cause gangrene of the distal portions of the extremities, nose, ear lobes, and genitalia. This vasculitic process may also result in loss of intravascular colloid with subsequent hypovolemia and decreased tissue perfusion and, possibly, organ failure. Loss of electrolytes is common.

The mechanism of the development of epidemic typhus may be represented by the next phases:

1. Penetration of ***Rickettsia Prowazekii*** into the organism and reproduction in the endothelial cells of the vessels.
2. Destruction of the endothelial cells and penetration of rickettsia into the blood – rickettsiemia, toxinemia.
3. Functional violations of the vessels in all organs and tissues – vasodilatation, slowdown of the bloodstream.
4. Destructive and proliferative alterations of the capillaries with formation specific granulemas (nodules).
5. Formation of immunity.

The small hemorrhages in the conjunctivae are frequent. The heart usually shows slight gross changes. Microscopically the blood vessels show similar lesions to those observed in the skin, and sometimes there is considerable infiltration with mononuclear and polymorphonuclear cells. Thrombi are rarely found in the larger blood vessels.

The blood is usually duck colored and liver and kidneys show cloudy swelling. The spleen is somewhat enlarged during the early stages of the disease but tends to be normal in size later on. It is often very soft and then may rupture from being handled at autopsy. Microscopically, engorgement with blood, with extensive phagocytosis of red blood corpuscles and diminution of lymphoid elements, is commonly present.

The lesion in the brain, particularly in the basal ganglia, medulla and cortex of the cerebrum, and more rarely in the white matter and cerebellum, correspond in size to miliary tubercles and are secondary to lesions of the small blood vessels and capillaries, as in the skin. They first consist of a collection of large cells of vascular and perivascular origin, endothelium, and monosytes, with necrosis resulting from occlusion of the vessels.

CLINICAL MANIFESTATIONS

Epidemic typhus is cyclic infectious disease. There are the next periods in the course of the disease: incubation period (it's duration is from 6 till 23 days); initial period till appearance of the rash (it's duration is 4-5 days), period of climax – from appearance of the rash till normalization of the temperature (it's duration is from 4-5 days till 8-10 days) and period of convalescence (it's duration is 2-3 weeks).

After an incubation period, the onset of illness is abrupt, with prostration, severe headache, chills, myalgia, and rapidly rising temperatures of 38.8 to 40.0°C. The fever worsens quickly and becomes unremitting and the patient is soon prostrated by the illness. There is no eschar Giddiness, backache, anorexia, nausea are observed in the patients. The appearance of the patient is typical. The face is edematous, flushed. Eyes are brilliant with injected sclera ("rabbit's eyes"). Enanthem (small hemorrhages) on the basis of uvula is marked on the second-third day of the disease (symptom of Rosenberg). The petechial rash may be revealed on transitive folds of conjunctiva from the third-forth day (symptom of Kiary - Avcyn). The early sign is tremor of the tongue, it's declining to the side (symptom Govorov-Godeljae) due to bulbaric disorders. Splenomegaly is marked on the 3-4 day of the disease in the majority of the patients.

Climax period is characterized by development of all clinical manifestations of the disease. The temperature is definite high level (febris remittans). Temperature decreases frequently on the 3-4, 8-9 and 12-13 day of the disease and then the temperature increases again. Climax period is accompanied by intoxication and damage of the central nervous system. The appearance of the rash is an important sign of climax period. A rash begins on the upper trunk by the fifth day of fever and later becomes generalized, involving all of the body except the face, palms, and soles. Initially, this rash is macular; without treatment, it becomes maculopapular, petechial, and confluent. Photophobia, with considerable conjunctival injection and eye pain, is frequent. The tongue may be dry, brown, and furred. Skin necrosis and gangrene of the digits have been noted in severe cases.

The circulatory system. Very outspoken is cardiac weakness due to myocardial degeneration. The heart sounds are very weak and the pulse feeble, rapid and irregular. The blood pressure often is very low, especially the diastolic, and may remain so throughout the disease. Bradycardia may be marked during convalescence.

The Respiratory System. Cough may appear in the first days, but usually is first troublesome about the time of the eruption. By the end of a week, the cough becomes loose and rales of various types may be noted.

The Alimentary Tract. Constipation is usually noted. Very marked is the tendency of the mouth and tongue to become dry and sordes to collect on the teeth. It is often difficult to get the patient to protrude his tongue when told to do so. In the patients with epidemic typhus splenomegaly and hepatomegaly (from one till second

week) are marked.

The Nervous System. Clouding of the consciousness may be as marked in this disease. Dull aching frontal headache is common and is an early predominating symptom. It frequently diminishes before the eruption appears. A dull stuporous state soon comes on. Delirium is marked in some cases. There are often the faces and mental state of alcoholic intoxication. It may be meningitis or meningoencephalitis.

Untreated disease is fatal in up to 40 percent of cases, with outcome depending primarily on the condition of the host. Patients with untreated infections develop renal insufficiency and multivisceral involvement, with prominent neurologic manifestations in 12 percent of cases.

Signs, symptoms, and potential complications of typhus are due to hematogenous spread of organisms with resultant endothelial proliferation and vasculitis.

The central nervous, musculoskeletal, and cardiovascular systems may be involved, as well as the skin, lungs, and kidneys. Multiorgan system involvement is possible.

Vasculitis may result in hypovolemia, electrolyte disturbances, and digital gangrene.

Hemodynamic status and fluid/electrolyte replacement should be diligently monitored.

Secondary infections, such as bacterial pneumonia, should be treated appropriately.

Bronchitis, otitis media, parotitis, nephritis, trombosis of various vessels, both abdominal and peripheral may be present.

DIAGNOSIS

In the period of the climax the differential diagnosis is performed with typhoid fever, ornithosis, drug disease, leptospirosis, infectious mononucleosis, trichineilosis, meningococcemia, brucellosis, malaria, rubella, measles, meningitis.

Typhus is a vasculitic process that is capable of causing various abnormal laboratory values. Any organ may be affected, and multiorgan system dysfunction or failure may occur if the illness is not diagnosed and treated in the early stages. These abnormalities, listed by organ system, may include the following: renal – azotemia/proteinuria; hematologic – leukopenia (common in the early stages of disease), WBC count normal/mildly elevated later, thrombocytopenia; hepatic – mild transaminase elevations; metabolic – hypoalbuminemia/electrolyte abnormalities (particularly hyponatremia).

Indirect immunofluorescence assay (IFA) or enzyme immunoassay (EIA) testing can be used to evaluate for a rise in the immunoglobulin M (IgM) antibody titer, which indicates an acute primary disease.

Brill-Zinsser disease can be confirmed in a patient with a history of primary epidemic typhus who has recurrent symptoms and signs of typhus and a rise in the immunoglobulin G (IgG) antibody titer, which indicates a secondary immune response.

IFA and EIA tests can be used to confirm a diagnosis of typhus, but they do not identify the various rickettsial species.

Polymerase chain reaction (PCR) amplification of rickettsial DNA of serum or skin biopsy specimens can be used for diagnosing typhus.

The complement fixation (CF) test is a serological test that can be used to demonstrate which specific rickettsial organism is causing disease by detection of specific antibodies.

Rickettsia may be observed in tissue sections using Giemsa or Gimenez staining techniques.

TREATMENT

The treatment of the patient is complex: etiotropic, pathogenetic and symptomatic. The goals of pharmacotherapy are to reduce morbidity, to prevent complications, and to eradicate infection. Specific antimicrobial therapy effective against rickettsia should be used. Tetracycline and chloramphenicol are used as antirickettsial agents for the treatment of typhus. The recommended dose for tetracycline is 0.3-0.4g, chloramphenicol – 0.5g four times per day. Usually antibiotics are abolished from the third day of the normal temperature. Azithromycin and rifampicin have been shown to be effective in small trials conducted in areas with known doxycycline resistance.

Pathogenetic therapy includes heart (corglycon, strophantin) and vascular (cordiamin, ephedrine, mezaton) remedies. In the serious course the disintoxicative and dehydrative therapy is performed. Sometimes in the case of the marked exciting bromides, aminaszin, barbiturates, seduxen are prescribed. The patients may walk from the 7-8 day of the normal temperature. The discharge of the patients from the hospital may be realized at the 12 day of the normal temperature.

PREVENTION

Control of the human body louse and the conditions that foster its proliferation is the mainstay in preventing louse-borne typhus.

Typhus vaccine is prepared from formaldehyde-inactivated rickettsiae Prowazekii grown in embryonated eggs. Typhus vaccination is suggested for special risk group.

BRILL-ZINSSER DISEASE

Brill-Zinsser disease is a recrudescent, mild form of epidemic typhus occurring years after the acute disease, probably as a result of immunosuppression or old age. Nathan Brill first identified recrudescent typhus in New York in 1898. In 1923, Hans Zinsser noted that more than 90 percent of patients with recrudescent typhus had emigrated from typhus-endemic areas of Europe. Strains of R. Prowazekii indistinguishable from classic strains were isolated from patients with recrudescent typhus. Furthermore, R. Prowazekii was isolated from the lymph nodes of patients undergoing elective surgery who had had typhus years earlier. After a patient with typhus is treated with antibiotics and the disease appears to be cured, Rickettsia may linger in the body tissues. Months, years, or even decades after treatment, organisms may reemerge and cause a recurrence of typhus. How the Rickettsia organisms linger silently in a person and by what mechanism recrudescence is mediated are unknown. Thus, the typhus rickettsiae can remain dormant for years and can reactivate with waning immunity.

It occurs in the United States primarily in immigrants from Eastern Europe whose initial infection was early.

Brill-Zinsser disease is an acute cyclic disease. Brill-Zinsser disease is characterized by sporadic morbidity in absence of the louse.

In Brill-Zinsser disease the pathogenesis and morbid anatomy are similar epidemic typhus, however the process is less marked, because the concentration of rickettsia Prowazekii is small in the blood. The course of Brill-Zinsser disease is lighter than epidemic typhus, but the patients have all typical symptoms of the disease.

The initial period is accompanied by moderate intoxication. Headache, disorder of sleep, increase of the temperature till 38-39° are marked. Enanthema is observed rarely (in 20% of the cases). The climax period is usually 5-7 days. It is characterized by moderate hyperthermia (38-39°) of remittent or rarely constant type.

The sighs of the damage of the central nervous system are marked moderate. Meningeal sighs are revealed rarely.

The rash is observed in 60-80%of the patients. The sighs of the damage of the cardiovascular system are marked frequently. Enlarged liver and spleen are revealed inconstantly.

In Brill-Zinsser disease the -complications develop rarely. It may be – pneumonia, thrombosis, thrombophlebitis. The treatment is such as in epidemic typhus.

The differentiation of primary louse-borne typhus is made by showing that the antibody produced is IgM (primary louse-borne) or IgG (Brill-Zinsser disease).

Q FEVER

Q-fever – is an acute zoonotic infectious disease, which caused by Coxiella burnetii, characterized by acute benignant course with polymorphous clinical manifestations, fever, and intoxication.

ETIOLOGY

The causative organism is Coxiella burnetii. It belongs to genus Coxiella, family Rickettsiaceae. C. Burneti has ability passing through bacterial filters. They may transform into L-form by action of antibiotics. This small gram-negative immobile microorganism exists in two antigenic forms: phase I and phase II. When C. burnetii is passaged in cell cultures or embryonated eggs, its lipopolysaccharide undergoes changes that result in an antigenic shift called phase variation. In humans and other animals, the organism exists in the phase I form, which is extremely infectious. Passage in cell culture or embryonated eggs results in a shift to the phase II form, which is avirulent. The ability of C. burnetii to form spores allows it to survive in harsh environments. Indeed, it can survive for more than 40 months in skim milk at room temperature and is readily recovered from soil up to 1 month after contamination. Three different plasmids have been described in various isolates of C. burnetii. This microorganism multiplies intracellulary.

EPIDEMIOLOGY

Q-fever is a zoonosis. The primary sources of human infection are infected cattle, sheep, and goats. However, infected cats, rabbits, and dogs have also been shown to transmit C. burnetii to humans. The reservoir in nature includes mammals, birds, and ticks; the last is an important vector in infecting mammals. A strong association between the disease and exposure to farm animals exists. Furthermore, because the organism is reactivated in pregnant animals, a strong association between the disease and contact with parturient animals (especially cows, sheep, goats, dogs, cats, rabbits) also exists. C. burnetii localizes to the uterus and the mammary glands; infection is reactivated during pregnancy, and high concentrations of C. burnetii are found in the placenta. Aerosol from newborn animals and their placentas can spread Q-fever. Other modes of transmission include aerosol from contaminated wool, hides, and dust; ingestion of raw milk or goat cheese; blood transfusions; and tick bites. Disease is highly infectious. In rare instances, human-to-human transmission has followed childbirth by an infected woman or autopsy on an infected patient. Sexual transmission has been demonstrated experimentally in mice, as has transmission during artificial insemination in cattle. Whether C. burnetii is sexually transmitted in humans is not yet known. It is evident that the persons at risk for Q-fever include abattoir workers, veterinarians, and others who vocationally or avocationally come into contact with infected animals.

Q-fever exists worldwide. A seroprevalence study of blood donors in Marseille, France, showed that 4% of donors had antibodies to C burnetii. Similar studies in other European countries have shown figures of 5-30%, with lower figures seen in urban areas and higher figures in rural zones.

Patients of all ages can contract Q-fever, but it seems to be more prevalent in men between the ages of 30 and 70 years. After exposure, women and children are more commonly asymptomatic than men and adults.

Q-fever is characterized by spring-summer seasonal prevalence (period of mass cattle calving and maximal tick activity).

PATHOGENESIS

Q-fever is reticuloendotheliosis without development of panvasculitis.

There are next links of the pathogenesis:

1. inoculation of the agent into the organism through the damaged mucous membranes and/or skin;
2. lymphagenic spread of the agent into the circulative system;
3. primary rickettsiaemia;
4. dissemination of the rickettsia into the parenchimatous organs of the reticuloendothelial system;
5. reproduction and development of rickettsiae in the histiocytes and macrophages;
6. secondary rickettsiaemia and toxinemia with dissemination into new focuses of the reticuloendothelial system;
7. development of the allergic manifestations;
8. formation of the immunity and convalescence.

CLASSIFICATION

By duration: acute, subacute, chronic.

By severity: mild, moderate, severe.

Clinical forms: pneumonic, septic, flu-like, nervous, typhoid, pulmonary, meningeal, brucellosis-like, etc.

CLINICAL MANIFESTATIONS

Abrupt onset of high fever with or without a flulike illness is common. The incubation period for acute Q-fever ranges from 3 to 39 days (more often – 12-20 days). Q-fever can manifest various signs; no one classic presentation exists. The major clue is the epidemiologic circumstance, exposure to parturient mammals or their newborn, and tick bites. The most common presentation of Q-fever may vary with geography. For example, in the Basque region of northern Spain, pneumonia is a common finding, whereas in southern Spain, hepatitis predominates.

The clinical presentations include flu-like syndromes, prolonged fever,

pneumonia, hepatitis, pericarditis, myocarditis, meningoencephalitis, and infection during pregnancy. The symptoms of acute Q-fever are nonspecific; common among them are fever, extreme fatigue, and severe headache. Other symptoms include chills, sweats, nausea, vomiting, and diarrhea, which occur in 5 to 20 percent of patients. Arthralgias can occur. Cough develops in about half of all patients with Q-fever pneumonia. Hepatitis is a common manifestation and usually is associated with elevated hepatic transaminase levels, since Q-fever rarely causes jaundice or acute gastro-intestinal symptoms.

Neurologic manifestations of acute Q-fever are uncommon. However, in one outbreak in the West Midlands of the United Kingdom, 23 percent of 102 patients had neurologic signs and symptoms as the major manifestation of acute Q-fever. A nonspecific skin rash may be evident in some patients. Uncommon manifestations of acute Q-fever include optic neuritis, extrapyramidal neurologic disease, Guillain-Barre syndrome, inappropriate secretion of antidiuretic hormone, epididymitis, orchitis, priapism, hemolytic anemia, mediastinal lymphadenopathy mimicking lymphoma, pancreatitis, erythema nodosum, and mesenteric panniculitis. Chest radiography may show an opacity that is indistinguishable from those seen in pneumonia of other causes. Multiple rounded opacities are common. In the appropriate epidemiologic setting, these opacities are highly suggestive of Q-fever pneumonia; however, right-sided endocarditis resulting in septic pulmonary emboli can produce the same radiographic appearance.

Chronic Q-fever. There are several clinical forms as a result of chronic Q-fever: endocarditis, hepatitis, meningoencephalitis, osteomyelitis. Endocarditis with negative culture findings is, by far, the most common manifestation of chronic Q-fever. It can occur months to years after the acute infection. Symptoms include fever, fatigue, dyspnea, and rash from septic thromboembolism. This infection usually occurs in patients with previous valvular heart disease, immunosuppression, or chronic renal insufficiency. Fever is usually absent or, if present, is low grade. Patients may have nonspecific symptoms for up to 1 year before diagnosis. Valvular vegetations have been seen in only 12% of patients with transthoracic echocardiograms, but the rate of detection may be higher with the use of transesophageal echocardiography. A high index of suspicion is necessary for a correct diagnosis. All patients with valvular heart disease and an unexplained purpuric eruption, renal insufficiency, stroke, and/or progressive heart failure should be tested for C. burnetii infection. Patients with chronic Q-fever have hepatomegaly and/or splenomegaly. These two findings, especially in combination with positive rheumatoid factor, high erythrocyte sedimentation rate, high C-reactive protein level, and/or increased gamma globulin concentrations, suggest this diagnosis. Other manifestations of chronic Q-fever include infection of vascular prostheses, aneurysms, and bone.

Complications: acute respiratory distress syndrome, thrombocytopenia, endocarditis caused by chronic infection as well as infection of vascular aneurysms and prostheses, spontaneous abortion and premature labor.

DIFFERENTIAL DIAGNOSIS

Similar symptoms can occur with many other infections: influenza, typhoid fever, louse-borne typhus, sepsis, brucellosis, leptospirosis, tuberculosis, ornithosis, viral hepatitis.

DIAGNOSIS

The routine laboratory tests are nonspecific; there is usually leukopenia with neutropenia and relative lympho-, and monocytosis, sometimes – anemia. The ESR usually normal or deviates a little from the normal. Thrombocytopenia is present in about 25% of patients, and reactive thrombocytosis frequently develops during recovery. This thrombocytosis may account for cases of deep-vein thrombophlebitis complicating acute Q-fever in some series.

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

The transparent or opalescent cerebrospinal fluid flowing in lumbar puncture is at normal or elevated pressure. Its protein content is normal or slightly increased; the cytosis is increased at the expense of lymphocytes (30-1500 cells per mm^3). The sugar and chloride content is normal. The C. Burneti is often discovered in the cerebrospinal fluid. But more often the results of liquor investigation indicate of meningism presence.

An elevated hepatic transaminase level is a common finding and is present in nearly 70% patients who require hospitalization. There are hypergammaglobulinemia and decrease of prothrombin index as a result of protein-synthesis function damages.

C. burnetii can be isolated from buffy-coat blood samples or tissue specimens by a shell-vial technique; however, most laboratories are not currently permitted to attempt the isolation of C. burnetii, since it is considered highly infectious.

The diagnosis is based on a high index of suspicion suggested by the epidemiologic features and is proven by serologic testing.

Determination of antibodies to C. burnetii can be achieved by means of complement fixation, indirect immunofluorescent antibody testing, and enzyme-linked immunosorbent assay. These tests are performed in reference laboratories, and indirect immunofluorescent antibody testing is the reference method of choice. Seroconversion generally occurs between days 7 and 15 and is almost always present by 21 days.

In chronic disease, a single elevated level is often diagnostic.

Culturing this organism can be accomplished, but this is dangerous because

laboratory-transmitted cases are reported.

Polymerase chain reaction (PCR) can be used with tissue specimens, but these are not generally available commercially.

A chest radiograph is the only imaging study that is likely to be useful. An atypical pneumonia pattern may be observed, similar to the pattern seen with pneumonia caused by viruses and Mycoplasma, Chlamydia, and Legionella species.

In the rare patient with prominent neurologic symptoms, CT scanning of the brain may be indicated.

In cases of Q-fever endocarditis, the cardiac echocardiogram demonstrates vegetations in only 12% of cases.

Pericardial effusion may also be seen in Q-fever.

TREATMENT

Treatment of Q-fever is etiotropic, symptomatic, and supportive. Bed rest and mild analgesic-antipyretic therapy (aspirin, ibuprofen) often are helpful in relieving the lethargy, malaise, and fever associated with the disease. The prescription anti-inflammatory and antihistamine drugs are shown in connection with allergic reorganization of the organism, especially in prolonged and chronic forms 0f the disease with serious course.

The most effective specific medicines are antibiotics of the tetracycline group. Tetracycline is prescribed on 2g in a day till 7-10 days of the normal temperature. Treatment of acute Q-fever with doxycycline (100 mg twice daily for 14 days) is usually successful too. Fluoroquinolones are also effective. Treatment of chronic Q-fever should include at least two antibiotics active against C. burnetii. The optimal duration of antibiotic therapy for chronic Q-fever remains undetermined.

The prognosis with acute Q-fever is excellent, with a low mortality rate (about 1%) in hospitalized patients. Children usually are more mildly affected than adults.

Chronic Q-fever has a mortality rate of about 25%.

PREVENTION

Prophylaxis includes complex veterinary, antiepidemiological and sanitary-hygienic measures. The specific prophylaxis is performed out with using killed or living vaccine. In endemic areas of Q-fever the persons, working with animals, must be vaccinated.

MARSEILLES FEVER

Marseilles fever is acute rickettsial transmissible disease with benignant course, is characterized by presence of primary affect, regional lymphadenitis, and general maculopapular rash.

The names for this disease vary with the region in which it occurs; examples include Mediterranean spotted fever (also known as boutonneuse fever), Kenya tick typhus, Indian tick typhus, Israeli spotted fever, and Astrakhan spotted fever. Whatever the designation, the clinical manifestations are similar.

ETIOLOGY

The etiologic agent that causes Mediterranean spotted fever is Rickettsia conorii. It is a typical spotted fever group rickettsia, having more than 90 percent DNA homology with Rickettsiae. There are also cross - reactive protein, and lipopolysaccharide antigens and cross -protection antigens is shared among R. Conori, R. Siberia and R. Rickettsiae. It has as toxic as hemolytic activity. Rickettsiae are obligate, intracellular gram-negative coccobacilli that measure 1 μm X 0.3 μm and are found within the cytoplasm and occasionally the nucleus of eukaryotic cells.

EPIDEMIOLOGY

Mediterranean spotted fever is transmitted by the common dog tick Rhipicephalus sanguineous. Rh. sanguineous is the vector and reservoir. The dog constitutes the reservoir of the R. Conori. Dogs have been shown to be susceptible to inoculation and their blood has been proved to be infective both for man and monkeys. R. Conori is maintained transovarially in thicks and is transmitted to humans by tick bite. The cases occur mainly in warm months with the peak incidence in July, August, and September in many Mediterranean locations.

Mediterranean spotted fever is prevalent in southern Europe, Africa, and central Asia, including India. The frequency of travel-associated Mediterranean spotted fever has increased worldwide because of increased travel to endemic areas, including ecotourism.

Susceptibility is general. After disease life-long immunity develops.

PATHOGENESIS

Pathogenesis is such as rickettsioses of the group of louse-borne typhus , but the changes of the vessels are less marked. The pathophysiologic hallmark of R conorii infection is the invasion of vascular endothelial cells by the organism, causing endothelial injury and tissue necrosis, which is illustrated by the tache noire or eschar at the tick bite site. The primary affect is the local inflammation of the skin on the place of the reproduction of rickettsiae with necrosis in the center. The black

crust appears on the 5-8 day till rising of the temperature. The dermal and epidermal necrosis and perivascular edema are the consequences of endothelial injury by R. Conori. Necroses of fatal cases reveal disseminated vascular infection and injury by R. Conori including meningoencephalitis and vascular lesions in kidneys, lungs, gastrointestinal tract, liver, pancreas, heart, spleen, and skin. Thrombosis is not an important pathogenic mechanism in this infection, but deep venous thrombosis can occur late in the course of illness.

CLINICAL MANIFESTATIONS

The incubation period of Mediterranean spotted fever is approximately 3-16 (more often – 5-7) days after an often-unnoticed, painless tick bite.

There are 3 periods of disease:

- initial period (from the first days of fever to rash appearance, it last 2-4 days);
- height of disease (from rash appearance to normalization of body temperature, it last 3-10 days);
- recovery period (after normalization of body temperature).

The onset of disease is abrupt with intense headache, chills, fever (39-40ºC), arthralgias and myalgias. Dizziness, malaise, insomnia, backache, anorexia, nausea, vomiting, diarrhea, pain in abdominal region are observed in the patients. The face is edematous and hyperemic; eyes are brilliant with injected sclera.

The primary affect («black spot») is an early sign of the disease. The crust usually falls on 4-5 day of the normal temperature. The localization of the primary affect is the strips of the skin covering by clothes. It is revealed difficulty, because the bite of the tick is painless. On the 3-4 day of the disease the rash appears on the abdomen and then on the chest and alone all the body, including palms and reams. There is regional lymphadenitis. The skin rash in this disease is usually maculopapular (d – 0,2-1 sm) but is sometimes vesicular, and there is an inoculation eschar. There is no itch. The changes from the side of the, internal organs are such as other rickettsioses. Often the spleen is increased, the liver is increased rarely. The meningeal syndrome is no typical. Retinopathy, sensorineural hearing loss, and other neurologic manifestations (although rare) may be occurring.

The complications occur rarely. It may be pneumonia, phlebitis of lower extremities (the main vascular complication, deep vein thrombosis possible), neurologic involvement, autoimmune anemia, cryoglobulinemia, respiratory distress syndrome, multi-organ failure.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of Mediterranean spotted fever includes epidemic typhus, measles, rubella, malaria, Q-fever, hepatitis, meningitis.

DIAGNOSIS

The diagnosis of these other tick-borne spotted fevers is based on clinical and epidemiologic findings and is confirmed by isolation of rickettsiae or by serology. In an endemic area, patients presenting with fever, rash, and/or a skin lesion consisting of a black necrotic area or a crust surrounded by erythema should be considered to have one of these rickettsial spotted fevers. History typically includes physical contact with dogs in endemic areas.

The leukopenia, lymphocytosis, the ESR is accelerated moderately.

Serologic assays are sometimes difficult to interpret, since members of the spotted fever group have extensive cross-reactivity. In some cases, R conorii can be isolated from blood or skin biopsy at the eschar site.

Polymerase chain reaction or western blot studies can be used to differentiate R conorii from rickettsia africae. Species isolation should be considered in patients with unusual cases, including severe disease, and those traveling from areas with poorly defined rickettsial activity.

Currently, indirect fluorescent antibody is the most commonly used test to confirm the diagnosis of Mediterranean spotted fever. Serum specimens should be collected early in the disease course.

R conorii may be cultured from blood samples using VERO cells, primary chicken embryo, fibroblast, and other cell lines or by intraperitoneal inoculation of adult male guinea pigs.

Histologic Findings

Characteristic histopathologic findings at the site of the primary lesion consist of epidermal ulceration, hyperplasia of the endothelium of the small dermal antinodes, and perivascular infiltrates in the dermis.

TREATMENT

The treatment is such as the other Rickettsioses.

The goals of pharmacotherapy are to reduce morbidity, to prevent complications, and to eradicate the infection. Patients with Mediterranean spotted fever typically improve within 24 hours after initiation of therapy, and a delay in response should cast doubt on the diagnosis.

Antibiotics:

The course of Mediterranean spotted fever can be shortened with appropriate treatment. The preferred drug is doxycycline (100 mg PO q12h). Other effective treatments include the following: ciprofloxacin (200 mg IV q12h or 750 mg PO q12h), levofloxacin (500 mg PO qd), chloramphenicol (50-60 mg/kg/d PO q6h in 4 divided doses), macrolides such as azithromycin (500 mg PO qd) and clarithromycin (500 mg PO bid) (These have been shown to be efficacious in children and can be used as alternatives to doxycycline in adults.)

Mediterranean spotted fever is usually a benign disease, and fatalities are uncommon. A clinically severe form of the disease, associated with a 50 percent mortality rate, has been observed in patients with diabetes, alcoholism, or heart failure.

PREVENTION

Prophylaxis in endemic areas includes obligatory registration of the dogs every year, the processing of the dogs and the places of the ticks. To prevent infection by rickettsiae, precautions should be taken to avoid contact with ticks. Protective clothing should be worn, preferably impregnated with permethrin or another pyrethroid. Topical repellents can be used on any exposed skin; however, frequent application is recommended because of short-lasting effect (approximately 1-2 h per application). Daily self-checks and removal of ticks should be performed during travel.

BRUCELLOSIS

Brucellosis – zoonotic infectious disease, which caused by any of four species of Brucella genus, characterized by multiple organ affections with primary involvement in pathological process musculoskeletal and nervous systems.

ETIOLOGY

Among the 4 Brucella species known to cause disease in humans (***B abortus, B melitensis, B canis, B suis***). Human brucellosis can be caused by: Brucella melitensis (the most common cause worldwide) is acquired primarily from goats, sheep, and camels; ***Brucella abortus*** from cattle; ***Brucella suis*** from hogs; and ***Brucella canis*** from dogs. B melitensis is thought to be the most virulent and causes the most severe and acute cases of brucellosis. ***B melitensis*** is also the most prevalent worldwide. A prolonged course of illness, often associated with suppurative destructive lesions, is associated with ***B suis*** infections. ***B abortus*** is associated with mild-to-moderate sporadic disease that rarely causes complications. ***B canis*** infection has a disease course that is indistinguishable from ***B abortus*** infection. B canis infection has an insidious onset, causes frequent relapses, and does not commonly cause chronic brucellosis. These small aerobic gram-negative bacilli are unencapsulated, nonmotile, non-spore-forming, facultative intracellular parasites. These organisms are shed in large numbers in the animal's urine, milk, placental fluid, and other fluids. Exposure to infected animals and animal products causes brucellosis in humans. Brucellae are killed by boiling or pasteurization of milk and milk products. They survive for up to 8 weeks in unpasteurized, white, soft cheese made from goat's milk and are not killed by freezing. The organisms remain viable for up to 40 days in dried soil contaminated with infected-animal urine, stool, vaginal discharge, and products of conception and for longer periods in damp soil.

EPIDEMIOLOGY

Brucellosis causes more than 500,000 infections per year worldwide. The heaviest disease burden lies in countries of the Mediterranean basin and Arabian Peninsula, and the disease is also common in India, Mexico, and South and Central America. Brucella is transmitted most commonly through the ingestion of untreated milk or milk products, raw meat, or bone marrow. However, the organism can be contracted via inhalation during contact with animals, especially by children and by slaughterhouse, farm, and laboratory workers. Other routes of infection for at-risk workers include skin abrasion, autoinoculation, and conjunctival splashing. The organism has been transmitted from person to person through the placenta, during breast feeding, and (in rare instances) during sexual activity. Worldwide, brucellosis

is more common in males than in females. Persons in their third to fifth decades of life were most commonly affected. Brucellosis in children comprises 3-10% of reported cases worldwide, with a heavier burden in endemic areas. Elderly persons typically develop chronic brucellosis.

PATHOGENESIS

Brucella species have a unique ability of invading both phagocytic and nonphagocytic cells and surviving in the intracellular environment by avoiding the immune system in different ways, explaining why brucellosis is a systemic disease and can involve almost every organ system.

After ingestion by phagocytes, approximately 15-30% of Brucella organisms survive. In polymorphonuclear or mononuclear phagocytic cells, the bacteria use numerous mechanisms to avoid or suppress bactericidal responses. Brucella species have relatively low virulence, toxicity, and pyrogenicity, making them a poor inducer of some inflammatory cytokines such as tumor necrosis factor (TNF) and interferons. Also, the bacteria do not activate the alternative complement system.

Inflammatory responses or granulomas may develop, and caseation, necrosis, and abscess formation have been described. Endogenous interleukin (IL)-12 has a strong inducing effect on interferon g-producing T cells, which also play a key role in the host's defense against Brucella infection; in contrast, IL-10 downregulates protective immunity to Brucella. Intracellular multiplication of the organism takes place in lymph nodes and reticuloendothelial tissues. Other organs may also be affected through hematogenous spread.

Immunity to Brucella is determined by phagocytosis mediated by specific antibodies and by cell-mediated mechanisms. Brucella organisms are phagocytosed by polymorphonuclear leukocytes and by activated macrophages. Brucella antigens are capable of inducing the production of specific antibodies. Serum IgM antibodies appear early after infection and are followed later by IgG and IgA.

Susceptibility to intracellular killing differs among species, with B abortus readily killed and B melitensis rarely affected; this might explain the differences in pathogenicity and clinical manifestations in human cases of brucellosis.

CLINICAL MANIFESTATIONS

Symptoms of brucellosis are protean in nature, and none is specific enough to support the diagnosis.

The incubation period lasts for about 2 days to 2 months. The onset of symptoms may be either abrupt (over 1 to 2 days) or gradual (over 1 week or more). The most common symptoms are fever, chills, diaphoresis, headaches, myalgia, fatigue, anorexia, joint and low-back pain, weight loss, constipation, sore throat, dry cough, lymphadenopathy, and hepatosplenomegaly. Fever is sign of brucellosis, occurring in

80-100% of cases. It is intermittent in 60% of patients with acute and chronic brucellosis and undulant in 60% of patients with subacute brucellosis. Fever can be associated with a relative bradycardia and with chills. Constitutional symptoms of brucellosis include anorexia, asthenia, fatigue, weakness, and malaise and are very common (>90% of cases). Bone and joint symptoms include arthralgias, low back pain, spine and joint pain, and, rarely, joint swelling. Neuropsychiatric symptoms of brucellosis are common despite the rare involvement of the nervous system. Headache, depression, and fatigue are the most frequently reported neuropsychiatric symptoms. Gastrointestinal symptoms, present in 50% of patients, include abdominal pain, constipation, diarrhea, and vomiting. Neurologic symptoms of brucellosis can include weakness, dizziness, unsteadiness of gait, and urinary retention. Symptoms associated with cranial nerve dysfunction may affect persons with chronic CNS involvement. Cough and dyspnea develop in up to 19% of persons with brucellosis; however, these symptoms are rarely associated with active pulmonary involvement. Pleuritic chest pain may affect patients with underlying empyema.

Subclinical, acute, subacute, and chronic infections are the classic categorizations of brucellosis. Localized and relapsing forms have also been described.

Subclinical brucellosis: Disease is usually asymptomatic, and the diagnosis is usually established incidentally after serologic screening of persons at high risk of exposure. Culture data are usually unrevealing.

Acute or subacute brucellosis: Disease can be mild and self-limited (e.g., B. abortus) or fulminant with severe complications (e.g., B. melitensis). Associated symptoms can develop at 2-3 months and 3-12 months prior to diagnosis, respectively.

Chronic brucellosis: The diagnosis is typically made after symptoms have persisted for 1 year or more. Low-grade fevers and neuropsychiatric symptoms predominate. Results of serologic studies and cultures are often negative; without confirmatory evidence, many authorities doubt the existence of chronic disease. Many patients have persistent disease caused by inadequate initial therapy, and underlying localized disease may be present.

Residual brucellosis: constant changes in different organs and tissues in patients with chronic brucellosis.

Localized complications of brucellosis are typically observed in patients with acute disease or chronic untreated infection. Osteoarticular, genitourinary, and hepatosplenic involvement are most common. Cultures of involved tissue sites and serology can be diagnostic.

Physical findings in patients with brucellosis vary and are nonspecific for the disease.

Bones and joints. Although monarticular septic arthritis occurs, 30 to 40 percent

of patients have reactive asymmetric polyarthritis involving the knees, hips, shoulders, and sacroiliac and sternoclavicular joints.

Brucella osteomyelitis commonly affects the lumbar vertebrae, starting at the superior end plate (an area with a rich blood supply) and occasionally progressing to involve the entire vertebra, disk space, and adjacent vertebrae. Extraspinal brucella osteomyelitis is rare. In brucella septic arthritis and osteomyelitis, the peripheral white cell count is normal, while the erythrocyte sedimentation rate may be either normal or elevated.

Heart cardiovascular complications of brucellosis include endocarditis, myocarditis, pericarditis, aortic root abscess, mycotic aneurysms, thrombophlebitis with pulmonary aneurysm, and pulmonary embolism. Brucella endocarditis may develop on valves previously damaged by rheumatic fever or congenital malformation but also occurs on previously normal valves. The clinical features are indistinguishable from those of endocarditis caused by other organisms.

Respiratory tract. Brucella can produce respiratory symptoms. A flulike illness with sore throat, tonsillitis, and dry cough is common and usually mild. Hilar and paratracheal lymphadenopathy, pneumonia, solitary or multiple pulmonary nodules, lung abscesses, and empyema have been reported.

Gastrointestinal tract. Gastrointestinal manifestations of brucella infection are generally mild and may include nausea, vomiting, constipation, acute abdominal pain, and/or diarrhea. Pathologic examination of the liver may reveal any of several changes, including noncaseating granuloma, suppurative abscesses, or mononuclear cell infiltration. Hepatic and splenic enlargement may be documented in 15 to 20 percent of cases, and abscesses may develop in the liver and spleen. Mild jaundice may be evident, with elevated levels of bilirubin and hepatic enzymes.

Genitourinary tract. Various genitourinary infections have been attributed to brucella, including unilateral or bilateral epididymoorchitis, which is a self-limiting manifestation. Prostatitis, seminal vesiculitis, dysmenorrhea, tuboovarian abscess, salpingitis, cervicitis, and acute pyelonephritis have also been documented. Brucella has been cultured from the urine in up to 50 percent of cases of genitourinary tract infection.

Central nervous system. Neurobrucellosis is uncommon but serious and includes meningoencephalitis, multiple cerebral or cerebellar abscesses, ruptured mycotic aneurysms, myelitis, Guillain-Barre syndrome, cranial nerve lesions, hemiplegia, sciatica, myositis, and rhabdomyolysis. Papillitis, papilledema, retrobulbar neuritis, optic atrophy, and ophthalmoplegia due to lesions in cranial nerves III, IV, and VI may occur in Brucella meningoencephalitis. Cerebrospinal fluid (CSF) pressure is usually elevated; the fluid may appear clear, turbid, or hemorrhagic; the protein concentration and cell count (predominantly lymphocytes) are elevated; and the glucose concentration may be either reduced or normal. In brucella meningitis, the

organism may be cultured from the CSF.

Other manifestations. Splashing of the eyes with virulent brucellae or with organisms in veterinary vaccines may result in keratitis, corneal ulcers, uveitis, retinal detachment, and endophthalmitis.

Skin manifestations of brucellosis are uncommon. They include maculopapular eruptions, purpura and petechiae, chronic ulcerations, multiple cutaneous and subcutaneous abscesses, discharging sinuses, superficial thrombophlebitis, erythema nodosum, and pemphigus.

Brucellosis during human pregnancy can cause fetal death. Brucella has been isolated from the human placenta and fetus.

Endocrinologic findings in brucellosis include thyroiditis, adrenal insufficiency, and the syndrome of inappropriate secretion of antidiuretic hormone.

DIFFERENTIAL DIAGNOSIS

Similar symptoms can occur with many other infections: malaria, typhoid fever, sepsis, epidemic typhus, leptospirosis, tularemia, Q-fever, tuberculosis, infectious mononucleosis, viral hepatitis, lymphogranulomatosis.

DIAGNOSIS

As mentioned above, symptoms and signs of brucellosis are unspecific; cultures and serology are usually necessary for diagnosis. Some general laboratory findings might suggest the diagnosis (e.g., leukopenia, relative lymphocytosis, and pancytopenia). Slight elevation in liver enzymes is a very common finding. The criterion standard test for diagnosis of brucellosis is the isolation of the organism from the blood or tissues (e.g., bone marrow, liver aspiration).

The sensitivity of blood cultures with improved techniques such as the Castaneda bottles is further improved by the lysis-centrifugation technique. With these methods, the sensitivity is approximately 60%. Subcultures are still advised for at least 4 weeks; thus, if brucellosis is suspected, the laboratory should be alerted to keep the cultures for 3-4 weeks, which is not done routinely for most bacterial cultures. Bone marrow culture is thought to be the criterion standard, since the reticuloendothelial system holds a high concentration of brucellae. Sensitivity is usually 80-90%. Any fluid can be cultured (synovial, pleural, cerebrospinal), but the yield is usually low. CSF evaluation: This reveals a mild-to-modest lymphocytic pleocytosis in 88-98% of in patients with neurobrucellosis. Protein levels are elevated in conjunction with normal glucose levels.

Serological testing is the most commonly used method of brucellosis diagnosis.

Serum tube agglutination test: This test measures antibodies against smooth LPS; it remains the most popular test tool for the diagnosis of brucellosis.

Other tests such as tray agglutination (TAT) and modified TAT, ELISA,

polymerase chain reaction (PCR) are also popular.

Chest radiography. Radiographic findings are typically absent in brucellosis, even in patients with prominent respiratory symptoms.

Findings observed in patients with active pulmonary involvement include hilar and paratracheal lymphadenopathy, pulmonary nodules, pleural thickening, and pleural effusion.

Spinal radiography. Radiographic findings in patients with osteoarticular disease occur later in the course of illness, usually 2-3 weeks after the onset of symptoms.

In patients with sacroiliitis, the most commonly observed abnormalities include blurring of articular margins and widening of the sacroiliac spaces.

Spondylitis-related abnormalities include anterosuperior vertebral angle epiphysitis, spinal straightening, narrowing of the intervertebral disc spaces, end-plate sclerosis, and osteophytes.

Radionuclide scintigraphy. This study is more sensitive for revealing skeletal abnormalities, especially early in the disease, when standard radiographic findings are usually normal.

Histologic Findings. Histologic findings in brucellosis usually include mixed inflammatory infiltrates with lymphocytic predominance and granulomas (in up to 55% of cases) with necrosis.

TREATMENT

No special diet is required for the treatment of brucellosis.

Although multiple antibiotics display in vitro activity against Brucella species, clinical response has been demonstrated with only a limited number of agents. Drugs that display clinical activity with low relapse rates include doxycycline, gentamicin and streptomycin, rifampin, and TMP-SMX. Other agents with potential roles include chloramphenicol, imipenem-cilastatin, and fluoroquinolones. When relapse has occurred, the development of antibiotic resistance does not appear to be the underlying cause.

Single-agent therapy for brucellosis has now been abandoned because of the high incidence of failure and relapse and the potential development of resistance. Relatively short courses (less than 8 weeks) of treatment with antibiotic combinations have similarly been associated with high rates of relapse. The combination of doxycycline and an aminoglycoside (streptomycin, gentamicin, or netilmicin) for 4 weeks followed by the combination of doxycycline and rifampin for 4 to 8 weeks is the most effective regimen. Doxycycline (which is preferred over tetracycline) is given orally in a dose of 100 mg twice daily. Streptomycin is given intramuscularly in a dose of 2 g once daily to patients under 45 years of age and in a dose of 1 g/d to older patients. Gentamicin is given intramuscularly or as a slow intravenous infusion (3 to 5 mg/kg per day in divided doses every 8 h). Tetracycline is given orally in a

dose of 250 mg every 6 h and rifampin as a single daily dose of 600 to 900 mg. An alternative regimen consists of the doxycycline/rifampin combination given for 8 to 12 weeks. The doxycycline/netilmicin (or doxycycline/streptomycin) combination is more effective than the doxycycline/rifampin combination in that rifampin reduces levels of doxycycline in plasma.

When used alone, fluoroquinolonessantibiotics with good intracellular penetration and efficacy against Brucella in vitroshave has been associated with the development of quinolone resistance and with high rates of failure and relapse. At present, clinical data are inadequate for the formulation of recommendations regarding the combination of fluoroquinolones with doxycycline, rifampin, or streptomycin.

Third-generation cephalosporins (ceftriaxone), although active in vitro against Brucella when used alone, have also been associated with a high incidence of clinical failure and relapse. These agents may be useful in combination with other drugs for the treatment of Brucella meningitis.

Pregnant women: Brucellosis treatment is a challenging problem with limited studies. The recommendation is a regimen of rifampin alone or in combination with trimethoprim-sulfamethoxazole (TMP-SMZ). However, TMP-SMX use by the end of pregnancy is associated with kernicterus.

In cases of neurobrucellosis, aortic root abscess, and endocarditis, rifampin should be added to the doxycycline/aminoglycoside combination. Cardiac surgery may be needed along with antibiotic therapy in the acute stage, particularly in cases of Brucella endocarditis and aortic root abscess. In instances of renal failure, doxycycline can be used safely. In contrast, the use of aminoglycosides requires facilities for the monitoring of plasma levels; if such facilities are not available, then the doxycycline/rifampin combination should be administered for 8 to 12 weeks.

Within 4 to 14 days after the initiation of therapy, patients become afebrile and constitutional symptoms disappear. The enlarged liver and spleen return to their normal size within 2 to 4 weeks. An acute, intense flare-up of symptoms may follow the start of treatment, especially that with tetracyclines. This reaction is transient and does not necessitate the discontinuation of therapy. In endemic areas the coexistence of brucellosis and tuberculous spondylitis may result in a failure to respond to appropriate treatment. Treated patients whose infections are apparently cured should be followed up clinically and serologically, with repeat blood cultures, every 3 to 6 months for 2 years.

PROGNOSIS

Deaths attributable to brucellosis should be avoidable. Even before the discovery of antibiotics, mortality was less than 2 percent and endocarditis was most frequently the cause of death. Morbidity due to brucellosis remains significant; its severity

depends on the infecting Brucella species and is greatest with B. melitensis. Spinal damage, paraplegia, and other neurologic deficits may occur. Nerve deafness due to meningitis or secondary to treatment with streptomycin has been documented.

PREVENTION

Efforts at prevention should be aimed at the source of infection. Immunization of animals and boiling or pasteurization of milk and milk products are important. Inform persons with an occupational risk for brucellosis about the use of protective devices (goggles, masks, gloves) to avoid exposure to aerosols, body fluids, and inadvertent vaccine exposure. Inform travelers to endemic areas about appropriate dietary hygiene. Advise laboratory personnel about the potential diagnosis so they will use biosafety level-3 precautions when in contact with suspicious specimens. Workers in the meat and dairy industries have been vaccinated; the vaccine has markedly reduced the rate of infection. However, immunity is short-lived, and vaccination should be repeated every 2 years.

SEPSIS

The problem of sepsis is characterized by: difficulties in diagnosis; expensive therapy; high mortality rates; Sepsis is one of the most severe and frequent infections. The death rate in sepsis is very high. Sepsis (from Greek sepsis - "putrefaction") is a generalized infectious disease developing due to the presence of an infection focus in the organism. It has its own etiological, epidemiological, clinical, immunological and pathological characteristics. Sepsis is not contagious, it cannot be reproduced experimentally. Sepsis is a disease caused by different microorganisms and characterized by absence of cyclic course, stereotypic manifestation, and also depression of barrier systems of the organism. Infectious diseases are differenced from the other diseases by specificy of the agent, cyclic of the course, development of immunity after disease. Sepsis has essential differences from the other infectious diseases: Sepsis is polyetiological disease. The agents of sepsis may be different microorganisms-aerobia and anaerobia. There is ho united entrance gates. There is no cyclicy of the course. Immunity is not developing in sepsis. Sepsis syndromes are clinically defined on a spectrum of increasing disease severity as sepsis, severe sepsis, and septic shock. Sepsis is the presence of SIRS (systemic inflammatory response syndrome) in the setting of infection. Severe sepsis is infection with evidence of endorgan dysfunction as a result of hypoperfusion. (Polyorgan failure). SIRS criteria (R. Bone). Meeting SIRS criteria is defined by the having at least 2 of the following 4 abnormalities: 1. Temperature higher than 38°C or lower than 36°C; 2. Heart rate greater than 90 beats per minute; 3. Respiratory rate greater than 20 breaths per minute; 4. WBC count higher than 12,000/mm3 or lower than 4,000/mm3 or with more than 10% immature forms (bands). Sepsis it is SIRS criteria + documentary Bacteriemia (that confirmatory with help of blood culture; Serious sepsis it is Sepsis + organs dysfunction; Septic shock it is sepsis + hypotension. Septic shock is severe sepsis with persistent hypotension despite fluid resuscitation and resulting tissue hypoperfusion. Sepsis - the systemic inflammatory answer of an organism to an infection on background immunodeficiency (or without this), described by infringement of balance of mediators of immune reactions, defeat of vascular. Bacteriemia is defined by the isolation of bacteria from the peripheral blood. Bacteriemia is not obligate sepsis endothelium, epithelial barrier of an intestine and formation poliorgans of failure. Bacteremia is defined as the presence of viable bacteria within the liquid component of blood. Bacteremia may be primary (without an identifiable focus of infection) or, more often, secondary (with an intravascular or extravascular focus of infection). While sepsis is commonly associated with bacterial infection, bacteremia is not a necessary ingredient in the activation of the inflammatory response that results in severe sepsis. In fact, septic shock is associated with culture-positive bacteremia in only 30-50% of cases.

Septicaemia is a term used to denote those clinical states in which bacteria are present in the bloodstream and cause systemic symptoms such as fever and hypotension. It is the most common cause of the systemic inflammatory response syndrome. However, the manifestations of septicaemia can also be induced by non-bacterial infectious agents, by nonliving bacterial or fungal products, or by a variety of non-infectious conditions such as major trauma, bums, or pancreatitis. Septicemia is an acute condition; most cases of infective endocarditis or miliary tuberculosis would not be included, even though many of the symptoms and signs are the same. Lastly, septicaemia has a connotation of urgency; unless the right things are done quickly, the patient is likely to die.

ETIOLOGY

Almost any bacterium known to man may cause septicaemia on occasion. However, some organisms do so regularly in healthy people, while others need considerable assistance even to cause disease in sick people. Anything is possible, but not everything is equally frequent, and useful clinical information can be gained from a consideration of the circumstances under which the septicaemia arose. Neisseria gonorrhoeae; Saphylococcus aureus (MRSA, MRSE); Sreptococcus pneumonia; Non-typhoidal salmonellae; Strep. Faecalis; Neisseria meningitides; Listera monocytogenes; Esherichia coli, Pseudomonas, etc.; The most frequent etiologic factor of sepsis are auto- or external microflora. These agents are staphylococci, streptococci, colibacilla and other so called conditionally pathogenic microorganisms. Rarely, a reason of the sepsis may be obligate parasites. The septic agent may be blue pus bacillus, gonococci, meningococci, bacillus anthracis, salmonella, fungi and others. But, at the last time staphylococcus is found more often than others. Staphylococcus aureus plays the most important role in the pathology of human. Now most important role as etiological agent of sepsis plays Gram-negative bacteria.

EPIDEMIOLOGY

Staphylococcous infection is widely spread among hospitalized persons. Intrahospital distribution is the typical feature of epidemiology of staphylococcous infection. Intrahospital infections are characterized by large quantity of the sources of infection, multiply ways and factors of transmission of the agent and persons with increased risk of the infection. The sources intrahospital infection is the patients with different forms of staphylococcous purulent infection, carriers of staphylococcus. Carriers of staphylococcus from medical personnel play an important role in the conditions of the hospital. The ways and factors of transmission of staphylococcous infections are different: respiratory-drug, contact and alimentary. Transmission of the agent may be realized by alimentary way. For example, it is possibly infection of infants in born-hause with solutions for drink and milk, using for supplementary

nourishment. Staphylococcous infection has sporadic character in observance of sanitary-antiepidemic regime. Epidemic outbreaks of intrahospital staphylococcous infections may be in violation of regime. Staphylococcous infection develops as rule in persons with decreased nonspecific resistance, with different infectious diseases (especially, viral etiology), after chronic diseases, in persons after massive doses of immunodepressors, antibiotics, hormones, X-ray therapy.

PATHOGENESIS

Sepsis is characterized by a similar response to infection, although on a systemic level, resulting in diffuse endothelial dysfunction. In the case of bacterial infection, the inciting event is the interaction with the host immune cells of endotoxins (LPS) contained within the bacterial cell wall of gram-negative organisms. In gram-positive organisms, this interaction occurs with either cell wall components or exotoxins released by the organism. As a result of these interactions, cellular activation occurs with the release of cytokine and noncytokine mediators, the most notorious of which are tumor necrosis factor-alpha (TNF-alpha), interleukin 1 (IL-1), and interleukin 6 (IL-6), («storm of cytokines»). These factors are implicated in the diffuse activation of a systemic inflammatory response. As a result, mediators with vasodilatory and endotoxic properties are released systemically, including prostaglandins, thromboxane A2, and nitric oxide. This results in vasodilation and endothelial damage, which leads to hypoperfusion and capillary leak (but next - hiperdinamic rection and spasm of vesels). In addition, cytokines activate the coagulation pathway, resulting in capillary microthrombi and endorgan ischemia. The prevailing theory has been that sepsis represents an uncontrolled inflammatory response. Numerous trials were conducted of agents that block the inflammatory cascade - corticosteroids, antiendotoxin antibodies, tumor necrosis factor (TNF) antagonists, interleukin-1–recep-tor antagonists, and other agents. The failure of antiinflammatory agents led investigators to question whether death in patients with sepsis results from uncontrolled inflammation. The theory that death from sepsis was attributable to an overstimulated immune system was based on studies in animals that do not seem to reflect the clinical picture in humans These studies used large doses of endotoxin or bacteria; consequently, levels of circulating cytokines such as tumor necrosis factor a (TNF-a) were exponentially higher in animals than they are in patients with sepsis. In these studies, the animals died from “cytokine storm,” and compounds and macromolecules that block these mediators improved survival. Mononuclear cells from patients with burns or trauma have reduced levels of Th1 cytokines but increased levels of the Th2 cytokines interleukin-4 and interleukin-10, and reversal of the Th2 response improves survival among patients with sepsis. Apoptotic cell death may trigger sepsis-induced anergy. Although the conventional belief was that cells die by necrosis, recent work has shown that cells can die by

apoptosis - genetically programmed cell death. In apoptosis, cells “commit suicide” by the activation of proteases that disassemble the cell. Large numbers of lymphocytes and gastrointestinal epithelial cells die by apoptosis during sepsis. A potential mechanism of lymphocyte apoptosis may be stress-induced endogenous release of glucocorticoids. Neutrophils have been regarded as double-edged swords in sepsis. Although neutrophils were thought to be essential for the eradication of pathogens, excessive release of oxidants and proteases by neutrophils was also believed to be responsible for injury to organs. Because of the intrapulmonary sequestration of neutrophils and the frequent complication of the acute respiratory distress syndrome in patients with sepsis, this link between overly exuberant neutrophil activation and organ injury was thought to affect the lungs in particular. Although findings from studies in animals implicated neutrophil-mediated injury, other studies in which granulocyte colony - stimulating factor (G-CSF) was used - to increase the number of neutrophils and enhance their function - demonstrated improved survival among patients with sepsis. Autopsy studies in persons who died in the intensive care unit show that the failure to diagnose and appropriately treat infections with antibiotics or surgical drainage is the most common avoidable error.

The factors of risk, promoting the penetration of the normal germs of skin and mucous membranes into internal mediums of the macroorganism, may be different causes: injuries, inflammations, trophic disorders, aggression of different microflora, congenital anomalies. The following distribution of microbes in macroorganism may go by different ways - via blood, lymph and direct methastasing. The intermediate localization of the process appears. It may be phlegmon, abscess or other destructive processes. The process is sepsis, when it has generalized character with damage of liver, spleen, lungs, kidneys, and vessels and other organs and systems. The agent of sepsis, penetrating into tissues, causes an inflammatory process. In some cases the process develops impetuously. The purulent inflammatory focus arises on the place of the penetration with reproduction of microbes (primary focus). But in the other cases inflammatory manifestations are less expressive and rapidly disappear, but agent penetrates inside tissues by lymphatic and blood ways and causes inflammatory focus in the distant place. These inflammatory focci may lead to development of sepsis, in corresponding change of reactivity and resistance of the organism. The entrance gates of infection may be in any organ and tissue. The primary focus is more frequently in tissues with the large quantity of lymphatic and blood vessels. For example, in wound sepsis the skin is entrance gates. In urosepsis and gynecological sepsis mucous membranes are entrance gates. Prolonged course of sepsis is marked in patients with localization septic and primary foci in bones, muscles, urogenital system. In some cases, there are no visual foci, except the primary septic focus. These forms are called septicemia. But in the other cases, metastatic secondary purulent foci are formed. These forms are named pyemia. But, also there is possible a transitional

form - septicopyemia. The distribution of infection is realized from the primary focus by blood and lymphatic ways. The distribution of the agents is realized by veins too, with formation of thrombosis and thrombophlebitis. Microbes and their toxins may penetrate to lymphatic vessels and cause lymphangites and lymphadenites. Metastases may be as an infiltrations, phlegmons, and abscesses. The purulent infiltrates may appear in the intestine too. In the serous cavities they are characterized by purulent exudations (arthritis, pleurisy, peritonitis, and pericarditis). The localization of metastases in the lungs is on the first place, kidneys are on the second place, then - other organs. Allergic component has an important role in pathogenesis of the septic process. Primary and secondary septic foci transfer into a source of sensibilisation of human organism. In sepsis the violations of metabolism, acid-alkaline balance, deep changes of balance of proteins and vitamins are observed. Anemia develops due to damage of bone marrow. DIC-syndrome plays an important role in the development of septic state and complications. In some cases of sepsis DIC-syndrome comes out on the first plan and causes fatal outcome in considerable degree. In sepsis dysbalance of immune system has the pathogenetic meaning. Immune deficiency is manifested by decrease of quantity of T-helpers; reduce of activity natural killers and phagocytic activity of granulocytes. These changes lead to development of generalized infectious inflammatory process. In sepsis pathologoanatomy alterations are very various. Petechial rash is marked on the skin. Hemorrhages are observed in organs and tissues, especially on mucous membranes. The alteration of myocardium is marked from turbid swelling till excessive lipid dystrophy. Erosions are revealed in endocardium. Thrombosis of veins is often observed. Spleen is enlarged. There is a turbid swelling or lipid infiltration in liver. Lymphatic nodes are increased. There are plural hemorrhages in kidneys. Also, they are marked in the gastrointestinal tract. Hemorrhages are observed in the adrenal glands. There is edema in the lungs. Sometimes there are foci of bronchopneumonia. The infarction foci are not rare. There are edema and hyperemia of brain's substance. In sepsis with metastases (pyemia) purulent process are observed in brain (purulent meningoencephalitis), lungs, kidneys, thyroid gland. Besides that, purulent pleurisies, peritonitis, pericarditis, phlegmons are observed in different patients.

CLASSIFICATION

A number of features are taken into account in classification: 1) etiology, 2) infection atrium (location of the focus), 3) clinico-mofphological. According to the etiology, the following types of sepsis can be defined: streptococcal, staphylococcal, pneumococcal, gonococcal, pyocyanic, colibacillary, anthracic, tuberculous, mycotic. Depending of the infection atrium (location of the septic focus) sepsis is classified as therapeutic (parainfection), through skin (from furuncles, wounds and traumas of a skin); real surgical through operations; obstetrics (after delivery etc.); tonsillar,

uterine, otogenic, odontogenic, umbilical, veselsgenic (with the septic center in vessels or cavities of heart); cryptogenic. In cryptogenic (from Greek kryptos - secret) sepsis the infection atrium is absent. According to clinic and morphological features there are 4 clinic and anatomical forms of sepsis: septicemia, septicopyemia, septic (bacterial) endocarditis and chronic septicemia. Sepsis syndromes are clinically defined on a spectrum of increasing disease severity as sepsis, severe sepsis, and septic shock. Sepsis is the presence of SIRS in the setting of infection. Severe sepsis is infection with evidence of end-organ dysfunction as a result of hypoperfusion. Septic shock is severe sepsis with persistent hypotension despite fluid resuscitation and resulting tissue hypoperfusion. To define the septic process, there are the criteria proposed by in concert with recommendation of the American Colleague of Physicians and Society of Critical Care. The following were used, modified from references. Renal: serum creatinine concentration of >240 micromol/L, urea concentration of >14 mmol/L, urine output<30 ml per hour. Hepatic: total bilirubin concentration of >36 mmol/L. Pulmonary: pneumonia or adult respiratory distress. Cardiovascular: episode of septic shock (systolic blood of <90 mm Hg, tachycardia of >120 beats per minute, urine output <30 ml per hour, necessity to infuse catecholamines and corticosteroids). Gastrointestinal: upper gastrointestinal bleeding, or prolonged adynamic ileus. Hematological/coagulation: anaemia disseminated intravascular coagulation syndrome. Central nervous system: depression of consciousness, euphoria. Nutrition: arrested wound healing, or albumin value of <40 gL.

Stages of sepsis. 1. Bacteriaemia; 2. Onset of symptoms of systemic inflammatory response; 3. Sepsis; 4. Serious sepsis; 5. Septic shock; 6. Onset of symptoms polyorgans deficiency. Polyorgan failure. The pathological condition which is formed and progresses as a result of heavy nonspecific reaction of an organism to damage or an infection and is accompanied by an inconsistency of two and more organ-functional systems. Purulent-resorptive fever is characterized by presence of purulent foci, wave-like course, and general intoxication. Septicemia is characterized by severe general state, hectictemperature, severe disorders of central nervous system and cardiovascular system. Septicopyemia. This is combination of septicemia and presence of secondary purulent foci in different organs. Chronic sepsis. There are purulent foci in anamnesis in this form. The disease is accompanied by prolonged wave-like fever, presence of period of remission and relapses, periodical formation of purulent foci. In accordance with duration of the course the next form of the diseases are differed: Fulminant sepsis (24-48 hours); Acute sepsis (from 5-7 days till some weeks); Subacute sepsis (3-4 months); Chronic sepsis (from some months till one year and more). In accordance with date of appearance of the process the next variants are differed: Early sepsis (till 3 months from appearance of the primary focus) Late sepsis (later than 3 months). In accordance with character of

microorganism sepsis is differed on: 1. Sepsis, caused by gram-positive flora. It leads, in rarely, to development of septicopyemia. 2. Sepsis, caused by gram-negative flora. Infectious-toxic shock may be in such cases.

CLINICAL MANIFESTATIONS

There is no any specific incubation in septic patients. In one cases, septic process develops for weeks and months after localized focus (abscess), but in the other cases sepsis may be on its background. The complaint of these patients are different as a clinical manifestations -weakness, headache, pain in joints, chill with following sweats or chilling, dry mucous membrane of the mouth, poor appetite, sometimes - diarrhea. The fever is frequently of hectic character in the patients with sepsis. The different variants of the temperature may be - remittent and intermittent types, sometimes, - the temperature is higher in the morning (the reversal type). The temperature may be not high in weak, cachestic patients and elders. Patient's skin is pale, moist and even icteric in severe cases. The different rashes are observed. Rash of hemorrhagic type is marked more frequently, sometimes - pustules, ulcers, erythema. Eruption may be on the skin of the trunk, limbs and face. The mucous membranes of the lips, oral cavity are dry and may have erosions, ulcers, fissures, bleeding sickness. Often, there are hemorrhages of conjunctiva. The pulse is frequent. The arterial pressure decreases. Heart is enlarged. There are a systolic murmur above cardiac apex, tachycardia and "pendulous" rhythm during auscultation. The alterations of myocardium are revealed on cardiogram. The type of this alteration is diffuse or diffuse-focal. Sometimes, the sighs of the injury of endocardium and the large peripheral vessels are revealed (arteritises, phlebitises). The alterations of the respiratory tract are revealed frequently in the patients with sepsis: dyspnoe, bronchitis and pneumonia. Pneumonia has tendency to formation of abscesses. Inrarely, serous, purulent, hemorrhagic and mixed pleurisy arise in the patients. There is a dry coated tongue in these patients. An appetite decreases. Sometimes, vomiting arises. Spleen is frequently enlarged, soft consistention. Liver also increases and painful on palpation; the abscesses may arise inside of abdominal cavity. Septic patient have often a disorders of kidneys and urinary track. Sometimes toxic nephrites, purulent paranephrites arise. The alterations of uterus, perimetrium may be in women. The primary location of inflammatory process is marked inrarely in urogenital organs. Osseous-muscular system is involved to pathologic process, too. There are reports about the serous and purulent mono- and polyarthritis, foci of osteal destruction, degeneration of born marrow, myocytes. Also, the osteal tissue may be site of the primary foci (osteomyelitis). The different manifestations may be from nervous system, such as – a meningismus, purulent meningitis, cerebral and spinal hemorrhages and hemorrhages into the vegetative ganglions.

The signs of anemia are revealed in the blood – decreased of quantity

erythrocytes, hemoglobin. Also, there are signs of the anisocytosis, poikilocytosis and thrombocytopenia. Neutrophilic leukocytosis with shift to myelocytes, increased ESR are marked. Leucopenia may be in cachestic patients with fulminant forms of sepsis. The biochemical changes of the blood are expressive in the patient with sepsis. Increased content of bilirubin and increased activity of transaminases are marked. In sepsis the proteins of serum blood are sharply changed. A quantity of albumins decreases and globulins increased. The changes of concentration of IgA, IgG, IgM depend upon gravity of the course and outcomes of sepsis.

Fulminant sepsis is a rare form, for example, meningococcal sepsis. It has several synonyms. There are – fulminant meningococcemia, acutest meningococcal sepsis, Waterhouse-Friedrichen syndrome. It is the more severe, unfavorable form of meningococcal infection. Its base is infectious-toxic shock. Fulminant sepsis is characterized by acute sudden onset and impetuous course. The temperature of the body rises up to 40-41°C. It is accompanied by a chill. However, hypothermia may be for some hours. Hemorrhagic plentiful rash appears at the first hours of the disease with tendency to confluence and formation large hemorrhages, necroses. The skin is pale, but with a total cyanosis. Patients are anxious and excited. The cramps are observed frequently, especially in children. The recurrent bloody vomiting arises inrarely. Also, a bloody diarrhea may be too. Gradually, a prostration becomes more excessive and with lose of the consciousness.

Acute sepsis is frequent form of sepsis. Staphylococcous sepsis is occurrs very frequently. It is accompanied by considerable fatal outcomes. In the majority of the cases the onset of disease is an acute with chill and increase of the temperature. Fever may be of different character: constant, intermittent, remittent and incorrect. Sometimes sepsis may be with subfebril temperature. Anemia increases in the majority of the patient, because the skin is pale. Sometimes skin has icteric shade due to haemolysis or toxic hepatitis. The rash is in the shape of petechia. Rash is localized on the skin of the chest, forearms, hands, upper extremities, on the mucous membrane of the mouth, conjunctiva and all gastrointestinal tract. Hemorrhages on the mucous membrane of gastrointestinal tract may evoke bloody vomiting and diarrhea. The sizes of hemorrhages are different - from small points till large hemorrhages. An appearance of hemorrhagic rash is explained by present of hemorrhagic vasculitis. Rash may be purulent or erythematosus character due to infectious-allergic dermatitis. The damage of joints is observed in 25-30% of the causes. The large joints are injured more frequently. The joints are edematous. There is hyperemia of the skin over joints. The motions are painful. In sepsis symptoms, connecting with injury of the different organs and system are always expressed. They appear as a result of expressive intoxication, or as primary or secondary purulent inflammatory process. The symptoms, connecting with injury of cardiovascular system are revealed more frequently.

Staphylococcous sepsis may be without injury of endocardium. In this case the clinical symptoms are evoked by dystrophic changes of endocardium. Tachycardia, decreased - arterial pressure, pains - in the heart of indefinite character, enlargement of the borders of the heart, muffled heart sounds are observed. The injury of the vessels may be manifested in the form of phlebitis, development of thromoembolism and also embolism of the small vessels of the skin and internal organs, in this violation of coronary circulation. Oxygenic insufficiency and injury of the respiratory center leads to breathlessness. In the some patient bronchitis, pneumonia, abscesses and pleurisy are observed. Hemorrhagic pleurisy is more typical for staphylococcous sepsis. In staphylococcus sepsis the typical sign is increased liver. The severe septic hepatitis may be observed with development of jaundice and violation of the all functions of the liver and also cholangitis, abscesses. Enlarged spleen (septic mesenchymic spleenitis) is the frequent symptom. Spleen is soft in an acute period, because it is difficult to define spleen on palpation. However, enlarged spleen is clearly defined on percussion. In prolonged course of sepsis spleen becomes dense. The injury of kidneys has essential meaning in clinic of sepsis. In acute process the local nephritis of microbial embolic origin develops, diffusive nephritis develops later. The symptoms of the injury of nervous system are the principal clinical manifestations in the patient with sepsis. In acute sepsis consciousness is preserved even in high temperature. In this period severe headache, sweat, violation of the sleep and dizziness are usual complaints of the patients. In severe cases depression, irritation, sometimes excitement are observed in the patients. Due to edema of the brain meningeal syndrome may be too. It is possible development of the secondary purulent meningitis. The appearance of meningitis is characterized by intensification of headache, addition of vomiting, development of meningeal symptoms. Meningoencephalitis, arachnoiditis and abscess may develop. The course of acute sepsis is from 2 weeks till 3 months. Thus, clinic of acute sepsis is characterized by severe course, marked symptoms of intoxication and symptoms of the injury of separate organs. The frequent manifestation of acute sepsis is development of bacterial endocarditis and purulent inflammatory focuses in different organs (phlebitis, abscesses, pneumonia, pleurisy, pancreatitis, cholangitis, osteomyelitis, otitis, cystitis, violations of brain's blood circulation, hemorrhage into retina of the eye and other.

Subacute sepsis. The duration of this sepsis is 3-4 months. It is differenced from an acute sepsis by lesser intensity of symptoms. Metastases appear more rarely than in acute sepsis. The prognosis is better in this form. This form of sepsis arises in the injury of the heart with rheumatic process. Chronic sepsis is characterized by prolonged course (till one year and more).This form is accompanied with remissions and aggravations with a severe morphologic alteration. Chronic sepsis has a wound origin, for example, the septic in the inflammatory process of the billiary tract and

portal vein. In some cases, billiary tract is secondary infected due to of any general cyclic infectious disease. In the other cases, billiary tract may be as septic focus. The so-called peripheral signs of septic endocarditis are 1) petechial hemorrhages in the conjunctiva near the internal angle of the lower eyelid (Lukin - Libman spots); 2) nodular thickening on the palm surface of the hand (Osier's nodes); 3) thickening of the nail phalanges ("drum sticks"); 4) necrosis foci in the subcutaneous fat; 5) hemorrhages to the skin and subcutaneous fat (Jeinway's spots); 6) jaundice. At present only Oslier's nodes are observed in all instances. Thromboembolic complications are frequent, as the source of thromboembolism, thromboendocarditis, is most commonly localized in the left heart. Thromboembolism frequently becomes generalized and dominates in the clinical picture of the disease. These are the cases of thromboembolic syndrome. The embolisms give the rise to infarctions in the lungs, spleen, kidneys, retina, skin necrosis, gangrene of the extremities, intestine, foci of softening in the brain. In spite of the presence of streptococci in the thrombi, suppuration in the tissue is absent which suggests hyperergic reaction of the organism in septic endocarditis. The outcomes of the disease depend from the premorbid condition, opportunity, of the therapy and its effectiveness. The prognosis of sepsis is frequently unfavorable, especially for an infants and elder patients.

DIAGNOSIS

Clinical diagnosis is based on symptomes. After that: 1. Estimation CBA; 2. Express test – coloring swab of blood; 3. Serial blood samples for blood culture (2 day - 10 blood samples); 4. Superficial infection is diagnosed by isolation of the organism from infected tissues; 5. Invasive infection can be confirmed by isolation of the organism from a normally sterile site such as blood; 6.Throat swabs are of limited value due to the frequency of unapparent Streptococcal carriage; 7. Definitive identification depends on specific serogrouping procedures. Bacteriologic investigations are an important diagnostic test in sepsis. During 2 days 5 times a day must be examined blood of method blood culture. The results of the bacteriologic investigations never must be account without data of the history, clinical features and other laboratory tests. The positive bacteriologic results are not always in septic patients. The negative results are especially frequent in culture of the blood. In sepsis the excretion of the agent and estimate of received results are in rarely complicated problem. It is connected with that in sepsis the circulation of agent in the blood is no constant. A quantity of the agent in the blood is oscillated and may be insignificant. The treatment by antibiotics has a large influence on bacteremia. It is necessary to perform a differentiation with different diseases with prolonged-fever, rigors, sweating and various eruptions. Other investigations: Prothrombin time (PT), activated partial thromboplastin time (APTT), and D-dimer, protein C, protein S, and antithrombin levels were obtained at each time point. Platelet counts were determined

from EDTA anticoagulated blood samples obtained before study drug infusion and on study days 4 and 6. Serum for IL-6 determinations was obtained before infusion and daily through to study day. The following seven additional biomarkers: prothrombin fragment F1.2, thrombin–antithrombin complex (TAT), plasminogen activator inhibitor (PAI)-1, thrombin activatable fibrinolysis inhibitor (TAFI), α2-antiplasmin (α2-AP), plasminogen, and soluble thrombomodulin (sTM). Post hoc measurements of the concentrations of four additional inflammatory cytokines, namely tumor necrosis factor (TNF)-α, IL-1β, IL-8, and IL-10, were also performed in the citrated plasma. The assay detection limit was 20 pg/ml for TNF-α, IL-1β and IL-10, and 100 pg/ml for IL-8.

DIFFERENTIAL DIAGNOSIS

Typhoid fever and paratyphoid remind sepsis by fever, pale skin, enlarged liver and spleen. But, they are differenced from septic process by cyclic course, not so excessive anemia and rarity of the hemorrhagic eruptions, isolation of the agent of typhoid fever and paratyphoid, results of IHA-test (indirect hemagglutination reaction) help in the decision of the problem.

Sepsis should be differentiated with pneumonia, because pneumonia must be as result of sepsis. The following systematic observation and the metastatic foci in joints, endocardium and brain's membranes are usually helpful for decision of this problem.

In epidemic typhus there are typical clinical symptoms. They are Kjary-Auvcyne's symptom, Govorov-Godelyae's symptom, Rosenberg's symptom early enlargement of spleen. Typical eruption appears on the 4-5 day of the disease. Serologic methods are very useful, especially for the final diagnosis.

Tropical malaria, also, is accompanied by a prolonged fever and hepatosplenomegaly. The typical features of the fever in tropical malaria are prolonged paroxysms (to 24-36 hours and over), poorly marked an apyrexia periods. Rigor and sweating are less marked, that is caused by some fluctuation of temperature. These attacks are accompanied by severe headache, low back pain, nausea and sometimes by vomiting. Abdominal pains and watery stools appear inrarely. The indications of the patients about location in the focus of malaria, departure to tropical countries have an important epidemiological meaning. Microscopic blood examination (blood smear and thick drop) are needful and reliable laboratory methods for diagnostics of malaria.

Four diseases are problems for differential diagnostics: tuberculosis, collagenoses (a lupus erythematosus and so called "non-differentiated" collagenoses or diffuse diseases of connective tissue), malignant neoplasm (especially hepatomae and hypernephromae, also as a lymphogranulomatosis and leukemia).

In some cases, tuberculosis, especially its milliary forms in young patients, is

difficult for diagnostics. The fever sometimes of hectic type, dyspnea, sweating may be as in sepsis. It is necessary carefully to study of the epidemiological data, repeated radiological investigation and culture of the blood. Also, the hectic fever, sweating may be in acute period of brucellosis. In brucellosis there are a little violations of the general state of the patients. There is no the hemorrhagic syndrome. In the second stage there are signs of the locomotor system infractions. In the early stages of the brucellosis, positive results of Wright reaction are marked, and ELISA test is positive.

At the last time it is necessary to allow for increased rate of the fungal infections in diagnostics of sepsis. In the main, they are candidiasis of the bronchopulmonal, intestine, urogenital and osseous systems. Fungi of genus Candida albicans have the most meaning among fungal injures. Fungi Candida albicans are revealed in the normal flora of the oral cavity, intestine.

It is necessary to perform differential diagnosis of sepsis with intestine yersiniosis. This disease may have prolonged (more 3 months), relapsing course. In prolonged yersiniosis alteration of the periods of relapses and remissions is observed. The period of relapse is characterized by prolonged fever, reactive polyarthritis, myocarditis, prolonged gastroenteritis, hepatolienal syndrome and erythema. The repeated cultures are performed on special mediums for determination of the agent's origin: blood, sugar, billiary broth. It is recommended to take the blood in a quantity 15-20 ml on 80-100 ml of the medium. The agent may be revealed from hemorrhagic elements, sputum, urine, content of abscess and other materials.

TREATMENT

Early recognition of sepsis is a key to successful treatment. Treatment including: 1. Antibacterial therapy. 2. Anticoagulation (every 3-d hour). 3. Antienzymes therapy: Gordox, Trasylolum, Contricalum. Immunal therapy: antistaphylococcal immunoglobulins, staphylococcal anatoxin. Extracorporal methods of desintoxication: a) hem sorption; b) immunosorbtion; c)exchange plasmapheresis; d) plasmcytopheresis.

Antibiotics are used in massive doses and during for a long time. Its choice is realized under control of antibioticogram. Popular preparations with a little toxic are prescribed before revelation of the agent and its sensibility to antibiotics. It is recommended that antibiotic therapy be administered within the first hour of recognition of septic shock, and delays in antibiotic administration have been associated with increased mortality. Selection of particular antibiotic agents is empirically based on an assessment of the patient's underlying host defenses, the potential source of infection, and the most likely responsible organisms. Antibiotic choice must be broad spectrum, covering gram-positive, gram-negative, and anaerobic bacteria when the source is unknown. Treatment due to antibiotic very

often is empiric! In what follows antibiotics are prescribed in accordance with sensibility of microflora to antibiotics. Semisynthetic penicillins are used in case of resistant staphylococcus to benzylpenicillin. Percent of resistant staphylococcus is high (more than 80%). Oxacillin is used in dosage 10-12 g in a day for adults. Cephalosporins are prescribed in allergy to penicillin. Lincomycin, kanamicyn, vancomycin are prescribed in case of allergy to cephalosporins and different combinations of remedies. The middle course of antibiotic therapy is 4-6 weeks. Five antibiotics are considered more effective in the treatment of the patients with sepsis: rifampicin, gentamicin, kanamicin, ristomicin, cephalosporins. Imipenem and cilastatin (Primaxin) carbapenem with activity against most gram-positive organisms (except MRSA), gram-negative organisms, and anaerobes; used for treatment of multiple organism infections in which other agents do not have wide-spectrum coverage or are contraindicated because of their potential for toxicity. Has been used as single-drug therapy for sepsis. For adult 500 mg IV q6h. Vancomycin (Vancocin) Gram-positive coverage and good hospital-acquired MRSA coverage. Now used more frequently because of high incidence of MRSA. Should be given to all septic patients with indwelling catheters or devices. Advisable for skin and soft-tissue infections. For adult 1 g or 15 mg/kg IV q12h. Teucoplanin. Adult: I.V., 1th day: 6 mg/kg (400 mg) 2 time a day , from 2th day: 400 mg 1 time a day. Metronidazole. Imidazole ring-based antibiotic active against various anaerobic bacteria and protozoa; usually used with other antimicrobial agents except when used for Clostridium difficile enterocolitis in which monotherapy is appropriate. For adult loading dose: Infuse 15 mg/kg IV over 1 h (1 g per 70 kg). Maintenance dose: Infuse 7.5 mg/kg IV over 1 h q6-8h (500 mg per 70 kg) beginning 6 h after loading dose; not to exceed 4 g in 24 h. Levofloxacin. Fluoroquinolone with excellent gram-positive and gram-negative coverage. Excellent agent for pneumonia. Excellent abdominal coverage as well. High urine concentration and therefore reduce dosing in urinary tract infection. Adult. 750 mg IV q24h for pneumonia 500 mg IV q24h for abdominal source 250 mg IV q24h for urinary source. Cefepime (Maxipime). Fourth-generation cephalosporin. Gram-negative coverage comparable to ceftazidime but has better gram-positive coverage (comparable to ceftriaxone). Poor capacity to cross blood-brain barrier precludes use for treatment of meningitis. For adult 1-2 g IV q12h; pseudomonal infections require higher doses.

Recombinant human activated protein C, an anticoagulant, is the first anti-inflammatory agent that has proved effective in the treatment of sepsis. In patients with sepsis, the administration of activated protein C resulted in a 19.4 percent reduction in the relative risk of death and an absolute risk reduction of 6.1 percent. Activated protein C inactivates factors Va and VIIIa, thereby preventing the generation of thrombin. It was estimated that early aggressive therapy that optimized cardiac preload, afterload, and contractility in patients with severe sepsis and septic

shock improved the likelihood of survival. Drotrecogin alfa (Xigris) Activated protein C (APC) is an endogenous protein that has natural anticoagulant and anti-inflammatory effects. Its levels are low in septic shock, which is hypothesized to exacerbate the proinflammatory response and microthrombus formation in end-organ vascular beds that leads to organ dysfunction. Exogenous administration of APC has been shown to improve the mortality in a very ill subset of patients with septic shock. Having an anticoagulant effect, use of APC increases the risk for serious bleeding. For adult 24 mcg/kg/h IV continuous infusion for 96 h; ideally, initiate within 48 h of sepsis onset.

Volume resuscitation – it is volume infusions of colloid or crystalloid, vasoactive agents, and transfusions of red cells to increase oxygen delivery. Resuscitation end points chosen for assessment of the adequacy of oxygen delivery were the normalization of values for mixed venous oxygen saturation, lactate concentration, base deficit, and pH. Early therapeutic intervention to restore balance between oxygen delivery and oxygen demand improved survival among patients presenting with severe sepsis. The use of objective measures, including lactate concentration, base deficit, pH, and possibly central venous oxygen saturation, in the follow-up of patients who are receiving resuscitation therapy is advisable. These agents are standard intravenous fluids used for volume resuscitation, referred to as crystalloids.

Isotonic crystalloid fluids expand intravascular volume and also diffuse through capillary endothelium into interstitial tissue spaces. Typically, about 30% of administered isotonic fluid stays intravascular; therefore, large quantities may be required to maintain adequate circulating volume. It is important to watch for signs of over-resuscitation, which include respiratory difficulty, low oxygen saturation, crackles on lung examination, or peripheral or periorbital edema. Normal saline (NS), lactated Ringers (LR) Both fluids are essentially isotonic and have equivalent volume-restorative properties. While some differences between metabolic changes are seen with administration of large quantities of either fluid, for practical purposes and in most situations, differences are clinically irrelevant. Importantly, hemodynamic effect, morbidity, and mortality are not demonstrably different in resuscitation with isotonic sodium chloride solution or lactated Ringer solution. For adult 1-2 L IV initially, followed by reassessment of hemodynamic response; titrate further 500-mL boluses q15min to urine output >0.5 mL/kg/h (30-50 mL/h in most adults) or CVP >8-12 mm Hg.

Colloid solutions provide an oncotically active substance that expands plasma volume to a greater degree than do isotonic crystalloids and reduce the incidence of pulmonary and cerebral edema. About 50% of the administered colloid stays in the intravascular space. Despite the theoretical benefit of a colloid solution, no clear evidence has shown a benefit of a colloid solution over standard crystalloid

resuscitation in the initial treatment of septic shock. Albumin (Albuminar). For certain types of shock or impending shock; useful for plasma volume expansion and maintenance of cardiac output; a solution of isotonic sodium chloride solution and 5% albumin is available for volume resuscitation. Adult. 250-500 mL IV over 20-30 min, with reassessment of hemodynamic response. Rivers et al brought this issue to the forefront with a landmark study in 2001, where they instituted a treatment protocol for patients with septic shock, termed Early Goal Directed Therapy (EGDT). EGDT emphasizes early recognition of patients with potential sepsis in the ED, early broad-spectrum antibiotics, and a rapid crystalloid fluid challenge, followed by goal-directed therapy for those patients who remain hypotensive or severely ill after this initial therapy. In the study by Rivers et al, the patients who did not respond to an initial fluid challenge (20-30 mL/kg bolus) and antibiotics received a CV catheter in the internal jugular or subclavian vein to measure central venous pressure (CVP) and an arterial catheter to directly measure arterial blood pressure. The first step involves titrating crystalloid fluid administration to CVP by administering 500-mL boluses of fluid until the CVP measures between 8 and 12 mm Hg. CVP is a surrogate for intravascular volume, as excess circulating blood volume is contained within the venous system. Patients with septic shock will frequently require 4-6 L or more of crystalloid to achieve this goal. Clinical signs of volume overload should be monitored as well, including developing periorbital or extremity edema, crackles on pulmonary examination, increasing oxygen requirement, or increased difficulty breathing. In patients who are mechanically ventilated, the target CVP goal is 12-15 mm Hg due to increased intrathoracic pressure. The second step, if the patient has not improved with fluid alone, is to administer vasopressors to attain a mean arterial pressure (MAP) greater than 65 mm Hg. The third step is to evaluate the central venous oxygen saturation (ScvO2), which is measured from the CV line in the superior vena cava. ScvO2 is the oxygen saturation of blood returning from tissue capillary beds, and it reflects the difference between overall oxygen supply and demand. Similar to lactate, ScvO2 is an indicator of adequate tissue oxygenation. A SvO2 of less than 70% is considered abnormal and indicative of suboptimal oxygen delivery compared with oxygen demand. An initial assessment of airway and breathing is very important in a patient with septic shock. Supplemental oxygen should be administered to all patients with suspected sepsis. Early intubation and mechanical ventilation should be strongly considered for patients with an oxygen requirement, dyspnea or increased respiratory rate, persistent hypotension, or those with evidence of poor peripheral perfusion. Patients with suspected septic shock require an initial crystalloid fluid challenge of 20-30 mL/kg (1-2 L) over a period of 30-60 minutes with additional fluid challenges at rates of up to 1 L over 30 minutes. Crystalloid administration is titrated to a CVP goal between 8 and 12 mm Hg or signs of volume overload (dyspnea, pulmonary rales, or pulmonary edema on

the chest radiograph). A fluid challenge refers to the rapid administration of volume over a particular time period followed by an assessment of the response. Patients with septic shock often require a total 4-6 L or more of crystalloid resuscitation. Colloid resuscitation (with albumin or hetastarch) has not previously been shown in meta-analyses to have any benefit over isotonic crystalloid resuscitation (isotonic sodium chloride solution or lactated Ringer solution). The SAFE trial enrolled 7000 ICU patients requiring fluid resuscitation, only about 1200 of who had severe sepsis. Overall, there was no difference between the two treatment groups; however, there was a trend toward improved outcome in patients with severe sepsis who received 4% albumin versus normal saline. These data are inconclusive, especially regarding the initial resuscitation phase for septic shock in the ED, and crystalloid resuscitation is recommended.

Administration of high doses of corticosteroids (e.g., 30 mg of methylprednisolone per kilogram of body weight) does not improve survival among patients with sepsis and may worsen outcomes by increasing the frequency of secondary infections. The proposed explanation for the physiological response to corticosteroids (despite normal or elevated plasma cortisol levels) is desensitization of corticosteroid responsiveness with down-regulation of adrenergic receptors.

Catecholamines increase arterial pressure through effects on adrenergic receptors of the vasculature; corticosteroids increase the expression of adrenergic receptors. Antihistamine remedies are prescribed for decrease of allergic manifestations.

Prolonged antibiotic therapy may become by reason of candidomicosis, dysbacteriosis. Fluconazol are prescribed for treatment and prophylaxis of candidomicosis and dysbacteriosis. Hyperimmune antistaphylococcal plasma is used for increase of specific resistance of the organism. This plasma may be received from donors, immunized by staphylococcal anatoxin. Plasma is injected intravenously to adults - a 100-200 ml, but children - 5 ml per kg of weight a week. Staphylococcal gamma-globulin is prescribed a 3-6 ml per one injection also with similar purpose. Antiferments (contrykal, gordox) are used for suppression of proteolytic activity in the foci of damage. Ascorbic acid (5% solution - 30-40 ml intravenously) is used for protection of cell membranes.

Specific therapy is no sufficient inrarely. This fact may be explained by essence of septic process. It is necessary increase of resistance of macroorganism and barrier functions of its separate systems. Diet, injections of vitamins, immunocorrecting remedies have an important meaning in these cases. In severe cases, antibiotics are prescribed in complex with a glucocorticoids - 0,5 mg of prednisolone per 1 kg of patient's weight daily at first three days, then in decrease doses, with purpose of a desensibilization and desintoxication. Course of the medical course is 12-14-18 days. Cardiovascular remedies, antiferments intravenous injection

of sodium chloride isotonic and Ringer-Lock's solution, ferrum preparations, anabolic hormones are prescribed by evidences.

PREVENTION

It is necessary to perform opportune treatment of primary foci. The measures, directing on increase of resistance of the organism have an important meaning. These measures are rational diet, regime of work and rest, physical tempering. Staphylococci are more frequent etiological factor of sepsis, because prophylaxis of intrahospital staphylococcal infection is necessary. The early revealing and prohibition of work of medical personnel with purulent inflammatory diseases (sore throat, pyodermia) and opportune hospitalization of the patients with staphylococcal infection in special departments or wards. It is necessary the revealing of prolonged bacteriocarriers of hospital strains of staphylococcuses and its sanation for patients with immunodeficiency and operating-room.

LISTERIOSIS

Listeria is the common name for the pathogenic or disease-causing bacterium known as Listeria monocytogenes. It is a food borne illness that when ingested causes an infection known as listeriosis.

ETIOLOGY

Listeria monocytogenes is a non-sporing, Gram-positive bacillus that can be cultivated under aerobic and anaerobic conditions on a range of laboratory media between pH 6 and pH 9, and at temperatures between 1 and 45°C, although optimum growth occurs between 30 and 37°C. Morphologically, L. monocytogenes resembles a diphtheroid, from which it is distinguishable in a hanging-drop preparation by its characteristic; tumbling; motility. L. monocytogenes is the only human pathogen in the genus, six other species of Listeria have been described, namely L. innocua, L. ivanovii, L. seeligeri, L. welshimeri, L. grayi, and L. murrayi. Whereas L. monocytogenes is the only species likely to be isolated from blood, cerebrospinal fluid, pus or tissues, other Listeria spp. may be found in faeces, food, soil, water, sewage sludge, and decaying vegetation. Some food-processing methods (heating, chilling, freezing, chemical treatment) may cause sublethal injury to the microbial flora, and new approaches leading to the efficient recovery of sublethally injured Listeria spp. from foods are currently being investigated. L. monocytogenes is subdivided into serotypes on the basis of somatic (O) and flagellar (H) antigens. Eleven serotypes (1/2a, 1/2b, 1/2c, 3a, 3b, 4a, 4b, 4c, 4d, and 4e) are currently recognized. When it is grown, Listeria can be confused with other less harmful contaminants and disregarded. Second, while most bacteria grow poorly when temperatures fall below 40°F, Listeria survives at temperatures from below freezing to body temperature, and grows best at the 0°F to 50°F range, which includes the temperature range used for freezing and refrigeration.

EPIDEMIOLOGY

Listeria is ubiquitous in the environment, and can be isolated from wild and domestic animals, birds, insects, soil, wastewater, and vegetation. Most infections are due to food-borne transmission. A substantial minority of infections are transmitted by other modes. Transmission can occur transplacentally or via an infected birth canal. Isolated incidences of cross-infection in neonatal nurseries have been reported. The bacterium easily comes into contact with farm animals as it has been found to be present in grazing areas, stale water, and poorly prepared animal feed. In addition to being present in the environment, Listeria can live in the intestines of humans, animals and birds for long periods of time without causing infection. Because Listeria is present in nearly every environment - including in some food processing facilities -

numerous opportunities for contamination exist during the food production process. While the general public need not be especially concerned with preventing listeriosis, several segments of the population are at risk, and need to be informed of that risk so proper precautions can be taken to prevent listeriosis. Due to its unusual growth capabilities, Listeria may be transferred in common ready-to-eat foods that have been kept properly refrigerated. Thus, Listeria presents many challenges because of its ability to grow in diverse environments. These host factors, along with the amount of bacteria ingested and the virulence of the strain, determine the risk of disease. Pregnant women are about 20 times more likely than other healthy adults to contract listeriosis. About one-third of listeriosis cases happen during pregnancy. There is no routine screening test for susceptibility to listeriosis during pregnancy, as there is for rubella and some other congenital infections. Newborns, rather than the pregnant women themselves, suffer the serious effects of infection in pregnancy. In addition to pregnant women, fetuses, and newborns, persons with weakened immune systems due to treatment, particularly transplant recipients and persons receiving treatment for lymphoma, but also other cancer victims, are at significantly increased risk for Listeria infection. Persons with AIDS suffer listeriosis 65-145 times more frequently than the general population. Persons who take glucocorticosteroid medications (also called cortisone) are also at increased risk .The elderly and certain debilitated patients (such as those on dialysis or alcoholics) are at minor increased risk for listeriosis. Epidemiological patterns of human listeriosis. There are two main epidemiological patterns for human listeriosis. 1. Epidemic disease: (a) community-acquired outbreaks of common-source, food-borne listeriosis; (b) hospital-acquired outbreaks, spread by cross-infection. 2. Sporadic infections: (a) isolated cases of community-acquired, food-borne listeriosis; (b) sporadic, localized skin and eye infections acquired occupationally by workers with animals or their products. Food-borne listeriosis. Sporadic cases of food-borne listeriosis have been attributed to the consumption of undercooked chicken, undercooked hot-dogs, turkey franks, ice-cream, and other dairy products. A large case-control study of dietary risk factors in sporadic listeriosis by the Listeria Study Group, United States Center for Disease Control showed that cases were more likely than matched controls to have eaten soft cheeses or food purchased from store delicatessen counters. In immunosuppressed patients, eating undercooked chicken also increased the risk of listeriosis.

PATHOGENESIS

LM – it is classic intracellular parasite, that able penetrate inside cells by means of phagocytosis. At period of diseases LM may damage various tissue and cells. The virulence of L. monocytogenes. This is related to the production of specific toxins, including listeriolysin O and haemolysin. The body’s defense against Listeria monocytogenes and other intracellular pathogens is called “cell-mediated immunity”

because it depends on our cells (as opposed to our antibodies), especially lymphocytes called “T-cells.” Therefore, it is not surprising that individuals whose cell-mediated immunity is suppressed are more susceptible to the devastating effects of Listeriosis. Pregnant women naturally have a depressed cell-mediated immune system; many think that this occurs so that the mother’s immune system will not reject the fetus. In addition, the systems of fetuses and newborns are very immature; they are extremely susceptible to intracellular pathogens. Other adults, especially transplant recipients and lymphoma patients, are given necessary therapies with the specific intent of depressing immune T-cells, and these individuals become especially susceptible to Listeria monocytogenes as well. The factors that influence whether invasive disease will occur include the virulence of the infecting organism, the susceptibility of the host, and the size of the infecting dose of bacteria.

The transmission of L. monocytogenes infection in food, this requires penetration of the organism through the intestine. Multiplication can then occur in various types of cells including non-immune phagocytes and cells of Peyer's patches. The production of listeriolysin O is thought to permit pathogenic Listeria spp. to disrupt vacuolar membranes and pass from the phagosome into the cytoplasm, where conditions for multiplication may be more favorable. Host susceptibility. This is related to cell-mediated immunity and most listeriosis occurs in people in whom this is depressed by pregnancy, disease, or immunosuppressive or cytotoxic therapy. Although reports of listeriosis in patients with AIDS may seem infrequent, listeriosis occurs at least 300 times more often in such patients, although other opportunistic infections are more common. In experimental mice, susceptibility to listeria infection can be genetically linked. Most infections occur after oral ingestion, with access to the systemic circulation after intestinal penetration. Protection against Listeria is mediated via lymphokine activation of T cells on macrophages and by interleukin-18. CNS infection may manifest as meningitis, meningoencephalitis, or abscess. Endocarditis another possible presentation. Localized infection may manifest as septic arthritis, osteomyelitis, and, rarely, pneumonia.

CLINICAL MANIFESTATIONS

L. monocytogenes can cause a wide range of clinical presentations from asymptomatic carriage or a mild, influenza-like illness to fatal septicaemia and meningoencephalitis. The following syndromes are recognized: (1) maternofetal listeriosis; (2) neonatal listeriosis; (3) listeriosis in children and adults: (a) septicaemia, (b) meningoencephalitis, (c) other localized infections.

The most common clinical manifestation is diarrhea. A mild presentation of fever, nausea, vomiting, and diarrhea may resemble a gastrointestinal illness. The microorganism has gained recognition because of its association with epidemic gastroenteritis. Bacteremia and meningitis are more serious manifestations of disease

that can affect individuals at high risk. Unless recognized and treated, Listeria infections can result in significant morbidity and mortality. Disease may be a self-limited gastrointestinal tract illness or a more severe CNS infection or bacteriemia. Examination depends on the organ system involved. Febrile gastroenteritis. L monocytogenes can produce food-borne diarrheal disease, which is typically noninvasive. The median incubation period is 1-2 days, with diarrhea lasting anywhere from 1-3 days. The prevalence of diarrheal illness is high in individuals exposed to inocula of Listeria. Patients present with fever, myalgias, and diarrhea and recover with supportive care. Listeria septicaemia. This occurs mainly in patients with malignancies, in transplant recipients, and in immunosuppressed and elderly people. Most present with fever, hypotension, and shock but a third to a half develop meningitis, which may be the presenting feature.

Listeria has a predilection for the brain parenchyma, especially the brain stem, and the meninges. Mental status changes are common. Seizures, both focal and generalized, occur in at least 25% of patients. Cranial nerve deficits may be present. Strokelike syndromes with hemiplegia may occur. Nuchal rigidity is less common. Movement disorders may include tremor, myoclonus, and ataxia. Patients may present with encephalitis, especially of the brainstem. Meningitis is possible. Ventriculitis, particularly of the fourth ventricle, may develop. Cervical myelitis has been reported. Brain abscess occurs in 10% of CNS infections, often located in the thalamus, pons, and medulla. This uncommon complication is associated with high mortality. Listeria meningoencephalitis may start abruptly but in adults it can also develop insidiously, with progressive focal neurological signs even in the absence of a brain abscess. Most patients have meningism, but fever may not be marked, particularly in elderly or immunosuppressed people. Listeriosis should be considered in any patient with an acute brain-stem disorder associated with fever, particularly if there are no risk factors for cerebrovascular disease.

Listeria may proliferate in the placenta and cause infection due to impaired cell-mediated immunity during pregnancy. CNS infection is very rare during pregnancy, although it is observed frequently in other compromised hosts. Fever, myalgias, arthralgias, back pain, and headache are classic symptoms of bacteremia. Symptoms may mimic those of a flulike illness. The infection may be mild and self-limited. Listeriosis during pregnancy usually occurs during the third trimester, when cell-mediated immunity is at its lowest. Preterm labor and/or delivery is common. Abortion, stillbirth, and intrauterine infection are possible. Neonatal infection (granulomatosis infantisepticum): Two forms are described. Early-onset sepsis, with Listeria acquired in utero via transplacental transmission, results in premature birth. Listeria can be isolated in the placenta, blood, meconium, nose, ears, and throat, among other sites, and manifests as abscesses and/or granulomas. Late-onset meningitis is acquired through vaginal transmission, although it also has been

reported with cesarean deliveries. Maternofetal listeriosis can occur at any time during pregnancy. The mother may develop a fever, with headache, myalgia, and back pain, associated with the bacteraemic phase of the disease. Lower back pain may mimic urinary-tract infection. Transplacental infection causes amnionitis, usually leading to either spontaneous septic abortion or premature labour with the delivery of an infected fetus or baby. Neonatal listeriosis of early onset has a high mortality and results from intrauterine infection. Usually, the mother has had an influenza-like illness before the onset of labour. The liquor is meconium-stained and the baby septic and jaundiced, with signs of purulent conjunctivitis, bronchopneumonia, meningitis, or encephalitis. Granulomas affecting many organs are a unique feature of this disease, which is therefore also termed granulomatosis infantisepticum. Late-onset disease occurs after several days to weeks in a baby who is initially healthy. Although the mother's genital tract is the usual source of infection, spread in nurseries and labour suites has also been described.

Hospital-acquired listeriosis. Clusters of cases of late-onset neonatal listeriosis have been reported from a number of countries. Poor hand hygiene, close contact between infected patients and their mothers, and fomites such as rectal thermometers, contaminated resuscitation equipment, and contaminated mineral oil used to bathe newborn infants have all been implicated. Both person-to-person and food-borne spread have been suspected in outbreaks amongst adult immunosuppressed patients in hospital.

Occupationally acquired listeriosis. Eye and skin infections without systemic involvement have occasionally been reported in agricultural, veterinary, and laboratory workers who have been directly exposed to infected animals or culture material.

Other localized infections. These are rare and occur mainly in immunosuppressed people. They include osteomyelitis, septic arthritis, cholecystitis, abscesses, and peritonitis. They usually result from seeding during an initial bacteraemic phase, but can also result from direct, occupational exposure.

DIAGNOSIS

Methods are becoming available for the rapid detection of Listeria spp. in clinical specimens and in food. These include immunoassays, DNA probe assays, and a two-step, nested polymerase chain reaction that may offer a means of detecting L. monocytogenes DNA retrospectively in preserved clinical specimens. Healthcare providers frequently overlook Listeria as a possible cause of illness due to its unusual growth capabilities. First, laboratories sometimes have a difficult time growing Listeria. Microbiological diagnosis. Definitive microbiological diagnosis of invasive listeriosis is made by blood culture. This diagnosis may be supported by the microscopic demonstration of Gram-positive bacilli in a stained smear, and by culture

of the organism from meconium, nose or eye swabs, urine, cerebrospinal fluid, blood, tracheal aspirate, placental tissue, and/or lochia. Cultures from sites such as the vagina or faeces have the disadvantage that a positive result is not diagnostic of listeriosis and may show carriage of L. monocytogenes only. Moreover, antenatal vaginal examination to obtain a high vaginal or endocervical swab is not without risk to the pregnancy. Serological tests. Tests for listeria antibodies in maternal and cord blood samples are unhelpful. They are unsuitable for screening either symptomatic patients or asymptomatic pregnant women who are worried that they could have become infected from eating a high-risk food.

The common markers of bacterial infection, such as assays of C-reactive protein, may support a clinical diagnosis of listeriosis while the results of bacterial culture are awaited. Serial, quantitative estimations of C-reactive protein may be helpful in monitoring the efficacy of antimicrobial chemotherapy. Blood cultures should be performed. Blood culture results are positive in 60-75% of patients with CNS infections. Listeria demonstrates "tumbling motility" in wet mounts of CSF. Listeria organisms are motile in wet mounts of CSF. CSF Gram stain results are positive in less than 50% of patients. CSF analysis reveals pleocytosis, and CSF protein levels are moderately elevated. CSF glucose levels may be low, and if so, are associated with a poor prognosis. Laboratory results that show diphtheroids should prompt heightened awareness for the possibility of Listeria infection, particularly in immunocompromised patients.

CSF culture findings are positive in nearly 100% of patients. Serologic testing is not reliable. Stool cultures are neither sensitive nor specific. Imaging Studies. MRI is superior to CT scan for demonstrating CNS disease, especially in the brainstem. Transesophageal echocardiography should be performed if endocarditis is suspected. Lumbar puncture should be performed if CSF infection is suspected.

TREATMENT

Person-to-person transmission does not occur; therefore, isolation precautions are not necessary. Intravenous antibiotics must be started immediately when the diagnosis is suspected or confirmed. There have been no controlled clinical trials of antibiotic treatments for listeriosis, and views about the optimal antibiotic regimen are generally based on small series, historical comparisons, and clinical experience.

L. monocytogenes is generally susceptible in vitro to the aminoglycosides (e.g. gentamicin), ampicillin, benzylpenicillin, chloramphenicol, ciprofloxacin, erythromycin, imipenem, mezlocillin, rifampicin, some sulphonamides, tetracyclines, trimethoprim, and vancomycin. The organism is only moderately susceptible to some cephalosporins (cefazolin, cefotaxime, ceftriaxone) and resistant to most others, including the oral cephalosporins and ceftazidime. Some strains are partly resistant to penicillin, but synergy can be demonstrated in vitro between ampicillin and

gentamicin, and between mezlocillin and gentamicin, combinations that are bactericidal, as is gentamicin alone. The current consensus favors a combination of ampicillin and gentamicin as the treatment of choice for listeriosis. Because of its potential for fetal toxicity, gentamicin is best avoided in pregnancy, when ampicillin or amoxycillin may be used alone. Successful treatment has also been reported with intravenous chloramphenicol and with co-trimoxazole. Treatment failures have been reported with penicillin alone and with cephalosporins, despite apparent in vitro susceptibility. Ciprofloxacin has in vitro activity against Listeria spp. but it has not yet been evaluated in listeriosis. The appropriate duration of therapy also remains unsettled. A period of 2 weeks has been sufficient in some series, but recurrence after 14 days of treatment has been noted, particularly in immunosuppressed patients, so 3 to 6 weeks of treatment is probably safer. This longer course, which should also be considered in neonatal listeriosis, is likely to improve the outcome when organisms are sequestered in deep granulomatous tissues. In cases of genuine penicillin allergy, effective treatment is difficult. A tetracycline such as minocycline, which penetrates the cerebrospinal fluid relatively well, may be considered in combination with gentamicin. Some success has been reported with co-trimoxazole and with chloramphenicol. Vancomycin has also been proposed, but there is at present insufficient information to recommend it. Antibiotic therapy is the treatment of choice. Bacteremia should be treated for 2 weeks if the patient is immunocompetent. Longer courses may be required in the immunocompromised patient. Meningitis should be treated for 3 weeks; endocarditis, for 4-6 weeks; and brain abscess, for at least 6 weeks. Ampicillin is generally considered the preferred agent, but other agents may be acceptable. Gentamicin is added frequently for synergy, but it may be discontinued after 1 week of clinical improvement in order to decrease the chance of renal toxicity or ototoxicity. Empiric antimicrobial therapy must be comprehensive and should cover all likely pathogens in the context of the clinical setting. Ampicillin (Adult 2 g IV q4h, Pediatric, 200-400 mg/kg/d IV divided q4h). Trimethoprim-sulfamethoxazole (Adult 20 mg/kg/d of trimethoprim IV divided q6h). Chloramphenicol (Adult 50-100 mg/kg/d PO/IV divided q6h for 10 d; not to exceed 4 g/d. Pediatric 50-75 mg/kg/d PO/IV divided q6h).

PROGNOSIS

Despite antibiotic therapy, the mortality of septicaemia and meningoencephalitis with L. monocytogenes remains high (20-50 per cent). There is significant long-term morbidity in the survivors. Efforts should therefore continue to be focused on the prevention of this infection by improvement in the microbiological safety of methods of food production and preparation, and by education of the public so that vulnerable people can avoid high-risk foods.

TETANUS

Tetanus is an infectious disorder characterized by increased muscle tone and spasms caused by the release of the neurotoxin tetanospasmin by ***Clostridium tetani*** following inoculation into a human host. Tetanus occurs in several clinical forms, including generalized, cephalic, localized, and neonatal disease.

ETIOLOGY

Infectious agent ***C. tetani*** is a slender, gram-positive, anaerobic rod that may develop a terminal spore, giving it a drumstick appearance. The organism is sensitive to heat and cannot survive in the presence of oxygen. The spores, in contrast, are very resistant to heat and the usual antiseptics. They can survive autoclaving at 121°C for 10-15 minutes. The spores are also relatively resistant to phenol and other chemical agents. The spores are widely distributed in soil and in the intestine and feces of horses, sheep, cattle, dogs, cats, rats, guinea pigs, and chickens. Manure-treated soil may contain large numbers of spores. In agricultural areas, a significant number of human adults may harbor the organism. The spores can also be found on skin surfaces and in contaminated heroin. There is no laboratory findings characteristic of tetanus. The diagnosis is entirely clinical and does not depend upon bacteriologic confirmation. ***C. tetani*** is recovered from the wound in only 30% of cases, and can be isolated from patients who do not have tetanus. Laboratory identification of the organism depends most importantly on the demonstration of toxin production in mice. Reservoir microrganisms are found primarily in the soil and intestinal tracts of animals and humans.

Tetanospasmin is formed in vegetative cells under plasmid control. It is a single-polypeptide chain. With autolysis, the single-chain toxin is released and cleaved to form a heterodimer consisting of a heavy chain (100 kDa), which mediates binding to nerve-cell receptors and entry into these cells, and a light chain (50 kDa), which acts to block neurotransmitter release. The amino acid structures of the two most powerful toxins known, botulinum toxin and tetanus toxin, are partially homologous.

EPIDEMIOLOGY

Tetanus is not contagious from person to person. It is the only vaccine-preventable disease that is infectious, but not contagious. Tetanus occurs sporadically and almost always affects nonimmunized persons, partially immunized persons, or fully immunized individuals who fail to maintain adequate immunity with booster doses of vaccine. Although tetanus is entirely preventable by immunization, the burden of disease is large worldwide. The disease is common in areas where soil is

cultivated, in rural areas, in warm climates, during summer months, and among males. In countries without a comprehensive immunization program, tetanus occurs predominantly in neonates and other young children. In Europe and other nations with successful immunization programs, neonatal tetanus is rare and the disease affects other age groups and groups inadequately covered by immunization (such as nonwhites).

The true incidence of tetanus is not known, but is estimated to be between 500,000 to one million cases per year worldwide. The majority of cases occur in developing countries, with 50% of those cases occurring in neonates. This is partly because the coverage of antenatal care is very low and only 31% of pregnant women are immunized with tetanus toxoid, and partly because trained personnel assist fewer than 10% of deliveries. In rare instances, outbreaks of tetanus among injecting drug users have occurred.

Transmission is primarily by contaminated wounds (apparent and inapparent). The wound may be major or minor. In recent years, however, a higher proportion of cases had minor wounds, probably because severe wounds are more likely to be properly managed. Tetanus may follow elective surgery, burns, deep puncture wounds, crush wounds, otitis media (ear infections), dental infection, animal bites, abortion, and pregnancy. In a few cases the portal of entry is either trivial e.g. rose thorn in the finger. Tetanus, however, does not occur only in classic "puncture" wounds. Therefore, relying on "proper wound management" alone will not effectively eliminate tetanus in adults. Patients of all ages must continue to be adequately immunized. The incubation period, which is the time between the introduction of spores in the body and the first clinical symptoms, varies from 1 day to several months (usually 3-21 days). Most cases occur within 14 days. The duration of incubation, as well as the interval between first symptoms and generalized spasms (the period of onset), determine the severity of the disease and therefore the prognosis. In general, the shorter the period from injury to onset of symptoms and the shorter the time interval between symptoms and spasms, the more severe the tetanus will be.

PATHOGENESIS

Contamination of wounds with spores of C. tetani is probably frequent. Germination and toxin production, however, take place only in wounds with low oxidation-reduction potential, such as those with devitalized tissue, foreign bodies, or active infection. C. tetani does not itself evoke inflammation, and the portal of entry retains a benign appearance unless infection with other organisms is present.

Toxin released in the wound binds to peripheral motor neuron terminals, enters the axon, and is transported to the nerve-cell body in the brainstem and spinal cord by retrograde intraneuronal transport. The toxin then migrates across the synapse to

presynaptic terminals, where it blocks release of the inhibitory neurotransmitters glycine and gamma-aminobutyric acid (GABA). The blocking of neurotransmitter release by tetanospasmin, a zinc metalloprotease, involves the cleavage of protein critical to proper function of the synaptic vesicle release apparatus. With diminished inhibition, the resting firing rate of the alpha motor neuron increases, producing rigidity. With lessened activity of reflexes, which limits polysynaptic spread of impulses (a glycinergic activity), agonists and antagonists may be recruited rather than inhibited, with the consequent production of spasms. Loss of inhibition also may affect preganglionic sympathetic neurons in the lateral gray matter of the spinal cord and produce sympathetic hyperactivity and high circulating catecholamine levels. Tetanospasmin, like botulinum toxin, may block neurotransmitter release at the neuromuscular junction and produce weakness or paralysis; recovery requires sprouting of new nerve terminals.

In local tetanus, only the nerves supplying the affected muscles are involved. Generalized tetanus occurs when toxin released in the wound enters the lymphatics and bloodstream and is spread widely to distant nerve terminals; the blood-brain barrier blocks direct entry into the central nervous system. If it is assumed that intraneuronal transport times are equal for all nerves, short nerves are affected before long nerves: this fact explains the sequential involvement of nerves of the head, trunk, and extremities in generalized tetanus.

CLINICAL MANIFESTATIONS

Rapid case identification of tetanus is important clinically because hospitalization may be required. The case-fatality ratio in the developed counties, in 1995-1997 was 11% from a case-fatality ratio of 91% was reported in 1947. The mortality rate is highest for young children or people older than 60 years (40%) compared with those aged 20-59 years (8%). The mortality rate is 30% for people who require mechanical ventilation but only 4% for those who do not.

Acute onset of painful muscular contractions (usually of the muscles of the jaw and neck) and generalized muscle spasms without other apparent medical cause. Tetanus may be localized at the site of injury resulting in local pain and rigidity often with a low mortality. When local tetanus follows head, facial injuries or chronic otitis media, cephalic tetanus can occur which is a local variant (often involving cranial nerves particularly the seventh cranial nerve) but has a higher mortality. Both of these may progress to the more common generalized form, which may present with pain, stiffness, rigidity, trismus (rigidity of the masseter muscles), dysphagia, opisthotonus and spasms. The clinical pattern of generalized tetanus consists of severe painful spasms and rigidity of the voluntary muscles. The characteristic symptom of "lockjaw" involves spasms of the masseter muscle. It is an early symptom, which is followed by progressive rigidity and violent spasms of the trunk and limb muscles.

Spasms of the pharyngeal muscles cause difficulty in swallowing. Death usually results from interference with the mechanics of respiration. On the basis of clinical findings, different forms of tetanus have been described. Generalized tetanus is the most common type (about 80%) of reported tetanus. The disease usually presents with a descending pattern. The first sign is trismus or lockjaw, followed by stiffness of the neck, difficulty in swallowing (spasms of the pharyngeal muscles), and rigidity of abdominal muscles.

Other symptoms include a temperature rise of 2°-4°C above normal, sweating, elevated blood pressure, and episodic rapid heart rate. Spasms may occur frequently and last for several minutes. Spasms are usually worst during the first 2 weeks with autonomic instability following some days after the onset of spasms and often peaking during the second week of the disease. Rigidity may continue after the spasms and autonomic disturbances have started to improve. Spasms continue for 3-4 weeks. Complete recovery may take months.

Local tetanus is an uncommon form of the disease, in which patients have persistent contraction of muscles in the same anatomic area as the injury. These contractions may persist for many weeks before gradually subsiding. Local tetanus may precede the onset of generalized tetanus, but is generally milder. Only about 1% of cases are fatal. Cephalic tetanus is a rare form of the disease; occasionally occurring with otitis media (ear infections) in which C. tetani is present in the flora of the middle ear, or following injuries to the head. There is involvement of the cranial nerves, especially in the facial area.

Neonatal tetanus is a form of generalized tetanus that occurs in newborn infants. It develops in children born to inadequately immunized mothers, frequently after unsterile treatment of the umbilical cord or its stump. Poor feeding, rigidity, and spasms are typical features of neonatal tetanus

Maternal tetanus defined as tetanus occurring during pregnancy or within 6 weeks after any type of pregnancy termination. It includes postpartum or puerperal tetanus resulting from septic procedures during delivery, postabortal tetanus resulting from septic abortion and tetanus incidental to pregnancy, resulting from any type of wound during pregnancy.

Estimation of severity grade in tetanus is very important for planning of therapy tactic. A rating scale for the severity and the prognosis of tetanus is described below.

- Score one point for each of the following:
- Incubation period less than 7 days
- Period of onset less than 48 hours
- Acquired from burns, surgical wounds, compound fractures, septic abortion, umbilical stump, or intramuscular injection
- Narcotic addiction

- Generalized tetanus
- Temperature greater than 104°F (40°C)
- Tachycardia greater than 120 beats per minute (>150 beats per minute in neonates)

Total score indicates the severity and the prognosis as follows:

- Score of 0-1 indicates mild severity with less than a 10% mortality rate.
- Score of 2-3 indicates moderate severity with a 10-20% mortality rate.
- Score of 4 indicates severe tetanus with a 20-40% mortality rate.
- Score of 5-6 indicates very severe tetanus with greater than a 50% mortality rate.
- Cephalic tetanus is always severe or very severe. Neonatal tetanus is always very severe.

One of the complications of tetanus is laryngospasm (spasm of the vocal cords) and/or spasm of the muscles of respiration leads to interference with breathing. Aspiration pneumonia is a common late complication of tetanus. Fractures of the spine or long bones may result from sustained contractions and convulsions. Hyperactivity of the autonomic nervous system may lead to hypertension and/or an abnormal heart rhythm. Nosocomial infections are common because of prolonged hospitalization. Secondary infections may include sepsis from indwelling catheters, hospital-acquired pneumonias, and decubitus ulcers. Pulmonary embolism is particularly a problem in drug users and elderly patients.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis includes dystonic drug reactions, meningitis/encephalitis, rabies, tetanus, strychnine poisoning, facial pathology (jaw stiffness, dental abscess). In neonates, one also has to exclude hypocalcaemia, hypoglycaemia, meningitis and meningoencephalitis, seizures due to other etiology.

DIAGNOSIS

The diagnosis of tetanus is based entirely on clinical findings. Tetanus is unlikely if a reliable history indicates the completion of a primary vaccination series and the receipt of required booster doses. Wounds should be cultured in suspected cases. However, C. tetani can be cultured from wounds of patients without tetanus and frequently cannot be cultured from wounds of patients with tetanus. The leukocyte count may be high. Cerebrospinal fluid examination yields normal results. Serum antitoxin levels of 0.01 or higher are considered protective and make tetanus unlikely, although rarely cases have been reported despite the presence of protective antitoxin levels. Serum muscle enzyme levels (e.g., creatine kinase, aldolase) may be elevated.

Electromyography may show continuous discharge of motor subunits and shortening or absence of the silent interval normally observed after an action

potential. Nonspecific changes may be evident on electrocardiography.

TREATMENT

The goals of therapy are to eliminate the source of toxin, neutralize unbound toxin, prevent muscle spasms, and provide support¾especially respiratory support¾until recovery. Patients should be admitted to a quiet room in an intensive care unit, where observation and cardiopulmonary monitoring can be maintained continuously but stimulation can be minimized. Protection of the airway is vital. Wounds should be explored, carefully cleansed, and thoroughly debrided.

Although of unproven value, antibiotic therapy is administered to eradicate vegetative cells¾the source of toxin. The use of penicillin (10 to 12 million units intravenously, given daily for 10 days) has been recommended, but metronidazole (500 mg every 6 h or 1 g every 12 h) is preferred by some experts on the basis of this drug's excellent antimicrobial activity, a survival rate higher than that obtained with penicillin in one nonrandomized trial, and the absence of the GABA antagonistic activity seen with penicillin. Clindamycin and erythromycin are also alternatives for the treatment of penicillin-allergic patients. Additional specific antimicrobial therapy should be given for active infection with other organisms.

Antitoxin serum is given to neutralize circulating toxin and unbound toxin in the wound, antitoxin effectively lowers mortality; toxin already bound to neural tissue is unaffected. Human tetanus immune globulin (TIG) is the preparation of choice and should be given promptly. The dose is 3000 to 6000 units intramuscularly, usually in divided doses because the volume is large. The optimal dose is not known, however, and results from one study indicated that a 500-unit dose was as effective as higher doses. Pooled intravenous immunoglobulin may be an alternative to TIG. It may be best to administer antitoxin before manipulating the wound; the value of injecting a dose proximal to the wound or infiltrating the wound is unclear. Additional doses are unnecessary because the half-life of antitoxin is long. Antibody does not penetrate the blood-brain barrier. Intrathecal administration should be considered experimental. Equine tetanus antitoxin (TAT) is also available. It is cheaper than human antitoxin, but its half-life is shorter and its administration commonly elicits hypersensitivity and serum sickness. Doses of up to 100,000 units are given, part intramuscularly and part intravenously, but 10,000 units may suffice.

Many agents, alone and in combination, have been used to treat the muscle spasms, which are painful and can threaten ventilation by causing laryngospasm or sustained contraction of ventilatory muscles. The ideal therapeutic regimen would abolish spasmodic activity without causing oversedation and hypoventilation. Diazepam, a benzodiazepine and GABA agonist, is in wide use. The dose is titrated, and large doses (250 mg/d or more) may be required. Lorazepam, with a longer duration of action, and midazolam, whose short half-life necessitates administration by continuous intravenous infusion, are other options. Barbiturates and

chlorpromazine are considered second-line agents. Mechanical ventilation and therapeutic paralysis with a nondepolarizing neuromuscular blocking agent may be required for the treatment of spasms unresponsive to medication or spasms that threaten ventilation. However, prolonged paralysis after the discontinuation of therapy with such agents has been described, and both the need for continued paralysis and the occurrence of complications should be assessed daily. Alternative agents include propofol, which is expensive, and dantrolene and baclofen, which are being investigated in the hope of shortening the period of therapeutic paralysis.

Respiratory care, intubation or tracheostomy, with or without mechanical ventilation, may be required for hypoventilation due to oversedation or laryngospasm or for the avoidance of aspiration by patients with trismus, disordered swallowing, or dysphagia. The need for these procedures should be anticipated, and they should be undertaken electively and early. Ventilation many patients with the generalized form of tetanus will require intubation and ventilation both for airway protection and respiratory support particularly if their forced vital capacity is less than 1200 ml (normal 4000 - 5000 ml) and their peak negative inspiratory pressure is less than 35 cm H2O (normal 75 to 100 cm H2O). Patients should all receive intermittent positive pressure ventilation (IPPV) with at least 5 cm H_2O of positive end expiratory pressure (PEEP) provided there is no contraindication to PEEP. In the later stages of the disease other modes of ventilation may be introduced to allow an appropriate component of spontaneous ventilation (synchronized intermittent mandatory, continuous positive airway pressure or biphasic positive airway pressure ventilation). This allows reduction of sedation (if the primary pathology is improving), may minimize muscle wastage and may reduce the likelihood of critical illness neuropathies or myopathies.

The optimal therapy for sympathetic overactivity has not been defined. Agents that have been considered include labetalol (an alpha- and beta-adrenergic blocking agent that is recommended by some experts but that reportedly has caused sudden death), esmolol administered by continuous infusion (a beta blocker whose short half-life may be advantageous in the event of severe hypertension from unopposed alpha-adrenergic activity), clonidine (a central-acting antiadrenergic drug), and morphine sulfate. Parenteral magnesium sulfate and continuous spinal or epidural anesthesia have been used but may be more difficult to administer and monitor. The relative efficacy of these modalities has yet to be determined. Hypotension or bradycardia may require volume expansion, use of vasopressors or chronotropic agents, or pacemaker insertion.

Additional therapeutic measures include hydration to control insensible and other fluid losses, which may be significant; the meeting of the patient's increased nutritional requirements by enteral or parenteral means; physiotherapy to prevent contractures; and administration of heparin or another anticoagulant to prevent

pulmonary emboli. Bowel, bladder, and renal function must be monitored. Gastrointestinal bleeding and decubitus ulcers must be prevented, and intercurrent infection should be treated. Fluid balance is important due to increased losses from sweating, salivation and GIT losses. Being fluid replete may help to manage the autonomic instability. Acute renal failure is fairly common in generalized tetanus and may be due to the fluid shifts, cardiovascular instability and rhabdomyolysis.

Feeding a nasogastric tube (NGT) should be passed on admission and can be used immediately for drugs provided there is no ileus and nasogastric feeds can be commenced as soon as possible. The regular tube feeds with additional supplementation with vitamins and trace elements must be given. The daily caloric requirements in well-controlled tetanus will be within 15% of the predicted requirements. Early enteral feed is recommended. If this is not possible then total parenteral nutrition should be commenced early. Some units would advocate prophylaxis for stress ulcers if the patient is not being fed enterally and this may be appropriate during the period of high sympathetic outflow.

Patients recovering from tetanus should be actively immunized because immunity is not induced by the small amount of toxin that produces disease.

PROPHYLAXIS

Active Immunization of all partially immunized and unimmunized adults should receive vaccine, as should those recovering from tetanus. The primary series for adults consists of three doses: the first and second doses are given 4 to 8 weeks apart, and the third dose is given 6 to 12 months after the second. A booster dose is required every 10 years and may be given at mid-decade ages¾35, 45, and so on. Combined tetanus and diphtheria toxoid (Td) adsorbed (for adult use), rather than single-antigen tetanus toxoid, is preferred for persons over 7 years of age.

Proper wound management requires consideration of the need for passive immunization with TIG and active immunization with vaccine, preferably Td in persons over age 7. For clean minor wounds, Td is administered to persons who have:

- unknown tetanus immunization histories;
- received fewer than three doses of adsorbed tetanus toxoid;
- received three or more doses of adsorbed vaccine, with the last dose given more than 10 years previously;
- received three doses of fluid (nonadsorbed) vaccine.

The recommendations for contaminated or severe wounds are identical, except that vaccine should be given to those who have received three or more doses of adsorbed tetanus toxoid if more than 5 years have elapsed since the last dose. Passive immunization with TIG is not recommended for clean minor wounds but is given for all other wounds if the patient's vaccination history indicates unknown or partial immunization. The dose of TIG for passive immunization of persons with wounds of

average severity is 250 units intramuscularly, which produces a protective antibody level in the serum for at least 4 to 6 weeks; the appropriate dose of TAT is 3000 to 6000 units. Vaccine and tetanus antitoxin should be administered at separate sites in separate syringes.

Measures aimed at preventing neonatal tetanus include maternal vaccination, even during pregnancy; efforts to increase the proportion of births that take place in the hospital; and the provision of training for nonmedical birth attendants.

RABIES

Rabies (hydrophobia, lyssa) is a viral neuroinvasive disease that causes acute encephalitis in warm-blooded animals. It is zoonotic (transmitted by animals), most commonly by a bite and infected secretions, usually saliva from an animal, but occasionally by other forms of contact (aerosol or the ingestion or transplantation of infected tissues). It is fatal if left untreated. In some countries it is a significant killer of livestock.

The term is derived from the Latin rabies, "madness". This, in turn, may have come from the Sanskrit rabhas, "to do violence". The Greeks derived the word "lyssa", which is derived from "lud" or "violent", this terminology is used in the name of the genus of rabies lyssavirus.

ETIOLOGY

The rabies virus is a member of the Lyassavirus of the Rhabdoviridae family, it is single-stranded RNA, enveloped virus, helical symmetry, infectivity destroyed by lipid solvents, 6-7 nm spike projections are present on the envelope, characteristic bullet-shaped appearance. Virion with a length of about 180 nm and a cross-sectional diameter of about 75 nm. The RNA genome of the virus encodes five genes whose order is highly conserved. These genes are nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G) and the viral RNA polymerase (L). Exceeding wide range of hosts. Rabies virus have been adapted to growth in a wide variety of primary and continuous cell systems, not only from cells of warm blooded animals but also ones of poikilothermic vertebrate origin. The virus is grown in human diploid cells for the purpose of producing a vaccine. It has also been adapted to growth in avian embryos. Monoclonal and polyclonal studies of rabies isolates from many animal studies worldwide have led to the following classification of the rabies group of Rhabdoviridae, genus Lyssavirus.

There are 6 serotypes of the virus: I –Prototype rabies virus, II – Lagos bat, III – Mokola, IV – Duvenhage, V – EBL-1, VI – EBL-2. Lagos bat, Mokola and Duvenhage viruses have been isolated from various animals in a number of African countries. Their natural hosts are unknown and are thought to be bats or rodents. European bat lyssaviruses-1 (EBL-1) and EBL-2 have been isolated from European bats. Duvenhage and EBL-2 viruses have been associated with human infection that resulted in a rabies-like illness and death.

EPIDEMIOLOGY

Any warm-blooded animal, including humans, may become infected with the rabies virus and develop symptoms. Indeed the virus has even been adapted to grow in cells of poikilothermic vertebrates though natural transmission has only been documented among mammals. Most animals can be infected by the virus and can

transmit the disease to humans. Rabies exists in two epidemiologic forms: urban, propagated chiefly by unimmunized domestic dogs and/or cats, and sylvatic propagated by bats, monkeys, raccoons, foxes, skunks, cattle, wolves, dogs, mongoose (normally yellow mongoose) or cats provide the greatest risk to humans. Rabies may also spread through exposure to infected domestic farm animals, groundhogs, weasels, bears and other wild carnivores. Rodents (mice, squirrels etc) are seldom infected. The virus is usually present in the nerves and saliva of a symptomatic rabid animal.

There are three vectors for rabies:

1. Usually the bite or scratch of an infected animal, which introduces the virus through the skin or mucous membrane. In many cases the infected animal is exceptionally aggressive, may attack without provocation, and exhibits otherwise uncharacteristic behavior.
2. Aerosol transmission from an infected animal, usually a bat. Infection by aerosol transmission had been demonstrated in experimental animals and has been implicated in human infection in rabies-infected bat caverns and in several laboratory accidents.
3. Tissue transplants (such as corneas) from infected humans. There have been at least 6 recorded cases of humans contracting the disease from transplants of corneas from infected donors. Transmission between humans is extremely rare.

