Typhus
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Etiological agent: obligate intracellular bacteria *Rickettsia prowazekii, Rickettsia typhi, Rickettsia felis* (2) and *Orientia tsutsugamushi* (3).

Domain: Eukaryota
Phylum: Proteobacteria
Class: Alphaproteobacteria
Subclass: Rickettsiidae
Order: Rickettsiales
Family: Rickettsiaceae
Genus: *Rickettsia*
Species: *Rickettsia prowazekii*
  *Rickettsia typhi*
  *Rickettsia felis*

Genus: *Orientia*
Species: *O. tsutsugamushi* (6).

Typhus refers to a group of obligate protozoans known as rickettsial organisms that may result in an acute illness. The disease is transmitted by arthropod vectors to humans. There are three different variations of this disease known as epidemic or “louse-borne” typhus, murine typhus, and scrub typhus. There is also a latent for known as Brill-Zinsser disease which is related to epidemic typhus. *Rickettsia prowazekii* is responsible for the epidemic typhus and the potential for Brill-Zinsser disease, *Rickettsia typhi* and *Rickettsia felis* contract murine typhus, while scrub typhus is caused by *Orientia tsutsugamushi* (1). These are all small, gram-negative coccobacilli-shaped bacteria that utilize the intracellular organelles of many animals(2).

**Epidemic Typhus:**

The body louse (*Pediculus corporis*) is the arthropod vector of epidemic typhus, while its host is the human. *Rickettsia prowazekii* live is the louse’s alimentary tract and is released onto the human’s skin through defecation while feeding on a blood meal. The human then scratches at the site and protozoan is pulled into the wound, traveling into the bloodstream, subsequently causing rickettsemia to develop. (1).

The epidemic typhus is considered the most dangerous of the typhus variants (2).
Concerning the virulence factor of typhus as an obligate intracellular bacteria, once the Rickettsia parasite has entered the body make their home inside the endothelial cells of the arterial, small venous, and capillary vessels. As the organism proliferates the endothelial cells enlarge and result in multiorgan vasculitis. Gangrene may develop as thrombosis of supplying blood vessels cuts off circulation to distal portions of the human host’s extremities, ear lobe, genitalia, or nose. Hypovolemia and decreased tissue perfusion leading to organ failure may also occur due to the vasculitis process causing loss of intravascular colloid(1). The vasculitic process can also affect the central nervous system, varying from brain fog or dullness of mentation all the way to coma. Patients with active epidemic typhus will experience fatigue, high fever (105 F), headache, nausea/vomiting, and diarrhea. Some patients also report having a cough, joint/back pain or abdominal pain. After four to seven days a distinctive rash that may cover the entire body except the palms of the hands and the bottom of the feet. The vasculitic process may also cause the patient to develop the additional symptom of petechia (bleeding into the skin). Symptoms usually abate within two weeks barring complications or death. Untreated, the mortality rate of epidemic typhus is as low as 20%, in healthy individuals, to 60% in elderly or debilitated patients(2). Due to the 5-14 day incubation period of most of the typhus causing rickettsial diseases, patients that have traveled to areas with a higher rate of infections may not experience trips until they have returned home and make associating symptoms more difficult(3). Patients may develop a more severe form if they have a glucose-6- phosphate dehydrogenase (G6PD) deficiency(4).

Although some patients appear to be cured from the epidemic typhus, Rickettsia prowazakii may linger in the tissues of the body. This is known as Brill-Zinsser disease. Months, years, or longer after treatment, the organism may cause a recurrence of the typhus disease(1), although it is generally of a less sever nature and carries a lower mortality rate. Approximately 15% of the people with a history of epidemic typhus will test positive for Brill-Zinsser disease(2).

Cases of epidemic typhus occur in certain regions of the Himalayas, Northern China, Africa, Central and South America. Outbreaks most often happen when favorable conditions for
the transmission of lice in a community arise(2).

