Abstract
National Institute of Allergy and Infectious Diseases has classified all the emerging infectious diseases agents under three categories. Among Category A priority pathogens comes *Bacillus anthracis* – the causative agent of Anthrax. It is a gram positive spore bearing bacteria, and the disease is typically associated with grazing animals, and affects the people as a zoonosis. The disease can be classically transmitted by three routes namely: cutaneous, gastrointestinal and pulmonary, with a fourth route recently identified as “injection anthrax”, seen in intravenous drug abusers. Cutaneous anthrax is the commonest form in humans, accounting for 95% of all the cases. There are two main virulence factors of this bacteria, a capsule and an exotoxin, each carried by a separate toxin. Two models have been used for explaining the pathogenesis of this infection. The earlier one or “Trojan horse” model is now replaced with “jail-break” model. Centers for disease control (CDC) has issued updated guidelines for diagnosis, post-exposure prophylaxis and treatment. For immunization, anthrax vaccine absorbed is available.

Key Words: Anthrax, bioterrorism, emerging threats

Introduction
Infectious disease is one of the few genuine adventures left in the world (Hans Zinsser; 1878–1940).

Emerging infectious diseases can be defined as infectious diseases that have newly appeared in a population or have existed but are rapidly increasing in incidence or geographic range or that are caused by one of the National Institute of Allergy and Infectious Diseases Category A, B, or C priority pathogens. Category A pathogens are those organisms/biological agents that present highest threat to national security and public health because they (i) are easily transmissible, (ii) result in high mortality rates with a potential for major public health impact, (iii) might lead to widespread panic among society, and (iv) demand special action for public health protection. Among the Category A priority pathogens, the list is topped by none other than *Bacillus anthracis*, the causative agent of anthrax.[1]

Anthrax constitutes one of the eleven major zoonotic diseases in India as listed by Roadmap to Combat Zoonoses in India. The actual incidence of anthrax in this country is not yet known, thanks to underreporting.[2] Although many parts of India bear enzootic focus for animal anthrax, it seems to be less frequent in northern parts of the country and sporadically reported from southern parts.

The Pathogen
*Bacillus anthracis* is a Gram-positive sporebearer that causes the disease. As this disease is associated with grazing animals mainly, it is zoonotic for the persons associated with it. Classically, the disease is contracted by three means of exposure: cutaneous, gastrointestinal, and inhalational. However, recently, a new form has been recognized and deemed “injection anthrax,” as it is associated with *B. anthracis*-contaminated needles in intravenous drug abusers.[3]

Cutaneous form is the most common form in humans, accounting for 95% of all the cases.[4] This form has the lowest mortality rate, 1% with antibiotics and 20% without. On the contrary, the highest mortality rate
is associated with inhalation type - 45% even with antibiotic treatment and >97% without. Perhaps, gastrointestinal form bears similar mortality rate as that of pulmonary counterpart but goes largely underdetected and occurs mostly in developing countries. [8]

**The Arsenals**
There are two main virulence factors of the bacteria, namely, a capsule and an exotoxin. Each one is carried on a separate plasmid, pXO1 and pXO2, respectively.[9] The exotoxin is tripartite in nature consisting of three parts - a receptor-binding protective antigen (PA), lethal factor (LF) and edema factor (EF). When PA is bound to LF or EF, this becomes lethal toxin or edema toxin. The vegetative form may cause infection in the laboratory, but the spore is the infectious form in nature. [9]

**Pathogenesis**
Regarding pathogenesis of infection, two models are exemplified. First one is Trojan horse model (Guidi-Rontani, 2002). This model was reassessed later and was followed by a "jail break" model.

The first one - the Trojan horse model revolves around pulmonary anthrax. This hypothesis states - (i) Spores germinate beyond the lungs in the lymphatics, being carried there by alveolar macrophages. (ii) A germination operon (gerX) was involved in this. [10] The alveolar macrophages were named Trojan horse cells as they led to disseminated disease by transporting spores from lungs to mediastinal group of lymph nodes. (iii) Finally, the bacteria escape the lymph nodes, enter the blood stream, leading to bacteremia and death.