The rabies virus survives in widespread, varied, rural fauna reservoirs. However, in Asia, parts of America and large parts of Africa, dogs remain the principal host. Mandatory vaccination of animals is less effective in rural areas. Especially in developing countries, pets may not be privately kept and their destruction may be unacceptable. Rabies is found in animals in all regions of the world except Australasia and Antarctica. Oral vaccines can be safely distributed in baits, and this has successfully reduced rabies. There are an estimated 55,000 human deaths annually from rabies worldwide, with about 31,000 in Asia, and 24,000 in Africa. One of the sources of recent flourishing of rabies in East Asia is the pet boom. China introduced in the city of Beijing the “one-dog policy” in November 2006 to control the problem. India has been reported as having the highest rate of human rabies in the world, primarily because of stray dogs. In most areas of the world, the dog is the most important vector of rabies virus for humans. However, the wolf (in eastern Europe and Arctic regions), the mongoose (in South Africa and the Caribbean), the fox (in western Europe), and the vampire bat (in Latin America) also may be prominent vectors.

Feline rabies is now reported more frequently than canine rabies; thus the vaccination of domestic cats is extremely important. Rodents and lagomorphs are rarely infected with rabies virus. Although rabies in wildlife is common throughout both the developed and the undeveloped world, most cases of postexposure

prophylaxis are associated with domesticated animals such as dogs and cats.

PATHOGENESIS

The rabies virus attacks nervous tissue and appears to replicate almost exclusively in neuronal cells. Once introduced through the skin or mucous membrane, the virus begins replicating in the striated muscles at the wound. The virus can replicate in muscle cells for hours or weeks, or it can migrate immediately to the nervous system via unmyelinated sensory nerve endings at the inoculation site. Migration to the nervous system is via the nearest sensory or motor neuron in the ganglion at the base of the spinal cord or to the spinal cord itself. The peripheral nervous system is exposed at the neuromuscular and/or neurotendinous spindles of unmyelinated sensory nerve cell endings. The virus then spreads centripetally up the nerve to the CNS (It can then be transported back to the wound site or up to the brain via the central nervous system.) probably via peripheral nerve axoplasm, at a rate of approximately 3 mm/h. It is possible however, that the virus also moves across cell-to-cell junctions, and not just among nerve trunks. Possible receptors for the virus are: acetylcholine receptors, gangliosides, and phospholipids. The rabies RNA most likely competes with host RNA, impairing neural functions. Neurologic damage is exacerbated by the production of certain cytokines, such as tumor necrosis factor-alpha. In addition, the bodies own immune response to rabies includes the production of nitric oxide, which may act as a toxin to the CNS. One of the determining factors of rabies virulence is the glycoprotein (GP) which makes up the viral membrane. In particular, the amino acid site at position 333 seems to be critical to pathogenicity. Argine or lysine residues at this site seem to confer virulence. Substituting different amino acids at this position resulted in viruses which were attenuated. The attenuated viruses spread more slowly in the CNS and do not seem able to infect certain types of nerve fibers. Reverting to the original amino acid (arginine) at the site restores neurovirulence. Viremia has been documented in experimental conditions but is thought not to play a role in naturally acquired disease. It replicates almost exclusively within the gray matter and then passes centrifugally along autonomic nerves to other tissues the salivary glands, adrenal medulla, kidneys, lungs, liver, skeletal muscles, skin, and heart. Passage of the virus into the salivary glands and viral replication in mucinogenic acinar cells facilitate further transmission via infected saliva.

In aerosol transmission, the virus enters the body through the nasal epithelium and is subsequently transported to the olfactory bulb. It is thought that the virus replicates in the neurons of the olfactory bulb before spreading to other neurons in the brain.

Rates of infection and mortality are highest from bites on the face, intermediate from bites on the hands and arms, and lowest from bites on the legs. Cases of human

rabies with an extended incubation period (2 to 7 years) have been reported, but they are rare. Host immune responses and viral strains also influence disease expression. Neurological research has suggested that death from rabies is not a result of structural damage caused by the virus, but rather a result of functional alteration of neurons.

CLINICAL MANIFESTATIONS

Two principal forms of rabies are recognized: an excitatory or "furious" form, and a paralytic or "dumb" form. The term “furious rabies” refers to man in which aggression (the excitative phase) is pronounced. “Dumb or paralytic rabies” refers to man in which the behavioral changes are minimal, and the disease is manifest principally by paralysis.

Furious form. This is the classic “mad-syndrome,” although it may be seen in all species. It is more common form and it is characterized by hyperexcitability, spasms and hydrophobia.

Paralytic form: This is first manifest by ascending paralysis of the throat and masseter muscles, often with profuse salivation and inability to swallow. Hydrophobic episodes. The paralysis progresses rapidly to all parts of the body, and coma and death follow in a few hours.

Survival tends to be longer for patients with "dumb" rabies than those with "furious" rabies.

Incubation period: 20 days to 2 months. However, the period can be as short as a few days or as long or longer than 6 years. The incubation period of rabies is exceedingly variable. Anecdotal evidence in the past has suggested that the incubation period could be as long as 21 years.

The incubation period appears to be determined by several factors: site of the bite wound; proximity to the CNS; severity of the bite; type of virus; quantity of virus injected into the site; age of the patient; immune status of the host.

Rabies develops with three main phases: prodromal period, acute neurological period, and coma. The onset of symptoms follows these general stages:

Prodromal stage. Prodromal or premontive symptoms are mild and nonspecific. They include: a slight fever, chills, malaise, headache, anorexia, nausea, sore throat (the beginnings of hydrophobia), photophobia, musculoskeletal pain, and a persistent loose cough. This stage usually lasts 2-10 days. A specific early symptom is local or radiating pain, burning, or itching, a sensation of cold, and/or tingling at the inoculation bite These sensations, which may be related to the multiplication of virus in the dorsal root ganglion of the sensory nerve supplying the area of the bite, are reported by 50 to 80 percent of patient.

Acute encephalitis similar to other viral encephalitides. This stage usually lasts 2 to 7 days. Confusion, hallucinations, combativeness, bizarre aberrations of thought, muscle spasms, meningismus, opisthotonic posturing, seizures, and focal paralysis

soon appear. Patients experience nervousness, anxiety, agitation, marked restlessness, apprehension, irritability, hyperesthesia, sensitivity to loud noises, hydrophobia, excessive salivation (1 to 1.5 liters in 24 hours), lacrimation (secretion of tears), and perspiration. As the virus begins replicating in the brain, impairment of the cranial nerve occurs. This causes eye conditions: palsies, lack of parallelism of the visual axes of the eyes, asymmetrical dilation of constriction of the pupils, and an absence of corneal reflexes. At the same time, there is weakness of facial muscles and hoarseness. Systemic symptoms are severe, and they include: tachycardia or bradycardia, cyclic respirations, urinary retention, and subfibril temperature. Evidence of upper motor neuron paralysis, with weakness, increased deep tendon reflexes, and extensor plantar responses, is the rule. Paralysis of the vocal cords is common.

Characteristically, the periods of mental aberration are interspersed with completely lucid periods, but as the disease progresses the lucid periods get shorter until the patient lapses into coma.

Coma, or terminal phase. This phase is characterized by generalized flaccid paralysis. Cranial nerve involvement causes diplopia, facial palsies, optic neuritis, and the characteristic difficulty with deglutition. Hydrophobia is experienced by 17% to 80% of rabies patients. In this stage there are forceful, painful muscle spasms of the throat, which expel any liquids administered orally. It is suspected that this is an exaggerated protective reflex of the respiratory tract. The patient experiences apnea (interruption or halt of breathing while swallowing). Cyanosis and death can occur in this phase. In addition, the patient's difficulty in swallowing results in a frothy saliva which drools from the patient's mouth because of growing muscular weakness. Eventually, a variety of stimuli (the mention of water, a tactile sense or scent of water, the thought of water, etc.) can cause uncontrollable spasms and drool. Hydrophobic episodes last for 1-5 minutes. Involvement of the amygdaloid nucleus may result in priapism and spontaneous ejaculation. Eventually, the patient experiences peripheral vascular collapse, coma, and death. The patient lapses into coma, and involvement of the respiratory center produces an apneic death.

Death or in rare cases recovery. Recovery is very rare and a number of late complications may appear. These include inappropriate secretion of antidiuretic hormone, diabetes insipidus, cardiac arrhythmias, vascular instability, adult respiratory distress syndrome, gastrointestinal bleeding, thrombocytopenia, and paralytic ileus.

Rabies is usually 100% fatal if untreated. If symptoms have appeared, the victim usually dies in spite of subsequent immunization and treatment with rabies immunoglobulin. There are only three documented cases of patients recovering from rabies infection.

DIAGNOSIS

Diagnosis by bite and symptom history is not necessarily accurate, because such history cannot be established in 22% to 40% of the cases. Diagnosis is confirmed by isolation of the virus from the patient's saliva, throat, corneal impression, facial skin, or skin from the hair-covered occipital part of the neck. Electron micrographs can confirm Negri bodies (oval or round eosinophilic masses) in the brain, usually in the cornu Ammonis. However, Negri bodies, which consist almost entirely of viral nucleocapsid, cannot be found in approximately 30% of human rabies cases.

Laboratory results may indicate: elevated white blood count; increased number of polymorphonuclear cells; increased number of monoculear cells; elevated levels of urinary glucose, acetone, and protein; abnormal number of cells in the cerebrospinal fluid.

Early in the disease, hemoglobin values and routine blood chemistry results are normal; abnormalities develop as hypothalamic dysfunction, gastrointestinal bleeding, and other complications ensue. The peripheral white blood cell count is usually slightly elevated (12,000 to 17,000/uL) but may be normal or as high as 30,000/uL.

The deference method for diagnosing rabies is by performing PCR or viral culture on brain samples taken after death. The diagnosis can also be reliably made from skin samples taken before death. It is also possible to make the diagnosis from saliva, urine and cerebrospinal fluid samples, but this is not as sensitive. Inclusion bodies called Negri bodies are 100% diagnostic for rabies infection, but found only in 20% of cases.

The diagnosis of animal and human rabies can be made by 4 methods: (1) histopathology (2) virus cultivation (3) serology (4) virus antigen detection. Although each of the first 3 methods have distinct advantages, none provide a rapid definitive diagnosis.

Histopathology - The detection of viral antigen in infected tissue (e.g., corneal impression smears, skin biopsies, or brain). Negri bodies are pathognomonic of rabies. However, Negri bodies are only present in 71% of cases. The neuropathology of rabies resembles that of other viral diseases of the CNS: hyperemia, varying degrees of chromatolysis, nuclear pyknosis, and neuronophagia of the nerve cells; infiltration by lymphocytes and plasma cells of the Virchow-Robin space; microglial infiltration; and parenchymal areas of nerve cell destruction. In experimental animal models, adenohypophyseal infection with rabies virus, with reduction in growth hormone and vasopressin release, is common. The most characteristic pathologic finding of rabies in the CNS is the formation of cytoplasmic inclusions called Negri bodies within neurons. Each eosinophilic mass measures approximately 10 nm and is made up of a finely fibrillar matrix and rabies virus particles. Negri bodies are

distributed throughout the brain, particularly in Ammon's horn, the cerebral cortex, the brainstem, the hypothalamus, the Purkinje cells of the cerebellum, and the dorsal spinal ganglia. Negri bodies are not demonstrated in at least 20 percent of cases of rabies, and their absence from brain material does not rule out the diagnosis.

Virus cultivation – The most definitive means of diagnosis is by virus cultivation from infected tissue. Tissue culture lines, such as WI-38, BHK-21, or CER. Since rabiesvirus induce minimal CPE, IF is routinely used to detect the presence of rabiesvirus Ag in the tissue culture. The more commonly used method for virus isolation is by the inoculation of saliva, salivary gland tissue and brain tissue intracerebrally into infant mice. The mice should develop paralysis and death within 28 days. Upon death, the brains are examined for the presence of the virus by immunofluorescence.

Serology. The serologic demonstration of acute infection, circulating antibodies appear slowly in the course of infection but they are usually present by the time of onset of clinical symptoms. The most commonly used serological tests were the mouse infection neutralization test (MNT) or the rapid fluorescent focus inhibition test (RFFIT). These tests have now been largely superseded by EIAs. Serology had been reported to be the most useful method for the diagnosis of rabies.

Rapid virus antigen detection - in recent years, virus antigen detection by IF had become widely used. The potentially infected tissue is incubated with fluorescein-labeled antibody. The cells are examined by fluorescent microscopy for the presence of fluorescent intracytoplasmic inclusions. The specimens which are usually used are corneal impressions (obtained by gently abrading the cornea with a microscopic slide) or neck skin biopsy (the cells examined are the sensory nerves). In an American series, IF of corneal impressions or neck skin impressions was diagnostic only in 50% of cases early in the course of the clinical illness.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis in a case of suspected human rabies may initially include any cause of encephalitis, particularly infection with viruses such as herpesviruses, enteroviruses, and arboviruses (e.g., West Nile virus). The most important viruses to rule out are herpes simplex virus type 1, varicella-zoster virus, and (less commonly) enteroviruses, including coxsackieviruses, echoviruses, polioviruses, and human enteroviruses 68 to 71. In addition, consideration should be given to the local epidemiology of encephalitis caused by arboviruses belonging to several taxonomic groups, including eastern and western equine encephalitis viruses, St. Louis encephalitis virus, Powassan virus, the California encephalitis virus serogroup, and La Crosse virus. Rabies may also present as an ascending paralysis resembling the Landry/Guillain-Barre syndrome (dumb rabies, rage tranquille). Initially, this clinical pattern was reported most frequently among persons bitten by

vampire bats who were given postexposure rabies prophylaxis. Paralytic rabies also occurs in Southeast Asia among persons with canine exposures.

TREATMENT

In cases of animal bites, dogs and cats in a rabies endemic area should be held for 10 days for observation. If signs develop, they should be killed and their tissue examined in the laboratory. Wild animals are not observed but if captured, the animal should be killed and examined.

Wound treatment - surgical debridement should be carried out: scrubbed with soap and then flushed with water. The wound should not be sutured up. Quaternary ammonium compounds such as 1 to 4% benzalkonium chloride or 1% cetrimonium bromide are useful because they inactivate the rabies virus. However, 0.1% benzalkonium solutions are less effective than 20% soap solutions. Usually tetanus toxoid and antibiotics should be administered.

Passive immunization – human rabies immunoglobulin (HRIG) around the area of the wound; to be supplemented with an i.m. dose to confer short term protection. There is convincing evidence that combined treatment with rabies immunoglobulin and active immunization is much more effective than active immunization alone. Equine rabies immunoglobulin (ERIG) is available in many countries and is considerably cheaper than HRIG, but it frequently may cause serum sickness. Fifty percent of the total dose of 20 units per kilogram for HRIG and 40 units per kilogram for equine antiserum is given by local infiltration of the wound, and the rest is administered intramuscularly into the gluteal region.

Active immunization – Several types of live attenuated vaccines are available for use in animals, but they are considered to be unsuitable for humans. The vaccines which are available for humans are present are inactivated whole virus vaccines.

Nervous tissue preparation – this consisted of a 5% suspension of infected animal nervous tissue which had been inactivated (e.g. the Semple vaccine was derived from phenol-inactivated infected rabbit brain), these preparations are now out of date as they were associated with the rare complication of demyelinating allergic encephalitis. This appears to be related to myelin basic protein in the vaccine. This complication was shown to occur in 4.6 cases for 1000 persons vaccinated by the Semple vaccine. The case-fatality proportion was 3.13%. The Semple vaccine is still used in some developing countries. A suckling mouse brain vaccine is used in some Central and S. American countries.

Duck embryo vaccine – this vaccine strain is grown in embryonated duck eggs and is inactivated with B-propriolactone. This vaccine has a lower risk of allergic encephalitis. However, it is considerably less immunogenic and does have minor side effects. Almost all vaccines experience local reactions, 33% have constitutional symptoms such as fever, malaise, myalgia, and generalized lymphadenopathy.

Human diploid cell vaccine (HDCV) – HDCV was introduced in 1978. It is a grown on WI-38 (US) or MRC-5 (Europe) cells. The vaccine is highly effective, in several studies, antibodies have been demonstrated in 100% of all recipients. Serious adverse reactions to HDCV are extremely rare. However, the vaccine is very expensive ($100 for 6 doses), as human cell cultures are more difficult to handle than other animal cell culture systems. 5 or 6 doses of the vaccine is normally i.m. However, several studies suggest than smaller intradermal doses of HDCV may be as effective and thus it may be considered for use in poor developing countries.

Another inactivated vaccine is widely used in China. It is derived from virus grown in primary hamster kidney cells and cost less than the other diploid cell culture vaccines. The vaccine had been shown to be as effective as HDCV. Efforts are being made to use other inexpensive cell culture systems such as VERO cells.

Treatment is nonspecific.

Vaccination schedule:

1. The pre-exposure vaccination schedule consists of three doses, given as follows:

- First dose given.
- Second dose given 7 days after first dose.
- Third dose given 21 days or 28 days after first dose.

2. If the decision is made to begin the rabies vaccine shots and you have never been vaccinated against rabies:

- you should get five doses of the rabies vaccine - first dose immediately, then additional doses 3, 7, 14, and 28 days after the first dose.
- you should also get a shot of Rabies Immune Globulin at the same time as the first dose of rabies vaccine.

3. If you have been previously vaccinated against rabies:

- you should get two doses of the rabies vaccine -- the first dose immediately, and the second dose three days later.
- you do not need to get a shot of rabies immune globulin.

PREVENTION

Preexposure prophylaxis. Persons who are regularly at high risk of exposure, such as vets, laboratory workers, animal handlers and wildlife officers should be considered for preexposure prophylaxis by active immunization with the cell culture vaccine. Immunization normally consists of 3 doses of vaccine. Antibody can be demonstrated in the sera of virtually 100% of those vaccinated if the diploid cell culture vaccine is used. Booster doses should be offered to persons at continuing risk every one to three years. Local treatment of wounds should always be carried out in exposed persons who have been vaccinated previously. The WHO expert committee considers that local infiltration with antiserum is optional and systemic passive

immunization contraindicated.

Post-exposure prophylaxis. Treatment after exposure, known as post-exposure prophylaxis or “P.E.P.”, is highly successful in preventing the disease if administered promptly, generally within ten days of infection. Thoroughly washing the wound as soon as possible with soap and water for approximately five minutes is very effective at reducing the number of viral particles. If available, a virucidal antiseptic such as povidone-iodine, iodine tincture, aqueous iodine solution or alcohol (ethanol) should be applied after washing. Exposed mucous membranes such as eyes, nose or mouth should be flushed well with water. Patients receive one dose of HRIG and five doses of rabies vaccine over a twenty-eight day period. One-half the dose of the immunoglobulin is injected in the region of the bite, if possible, with the remainder injected intramuscularly away from the bite. This is much less painful compared with administering the immunoglobulin through the abdominal wall with a large needle, as was done in the past. The first dose of rabies vaccine is given as soon as possible after exposure, with additional doses on days three, seven, fourteen, and twenty-eight after the first. Patients that have previously received pre-exposure vaccination do not receive the immunoglobulin, only the post-exposure vaccinations on day 0 and 3.

In instances when post-exposure prophylaxis is administered as a precaution (e.g. a person wakes up and finds a bat in the room they were sleeping in), it is now mainly given in the gluteal region and deltoid (upper arm). The number of shots delivered to the gluteal area on the first day is determined by weight, and it is not uncommon to require three of these shots. Subsequent shots of the immunoglobulin (to build longer term immunity to rabies) are given to the arm. Recipients of the vaccine have reported that these shots are no more painful than normal shots (such as tetanus boosters). This use of post-exposure prophylaxis has come in for heavy criticism.

Most official documentation on rabies on the internet and otherwise warn that treatment becomes futile with the onset of prodrome (when symptoms begin to appear). These texts are written to convince the layman not to delay seeking treatment (and rightly so). However, this may also lead them to falsely conclude that their situation is not urgency and that treatment is possible up until the very end of the incubation period, as it may last from 1 to 3 months on average; or it may at least convince them that it is safe to delay treatment by a few days. While the virus is treatable only during the incubation period, it is important to note that it is not treatable during its entirety. Rabies is fully treatable while the virus is present in tissues composed of cells other than neurons, such as skin and muscle. However, once the infection spreads to a neuron, the virus is sequestered from the immune system and will eventually make its way to the spinal cord and then to the brain. Treatment at this point may not be effective, even though symptoms may begin to appear weeks or even months later. Therefore, it is highly recommended that P.E.P.

be administered as soon as possible. Begun without delay, or very little delay, P.E.P. is 100% effective against rabies. In the case where there has been a significant delay in administering P.E.P., the treatment should be administered regardless of that delay, as it may still be effective if it is not too late.

Failure of prophylaxis. HDCV has been used to treat many thousands of people exposed to possible rabid animals in the past 12 years and its efficacy has been proven. At least 16 people treated with HDCV after exposure have died of rabies. All of the patients had major exposures and in the majority, the incubation period was short, 21 days or less. Treatment was frequently not started promptly within 24 hours and only half received combined serum and vaccine. At least one person has died despite optimum treatment.

CONTROL

Urban – canine rabies accounts for more than 99% of all human rabies cases and over 90% of all human post-exposure treatments worldwide. In the past, the Scandinavian countries were able to rid themselves of rabies by sanitary control alone, which included stray dog control. Other countries, such as the UK, have used these techniques allied with quarantine and/or vaccination to eradicate and then maintain freedom from the disease. Currently, the importation of mammals into the UK is controlled by the Rabies order. It applies to a wide range of mammals but livestock including horses, which are covered by separate regulations. The animals must be vaccinated on arrival. Effective animal vaccines are available.

Wildlife – canine rabies can be controlled because in general, dogs live in close association with man and are therefore within physical reach. An attempt was made to vaccinate foxes in an attempt to create an immune barrier at the entrance to the Rhone valley in 1978. The live attenuated virus was contained in small plastic blister packages fixed under the skin of chicken heads used as bait, and 4050 of these were distributed over an area of 335km^2. With continued field trials, Switzerland has been freed of rabies. Other field trials are being set up.

ANTHRAX

Anthrax is an acute bacterial infection caused by Bacillus anthracis. The name anthrax (from the Greek for coal) refers to the typical black eschar that is seen on affected area. It occurs most frequently in herbivorous animals. It is a zoonosis to which most mammals, especially grazing herbivores, are considered susceptible. Human infections result from contact with contaminated animals or animal products, and there are no known cases of human-to-human transmission. Human anthrax is not common, and only one of us has seen a case. Cutaneous anthrax, the most common form, is usually curable. A small percentage of cutaneous infections become systemic, and these can be fatal. Systemic infection resulting from inhalation of the organism has a mortality rate approaching 100 percent, with death usually occurring within a few days after the onset of symptoms. The rate of mortality among persons with infection resulting from ingestion is variable, depending on the outbreak, but it may also approach 100 percent. Whatever the portal of entry, systemic anthrax involves massive bacteremia and toxemia with nondescript initial symptoms until the onset of hypotension, shock, and sudden death. Manifestations of advanced disease, including shock and sudden death, are believed to result from the action of the exotoxin complex secreted by anthrax bacilli. The efficacy of therapy, if initiated during the incubation period, and the rapid course of the disease once symptoms appear make early intervention an absolute necessity.

ETIOLOGY

B. anthracis is a nonmotile, gram-positive, aerobic rod 1.2 to 10 μm in length and 0.5 to 2.5 μm in width that is capable of forming central or terminal spores. Oxygen is required for sporulation but not for germination of spores, and sporulation does not take place in living animals. The rectangular shape of the individual bacteria gives chains of B. anthracis a boxcar-like appearance. On blood agar, virulent B. anthracis usually forms nonhemolytic or weakly hemolytic, grayish-white, rough colonies; however, if the medium contains bicarbonate and incubation takes place in the presence of excess CO_2, the colonies are smooth and mucoid. Virulent strains of B. anthracis are pathogenic for animals, including mice and guinea pigs. Known virulence factors include three proteins collectively called anthrax toxin (see below) and an antiphagocytic capsular polypeptide composed of D-glutamic acid residues linked by peptide bonds involving the gamma carboxyl group.

The genes that determine the production of anthrax toxin and that of capsular polypeptide are located on separate plasmids of B. anthracis. Determination of susceptibility to bacillus phage gamma and demonstration of species-specific antigens are helpful in laboratory identification of B. anthracis. Spores of B. anthracis

can survive for years in dry earth but are destroyed by boiling for about 10 min, by treatment with oxidizing agents such as potassium permanganate or hydrogen peroxide, or by dilute formaldehyde. Most strains of B. anthracis are susceptible to penicillin.

EPIDEMIOLOGY

The distribution of anthrax is worldwide. All animals are susceptible to varying degrees, but the disease is most prevalent among domestic herbivores (including cattle, sheep, horses, and goats) and wild herbivores.

Grazing animals become infected when they are foraging for food in areas contaminated with spores of B. anthracis under appropriate climatic conditions. Anthrax in herbivores tends to be severe, with a high mortality rate. Terminally ill animals have overwhelming bacteremic infections and often bleed from the nose, mouth, and bowel, thereby contaminating soil or watering places with vegetative B. anthracis that can subsequently sporulate and persist in the environment. The carcasses of infected animals provide additional potential foci of contamination.

Epidemics among animals may spread from an initial focus to contiguous geographic areas in a pattern consistent with the movement of infected animals. Biting flies have also been implicated as vectors for the spread of anthrax, and vultures that feed on infected carcasses occasionally spread spores from a contaminated area to noncontiguous areas, probably by the contamination of surface water pools.

The natural resistance of humans to anthrax is greater than that of herbivorous animals. It is difficult to determine the annual worldwide incidence of human anthrax, because many cases do not receive medical attention and are not reported. Estimates of 20,000 to 100,000 cases per year have been made. Human cases are classified as agricultural or industrial on the basis of the epidemiologic setting in which they occur. Agricultural cases result most often from contact with animals that have anthrax (for example, during skinning, butchering, or dissecting), from bites of contaminated or infected flies, and (in rare instances) from consumption of contaminated meat. Industrial cases are associated with exposure to contaminated hides, goat's hair, wool, or bones. Anthrax in animals has been a long-standing problem in Iran, Turkey, Pakistan, and Sudan, and the probability is high that animal products (especially goat's hair) originating from these areas will be contaminated with anthrax spores.

Large epidemics of anthrax occurred in Zimbabwe between 1978 and the early 1980s. The outbreak in Zimbabwe involved more than 9700 cases of agricultural anthrax in humans. This massive outbreak occurred during wartime and was associated with disruption of the veterinary and medical infrastructure and the cessation of veterinary anthrax vaccination programs.

Another outbreak was observed in the former Soviet Union at Sverdlovsk in 1979. Initially, the cases in Sverdlovsk were reported to be cutaneous and gastrointestinal anthrax and were attributed to exposure to meat from infected animals. Intense international interest was stimulated by the suspicion that the release of B. anthracis from a nearby military facility was responsible for the outbreak. Recent analyses of epidemiologic data from the Sverdlovsk outbreak and autopsy findings on most of the fatal cases determined that the disease was, in fact, inhalation anthrax.

Before the introduction of hygienic measures in the 1960s, including vaccination, inhalation anthrax developed in special population. The workers in goat-hair mills, for example, were regularly exposed to high concentrations of viable anthrax spores. Nevertheless, for reasons that are not understood, few cases of inhalational anthrax occurred among them. When dispersed in the atmosphere as an aerosol, anthrax spores can present a respiratory hazard even far downwind from the point of release, as demonstrated by animal tests on Gruinard Island in the United Kingdom, and by an accidental release from a military biologic facility in the city of Sverdlovsk in the former Soviet Union

Hardiness and dormancy of anthrax have allowed anthrax spores to be developed as biologic weapons by a number of nations, although their only known use in war was by the Japanese army in Manchuria in the 1940s. As example of bioterrorism is outbreak in US. Letter containing anthrax spores was mailed in US on October 2001. That led to 5 cases of inhalational anthrax among postal workers who were employed at that major facility or who handled bulk mail originating from that facility. And 2 fatal cases of inhalational anthrax have been reported.

PATHOGENESIS

B. anthracis is an extracellular pathogen that can evade phagocytosis, invade the bloodstream, multiply rapidly to a high population density in vivo, and kill quickly. Capsular polypeptide and anthrax toxin are the principal virulence factors of B. anthracis. The capsule of B. anthracis consists of poly-D-glutamic acid and confers resistance to phagocytosis. Anthrax toxin consists of three proteins called protective antigen (PA), edema factor (EF), and lethal factor (LF). The major virulence factors of B. anthracis are encoded on two virulence plasmids, pXO1 and pXO2. The toxin-bearing plasmid, pXO1, is codes for the genes that make up the secreted exotoxins. The smaller capsule-bearing plasmid, pXO2, is codes for three genes (capB, capC, and capA) involved in the synthesis of the polyglutamyl capsule.

The exotoxins are thought to inhibit the immune response mounted against infection, whereas the capsule inhibits phagocytosis of vegetative anthrax bacilli. The expression of all known major virulence factors is regulated by host-specific factors such as elevated temperature (>37°C) and carbon dioxide concentration (>5 percent),

and by the presence of serum components.

Bacillus anthracis endospores reach a primary site in the subcutaneous layer, gastrointestinal mucosa, or alveolar spaces. For cutaneous and gastrointestinal anthrax, low-level germination occurs at the primary site, leading to local edema and necrosis. Endospores are phagocytosed by macrophages and germinate. Macrophages containing bacilli detach and migrate to the regional lymph node. Vegetative anthrax bacilli grow in the lymph node, creating regional hemorrhagic lymphadenitis. Bacteria spread through the blood and lymph and increase to high numbers, causing severe septicemia. High levels of exotoxins are produced that are responsible for overt symptoms and death. In a small number of cases, systemic anthrax can lead to Meningeal involvement by means of lymphatic or hematogenous spread. In cases of pulmonary anthrax, peribronchial hemorrhagic lymphadenitis blocks pulmonary lymphatic drainage, leading to pulmonary edema. Death results from septicemia, toxemia, or pulmonary complications and can occur one to seven days after exposure. Vegetative anthrax bacilli secrete two exotoxins that are active in host cells. Edema toxin is a calmodulin - dependent adenylate cyclase that increases intracellular levels of cyclic AMP (cAMP) on entry into most types of cell. This is believed to alter water homeostasis, resulting in massive edema.

Lethal toxin is a zinc metalloprotease that causes a hyperinflammatory condition in macrophages, activating the oxidative burst pathway and the release of reactive oxygen intermediates, as well as the production of proinflammatory cytokines, such as tumor necrosis factor α and interleukin-1b, that are responsible for shock and death.

Histologically, the lesion in cutaneous anthrax is characterized by necrosis, vascular congestion, hemorrhage, and gelatinous edema. The number of leukocytes is disproportionately small in comparison with the amount of tissue damage. The clinical description of this lesion as a "malignant pustule" is not in concordance with the pathologic findings.

CLINICAL MANIFESTATIONS

Approximately 95% percent of human cases of anthrax are the cutaneous form and about 5% the inhalation form. Gastrointestinal anthrax is rare. Anthrax meningitis occurs in a small percentage of all cases and is a frequent complication of overwhelming B. anthracis bacteremia.

The cutaneous lesion in anthrax is most often found on exposed areas of skin. In Zimbabwe, lesions in children under 5 years old were significantly more likely to be on the head, neck, or face and less likely to be on the upper limbs than lesions in adults. This distribution correlates with the fact that children have less contact with carcasses of infected animals and are more likely to acquire infection through fly bites.

Within days after inoculation of B. anthracis spores into the skin, a small red macule appears. During the next week, the lesion typically progresses through papular and vesicular or pustular stages to the formation of an ulcer with a blackened necrotic eschar surrounded by a highly characteristic, expanding zone of brawny edema. The early lesion may be pruritic, and the fully developed lesion is painless. Small satellite vesicles may surround the original lesion, and painful nonspecific regional lymphadenitis is common. Most patients are afebrile, with mild or no constitutional symptoms; in severe cases, however, edema may be extensive and associated with shock. Spontaneous healing occurs in 80-90 % of untreated cases, but edema may persist for weeks. In the 10-20% of untreated patients who have progressive infection, bacteremia develops and is often associated with high fever and rapid death. The differential diagnosis includes staphylococcal skin infections, tularemia, plague, and orf. Cutaneous anthrax should be considered when patients have painless ulcers associated with vesicles and edema and have had contact with animals or animal products.

Inhalational anthrax is rare, usually occurring after the inhalation of pathogenic endospores from contaminated animal hides or products. The frequent similarity of the presenting symptoms of inhalation anthrax (woolsorters' disease) to those of severe viral respiratory diseases makes early diagnosis difficult. After 1 to 3 days, an acute phase supervenes, with increasing fever, dyspnea, stridor, hypoxia, and hypotension usually leading to death within 24 h. Occasionally, patients present with fulminant disease. A characteristic radiologic finding associated with hemorrhagic mediastinitis is symmetric mediastinal widening.

Symptoms of gastrointestinal anthrax are variable and include fever, nausea and vomiting, abdominal pain, bloody diarrhea, and sometimes rapidly developing ascites. Diarrhea is occasionally massive in volume, causing hemoconcentration and severe contraction of intravascular volume. The major features of oropharyngeal anthrax are fever, sore throat, dysphagia, painful regional lymphadenopathy, and toxemia; respiratory distress may be evident. The primary lesion is most often on the tonsils.

Involvement of the meninges by B. anthracis is a rare complication of anthrax. The most common portal of entry is the skin, from which the organisms can spread to the central nervous system by hematogenous or lymphatic routes. Anthrax meningitis also occurs in cases of pulmonary and gastrointestinal anthrax. Anthrax meningitis is almost always fatal, with death occurring one to six days after the onset of illness, despite intensive antibiotic therapy. In the few cases in which patients have survived, antibiotic therapy was combined with the administration of antitoxin, prednisone, or both. Common meningeal symptoms and nuchal rigidity, the patient has fever, fatigue, myalgia, headache, nausea, vomiting, and sometimes agitation, seizures, and delirium. The initial signs are followed by rapid neurologic degeneration and death.

The pathological findings are consistent with hemorrhagic meningitis, with extensive edema, inflammatory infiltrates, and numerous gram-positive bacilli in the leptomeninges. The cerebrospinal fluid is often bloody and contains many gram-positive bacilli. Examination at autopsy finds extensive hemorrhage of the leptomeninges, which gives them a dark red appearance described as “cardinal’s cap.”

DIFFERENTIAL DIAGNOSIS

In cutaneous anthrax, the painless, blackened, necrotic eschar is limited to the late stages of the infection. The ulcerative eschar of cutaneous anthrax must be differentiated from other papular lesions that present with regional lymphadenopathy. If the lesion is purulent and the regional lymph nodes are palpable, staphylococcal lymphadenitis is the most likely cause, although cutaneous anthrax lesions can be superinfected with pyogenic bacteria.

DIAGNOSIS

B. anthracis is present in large numbers in cutaneous lesions of anthrax and can be demonstrated by Gram's staining, direct fluorescent antibody staining, or culture unless the patient has been treated with antibiotics. A small proportion of patients with anthrax have bacteremia, but the disease may progress to death before blood cultures become positive. Patients with anthrax meningitis have bloody spinal fluid containing large numbers of B. anthracis organisms demonstrable by staining or culture.

A tests for antibody to B. anthracis are useful in confirming the diagnosis of anthrax. Specific enzyme-linked immunosorbent assays that show a quadrupling of the titer of antibodies against these components are diagnostic of past infection or vaccination. Immunologic detection of the exotoxins in blood during systemic infection is possible with similar tests if antibodies to anthrax toxins are available, but those tests are unreliable for diagnosis.

The anthraxin skin test, consisting of subdermal injection of a commercially produced chemical extract of an attenuated strain of B. anthracis, is available for the diagnosis of acute and previous cases of anthrax.

The virulence of suspected isolates of B. anthracis can be demonstrated by inoculation of guinea pigs; death occurs within 24 h with positive cultures of heart blood.

Patients with mild disease usually have normal leukocyte counts, but patients with disseminated disease typically have polymorphonuclear leukocytosis. A sensitive and specific polymerase chain reaction method developed for the detection of spores of B. anthracis may be useful for rapid testing of potentially contaminated animal or agricultural products. This new diagnostic techniques have focused on the

use of the polymerase chain reaction to amplify markers specific to B. anthracis.

TREATMENT

Pharmacologic therapy for anthrax. Penicillin and doxycycline are used for the treatment of anthrax. Intravenous administration is recommended in cases of inhalational, gastrointestinal, and meningeal anthrax. Cutaneous lesions should be cleaned and covered, and used dressings should be decontaminated. Cutaneous anthrax with signs of systemic involvement, extensive edema, or lesions on the head and neck also requires intravenous therapy. Streptomycin had a synergistic effect with penicillin in experiments and may also be given for inhalational anthrax. Despite early and vigorous treatment, the prognosis of patients with inhalational, gastrointestinal, or meningeal anthrax remains poor.

Antibiotic therapy should be continued for at least 14 days after symptoms abate. In cutaneous anthrax, treatment with oral penicillin renders lesions sterile after 24 hours, although they still progress to eschar formation. Chloramphenicol, erythromycin, tetracycline, or ciprofloxacin can be administered to patients who are allergic to penicillin. If resistance to penicillin and doxycycline is suspected and antibioticsusceptibility data are not available, ciprofloxacin may be administered empirically. Doxycycline and tetracycline are not recommended for pregnant women or children, and the effects of ciprofloxacin in pregnant women have not been determined.

For inhalation anthrax, high-dose penicillin therapy (2 million units at 2-h intervals) is recommended; for gastrointestinal anthrax or anthrax meningitis, the recommended regimen is the same.

For culturing cutaneous lesions, gentle sampling with a moist, sterile applicator is preferred. Excision of the eschar is contraindicated and might hasten systemic dissemination. Lesions should be covered with sterile dressings that are changed regularly. Soiled dressings should be autoclaved and properly disposed of. In cases of extensive edema, meningitis, or swelling in the head-and-neck region, corticosteroid therapy should be initiated. Supportive therapy should be initiated to prevent septic shock and fluid and electrolyte imbalance, and to maintain airway patency.

The understanding that anthrax is a toxigenic condition suggests the potential of antitoxin therapy. The central importance of lethal toxin is supported by much research. A rational case can be made for passive immunization with anthrax antitoxin in addition to antibiotic therapy in severely ill patients with anthrax, but no appropriate antitoxin is commercially available.

PROPHYLAXIS

Inhalation anthrax was essentially eliminated in England before 1940 through the development of methods to decontaminate wool and goat's hair and the

improvement of working conditions for handlers of animal products.

Nonliving vaccines consisting of alum-precipitated or aluminum hydroxide-adsorbed extracellular components of unencapsulated B. anthracis are used in Europe and US for the immunization of agricultural workers, veterinary personnel, and others at risk of exposure to anthrax. The major active component of these vaccines is PA.

Live attenuated vaccines containing spores of B. anthracis are used in both developed and developing countries to immunize domestic herbivores. Bacterial strains for anthrax vaccine were made by rendering virulent strains free of one or both plasmids. Pasteur prolongly incubated of B. anthracis cultures at 42°C and the strain became avirulent and encapsulated and no express exotoxin components. The basis for attenuation of the current Sterne spore vaccine is loss of the plasmid that encodes capsular polypeptide.

Improved anthrax vaccines for humans are needed, because the current vaccines are impure and chemically complex, elicit only slow-onset protective immunity, provide incomplete protection, and cause significant adverse reactions. In addition to agricultural and industrial anthrax, the possible use of B. anthracis as an agent of biological warfare is a stimulus for the development of an improved vaccine. Current strategies for vaccine development include purification of candidate protective antigens, expression of protective antigens in recombinant microbial vaccines, and construction of improved live attenuated strains of B. anthracis.

Carcasses of animals that succumb to anthrax should be buried intact or cremated. Necropsy or butchering of infected animals should be avoided, because sporulation of B. anthracis occurs only in the presence of oxygen.

PLAGUE

Plague is an acute, febrile, zoonotic disease caused by infection with Yersinia pestis. Although human cases are infrequent and are curable with antibiotics, plague is one of the most virulent and potentially lethal infectious diseases known. The plague bacterium occurs in widely scattered foci in Asia, Africa, and the Americas, where its usual hosts are wild and peridomestic rodents. It is transmitted to humans typically by flea bite and less commonly by direct contact with infected animal tissues or by airborne droplet. The principal clinical forms of plague are bubonic, septicemic, and pneumonic. Most cases are sporadic, occurring singly or in small clusters, although the potential for epidemic spread still exists in some countries.

Plague's deadly epidemic potential is notorious and well documented. The Justinian pandemic (542 to 767 A.D.) spread from central Africa to the Mediterranean littoral and thence to Asia Minor, causing an estimated 40 million deaths. The second pandemic began in central Asia, was carried to Sicily by ship from Constantinople in 1347, and swept through Europe and the British Isles in successive waves over the next four centuries. At its height, it killed as many as a quarter of the affected population and became known as the Black Death. In the third (modern) pandemic, plague appeared in Yunnan, China, in the latter half of the nineteenth century; established itself in Hong Kong in 1894; and spread by ship to Bombay in 1896 and subsequently to major port cities throughout the world, including San Francisco and several other West Coast and Gulf Coast ports in the United States. The plague bacillus was first cultured by Alexandre Yersin in Hong Kong in 1894. In 1898, Paul-Louis Simond, a French scientist sent to investigate epidemic bubonic plague in Bombay, identified the bacillus in the tissues of dead rats and proposed transmission by rat fleas. Waldemar Haffkine, also in Bombay at that time, developed a crude vaccine.

By 1910, plague had circled the globe and established itself in rodent populations on all inhabited continents other than Australia. After 1920, however, the spread of plague was largely halted by international regulations that mandated control of rats in harbors and inspection and rat-proofing of ships. Before the third pandemic subsided, it resulted in an estimated 26 million plague cases and more than 12 million deaths, the vast majority in India. From 1969 through 1993, a median of 1356 human plague cases were reported annually to the World Health Organization, with around 10 to 15 countries reporting cases each year. Plague has practically disappeared from cities and now occurs mostly in rural and semirural areas, where it is maintained in wild rodents.

Plague, because of its pandemic history, remains one of three quarantinable diseases subject to international health regulations (the other two being cholera and yellow fever). The alarm that plague is still able to evoke was highlighted by the

public panic over and exaggerated international response to reports of outbreaks of bubonic and pneumonic plague in India in 1994.

ETIOLOGY

Y. pestis is a gram-negative coccobacillus in the family Enterobacteriaceae. It is microaerophilic, nonmotile, nonsporulating, oxidase and urease negative and biochemically unreactive. The organism is nonfastidious and infective for laboratory rodents. It grows well, if slowly, on routinely used microbiologic media (e.g., sheep blood agar, brain-heart infusion broth, and MacConkey agar). Y. pestis can multiply within a wide range of temperatures (-2°C to 45°C) and pH values (5.0 to 9.6), but optimal growth occurs at 28°C and at pH ~7.4. When incubated on agar plates, colonies are pinpoint in size at 24 h and 1 to 2 mm in diameter at 48 h. Colonies are gray-white with irregular surfaces that are often described as having a "hammered-metal" appearance when viewed microscopically. In broth culture, Y. pestis grows without turbidity in clumps clinging to the sides of tubes. The virulence of this bacterium results from the 32 Y. pestis chromosomal genes and two Y. pestis – specific plasmids, constituting the only new genetic material acquired since its evolution from its predecessor. These acquired genetic changes have allowed the pathogen to colonize fleas and to use them as vectors for transmission.

