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Prevention and Treatment Approaches to Deal with Plague as a Biological Weapon

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ABSTRACT

Introduction: Biological attacks are a phenomenon that started on a serious note in the twentieth century and such weapons are being developed every day.
The agent of plague is one of those listed as biological weapons by the Weapons Convention. So, the danger of its biological or bioterrorist applications by the enemy is possible and poses a serious threat. The purpose of compiling this article is to update information of health personnel about plague and the bioterrorist aspect of this disease.
Methods: This article is a review study which had been undertaken based on articles searched from the library and the internet (1990–2016).
Results: More than 2000 species of bacteria have been identified in three main groups of bacillus (rod-shaped), cocci (round and oval) and spiral (helical) but only approximately 100 species have been identified as pathogenic and less than 10 species are used as suitable biological agents for military application and the plague agent is one of them. Yersinia pestis is a type of gram-negative anaerobic coccobacillus from the Enterobacteriaceae family and if it is stained with Wright, Giemsa or Wayson it can be seen as bipolar under a microscope.
Conclusion: Nowadays, despite development of science and technology, humans are not able to predict time and location of this type of attack. So, we should be prepared for this unavoidable eventuality. Considering the importance and necessity of preparing to deal with attacks, authors of such studies and professionals should consciously plan and try to prepare against these dangers.

Keywords: Bioterrorism, Plague, Biological Attacks

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Introduction

Plague is a bacterial zoonotic disease which is caused by Yersinia pestis. Natural hosts of plague are rodents (a type of rodent such as mouse) [1]. The disease is usually contagious by the bite of flea but sometimes it leads to respiratory plague by aerosols. Plague has had deep effects in history, pattern of the world's population, health status and even the history of art [1, 2]. Throughout history, plague has been considered as one of the deadliest and most terrible pathogens known to man. Even in some regions, mortality has been so high that there were not enough living people to bury the dead [3, 4].

The first pandemic of the disease was in 541 AD in Egypt and from there to Europe and led to severe casualties and reduction of more than 50 percent of the population in Europe, Africa and Asia. The second pandemic occurred in 1346 AD and left approximately 20–30 million dead. In that period, plague was slowly transmitted through movements of infected humans and mice from a village to another and more quickly from a country to another by ships. The third plague pandemic started in 1855 AD in China and was spread to other regions. Eventually, it led to the death of 12 million Chinese and Indians [1, 5].

Since 1980, plague was again increasingly reported with vast majority of cases being seen in East Africa and Madagascar. Public health concerns about the current status of plague can be mentioned as a justification to not be indifferent about the disease. Improvement of monitoring strategies on plague is completely necessary to achieve a clear image of the plague status in a region [6]. Approximately 2652 deaths caused by plague were reported in the period between 1985 and 1999. Most deaths were reported from Africa [7]. Despite advances in medical technology, the disease is still seen as an endemically around the world and is still prevalent in more than 20 countries [3, 8].

Currently, small outbreaks of plague continue throughout the world [9]. Now, major outbreaks of the disease are not possible due to identification of the bacterial agent and antibiotic treatment but the agent as a biological weapon is a big threat to the world. Plague is one of the few diseases, which spreads very quickly. If it spreads in a small area, it may be transmitted to other areas and become pandemic. The epidemiology, course of the disease, ways of transmission and so on are naturally different during natural occurrence of plague compared with intentional outbreak of the disease [1].

History of the plague agent as a weapon

In the fourteenth century, Tatar invasion forces, by hurling the diseased cadavers into Caffa city caused an outbreak of the disease in large numbers and killed many of them. Japan used this weapon widely in the Second World War and Russia used it during the siege of Stalingrad by Germans. In 1932–1945, Japan tested for biological wars on Manchurian prisoners in China and after infecting them with the plague agent and other microorganisms biologically, they attackted some Chinese cities. In that war, Japan released each time approximately fifteen million fleas infected with plague bacillus from an aircraft on the people so that Japanese forces were not immune from these attacks. In one of the camps, approximately ten thousand Japanese army soldiers were infected with plague and other diseases [9].

The offensive biological weapons program against Iraq has become clear and evident in the past few years for the whole world. Meanwhile, some countries such as the United States of America and Israel have conducted several researches about this type of weapon since the past decades and they are of the view that this type of terror may take place and support the manifestations of state terrorism [10].