*R. prowazekii* has been tracked to active infections in the central and eastern portions of the United States in relationship to the flying squirrel (Glaucomys volans) as the host(2) and the fleas transmitting the disease to humans through inhalation of the fleas excrement or by rubbing it into an open wound such as a bite(1).

Some research has reported positive transmission of some rickettsial disease following transfusions or organ transplantation, but is still considered very rare (3).

**Diagnosis:**

Diagnosis of epidemic typhus is done through patient's clinical history of symptoms, physical exam, and bloodwork/tissue samples to identify the bacterial genus and species. PCR testing of biopsies from areas of lesions within the rash and serum samples are used to narrow down the bacterial identification. Tissue samples, usually from the skin, can also localize the bacteria through immunohistological staining. During later stages of typhus, or after treatment with antibiotics, significant titers of anti-rickettsial antibodies can be detected by the immunological techniques(2). Detection of specific antibodies from certain species of rickettsial organisms can be detected using complement fixation (CF) tests. Serology tests showing a rising IgM titres during the acute infection stage and rising IgG in the latent Brill-Zinsser disease stage can also be used to diagnose the disease(4).

**History:**

Girolamo Fracastro (1476-1553), a Veronese physician, first described the rash now associated with typhus as lenticulae("small lentils"), puncticulae ("small pricks"), and petechiae ("bites")(7).

During the siege of Granada in 1489, there was written description of a disease that was most likely epidemic typhus. The writings described the death of over 17,000 Spanish troops with symptoms of delirium, rash, and sores. 1494 French troops stationed in Italy lost 30,000 soldiers to typhus. Then during the Thirty Years War (1618-48) in Europe, typhus was a major problem. This was mainly due to crowded cities, poor hygiene, and heavy rains for marching soldiers. In 1643, both Parliamentarian and Royalist armies were so ravaged by typhus that the country basically became one huge hospital(7).English authorities in 1759 estimated that about 25% of all prisoners in England were dying of the same type of disease per year(2). The name “typhus” was not notated until 1760, after the Greek word for “smoke” or “stupor” from the delirium that can develop(5). Due to the thatched roofs, close quarters, wartime living conditions and propagation of slum like areas, Europe experience many epidemics of typhus raging for several centuries. It is estimated by some historians that more of Napoleon’s troops were killed by typhus than by combat power of the Russian soldiers during their 1812 retreat from Moscow. During the Crimean War from 1854-6, nearly twice as many soldiers died from disease like typhus than from combat wounds(7).

Many researchers confused typhus and typhoid fever as the same illness because of the similar presentations. During 1829 the French physician Pierre Louis (1787-1872) officially
coined the term "typhoid" which means "like typhus". In 1835-36, William Wood Gerhard (1809-72) studied a typhus outbreak amongst Irish immigrants in Philadelphia to greater understand the differences between them. The biggest difference found between patients during autopsy was the presence of inflamed lesions in the small intestines of typhoid patients which was absent in typhus patients(7).

Ireland and America’s records show several period of epidemic typhus during the 1830’s, accounting for over 100,000 death(7).

In 1909, the body louse (Pediculus humanus corporis) was found to be the vector that transmits typhus by Charles Nicolle. Summing up these conclusions about the transmission and vector of the disease won him the Nobel Prize in 1928(7). In 1916, D.C. Henrique da Rocha Lima, a Brazilian doctor doing research on typhus in Germany localized the cause of epidemic typhus(2). However the first vaccine was not produced until 1937(7) which meant that there were still an estimated over 3 million deaths attributes to typhus during WWI(3). During the Holocaust, German concentration camps were notorious for typhus outbreaks. Anne Frank died from typhus in a camp at the age of just 15 years old(7).

Control:

Maintenance and cleanliness of areas with close quarters and better hygiene are some of the most important methods of prevention. The vaccine produced in 1937 by Rudolph Weigl did help reduce outbreaks during the time, especially in slums and high war areas, some researchers debate the overall coverage of the vaccine. The vaccine was created with the use of some of the first testing on guinea pigs and then even on human “feeders” by lice with a formaldehyde-deactivated, R. prowazekki strand. DDT was used widely at the end of WWII and after a few epidemics in Africa, Eastern Europe, Asia, and the Middle east to kill the lice that transmit the disease. However, due to the toxicity and risk from DDT, the use of it has been banned in the U.S. since 1972(2).

