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Master's Thesis

ETIOLOGY OF PLAGUE

AND TRANSMISSIOM CAUSE BY YERSINIA PESTIS

223 Nursing

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CONTENTS

ABSTRACT

Yersinia pestis is a facultative anaerobic gram negative rod-shaped bacterium. It is known to be an agent for the plague, an acute infectious zoonotic disease which is particularly dangerous for humans and some animals, mainly rodents, from which the infection is transferred to humans via fleas. This disease is characterized by lesion of the mucous membranes, skin, lymph nodes, lungs, and sepsis. There are several clinical forms of the plague: a) cutaneous, bubonic, skin-bubonic; b) primary septic, secondary septic; and c) primary pneumonic, secondary pneumonic. The bubonic plague is occurred very often (70-80%), less septic (15-20%), and pneumonic (5-10%) forms of the plague. All these forms were responsible for huge mortality during the epidemics throughout the world.

The world history shows three worst pandemics of plague. It is believed that each biovar of *Yersinia pestis* (*Antiqua, Medievalis, Orientalis*) is responsible for each of the historic pandemics of plague. Plague belongs to natural and indirect zoonotic infections. The sources of infection are wild rodents and lagomorphs, the location of which may be latent foci of infection. The mechanism of transmission of disease is diverse, often transmissible but airborne way of distribution is also possible (in case of pneumonic plague).

As plague refers to the particularly dangerous infections, the laboratory studies of pathological material are very important and conducted in several stages in order to differentiate it from other diseases. The treatment of the plague depends upon the form of the disease.

INTRODUCTION

For many centuries the plague that was called “Black Death” has caused a huge amount of deaths throughout the world. It brought more fear that any other infectious disease known in the human history. Despite the fact that the plague was studied for many years and it is already known a lot about the pathogenesis and treatment of plague, this very dangerous disease is still exist in the 21st century. The causative agent of plague, *Yersinia pestis*, is a facultative anaerobic gram-negative rod-shaped bacterium. The genetic studies revealed that the genome of this pathogen consists of one circular chromosome and three plasmids. These plasmids play very important role in the pathogenesis of disease as they carry genes that encode specific proteins which are essential for the virulence of *Yersinia pestis*. Even though the plague is an acute zoonotic disease that remains dangerous for people and some animals, the laboratory diagnostics and possible treatment are now available in different countries.

CHAPTER 1. GENERAL CHARACTERISTIC of YERSINIA PESTIS. EPIDEMIOLOGY, TRANSMISSION and PATHOGENESIS of DISEASE

The causative agent of plague belongs to the family *Enterobacteriaceae*, the genus Yersinia, the type of *Yersinia pestis*. First swine pathogen was opened and described in 1894 by Alexandre Yersin and the Japanese bacteriologist Shibasaburo Kitasato during the plague in Hong Kong. Bacteria that cause plague repeatedly changed its taxonomic nomenclature.

Yersinia pestis is facultative anaerobic, non-motile, gram-negative, oval rods with a characteristic bipolar coloring, its length is 0.7-1.5 and width is 0.3-0.5 mm. Spores do not form, but delicate capsule is formed. A characteristic feature is polymorphism. The bacteria can grow on the ordinary nutrient media at the optimal temperature of 28 °C. Growth at selective media is characterized by formation of white loose sediment and gentle film with threads as stalactites. On solid media colonies are characterized as follows: compacted center surrounded by jagged edge that looks like a lace. *Yersinia* has a saccharolytic activity and fermented a number of carbohydrates, such as glucose, galactose, arabinose, xylose, mannitol to acid; indole is not formed, do not thin a gelatin (Clayton O. Jarrett, 2004).

The complete genome sequence of *Yersinia pestis* strain CO92 contains a single circular chromosome of 4.65 megabase (Mb) chromosome and three plasmids of 96.2 kilobases (kb), 70.3 kb, and 9.6 kb, respectively. The average G+C content is 47.64%. *Yersinia pestis* is a pathogen that has undergone significant genetic change and provides a unique understanding the ways in which new and highly infectious pathogens evolve. *Yersinia pestis* is very closely related to the gastrointestinal pathogen (*Yersinia pseudotuberculosis*), and it has been

