BIOLOGICAL AGENTS
Plague – A Review[1]

by
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AETIOLOGY
PLAGUE IS CAUSED BY the bacterium Yersinia pestis, a small Gram-negative, non-motile coccobacillus, which has a characteristics bipolar "safety-pin" appearance when stained.

Although this organism is non-sporing, it may remain viable for weeks in sputum at room temperature, for 2 to 30 days in water, for two weeks in moist grain, or for months if frozen. It can be destroyed quickly in sunlight, by boiling, or by exposure to dry heat (less than 72°) or steam, or simple disinfectants, such as Lysol or chloride of lime[2].

EPIDEMIOLOGY
Yersinia pestis is a natural pathogen of rats, squirrels, rabbits and cats, but will occasionally be transmitted to humans via the rat-flea. The flea acquires the pathogen from infected rodent blood, and bacteria' proliferation causes an obstruction in the insect's gut. The flea is unable to feed and will attack almost any other host (especially humans) in order to try to obtain blood. Bacteria, which are regurgitated by the feeding flea, are then able to infect the human. The flea may remain infective for months[4].

The pathogen may also be transmitted by inhalation of bacteria or by the bite or scratch of infected animals. Human-to-human transmission is possible, through inhalation of sputum aerosols, especially under favourable conditions, such as overcrowding [4].

Yersinia pestis is found in all continents except Australia. Recent sporadic outbreaks have occurred in Africa and South America. Plague is endemic in Indonesia, Burma and Vietnam.

PATHOLOGY
Antigenic Composition. Y. pestis possesses several important antigens. [1,3,5]
   a) **Antigen** - a lipopolysaccharide-protein complex which is toxic for animals.
   b) **Capsular antigen** - a heat-labile antiphagocytic glycoprotein-lipoprotein known as fraction[11,3].
   c) **V/W antigen** - comprised of a protein (V) and a lipoprotein (W), is an antiphagocytic virulence factor. These antigens are synthesised at 37°C. The V antigen is a cytoplasmic protein of molecular weight 37,000 Da. The W lipoprotein has a weight of 140,000 Da and is excreted.[5] The precise physiological roles of these proteins has not yet been elucidated'.
   d) **Proteinaceous murine toxin** - found in the cell envelope, it is released when cell autolysis occurs. It is comprised of either five or ten subunits of 24,000 Da. This protein is highly toxic to mice and rats. The mode of action is believed to be as an adrenaline blocker[6].
   e) **Pesticin 1 and Pesticin 11** - bacteriocins which inhibit strains of Y enterocolitica and Y pseudotuberculosis.

f) **Plasmid-coded outer membrane proteins (POMPS)** - these are produced during the infection.
g) **Lipopolysaccharide endotoxin** – very little information is available about the antigen.

Virulence factors. A 72 kb plasmid codes for the V and W antigens, PONTs (only during infection), and is responsible for the pathogen's cytotoxicity in macrophages and resistance to phagocytosis by macrophages. It also stipulates a requirement of Ca for the bacteria at 37°C'. Loss of this plasmid induces a profound loss of virulence'. The precise reason for the requirement for calcium has not yet been elucidated, but it may be necessary for the adoption of the pathogen to a higher temperature environment.

A 9 kb plasmid is necessary for the synthesis of pesticin, coagulase, and fibrinolysin. The absence of this plasmid results in a major reduction of virulence.

Another plasmid, of about 100k b, is also important in the pathogenicity of the microorganism. It codes for the murine toxins.

The synthesis of the capsular antigen, and the ability of the organism to accumulate exogenous haemin (by a pigment-binding surface component (Pgm) and use it as a source of iron, are controlled by genes on the chromosome. Bacteria which are Pgm- are avirulent.

Pathogenic sequence. At 28·c (flea body temperature), Yersinia pestis does not possess the glycoprotein capsular antigen or the V/W antigen. When bacteria enter the dermal lymphatics of the human they are phagocytes by polymorphonuclear lymphocytes (PMNs), which, in most cases, leads to the death of the bacteria. If pathogens do survive, the capsular and V/W antigens are produced in the macrophage[3].

They are then carried to the regional lymph nodes. Bacteria which persist are then able to proliferate in the lymph nodes, which become inflamed and enlarged (buboes). This form of the disease in known as bubonic plague and has a mortality of about 75 per cent in untreated patients.

If haemorrhagic necrosis of the inflamed lymph nodes occurs, and the pathogen is able to disseminate via the bloodstream, it may infect many sites, especially the liver, spleen and CNS. Haemorrhagic parenchymatous lesions may form, which may cause disseminated intravascular coagulation. Blocking of blood vessels to the organs may occur, leading to death and scarring of tissue. If the disease spreads to the respiratory system (10 - 20 per cent of cases), the pneumonic plague may result. This is associated with almost 100 per cent mortality if not treated promptly [3].

Primary pneumonic plague occurs when patients inhale aerosolised sputum from other pneumonic plague sufferers.

CLINICAL MANIFESTATIONS
Bubonic plague. Within a few (1-6) days of infection, the patient will usually show an abrupt onset of fever, tachycardia, general malaise, and aching extremities and back'. Lymph nodes will become extremely tender, and shortly after, painful buboes will form in the armpits, groin, or neck. There is often pronounced oedema of the lymphatic area. The surrounding skin will exhibit dark blotches (hence "black death") from bleeding into the skin.

If the disease becomes bacteraemic, the patient will show signs of prostration, shock, delirium, and will usually die within 3-5 days from the onset of these symptoms.

Septicaemic infections may show characteristics similar to gastrointestinal infections and swelling of the lymph nodes may not be as prominent. In these cases, nausea, vomiting, diarrhoea, and abdominal pain are more symptomatic. Initial symptoms may also include pharyngitis, coughing of frothy or bloody sputum, shortness of breath, and meningitis. Death will usually occur within 48 hours.

Pneumonic plague. Primary pneumonic plague from inhalation of aerosolised infectious sputum usually has a short incubation period - symptom normally appear within 24 hours. There is an explosive onset of high fever, tachycardia, restlessness, tachypnoea, intense headache and prostration. A persistent cough, with profuse watery, blood-tinged sputum, will develop. Rales can usually be noted, and respiratory distress follows.

Gross haemorrhaging of the lung tissue, and exudation of watery sputum are common physical symptoms of this disease.

If untreated, most patients will die within three days[8].

Pulmonary signs may be lacking until the final day'. In the first few days, there may often be a marked contrast between the extreme prostration of the patient, and the negligible physical symptoms in the chest.

DIAGNOSIS

Laboratory diagnosis. Positive identification is usually made by isolation of the pathogen from lymph nodes, blood or sputum, or by fluorescent antibody assays of clinical smears. Although weakly Gram-negative, the characteristic "safety-pin" appearance is best achieved with Giemsa or Wayson's stains. However, isolation of bacteria is not usually possible until 48- 96 hours after infection, by which time the patient will either have died, or be beyond antibiotic treatment. Therefore, diagnosis must be made on clinical grounds - laboratory diagnosis is only used as confirmation.

Differential diagnosis. These include staphylococcal, streptococcal, or Pasteurella lymphadenitis and sepsis, tularaemia, bacterial sepsis, or anthrax. Plague pneumonia and anthrax pneumonia have similar symptoms, although plague patients have pulmonary infiltrates, which are normally absent in anthrax.

TREATMENT

Streptomycin, gentamycin, tetracycline, chloramphenicol are all effective antibiotics. Streptomycin given intramuscularly (4-8 g 1day) appears to produce good results, as does chloramphenicol given intravenously for the first 48 hours.

Recommended Therapy. The recommended therapy is:

- 7.5 mg-15 mg 1kg of streptomycin intramuscularly every 12 hours; and 5 mg-10 mg /kg of tetracycline intravenously every 6 hours given concurrently. Streptomycin therapy can be discontinued when the patient becomes afebrile. Tetracycline should be continued for at least 3-4 days after the disappearance of fever.
  Patients with suspected CNS infiltration should be given 12.5mg-25mg /kg of chloramphenicol either orally or intravenously every 6 hours instead of tetracycline.
- If streptomycin-resistant strains are suspected, gentamycin is an effective substituted.

Patients must be strictly isolated until at least 3 days after the completion of successful antibiotic therapy. People in contact with patients should be quarantined, given concurrent antibiotic prophylaxis (tetracycline or trimethoprim-sulfamethoxazole), and surveyed for 7 days.

It must be noted that unless specific antibiotic therapy is instigated within 15 hours of the onset of symptoms, the course of the infection will not be altered. Ideally, therapy should be started within 8-24 hours of infection.

After a favourable response to antibiotic therapy, it is not uncommon for patients to suffer a brief, febrile, self-limiting illness. Supportive care may include oxygen therapy and tracheostomy. The surrounding environment should be disinfected as much as possible.

SUSCEPTIBILITY OF POPULATION
The susceptibility of the general population appears to be high. Even vaccinated individuals may not have permanent or solid immunity. Secondary spread is possible unless strict quarantine precautions are observed. Immunity following an infection is relative - it may not be adequate against a large challenge.

PREVENTION
Several vaccines are available:

a) Attenuated/formalin killed vaccine. Currently given to medical personnel and others considered to be at risk. However, boosters need to be given every 6 months. Tetracycline or trimethoprim- sulfamethoxazole prophylaxis may also be administered concurrently.
b) Avirulent living plague bacilli. Very little information is available.

POTENTIAL AS A BW AGENT
A BW attack would probably be via aerosol, so plague pneumonia would be the most likely outcome. This disease has a short incubation period, with initial symptoms being non-specific and hard to diagnose, and, unless the diagnosis is made early, and antibiotic therapy initiated rapidly, mortality would be high.

The disease has high infectivity (as few as 1000 organisms inhaled can cause illness) and is able to be spread from person to person. Unless quarantine procedures were implemented promptly, large numbers of personnel could become infected.

Antibiotic therapy needs to be aggressive, both for patients and those under surveillance. This could lead to a drain on medical personnel and resources. Strict isolation programmes may also severely drain effective manpower.

Although vaccines do exist, they only provide temporary immunity, and boosters need to be given regularly.

The use of antibiotic-resistant strains of E pestis is a possibility. Antibiotic resistance can be cultivated in the laboratory, and both tetracycline and streptomycin- resistant strains have been isolated from clinical specimens.

Although the organism has a moderately high persistence in moist environments, it does not survive well in dry conditions, and would probably not remain viable for long periods of time in aerosol form.

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