Treatment:

Antibiotic therapy, such as azithromycin, doxycycline, tetracycline or chloramphenicol, are recommended to treat both epidemic and endemic typhus. A full course of these antibiotics can cure most patients infected but full cure may take longer or more extended treatment in patients that are over the age of 60 or otherwise immuno-compromised. In these patients, the patient's prognosis may still be only fair to poor due to complications such as renal insufficiency, pneumonia, or central nervous system damage(2).

Murine Typhus/Scrub Typhus Variants:

The three variants of typhus have much in common but the following shows the differences in murine and scrub typhus versus epidemic typhus. Murine typhus is caused by R. typhi and R. felis, which is hosted by rats, mice, cats, and opossums, and transmitted by the fleas that feed on them. Areas that have poor hygiene, impoverished areas, and crowded living conditions have a higher prevalence of endemic typhus. It has been found patients that have been previously exposed to R. typhi has been shown to maintain subsequent, long-lasting immunity to reinfection. R. felis is related to fleas found on opossums and cats, and has been reported in
southern California and southern Texas. Occurrences increase during spring and summer months when fleas are most active. In Galveston, Texas during 2013, 12 patients with murine typhus were identified which may point towards a re-emergence of *R. typhi* in the rat population or a new cycle of *R. felis* in the opossum/feline population(1). Travis County, Texas (including Austin, TX) was declared to be endemic for murine typhus in 2011 with 53 cases diagnosed(2).

Murine typhus occurs in many locations internationally, especially the subtropical and temperate coastal areas. Researchers believe that the incidence of murine typhus is probably greatly underestimated in endemic regions.

Scrub typhus is caused by the organism *Orientia tsutsugamushi* and has been reported across the western Pacific region, Indian subcontinent, and northern Australia. Although not classified with the other rickettsiae, *Orientia tsutsugamushi*, is very similar in presentation and treatment to the epidemic and endemic typhus diseases. The symptoms are overall very similar as a milder form of epidemic typhus but patients may also present with a papule with black eschar at the bite site, lymphadenopathy, and more prominent gastrointestinal symptoms(5). Many cases of scrub typhus go undiagnosed because of its difference in manifestation and lack of diagnostic laboratory testing. One study done in Malaysia found an incidence of scrub typhus to approximately 3% per month, and noted a reinfection of the same individuals due to a lack of immunity developed to *Orientia tsutsugamushi*, even after repeated infections(2). In northern Thailand and Laos, 25% of adults presenting with fever and negative blood cultures are diagnosed with scrub typhus. The mites that carry *Orientia tsutsugamushi*, thrive in areas of scrub vegetation (hence the name) and breed most during the rainy seasons or near water. US troops during WWII were continually at risk of contracting scrub typhus while fighting in the Pacific, and caused many deaths. No effective antibiotic treatments were available to treat scrub typhus prior to 1944. This remained a problem for troops that were stationed in Japan after the surrender(5). While the initial infection of scrub typhus is most often self-limiting, it can occasionally turn more severe or even fatal when not treated. Mortality rates of patients that go untreated varies from 4-40%.

No cases of scrub typhus have been identified as starting in the United States, but patients have been diagnosed with it after returning from endemic areas(3).

Both murine and scrub typhus share a somewhat milder version of the epidemic typhus pathophysiology and symptoms experienced by the patient. Murine typhus patients that undergo treatment have a mortality rate of just 1-4% and less than 1% mortality rate for treated scrub typhus patients. Between 1996-2011, a worldwide network that monitors travel-related disease and morbidity called GeoSentinel reported no fatalities in 16 cases of murine typhus and 13 cases of scrub typhus(2).

Works Cited:


