

MINI REVIEW

PLAGUE — THE HIDDEN OLD NEMESIS

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ABSTRACT

Plague is a disease of rodents carried to man by fleas and is non-existent in Pakistan. It represents a typical example of the evolution of human disease from an infection, originally confined to wild animals. Due to the closeness of Pakistan with India, the danger exists where it can become entrenched in the wild animals. It should be considered in the differential diagnosis in patients who live in the endemic area or have exposure to animals known to harbor the vector. An attempt has been made in this review to understand the bionomics, clinical findings, diagnosis, epidemiology and prevention of the disease.

Keywords: Disease, epidemiology, infection, plague, rodents.

1. INTRODUCTION

1.1. Historical Background

Plague is a disease of antiquity that has caused three pandemics¹, the first in the 6th century (the Justinian plague), the second in the 14th century (the Black Death) and the third that started in China in 1860's and linger till date. About 200 million casualties have been suggested as the credible number of plague death throughout the recorded history. The devastation caused by bubonic and pneumonic plague dwarfs that of most other infectious diseases^{2,3}.

1.2. Etiology

The genus *Yersinia*, a member of the family Enterobacteriaceae consists of 11 species, of which 3 are human pathogens (*Y. pestis*, *Y. pseudotuberculosis* and *Y. enterocolitica*). The type *Yersinia pestis* is a facultative anaerobic bacterium that is gram-negative, non-motile, non-spore forming coccobacillus that exhibits bipolar staining with Giemsa, Wright's or Wayson staining. Three classic biovars of *Y. pestis* have been identified including biovar Antiqua, Medievalis, and Orientalis, which are linked to respective pandemics and have distinct geographic distributions^{3,4}.

1.3. Epidemiology

Plague is a zoonotic disease that primarily affects

rodents but humans play no role in the long-term survival of *Y. pestis*. Over 1500 species of fleas have been identified while over 200 mammalian species in 73 genera have been reported to be naturally infected with *Y. pestis*. Rodents are considered as an important host for plague throughout the world and the domestic rats, *Rattus rattus* and *Rattus norvegicus*, are the most dangerous reservoirs of plague. The most efficient vector of infection to humans is the oriental rat fleas i.e. *Xenopsylla cheopis* and *Xenopsylla astia*. The risk of spread of plague from rats to humans is positively correlated with the density of rats, the number of fleas per animal (flea index) and the *Y. pestis* infection rates in sampled rats and rat fleas^{3,5}.

The oriental rat flea, a classic vector for plague, can ingest 0.03–0.5 µl of blood from bacteremic rodent⁶. The ingested organism multiplies in the gut of flea and helped by an enzyme coagulase that blocks its proventriculus so that no food can pass through. After blockage of the proventriculus, the flea gets no nutrition and become hungrier, loses its natural host selectively for rodents and more readily bites a human. While not all blocked fleas transmit plague, blocking is an important process in ensuring transmission. However, spread by unblocked fleas is exceedingly rare. It has also been suggested that

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as many as 11,000–24,000 bacilli are regurgitated by the flea into the mammalian host. Both *X. cheopis* and *X. astia* appear to be capillary feeders, however, the feeding methods i.e. capillary or wound (pool feeding) for the vast majority of fleas are still undetermined^{5,6}.

1.4. Epidemiological Forms

1.4.1. Urban plague

This cycle predominates during the time of poor sanitation, e.g. wartime when domestic rats proliferate and come in contact with fleas in the sylvatic cycle. It may also occur when wild rodents come into contact with domestic city rats (during drought when wild rodents forage for food) and their fleas then transmit the bacteria to domestic rats³⁻⁵.

1.4.2. Sylvatic plague

The enzootic (sylvatic) cycle consist of transmission among wild rodents by fleas that constitute reservoirs from which plague can be introduced into the commensal rat population of human communities, thus initiating epizootic danger to man. The epizootic cycle proceeds towards epidemic and is commonly indicated by a high rodent mortality³⁻⁵.

2. DIAGNOSTIC LABORATORY TEST

Plague may be suspected in febrile patients who have been exposed to rodents in known endemic areas. The specimen should be collected before antibiotic treatment is started and since *Y. pestis* is a highly infectious pathogen, therefore, specimens should be handled with care. The blood specimen is taken for culture and aspirates of enlarged lymph nodes for both smear and culture. In case of pneumonia, sputum is used but in possible cases of meningitis cerebrospinal fluid (CSF) is taken for smear and culture and should be incubated at room temperature. The organism in smears is capsulated and shows bipolar staining (safety pin appearance) with methylene blue, Giemsa or Wayson rapid stain. The organism grows on both MacConkey's and Blood agar, although colonies grow somewhat more slowly than those of other Enterobacteriaceae. The plague laboratory data are non-specific as the white blood cells count is usually elevated with left shift,

while platelets are decreased or normal⁵⁻⁸. Polymerase chain reaction (PCR) is another technique that has been used successfully in the detection of *Yersinia pestis* in fleas⁶.

3. METHODS OF CONTROL

3.1. Preventive Measures

Deratization i.e. destruction of rats by poisoning or trapping is one of the major methods of rat control. All rodenticides should be used with great care as they can infect humans as well. Following are some methods to be considered as preventive measures for complete rat control^{5,7-12}:

- In most of the cases, warfarin may be used which has fewer disadvantages than other poisons due to its slow action and creates no suspicion in rats.
- Bait-ground cereals are used as the basis for bait.
- Rat-proofing of buildings, houses and warehouses should be made considering the borrowing and climbing habit of the rats.
- Reduction of harborages of rats by the proper garbage disposal.
- Survey of rodent population periodically to determine the effectiveness of sanitary programs and to evaluate the potential for epizootic plague; rat control should always be preceded by measures to control fleas.
- Control of rats on ships and docks by periodic fumigation along with the destruction of rats and their fleas in vessels and in cargoes, especially containerized cargoes before shipment and on arrival from plague endemic locations.
- At present cyanogens (calcium cyanide) is employed as a fumigant and active immunization (wide infra) should also be done.

3.2. Control of Patients, Contacts and Immediate Environment Notification

In order to control the number of affected patients, early diagnosis is mandatory. Once diagnosed positive the case should be immediately reported to local health authority as case reports of suspected and confirmed patients are universally required by

international health regulations^{5,7-9}. Following are some important aspects to be taken into account in order to control the number of affected patients such as:

3.2.1. Immunization

Both antibiotics and vaccines have been used to prevent *Y. pestis* infections. Usually, antibiotics are given as prophylactic measures only to close contacts of pneumonic plague patients and in this regard tetracyclines are the most popular antibiotics for plague prophylaxis. Apart from antibiotics, there are two types of plague vaccines currently used in various parts of the world. The live vaccine is derived from a pgm-attenuated strain, usually related to EV76, while the killed vaccine uses a formalin-fixed virulent strain of *Y. pestis*. There has been an increasing interest in developing a new plague vaccine for a number of reasons. First, the current vaccine causes an adverse reaction in a significant percentage of users, although the reactions are generally mild but can be severe in some cases. In addition, the antibodies directed against the vaccine become weaker relatively quickly requiring booster doses every 1 to 2 years. Finally, experimental evidence indicates that the plague vaccine does not provide immunity against the pneumonic form of the disease^{5,10-16}.

3.2.2. Treatment

Streptomycin has been used to treat plague for more than 45 years and still remains the drug of choice with chloramphenicol and tetracycline used as alternative agents. Aminoglycosides and some sulfa drugs including sulfamethoxazole-trimethoprim have also been found active against plague but insufficient outcome studies have been performed on them and therefore they are not recommended as the first-line therapy. The close contacts should be treated with prophylactic tetracycline especially if the index case has pneumonia^{5,18-20}.

3.2.3. Isolation

For patients with bubonic plague (if there is no cough and chest x-ray is negative) drainage and secretion precautions are indicated for 48 hours after

the start of effective therapy. For patients with pneumonic plague, strict isolation with precautions against the airborne spread is required until 48 hours of appropriate antibiotic therapy has been completed with a favorable clinical response^{5,18,19}.

3.2.4. Concurrent disinfection

Concurrent disinfection of sputum and purulent discharges and articles should be soiled therewith^{5,18,19}.

3.2.5. Terminal disinfection

The bodies of people and carcasses of animals that died of plague should be handled with strict aseptic precautions^{5,18,19}.

3.2.6. Quarantine

Those who have been in household or face to face contact with patients with pneumonic plague should be provided with chemoprophylaxis and placed under surveillance for 7 days. However, those who refuse chemoprophylaxis should be maintained in strict isolation with careful surveillance for 7 days^{5,18,19}.

3.2.7. Investigation of contacts and sources of infection

A search should be carried out for people with household or face to face exposure to pneumonic plague, sick or dead rodents and their fleas. Flea control must precede or coincide with anti-rodent measures. Dust the rodent runs, harborages and burrows in and around known or suspected plague areas with an insecticide labeled for flea control and known to be effective against local fleas. The bodies and clothing of residents in the immediate vicinity should also be dusted^{5,21-23}.

3.3. Epidemic Measures

The following epidemic measures should be taken into account such as^{5,9,10,17,22-27}:

- Investigate all suspected plague deaths with autopsy and laboratory examinations when indicated.
- Develop and carry out case findings.
- Establish the best possible facilities for diagnosis and treatment. Alert existing medical facilities

to report cases immediately and to use full diagnostic and therapeutic services.

- An attempt should be made to mitigate public hysteria by appropriate informational and educational releases through the press and news media.
- Institute intensive flea control in expanding circle form known foci.
- Implement rodent destruction within affected areas only after satisfactory flea control has been accomplished.
- Protect all contacts such as field workers against fleas, dust clothing with insecticide powder and use insect repellents daily.

3.4. International Measures

Some important protective measures to be carried out internationally may include as^{5,9,10,17,22-27}:

- Notification should be sent within 24 hours by Government to WHO and adjacent countries.
- Measures applicable to ships, aircraft and land transport arriving from plague areas are specified in International Health Regulations.
- All ships and planes should be free of rodents or periodically de-ratted.
- Rat proof buildings must be built at sea and airports. Appropriate insecticides should be used and rats must be eliminated with effective rodenticides.
- For international travelers, international regulations require that prior to their departure on an international voyage from an area where there is an epidemic of pulmonary plague, those suspected of significant exposure shall be placed in isolation for 6 days after last exposure. On arrival of any suspected infested ships or aircraft, travelers may be disinfected and kept under surveillance for a period of not more than 6 days from the date of arrival.

4. CONCLUSION

The tiny insect toppled the world's social structure especially in Europe and altered medieval society forever. We are lucky to have the knowledge and resources (vaccines and antibiotics) to protect against this scourge.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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