EPIDEMIOLOGY

Y. pestis is maintained in enzootic cycles involving relatively resistant wild rodents and their fleas in mostly remote, lightly populated areas of Asia, Africa, and the Americas and in limited rural foci in extreme southeastern Europe near the Caspian Sea. Plague is a zoonotic disease that primarily affects rodents; humans are incidental hosts. Survival of the bacillus in nature depends on flea-rodent interaction, and human infection does not contribute to the bacteria's persistence in nature. Of the 1500 flea species identified, only 30 of them have been shown to act as vectors of plague. The most prominent of these vectors is Xenopsylla cheopis (oriental rat flea); however, Oropsylla montana has been incriminated as the primary vector for this disease in North America. Y. pestis can multiply to enormous numbers in the foregut (proventriculus) of these fleas, resulting in a bolus of organisms and clotted blood that blocks the passage of subsequent blood meals. Regurgitation by a "blocked" flea while it feeds facilitates transmission of the plague bacillus to the new host.

Plague in populated areas is most likely to develop when sanitation is poor and rats are numerous especially the common black or roof rat (Rattus rattus) and the larger brown sewer or Norway rat (R. norvegicus). A high mortality rate from plague in these susceptible rat populations forces their fleas to seek alternative hosts, including humans.

Except for large outbreaks of pneumonic plague in Manchuria in the early part

of the twentieth century, person-to-person respiratory transmission of plague during the third pandemic has occurred only sporadically and has been limited to clusters of close contacts of pneumonic plague patients, such as household members and caregivers. The 1994 outbreak of pneumonic plague in the city of Surat, India, although reported to be extensive, most likely involved fewer than 100 cases and 50 deaths.

From 1979 through 1993, 16,312 human plague cases and 1668 deaths (mortality, 10 percent) were reported by 20 countries to the World Health Organization. The WHO reports that, in 2003, 9 countries reported a total of 2118 plague cases and 182 deaths, 98.7% and 98.9% of which were reported from Africa, respectively. International health regulations require immediate reporting of plague cases.

Plague can be transmitted during the skinning and handling of carcasses of wild animals such as rabbits and hares, prairie dogs, wildcats, and coyotes. Such direct inoculation of mammal-adapted organisms is associated with primary septicemia and high mortality. Oropharyngeal plague can result from the ingestion of undercooked contaminated meat and perhaps from the manual transfer of infected fluids to the mouth during the handling of infected animal tissues.

PATHOGENESIS

Y. pestis is among the most invasive bacteria known. The mechanisms by which the organism causes disease are incompletely understood, but both chromosome- and plasmid-encoded gene products are probably involved. Three plasmids encode for a variety of known or presumed virulence factors, including the F1 envelope antigen, which confers bacterial resistance to phagocytosis by polymorphonuclear leukocytes (PMNs) in vitro; a murine exotoxin; the V antigen, which is essential for virulence, may immunocompromise the host by suppressing the synthesis of interferon g and tumor necrosis factor a, and stimulates protective immunity in laboratory animals; pesticin, a bactericidal protein of unknown function and importance; a protease that can activate plasminogen and degrade serum complement and that is thought to play a role in the dissemination of Y. pestis from peripheral sites of infection; a coagulase; and a fibrinolysin. A lipopolysaccharide endotoxin, believed to be chromosomally encoded, is probably important in the pathogenesis of septicemic plague and disseminated intravascular coagulation (DIC).

Y. pestis organisms inoculated through the skin or mucous membranes usually invade cutaneous lymphatic vessels and reach regional lymph nodes, although direct bloodstream inoculation may take place. Mononuclear phagocytes, which can phagocytize Y. pestis organisms without destroying them, may play a role in dissemination of the infection to distant sites. Plague can involve almost any organ, and untreated plague generally results in widespread and massive tissue destruction.

In the early stages, infected lymph nodes are characterized by edema and congestion without inflammatory infiltrates or apparent vascular injury. Fully developed buboes contain huge numbers of infectious plague organisms and show distorted or obliterated lymph node architecture with vascular destruction and hemorrhage, serosanguineous effusion, necrosis, and a mild neutrophil infiltration. At this stage, the effusion often involves perinodal tissues. If several adjacent lymph nodes are involved, a boggy edematous mass can result.

Primary septicemic plague results from the direct inoculation of infected fluids or tissues or from an infective flea bite in the apparent absence of a bubo; secondary septicemic plague occurs when lymphatic and other host defenses are breached and the plague bacillus multiplies within the bloodstream. In either primary or secondary septicemic plague, renal glomeruli often contain fibrin thrombi. Diffuse interstitial myocarditis with cardiac dilatation may develop. Multifocal necrosis of the liver is common, as is diffuse hemorrhagic splenic necrosis. If DIC ensues, vascular necrosis may lead to widespread cutaneous, mucosal, and serosal ecchymoses and petechial rash.

Pneumonic plague arises from primary exposure to infective respiratory droplets from a person or cat with respiratory plague or secondary to hematogenous spread in a patient with bubonic or septicemic plague. Pneumonic plague can also result from accidental inhalation of Y. pestis in the laboratory. Primary plague pneumonia generally begins as a lobular process and then extends by confluence, becoming lobar and then multilobar. Plague organisms typically are most numerous in the alveoli. Secondary plague pneumonia begins more diffusely, with organisms usually most numerous in the interstitium. In untreated cases of both primary and secondary plague pneumonia, diffuse hemorrhage, necrosis, and scant neutrophilic infiltration develop.

CLINICAL MANIFESTATIONS

Plague is characterized by a rapid onset of fever and other systemic manifestations of gram-negative bacterial infection. If it is not quickly and correctly treated, plague can follow a toxic course, resulting in shock, multiple-organ failure, and death. In humans, the three principal forms of plague are bubonic, septicemic, and pneumonic. Bubonic plague, the most common form, is almost always caused by the bite of an infected flea but occasionally results from direct inoculation of infectious tissues or fluids. Septicemic and pneumonic plague can be either primary or secondary to metastatic spread. Unusual secondary forms include plague meningitis, endophthalmitis, pharyngeal plague, and lymphadenitis at multiple sites. Primary plague pharyngitis has been documented by culture of organisms from throat swabs, but its clinical and epidemiologic features have not been completely described. The following are the mortality rates associated with the different types of

plague: Pneumonic plague - untreated - 100%, treated - 50%; bubonic plague - untreated - 50%-90%, treated - 10%-20%; septicemic plague - 20%-25%.

Bubonic plague usually has an incubation period of 2 to 6 days, occasionally longer. Typically, the patient experiences chills; fever, with temperatures that rise within hours to 38°C or higher; myalgias; arthralgias; headache; and a feeling of weakness. Soon ¾ usually within 24 h ¾ the patient notices tenderness and pain in one or more regional lymph nodes proximal to the site of inoculation of the plague bacillus. Because fleas often bite the legs, femoral and inguinal nodes are most commonly involved; axillary and cervical nodes are next most commonly affected. The enlarging bubo becomes progressively painful and tender, sometimes exquisitely so. The patient usually guards against palpation and limits movement, pressure, and stretch around the bubo. The surrounding tissue often becomes edematous, sometimes markedly so, and the overlying skin may be erythematous, warm, and tense. Inspection of the skin surrounding or distal to the bubo sometimes reveals the site of a flea bite marked by a small papule, pustule, scab, or ulcer. Large eschars develop rarely. A list of lymphadenitic conditions that could be confused with a plague bubo would include Staphylococcus aureus and group A beta-hemolytic streptococcal infections, cat-scratch disease, and tularemia. The bubo of plague is distinguishable from lymphadenitis of most other causes, however, by its rapid onset, its extreme tenderness, the accompanying signs of toxemia, and the absence of cellulitis or obvious ascending lymphangitis.

Treated in the uncomplicated state with an appropriate antibiotic, bubonic plague usually responds quickly, with defervescence and alleviation of other systemic manifestations over 2 to 5 days. Buboes often remain enlarged and tender for a week or more after the initiation of treatment and can become fluctuant. Without effective antimicrobial treatment, patients with typical bubonic plague manifest an increasingly toxic state of fever, tachycardia, lethargy leading to prostration, agitation and confusion, and (occasionally) convulsions and delirium. Secondary plague sepsis may result in an alarmingly rapid and refractory cascade of DIC, bleeding, shock, and organ failure.

Septicemic plague is a progressive, overwhelming bacterial infection. Primary septicemia develops in the absence of apparent regional lymphadenitis, and the diagnosis of plague often is not suspected until preliminary blood culture results are reported to be positive by the laboratory. Y. pestis, however, can also be cultured from the blood of most bubonic plague patients, and bacteremia should be distinguished from septicemia, in which the patient is desperately ill and requires aggressive care. Patients with septicemic plague often present with gastrointestinal symptoms of nausea, vomiting, diarrhea, and abdominal pain, which may further confound the correct diagnosis. Petechiae, ecchymoses, bleeding from puncture wounds and orifices, and gangrene of acral parts are manifestations of DIC;

refractory hypotension, renal shutdown, obtundation, and other signs of shock are preterminal events.

Of all forms of the disease, pneumonic plague develops most rapidly and is most frequently fatal. The incubation period for primary pneumonic plague is rarely longer than 1 to 4 days. The onset is most often sudden, with chills, fever, headache, myalgias, weakness, and dizziness. Pulmonary signs, including cough, sputum production, chest pain, tachypnea, and dyspnea, typically arise on the second day of illness and may be accompanied by hemoptysis, increasing respiratory distress, cardiopulmonary insufficiency, and circulatory collapse. In primary plague pneumonia, the sputum is most often watery or mucoid, frothy, and blood-tinged, but it may become frankly bloody. Pulmonary signs in primary pneumonic plague may indicate involvement of a single lobe in the early stage, with rapidly developing segmental consolidation before bronchopneumonic spread to other lobes of the same and opposite lungs. Liquefaction necrosis and cavitation may occur early in areas of consolidation and may or may not leave significant residual scarring.

Secondary plague pneumonia manifests first as diffuse interstitial pneumonitis in which sputum production is scant; since the sputum is more likely to be inspissated and tenacious in character than the sputum found in primary pneumonia, it may be less infectious. Observers in the early twentieth century remarked on the relative lack of auscultatory findings, the usual presence of toxemia, and the frequency of sudden death in patients with pneumonic plague as compared to patients with other bacterial pneumonias. Meningitis is an unusual manifestation of plague. Although meningitis may be a part of the initial presentation of plague, its onset is often delayed and is a manifestation of insufficient treatment. Recent cases in the United States have occurred during the first and second weeks of antibiotic treatment for bubonic plague. Chronic relapsing meningeal plague over periods of weeks or even months was described in the preantibiotic era. The affected patients typically presented with fever, headache, meningismus, and pleocytosis.

Plague pharyngitis presents as fever, sore throat, cervical lymphadenitis, and headache and is often indistinguishable clinically from pharyngitis of other infectious etiologies. Caregivers working in plague-endemic areas must be alert to the possibility of plague to avoid misdiagnosis leading to delayed and/or inappropriate treatment.

DIAGNOSIS

The possibility of plague should be strongly considered in febrile patients from endemic areas who have history of exposure to rodents. Rapid recognition of the classic symptoms of this disease and laboratory confirmation are essential to instituting lifesaving therapy. Plague should always be considered when a previously healthy person presents with septic shock in the southwestern United States, India

and South Asia. When the diagnosis of plague is being considered, close communication between clinicians and the diagnostic laboratory and between the diagnostic laboratory and a qualified reference laboratory is essential.

When plague is suspected, specimens should be collected promptly for laboratory studies, chest roentgenograms should be obtained, and specific antimicrobial therapy should be initiated pending confirmation. Appropriate diagnostic specimens for smear and culture include citrated or heparinized whole blood from all patients with suspected plague, bubo aspirates from those with suspected buboes, sputum samples or tracheal aspirates from those with suspected pneumonic plague, and cerebrospinal fluid (CSF) from those with suspected plague meningitis. Since early buboes are often exquisitely tender and are seldom fluctuant or necrotic, these lesions usually require aspiration under local anesthesia and after surface decontamination with an injection of 1 to 2 mL of normal saline (sterile but nonbacteriostatic) through a 20- to 22-gauge needle. A variety of appropriate culture media (including brain-heart infusion broth, sheep blood agar) should be inoculated with a portion of each specimen. Moreover, for each specimen, at least one smear should be examined immediately with Wayson or Giemsa stain and at least one with Gram's stain; a smear should also be submitted for direct fluorescent antibody testing. An acute-phase serum specimen should be tested for antibody to Y. pestis; whenever possible, a convalescent-phase serum specimen collected 3 to 4 weeks later should also be tested. When a patient dies and plague is suspected, appropriate autopsy tissues for culture and fluorescent antibody testing include buboes, all solid organs (especially liver, spleen, and lung), and bone marrow.

Laboratory confirmation of plague depends on the isolation of Y. pestis from cultures of body fluids or tissues. Y. pestis strains are readily distinguished from those of the closely related species Yersinia pseudotuberculosis by differences in biochemical profile, temperature-dependent susceptibility to lysis by a Y. pestis-specific bacteriophage, and motility. Automated bacteriologic test systems can be used to assist in the identification of isolates as Y. pestis, but such strains can be misidentified (e.g., as Y. pseudotuberculosis) or overlooked if these systems are improperly programmed.

The specificity of a positive passive-hemagglutination test requires confirmation with the F1 antigen hemagglutination-inhibition test. A few plague patients seroconvert to F1 antigen as early as 5 days after the onset of illness. Most seroconvert between 1 and 2 weeks after onset; a few seroconvert 3 weeks or more after onset; and a few (fewer than 5 percent) fail to seroconvert at all. Early, specific antibiotic treatment may delay seroconversion by several weeks. After seroconversion, positive serologic titers diminish gradually over months to years. Enzyme-linked immunosorbent assays for IgM and IgG antibodies to Y. pestis have only recently been developed.

Visualization of characteristic bipolar bacilli in a Giemsa- or Wayson-stained smear constitutes supportive evidence of plague. Tularemia, especially the glandular, typhoidal, and pneumonic forms, can sometimes be confused clinically and epidemiologically with plague, but the results of microbiologic and serologic tests should readily distinguish these two diseases.

Patients with plague typically have WBC counts of 15,000 to 25,000/uL, with a predominance of PMNs and a left shift. Leukemic reactions with WBC count as high as 100,000/uL can occur. Modest thrombocytopenia is usually documented, and fibrin-fibrinogen split products are often detected even in patients without frank DIC. Serum levels of aminotransferases and bilirubin may be elevated. Chest roentgenograms of patients with pneumonic plague usually show patchy bronchopneumonic infiltrates as well as lobar or segmental consolidation with or without confluence; they occasionally show cavitation. Stained sputum samples usually contain PMNs and characteristic bipolar-staining bacilli. In Y. pestis septicemia, visualization of the characteristic bacilli in a routine blood smear or a buffy-coat smear is an uncommon but grave prognostic sign. In patients with plague meningitis, pleocytosis with a predominance of PMNs is the rule, and the characteristic bacilli are usually visible in stained CSF smears. Proteinuria may be present, and renal function test findings may be abnormal. Hypoglycemia may be observed. Lymph node aspirates often demonstrate Y pestis. In patients with pharyngeal plague, Y pestis is cultured from throat swabs.

TREATMENT

All patients with suspected plague and signs of pneumonia should be placed in strict respiratory isolation for 48-72 hours after antibiotic therapy is initiated and kept there until pneumonia has been ruled out or until sputum culture have shown negative findings. Report patients thought to have plague to the local health department and to the WHO. Alert laboratory personnel to the possibility of the diagnosis of plague. All fluid specimens must be handled with gloves and mask to prevent aerosolization of the infected fluids.

Streptomycin is the drug of choice. Alternative antibiotics include the tetracyclines and chloramphenicol; these agents are usually given orally with initial loading doses but may be given intravenously to critically ill patients and to patients unable to tolerate oral medication. Gentamicin is increasingly used for the treatment of plague in the United States because of its ready availability; it is probably as effective as streptomycin, although results of controlled studies have not yet been published. Penicillins, cephalosporins, and macrolides are suboptimal and should not be used. Doxycycline may be as effective as other tetracyclines or even more so, but comparative evaluations have not been made. Trimethoprim-sulfamethoxazole has been used successfully to treat bubonic plague but is not considered a first-line

choice. Chloramphenicol is indicated for the treatment of plague meningitis, pleuritis, endophthalmitis, and myocarditis because of its superior tissue penetration; it is used alone or in combination with streptomycin. In general, antimicrobial treatment should be continued for 10 days or for at least 3 days after the patient has become afebrile and has made a clinical recovery. Patients initially given intravenous antibiotics may be switched to oral regimens upon clinical improvement. Such improvement is usually evident 2 or 3 days after the start of treatment, even though fever may continue for several more days; as noted earlier, buboes can persist for days or even weeks. Hemodynamic monitoring and ventilatory support are performed as appropriate. Intravenous fluids, epinephrine, and dopamine are implemented as necessary for correction of dehydration and hypotension.

Patients with these disorders require intensive monitoring and close physiologic support, as outlined elsewhere. Buboes may require surgical drainage. Abscessed nodes can cause recurrent fever in patients who have apparently recovered; this relation may be occult if intrathoracic or intraabdominal nodes are involved. Viable Y. pestis organisms have been isolated from affected nodes 1 to 2 weeks after clinical recovery from acute disease. Antibiotic-resistant strains of Y. pestis have rarely been identified, and the plague bacillus is considered to be genetically stable.

PREVENTION AND CONTROL

Persons at greatest risk for plague are those who live, work, and participate in outdoor recreational activities in areas which plague is enzootic. Surveillance, education, and environmental management are the cornerstones of prevention and control. Personal protective measures include the avoidance of areas with known epizootic plague (which may be posted) and of sick or dead animals; the use of repellents, insecticides, and protective clothing when at risk of exposure to rodents' fleas; and the wearing of gloves when handling animal carcasses. Short-term antibiotic prophylaxis is recommended for persons known to have had face-to-face or other direct contact with a patient with suspected or confirmed pneumonic plague; it may also be advisable occasionally for persons who are unable to avoid an area where a plague outbreak is in progress or who are caring for patients with plague. To decrease the risk of pneumonic transmission, all patients in whom plague is suspected should be placed in respiratory isolation (to prevent droplet spread) until pneumonia has been ruled out or until 48 h of specific antimicrobial therapy has been administered, after which only standard precautions are generally necessary.

Rodent food (garbage, pet food) and habitats (brush piles, junk heaps, woodpiles) should be eliminated in domestic, peridomestic, and working environments; buildings and food stores should be rodent-proofed. The control of fleas with insecticides is a key public health measure in situations where epizootic

plague activity places humans at high risk; this effort includes dusting and spraying of rodent burrows, rodent runs, and other sites where rodents and their fleas are found. In plague-endemic areas persons should keep their dogs and cats free of fleas and restrained. The decision to control plague by killing rodents should be left to public health authorities, and such a program should be carried out only in conjunction with effective flea control. Killing of rodents has no lasting benefit without environmental sanitation.

A killed, whole-cell plague vaccine can be used. The efficacy of this vaccine in humans has not been evaluated in controlled studies, although reviews of vaccine use during the Vietnam War provide indirect evidence that it is at least partially protective against plague transmitted by fleas. The vaccine does not appear to offer protection against primary pneumonic plague. As recommended by the manufacturer, primary immunization consists of a series of three injections followed by booster doses as warranted (at intervals of 6 months or more). The degree and duration of the immune response vary, and persons at continuing risk may need to have their antibody levels monitored. Vaccination is recommended for laboratory personnel who routinely work with Y. pestis and should also be considered for persons whose vocation brings them into regular contact with wild rodents and their fleas in areas experiencing enzootic or epizootic plague. Military personnel in some situations are vaccinated, but vaccination is not routinely indicated for civilians living in areas with enzootic plague, for medical personnel, for travelers to countries that have reported plague cases, or for the control of plague epidemics.

TULAREMIA

Tularemia is an acute, febrile, granulomatous, infectious zoonosis caused by the aerobic gram-negative pleomorphic bacillus ***Francisella tularensis***. Although tularemia has likely existed since ancient times, the disease was first described in Japan in 1837. In 1911, a plaguelike disease in ground squirrels was described in Tulare County, California (tulare is an Aztec word for the tule reed, a marsh plant commonly found in that area), and was later found to be caused by the bacterium now known as ***F. tularensis***. Edward Francis studied the causative organism further, named the disease, and, in 1928, described his experience. Humans of any age, sex, or race are universally susceptible to this systemic infection. Tularemia is primarily a disease of wild animals and persists in contaminated environments, ectoparasites, and animal carriers. Worldwide, more than 100 species of animals, birds, amphibians, and arthropods host ***F tularensis***. The bacillus may also be found in mud and water. Human infection is incidental and usually results from interaction with biting or blood-sucking insects, wild or domestic animals, or the environment. Tularemia occurs throughout the Northern Hemisphere, except for in the United Kingdom. Cases have been reported in the United States, the former Soviet Union, Japan, Canada, Mexico, and Europe. Tularemia has not been reported in Africa and South America.

ETIOLOGY

F. tularensis is the etiologic agent of tularemia, which, with rare exceptions, is the only disease produced by this genus. The organism is a small, gram-negative, pleomorphic, nonmotile, non-spore-forming bacillus measuring 0.2 to 0.7 um. Bipolar staining results in a coccoid appearance. The organism is a thinly encapsulated, nonpiliated strict aerobe that invades host cells.

EPIDEMIOLOGY

In nature, ***F. tularensis*** is a hardy organism that persists for weeks or months in mud, water, and decaying animal carcasses. Dozens of biting and blood-sucking insects, especially ticks and tabanid flies, serve as vectors. Animal reservoirs include wild rabbits, squirrels, birds, sheep, beavers, muskrats, and domestic dogs and cats.
The two main biovars of ***F. tularensis*** (type A) and palearctica (type B). Type A produces more serious disease in humans; without treatment, the associated fatality rate is approximately 5 percent. Type B produces a milder, often subclinical infection that is usually contracted from water or marine mammals.

Ticks pass the organism to their offspring via a transovarian route. The organism is found in tick feces but not in large quantities in tick salivary glands. F. tularensis is transmitted frequently during blood meals taken by embedded ticks

following hours of attachment. It is the taking of a blood meal through a fecally contaminated field that transmits the organism. Tularemia is more common among men. Person-to-person transmission is rare or nonexistent. Transmission of the organism by ticks and tabanid flies takes place mainly in the spring and summer. However, continued transmission in the winter months by trapped or hunted animals has been documented. The organism is extremely infectious.

PATHOGENESIS

The most common portal of entry for human infection is through skin or mucous membranes, either directly through the bite of a tick, other arthropods, or other animals or via inapparent abrasions. Inhalation or ingestion of F. tularensis can also result in infection. Although more than 100 organisms are usually required to produce infection via the oral route (oropharyngeal or gastrointestinal tularemia), fewer than 50 organisms will result in infection when injected into the skin (ulceroglandular/glandular tularemia) or inhaled (pneumonia). After inoculation into the skin, the organism multiplies locally; within 2 to 5 days (range, 1 to 10 days), it produces an erythematous, tender, or pruritic papule. The papule rapidly enlarges and forms an ulcer with a black base (chancriform lesion). The bacteria spread to regional lymph nodes, producing lymphadenopathy (buboes), and, with bacteremia, may spread to distant organs.

Tularemia is characterized by mononuclear cell infiltration with pyogranulomatous pathology. The histopathologic findings can be quite similar to those in tuberculosis, although tularemia develops more rapidly. As a facultatively intracellular bacterium, F. tularensis is capable of parasitizing both phagocytic and nonphagocytic host cells and of surviving intracellularly for prolonged periods. In the acute phase of infection, the primary organs affected (skin, lymph nodes, liver, and spleen) include areas of focal necrosis, initially surrounded by polymorphonuclear leukocytes. Subsequently, granulomas form with epithelioid cells, lymphocytes, and multinucleated giant cells surrounded by areas of necrosis. These areas may resemble caseation necrosis but later coalesce to form abscesses.

Conjunctival inoculation can result in infection of the eye, with regional lymph node enlargement (preauricular lymphadenopathy, Parinaud's complex). Aerosolization and inhalation or hematogenous spread of organisms can result in pneumonia. In the lung, an inflammatory reaction with foci of alveolar necrosis and cell infiltration (initially polymorphonuclear and later mononuclear) with granulomas develops. Chest roentgenograms usually reveal bilateral patchy infiltrates rather than large areas of consolidation. Pleural effusions are common and may contain blood. Lymphadenopathy occurs in regions draining infected organs. Therefore, in pulmonary infection, mediastinal adenopathy may be evident, while patients with oropharyngeal tularemia develop cervical lymphadenopathy. In gastrointestinal or

typhoidal tularemia, mesenteric lymphadenopathy may follow the ingestion of large numbers of organisms. The term typhoidal tularemia may be used to describe severe bacteremic disease, irrespective of the mode of transmission or portal of entry. Meningitis has been reported as a primary or secondary manifestation of bacteremia. Patients may also present with fever and no localizing signs.

Infection with F. tularensis stimulates the host to produce antibodies. However, this antibody response probably plays only a minor role in the containment of infection. In contrast, cell-mediated immunity, which develops over 2 to 4 weeks, plays a major role in containment and eradication of the infection. Macrophages, once activated, are capable of killing F. tularensis.

Immunospecific protection against tularemia can be afforded either by natural infection or by vaccination with live attenuated strains of F. tularensis. Killed vaccines, on the other hand, induce no protection against virulent F. tularensis. After natural infection or vaccination, serum antibodies to surface-exposed carbohydrate antigens predominate, whereas T cell determinants are located on membrane proteins beneath the bacterial capsule. T cell responses are thought to be due to priming by the organism. Recent investigations of neutrophils in cases of tularemia have suggested that PMNs are needed for defense against primary infection. PMNs may restrict the growth of F. tularensis before the organism becomes intracellular.

CLINICAL MANIFESTATIONS

Tularemia often starts with a sudden onset of fever, chills, headache, and generalized myalgia and arthralgia, malaise, and fatigue. Develop 1 of 6 well-recognized clinical forms: ulceroglandular tularemia, glandular tularemia, oculoglandular tularemia, oropharyngeal tularemia, pneumonic tularemia, and typhoidal (septicemic) tularemia.

An incubation period of 2 to 10 days is followed by the formation of an ulcer at the site of penetration, with local inflammation. The ulcer may persist for several months as organisms are transported via the lymphatics to the regional lymph nodes. These nodes enlarge and may become necrotic and suppurating. If the organism enters the bloodstream, widespread dissemination as well as signs and symptoms of endotoxemia may result.

Most patients with tularemia (75 to 85 percent) acquire the infection by inoculation of the skin. In adults, the most common localized form is inguinal/femoral lymphadenopathy; in children, it is cervical lymphadenopathy. About 20 percent of patients develop a generalized maculopapular rash, which occasionally becomes pustular. Erythema nodosum occurs infrequently. The clinical manifestations of tularemia have been divided into various syndromes.

Ulceroglandular and glandular tularemia account for approximately 75 to 85 percent of cases. The predominant form in children involves cervical or posterior

auricular lymphadenopathy and is usually related to tick bites on the head and neck area. In adults, the most common form is inguinal/femoral lymphadenopathy resulting from insect and tick exposures on the lower limbs. In cases related to wild game, the usual portal of entry for F. tularensis is either an injury sustained while skinning or cleaning an animal carcass or a bite (usually on the hand). Epitrochlear lymphadenopathy/lymphadenitis is common in patients with bite-related injuries.

In ulceroglandular tularemia, the ulcer is erythematous, indurated, and nonhealing, with a punched-out appearance that lasts from 1 to 3 weeks. The papule may begin as an erythematous lesion that is tender or pruritic; it evolves over several days into an ulcer with sharply demarcated edges and a yellow exudate. The ulcer gradually develops a black base, and simultaneously the regional lymph nodes become tender and severely enlarged. The affected lymph nodes may become fluctuant and drain spontaneously, but usually the condition resolves with effective treatment. Late suppuration of lymph nodes has been described in up to 25 percent of patients with ulceroglandular/glandular tularemia. Examination of material taken from these late fluctuant nodes after successful antimicrobial treatment has revealed sterile necrotic tissue. In 5 to 10 percent of patients, the skin lesion may be inapparent, with lymphadenopathy plus systemic signs and symptoms the only physical findings. This clinical syndrome is designated glandular tularemia. Conversely, a tick or deerfly bite on the trunk may result in an ulcer without evident lymphadenopathy.

Oculoglandular Tularemia In about 1 percent of patients, the portal of entry for F. tularensis is the conjunctiva. Usually, the organism reaches the conjunctiva through contact with contaminated fingers. The inflamed conjunctiva is painful, with numerous yellowish nodules and pinpoint ulcers. Purulent conjunctivitis with regional lymphadenopathy (preauricular, submandibular, or cervical) is evident. Because of debilitating pain, the patient may seek medical attention before regional lymphadenopathy develops. Painful preauricular lymphadenopathy is unique to tularemia and distinguishes it from cat-scratch disease, tuberculosis, sporotrichosis, and syphilis. Corneal perforation may occur.

Oropharyngeal and Gastrointestinal Tularemia Rarely, tularemia follows the ingestion of contaminated undercooked meat, the oral inoculation of F. tularensis from the hands in association with the skinning and cleaning of animal carcasses, or the consumption of contaminated food or water. Oral inoculation may result in acute, exudative, or membranous pharyngitis associated with cervical lymphadenopathy or in ulcerative intestinal lesions associated with mesenteric lymphadenopathy, diarrhea, abdominal pain, nausea, vomiting, and gastrointestinal bleeding. Infected tonsils become enlarged and develop a yellowish-white pseudomembrane, which can be confused with that of diphtheria. The clinical severity of gastrointestinal tularemia varies from mild, unexplained, persistent diarrhea with no other symptoms to a

rapidly fulminant, fatal disease. In fatal cases, the extensive intestinal ulceration found at autopsy suggests an enormous inoculum.

Pulmonary Tularemia pneumonia presents as variable parenchymal infiltrates that are unresponsive to treatment with b-lactam antibiotics. Tularemia must be considered in the differential diagnosis of atypical pneumonia in a patient with a history of travel to an endemic area. The disease can result from either inhalation of an infectious aerosol or spread to the lungs and pleura after bloodstream dissemination. Inhalation-related pneumonia has been described in laboratory workers after exposure to contaminated materials and is associated with a relatively high mortality rate. Exposure to F. tularensis in aerosols from live domestic animals or dead wildlife (including birds) has been reported to cause pneumonia. Hematogenous dissemination to the lungs occurs in 10 to 15 percent of cases of ulceroglandular tularemia and in about half of cases of typhoidal tularemia. Previously, tularemia pneumonia was thought to be a disease of older patients, but as many as 10 to 15 percent of children with clinical manifestations of tularemia have parenchymal infiltrates detected by chest roentgenography. Patients with pneumonia usually have a nonproductive cough and may have dyspnea or pleuritic chest pain. Rentgenograms of the chest usually reveal bilateral patchy infiltrates (described as ovoid or lobar densities), lobar parenchymal infiltrates, and cavitary lesions. Pleural effusions may have a predominance of mononuclear leukocytes or PMNs and sometimes red blood cells. Empyema may develop. Patients with tularemia pneumonia can have blood cultures positive for F. tularensis.

Typhoidal Tularemia Once thought to represent up to 10 percent of all cases of tularemia. In this presentation, fever develops without apparent skin lesions or lymphadenopathy. In the absence of a history of possible contact with a vector, diagnosis can be extremely difficult. Blood cultures may be positive and patients may present with classic sepsis or septic shock in this acute systemic form of the infection. Typhoidal tularemia is usually associated with a huge inoculum or with a preexisting compromising condition. High continuous fevers, signs of endotoxemia, and severe headache are common findings. The patient may be delirious and may develop prostration and shock. If presumptive antibiotic therapy in culture-negative cases does not include an aminoglycoside, the mortality rate can approach 30 percent.

Other Manifestations F. tularensis infection has been associated with meningitis, pericarditis, hepatitis, peritonitis, endocarditis, osteomyelitis, and sepsis and septic shock with rhabdomyolysis and acute renal failure. In the rare cases of tularemia meningitis, a predominantly lymphocytic response can be demonstrated in cerebrospinal fluid.

DIAGNOSIS

When patients in endemic areas present with fever, chronic ulcerative skin lesions, and large tender lymph nodes, a diagnosis of tularemia should be made presumptively, and confirmatory diagnostic testing and appropriate therapy should be undertaken. When the possibility of tularemia is considered in a patient with this presentation in a nonendemic area, an attempt should be made to determine whether the individual has come into contact with a potential animal vector. The level of suspicion of tularemia should be especially high in hunters, trappers, game wardens, veterinarians, laboratory workers, and individuals with a history of exposure to an insect or other animal vector. However, up to 40 percent of patients with tularemia have no known history of epidemiologic contact with an arthropod or other animal vector.

The characteristic presentation of ulceroglandular tularemia does not pose a diagnostic problem, but a less classic progression of regional lymphadenopathy or glandular tularemia must be differentiated from other diseases. The skin lesion may resemble those seen in sporotrichosis; skin infection with Staphylococcus aureus, Streptococcus pyogenes, or Mycobacterium marinum; syphilis; anthrax; rat-bite fever (due to Spirillum minus); or rickettsiosis (scrub typhus). In the latter infections, regional lymphadenopathy is usually not as impressive as in tularemia. The lymphadenopathy of tularemia (especially glandular tularemia) must be differentiated from that of plague, lymphogranuloma venereum, and cat-scratch disease. In children, the differentiation from cat-scratch disease is made more difficult by the chronic papulovesicular lesion associated with Bartonella henselae infection.

Oropharyngeal tularemia can resemble and must be differentiated from pharyngitis due to group A beta-hemolytic streptococci, Arcanobacterium haemolyticum, or Corynebacterium diphtheriae as well as from infectious mononucleosis. Tularemia pneumonia may resemble any of the atypical pneumonias, including those due to various viruses, Mycoplasma pneumoniae, Chlamydia pneumoniae, Chlamydia psittaci, Legionella pneumophila, Coxiella burnetii, and (occasionally) Histoplasma capsulatum. Typhoidal tularemia may resemble typhoid fever, other Salmonella bacteremia, rickettsial infections, brucellosis, infectious mononucleosis, acquired toxoplasmosis, miliary tuberculosis, sarcoidosis, and hematologic or reticuloendothelial malignancies.

Direct microscopic examination of polychromatically stained tissue smears or clinical specimens reveals F. tularensis organisms, singly and in groups, both intra- and extracellularly. Gram's staining of clinical or biopsy material is of little value, as the small, weakly staining organisms cannot be readily distinguished from the background. An indirect fluorescent antibody test with commercially available antisera can be useful, although false-positive results due to Legionella species have been reported.

The diagnosis of tularemia is most frequently confirmed by serologic testing. In the standard tube agglutination test, a single titer of 1:160 is interpreted as a presumptive positive result. A fourfold increase in titer between paired serum samples collected 2 to 3 weeks apart is considered diagnostic. False-negative serologic responses are obtained early in infection; up to 30 percent of patients infected for 3 weeks have sera that test negative. Late in infection, titers into the thousands are common, and titers of 1:20 to 1:80 may persist for years. A microagglutination test that may be as much as 100-fold more sensitive than the standard tube agglutination test has been described and is currently being used in many clinical microbiology laboratories. Enzyme-linked immunosorbent assays have proven useful for the detection of both antibodies and antigens. Analysis of urine for F. tularensis antigen has yielded promising results in clinical trials, but facilities for this type of analysis are not widely available. A skin test for delayed hypersensitivity to F. tularensis turns positive during the first week of illness and remains positive for years. The skin-test antigen, which is not commercially available, can boost titers of agglutinating antibody.

Culture and isolation of F. tularensis are difficult. In one study the organism was isolated in only 10 percent of more than 1000 human cases, 84 percent of which were confirmed by serology. The medium of choice is cysteine-glucose-blood agar. F. tularensis can be isolated directly from infected ulcer scrapings, lymph-node biopsy specimens, gastric washings, sputum, and blood cultures. Colonies are blue-gray, round, smooth, and slightly mucoid. On media containing blood, a small zone of alpha hemolysis usually surrounds the colony. Slide agglutination tests or direct fluorescent antibody tests with commercially available antisera can be applied directly to culture suspensions for identification.

The polymerase chain reaction has been used to detect F. tularensis DNA, primarily in blood. However, this test has not been shown to be more sensitive than direct culture and at present remains a research tool.

TREATMENT

F. tularensis cannot be subjected to standardized antimicrobial susceptibility testing because the organism will not grow on the media used. A wide variety of antibiotics, including all b-lactam antibiotics and the newer cephalosporins, are ineffective for the treatment of this infection. Recent studies indicated that third-generation cephalosporins were active against F. tularensis in vitro, but clinical case reports suggested a nearly universal failure rate of ceftriaxone in pediatric patients with tularemia. Although in vitro data indicate that imipenem may be active, therapy with imipenem, sulfanilamides, and macrolides is not presently recommended because of the lack of clinical data. Fluoroquinolones have shown promise in terms of their relatively low toxicity and their potential for oral administration.

Chloramphenicol and tetracycline have been used successfully for treatment of the acute stages of tularemia but have been associated with higher relapse rates (up to 20 percent) than conventionally used agents. F tularensis is naturally resistant to penicillins and first-generation cephalosporins.

Streptomycin is considered the drug of choice (DOC). Streptomycin, given intramuscularly at a dose of 7.5 to 10 mg/kg every 12 h, is considered the drug of choice for adults. In severe cases, 15 mg/kg every 12 h may be used for the first 48 to 72 h. Streptomycin is also considered the drug of choice for children; the appropriate dose is 30 to 40 mg/kg daily in two divided doses administered intramuscularly. In children, after a clinical response is demonstrated at 3 to 5 days, the dose can be reduced to 10 to 15 mg/kg daily in two divided doses. Therapy is typically continued for 7 to 10 days; however, in mild to moderate cases of tularemia in which the patient becomes afebrile within the first 48 to 72 h of streptomycin treatment, a 5- to 7-day course has been successful.

Gentamicin, at a dose of 1.7 mg/kg given intravenously or intramuscularly every 8 h, is also effective. The published experience in adults consists of two reports describing, respectively, nine and eight patients who were treated effectively with gentamicin. The eight patients in one of the reports all had fever before treatment, and all eight became afebrile within 24 to 72 h. In a recent pediatric study, other symptoms, such as tender lymphadenitis and pharyngitis, also responded within 24 to 72 h of the start of gentamicin therapy.

Virtually all strains of F. tularensis are susceptible to streptomycin and gentamicin. In successfully treated patients, defervescence usually occurs within 2 days, but skin lesions and lymph nodes may take 1 to 2 weeks to heal. When therapy is not initiated within the first several days of illness, defervescence may be delayed. Relapses are uncommon with streptomycin or gentamicin therapy. Late lymph-node suppuration, however, occurs in approximately 40 percent of children, regardless of the treatment received. These nodes have typically been found to contain sterile necrotic tissue without evidence of active infection. Patients with fluctuant nodes should receive several days of antibiotic therapy before drainage to minimize the risk to hospital personnel. Unlike streptomycin and gentamicin, tobramycin is ineffective in the treatment of tularemia and should not be used.

If tularemia goes untreated, symptoms usually last 1 to 4 weeks but may continue for months. The mortality rate from severe untreated infection (including all cases of untreated tularemia pneumonia and typhoidal tularemia) can be as high as 30 percent. However, the overall mortality rate for untreated tularemia is less than 8 percent. Mortality is less than 1 percent with appropriate treatment. Poor outcomes are often associated with long delays in diagnosis and treatment. Lifelong immunity usually follows tularemia.

PREVENTION

The prevention of tularemia is based on avoidance of exposure to biting and blood-sucking insects, especially ticks and deerflies. An intradermal vaccine made from live attenuated F. tularensis is available from the Centers for Disease Control and Prevention. This vaccine is effective in reducing the frequency and severity of infection. Vaccination of high-risk individuals working with large quantities of cultured organisms is recommended. Others who come into contact with the organisms, such as veterinarians, hunters, or game wardens, should consider vaccination, particularly if they live in endemic areas. The avoidance of skinning wild animals especially rabbits and the wearing of gloves while handling animal carcasses, decrease the risk of transmission. Use of insect repellents and preparations that prevent tick attachment as well as prompt removal of ticks can be helpful. Prophylaxis of tularemia has not proved effective in patients with embedded ticks or insect bites.

SMALLPOX

Smallpox is an acute contagious disease caused by the variola virus (Poxvirus variolae), which characterized by severe intoxication and specific eruption on the mucous and skin.

The pox part of smallpox is derived from the Latin word for “spotted” and refers to the raised bumps that appear on the face and body of an infected person.

Smallpox outbreaks have occurred sporadically for thousands of years, but, after a successful global vaccination program, the disease has now been eradicated. The last endemic case of variola major was reported in Bangladesh in 1975; the last endemic case of variola minor was reported in Somalia in 1977. In 1979, a laboratory accident in Birmingham, England, resulted in a single case of the disease. Smallpox is authorized to be kept for research purposes only at 2 World Health Organization reference laboratories. One is the US Centers for Disease Control and Prevention (CDC) in Atlanta, Ga, and the other is the State Research Centre of Virology and Biotechnology, also known as the VECTOR Institute, in Koltsovo, Russia. Routine smallpox vaccinations was stopped in 1972 and smallpox was declared eradicated in 1980 after a worldwide vaccination program. However, in the aftermath of the events of September and October, 2001, there is heightened concern that the variola virus might be used as an agent of bioterrorism.

ETIOLOGY

Poxviruses (members of the Poxviridae family) can infect both humans and animals. Poxviridae consist of 2 families: Chordopoxviridae, which infect vertebrates, and Entomopoxviridae, which infect insects. Chordopoxviruses are subdivided into eight genera of which the orthopoxviruses have been the most important for man. The orthopoxviruses include smallpox (variola), monkeypox, vaccinia, cowpox, buffalopox, cantagalo, and aracatuba viruses. The parapoxviruses include orf virus, bovine papular stomatitis virus, pseudocowpox virus, deerpox virus, and sealpox virus. Yatapoxviruses include tanapox virus and yabapoxviruses, which are found primarily in Africa. Molluscipoxviruses include the human poxvirus, molluscum contagiosum virus. Smallpox and molluscum contagiosum are specific to humans. The other viruses cause rare zoonotic infections in humans. Vaccinia virus, which has been used for vaccination, can also infect humans.

Poxviridae are linear double-stranded DNA viruses that replicate in the cytoplasm. Smallpox is a double-stranded, 135- to 375-kilobase (kb) DNA virus that replicates in the cytoplasm of the host cell and forms B-type inclusion bodies (Guarnieri bodies), unlike herpes viruses, which replicate in the nucleus. The orthopoxviruses are among the largest and most complex of all viruses. The virion is brick-shaped with a diameter of approximately 200 nm.

EPIDEMIOLOGY

Humans are the only natural hosts of variola. Smallpox is not known to be transmitted by insects or animals.

Smallpox spreads very easily from person to person.The smallpox virus is transmitted mainly through the airborne route and adheres via droplet spread of viral particles onto the mucosal surfaces of the oropharyngeal and respiratory tract. This transmission occurs through close personal contact. Respiratory spread over long distances has been reported. Smallpox also can be spread through direct contact with infected bodily fluids or contaminated objects such as bedding or clothing. Rarely, smallpox has been spread by virus carried in the air in enclosed settings such as buildings, buses, and trains. Pregnant women with smallpox tend to develop hemorrhagic disease, but intrauterine infection occurs in even the mildest maternal infections, resulting in premature delivery and high fetal and neonatal mortality rates.

A person with smallpox is sometimes contagious with onset of fever (prodrome phase), but the person becomes most contagious with the onset of rash. The highest intensity of viral shedding is during the first 10 days of the rash. The infected person is contagious until the last smallpox scab falls off. Infection rates among close contacts of infected persons have been reported to be between 37% and 88%. Survivors of natural smallpox infection acquire lifelong immunity.

PATHOGENESIS

The replication of poxviruses is equally complex. Infection is initiated by attachment of the poxvirus to one of several cellular receptors. The virus can then enter the cell via numerous mechanisms. Unlike other DNA viruses, poxviruses replicate in the cytoplasm. The virus contains all the elements for genomic replication, but cellular functions appear necessary for complete viral maturation.

Implantation of just a few virions of smallpox into the oropharynx or respiratory tracts can cause infection. The virus infects macrophages during the first 72 hours of the incubation phase. The virus migrates and multiplies in the regional lymph nodes, resulting in asymptomatic viremia by the fourth day. The virus multiplies in the spleen, bone marrow, and lymph nodes, resulting in a symptomatic secondary viremia (ie, fever, toxemia) by the eighth day. Finally, the virus re-enters the blood in leukocytes, producing fever and toxemia, and then passes from leukocytes to adjacent cells in small blood vessels of the dermis and beneath the oropharyngeal mucosa, leading to the initial onset of the enanthem and exanthem, at which point (approximately day 14) the patient becomes infectious.

The spleen, lymph nodes, kidneys, liver, bone marrow, and other viscera may contain large amounts of smallpox virus.

CLINICAL MANIFESTATIONS

There are two clinical forms of smallpox: variola major and variola minor, each of which confers immunity against the other.

During the first half of the 20th century, all outbreaks of smallpox in Asia and most in Africa were due to variola major. The case fatality rate was 20%-30% or more in unvaccinated persons. Variola minor carried a case fatality rate of 1% or less and was endemic in some countries in Europe, North America, South America, and many parts of Africa.

Variola major is the more severe and common form of smallpox. It causes more extensive rash and fever. There are four types of variola major smallpox: Ordinary smallpox – the most common form, which accounts for 90% or more of smallpox cases. Modified smallpox – a mild form that develops in previously vaccinated persons. Flat smallpox (malignant smallpox) – a severe variety of smallpox in which lesions do not project above the skin surface. Hemorrhagic smallpox (fulminant smallpox) – a rare, very severe, highly fatal variety of smallpox in which hemorrhages develop in the skin and mucous membranes. Flat and hemorrhagic smallpox usually are fatal. Variola minor is a less common presentation of smallpox, and a much less severe disease, and much less virulent. Variola sine eruptione (variola sine exanthemata) is another less-common form of smallpox. In addition, a pharyngeal form of smallpox develops in immunized individuals; this form presents with a spotty enanthem over the soft palate, uvula, and pharynx. An influenzalike form of smallpox exists but rarely results in a rash. Both of these forms are relatively mild, usually affect individuals who have been previously immunized, and do not cause mortality. A pulmonary form of smallpox characterized by severe symptoms, cyanosis, and bilateral infiltrates has been described in individuals with little or no smallpox immunity. The mortality rate of this type is undetermined.

Clinical manifestation of the ordinary type of Variola major infection includes following periods: incubation, prodrome (initial symptoms), early rash, pustular rash, pustules and scabs, resolving scabs.

Exposure to the virus is followed by an incubation period during which people do not have any symptoms and may feel fine. Incubation periods are typically 10-14 days but can range from 7-17 days. Intrauterine infections rarely occur and usually have shorter incubation periods. Patients exposed to smallpox through routes other than the person-to-person respiratory route also have shorter incubation periods. Prior immunization, VIG, and, possibly, antiviral chemotherapy may extend the incubation period. During this time, people are not contagious.

The first symptoms of smallpox include fever, malaise, head and body aches, and sometimes rigors and vomiting. The fever is usually high, ranges from 38.8-40°C. At this time, people are usually too sick to carry on their normal activities. This is called the prodrome phase and may last for 2 to 4 days. Smallpox may be

contagious during the prodrome phase, but is most infectious during the first 7 to 10 days following rash onset.

A rash emerges first as small red spots on the face, in the mouth and pharynx, and on the forearms. The initial lesions are shotty and do not disappear with pressure.These spots develop into sores that break open and spread large amounts of the virus into the mouth and throat. At this time, the person becomes most contagious.

Around the time the sores in the mouth break down, a rash appears on the skin, starting on the face and spreading to the arms and legs and then to the hands and feet. Usually the rash spreads to all parts of the body within 24 hours. As the rash appears, the fever usually falls and the person may start to feel better. By the third day of the rash, the rash becomes raised bumps. By the fourth day, the bumps fill with a thick, opaque fluid and often have a depression in the center that looks like a bellybutton. (This is a major distinguishing characteristic of smallpox). The bumps (papules) become pustules – sharply raised, usually round and firm to the touch as if a small round object is under the skin. At this time, the fever often rises again and remains high until scabs form over the bumps. The pustules begin to form a crust and then scab. By the end of the second week after the rash appears, most of the sores have formed scabs.

The scabs begin to fall off, leaving marks on the skin that eventually become pitted scars. Most scabs will have fallen off three weeks after the rash appears. The scabs begin to separate, leaving marks on the skin that eventually become pitted scars. Most scabs separate by the third week after the rash appears. The person is contagious until all of the scabs are gone. Scabs have fallen off. Person is no longer contagious.

The smallpox rash has a centrifugal distribution, with more lesions on the arms and legs than on the trunk. Rash on the palms and soles is common. As a comparison, a chickenpox rash has a centripetal distribution, with more lesions on the trunk and with fewer or no lesions on the palms and soles.

Most patients report severe headaches and spinal pain. Few patients develop neuropsychiatric symptoms (hallucinations, delirium, depression and psychosis, manic depression). Autopsies of patients with smallpox have demonstrated perivenular demyelination.

Currently, the clinical diagnosis of smallpox is based on several criteria. The major criteria are: 1) a febrile prodrome 1-4 days before rash onset; 2) the classic smallpox lesions (ie, deep-seated, firm, round, well-circumscribed lesions); 3) lesions that are at the same stage of development. The minor criteria include: 1) a centrifugal distribution of lesions, with the first lesions on the oral mucosa or palate, face, or forearms; 2) a toxic or moribund appearance; 3) the slow evolution of lesions of 1-2 days per stage; 4) lesions that appear on the palms and soles.

Ten to 20% of patients with smallpox develop ophthalmic complications (variola residua). Conjunctivitis is most common, appearing 5 days after rash onset. Some patients develop painful pustules and bulbar conjunctivitis. During epidemics, corneal ulceration was common (complicated by bacterial superinfection and perforation). Two to 5% of children develop osteomyelitis (osteomyelitis variolosa) due to viral invasion of the bone rather than to secondary infection. Other complications are skin infections (furuncles and/or abscesses), sepsis, pockmarks; arthritis, symmetrical elbow joint involvement; pulmonary edema, pneumonitis; encephalitis (1 in 500 cases) and dehydration.

The mortality rate in patients with untreated smallpox is 30% or higher (range, 15-50%) in an unvaccinated population and 3% in a vaccinated population. The more severe hemorrhagic and malignant forms of smallpox are usually fatal. Death rate in patients with Variola minor infection is 1% or less.

DIAGNOSIS

Variola virus can be detected with electron microscopy, virus culture from live cells, or DNA analysis using PCR.

Cell culture is seldom used because it is not as effective as the other methods and because it requires the use of live virus, which, in turn, requires the use of a biosafety level 4 (BSL-4) laboratory.

PCR and electron microscopy can be used to examine inactivated samples and therefore do not require such high levels of isolation and can be performed in local laboratories. Electron microscopy can help identify the virus as a member of the Orthopoxvirus genus (presence of brick-shaped virions), but it cannot help determine the exact species. PCR can be used to identify the species (variola) and can even distinguish minor genetic variations in the different strains. PCR can amplify small and specific lengths of DNA and can accurately differentiate variola virus DNA from other species in the genus. The sensitivity is 5-10 copies of DNA. PCR can be useful to distinguish between chickenpox and smallpox.

Serologic testing is not useful for rapid diagnostic purposes. No imaging studies assist in making the diagnosis of variola infection. Lumbar puncture may be included in the workup for hemorrhagic variola to exclude meningococcemia.

Smallpox skin specimen should be collected with precautions in place. The CDC recommends the following procedures for handling specimens obtained from a patient thought to be infected with the smallpox virus:

- Specimens should be collected by someone who has recently been vaccinated (or who is vaccinated that day) and who wears gloves and a mask.
- To obtain vesicular or pustular fluid, the lesions may need to be opened with the blunt edge of a scalpel. The fluid can then be harvested on a cotton swab. Scabs can be picked off with forceps.

- Specimens should be deposited in a Vacutainer tube. The tube should be sealed with adhesive tape at the juncture of the stopper and the tube. This tube, in turn, should be enclosed in a second durable and watertight container.
- State or local health department laboratories should be contacted immediately for proper specimen shipping protocols.
- Laboratory examination should be performed only in designated BSL-4 laboratories. Once established that an epidemic is caused by the smallpox virus, clinically similar cases would not require further laboratory testing.

Differentials are performed with enteroviruses, erythema multiforme (Stevens-Johnson Syndrome), herpes simplex, herpes zoster, impetigo, influenza, malaria, meningitis, meningococcemia, molluscum contagiosum, poxviruses, rickettsialpox, rocky mountain spotted fever, syphilis, vaccinia, varicella-zoster virus.

TREATMENT

No known treatment is effective for smallpox. Medical management of smallpox is mainly supportive. Supportive care in patients with symptomatic smallpox consists of the following:

- The patient should be isolated until all scabs have fallen off (about 3-4 wk after rash onset) to prevent transmission of the smallpox (variola) virus to nonimmune persons.
- The fluid and electrolyte balance should be monitored and maintained to avoid dehydration.
- Medications are given for fever and pain.
- Good nutritional support is maintained.
- Skin care should be instituted.
- Complications should be monitored for and treated.
- Unless the diagnosis of smallpox is confirmed in a laboratory, patients should receive smallpox vaccination if they will be isolated with other patients with confirmed or suspected smallpox to prevent accidental transmission.

New drugs are under investigation; one of these drugs is cidofovir, which has shown good results in the laboratory.

PREVENTION

In a smallpox outbreak, patients with confirmed or suspected smallpox may be isolated in several ways. The goal of isolation is to prevent transmission of smallpox from an infected patient to nonimmune individuals while maintaining an appropriate care and comfort level for the patient. Medical personnel should consult with public health officials to determine the most appropriate method for isolation of patients with smallpox. If a patient with confirmed or suspected smallpox requires hospital care, the following steps must be taken while the patient is hospitalized: The patient

should be kept in strict airborne and contact isolation in a room with negative air pressure (and individual high-efficiency particulate air [HEPA]–filtered ventilation exhaust, if available). This room should have private shower and bathroom facilities and not share ventilation with any other part of the hospital.

Unvaccinated personnel who enter and leave the isolation room should wear protective clothing, including gowns, masks (properly fitted N95 respirator masks), gloves, protective eyewear, and surgical booties. Recently successfully vaccinated personnel should exercise contact precautions (eg, gowns, gloves) and should wear a surgical mask and eye protection, as indicated, for procedures in which contact with body fluids is possible.

All protective clothing should be removed and placed into biohazard waste disposal containers before leaving the isolation room and re-entering other areas of the hospital. All infectious waste and contaminated protective clothing should be disposed of or sterilized in an appropriate manner (incineration for disposable materials; autoclaving, ethylene oxide decontamination, or laundering in hot water and bleach for reusable equipment or clothing). Public-health officials should be consulted for specific waste-disposal and decontamination guidelines.

Personnel entering the isolation room or handling infectious waste or clinical specimens from the patient should be vaccinated or have documented successful recent smallpox vaccinations (within 3 years). Public health officials should be contacted for vaccination requests.

Nonhospital isolation: Public-health officials should be consulted before nonhospital isolation is initiated. Patients with confirmed or suspected smallpox who do not require hospital care may be isolated in nonhospital facilities that do not share ventilation systems with other facilities. These facilities should have appropriate climate-control capabilities (heating and air conditioning), running water, and bathroom facilities. If patients with suspected or confirmed smallpox are isolated together, all patients should receive smallpox vaccination to prevent accidental transmission due to misdiagnosis. All persons entering these facilities must have documented successful recent smallpox vaccinations (within 3 years).

One of the best ways to prevent smallpox is through vaccination. Vaccine given to individuals before exposure to smallpox can completely protect them. Vaccination within 3 days after exposure prevents or greatly lessens the severity of smallpox in most people. Vaccination 4-7 days after exposure likely offers some protection from disease or may decrease the severity of disease. Vaccination does not protect patients with smallpox who have already developed a rash.

The vaccine should be administered to all persons who had contact with a patient confirmed to have smallpox. Additionally, the vaccine should be administered to personnel without contraindications who will be involved in the future evaluation or care of patients possibly infected, if not already a contact.

The various vaccines available and being tested. First-generation vaccines are composed of vaccinia virus derived from calf lymph or chicken embryos, have little attenuation, and represent the majority of the vaccine stockpile. Second-generation vaccines are viruses taken from first-generation vaccines that are then sterilely tissue-cultured with the aim of decreasing adverse outcomes. Lastly, third-generation vaccines use replication-deficient viruses that are highly attenuated, again with the aim of decreasing side effects and adverse outcomes.

VIG is indicated when the vaccination is contraindicated.

The patient and any individual who came into contact with the patient up to 17 days prior to the illness (including the treating physician and nursing staff) should remain in isolation until a definite diagnosis is made.

After the disease was eliminated from the world, routine vaccination against smallpox among the general public was stopped because it was no longer necessary for prevention.

MONKEYPOX

Monkeypox is zoonotic natural-focal like smallpox disease, caused by monkeypox virus.

ETIOLOGY

The monkeypox virus is a member of the genus orthopox (family Poxviridae). The infection was first seen in laboratory monkeys in 1958, thus, the name monkeypox, although rodents are believed to be the major reservoir in Africa.

Genomic sequencing of US, western African, and central African monkeypox isolates have confirmed the existence of 2 distinct monkeypox clades. The isolates from the United States were identical to the western African isolates. The disease course for individuals infected with the western African isolates is milder with less human-to-human transmission than for those infected with isolates from central Africa. In 2010, a dosage comparison using a prairie dog animal model reconfirmed that the Congo Basin strain of monkeypox virus is more virulent than the West African strain of monkeypox virus.

EPIDEMIOLOGY

Monkeypox virus is a zoonotic virus. Transmission can occur from contact with ill animals or animal reservoirs from Western Africa (eg, prairie dogs, rabbits, rats, mice, squirrels, dormice, monkeys, porcupines, gazelles). Additionally, preparing or ingesting infected animals can transmit monkeypox infection. Finally, direct cutaneous (skin-to-skin) or respiratory contact with an animal or person who is infected can transmit the infection.

Outbreaks in western and central Africa have been linked to exposure to rats, rabbits, squirrels, monkeys, porcupines, and gazelles. Inhabitants of remote tropical rain forests may become infected from direct contact while capturing, slaughtering, and/or preparing these animals for food; ingestion has also been linked to infection.

Respiratory droplets and direct contact with mucocutaneous lesions or fomites have been postulated as routes of human-to-human transmission.

CLINICAL MANIFESTATIONS

Monkeypox can cause a syndrome clinically similar to smallpox but overall is less infectious and less deadly.

The incubation period averages 12 days, ranging from 4-20 days.

In the prodrome or preeruptive stage (lasts 1-10 d), fever is commonly the first symptom (usually 38.5-40.5°C). The febrile illness is often accompanied by chills, drenching sweats, severe headache, backache, myalgia, malaise, anorexia, prostration, pharyngitis, shortness of breath, and cough (with or without sputum). The

most reliable clinical sign differentiating monkeypox from smallpox and chickenpox is enlarged lymph nodes (lymphadenopathy appears within 2-3 days after the fever), especially the submental, submandibular, cervical, and inguinal nodes.

In the exanthem (eruptive) stage, most persons develop a rash within 1-10 days after the onset of fever. The rash often starts on the face and then spreads to the rest of the body. It persists for 2-4 weeks until all lesions have shed the crusts. Encephalitis with immunoglobulin M found in the cerebrospinal fluid has been reported.

With regard to enanthema, nonspecific lesions and inflammation of the pharyngeal, conjunctival, and genital mucosae have been observed.

In the exanthem stage, within a particular body region, lesions evolve synchronously over 14-21 days, similar to the development of lesions with smallpox. However, unlike smallpox, skin lesions may appear in crops. In contrast to smallpox, the lesions do not have a strong centrifugal distribution. Lesions progress from macules to papules to vesicles and pustules; umbilication, crusting, and desquamation follow. Most lesions are 3-15 mm in diameter.

The face, the trunk, the extremities, and the scalp are involved. Lesions appear in covered and uncovered areas. Lesions may be seen on the palms and the soles. Necrosis, petechiae, and ulceration may be features. Pain is unusual, and, if it occurs, it is often associated with secondary bacterial infection. Pruritus may occur.

In patients who have been previously vaccinated against smallpox, a milder form of disease occurs. In children, the lesions may appear as nonspecific, erythematous papules that are 1-5 mm in diameter and suggestive of arthropod bite reactions. Subtle umbilication may be seen.

In the African outbreaks, 20% of unvaccinated patients developed a confluent, erythematous eruption on the face and the upper part of the trunk, which some authors have termed the septicemic rash of monkeypox.

Hemorrhagic and flat forms, which can be seen with smallpox, have not been reported in patients with monkeypox. Deep pock scars can result as the lesions resolve.

Uncomplicated cases resolve in 2-4 weeks, with only pock scars remaining.

Complications include pitted scars, deforming scars, secondary bacterial infection, bronchopneumonia, respiratory distress, keratitis, corneal ulceration, blindness, septicemia, and encephalitis.

Mortality rates ranging from 1-10% have been reported in Africa, but no fatalities occurred in the United States 2003 outbreak. Death rates are disproportionately high in African children. Health status, comorbidities, vaccination status, and severity of complications influence the prognosis in the United States and Africa.

DIAGNOSIS

A viral culture should be obtained from an oropharyngeal or nasopharyngeal swab. A skin biopsy specimen of the vesiculopustular rash or a sample of the roof of an intact vesiculopustule should be analyzed.

Tissue for PCR of DNA sequence-specific for the monkeypox virus may be obtained.

Paired sera for acute and convalescent titers may be analyzed. Serum collected more than 5 days for IgM detection or serum collected more than 8 days after rash onset for IgG detection was most efficient for the detection of the monkeypox virus infection.

A Tzanck smear can help differentiate monkeypox from other nonviral disorders in the differential diagnosis. However, a Tzanck smear does not differentiate a monkeypox infection from smallpox or herpetic infections.

Histologically, papular lesions show acanthosis, individual keratinocyte necrosis, and basal vacuolization. This is accompanied by a superficial and deep perivascular, lymphohistiocytic infiltrate in the dermis. Lesions in the vesicular stage demonstrate spongiosis with reticular and ballooning degeneration. Multinucleated epithelial giant cells may be seen. Pustular lesions are characterized by epidermal necrosis with numerous eosinophils and neutrophils, many displaying karyorrhexis. Necrosis may extend through full-thickness epidermis with sharp lateral demarcation from adjacent intact epidermis. The associated perivascular infiltrate includes eosinophils and neutrophils in addition to lymphocytes and histiocytes. Petechial lesions demonstrate secondary vasculitis. Amphophilic intranuclear structures suggestive of viral inclusions may be seen in keratinocytes.

Immunohistochemistry staining for orthopox viral antigens can be performed in a reference laboratory. With electron microscopy, intracytoplasmic, round-to-oval inclusions with sausage-shaped structures centrally, measuring 200-300 μm, are observed. Inclusions are consistent with orthopox viruses, permitting differentiation from parapox and herpes viruses.

Confirmed case. Meets 1 or more of the following laboratory criteria:

- Isolation of the monkeypox virus in culture from a sample obtained from the patient.
- Demonstration of the monkeypox virus on PCR in a specimen obtained from the patient.
- Demonstration of the orthopox virus by electron microscopy in samples obtained from the patient in the absence of exposure to other orthopoxviruses.
- Demonstration of the monkeypox virus by immunohistochemical methods in samples obtained from the patient in the absence of exposure to another orthopoxvirus.

Probable case. This is contact that meets current epidemiologic criteria. It is the

occurrence of fever and vesicular-pustular rash, with the onset of the first sign or symptom at most 21 days after the last exposure, meeting the epidemiologic exposure.

Suspected case. This is contact that meets current epidemiologic criteria. It the occurrence of fever or unexplained rash and 2 or more other signs or symptoms, with the onset of the first sign or symptom at most 21 days after exposure, meeting the epidemiologic criteria. Symptoms are as follows: chills and/or sweats, lymphadenopathy, sore throat, cough, shortness of breath, headache, and backache.

TREATMENT

The disease is usually self-limited; resolution occurs in 2-4 weeks.

Patients often feel poorly during the febrile stage of the illness; therefore, bedrest along with supportive care may be necessary. Hospitalization may be necessary in more severe cases; a negative pressure room is preferable.

To avoid infection of health care workers and close contacts, airborne and contact precautions should be applied.

The CDC recommends a smallpox vaccination within 2 weeks of exposure, ideally within 4 days, for exposed health care workers and household contacts of confirmed cases.

Cidofovir has been suggested as a possible treatment option in severe, life-threatening cases only.

PREVENTION

Contact and respiratory isolation precautions should be exercised to prevent the spread of disease. Direct contact with skin lesions or fomites is considered infectious until the crust detaches from the last skin lesion. Patients and unexposed contacts should wear masks until respiratory symptoms resolve.

Health care workers and others who are asymptomatic and in contact with patients who are infected must closely monitor their symptoms and their temperature for 21 days after the last known contact.

Importation of exotic animals as domestic pets poses a threat to the health of both people and animals by introducing nonindigenous pathogens. Animals, especially those implicated above (see epidemiology) or those in contact with them, demonstrating signs of respiratory distress, mucocutaneous lesions, rhinorrhea, ocular discharge, and/or lymphadenopathy should be quarantined immediately. Avoidance of contact, especially bites, scratches, and exposure to fluids/secretions, is essential. Guidance can be obtained from veterinarians, state/local authorities, and the CDC.
After the 2003 outbreak, the CDC implemented an immediate embargo on the importation of all rodents (order Rodentia) from Africa.

ERYSIPELAS

Erysipelas is a bacterial infection of the skin and subcutaneous tissue, which characterized by well demarcated areas of redness, heat, pain and swelling, and may be usually associated with fever and intoxication.

ETIOLOGY

Streptococci are the primary cause of erysipelas. Most facial infections are attributed to group A beta haemolytic streptococci (***Streptococcus pyogenes***), with an increasing percentage of lower extremity infections being caused by non–group A streptococci. Streptococcal toxins are thought to contribute to the brisk inflammation that is pathognomonic of this infection.

No clear proof has emerged that other bacteria cause typical erysipelas, although they clearly coexist with streptococci at sites of inoculation. Recently, atypical forms reportedly have been caused by ***Streptococcus pneumoniae***, ***Klebsiella pneumoniae***, ***Haemophilus influenzae***, ***Yersinia enterocolitica***, and ***Moraxella* species**, and they should be considered in cases refractory to standard antibiotic therapy.

The role of ***Staphylococcus aureus***, and specifically methicillin-resistant ***S. aureus***, remains controversial. No conclusive evidence demonstrates a pathogenic role for staphylococci in typical erysipelas. The infection's predictable response to penicillin, even when S. aureus is present, argues against S aureus as an etiologic agent. However, analogous to what occurs in bullous impetigo or staphylococcal scalded skin syndrome, exotoxins from coexisting S. aureus may account for the clinical presentation of bullous erysipelas.

EPIDEMIOLOGY

Source of infection are patients with erysipelas and other streptococci diseases (scarlet fever, angina, pneumonia, streptococcal impetigo etc.) and healthy carriers of streptococci. The organism may enter via a breach in the dermal barrier at a location some distance from the eventual site of clinical cellulitis. Contagiousness is insignificant.

Isolated cases are the rule with erysipelas, although epidemics have been reported. The incidence of erysipelas declined throughout the mid-20th century, possibly due to antibiotic development, improved sanitation, and decreased virulence.

In the past, the face was the most common site of infection. Now it accounts for only about 20% of cases. The legs are affected in up to 80% of cases.

Seasonality does not have essential value but number of erysipelas cases increases in summer and fall.

PATHOGENESIS

Obligatory condition for erysipelas development is preceding sensibilisation for Streptococcal antigen due to repeating infection or activation of endogenic infection.

Bacterial inoculation into an area of skin trauma is the initial event in developing erysipelas. Thus, local factors, such as venous insufficiency, stasis ulcerations, inflammatory dermatoses, dermatophyte infections, insect bites, and surgical incisions, have been implicated as portals of entry. The source of the bacteria in facial erysipelas is often the host's nasopharynx, and a history of recent streptococcal pharyngitis has been reported in up to one third of cases. Other predisposing factors include diabetes, alcohol abuse, HIV infection, nephrotic syndrome, other immunocompromising conditions, and vagrant lifestyle.

Preexisting lymphedema is a clear-cut risk factor for erysipelas. Recurrent erysipelas complicating the lymphedema from breast cancer treatment is well documented. Lymphoscintigraphy in patients with a first-time episode of lower extremity erysipelas has documented lymphatic impairment in both affected and nonaffected legs. Thus, subclinical lymphatic dysfunction is a risk factor for erysipelas.

In erysipelas, the infection rapidly invades and spreads through the lymphatic vessels. This can produce overlying skin "streaking" and regional lymph node swelling and tenderness.

Immunity does not develop to the inciting organism.

The histologic hallmarks of erysipelas are marked dermal edema, vascular dilatation, and streptococcal invasion of lymphatics and tissues. This bacterial invasion results in a dermal inflammatory infiltrate consisting of neutrophils and mononuclear cells. The epidermis is often secondarily involved. Rarely, bacterial invasion of local blood vessels may be seen.

CLINICAL MANIFESTATIONS

Incubation period in cases of exogenic infection varies from some hours up to 6-7 days; in cases of endogenic infection activation duration of this period is unknown.

Clinical classification includes following forms:

By the term of appearance: primary (first episode), relapsing (process appears on the same site after primary episode or previous relapse), recurrent or repeated (disease appears in two years or more after the first episode and usually has another localization).

By spread: localized (process has strictly restricted character), diffused (migrating, in one anatomical region), metastatic (formation of new foci with another

localization due to lymphogenic or hematogenic dissemination).

By character of inflammatory process: erythematous, erythematous-hemorrhagic, erythematous-bullous, bullous-hemorrhagic, phlegmonic, necrotic.

By severity: mild, moderate, severe.

The onset is usually abrupt with high fever, chills, and weakness. In severe cases may be vomiting, convulsions and delirium. This symptoms begin before the onset of the skin lesions and usually are present within 24-48 hours of cutaneous involvement. Pruritus, burning, and tenderness are typical complaints.

Erysipelas begins as a small erythematous patch that progresses to a fiery-red, indurated, tense, and shiny plaque.

Erysipelas predominantly affects the skin of the lower limbs, but when it involves the face it can have a characteristic butterfly distribution on the cheeks and bridge of the nose. Affected skin is distinguished from other forms of cellulitis by a well-defined (well-demarcated), raised border. The affected skin is red, swollen and may be finely dimpled (like an orange skin). Local signs of inflammation, such as warmth, edema, and tenderness, are universal.

Lymphatic involvement often is manifested by overlying red streaks extending proximally along superficial lymphatics from the site of infection (lymphangitis) and regional lymphadenopathy.

More severe infections may exhibit numerous vesicles and bullae along with petechiae and even frank necrosis.

With treatment, the outcome is good. It may take a few weeks for the skin to return to normal. The lesion often desquamates and can resolve with pigmentary changes that may or may not resolve over time. Peeling is common.

In some patients, the bacteria may travel to the blood. These results in a condition called bacteremia. The infection may spread to the heart valves, joints, and bones.

The most common complications of erysipelas include abscess, gangrene, and thrombophlebitis. Less common complications (<1%) are acute glomerulonephritis, endocarditis, septicemia, and streptococcal toxic shock syndrome. Rare osteoarticular complications involve joints contiguous with the erysipelas plaques and include bursitis, osteitis, arthritis, and tendinitis.

The prognosis for patients with erysipelas is excellent. Complications of the infection usually are not life threatening, and most cases resolve after antibiotic therapy without sequelae.

However, local recurrence has been reported in up to 20%-30% of patients with predisposing conditions (compromised immune systems or compromised lymphatic systems). Because erysipelas can damage the lymphatic system, the infection itself can be a setup for recurrence. This can lead to disfiguring and disabling healing reactions, such as elephantiasis nostras verrucosa.

DIAGNOSIS

In classic erysipelas, no laboratory workup is required for diagnosis or treatment.

Routine blood and tissue cultures are not cost-effective because they have an extremely low yield and results have a minimal impact on management. Cultures are perhaps best reserved for very immunosuppressed hosts in whom an atypical etiologic agent might be more likely.

Bacterial cultures from the portal of entry may be most helpful in persons with atypical clinical presentations.

Imaging studies are not usually indicated and are of low yield. MRI and bone scintigraphy are helpful when early osteoarticular involvement is suspected. In this setting, standard radiographic findings typically are normal. Differential diagnosis: erysipeloid, allergic dermatitis, gout, anthrax, insect bite, Lyme disease, pyoderma, thrombophlebitis.

TREATMENT

Hospitalization for close monitoring and intravenous antibiotics is recommended in severe cases and in infants, elderly patients, and patients who are immunocompromised.

Streptococci cause most cases of erysipelas; thus, penicillin has remained first-line therapy. Penicillin administered orally or intramuscularly is sufficient for most cases of classic erysipelas and should be given for 10-20 days.

A first-generation cephalosporin or macrolide, such as erythromycin or azithromycin, may be used if the patient has an allergy to penicillin. Cephalosporins may cross-react with penicillin and should be used with caution in patients with a history of severe penicillin allergy such as anaphylaxis.

Coverage for Staphylococcus aureus is not usually necessary for typical infections, but it should be considered in patients who do not improve with penicillin or who present with atypical forms of erysipelas, including bullous erysipelas. Some authors believe that facial erysipelas should be treated empirically with a penicillinase-resistant antibiotic, such as dicloxacillin or nafcillin, to cover possible S. aureus infection, but supporting evidence for this recommendation is lacking.

Two drugs, roxithromycin and pristinamycin, have been reported to be extremely effective in the treatment of erysipelas. Several studies have demonstrated greater efficacy and fewer adverse effects with these drugs compared with penicillin. Currently, the Food and Drug Administration has not approved these drugs in the United States, but they are in use in Europe.

Elevation and rest of the affected limb are recommended in erysipelas treatment to reduce local swelling, inflammation, and pain.

Saline wet dressings should be applied to ulcerated and necrotic lesions and changed every 2-12 hours, depending on the severity of the infection.

Debridement is necessary only in severe infections with necrosis or gangrene.

PREVENTION

Patients must keep their skin healthy by avoiding dry skin and preventing cuts and scrapes. This may reduce the risk for erysipelas.

Patients with recurrent erysipelas should be educated regarding local antisepsis and general wound care. Predisposing lower extremity skin lesions (e.g., tinea pedis, toe web intertrigo, stasis ulcers) should be treated aggressively to prevent superinfection. Use of compression stockings should be encouraged for as long as 1 month in previously healthy patients and long term in patients with lower extremity edema. Long-term management of lymphedema is essential. Long-term prophylactic antibiotic therapy generally is accepted, but no true guidelines are available. Treatment regimens should be tailored to the patient. One reported regimen is benzathine penicillin G at 2.4 MU intramuscularly every 3 weeks for up to 2 years. Two-week intervals have also been used.

ERYSIPELOID

Erysipeloid is an acute zoonotic bacterial infection which characterized with predominant affection of skin and joints.

ETIOLOGY

Erysipeloid is caused by the microorganism ***Erysipelothrix rhusiopathiae*** (insidiosa), which long has been known to cause animal and human infections. E. rhusiopathiae is a thin, gram-positive bacillus that may be straight or slightly curved. The microorganism is present in the soil and in poultry, fish, and birds.

E. rhusiopathiae has been shown to be eradicated from surfaces by the use of simple home disinfectants

EPIDEMIOLOGY

Infection with ***E rhusiopathiae*** occurs in worldwide distribution in a variety of animals, especially hogs. Erysipeloid is an occupational disease. Erysipeloid is more common among farmers, butchers, cooks, homemakers, and anglers. Direct contact between meat infected with ***E. rhusiopathiae*** and traumatized human skin results in erysipeloid. In animals, the organism causes swine erysipelas and several other diseases in poultry and sheep.

The infection is more likely to occur during the summer or early fall. Both sexes may be equally affected; however, erysipeloid seems to affect more males than females because of occupational exposure. Erysipeloid can affect any age group.

PATHOGENESIS

E. rhusiopathiae, which is highly resistant to environmental factors, enters the skin through scratches or pricks. In the skin, the organism is capable of producing certain enzymes that help it dissect its way through the tissues. It has recently been discovered that only pathogenic strains of E. rhusiopathiae are capable of producing the neuraminidase enzyme. This enzyme is speculated to help the microorganism invade tissues. Moreover, 2 adhesive surface proteins were discovered and their nucleotide sequence encoded. The proteins are named RspA and RspB and serve in helping the microorganism bind to biotic (collagen types I and IV) and abiotic (polystyrene) surfaces.

Meanwhile, the host's immune system is activated to start fighting against this foreign bacterium. The organism may escape immune surveillance and may spread in the body via the vascular system to the joints, heart, brain, CNS, and lungs. The organ most commonly affected other than the skin is the heart.

Histological Findings. The epidermis shows spongiosis, which may be severe enough to cause intraepidermal vesiculation. Marked edema of the papillary dermis

with dilatation of blood and lymphatic vessels occurs. In the reticular dermis, a perivascular inflammatory cell infiltrate made of neutrophil and eosinophils is observed.

CLINICAL MANIFESTATIONS

Incubation period are typically 2-3 days but can ranges from 1-7 days.

Erysipeloid may present in humans as one of 3 clinical forms: 1) cutaneous form: localized and diffuse; 2) cutaneous-arthrous form; 3) generalized or systemic infection as evidenced by bacteriemia.

In the first 2 forms of erysipeloid, patients present with local burning or pain at lesion sites. They may or not have fever, malaise, and other constitutional symptoms.

In the generalized form, patients present with fever, chills, weight loss, and a variety of other symptoms (e.g., joint pain, cough, headache), depending on the organ system involved.

Local changes are presented with following:

Localized cutaneous form (also known as erysipeloid of Rosenbach). Lesions most commonly affect the hands, mainly the webs of the fingers; however, any exposed area of the body may be affected. Lesions consist of well-demarcated, bright red-to-purple plaques with a smooth, shiny surface. Lesions are warm and tender. They leave a brownish discoloration on the skin when resolving. Sometimes vesicles may be present.

Diffuse cutaneous form. Multiple lesions appear on various parts of the body. Lesions are well-demarcated, violaceous plaques with an advancing border and central clearing.

Cutaneous-arthrous form characterized with development of interphalangeal joints arthritis. Fusiform intumescence of joints, stiffness and painfulness in the time of movement are present.

Systemic form of erysipeloid. Skin lesions may not be. If present, skin lesions appear as localized areas of swelling surrounding a necrotic center. Skin lesions also may present as several follicular, erythematous papules. Endocarditis is the most common, but still rare, manifestation of systemic erysipeloid.

Cutaneous forms of erysipeloid usually are self-limited even without treatment; therefore, skin-limited erysipeloid has a fairly good prognosis with no long-term sequelae. Cutaneous-arthrous form may lead to chronic recurrent arthritis and joints deformation. Prognosis of the systemic form of erysipeloid depends on the organ systems involved and on the extent of involvement. Early recognition and proper initiation of therapy is crucial to prevent sequelae.

Complications: permanent neurological damage (e.g., cerebrovascular accident); endocarditis with long-term valvular heart disease; septic arthritis with long-term joint diseases.

DIAGNOSIS

Several studies may be requested, depending on the clinical presentation.

- Gram stain may be performed on a skin scraping, which may show gram-positive rods; however, the stain often is negative because the infection is deep, and the microorganism is not reached with scraping.
- Bacterial culture on special media fortified with serum and at room temperature may be attempted. Culture of a biopsy from the leading edge of the lesion may reveal the organism.
- Blood culture aids in the diagnosis of systemic erysipeloid.
- Skin biopsy may be taken to confirm the diagnosis (see Histologic findings).

Imaging studies usually are ordered when an individual has the systemic form of erysipeloid, depending on the clinical presentation and probability of organ involvement.

- Echocardiography may be ordered, if endocarditis is suspected.
- CT or MRI of the brain may be used to rule out brain abscess or cerebral infarct.
- Radiography or CT of the chest may be ordered, if pleural effusion is suspected.
- Bone scan or MRI of bone may be performed, if osseous necrosis is suspected.

Differentials are performed with cellulitis, erysipelas panaritium, dermatitis, arthritis and sepsis.

TREATMENT

Empiric antimicrobial therapy must be comprehensive and should cover all likely pathogens in the context of the clinical setting.

The antibiotics of choice for the all forms of erysipeloid are penicillin or cephalosporin (Ceftriaxone). In patients who are allergic to penicillin, ciprofloxacin alone or erythromycin in combination with rifampin may be used. The microorganism is resistant to vancomycin, an important consideration in patients with endocarditis caused by E. rhusiopathiae.

The cutaneous forms of erysipeloid are self-limited and may remit spontaneously within 2-4 weeks; however, treatment with penicillin hastens the recovery and limits further progression of the disease.

Activity usually is not restricted. Individuals with the systemic form of erysipeloid may be advised to be on bed rest.

Individuals with the systemic form of erysipeloid may undergo surgery (e.g., cardiac valve replacement), pleural tap, or other procedures, depending on extent of organ involvement.

Procedures usually are not used in the cutaneous form of erysipeloid. Even a simple incision and drainage of lesions is not recommended as this may prolong the recovery time.

PREVENTION

Patients must be cautious while handling animals and animal products.

An important step in the prevention of infection may be to spray hazardous work areas (e.g., fishing boats, meat counters) with disinfectants.

BARTONELLOSIS

Until the early 1990s, ***Bartonella bacilliformis*** was the only member of the genus ***Bartonella*** and Carrión's disease was the first known human bartonellosis. It is only known to occur in endemic regions in the South American Andean valleys between 500 and 3200 m above sea level in Peru, Colombia and Ecuador. In the 1980s, during the years before effective anti-retroviral medication, the AIDS epidemic gave rise to a multi-fold of opportunistic infections, including bacillary angiomatosis that is caused by ***B. henselae*** or ***B. quintana***. Attempts to isolate the causative agents were successful to a much higher extent than before or ever since because of the immunocompromised state of the host. The AIDS epidemic in combination with the rapidly evolving molecular techniques created the necessary conditions for the onset and fast expansion of today's Bartonella research. Thus, bartonelloses are still referred to as emerging infections.

ETIOLOGY

Because of advances in genetics-based bacterial classification and taxonomy, the former genera Grahamella and Rochalimaea were soon merged into an expanded genus named Bartonella. Since its reclassification, the genus Bartonella is constantly expanding and by now comprises approximately 35 species and subspecies, many of which are reported pathogenic to humans. Although most diseases we are aware of today as related to Bartonella infections have been known for a long time, their etiology was not established until the 1990s.

The genus Bartonella is a member of the alpha sub-division of the phylum Proteobacteria. The genus Bartonella is a part of the order Rhizobiales. Members of the genus Bartonella are gram-negative rods, oxidase- and catalase-negative, and typically difficult to isolate. The bacteria can grow both on a free medium or intracellularly. The bacterium is haemin dependent and grows better with increased carbon dioxide pressure. The optimal growing temperature is 35-37°C for all Bartonella spp. except B. bacilliformis, which prefers 28°C. The latter also expresses a flagella-like B. schoenbuchensis and B. clarridgeiae but in contrast to other known Bartonella. The bacterium grows slowly. Primary isolation from infected humans may be very difficult and the first colony might be visible only after a prolonged incubation of 45 days. When subculturing, the generation time usually decreases successively to 4-5 days. Further, the appearance of the colonies changes after several passages from rough, adherent to smooth and less adherent colonies. This phenomenon is called phase variation and the mechanisms behind it are not fully known. It is likely caused by a variable expression of outer membrane proteins as a strategy for the bacteria to evade the host's immune response and permit adaptive interaction with different host structures. Bartonella spp. are facultative intracellular

bacteria. Bartonella may invade and persist in red blood cells and endothelial cells. Thus, it evades the host's immune response and increases its transmittability by blood-sucking arthropods.

The genomes of B. henselae H-1 and B. quintana (strain Toulose) contain a single circular chromosome and display a high degree of overall similarity. The size of the B. henselae genome was estimated to 1.93 Mb and B. quintana to 1.58 Mb. The backbone of the two genomes is homologous with the exception of one 55 kb prophage region and three genomic islands present in the B. henselae genome but absent in the B. quintana genome. These observations suggest that B. quintana is a reduced genomic derivative of B. henselae. This might be a consequence of the differences in vector-host ecology between the two species. B. quintana is more specialised in solely infecting humans with the body louse as a vector, whereas B. henselae is more of a generalist using vectors of broader host ranges. The utilization of host-restricted vectors is associated with accelerated rates of genome degradation.

EPIDEMIOLOGY

Bartonella infections are mainly regarded as zoonotic involving different modes of transmission, either directly from animal to human (e.g., through a cat scratch) or with arthropod vectors. Cats are the principal reservoir for Bartonella henselae, the main agent of cat-scratch disease (CSD) and B. clarridgeiae. Dogs could be one of the reservoirs for B. henselae, B. clarridgeiae, B. washoensis, B. elizabethae and B. vinsonii subsp. berkhoffii. Naturally infected reservoir hosts are generally asymptomatic or display minor symptoms of their infection. In contrast, incidentally infected hosts are normally symptomatic. Bacteremia with different Bartonella spp. in seemingly healthy animals has been reported in elk, cattle, deer, roe deer, rabbits, squirrels, cats, dogs, coyotes and rodent populations. Humans are thought to be the natural hosts of B. bacilliformis and B. quintana. Asymptomatic bacteremia in humans with both Bartonella spp. has been encountered. However, Carrion's disease may be fulminant with a high mortality rate if untreated.

Few vectors have been identified for Bartonella species: sandflies (Lutzomyia verrucarum) for Bartonella bacilliformis, body lice (Pediculus humanis corporis) for Bartonella quintana and cat fleas (Ctenocephalides felis) for Bartonella henselae. But there are other potential vectors, such as ticks and biting flies have been recently identified to harbor Bartonella DNA, including B. henselae.

PATHOGENESIS

A main feature in the pathogenesis of Bartonella is its propensity to invade mature erythrocytes and endothelial cells of its animal or human hosts. B. tribocorum experimental infections in rats have demonstrated persistent intra-erythrocytic bacteremia without causing haemolysis. A type IV secretion system is crucial for

invading the erythrocytes and for establishing the infection in an as yet elusive primary niche. From this niche, which is by some postulated to consist of endothelial cells and by others by bone marrow-stemmed erythrocyte progenitors (e.g., the erythroblast), the bacteria are seeded every 5 days into the bloodstream, which enables new rounds of erythrocyte invasion. The five-day seeding interval coincides with the symptom interval of trench fever. However, in immunocompetent hosts, the anti-Bartonella antibody response gradually prevents seeded bacteria to invade the erythrocytes thereby subsequently clearing the bacteremia.

Epidemiology of Bartonella infections

Species	Human	Animal reservoir	Pathophysiology
B. bacilliformis	reservoir	-	Carrion's disease, asymptomatic carriers
B. clarridgeiae	incidental host	cat	CSD, sepsis, endocarditis, splenomegaly
B. doshiae	incidental host	rat	CSD
B. elizabethae	incidental host	rat	endocarditis
B. grahamii	incidental host	mouse	Endocarditis, neuroretinitis
B. henselae	incidental host	cat	CSD, bacillary angiomatosis and peliosis, endocarditis, chronic bacteremia, neuroretinitis, encephalopathy, acute psychiatric symptoms, osteomyelitis, erythema nodosum
B. koehlerae	incidental host	cat	endocarditis, CSD
B. quintana	reservoir	-	trench fever, bacillary angiomatosis and peliosis, endocarditis, chronic bacteriemia, CSD
B. rochalimae	incidental host	unknown	chronic bacteremia, fever, cutaneous lesions, splenomegaly
B. tamiae	incidental host	unknown	chronic bacteremia, fever
B. vinsonii	incidental host	mouse, dog, coyote, foxes	endocarditis, fever and neurological disease
B. washoensis	incidental host	squirrel	fever and myocarditis

There is epidemiological evidence that this mechanism of antibody-mediated

cessation of hemotropic infection also applies to the natural course of B. quintana infections in humans. Another hallmark of Bartonella pathogenesis is its ability to induce angiogenesis that is seen in bacillary angiomatosis, verruga peruana and liver peliosis. In vitro studies have demonstrated the important role of the Bartonella VirB/VirD4 type IV secretion system also in the interaction with endothelial cells. The type IV secretion system of Bartonella exports Bartonella-translocated effector proteins (Beps) into the Endothelial cells leading to cytoskeleton rearrangement and the engulfment of bacterial aggregates (invasome formation), proinflammatory activation leading to the recruitment of circulating neutrophils and the thereby release of proangiogenic factors (such as vascular endothelial growth factor) and enhanced cell survival that is due to an anti-apoptotic effect. These effects promote the vasculoproliferative lesions. However, the exact mechanisms behind the processes are far from fully established.

Bartonella adhesion A (BadA) of B. henselae has recently been identified as an important pathogenicity factor. BadA is essential for the bacterium's binding to Endothelial cells, the activation of a key transcription factor in angiogenesis (hypoxia-inducible factor 1) and the induction of vascular endothelial growth factor. In B. quintana the BadA homologues are called variably expressed outer membrane proteins (Vomps) and they have been shown to mutate at a high frequency. There is evidence that BadA is an important host-interaction gene for Bartonella and, furthermore, the bacterium is able to modulate the badA gene expression by as yet unknown mechanisms.

CLINICAL MANIFESTATIONS

Carrión's disease. The clinical range is wide, going from asymptomatic infections via serious febrile forms with acute haemolytic anemia, to the angiomatous skin lesions which can be present from the onset or can be preceded by the febrile stage. The mortality of untreated cases varies between epidemics and ranges from 10-40% after 2-3 weeks. The disease is less severe in children and the mortality is far lower. If the course of the disease is favourable, the fever can last for 3 to 4 months. In 40-50% of cases of Oroya fever, concurrent salmonellosis (generally Salmonella typhimurium) complicates the illness and makes the prognosis less favourable. The superinfection causes fever with gastrointestinal symptoms and a deterioration of the patient's general condition.

Acute stage or Oroya fever. Incubation takes approximately 3 to 8 weeks (range 10-210 days). It begins insidiously with irregular intermittent febrile attacks with shivering, rapidly worsening anemia with tachycardia, pallor and (sub)icterus, severe headache with bone and joint pain. Other symptoms which may persist after the fever has ended include: enlargement of the liver and spleen, slightly painful on palpation; generalized painful swollen lymph nodes; myocarditis, pulmonary oedema

and anasarca; haemorrhagic diathesis as a result of the endothelial lesions (petechiae and tendency to thrombosis); neutrophilia. Necrotic foci are found in the liver, spleen and bone marrow. Spontaneous abortion, foetal death or transplacental transmission can occur. Neurobartonellosis due to involvement of the central nervous system takes the form of meningo-encephalitis with or without convulsions and with high mortality. Myelitis also occurs with spastic or flaccid paraplegia with sequelae which can be permanent. There is pleiocytosis of the cerebrospinal fluid. More focal and transient lesions of the spinal cord or of the cranial nerves are seen at the verruga stage.

Chronic stage or Verruga peruviana. The painless wart-like skin eruption results from the abnormal growth of blood vessels with the appearance of haemangiomas and the formation of angioblastic nodules. At this stage Bartonella can still be found more or less easily in the endothelial cells, but they are only very rarely found in the erythrocytes. The skin eruption usually appears 6 to 14 weeks after the acute stage. Both pathological conditions can be present at the same time, however. The skin eruption may initially be accompanied by a mild fever and arthralgia. The eruption is polymorphic. Some lesions disappear quickly, others persist or grow for some time only to shrivel and disappear, generally without leaving scars. There are three forms: 1) miliary form: the lesions are small (< 0.5 cm), very numerous and mainly found on the face, on the extensor surface of the limbs and on the trunk. They are initially macular and grow to small vascular, sometimes pedunculated and protruding nodules. Lesions are also present on the digestive and genito-urinary mucosa. Dysphagia, haematemesis, melaena, haematuria and metrorrhagia can occur; 2) nodular form: the nodules are larger, less numerous, deeper, chronic and mainly found around the elbows and knees. The mucous membranes are spared. The lesions appear in cycles for 2 to 3 months; 3) mular form: there are isolated pseudotumoural haemorrhagic nodules which macroscopically resemble granuloma pyogenicum.

Typical CSD is a syndrome of isolated lymphadenopathy with fever and no other signs or symptoms. Typical CSD is the most commonly recognized manifestation of infection with B henselae. Symptoms occur 1-7 weeks after infection and usually resolve spontaneously in immunocompetent individuals. The disease begins with an erythematous papule at the site of inoculation (cat scratch or bite). The papule appears 3 to 10 days after inoculation, and progresses through erythematous, vesicular, and papular crusted stages. Skin lesions other than the papule seen at the site of inoculation are rare, occurring in ~5% of patients infected with B. henselae. These consist of maculopapular and urticarial eruptions, granuloma annulare, erythema nodosum, erythema marginatum, and leukocytoclastic vascultis. The lesion persists for between 1 and 3 weeks.

Regional lymphadenopathy occurs 1 to 3 weeks after inoculation.

Lymphadenopathy is seen in all patients, and 85% of patients have only a single node involved. Lymphadenopathy occurs most frequently in the axillary and epitrochlear nodes, head and neck, and the groin. The nodal distribution reflects the fact that feline contact occurs most often with the hands. On ultrasound, nodes are multiple, hypoechoic, and highly vascularized with increased echogenicity of the surrounding soft tissues. On biopsy, nodes reveal granulomas with multiple microabscesses. Approximately 10% of nodes will suppurate, thereby requiring drainage.

Atypical CSD. Among the atypical manifestations are encephalopathy, neuroretinitis, Parinaud's oculoglandular syndrome, endocarditis, myocarditis, fever of unknown origin, osteomyelitis etc.

Systemic manifestations is mild in the majority of patients, and can include fever, generalized aches, malaise, anorexia, nausea, and abdominal pain. Of note is that <10% of patients have a fever higher than 39°C, and one-third are without fever.

Hepatosplenic manifestations occurs more than previously acknowledged in patients who are immunocompetent. Individuals present systemic symptoms, such as prolonged fever, and microabscesses in the liver and/or spleen. Physical examination findings are usually normal, with occasional detection of well-healed cutaneous scars secondary to cat scratches. Abdominal pain is a common complaint, usually described as episodic dull pain over the periumbilical and/or upper quadrant regions with high severity. Other presenting symptoms include weight loss, chills, headache and myalgias. Lymphadenopathy is present in about one half of cases. More than half of all patients will present with hepatomegaly, splenomegaly, or hepatosplenomegaly on physical examination. Jaundice, and elevated transaminase levels are not associated with this condition. Granulomatous disease in the spleen resulting from Bartonella can be severe enough to result in spontaneous splenic rupture. Patients will typically have an elevated erythrocyte sedimentation rate. White blood cell and platelet counts are normal or slightly elevated in most cases. Abdominal imaging is an important diagnostic step in patients with suspected hepatosplenic disease. On ultrasound, hepatic lesions seem hypoechoic. On computed tomographic scan, hepatic lesions seem either hypoattenuated relative to the liver, isoattenuated to the surrounding tissues, or only marginally enhanced. The diagnosis is based on characteristic defects in the liver and/or spleen and a positive B. henselae titer. In general, symptoms and visceral lesions regress within 6 months; however, there have been rare reports of residual calcification.

Pulmonary manifestations take the form of pneumonia or pleural thickening and/or effusion. Pulmonary disease appears 1 to 5 weeks after the appearance of lymphadenopathy. Systemic signs of infection, including fever, were present in 85%. Prognosis has been excellent, with complete recovery in a mean time of 2 months. One case in which a massive abscess involved the chest wall has been reported.

Neurologic manifestations are rare, occurring in 2-5% of infected patients. The

most common presentation is encephalopathy, accounting for 90% of cases that affect the nervous system. This complication may be more common in adults than in children. The onset is usually abrupt and occurs 1-6 weeks after the lymphadenopathy becomes apparent. Symptoms include headaches and mental status changes. Patients can become confused and disoriented, and their condition can deteriorate to coma. About 50% of patients have a fever. Combative behavior has been reported in as many as 40% of patients. In addition to mental status changes, patients with encephalopathy may present with a variety of neurologic findings, including weakness, nuchal rigidity, extensor plantar responses, hemiparesis and hyporeflexia or hyporeflexia. Seizures develop in 46% to 80% of patients. Recovery is usually complete in 2-10 days, with no sequelae.

Cerebrospinal fluid analysis typically yields normal results, although mononuclear pleocytosis and elevated cerebrospinal fluid protein have been reported in 20-30% of patients. Electroencephalography performed during the acute phase of illness reveals generalized slowing in 80% of patients, with complete normalization on follow-up. Only 19% of patients have abnormal findings on computerized tomographic scan or magnetic resonance imaging of the brain, and these include lesions of the cerebral white matter, basal ganglia, thalamus, and gray matter. Prognosis is generally excellent for patients with encephalopathy, with >90% of patients having complete, spontaneous recovery with no sequelae.

Less common neurologic complications include meningomyeloradiculopathy, manifesting with lower extremity paresthesias, weakness and sphincter dysfunction, facial nerve palsy, Guillain-Barre syndrome, epilepsy partialis continua, acute hemiplegia, transverse myelitis, Brown-Sequard syndrome and cerebral arteritis.

Ocular manifestations. Parinaud’s oculoglandular syndrome is the most common atypical presentation of CSD (~5% of patients) and is characterized by unilateral conjunctivitis with adjacent preauricular lymphadenopathy. Route of infection is thought to be direct conjunctival inoculation. Typical symptoms include foreign body sensation, unilateral eye redness, serous discharge, increased tear production, fever and regional lymphadenopathy. Examination of the palpebral conjunctiva on the involved side reveals necrotic granulomatous lesion 2-4 mm in diameter with ulceration of the conjunctival epithelium. Regional lymphadenopathy affects the preauricular, submandibular, or cervical lymph nodes. The granuloma typically disappears after several weeks without scarring.

Neuroretinitis (Leber idiopathic stellate retinopathy, Leber idiopathic stellate maculopathy), a form of optic neuropathy with optic disk swelling and macular stellate exudate, is the most common posterior segment ocular complication of Bartonella infection. Symptoms include fever, malaise and painless unilateral (rarely bilateral) visual loss with abrupt onset following cat exposure. Examination reveals decreased visual acuity, decreased color vision, and centrocecal scotoma. The optic

disc appears edematous, and exudates frequently surround the macula. On magnetic resonance imaging, unilateral enhancement at the optic nerve-globe junction is highly specific for B. henselae infection as cause for optic neuropathy. Macular exudates may take months to resolve and, even after resolution, patients may experience abnormal color vision and evoked potentials, subnormal contrast sensitivity, residual disk pallor, afferent pupillary defects, retinal pigment changes, and mildly decreased visual acuity. Long-term prognosis is good, but some individuals may acquire a mild postinfectious optic neuropathy.

There are reports of ocular Bartonella disease with optic disk edema and retinal detachment without the classic macular stellate exudate seen with neuroretinitis. Other posterior segment presentations of B. henselae infection include panuveitis with diffuse choroidal thickening, retinal vasoproliferative lesions, macular hole, vitreal detachment, vitritis, branch retinal artery and venous occlusions, retinal white spots, and papillitis. In HIV-positive patients, ocular B. henselae infection presents as a subretinal angiomatous mass associated with abnormal vascular network, which is best diagnosed by fluorescein angiography.

Hematologic manifestations. Hemolytic anemia has been reported in both adults and children and thrombocytopenic purpura in children. Bartonella has also been reported to be associated with development of lupus anticoagulant and prolongation of the activated partial thromboplastin time. Anecdotally, a case is known of a red blood cell enzyme deficiency with chronic hemolysis that worsened intensely with the development of systemic B. henselae infection, requiring transfusion therapy.

Orthopedic manifestations. Bone lesions are a rare complication of infection with B. henselae. Often, these lesions are osteolytic, and occur as an osteomyelitis (~0.3% of patients). Clinical manifestations of bony disease include fewer, local pain and tenderness over the affected bone and lymphadenopathy. The lytic lesions frequently occur in the context of systemic manifestations of Bartonella infection. Lymphadenopathy frequently occurs distant from the site of osteomyelitis, suggesting that bony infection occurs by hematogenous or lymphatic spread. Abnormalities on radiograph include lytic lesions, with occasional sclerosis or periosteal reaction. Lesions are sometime subtle on plain radiograph, and may require an MRI or radionuclide bone scan for diagnosis. In most patients, osteolytic disease is isolated to one bone (very rare multifocal bone marrow infection). Infection has been reported in the skull, sternum, vertebrae, clavicles, humerus, femur, tibia, acetabulum, metacarpals, and metatarsals. Biopsy reveals necrotizing granulomas of bone. Bony lesions have been associated with adjacent abscesses. Patients with osteomyelitis resulting from B henselae infection generally have an excellent prognosis.

Female gender, age of >20 years, and erythema nodosum were factors significantly associated with arthropathy in patients infected with Bartonella. The

most frequently affected joints were the knee, wrist, ankle, and elbow joints. Often, the disease is severe enough to incapacitate and limit activities of daily living. In most patients, arthropathy began within 1 week of the appearance of lymphadenopathy and persisted for greater duration than the lymphadenopathy. About 3% of cases of B. henselae infection had rheumatoid factor-negative arthritis/arthragia.

Renal manifestations. Renal complications of Bartonella infection are uncommon, with glomerulonephritis being the most frequently encountered. Glomerulonephritis secondary to B. henselae presents with gross or microscopic hematuria, low-grade proteinuria, and cola-colored urine, often accompanied by fever and lymphadenopathy. The renal disease can present as immunoglobulin A (IgA) nephritis, acute postinfectious glomerulonephritis or necrotizing glomerulonephritis. Affected patients have normal serum complement 3 levels, normal renal function, and renal biopsies may reveal mesangial hypercellularity, IgA deposition, interstitial infiltrate and/or complement 3 deposition consistent with acute glomerulonephritis.

Fever of unknown origin is defined as a documented daily temperature of 38° C for at least 14 days without diagnostic signs or symptoms of an obvious clinical disease. Bartonella infections, should always be considered as a diagnostic possibility in patients with fever of unknown origin and in patients with prolonged fever and abdominal pain, irrespective of exposure to cats. Approximately 30% of cases of fever of unknown origin caused by B. henselae had hepatosplenic involvement. There have also been reported cases of B. henselae presenting with intraabdominal lymphadenopathy, fever, and abdominal pain with no hepatosplenic disease.

Trench fever was recognized and described during World War I. Clinical presentations ranging from a mild to a more severe course. No fatalities were recorded. The incubation period was estimated to be 15-25 days in natural infection. The most common presentation (classic relapsing form) included an acute onset of fever (39-40°C) lasting 1-3 days followed by relapsing but decreasing episodes of fever every 5 days. Fever was accompanied by shin pain, headaches and dizziness. A typhoidal form characterized by a prolonged fever, splenomegaly and rash; and an abortive form, characterized by a brief, less intense course. A slightly furred tongue, conjunctivitis and a slow pulse relative to the severity of the fever were also reported. Epidemics among homeless populations have recently been reported. Thus, these epidemics have been referred to as urban trench fever. The epidemiological risk factors for trench fever include immunodeficiency, chronic alcoholism, homelessness and poor living conditions, louse infestation. An epidemic of trench fever was reported in refugee camps in Burundi in 1997. Some trench fever patients develop chronic bacteremia which is asymptomatic and can last for several years.

Cardiac manifestations. The most commonly reported cardiac manifestation of Bartonella infection is endocarditis. B. quintana has been reported to occur more

frequently than other Bartonella spp. (B. henselae, B. elizabethaea, B. koehlerae, B. alsatica) in cases of endocarditis. Bartonella species account for ~3% of cases of endocarditis. Presentation is insidious and subacute, with fever, dyspnea, bibasilar rales, cardiac failure, and cardiac murmur as presenting signs and symptoms. The aortic valve is usually involved, and vegetations are observed on echocardiography in 90% of patients.

Bartonella spp. may be involved in the aetiology of myocarditis. Myocarditis was suspected in a case of aggressive B. henselae endocarditis in an immunocompetent adult because of severely reduced left ventricular function although a heart biopsy specimen was not obtained. Another case of histologically verified B. henselae myocarditis was suspected in a case progressing to heart failure and heart transplantation. However, immunohistochemical staining and PCR for Bartonella were negative in myocardial biopsy specimens. It was hypothesised that the myocarditis in this case was caused by immune-mediated mechanisms secondary to CSD.

Arrythmogenic right ventricular cardiomyopathy/dysplasia is characterized biologically by progressive fibrofatty replacement of the right ventricular myocardium and clinically by life-threatening ventricular arrhythmias. Fibrofatty substitution also of the left ventricle is common in advanced disease and inflammatory infiltrates may be present. There are both sporadic and familial cases and specific chromosomal loci and five disease-causing genes have been identified in the latter group. These genes encode components of the desmosome which are important for providing tissues with mechanical strength. Impaired functioning of cell adhesion junctions may lead to myocyte detachment and death, accompanied by inflammation and fibrofatty repair. If infective mechanisms also have a role in the pathogenesis of arrythmogenic right ventricular cardiomyopathy/dysplasia and/or in the onset of malignant arrhythmias is under debate. However, myocarditis is a frequent finding in arrythmogenic right ventricular cardiomyopathy specimens and it has been postulated that infections contribute to the onset and the progression of the disease.

Pseudomalignancy. Infection simulating lymphoma is one of the most frequently reported for B. henselae, especially with lymphadenopathy in the neck and abdomen. The clinical picture is most confusing when splenic involvement occurs in the context of the so-called “B symptoms” of lymphoma, such as weight loss, night sweats, and prolonged fever. Hepatosplenic lesions and intraabdominal lymphadenopathy have been noted to have an appearance on both ultrasound and contrast-enhanced CT scan consistent with lymphoma.

Recently, Bartonella has been reported to mimic posttransplant lymphoproliferative disease in children who have undergone renal transplantation. Infection presented with fever, lymphadenopathy, and/or organomegaly 2 to 4 years

posttransplantation. In some of these patients, B. henselae infection was associated with acute rejection episodes that were reversed with intravenous corticosteroid therapy.

There are several reports in the literature in both adults and children of Bartonella infection presenting as a solitary mass in the breast. Initial clinical manifestations consist of a firm, mobile, tender breast mass, often in the lower outer quadrant of the breast, and inflammatory axillary lymphadenopathy. Disease in the breast has also presented as mastitis with soreness and erythema of the breast. Characteristic features of B. henselae infection of the breast are abscesses or granulomas in the breast parenchyma with bacteria in necrotic regions. Bartonella titers may be negative, but the bacteria may be detected on polymerase chain reaction analysis of nodal aspirate.

Although not a malignant process, B. henselae have been suggested in association with Kikuchi's disease, or histiocytic necrotizing lymphadenitis, in children. Another unusual presentation includes a patient with a solitary soft tissue mass overlying a lytic skull lesion, which was suggestive of Histocytosis X. In adults, B. henselae has presented similarly to pancreatic or biliary malignancy, pharyngeal cancer, and vascular neoplasms.

Bacillary angiomatosis. Bacillary angiomatosis is a proliferative vascular disease recognized predominantly in immunodeficient patients with B. quintana and B. henselae as aetiologic agents. Although this systemic disease can occur in various organ systems, skin lesions are most frequent, occurring in up to 90% of cases. Lesions consisting of numerous brown to violaceous or colorless vascular tumors of the skin and the subcutaneous tissue are difficult to differentiate from Kaposi's sarcoma, epithelioid hemangioma, and pyogenic granuloma. Disseminated disease may involve bone, liver, spleen, lymph nodes, the gastrointestinal and respiratory tracts, and bone marrow. Histologic examination with Warthin-Starry staining reveals vascular proliferation with numerous bacillary organisms.

Bacillary peliosis hepatis is a specific form of hepatosplenic Bartonella disease seen in the immunocompromised hosts. Patients present with gastrointestinal symptoms, fever, chills, and hepatosplenomegaly. The liver demonstrates characteristic dilated capillaries or blood-filled cavernous spaces. The typical duration of fever ranges from 1 week to 2 months.

DIAGNOSIS

There have been major advances in Bartonella diagnostics over the past 20 years. Before today’s methods were available, five diagnostic criteria for CSD were used: epidemiological data involving cat contact or cat scratches, the presence of a cutaneous inoculation site, regional lymphadenopathy, a granuloma present on histological examination of the lymph node biopsy or a positive skin test. Today, the

skin test is completely outdated and not in practice any more. In general, serologic testing is the most widely used method to diagnose Bartonella infection and indirect immunofluorescence is the reference method. Drawbacks include the lack of a Bartonella antibody response early in the course of the infection, the occurrence of variable antibody titers when different methods of antigen preparation are used and cross-reactions with antigens of distantly related genera such as Coxiella burnetii and Chlamydia pneumoniae. Western blot and cross-adsorption can be used to avoid the problem with cross-reactions and to differentiate between different Bartonella spp. typically; Bartonella endocarditis gives rise to high antibody titers.

Bartonella isolates from clinical samples are notoriously difficult to obtain. However, positive Bartonella cultures have become more common with improved techniques. The subculture of blood culture broth into shell vials or onto agar plates has been proven more efficient than the direct blood plating of infected blood. The blood sample should be frozen before the isolation attempt in order induce haemolysis and to release any intra-cellular bacteria.

Polymerase chain reaction (PCR) is, beside serology, the most important diagnostic tool for detecting Bartonella infections and has successfully been employed for various tissues. Many different target genes have been evaluated for diagnostic PCR, although the amplification of the house-keeping gene citrate-synthase (gltA) has been most widely used. gltA has the asset of providing the highest amount of nucleotide sequence data for Bartonella strain comparisons in public data bases. Furthermore, a species definition for the Bartonella genus has been defined on the basis of the gltA gene, which reinforces its usefulness. Instead of diagnostic conventional PCR, real-time PCR or quantitative PCR is preferable because of decreased risk of carryover contamination, higher speed, simplicity, reproducibility and quantitative capability.

Bartonella spp. may be detected in tissues by immunohistochemistry. Reported examples are valvular tissue in patients with Bartonella endocarditis and in skin biopsies of patients with bacillary angiomatosis. The intracellular presence of Bartonella spp. (endothelial cells or erythrocytes) has been visualized with staining with mouse monoclonal antibodies and using confocal microscopy.

TREATMENT

There are several difficulties in defining treatment recommendations for Bartonella infections. Bartonella infections display a wide range of clinical manifestations. The bacterium has both extra- and intracellular niches in the infected host and the course of the disease can be acute, relapsing or chronic depending on which Bartonella spp. is involved and the host's immune status.

There are some reported studies on susceptibilities to different antibiotic compounds but only two published randomized clinical trials for the treatment of

Bartonella infections. Azithromycin has been evaluated in such a study design for the treatment of CSD. Gentamicin and doxycycline were tested in a randomized open trial for the eradication of Bartonella quintana in patients with chronic bacteremia. Unfortunately, few prospective multi-centre randomized clinical trials that would be necessary to better define the treatment regimens have been carried out because of the comparatively infrequent occurrence of Bartonella infections.

Recommendations for the treatment of infections caused by Bartonella spp.

Form of bartonellosis	Agent	Dosage
Typical CSD	Azithromycin (for patients with extensive lymphadenopathy)	500 mg p.o. on the first day and 250 mg/day p.o. on 2 to 5 days
Trench fever / chronic B. quintana bacteremia	Doxycycline plus Gentamicin	200 mg p.o. once a day for 4 weeks 3 mg/kg i.v. once a day for 2 weeks
Endocarditis, suspected Bartonella, culture negative	Gentamicin plus Ceftriaxone plus Doxycycline	3 mg/kg/day i.v. for 14 days 2 g i.v. or i.m. once a day for 6 weeks 100 mg p.o. or i.v. twice a day for 6 weeks
Endocarditis, documented Bartonella, culture positive	Doxycycline plus Gentamicin or plus Rifampin	100 mg p.o. twice a day for 6 weeks 3 mg/kg/day i.v. for 14 days 300 mg p.o. twice daily for 14 days
Retinitis	Doxycycline plus Rifampin	100 mg p.o. twice a day for 4-6 weeks 300 mg p.o. twice a day for 4-6 wk
Bacillary angiomatosis	Erythromycin or Doxycycline	500 mg p.o. four times a day for ≥3 months 100 mg p.o. twice a day for 3 months
Bacillary peliosis	Erythromycin or Doxycycline	500 mg p.o. four times a day for ≥4 months 100 mg p.o. twice a day for 4 months
Carrion's disease Oroya fever	Chloramphenicol plus beta-lactam antibiotic or ciprofloxacin	500 mg p.o. or i.v. four times a day for 14 days 500 mg p.o. twice a day for 10 days
Carrion's disease Verruga peruana	Rifampin or streptomycin	10 mg/kg/day p.o. for 14 days 15-20 mg/kg/day i.m. for 10 days

In vitro, Bartonella spp. are susceptible to a wide range of agents including penicillins, cephalosporins, aminoglycosides, chloramphenicol, tetracyclines, macrolides, rifampin, fluoroquinolones and cotrimoxazole. Only aminoglycosides and rifampin have a reported bactericidal effect. The clinician deciding on the treatment for a patient with a suspected Bartonella infection has to consider many factors, as always, among which maybe the patient's immune status and the bacterium's both intra- and extracellular niches are the most important.

RAT BITE FEVERS

The bites of rodents, and of their predators such as cats and pigs, can transmit numerous diseases including Pasteurella multocida infection, tularaemia, tetanus, leptospirosis, rabies, arenavirus infection and lymphocytic choriomeningitis. Two distinct diseases are known as rat-bite fevers.

Rat-bite fevers are an uncommon systemic febrile illnesses typically transmitted by the bite of wild and laboratory rats or other small rodents (squirrels, gerbils etc.). These infections have a worldwide distribution and may be due to either of two different bacteria: Streptobacillus moniliformis or Spirillum minus which are commonly present in the oropharyngeal flora of rodents. Streptobacillary disease accounts for the vast majority of cases of rat-bite fever in the United States, while Spirillum minor infections occur mainly in Asia.

STREPTOBACILLUS MONILIFORMIS INFECTION

Illness following rat bites has been known in India for over 2000 years and the characteristic syndrome of rat-bite fever was recorded in the United States as early as 1839. The causative gram-negative bacillus, initially named Streptothrix muris rani, was recovered from an infected individual in 1916. In 1925, a blood culture isolate from a laboratory worker with fever, rash, and arthritis was called Streptobacillus moniliformis, based on its morphologic resemblance to a beaded necklace. In 1926, similar organism,

Haverhillia multiformis, was grown from the blood of patients during an epidemic disease resembling rat-bite fever in Haverhill, Massachusetts. Both H. multiformis and Streptothrix muris rani were subsequently shown to be identical to Streptobacillus moniliformis, the causative agent of Streptobacillary rat-bite fever.

ETIOLOGY

The taxonomic position of S. moniliformis (syn.: Actinomyces muris, Actinobacillus muris, Actinobacillus putorii, Streptomyces muris ratti, Haverhillia multiformis and Streptobacillus actinoides) is uncertain. Previously it was related to the actinobacilli. However, it appears to have more in common with the Mycoplasmatales.

The organism has been cultured from patients' bite wounds, blood, synovial and pericardial fluid, and from abscesses.

The organism is best visualized by staining with Romanovsky - Giemsa or Wayson stain. It is a gram-negative highly pleomorphic nonsporing, nonencapsulated bacterium which generally occurs as short coccobacillary forms or rods (0,3-0,7 μm in width and 1-5 μm in long), as well as chains and intertwining wavy filaments up to

150 μm long. The filaments may show spherical, oval or club-shaped gram-variable swellings up to 3 μm in diameter. If multiple, they give rise to a "string of beads" appearance - hence the description "moniliformis". In ageing cultures, filaments show degenerative changes, with the formation of granules and extracellular droplets, irregularity or failure of staining, and fragmentation. In fluid media and in vivo, pleomorphism is less pronounced. The organism is non-motile and non-acid fast.

The electrophoretic profiles of cellular proteins are characteristic and can be used to type strains, "Haverhill-fever" strains being distinguishable from "rat-bite-fever" strains.

Strains are antigenically homogenous, but L-phase variants lack an antigen present in the bacillary form. The species can be identified by fluorescence with a conjugated specific antiserum.

Blood, serum, ascitic fluid, or some other body fluid is required for growth. It may appear to be an obligate anaerobe on primary isolation, but is a facultative anaerobe on subculture. Optimum growth is probably best achieved on chocolate-blood agar or Tryptose Soy Agar, both enriched with 10-20% rabbit or horse serum, defibrinated blood, or ascites and incubated in a microaerophilic atmosphere with additional CO_2 (8-10% for primary isolation) and humidification.

Alternatively, media may be supplemented with a papain digest of ox liver. "Liquoid" (sodium polyanethol sulfonate), a substance sometimes added to trypticase soy broth or thioglycollate broth to inhibit the antibacterial activity of human blood, impedes growth of S. moniliformis in concentrations of at least 0,0125%.The optimal temperature for growth is 35-37°C, optimal pH 7.4-7.6. The choice of a fluid blood-culture medium is critical: it is recommend Brain Heart Infusion Broth with cysteine 0,05% and Panmede 2,5%, but without sodium polyanethol sulphonate - "Liquoid". This could be used in conjunction with a suitable L-phase fluid medium.

The organism is generally unreactive, with negative reactions for catalase, oxidase, indole production, nitrate reduction, and urease. It attacks sugars fermentatively. The end-products of glucose metabolism consist mainly of lactic with some succinic acid (without gas producing). galactose, glycogen, dextrin, raffinose and starch, and variably from fructose, maltose, mannose, salicin, lactose, sucrose, trehalose, and xylose, depending on the basal medium employed. Acid is not formed from sorbitol or mannitol. The alkaline phosphatase reaction is positive. Its pattern of hydrolysis of chromogenic enzyme substrates is characteristic.

It is inhibited or killed by concentrations of "Liquoid", as low as 0,025%. It is killed by a temperature of 55°C in 30 min or less.

The bacillary form is sensitive to penicillin (minimum inhibitory concentration: 0,015 mg/l) and to therapeutically attainable concentrations of cephalosporins, aminoglycosides, tetracycline, erythromycin, and clindamycin; less so to chloramphenicol. The L-phase variant is penicillin resistant, but sensitive to

tetracycline, and presumably to erythromycin.

EPIDEMIOLOGY

Organism is a part of the normal pharyngeal flora of up to 50% of wild and laboratory rats and can be recovered from the nasopharynx, middle ear, saliva, and urine. However, it may give rise to epizootic infection in rodents, characterized by swelling of the extremities, tenosynovitis, polyarthritis, lymphadenitis, cervical lymph-node abscesses, conjunctivitis, otitis media, pneumonia, septicaemia, and abortion.

Streptobacillary rat-bite fever is typically transmitted by the bite or scratch of wild or laboratory rats or mice, guinea-pigs, gerbils, squirrels and turkeys, or carnivores that prey upon these rodents, including cats, dogs, pigs, ferrets, and weasels. In some countries, 10% of those bitten by wild rats will be infected. A rat bite may not be suspected, as many are inflicted while the patient is asleep. Most cases probably occur in individuals (especially children) inhabiting crowded urban dwellings or rural areas infested with wild rats.

The infection may also be acquired by handling dead rats, with no apparent breach of intact skin. Laboratory staffs who work with rodents are also at special risk. Pathophysiologically, percutaneous inoculation probably produces rat-bite fever when local cutaneous defenses fail and bacteria disseminate. There are focal infiltrations of mononuclear cells within tissues invaded by streptobacilli in autopsies.

Oral ingestion of the organisms occurs in outbreaks of another form of rat - bite fever - Haverhill fever (erythema arthriticum epidemicum) and is not attributable to direct contact with animals. Potential sources of such outbreaks include foods such as turkey, raw milk and milk products or water contaminated with rodents excrement. Presumably, once ingested, S. moniliformis organisms gain access to the peripheral circulation by penetrating the gastrointestinal mucosa.

CLINICAL MANIFESTATIONS

After an incubation period of usually less than 10 days and often as little as 1 to 3 days, there is a sudden high fever with chill, vomiting, severe headache, myalgia, and muscle tenderness. The incubation period of S. moniliformis infection is from 2 to 10 days. A brief incubation period usually less than 10 days in duration (range 1-22 days) follows the bite of the rat.

There is abrupt onset of fever, chills, headache, vomiting, and severe migratory arthralgias and myalgias, vomiting and headache. Sore throat, cough and myalgia may also be features.

By that time, the wound itself has usually already healed, but local inflammation and lymphadenopathy occasionally occur. Regional lymphadenopathy is minimal or absent, in contrast to S. minor infection.

Seventy-five per cent of patients develop a rash 1 to 8 days later. Discrete erythematous macules, 1 to 4 mm in diameter, appear symmetrically on the lateral and extensor surfaces and over the joints. They are often most marked on the hands and feet (palms and soles), with associated petechiae, but also occur on the face. Papules, vesicles, and pustules with scabs have also been described. Within 2 to 4 days, a morbilliform or petechial rash appears on the palms, soles, and extremities and half of the patients develop arthritis, commonly involving the knees. Skin lesions may become purpuric or confluent or may eventually desquamate. The rash may occasionally contain small pustules. Diarrhoea and loss of weight are described in young children. Fever and other symptoms subside in a few days in treated cases, but fever may persist for 1 to 2 weeks, or relapse over several months and arthritis for many months in those untreated.

Rush is followed by a secondary rise in temperature and neutrophil leucocytosis accompanied in about two-thirds of cases by polyarthralgia. About half the patients develop an asymmetrical migratory polyarthralgia or arthritis, usually involving the knees, ankles, elbows, shoulders, and hips, and often associated with effusions. Joint pains may be the dominant symptom in patients with rat bite fever. Arthritis is common in S. moniliformis infections.

Occasionally fever may relapse in an irregular pattern for weeks or months, producing a clinical picture of fever of undetermined origin, or arthritis may persist for as long as 2 years. The acute infection may resolve completely or develop into a chronic relapsing disease.

A peripheral leucocytosis of 10000 to 30000 μl is usual and false-positive serological tests for syphilis are found in 15 to 25% of cases.

The liver function tests may be slightly abnormal, and prolonged prothrombin times can be demonstrable. The peripheral white blood cell count may range as high as 30000/mm^3 with leftward shift. Up to 25 % of patients have false-positive serologies for syphilis.

Haverhill fever (erythema arthriticum epidemicum) follows a similar clinical course after the patient has drunk unpasteurized milk or contaminated water. Vomiting, stomatitis, and upper respiratory-tract symptoms such as sore throat are said to be more prominent than in rat bite fever. When the infection has been due to ingestion of the pathogen (Haverhill fever), vomiting and pharyngitis are prominent symptoms.

Complications of S. moniliformis infection include abscesses of any organ. Severe infections can lead to bronchitis, pneumonia, metastatic abscess formation (including cerebral abscess), myocarditis, pericarditis with effusion, subacute glomerulonephritis, interstitial nephritis, splenitis or splenic abscess, amnionitis, and anaemia. Infective endocarditis, usually with underlying rheumatic or other valve disease, has been described. In infants and young children diarrhea and weight loss

may be prominent. Mortality of untreated cases overall ranges as high as 13%, and endocarditis in the preantibiotic era was uniformly lethal. The majority of these intravascular infections involved valves previously damaged by rheumatic valvulitis or calcification.

DIAGNOSIS

Clinically similar conditions such as tularaemia, leptospirosis, rickettsial and various viral infections will have been ruled out by appropriate serological tests. When the rash involves the palms and soles, rat-bite fever may mimic Rocky Mountain spotted fever or secondary syphilis. The presence of oligoarticular or migratory polyarthritis heightens concerns about disseminated gonococcal infection, septic arthritis, infective endocarditis, collagen vascular disease, and acute rheumatic fever. Unlike Spirillum minus infection (sodoku), the incubation period is short, the bite wound heals permanently with little local lymphadenopathy, the rash is morbilliform or petechial, and arthritis is common.

If Streptobacillary fever is suspected, and routine laboratory cultures are negative, the organism may sometimes be isolated by intraperitoneal inoculation of infected material into mice. In patients with infective endocarditis the differential diagnosis of the slow-growing microaerophilic organism will include Haemophilus aphrophilus, Cardiobacterium hominis, Actinomyces actinomycetencomitans, and Eikenella corrodens. A high or rising titer of agglutinins and complement-fixing or fluorescent antibodies may be detected in 2 to 3 weeks.

Alternatively, the diagnosis may be established by serological tests including agglutination, complement fixation and fluorescent-antibody tests. In the agglutination test, in which a formolized suspension of the organism is used, a titer of >80 or a rising titer is considered significant. Diagnosis of S. moniliformis infection is made by demonstration of the organism in blood, joint fluid, or exudate, by staining, and by culture.

Specific agglutinins appear within 2 weeks after the onset of symptoms and reach a maximum titer within 1 to 3 months. Diagnosis depends largely on cultures of pus, joint fluid and blood. S. moniliformis can be fastidious, but in appropriate culture media produces tangled chains of Gram-negative bacteria. Spirillum minus does not grow well in artificial media.

Streptobacillary fever is usually diagnosed by the isolation of Streptobac. moniliformis from blood, joint fluid or pus. If the isolation is unexpected, the organism may not be readily identified. Direct visualization of pleomorphic branching organisms stained by Romanovsky – Giemsa, Wayson, or gram-stained smears of blood, joint fluid, or pus may provide an early clue to the diagnosis.

Recent evidence suggests that fatty acid profiles on gas liquid chromatographs may hold some promise for rapid identification of S. moniliformis isolates. In addition, sodium-dodecyl-sulfate (SDS)-polyacrylamide gel electrophoresis patterns of cellular proteins may be useful for epidemiologic studies of Haverhill fever.

SPIRILLUM MINUS INFECTION (SODOKU)

This is an organism of uncertain classification first described by Carter (1888) in an Indian rat (Mus decu-manus). He referred to it as a 'minute blood-spirillum' and suggested the name ***Spirillum minor***. It was later described by Futaki and his colleagues (1916, 1917) as the cause of rat-bite fever in man. They used the name Spirochaeta morsus muris, but Robertson (1924) pointed out that it is a spirillum, not a spirochaete, and that the grammatically correct form of Carter's name is ***Spirillum minor***. In fact it is unlike other species of ***Spirillum***, which are unusually large saprophytic spiral bacteria, but as no one has been able to culture it satisfactorily in artificial media its true place is unknown. Morphologically it resembles C. jejuni and other 'thermophilic' campylobacters, so this chapter is as good a place as any to describe it. Perhaps the microaerobic culture methods recently developed for campylobacters will improve the chances of culturing Sp. minus.

The movements are rapid, like those of a vibrio. It is readily stained by ordinary aniline dyes, such as Loeffler's methylene blue, and Giemsa.

Spirillum minor is one of the two etiologic agents of rat-bite fever. ***Spirillum minor*** causes a significant portion of the cases of rat-bite fever in Asia, but rarely produces infection in the United States. In Japan, the infection is called sodoku (so: rat; doku: poison).

In the early years of this century, specimens from patients with sodoku were shown to contain spirochetes capable of infecting guinea pigs. These bacteria were initially called Spirocheta morsus muris or Sporozoa muris. The organism was renamed Spirillum minus in 1924 and is currently called Spirillum minor.

ETIOLOGY

Spirillum minor is a gram-negative, spiral organism that stains poorly, and is best demonstrated in blood, exudate, or body fluids by darkfield microscopy. Blood specimens may be stained with Wright's or Giemsa stain. The organism cannot be cultivated on artificial laboratory media.

Spirillum minor is a short, thick, gram-negative, tightly coiled spiral rod. The organism has two to six regular helical turns. Terminal polytrichous flagella confer darting motility, which can be demonstrated with dark-field examination. Spirillum minor cannot be cultured on artificial media.

Spirillum minor was formerly known as ***Spirochaeta*** or ***Spirillum morsus muris*** and ***Spirillum minor***. It may be found in the blood of up to 25 per cent of apparently healthy rodents and in eye discharge mouths of rats with interstitial keratitis and conjunctivitis. S. minus is a relatively thick, tightly coiled, Gram-negative spirillum (not a spirochaete), 2.5 to 5.0 μm long, with two to six (commonly three) spirals, resembling campylobacters. It darts about under the power of its

terminal flagella. Continuous culture on artificial media has not been achieved, but the organism can be demonstrated by inoculating material from the bite wound, regional lymph nodes, or blood intraperitoneally into mice or guinea-pigs. Organisms usually appear in the rodent's blood within 5 to 15 days of inoculation.

EPIDEMIOLOGY

The epidemiology of S. minor infections is similar to that of streptobacillary rat-bite fever, with the exception that oral ingestion has not been shown to cause spirillary disease. Numerous strains of Sp. minus have been isolated from mice, rats and human patients. In Japan about 3% of house rats appear to carry the organism. The spirilla are present in considerable numbers in the muscles of the tongue, which may account for the infectivity of the bite. In the serum of patients who have recovered from rat-bite fever spirochaeticidal bodies have been found.

The major route of transmission is through rat bites. Approximately 25 percent of tested rats are positive for S. minor in conjunctival and nasopharyngeal secretions, pulmonary lesions, and blood. Human-to-human transmission has not been documented.

Sodoku is found worldwide but is particularly common in Japan. It results from bites, scratches or mere contact with rodents or their predators including dogs, cats, and pigs.

PATHOGENESIS

In the human patient the organism is present in the swollen local lesion, the local lymph glands, and the blood, but is very difficult to demonstrate except by animal inoculation; at necropsy it can be found also in the kidneys. Microscopic examination of the blood is usually negative. The Wassermann reaction is said to be positive in about half the cases; and agglutinins to Proteus OXK may be present. The bacteriological diagnosis is best made by subcutaneous or intraperitoneal inoculation of blood taken at the height of a febrile paroxysm, or of serum expressed from the local lesion, into mice and guinea-pigs. Relapses of spirillary rat-bite fever have been postulated to be due to seeding of blood and distant foci during periodic reactivation of the primary bite lesion. The few available recorded autopsies show granulomatous inflammation at the original site of inoculation, with epithelial necrosis and mononuclear infiltration of the dermis. Regional lymph nodes are hyperplastic. Deep tissue specimens from distant areas of skin rash contain dilated blood vessels and round cell infiltrates. Liver, spleen, renal tubules, myocardium, and meninges may be hemorrhagic, with areas of necrosis in liver and kidney.

CLINICAL MANIFESTATIONS

Clinical picture of the spirillar form of rat-bite fever, or sodoku as it is called in

Japan. The incubation period is generally 7-21 days, but may extend to weeks or even months. Illness is ushered in by a acute febrile paroxysm accompanied by swelling of the lymphnodes and dark-red eruptions on the skin. Redness and swelling are noticeable at the site of the wound, which during the incubation period has generally healed satisfactorily. There are often pains in the limbs on the affected side. After 3 or 4 days the attack comes to an end, but is succeeded by another in a few days. These febrile paroxysms with intermittent afebrile periods may be repeated for months, or even years.

The initial bite wound heals promptly but then becomes painful, swollen, and purple approximately 1-4 weeks later, associated with regional lymphangitis and lymphadenitis. This local inflammatory lesion leads to a systemic illness characterized by fever, chills, headache, and malaise. Myalgias and arthritis are rare in this infection, contrasted with streptobacillary rat-bite fever. Severe manifestations including meningitis, cerebral abscess, encephalitis, endocarditis, myocarditis myocardial abscess, pleural effusion, chorioamnionitis, subcutaneous abscesses, and involvement of liver, kidney, and other organs are seen in about 10 per cent of cases. Relapses of fever, rash, and other symptoms lasting 3 to 6 days may occur between remissions of a week or so for 2 to 4 months and occasionally up to a year in untreated patients. Leukocytosis with peripheral white blood cell counts in the range of 10,000-20,000/mm3 may be observed, and up to 50 percent of patients have false-positive syphilis serologies. Next, the bite wound commonly progresses to chancre - like ulceration and induration with eschar formation. During the first week of fever, a blotchy violaceous or reddish - brown macular rash erupts over the extremities, face, scalp, and trunk, and then fades during subsequent afebrile intervals. Occasionally, the rash may be urticarial.

Without specific antibiotic therapy, fevers lasting 3-4 days recur at regular intervals between afebrile periods of 3-9 days. Spontaneous cure usually occurs within 1-2 months, but in some cases fever have relapses for years.

The most serious complication of untreated spirillary rat-bite fever is endocarditis. Most of these rare intravascular infections have been observed in patients with pre-existing valvular disease, but one reported case occurred on a normal aortic valve. The spectrum of reported complications also includes myocarditis, pleural effusions, hepatitis, splenomegaly, meningitis, epididymitis, conjunctivitis, and anemia. Mortality of untreated S. minor infections in the preantibiotic era was 2-10%.

DIAGNOSIS

As acute severe, febrile illness following a rat bite, or other contact with rodents or their predators, should raise the possibility of other rodent related infections such as Pasteurella multocida, which produces local pain and erythema

within a few hours of the bite, plague, tularaemia, leptospirosis, murine typhus and arenaviruses such as lymphocytic choriomeningitis and, in Africa, Lassa viruses. In the cases where rodent contact is unlikely the differential diagnosis is broadened to include other rickettsial diseases such as Rocky Mountain spotted fever, meningococcemia, erythema multiform, and Chlamydial and viral (especially coxsackie) infections. Ingestion of raw milk should also raise the possibility of brucellosis. In the absence of a history of rat bite or typical clinical features, other diagnoses that might enter into the differential diagnosis of relapsing fever would include Borrelia, malaria, and lymphoma. Since S. minor cannot be grown on synthetic media, initial diagnosis relies on direct visualization of characteristic spirochetes in blood, exudate, or lymph node tissue using Romanovsky - Giemsa or Wright's stain or dark-field microscopy. Organisms can also be recovered from mice or guinea pigs 1-3 weeks after intraperitoneal inoculation, with the precaution that the animals must be prescreened to rule out the presence of pre-existing spirochete infections. No specific serologic test is available for S. minor infection.

TREATMENT

Arsphenamine (salvarsan) or neoarsphenamine usually cuts the fever short, but complete cure of the disease is not always easy to obtain. More recent studies, however, suggest that it responds to treatment with penicillin and streptomycin (Hudemann and Mucke 1951, Golstein 1972). Penicillin is the drug of choice but may cause a Jarisch-Herxheimer reaction. Erythromycin, chloramphenicol and cephalosporins can be used in patients who are hypersensitive to penicillin. Rat-bite fever can be prevented by rodent control. The wearing of gloves by laboratory workers when handling rats is to be recommended, as is the use of specific-pathogen-free animals. In the event of a rodent bite, penicillin may be administered prophylactically after cleaning of the wound.

Treatment with parenteral benzylpenicillin is effective against both organisms. A course of 1,2 g 6 TD for 7-10 days is usually sufficient. Streptobacillary endocarditis requires 4-6 week treatment.

Both agents of rat-bite fever, S. moniliformis and S. minor, are sensitive to penicillin. Penicillin G 600,000 units intramuscularly every 12 hours is effective for either form of the disease, and therapy should continue for at least 10-14 days. The Jarisch-Herxheimer reaction may complicate initial therapy of S. minor infections. Oral tetracycline, 2 g/day, or intramuscular streptomycin, 15 mg/kg/day in two divided doses, are effective alternatives for treatment in case of penicillin allergy.

Penicillin-resistant L-variants are susceptible to streptomycin, tetracycline, and probably erythromycin. For patients hypersensitive to penicillin, erythromycin, chloramphenicol, tetracycline or cephalosporins can be used. There is information of successful Erythromycin usage.

Most patients respond promptly to therapy. For individuals who appear well after 5-7 days, therapy can be completed with oral penicillin 2 g/day. Fourteen days of oral penicillin 2 g/day is probably sufficient therapy for patients who present with mild disease.

Patients with endocarditis should be treated with intravenous benzylpenicillin, 4,8 to 14,4 g (8000000-24000000 U) daily for 4 to 6 weeks) by intramuscular injection for 4 weeks if the cultured organism has a sensitivity of 0,1 μg/ml. Addition of streptomycin improves bactericidal activity and eliminates L-forms.

The untreated mortality in Streptobacillus moniliformis infection was 10 to 13 per cent. Mortality in patients with endocarditis has been 53 per cent. Residual arthralgia persisting for as long as 10 years has been described.

PREVENTION

These infections can be prevented by rodent control, by encouraging laboratory workers to wear gloves and use correct techniques when handling rodents. to clean all rodent bite wounds, and to take prophylactic penicillin when bitten. Haverhill fever is prevented by avoiding consumption of raw milk, by monitoring water supplies, especially those not derived from the mains, and by controlling rat populations.

Following a rodent bite, the wound should be thoroughly cleaned, and tetanus prophylaxis should be administered if warranted by the patient's vaccination history. A 3-day course of oral penicillin 2 g/day would seem reasonable, although the prophylactic efficacy of penicillin in this setting is unknown, and the patient should be advised to report subsequent symptoms under any circumstances. Measures to limit the incidence of rat-bite fever include eradication of rats in urban areas, avoidance of nonpasteurized milk and potentially contaminated water, and the use of gloves by laboratory workers when handling rodents.

GLANDERS and MELIOIDOSIS

Glanders is a disease of equines caused by the bacterium ***Burkholderia (Pseudomonas) mallei***, which may be transmitted to human by air-droplet and contact ways. Glanders, a systemic disease that includes acute and chronic forms, involving the respiratory tract, has been distinguished from farcy, a cutaneous infection also caused by B. mallei.

Melioidosis is caused by the closely related species ***Burkholderia pseudomallei*** and ***Burkholderia mallei***, respectively. Whereas melioidosis is a significant cause of morbidity in south-east Asia, glanders is extremely rare.

The disease was first described by Whitemore in Rangoon in 1911. Pathogen of melioidosis is Malleomyces (Burkholderia) pseudomallei is morphologically close to Burkholderia mallei, put have a flagellums and subsequently mobile activity. It is Gram - negative.

Glanders of horses is a disease of antiquity, identifiable in the writings of Aristotle in the fourth century AD. Its communicability to man was recognized in the early nineteenth century. In 1882 the bacteriologists Friedrich Loffler and Wilhelm Schutz in Germany isolated and identified the causal agent, which they named the Bacillus mallei, now designated technically as the Pfeifferella mallei or Malleomyces mallei. In the early part of the twentieth century, equine glanders was present worldwide and was still relatively common in Europe and the United States. Over 200 000 horses were destroyed as a result of glanders during the First World War. However, no naturally acquired case has been reported in the United States or the United Kingdom since 1938, although occasional laboratory-acquired infections have occurred. This remarkable decline has been attributed variously to the compulsory slaughter of infected or seropositive animals, the decreasing use of the horse, and the removal of communal water troughs.

During World War I, Germany had a program of biologic sabotage against several countries, including the United States, whereby cultures of B. mallei and anthrax were distributed to undercover agents who attempted to infect livestock that were to be shipped to Allied countries.

Currently, glanders is still known to occur in parts of the Middle East, Africa, and Asia, although the true incidence is uncertain. Occasional cases have arisen amongst carnivore in non-endemic areas, probably through the ingestion of contaminated imported meat. The most recent such outbreak affected lions in Istanbul Zoo.

ETIOLOGY

B. mallei is an irregularly staining, Gram-negative bacillus that is atypical for a pseudomonad in giving a variable oxidase reaction and being non-motile. It cross-

reacts serologically with B. pseudomallei, and grows readily, although less luxuriantly than B. pseudomallei, on most culture media. Its rarity means that most microbiologists are unfamiliar with its characteristics, and it might easily be overlooked unless sought specifically.

EPIDEMIOLOGY

In solipeds, after infection, the disease usually follows a chronic course with a variable period of incubation, extending from several weeks to several months. Clinical cases in solipeds are manifested by a chronic nasal discharge from one or both nostrils, with or without visible ulceration of the nasal septum; chronic enlargement and hardening of the submaxillary lymph glands without outward discharge of pus; or the presence of pustules and ulcers (farcy buds) on the skin of the hindlegs or other parts of the body. Nonclinical, or latent, cases are essentially pulmonary in type, and the lesions remain in a concealed state (occult) in the lungs as tubercle-like nodules and suppurating foci. In many latent cases, the affected animal shows slight signs of lung trouble (altered breathing). Human glanders, which was rare even when equine glanders was common, most frequently occurs through occupational contact with diseased horses, from making an autopsy on a diseased animal, or from making laboratory cultures of the bacteria. Infection is thought usually to result from contamination of wounds, abrasions, or mucous membranes. The organism is particularly hazardous to laboratory workers, who probably acquire infection by inhalation and this route may also account for some naturally acquired cases. Person to person spread has occurred, so patients require isolation. The role of ingestion in human infections is uncertain. B. mallei is more delicate then B. pseudomallei and is usually considered to be an obligate parasite. It may, however, survive for up to 4 weeks in water, so infection from the inanimate environment is also a possibility.

Host of melioidosis – rodents (rats, mice). Possible role of livestock and domestic animals. Rout of transmission – through defects of skin or alimentary. Susceptibility of human is low, mainly in case of immunodeficiency or massive exposure of pathogen. There is no human – to human transmission.

PATHOGENESIS

Glanders pathogen penetrates in human organism through defected skin and mucous membrane. Bacteria are spread through lymph and blood in organism. Then typical septic process develops with abscess formation primary in lungs, muscles and skin. Suppurative osteomielytis, arthritis and formation of multiple pustules on skin and mucous membrane are typical. In case of chronic course of the disease affection of lungs are rare. Possible findings – pneumosclerosis, bronchoectasis and chronic abscesses.

CLINICAL MANIFESTATIONS

Incubation period on average is 4-5 days. The manifestations of glanders are similar to those of melioidosis. A spectrum of presentations is seen, ranging from occult infections, which are probably under-reported, to overwhelming sepsis resulting in severe toxaemia and widespread abscesses, culminating in delirium, shock, and death. Untreated, glanders may be fatal within days or may persist for many years with remissions and relapses. Onset is acute, with chill, myalgia, headache and increase of temperature up to 38-39ºC. Swelling of joints appears followed by papule with erysipelas-like erythema, then pustule with bloody content and subsequent transformation to ulcer. Regional lymphadenitis is typical. In 5-7 days after temporary decreasing of temperature there are second wave of intoxication and formation of secondary papules and nodes that transform in pustules and ulcers. Muscle abscesses are typical with suppuration from fistulas. There is tachycardia, hypotonia. From the respiratory tract typical complaints for dyspnea, discharge of purulent or bloody sputum, pain in chest. On auscultation moist reils are heard. X-ray examination shows focuses of specific pneumonia. In blood analysis neutrophil leucosytosis and ESR increasing are typical. Duration of acute form of glanders is 7-14 days. Mortality in pre antibiotic era was more than 90%.

Chronic form of glanders can persist for several years. More often is skin form. Typical symptoms are pustules, transforming to ulcers, lymphadenitis and multiple muscle abscesses with suppuration and further granulations, mainly in sural muscles. Multiple relapses are typical for chronic course of glanders.

Incubation period of melioidosis is from 4-10 days to several months. Acute form characterized with rapid onset, temperature 38-39ºC, myalgia, intensive headache, vomiting, abdominal pain, diarrhea, pleural pain. Often is cough with suppurative sputum, tachycardia, hypotonia, altered pulse. On X-ray examination pneumonic focuses are quite often. Liver and spleen are enlarged. In blood analysis - significant leucosytosis, increase of ESR. Toxic chock are often. If patients survive acute phase, multiple abscesses develops in lungs, kidneys, lever and other organs.

For chronic melioidosis it is typical formation of abscesses in one or several organs. Intoxication is not highly expressed. In case of accompanied diseases or immunodeficiency process can transform to septicemia with lethal outcome.

DIAGNOSIS

As with melioidosis, the clinical manifestations of glanders are rarely pathognomonic. The diagnosis thus hinges on an appropriate history is in an endemic area or laboratory exposure, and on isolation and identification of B. mallei from an appropriate clinical material. Serologic reactions – RA, RIA are used.

TREATMENT

As most human infections occurred in the pre-antibiotic era, data about treatment are scarce. There are few data regarding the antibiotic treatment of glanders, since the disease had largely disappeared by the time antibiotics became available. In vitro, ceftazidime, gentamicin, imipenem, doxycycline, and ciprofloxacin all have reliable activity against B. Mallei. There are reports on good response of infection to a combination of imipenem and doxycycline. Experimentally induced glanders also responds to a combination of sulfazine and trimethoprim. Treatment should be continued for at least 3 weeks and probably longer, depending on the patient's response. Long-term follow-up to detect relapse should be arranged. However, treatment of the disease in the setting of bioterrorism may be more difficult if the organism is drug-resistant. Treatment of melioidosis is similar to glanders

PREVENTION

There is no effective vaccine for either human or animal use, and prevention in those countries where glanders persists will depend on veterinary public-health measures.

FOOT AND MOUTH DISEASE

Foot and mouth disease (FMD) – is an acute viral disease, transmitted from animals to human with cyclic course and formation of vesicles and erosions on mucous of oral cavity and interfinger skin.

FMD in human was first described in 1764. Currently, FMD is still known to occur in Iran, Turkey and Afghanistan, although the true incidence is uncertain. There are several publications on incidents of FMD in European countries. Since January 2000, FMD has been reported in 28 countries, some of which have been free of the disease for decades. They include Argentina, Brazil, Cambodia, China, Russia, United Kingdom, est. The strain of the virus responsible for outbreak – the type O pan – Asia strain – first appeared in India in 1990 and spread both east and west.

ETIOLOGY

Pathogen is RNA – containing virus, family Picornaviridae, genus Aphtovirus. There is seven main types of virus: O, A, C, SAT.1, SAT2, SAT3 and Asia. Within each type there are several subtypes. Immunity is short lived and protects only against infection with the same type or closely related subtypes. It is stable in environment. The virus can survive in milk 25-30 hrs, on hair of animals – up to 4 weeks, in sausages – for 50 days. Fast inactivated when pH less 6,0 or more then 10.

EPIDEMIOLOGY

Host of infection are horned cattle, pigs, ships and goats. They contain virus in aftas and blood and discharge with saliva, milk, urine and dung. Discharge of virus with saliva and milk begins in incubation period and lasts usually for 10-12 day of disease. Routs of transmission are alimentary, through milk or during contact with animals. Aerogenic transmission is also possible. Susceptibility of human to FMD is not high.

PATHOGENESIS

Primary multiplication takes place in epithelial cells of mucosa or epidermal plicas of skin on place of inoculation with subsequent formation of specific vesicle. Then virus penetrates into bloodstream. Dissemination of virus is connected with formation of secondary afta on mucous layer of nose, mouth and conjunctivas. The virus concentrates in dermal capillaries that lead to formation of afta in intra finger spaces of palm and feet. General intoxication is also typical.

CLINICAL MANIFESTATIONS

Incubation period is from 2-5 to 7-10 days. Onset is acute with chill, high temperature, headache, myalgia, waist pain and loss of appetite. In 1-2 days dryness

and burning in mouth appear, in some patients urethral pain and photophobia. On mucous of mouth, lips, throat on expressed hyperemic base small vesicles appear. In 1-2 days they break with formation of afts of bright red color. Lymph nodes enlargement can be observed on examination. Swallowing is difficult, hyper salivation appears, tongue is edematous, and speech is rambling. Vesicles on skin also can be seen, most typically on intra finger spaces of palms and feet with painful inch and subsequent falling out of nails. Afts disappear after 3-5 days, together with fever and other symptoms. Convalescence period is for 10-15 days. In some cases diarrhea and vomiting are reported. During epizootics mild forms with poor symptoms are possible. In blood analysis there are leucopoenia and eosinophilia. Complications connected with secondary infections and include pneumonia, sepsis, and myocarditis.

DIAGNOSIS

Diagnosis are grounded on typical clinical manifestations and serologic tests, such us reaction of compliment fixation, biological test on guinea-pig is also used.

TREATMENT

Hospitalization of patient is necessary. There is no specific treatment. Local procedures - wetting of mucous of mouth with 3% hydrogen peroxide, 0,1% permanganate, 2% boric acid.

TOXOPLASMOSIS

Toxoplasmosis is infection caused by ***Toxoplasma gondii***, an obligate intracellular parasite. The infection produces a wide range of clinical syndromes in human.

ETIOLOGY

T gondii has been recovered from locations throughout the world, except Antarctica. Nicolle and Manceaux first described the organism in 1908 after they observed the parasites in the blood, spleen, and liver of a North African rodent, Ctenodactylus gondii. The parasite was named Toxoplasma (arclike form) gondii (after the rodent) in 1909. In 1923, Janku reported parasitic cysts in the retina of an infant who had hydrocephalus, seizures, and unilateral microphthalmia. Wolf, Cowan, and Paige (1937-1939) determined that these findings represented the syndrome of severe congenital T gondii infection.

T gondii has 2 distinct life cycles. The sexual cycle occurs only in cats, the definitive host. The asexual cycle occurs in other mammals (including humans) and various strains of birds. It consists of 2 forms, known as tachyzoites (the rapidly dividing form observed in the acute phase of infection) and bradyzoites (the slowly growing form observed in tissue cysts).

The sexual cycle begins in the gastrointestinal tract of the cat. Macrogametocytes and microgametocytes develop from ingested bradyzoites and fuse to form zygotes. The zygotes then become encapsulated within a rigid wall and are shed as oocysts. The zygote sporulates and divides to form sporozoites within the oocyst. Sporozoites become infectious 24 hours or more after the cat sheds the oocyst via feces. During a primary infection, the cat can excrete millions of oocysts daily for 1-3 weeks. The oocysts are very strong and may remain infectious for more than one year in warm humid environments.

EPIDEMIOLOGY

Transmission in acquired toxoplasmosis occurs mainly after the ingestion of cysts. Infection is in four stages: acute, subacute, chronic, and relapses. Organisms spread from the gut by lymphatics and the bloodstream throughout the body, reaching every organ, where they multiply intracellularly (acute stage). Termination of this stage depends upon the development of both cell-mediated and humoral immunity. Whenever the host is immunocompetent, the parasite encysts and will persist in host tissues without any inflammatory process as long as the cyst is not disrupted (chronic stage). If the host is or becomes immuno-compromised, there is a tendency for the cysts to release bradyzoites and Toxoplasma becomes an opportunistic infective agent. Among immunodeficient individuals, toxoplasmosis most often occurs in those

with defects of T-cell–mediated immunity, such as those with hematologic malignancies, bone marrow and solid organ transplants, or AIDS.

Congenital infection occurs transplacentally by transmission of tachyzoites when a previously uninfected woman acquires the infection during pregnancy.

T gondii oocysts, tachyzoites, and bradyzoites can cause infection in humans. Infection can occur by ingestion of oocysts following the handling of contaminated soil or cat litter or the consumption of contaminated water or food sources (e.g., unwashed garden vegetables). Transmission of tachyzoites to the fetus can occur via the placenta following primary maternal infection. Rarely, infection by tachyzoites occurs from ingestion of unpasteurized milk or by direct entry into the bloodstream through a blood transfusion or laboratory accident. Transmission can occur via ingestion of tissue cysts (bradyzoites) in undercooked or uncooked meat or through transplantation of an organ that contains tissue cysts. In Europe pork is the major source of T gondii infection in humans.

PATHOGENESIS

The ability of T gondii to actively penetrate host cells results in formation of a parasitophorous vacuole that is derived from the plasma membrane, which is entirely distinct from a normal phagocytic or endocytic compartment. Following apical attachment, the parasite rapidly enters the host cell in a process that is significantly faster than phagocytosis. The vacuole is formed primarily by invagination of the host cell plasma membrane, which is pulled over the parasite through the concerted action of the actin-myosin cytoskeleton of the parasite. During invasion, the host cell is essentially passive and no change is detected in membrane ruffling, the actin cytoskeleton, or phosphorylation of host cell proteins.

Tachyzoites proliferate, producing necrotic foci surrounded by a cellular reaction. Upon the development of a normal immune response, tachyzoites disappear from tissues. In immunodeficient individuals and in some apparently immunologically healthy patients, the acute infection progresses, resulting in potentially lethal consequences such as pneumonitis, myocarditis, and necrotizing encephalitis.

Tissue cysts form as early as 7 days after infection and remain for the lifespan of the host. The tissue cysts are up to 60 μm in diameter, each containing up to 60,000 organisms. They produce little or no inflammatory response but cause recrudescent disease in immunocompromised patients or chorioretinitis in congenitally infected older children.

When a mother is infected with T gondii during gestation, the parasite may be disseminated hematogenously to the placenta. When this occurs, infection may be transmitted to the fetus transplacentally or during vaginal delivery. If the mother acquires the infection in the first trimester and it goes untreated, the risk of infection

to the fetus is approximately 14-17%, and toxoplasmosis in the infant is usually severe. If the mother is infected in the third trimester and it goes untreated, the risk of fetal infection is approximately 59-65%, and involvement is mild or inapparent at birth. These different rates of transmission are most likely related to placental blood flow, the virulence and amount of T gondii acquired, and the immunologic ability of the mother to restrict parasitemia.

The most significant manifestation of toxoplasmosis in the fetus is encephalomyelitis, which may have severe results. Approximately 10% of prenatal T gondii infections result in abortion or neonatal death. In approximately 67-80% of prenatally infected infants, the infection is subclinical and can be diagnosed using only serological and other laboratory methods. Although these infants appear healthy at birth, they may develop clinical symptoms and deficiencies later in life.

Circulating immune complexes have been detected in sera from an infant with congenital toxoplasmosis and in older individuals with systemic, febrile, and lymphadenopathic forms of toxoplasmosis. However, these complexes did not persist after signs and symptoms resolved.

Alterations in subpopulations of T lymphocytes are profound and prolonged during acute acquired T gondii infection. These have been correlated with disease syndromes but not with disease outcome. Some patients with prolonged fever and malaise have lymphocytosis, increased suppressor T-cell counts, and a decreased helper-to-suppressor T-cell ratio. These patients may have fewer helper cells even when they are asymptomatic. In some patients with lymphadenopathy, helper cell counts are diminished for more than 6 months after infection onset. Ratios of T-cell subpopulations may also be abnormal in asymptomatic patients. Some patients with disseminated toxoplasmosis have a very marked reduction in T cells and a marked depression in the ratio of helper to suppressor T lymphocytes. Depletion of inducer T-lymphocytes in patients with AIDS may contribute to the severe manifestations of toxoplasmosis observed in these patients.

CLINICAL MANIFESTATIONS

Approximately 80-90% of immunocompetent patients with acute toxoplasmosis are asymptomatic. Some patients may have cervical lymphadenopathy with discrete, usually nontender, nodes smaller than 3 cm in diameter. Fever, malaise, night sweats, and myalgias have also been reported.

Patients may have symptoms of moderate pharyngitis. Retroperitoneal and mesenteric lymphadenopathy with abdominal pain may occur. Affection of an eye, as chorioretinitis is reported.

Clinical manifestations of toxoplasmosis in patients with AIDS often includes brain involvement (toxoplasmic encephalitis), with or without focal CNS lesions. Clinical findings include an altered mental state, seizures, weakness, cranial nerve

disturbances, sensory abnormalities, cerebellar signs, meningismus, movement disorders, and neuropsychiatric manifestations. The typical presentation is usually a subacute onset, with focal neurologic abnormalities in 58-89% of cases. However, in 15-25% of cases, the clinical presentation is more abrupt, with seizures or cerebral hemorrhage. Most commonly, hemiparesis and/or speech abnormality is the major initial manifestation. Brain stem involvement often produces cranial nerve lesions, and many patients exhibit cerebral dysfunction with disorientation, altered mental state, lethargy, and coma.

Less commonly, parkinsonism, focal dystonia, rubral tremor, hemichorea-hemiballismus, panhypopituitarism, diabetes insipidus, or syndrome of inappropriate antidiuretic hormone secretion may dominate the clinical picture. In some patients, neuropsychiatric symptoms such as paranoid psychosis, dementia, anxiety, and agitation may be the major manifestations.

Diffuse toxoplasmic encephalitis may develop acutely and can be rapidly fatal; generalized cerebral dysfunction without focal signs is the most common manifestation, and CT scan findings are normal or reveal cerebral atrophy.

Spinal cord involvement manifests as motor or sensory disturbances of single or multiple limbs, bladder or bowel dysfunctions, or both and local pain. Patients may present with clinical findings similar to those of a spinal cord tumor.

Cervical myelopathy, thoracic myelopathy, and conus medullaris syndrome have been reported.

Pulmonary toxoplasmosis (pneumonitis) due to toxoplasmosis is increasingly recognized in patients with AIDS who are not receiving appropriate anti-HIV drugs or primary prophylaxis for toxoplasmosis. The diagnosis may be confirmed by demonstrating T gondii in bronchoalveolar lavage (BAL) fluid.

Pulmonary toxoplasmosis mainly occurs in patients with advanced AIDS (mean CD4+ count of 40 cells/µL ±75 standard deviation) and primarily manifests as a prolonged febrile illness with cough and dyspnea. Symptoms of pulmonary toxoplasmosis may be clinically indistinguishable from Pneumocystis carinii pneumonia, and the mortality rate, even when treated appropriately, may be as high as 35%. Extrapulmonary toxoplasmosis develops in approximately 54% of persons with toxoplasmic pneumonitis.

Ocular toxoplasmosis, for example toxoplasmic chorioretinitis, is relatively uncommon in patients with AIDS; it commonly manifests as ocular pain and loss of visual acuity. Funduscopic examination usually demonstrates necrotizing lesions that may be multifocal or bilateral. Overlying vitreal inflammation is often present and may be extensive. The optic nerve is involved in as many as 10% of cases.

Invasion of T. gondii in gastrointestinal system may result in abdominal pain, diarrhea, and/or ascites due to involvement of the stomach, peritoneum, or pancreas. Acute hepatic failure due to toxoplasmosis has been reported, as has musculoskeletal

involvement.

DIAGNOSIS

The diagnosis of toxoplasmosis is confirmed with the demonstration of T. gondii organisms in blood, body fluids, or tissue. Isolation of T gondii from amniotic fluid is diagnostic of congenital infection by mouse inoculation. Lymphocyte transformation to T gondii antigens is an indicator of previous toxoplasmosis in adults.

Detection of T gondii antigen in blood or body fluids via ELISA technique indicates acute infection.

The Sabin-Feldman dye test is a sensitive and specific neutralization test for toxoplasmosis. It is used to measure primarily IgG antibody and is the standard reference test for toxoplasmosis. However, it requires live T gondii organisms; therefore, it is not available in most laboratories. High titers suggest acute toxoplasmosis.

The indirect fluorescent antibody test is used to measure the same antibodies as the dye test. Titers parallel dye test titers. The IgM fluorescent antibody test is used to detect IgM antibodies within the first week of infection, but titers fall within a few months.

The indirect hemagglutination test is easy to perform. However, it usually does not detect antibodies during the acute phase of toxoplasmosis. Titers tend to be higher and remain elevated longer.

The results from a double-sandwich IgM ELISA are more sensitive and specific than the results from other IgM tests. The results of the IgG avidity test may help differentiate those with acute infection from those with chronic infections better than alternative assays, such as assays that measure IgM antibodies. As is true for IgM antibody tests, the avidity test is most useful when performed early in gestation because a long-term pattern occurring late in pregnancy does not exclude the possibility that the acute infection may have occurred during the first months of gestation.

Polymerase chain reaction on body fluids, including CSF, amniotic fluid, BAL fluid, and blood, may be useful in the diagnosis.

Imaging Studies includes head CT scanning in cerebral toxoplasmosis. In most immunodeficient patients with toxoplasmic encephalitis, CT scans show multiple bilateral cerebral lesions in 70-80% of cases. Although multiple lesions are more common in persons with toxoplasmosis, they may be solitary; a single lesion should not exclude toxoplasmic encephalitis as a diagnostic possibility. MRI has superior sensitivity (particularly if gadolinium is used for contrast) to CT scanning, and MRIs often demonstrate a single or multiple lesions or more extensive disease not apparent on CT scans. Various positron emission tomography scanning, radionuclide scanning, and magnetic resonance techniques have been used to evaluate patients with AIDS

who have focal CNS lesions and to specifically differentiate between toxoplasmosis and primary CNS lymphoma.

Ultrasonographic diagnosis of congenital toxoplasmosis in a fetus is available at 20-24 weeks' gestation.

Skin tests that show delayed skin hypersensitivity to T gondii antigens may be useful as a screening test.

Antibody levels in aqueous humor or CSF may reflect local antibody production and infection at these sites.

Perform amniocentesis at 20-24 weeks' gestation if congenital disease is suggested.

TREATMENT

Outpatient care is sufficient for acquired toxoplasmosis in immunocompetent hosts and in persons with ocular toxoplasmosis. Inpatient care is appropriate initially for persons with CNS toxoplasmosis and for acute toxoplasmosis in immunocompromised hosts. Treatment is usually unnecessary in asymptomatic hosts, except in children younger than 5 years.

Currently recommended drugs in the treatment of toxoplasmosis act primarily against the tachyzoites form of T gondii; thus, they do not eradicate the encysted form (bradyzoite). Pyrimethamine is the most effective agent and is included in most drug regimens. Leucovorin (folinic acid) should be administered concomitantly to prevent bone marrow suppression. Unless circumstances preclude using more than one drug, a second drug (sulfadiazine, clindamycin) should be added. The efficacy of azithromycin, clarithromycin, atovaquone, dapsone, and cotrimoxazole is unclear; therefore, they should be used only as alternatives in combination with pyrimethamine. The most effective available therapeutic combination is pyrimethamine together with sulfadiazine or trisulfapyrimidines (combination of sulfamerazine, sulfamethazine, and sulfapyrazine). These agents are active against tachyzoites and are synergistic when used in combination.

Careful attention to dosing regimen is necessary because it differs depending on patient variables (immune status, pregnancy). Pyrimethamine may be used with sulfonamides, quinine, and other antimalarials and with other antibiotics.

Microorganisms that require exogenous folic acid and do not synthesize folic acid (pteroylglutamic acid) are not susceptible to the action of sulfonamides. Resistant strains are capable of using folic acid precursors or preformed folic acid. Sulfonamide antimicrobials exist as 3 forms in serum - free, conjugated (acetylated and possibly others), and protein-bound. The free form is considered therapeutically active. Sulfadiazine (Microsulfon) tablets 500 mg, can be used in daily dose 2-4 g PO. Dapsone (Avlosulfon) in tablets 25mg - 100mg can be used 50 mg PO qDay, with upward titration to 300 mg qDay. Reduce dosage as soon as possible to minimum maintenance level (25-400 mg/day).

Antiprotozoal agents are also used for the treatment. Pyrimethamine (Daraprim) in tablets 25mg in case of toxoplasmosis prescribed 50-75 mg qD PO for 1-3 weeks, then 25-37.5 mg qD PO for 4-5 weeks. Atovaquone (Mepron) in tablets 250mg for oral suspension 750mg/5mL is used in dose 750 mg PO BID x21 days. Macrolide antimicrobials, as Spiramycin and Azithromycin (Zithromax) also can be used in complex treatment.

Management of Toxoplasmosis in HIV-Infected patients includes empiric anti-T gondii therapy was deemed appropriate for all T gondii-seropositive, HIV-infected patients with focal brain lesions. Improvement on therapy constituted empiric evidence of toxoplasmosis, and brain biopsy was reserved for those who did not improve clinically. Because toxoplasmic encephalitis was the most common cause of focal brain lesions in AIDS patients, many unnecessary brain biopsies were avoided by this approach. However, the incidence of toxoplasmic encephalitis in patients with AIDS has decreased in recent years owing to the use of primary anti-T gondii prophylaxis and effective ART. In contrast, the frequency of CNS lymphoma has increased in patients with focal brain lesions. Therefore, empiric anti-T gondii therapy for all patients with focal brain lesion without an aggressive diagnostic work up may delay initiation of appropriate therapy and expose patients to potentially unnecessary and toxic regimens.

Corticosteroids can be administered to patients with toxoplasmic encephalitis with cerebral edema and intracranial hypertension. Duration of corticosteroid administration should be as short as possible (preferably no more than 2 weeks). The outcome of empiric regimens that include steroids should be interpreted with caution; improvement may be caused exclusively by reduction of inflammation or by response of CNS lymphoma to corticosteroid treatment.

Treatment of AIDS-associated toxoplasmic encephalitis is divided into acute and maintenance therapy. Acute therapy should be administered for no less than 3 weeks, and preferably for 6 weeks if tolerated. More prolonged acute therapy may be required in patients with severe illness who have not achieved a complete response. Thereafter, maintenance therapy is continued to avoid relapse. The improvement in immune function achieved by antiretroviral agents supports their prompt initiation in patients with toxoplasmic encephalitis. Currently, there is no definitive evidence that immune reconstitution inflammatory syndrome occurs in patients with toxoplasmic encephalitis started on antiretroviral therapy. Pyrimethamine is considered the cornerstone in the treatment of toxoplasmosis. The combination of pyrimethamine (a dihydrofolate reductase inhibitor) plus sulfadiazine (a dihydrofolate synthase inhibitor) is the standard regimen for treatment of toxoplasmic encephalitis (Table 1). This regimen exhibits synergistic activity against T gondii because it causes a sequential blockade in the pathway of folic acid synthesis. Sulfonamides other than sulfadiazine and trisulfapyrimidines (not available in the United States) are less

effective against T gondii. Patients receiving pyrimethamine should also be given folinic acid to prevent hematologic adverse effects. The recommended dose of folinic acid is 10-20 mg orally per day. Higher doses may be necessary in patients with persistent bone marrow suppression.

An initial response to pyrimethamine plus sulfadiazine is noted in 65-90% of patients. Unfortunately, adverse effects (primarily rash) may lead to discontinuation of this regimen in up to 40% of patients. Continuation of therapy and administration of antihistamines may be considered in patients with non-life-threatening dermatologic reactions. Sulfadiazine can also cause crystal-induced nephrotoxicity.

The combination of pyrimethamine plus clindamycin is as effective as pyrimethamine plus sulfadiazine during the acute phase of therapy. Rash and diarrhea are common adverse effects of pyrimethamine plus clindamycin. A randomized, prospective study reported that trimethoprim-sulfamethoxazole is as effective as pyrimethamine plus sulfadiazine for the treatment of toxoplasmic encephalitis.

Alternative regimens are needed for patients intolerant to sulfonamides and clindamycin. A number of agents exhibit anti-T gondii activity in vitro or in animal models, as well as in case reports. Additional studies are required before these agents can be recommended for routine use in patients with toxoplasmic encephalitis. These agents should be used in combination with pyrimethamine.

It appears that atovaquone oral suspension in combination with either pyrimethamine or sulfadiazine is an effective alternative for treatment of toxoplasmic encephalitis. These regimens resulted in a 77% clinical and radiologic response rate at 6 weeks, and a 5% rate of relapse during maintenance therapy.

Azithromycin and clarithromycin are effective either in vitro or in animal models of toxoplasmosis. A small study of toxoplasmic encephalitis in patients with AIDS reported that clarithromycin plus pyrimethamine resulted in clinical and radiologic response rates of 80% and 50%, respectively. A phase I/II study of azithromycin in combination with pyrimethamine reported a 67% response rate during the acute phase of therapy. Unfortunately, this regimen was associated with a 47% relapse rate. Although there are limited data, it appears that AIDS patients with extracerebral toxoplasmosis respond to pyrimethamine plus either sulfadiazine or clindamycin. The mortality rate in patients with pulmonary or disseminated toxoplasmosis may be higher than in patients with toxoplasmic encephalitis alone.

Current anti-T gondii regimens do not eradicate tissue cysts. This is likely to explain why, in the absence of effective ART, 50-80% of patients with AIDS who did not receive maintenance therapy experienced relapse of toxoplasmic encephalitis at 12 months. Patients with AIDS-associated toxoplasmosis should therefore be placed on a maintenance regimen upon completion of the acute phase of treatment. Maintenance therapy typically consists of the same drugs used for primary therapy but at lower dosages.

A prospective randomized study showed no significant differences in clinical outcomes of patients treated with maintenance therapy consisting of pyrimethamine plus sulfadiazine versus pyrimethamine plus clindamycin. However, another study reported a higher rate of relapse in patients receiving maintenance therapy with pyrimethamine plus clindamycin. Of note, patients in the latter study received a low dose of clindamycin (1,200 mg/day). Pyrimethamine plus sulfadiazine (but not pyrimethamine plus clindamycin) also provides prophylaxis against Pneumocystis pneumonia.

Pyrimethamine plus sulfadoxine has been reported to be effective as maintenance therapy. Unfortunately, adverse effects are relatively common. Alternatives for patients who do not tolerate conventional regimens include pyrimethamine alone, or pyrimethamine plus either atovaquone, clarithromycin, or azithromycin.

PREVENTION

Prevention of congenital toxoplasmosis includes serological screening of pregnant women, recommendations for prophylaxis, and serological follow-up for those who proved seronegative. The risk of fetopathy is reduced by a half by spiramycin. The recognition of fetopathy by intrauterine diagnosis and serial ultrasonography either allows elective termination or is a guide to the efficacy of treatment in utero.

T gondii-seronegative, HIV-infected persons should be instructed about measures to prevent acquisition of T gondii infection. These individuals should eat meat only if it is well cooked (internal temperature of 116°C, or no longer pink inside), and should wash their hands after touching undercooked meat. Fruits and vegetables should be washed prior to consumption. Patients should avoid contact with materials that may be contaminated with cat feces; handling cat litter boxes should be avoided, and gloves should be worn during gardening. Cat feces should be disposed of daily to avoid maturation of oocysts, and litter box can be cleaned by exposure to boiling water for 5 minutes.

Primary prophylaxis against toxoplasmosis is recommended in T gondii-seropositive patients with CD4 T-cell counts <100/μL regardless of clinical status, and in patients with CD4 T-cell counts <200/μL if an opportunistic infection or malignancy develops. Trimethoprim-sulfamethoxazole, pyrimethamine-dapsone, and pyrimethamine-sulfadoxine are effective in the prevention of toxoplasmic encephalitis in HIV-infected patients.

ABBREVIATION

AIDS	Acquired Immune Deficiency Syndrome
APC	Activated protein C
APTT	activated partial thromboplastin time
CNS	Central nervous system
CRP	C-reactive protein
CSD	Cat scratch disease
CSF	Cerebrospinal fluid
CSf	Colony - stimulating factor
CT	Computed Tomography
CVP	central venous pressure
DIC	Disseminated coagulopathy
DOC	Drug of choice
ELISA	enzyme-linked immunosorbent assay
EM	erythema migrans
ERIG	Equine rabies immunoglobulin
ESR	Erythrocyte sedimentation reaction
FMD	Foot and mouth disease
GABA	Gamma-aminobutyric acid
HDCV	Human diploid cell vaccine
HGA	Human granulocytic anaplasmosis
HIV	Human immunodeficiency virus
HLA	human leucocyte antigen
HME	Human monocytic ehrlichiosis
HRIG	Human rabies immunoglobulin
IL	interleukin
IPPV	Intermittent positive pressure Ventilation
LPS	Lipopolysaccharide
LPS	lipopolysaccharide
MRI	Magnetic resonance imaging
MRSA	methicillin-resistant Staphylococcus aureus
NGT	Nasogastric tube
PCR	polymerase chain reaction
PMN	Polymorphonuclear leukocytes
SDS	Sodium-dodecyl-sulfate
SIRS	systemic inflammatory response syndrome
SIRS	systemic inflammatory response syndrome
SPECT	Single photon emission computed tomography
TAT	Tetanus antitoxin
TBE	Tick-borne encephalitis
TIG	Tetanus immune globulin
TMP-SMZ	trimethoprim-sulfamethoxazole
TNF	Tumor necrosis factor
VIG	vaccinia immune globulin

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