However, in murine anthrax, it was found that vegetative bacilli grow at the spore entry site itself, be it Peyer's patches (gastrointestinal form) or dermis (cutaneous form). [10, 11] Question arises then why Trojan horse help is needed only for pulmonary anthrax, thus came the birth hour of "Jail-break model of dissemination". [12] In light of recent findings using animal models, this hypothesis proposes that (i) spores germinate at the site of initial entry into capsulated bacteria and start producing virulence factors, (ii) continuous growth increases exotoxin and protease concentration leading to epithelial/endothelial lining disruption, (iii) bacteria pass through damaged barrier, enter lymphatics, and then reach blood stream without any phagocytic transport help, leading to dissemination, and (iv) bacteria present in lymph nodes go on replicating at the same time, releasing virulence factors continuously.

However, to completely understand the pathogenesis, an ideal animal model is absolutely needed, and the quest for the Holy Grail is on.

**Clinical Forms**
Clinically, the cutaneous form of anthrax accounts for more than 95% of anthrax cases worldwide. It always starts as a small red itchy papule within 2–7 days of infection. By another 2 days, it develops into a blister which eventually ruptures. Ultimately, the whole lesion dries up into a scab called eschar, coal black in color - hence the name anthrax.

Pulmonary form, so aptly called wool-sorter's disease, is seen commonly among wool factory workers. The picture is that of hemorrhagic pneumonia with high case fatality rate.

Intestinal anthrax is rare and seen in primitive communities who eat the carcass of animals dying due to anthrax.

Anthrax meningitis or meningoencephalitis may occur from bacteremia, mostly as a complication of pulmonary form of the disease. The CSF is hemorrhagic, resembling that of cerebrovascular accident - especially subarachnoid hemorrhage. [13]

**Treatment and Prophylaxis**
Centers for Disease Control (CDC) has issued updated guidelines for postexposure prophylaxis and treatment, and the recommendations are

a. Uncomplicated cutaneous anthrax: for all strains regardless of penicillin susceptibility or susceptibility unknown:
   i. Ciprofloxacin 500 mg every 12 h or doxycycline 100 mg every 12 h or levofloxacin 750 mg every 24 h or moxifloxacin 400 mg every 24 h or clindamycin 600 mg every 8 h or alternatives for penicillin-susceptible strains or amoxicillin 1 g every 8 h or penicillin VK 500 mg every 6 h.

Duration of treatment for bioterrorism-related cases is for 60 days, and 7–10 days for naturally acquired infections. [13]

b. Antitoxin to be added to antibiotics for patients suspected to have systemic disease

c. Antitoxin might be human anthrax immunoglobulin (anthrasil) or monoclonal antibodies to the PA – oblitoxaximab or roxibacumab

d. Anthrax meningitis should be treated with at least three antimicrobial drugs, one of which should be clindamycin, and the treatment schedule should be of 60 days

e. PEP for inhalation anthrax in adults consists of ciprofloxacin and doxycycline as first-line drugs for 60 days along with anthrax vaccine absorbed (AVA).

Hygiene constitutes mainly of improvement of factory hygiene, proper sterilization of animal products like wool, and proper burial of animal carcasses suspected to be dying of anthrax.
For immunization, anthrax vaccine absorbed or AVA (Trade name-BioThrax) is available for human use. For pre-exposure prophylaxis, five doses are given to people at high risk of developing the disease. Postexposure prophylaxis is given after exposure to inhalational anthrax along with recommended antibiotics.\[14\]

**Conclusion**

Anthrax is enzootic in India, with annual infection rate running into tens of thousands. A focus of anthrax in sheep has been active in Andhra Pradesh – Tamil Nadu border area, causing many cutaneous and central nervous system infections in humans. There have been outbreaks in Karnataka and West Bengal, especially in villages of West Midnapore.\[15\] From the global epidemiological aspect, it is not only a natural infection but also a potential tool in biological warfare. In the year 2001, it was mailed to different parts of the USA, causing disease and death in many persons. FBI named it Amerithrax, and it was caused by a particular strain – Ames strain. After this, CDC Atlanta prepared guidelines for identification of anthrax Bacillus. It stated that any large Gram-positive Bacillus with the general morphology and cultural features of anthrax – nonmotile bacteria, which come nonhemolytic on blood agar and are catalase positive – can be given a presumptive report of anthrax. For preliminary confirmation, lysis by gamma phage and direct fluorescent antibody test would suffice.\[16\]

This dangerous disease occupies a twilight zone between emerging infectious disease and a potential bioterrorism agent. Probably early recognition and prompt treatment of the cutaneous form would go a long way in preventing an outbreak, as this is the most common form of this human scourge.

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**Conflicts of interest**

There are no conflicts of interest.

**What is new?**

‘Jailbreak model’ of dissemination and ‘Injection Anthrax’- a new variety are discussed

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