Biological weapons include infectious agents and toxins. The plague agent is one of the biological weapons listed by Weapons Convention. So, the danger of bioterrorist or biological applications by the enemy is a possibility and poses a serious threat [11]. Despite the very deep effect of the agent on social and economic statuses in the world, especially between sixth and 19th centuries, it was not identified until the late

nineteenth century [4]. Plague was isolated for the first time by Alexandre Yersin at 1894 in Hong Kong and after that it was found in all continents [12].

Generally, most industrial countries in the world modernize this type of weapon through technology and produce variety of biological weapons. Since production of the weapons is relatively simple and doesn't need any special technology or a wide environment, they are simply produced by terrorist groups. Plague is one of diseases which have its bacilli resources existing in animal reservoirs around the world. Therefore, preparing that is relatively simple [13]. The first terrorist measure through the plague agents was observed at 1995. At that time, a suspicious person who had received amounts of Yersinia pestis culture in Ohio by post was arrested [1].

Also, Japan used releasing fleas infected with plague against Chinese in the Second World War and caused the plague epidemic [11]. The aerosolized agent is the best way to carry out bioterrorist attacks and the most destructive ones too [7]. The most probable clinical picture after a biological attack will be primary pneumonic plague [1]. A cluster of cases of primary pneumonic plague could be owing to bioterrorism that should immediately be reported to the authorities. The plague epidemiology caused by bioterrorism may be different with its natural spread because intentional release of Yersinia pestis occurs most likely through infected sprays and leads to outbreak of the primary plague pneumonia [14]. The symptoms appear within 1–6 days after contact with the infected sprays and if it is not treated immediately, it leads to death [3]. One of the causes of bioterrorist attacks by Yersinia pestis is outbreak of plague pneumonia in a region where animal plague has been not seen before. It may have occurred in people who have no required ground and no report exists about previous death of rats [1].

In a report by the World Health Organization, if approximately 50 kilograms of the Yersinia pestis bacillus is sprayed over a city with 5 million population approximately, 150 thousands of residents will be infected with plague pneumonia and about 36 thousand people will die while a large number of people would flee to other areas and the disease will spread [11]. Based on available information, Russia, the United States of America, France and England have considerable reserves of the bacillus and have various methods of spraying the plague bacillus and releasing them without using flea [1, 15].

Methods

This article is a review study which has been written based on articles searched from library and internet resources (1990–2016).

How the disease spreads by natural events

1- Bubonic plague

The most common form of plague is bubonic plague. Due to lymphedema of the involved area, the disease was named bubonic plague. The incubation period of bubonic plague is 2–5 days but can occur within a few hours to 12 days. The bacillus enters the patient's body through biting of the skin by infected flea and this creates a bubo by attack on the lymphoid tissue. Also, by spreading along lymphatic channels, it causes severe sepsis and bacteremia and infection spreads to the lungs, liver, spleen and kidney. Meningitis is a key symptom of bubonic plague. Bubo is usually seen in inguinal areas (60 percent), armpits (30 percent), neck (10 percent) and epitrochlear (10 percent). Buboes are not larger than 5–10 centimeters and are very sensitive to touch. Erythematous are surrounded by a layer of blood as well as maculopapular lesions that are seen on the mouth of the bite injury. Swollen, painful along with large lymph nodes, fever, tachycardia, tachypnea, hypotension, and gastrointestinal problems in later stages of septic shock are other symptoms of bubonic plague. In natural outbreaks of plague, the flea, infected with the bacillus, bites humans and the bacillus enters the body. This event causes pain, fever and enlarged lymph glands, especially in the neck [5, 16].

1- Septicemic plague

Although the common form of the infection in the natural way is bubonic plague but in small

percentage of people the disease progresses towards septicemia without producing bubonic. This form of the disease is named primary septicemia plague and can be one of the complications of bubonic or pulmonary plague or may occur alone. Some symptoms of septicemic plague are vesicles, pustules, cyanosis of extremities, ecchymosis, petechiae, blackness of necrotic cyanotic organs (reason for being called Black Death), diffused abdominal tenderness with or without guarding, splenomegaly, hematochezia, black or tarry stools, gastrointestinal problems, bleeding from body cavities, varying degrees of mental status changes including mild confusion, delirium, coma and convulsions [16].

2- Pneumonic plague

A small percentage of patients with bubonic plague or septicemia are infected with pneumonic plague. Direct inhalation of the bacillus leads to pneumonic plague associated with bacteremia and sepsis. Incubation period of pneumonic plague is 2–3 days. If the infected people are not treated, they will die within 24 hours after onset of symptoms. Pneumonic plague is transmitted from a person to another person through respiratory aerosols. Primary pneumonic plague, which is caused by inhalation of infectious aerosols, is the most severe form of the plague although this form of the disease is not common. However, outbreak of respiratory plague has been reported [17].

Life cycle of plague reservoir

Natural reservoirs of the infection are wild rodents. Also, rabbits can be sources of the infection. More than rodents, various species operate as the host. A cat can be an important resource of zoonotic diseases. Plague primarily originates from wild rodents such as mice and squirrels. In an outbreak of the disease, rodents are infected and after death the infected and hungry fleas which live on the body are considered sources of the disease. If they bite humans or animals, they infect. Also, it is possible that people may become patients directly by touching infected rodents, rabbits and other wild carnivores that are fed through rodents. Pets such as dogs and cats may enter with the infected fleas, existing on their bodies, into houses [17].

Epidemiology of plague in biological wars

Epidemiology of plague through biological weapons is completely different with the natural outbreak of the disease. Intentional release of the disease agent is conducted through infected sprays and causes primary pneumonic plague in humans. Symptoms of the disease are similar to other acute respiratory diseases. The area of pandemic is related to some factors such as quantity of biological agents, features of used bacteria, environmental conditions and way of spraying the bacteria. If respiratory plague occurs in humans in regions where infection of animals has not been reported or there is no report about previous death of mice, a bioterrorist attack could be the reason. Symptoms of pneumonic plague are much more severe than other forms of plague and if it is not treated immediately almost all the patients will die [17].

Based on available information, some countries such as Russia and the United States of America have made and accumulated this type of weapon. Due to almost unique properties of biological weapons, medical staff will need a deep understanding of some key elements of biological defense to be able to deal with problems caused by a biological attack.

Identification of behavior of such victims, ways of checking spread of the agent and treatment selection are necessary. When the agent is known, it will be less difficult to manage the treatment post attack. Correct and perfect management and evaluation of a biological attack before identifying the disease agent will be complex and problematic. Understanding the damages, effects and severe complications of bioterrorist attacks is necessary and one cannot prevent the damages caused by this type of destructive operation [1].

Terrorist methods of releasing the infection

1- Spray of bacillus: At present, it seems that possibly the most common method to release the disease is spray of the plague bacillus. If this

method is used, the dominant form of the disease will be primary pneumonic plague.

2- Throwing containers containing the plague bacillus
3- Using infected fleas
4- Feeding infected corpses to rats in an area [17]

Pathogenesis of the disease in public attacks

Following inhalation of released sprays, the bacillus enters the lungs and causes primary pneumonic plague. The time interval between entrance of the bacillus and appearance of the first clinical symptoms is approximately 1–6 days. The first symptoms of the disease include fever, cough and shortness of breath. Gastrointestinal symptoms such as nausea, vomiting, abdominal pain and diarrhea are accompanied by other symptoms [17]. Symptoms of the primary pneumonic plague are similar to other progressive pneumonia and have no difference with secondary pneumonic plague but bubo doesn't exist in primary pneumonic plague and usually bilateral involvement is shown in chest radiography. The degree of contagiousness of primary pneumonic plague is more than others. Experiences show that a person infected with primary pneumonic plague can transmit the disease to 18 people. If the infected fleas or rodents are used for terrorist attacks, symptoms similar to bubonic plague occur [17].

Diagnosis

There is no rapid diagnostic test to detect plague. The used tests include Igm enzyme immunoassay, immunological staining and PCR polymerase chain reaction that of course are conducted in central laboratories not available publically. Indirect hemagglutination test, which is usually conducted, becomes positive many days or many weeks after outbreak of the disease. Gram stain makes sputum or blood of gram-negative coccobacillus patients recognize and the bipolar bacillus can be found in Wright, Giemsa or Wayson staining. Aspiration, staining and culture of drained sample from lymphadenopathy, sputum and blood will become positive in 24–48 hours but the final report can come in 6 days. A 10-cc syringe where 1–2 cc has been filled with normal saline is used to drain lymph nodes. First, the saline is injected in the nodes and then drained. Sampling should be conducted before starting the treatment. Since in bioterrorist attacks of plague, a large number of people are infected and diagnostic facilities encounter limitations in this wide area, the syndromic can be of help to diagnose patients. Sudden outbreak of the disease in a large number of people who have been healthy before and symptoms such as fever, cough, shortness of breath, chest pain and worsening of patients and death of people should make personnel of the health system suspicious that it could be a case of respiratory plague or respiratory anthrax [18].

Vaccination

Vaccine containing the killer bacillus was produced in the United States of America before 1999. The vaccine is used to prevent bubonic plague but doesn't prevent pneumonic plague. The vaccine is inoculated in people who work in laboratories of diagnosis of plague in plague endemic areas or people who work on mice infected with plague. Researches to make vaccine against pneumonic plague are continuing. In addition, safety resulting from the disease is relative and a large amount of the bacillus is broken for inoculation [19].

Treatment

Early diagnosis and treatment of plague improves the prognosis of patients. The factors which are crucial in plague include time of beginning antibiotics, the dose of the inhaled bacillus and quality of supportive measures. Classical treatment of plague is 30 mg streptomycin intramuscularly for 10 days. Therapeutic response is fast and fevers of most patients stop within 3 days. Another medicine gentamicin has not been approved by FDA but researches feel it is as effective as streptomycin. Since gentamicin is simply available and cheap, it can be applicable during wide outbreaks of the disease. Tetracycline and doxycycline can be suitable alternatives in the case of sensitivity to streptomycin. Chloramphenicol in amount of 6 mg kg/day is used intravenously in patients with

meningitis plague. Treatment with multiple antibiotics is not a priority. In outbreaks of the disease, which we face, for a high numbers of patients, oral doxycycline or tetracycline are suggested in case venous and muscular treatments are not used [20, 21].

Chemoprophylaxis after Exposure

During epidemics of pneumonic plague, all people who have 38.5 ° C fever or higher or cough should be immediately treated with intravenous antibiotics. Oral antibiotics can be used if there are not enough intravenous drugs. In infants with tachypnea, the treatment should be started as soon as possible. People without clinical symptoms who are in the house or hospital and in contact with untreated persons with pneumonic plague should be treated with chemoprophylaxis for 7 days and followed up for fever and cough. 500 mg/12h tetracycline and doxycycline or 25 mg/kg chloramphenicol every 6 hours for 7 days orally are chemoprophylaxis treatments. Preferred treatment of chemoprophylaxis is tetracycline and doxycycline [22, 23].

Control of infection

All those who have contacted pneumonic plague and have not taken medicine should be followed up during the first 7 days after contact and in the case of occurrence of fever and cough they should be immediately treated. Possibly, the surgical mask prevents transmission of pneumonic plague. If less than 48 hours pass from the start of the treatment, it is better for people who have been in near contact with them to use surgical masks in addition to taking prophylaxis medicine. They must avoid unnecessary contact and also take other respiratory precautions such as using gowns, gloves and goggles. It is better for patients to be isolated during the first 48 hours of treatment until appearance of signs of recovery. In case of crowds of patients, they can be hospitalized in common rooms after beginning the treatment. Also, it is better to avoid unnecessary displacement and movement of patients until infection is no more there [24].

Laboratory samples suspected to be plague should be sent by observing the standards of biosafety level 2 and should be prepared from suspected patients within 1–2 hours and immediately provided to the laboratory. Suitable treatment should be started before announcing results of the tests. Suspected cases should be reported to Center of Controlling Diseases. All residents in infected areas should be quarantined for 6 days after the last contact and if the symptoms occur treatment should be started. Victims who die should be buried by trained people by observing the health criteria [25, 26].

Conclusion

Nowadays, despite development of science and technology, humans are not able to predict time and location of this type of operation relatively. So, we should be prepared for unavoidable occurrence of such an event. Considering the importance and necessity of preparation to deal with these attacks, authors and professionals should consciously plan and try to prepare against these dangers. It should be noted that effective and efficient management is one of the most important things that can help deal with biological dangers and attacks.

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Conflict of Interest

There is not conflict of interest between the authors.

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