suggested that *Yersinia pestis* is a duplicate that evolved from *Y. pseudotuberculosis* serotype O:1b. *Yersinia pestis* seems to have rapidly adapted from being a mammalian enteropathogen found in the environment to a blood-borne pathogen of mammals. The genome of *Yersinia pestis* is fluid, and is capable of frequent change in its gene. Biovar *Orientalis* was the beginning of new ribotypes of *Yersinia pestis* in the environment following pandemic spreads shows that chromosomal changes are common in the environment. The gene achievement has been important in the evolution of *Yersinia pestis*. In addition to the 70-kb virulence plasmid (pYV/pCD1) found in all pathogenic *Yersinia*, it has acquired two unique plasmids that encode different virulent features. A 9.5-kb plasmid (pPst/pPCP1) encodes the plasminogen activator Pla, a putative invasion that is important for virulence by the subcutaneous path. A 100±110-kb plasmid (pFra/pMT1) encodes murine toxin Ymt and the F1 capsular protein, which enhances the spread of plague (Burland Valerie, et al 2002; Parkhill J. 2001).

High virulence of *Yersinia pestis* is mediated by V and W-antigens that provide the resistance of this microorganism to intracellular phagocytic destruction. In addition, the fraction I that is a capsular antigen partially protects the bacterium from phagocytosis by polymorph nuclear leukocytes. Other factors of virulence that are often responsible for the pathogenesis of the disease include bacteriocin. It is a monomeric protein (M 65 000 Da) that includes all amino acids, except cystine; it is accumulated in periplasmatic zone; thermally labile; UV activates the production of this protein; optimal pH is 6.0-8.0; Ca^{2+} activates; Fe^{3+}, Mg^{2+} inhibits; destroys the composition in glycan layer of murein lipoprotein. In addition, fibrinolysin that dissolves fibrin and fibrinogen in blood, plasma coagulase, and lipopolysacharose endotoxin are also destroyed by that protein (Brueggemann EE, 2006).

In pathological material (cadaver), the causative agent of the plague can be stored within a month. In the protein environment (blood, phlegm) for 4-5 months; in food it can be saved for 2-3 months, but it dies with 10-15 minutes at 55 °C. Under the sunlight the bacteria dies within 1-2 hours. *Yersinia pestis* is also sensitive to the action of different disinfecting agents. (Lee Ligon, 2006)

Epidemiology of disease

Plague is an acute infectious zoonotic disease that is particularly dangerous for people and some animals, mainly rodents (185 species), including rats, from which the infection is transferred to human via fleas. It is characterized by lesions of the mucous membranes, skin, lymph nodes, lungs, and sepsis.

In the history of mankind the three worst pandemic of plague are known that is divided into periods of 800 and 500 years old. The first great pandemic, which entered the annals, took place during the reign of Justinian in VI century. Between 532 and 580 years more than half of the population of the Eastern Roman Empire was died (about 100 million people). The second largest pandemic, known as "Black Death", swept across the world in the XIV century, with a maximum incidence in 1347-1351, respectively. It took about a quarter of the population of Europe. The third great pandemic began in the XIX century in China and reached Hong Kong in 1894. The plague was quickly spread from this major port to India, the Middle East, Brazil, California, and other regions of the world, because of ships that came together with infected rats. Approximately 10 million people died during the 20-year period of the pandemic (Lee Ligon, 2006).

It is believed that each biovar (*Antiqua, Medievalis, Orientalis*) is responsible for each of the historic pandemics of bubonic plague. Plague refers to natural and indirect zoonotic infections. The sources of infection are wild rodents

and lagomorphs (over 200 species), the location of which may be latent foci of infection (Casted D, 2004).

However, not all species have the same value to keep the disease agent. There are the main keepers of infection which serve as the main reservoir of infection in each type of foci. The main sources in the wild nature are marmots, squirrels, gerbil, field mice, and others. The main reservoir of infection in the city, harbor foci of plague, is synanthropic rats. They include the gray rat living in sewage pipes of big cities; black rat that live on ships and in the buildings; Alexandria or Egypt black rat. Dogs are completely resistant to the pathogen but they can infect fleas. There is the evidence of the role of camels as a source of infection for humans. The distribution of the “Black Plaque” infection is mainly due to transmission of the pathogen from infected animals to healthy ones. An exceptional role in this process plays fleas that parasitic on rodents. In the majority of rodents the acute form of plague is developed, but the rapid death of animals leads to the cessation of epizooty. While in hibernation, some rodents (squirrels and marmots) carry disease in a latent form, and next spring they become as a source of infection and contribute to the maintenance of natural foci of plague in this area (Gilligan C. A, Keeling M. J, 2000).

A sick person can under certain circumstances be a source of infection, like during the development of pneumonic plague, direct contact with the purulent content of Black Plaque tambourine, and as a result of infection of fleas in a patient with plague septicemia. The corpses of the dead people from the plague are often the direct cause of infection in others. The patients with pneumonic plague represent a particular danger of infection distribution.

Transmission of disease

The mechanism of transmission of disease is diverse, often transmissible (by bloodstream), but airborne way of distribution (in case of pneumonic plague, infection under laboratory conditions) is also possible. Carriers of the pathogen are fleas (about 100 species) and some types of mites that support the epizootic process in the nature and transfer the plague agent to synanthropic rodents, camels, cats, and dogs which may carry the infected fleas on themselves to human houses. A person is infected not just because of flea bite, but after rubbing the skin of feces or masses that regurgitate feeding. Bacteria that multiply in the gut of fleas, release coagulase, creating a "plug" (plague block), which prevents the flow of blood in its body. Any attempts of hungry insects to suck blood accompanied by eructation of infected mass on the surface of the skin at the bite area. Contagiousness of the fleas can be saved for 7 weeks in the average, and according to some sources - up to 1 year (Clayton O. Jarret el al., 2004; Gilligan C.A, 2000).

The contact (via broken skin and mucous membranes) during processing of the carcasses and skins of dead infected animals (rabbits, foxes, antelopes, camels, etc.) and alimentary (the consumption of meat) ways of plague infection are also possible (see Figure 1).

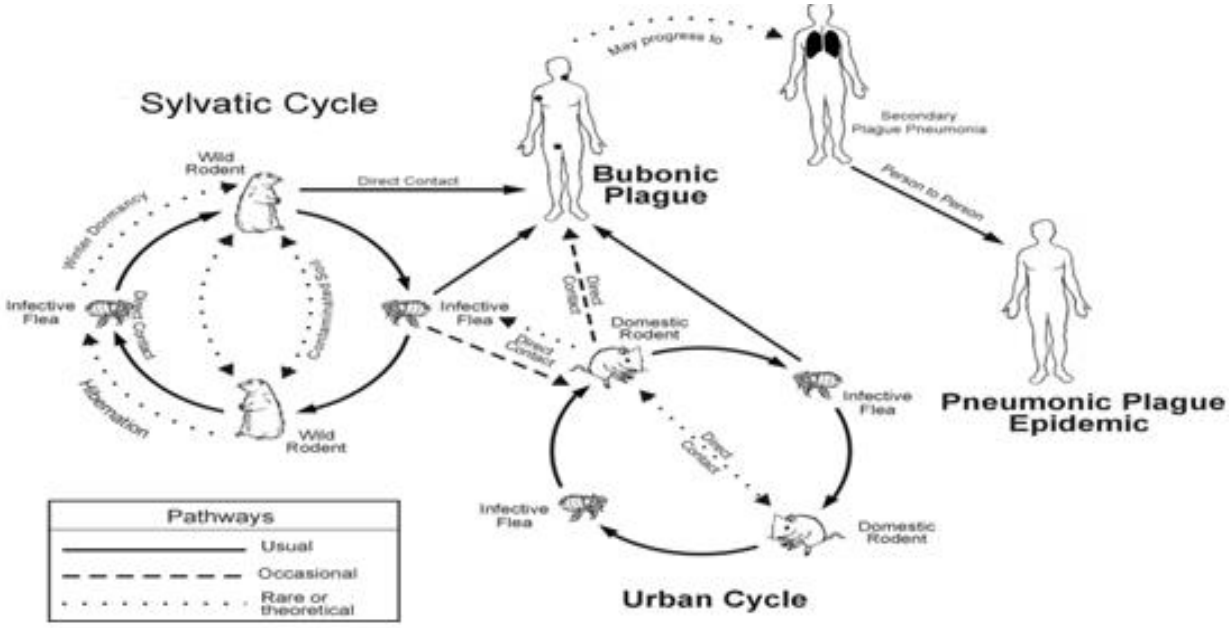

Figure 1**.** Transmission cycle of the plague (Neal R. Chamberlain, Ph.D., A.T. Still University/Kirksville College of Osteopathic Medicine, 2003).

Pathogenesis of the disease

When fleas that are infected with Yersinia pestis bite a person, a specific response in the place of the bite may take place, which is only occasionally pustules with hemorrhagic content or ulcers (cutaneous). Then the causative agent migrates through the lymph vessels without manifestation of lymphangitis to the regional lymph nodes where mononuclear cells capture it. Intracellular killing is inhibited by the antigens of the pathogen; it is not destroyed, but begins to multiply intracellulary with the development of the acute inflammatory response in the lymph node within 2-6 days. The reproduction of bacteria in macrophages of the lymph nodes leads to their rapid increase, fusion, and conglomerate formation (bubonic form). At this stage, the bacteria are also resistant to the phagocytosis by

the polymorph nuclear leukocytes through the protective effect of capsule and due to the lack of specific antibodies. Therefore, with the plague a typical hemorrhagic necrosis of the lymph nodes is developed; and a huge number of bacteria are able to get into the bloodstream and internal organs. As a result of this, the bacterial endotoxins are released, causing the intoxication of the organism. Thereafter, the agent enters the bloodstream and spreads throughout the body. Generalization of infection, which is not strictly required, may lead to the development of septic form which is accompanied by lesions of virtually all internal organs and the formation of the secondary tambourines. Especially dangerous of the epidemic positions is the elimination of the infection to the lung tissue with the development of secondary pneumonic form of the disease (airborne way of distribution). The lungs can be affected secondly in 10-20% of cases. The rapidly progressive pneumonia with widespread hemorrhagic necrosis is developed which is often accompanied by the formation of the pleural effusion. At the same time the specific tracheobronchial lymphadenitis is developed. Some patients have the distinct signs of sepsis without the formation of a distinct tambourine. This is a special form of bubonic plague (primary septic), in which the involvement to the lymphatic system is limited by its deeply located structures, or tambourines are so small that they can remain undetected because of the existence of distinct and acute symptoms of the intoxication (Wayson N.E, 2001).

Septic form of plague is characterized by the rapid appearance of the multiple secondary foci, which are accompanied by the massive bacteremia and toxemia, causing a complete suppression of the immune system and the development of sepsis. Under these conditions the degenerative changes in the cells of the internal organs are appeared very early.

The distinct endotoxemia with the gram-negative septicemia quickly leads to the formation of a paresis of the capillaries, the disruption of their microcirculation, the disseminated intravascular blood coagulation, the development of the trombohemorrhagic syndrome, deep metabolic disturbances in the tissues of the human organism, an infectious toxic encephalopathy, the acute renal failure, and other changes that are the main cause of the death in these patients (Wayson N.E, 2001).

CHAPTER 2. SYMPTOMS and DEVELOPMENT of PLAGUE

The incubation period is usually lasts 3-6 days, it is reduced to 1-2 days at the pneumonic form of the plague but can be extended to 8-10 days in grafted individuals. There are several clinical forms of the plague: a) cutaneous, bubonic, skin-bubonic; b) primary septic, secondary septic; and c) primary pneumonic, secondary pneumonic. The bubonic plague is occurred very often (70-80%), less septic (15-20%), and pneumonic (5-10%) forms of the plague (Cushing AH, 1982).

The plague is usually begins suddenly. The body temperature with a strong fever rapidly rises to 39 °C and above. Intoxication appears early and rapidly grows with the severe headaches, dizziness, sudden feeling of weakness, muscle aches, and sometimes vomiting. In some cases, the admixture of blood appears as bloody thick in vomit. Sometimes growing anxiety, unusual fussiness, and excessive mobility are observed in some patients. Violated consciousness and delirium may also occur. The coordination of movements is disturbed; speech becomes slurred; shaky walking can be also observed. The appearance of patients is changed: first the face is puffy and later becomes peaked with cyanotic tinges, and dark circles under the eyes and pained expression are presented.

The skin of the patients is hot and dry, the face and conjunctiva are hyperemic, often with a cyanotic tinges and hemorrhagic elements (petechiae which quickly become a dark purple). The mucose membrane of the oropharynx and soft palate are hyperemic with the point hemorrhages. Tonsils are often increased in size, swollen, sometimes with purulent coating. Tongue is thickened and covered with a characteristic white bloom ("grated with chalk"). The circulation of the blood is sharply distributed. The severe diarrhea is also occurred

in some patients. Urgency of defecation becomes more frequent (up to 6-12 times per day); the excrements contain impurities of blood and mucus.

Cutaneous form of the plague is rare (3-4%) and is usually the initial stage of skin-bubonic plague. First, spot appears on the skin, then papule, vesicle, pustule, and finally ulceration. Pustules are surrounded by red zone; filled with the dark blood content that is based on a solid red-purple base, which sharply increases when pushed. When the pustule bursts, the ulcers is formed, the bottom of which is covered by a dark crust. The plague sores on the skin stored for a long period, heal slowly, forming a scar.

Bubonic plague is characterized by the appearance of lymphadenitis (black plaque tambourine). The incubation period is usually lasts 3-6 days. In the place where the tambourine must develop, the patient feels pain, which hinder the movement of the feet, hands, and neck. Tambourine is a painful, enlarged lymph node or conglomerate of several nodes, together with the subcutaneous tissue, has a diameter of 1 to 10 cm and is localized in the inguinal region in 60-70% of patients. Besides, tambourines can develop in the axillary (15-20%) or cervical (5%) lymph nodes, or affect the lymph nodes of multiple locations simultaneously. (Gardner D, et al 2006) The tissue, that surrounds the lymph nodes, is involved in this process and provides a tambourine features: the tumor like formation of dense texture with indistinct contours that is sharply painful. The skin above the tambourine is hot when touching it; at first it is not changed, but then it becomes purplish-red. In addition, secondary bubbles with hemorrhagic content (plague phlyctenas) may appear around the tambourine. At the same time, other groups of lymph nodes (secondary tambourines) are increased in their sizes. Lymph nodes of the primary foci become softer at their puncture; purulent or hemorrhagic content are received, microscopic analysis of which reveals a large number of gram-

negative rods with bipolar staining. In the absence of antibiotic therapy decay lymph nodes are revealed, then a gradual healing will begin. Fever and chills are important symptoms, sometimes they are 1-3 days ahead of the appearance of tambourines. More than half of the patients feel pain in the abdomen that accompanied by anorexia, nausea, vomiting, and diarrhea which is sometimes with blood. Skin petechiae and hemorrhage are marked in 5-50% of patients, and at the later stages of the disease they may be extensive. Disseminated intravascular coagulation in a subclinical form is observed in 86% of cases. This syndrome is accompanied by severe clinical manifestations in the form of gangrene of the skin, fingers, on the limbs, and feet in 5-10% of cases (Gilligan C.A, 2000).

In case of a sharp reduction of nonspecific resistance of macroorganisms (bad nutrition, avitaminosis and immunodeficiency of different origin) plague pathogens can overcome the barriers of the skin and lymph nodes, get with blood flow and lymph flow into the general bloodstream, where cause the generalization of infection with the formation of secondary foci of infection in the liver, spleen, and other internal organs (septic plague). In some cases it develops from the beginning of clinical manifestations of plague (primary septic plague), in others - after the skin lesions and lymph nodes (secondary septic plague).

Primary septic plague begins abruptly, sharply, after incubation, which lasts from several hours to 1-2 days. Suddenly fever, general weakness, severe headache, nausea, vomiting are appeared; appetite disappears. The body temperature rises to 39 °C and above. After a few hours some mental disorders like agitation and lethargy are observed. The speech becomes slurred. Frequent vomiting begins; in the vomit admixture of blood is seen. The body temperature quickly reaches 40 °C and above. The face becomes puffy with cyanotic tone and sunken eyes. There is a marked tachycardia. Heart tone is relaxed and subdued;

blood pressure is degraded; frequent breathing and increased size of liver and spleen are observed. In most patients after 12-40 hours of the disease the signs of cardiovascular failure (enhanced tachycardia and hypotension) begin to develop; oliguria joins, then anuria; and hemorrhagic syndrome manifested by nosebleeds and admixture of blood in vomit, hemorrhages in different parts of the skin; in some cases - hematuria and the emergence of an admixture of blood in excrements. These changes are caused by infectious-toxic shock and characterized by hemorrhagic manifestations, reflecting the disseminated intravascular coagulation with the development of coagulopathy of consumption. In the absence of adequate medical care patients typically die within 48 hours. At this sepsis bacteremia so strongly expressed that the agent is easy to see using Gram strain of light layer of blood clots. The number of leukocytes in this form of plague is extremely high and reaches 40-60,000 in 1 ml^3 (Lee Ligon, 2006).

Secondary septic plague. At any time the bubonic plague can cause the generalization process and move in bubonic-septic form. In these cases the condition of patients very quickly becomes extremely difficult. Symptoms of intoxication increase very rapidly. The temperature after severe fever rises to high numbers. All signs of sepsis like muscle pain, severe weakness, headache, dizziness, unconsciousness, sometimes agitation, and insomnia are observed. There are small hemorrhages on the skin, possible bleeding from the gastrointestinal tract (vomit masses bloody), marked tachycardia, and a rapid drop in blood pressure. (Lee Ligon, 2006)

Primary pneumatic plague is the most dangerous form of the disease in the clinical and epidemiological meaning; the period from primary infection and infection of human via airborne contact to death ranges from 2 to 6 days. Typically, the disease has a very acute beginning. Against the background of full

health the strong chills (sometimes sharp, repeated), the rapid increase of body temperature, very severe headache, dizziness, often repeated vomiting suddenly appear. An ache in muscles and joints are seen; sleeping is disturbed. The examination in the first hours revealed tachycardia; dyspnea is accruing. At subsequent time the condition of patients is progressively deteriorated, increased weakness, and increased body temperature are observed. Typical flushing skin and conjunctiva are developed. Fast breathing becomes superficial. In the midst of pneumonic plague the signs of toxic affection of the central nervous system (CNS) are predominant (Kool JL, 2005). Mental condition of the patient is disturbed, and the patients become agitated or retarded. The coordination of movement is disturbed; tremor and difficult articulation are appeared. The speech becomes slurred. Acute sensitivity to light, cold, lack of fresh air. The affection of CNS by toxins of the pathogen leads to the infectious encephalopathy and cerebral hypertension, impaired consciousness on the type of its oppression, which is initially manifested as sopor and coma. On the 2-3 day the body temperature often exceeds 40 °C. Tachycardia corresponds to the severity of fever. Possible short-term extinction pulse or arrhythmia. An acute renal failure and hemorrhagic syndrome are developed. Progressive cyanosis and acrocyanosis indicate the disorder of microcirculation. Violation of breath is more pronounced than in the initial period, which is typical for the plague. There are specific features that indicate the development of right-side pneumonia. The cutting pain in the chest during inspiration and coughing are reinforced. The number of sputum is released with the development of the disease. The sputum detects impurities of bright-red blood that do not coagulate and always has a liquid consistency. In case of pulmonary edema the sputum is frothy and pink. Interstitial and alveolar pulmonary edema is developed, which is based on toxic affection of pulmonary micro-vessels with a sharp increase in their permeability. The duration is typically

less than 1.5-2 days. The diagnostic value in this period has the microscopy of sputum, which allows detecting a huge amount of bipolar stained rods. In the blood it is revealed a polymorph nuclear leukocytosis and toxic changes in blood cells (Gani R; Leach S, 2004).

If patients with pneumonic plague are not getting the adequate causal therapy, they will die in 3-4 days because of pronounced cardiovascular and respiratory failure. However, there is also a possible progress of plague when from the onset of the disease to death of the patient is no more than 1 day.

Secondary pneumonic plague has the same clinical signs as primary one. The only difference is that it develops in patients suffering from cutaneous or bubonic form of the disease. In these cases, on the 2-3 day of the disease cough and fever are appeared together with the minimum infiltrative changes in the lungs. These

symptoms rapidly grow and increase, the expressed dyspnea is developed; blood sputum and signs of respiratory failure are also observed. There is a large number of plague bacilli in the sputum (Kool JL, 2005; Gani R; Leach S, 2004). The features of defeat in case of bubonic and pneumonic plague are shown in Figure 2.

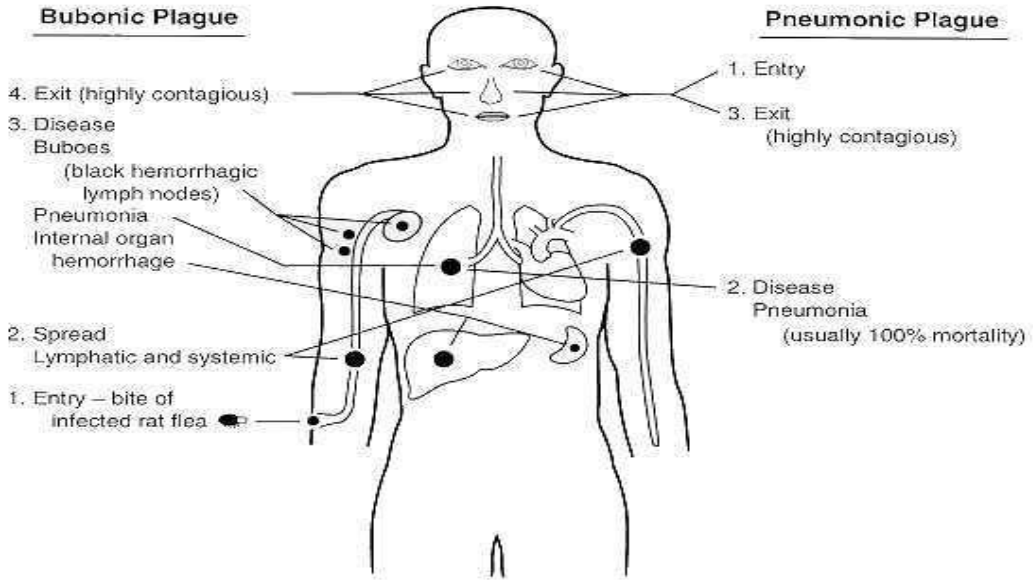

Figure 2. The features of defeat in case of bubonic and pneumonic plague (Kool JL, 2005).

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CHAPTER 3. LABORATORY DIAGNOSIS of PLAGUE. POSSIBLE TREATMENT and PREVENTION of the DISEASE

As the plague refers to the particularly dangerous infections, the laboratory studies of pathological material are carried out in special laboratories, where plague suits are required, with the execution of strict regime. The material for research includes the punctate with tambourine; sputum and material from the throat; the blood of the patient, and stool.

The laboratory diagnosis of plague is conducted in several stages:

1) Preliminary conclusion:

- Microscopic analysis of smears of blood, sputum, and body organs of cadavers. The smears are fixed in a mixture of Nikiforov, then Gram strained.
- For rapid diagnosis of disease the materials are processed by specific fluorescence serum - RIF.
- A serological testing is based on the identification of a specific antigen and antibody of the pathogen like RPHA, RTPHA, and neutralization reactions of antigen and antibody.

2) Final conclusion:

The inoculation of the investigated material on culture media, the isolation of pure culture, and its identification. To suppress the growth of other types of microorganisms the crystal violet is added to the media. The biological test is carried out on guinea pigs. The punctate of tambourines, blood, and other material are injected into the intraperitoneal cavity of the animals which are killed on 2-3 day, and the culture of plague bacteria are isolated from the organs.

The bubonic plague is differentiated from tularemia, “cat scratch” disease, purulent lymphadenitis, and venereal lymphogranulomatosis. The tambourine of

tularemia, unlike the plague one, has clear outlines, not associated with the skin and adjacent lymph nodes, because the phenomenon of periadenitis is missing. The tambourine develops slowly, then reach a large size by the end of the week; suppuration, if it occurs, is only on the third week of the disease. Fever and symptoms of intoxication during tularemia are expressed moderately.

"Cat scratch" disease very often occurs as a result of scratches, rarely because of a bite. After 1-2 weeks on the ground of scratching (bite) that has already healed, a small red spot is developed that turns into papules, vesicles, pustules, and finally a small ulcer size is formed. In 15-30 days after infection the regional lymphadenitis is developed. With the development of the tambourine the body temperature increased to 38-40°C; and the signs of intoxication are observed. Further course is benign; the lymph nodes are 3-5 cm in diameter; fluctuations and their softening are appeared in 2-3 weeks.

Possible treatment and prevention of the disease

In cases of plague the patients should be hospitalized immediately in a special plague hospital. If necessary, staff should wear the plague suit. All staff that contact with the patients remains in hospital for further assistance. Department, where the staff treats the patients, is isolated from the contact with other people.

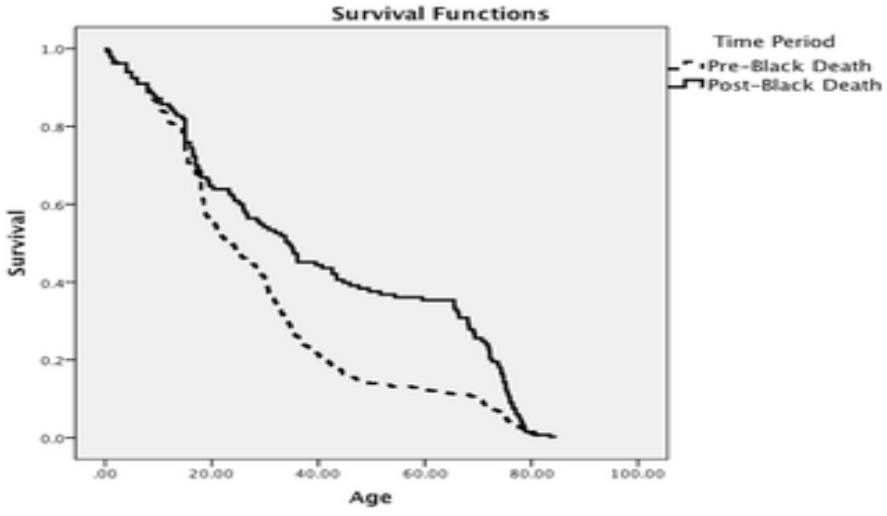
In the bubonic form of plague the patient is injected with antibiotics like streptomycin and tetracycline intravenously. In case of intoxication the saline solutions are injected intravenously. The drug dose is increased during the pneumonic and septic forms of plague. Antibiotic therapy lasts 7-10 days; biseptol, cardiovascular drugs, vitamins are also used (Ernest Jawetz, 2006).

In case of pneumonic or septic form of plague a plasmaphoresis is used. The effect of plasmaphoresis in the acute period of disease occurs almost immediately, the signs of intoxication are reduced, stabilizes blood pressure, muscle pain is subsided; shortness of breath decreases. With the current therapy for the bubonic

form, the mortality does not exceed 5-10%; but in other forms the rate of recovery is very high, if treatment is carried out in advance.

Methods of prevention of the plague include: prevention of disease outbreaks in natural foci**;** early diagnosis of the plague; accurate disinfection in the place of disease**;** and prevention of contamination of people who work with the materials of the patients. The specific preventive measures are carried out by the testimony using dry live vaccine EV. Duration of the immunity lasts from 6 months to 1 year (Josko D., 2004).

In Mortality Risk and Survival in the Aftermath of the Medieval Black Death research by Sharon N. DeWitte study that people who is older, skeletal short height, enamel hypoplasia, tibial periosteal lesions, cribra orbitalia, porotic hyperostosis. People with comorbidities, poor immune system had higher risks of death, than individuals who is younger, had bigger skeletal completion, healthy individuals that had healthy life style, with good immune system had higher rate of survival



Kaplan-Meier survivorship functions for the pre- and post-Black Death samples.

CONCLUSION

Yersinia pestis is an intracellular pathogen that causes an acute infectious disease of humans and some animals called plague. In the history the three worst pandemics of this disease are known that is divided into few periods. The different biovars of *Yersinia pestis* (*Antiqua, Medievalis, Orientalis*) are responsible for each of these pandemics of plague. The few clinical forms of this dangerous disease that possess its specific symptoms and treatment are described already. These forms are grouped into such categories as a) cutaneous, bubonic, skin-bubonic; b) primary septic, secondary septic; and c) primary pneumonic, secondary pneumonic. The bubonic plague is occurred very often, less septic and pneumonic forms of the plague (Cushing AH, 1982). The incubation period usually vary and depends on the form of plague and can be extended in grafted individuals.

The laboratory diagnostics of plague is an essential for determination of treatment and differentiation it from other infectious diseases. It is based on microscopic analysis of smears of blood, sputum, and body organs of cadavers that are Gram strained; the inoculation of the investigated material on selective culture media, the isolation of pure culture, and its identification are also necessary.

Therefore, the understanding of nature of this causative agent and pathogenesis of plague will give the opportunity to prevent the establishment of huge pandemics in the future. Moreover, the analysis of genome sequence of *Yersinia pestis* will allow comprehending the nature of those factors that are important for virulence of the pathogen.

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