

Scrub typhus-resurgence of a forgotten killer

Rickettsial diseases are an important cause of febrile illness. The infections are prevalent worldwide but are often undiagnosed/misdiagnosed leading to life-threatening condition. Tropical rickettsioses represent a diverse group of zoonotic infectious diseases caused by obligate intracellular gram negative, non-flagellate, and non-spore-forming *coccobacilli*.^[1] Based on genetic and antigenic data, the rickettsiae are divided into three groups, viz. spotted fever group, typhus group and scrub typhus group.^[2]

Scrub typhus, also called tsutsugamushi disease is caused by *Orientia tsutsugamushi*.^[3] It differs from other rickettsia species by its lack of polysaccharide cell wall^[4] and wide heterogeneity within the genus^[2] and thus deserves special emphasis during serological tests.

The disease is contracted via the bite of trombiculid mite larvae (chiggers) living in a wide range of vegetation type from scrubs (terrain between woods and clearings), primary forests to gardens, beaches etc. The epidemic period is influenced by activities of the infected mite which appear to occur more frequently during or after rainy seasons, thereby resulting in a spurt in cases during and after monsoon. Humans are accidental hosts and seen in people where activities bring them into contact with vector chiggers.

An estimated one billion people live in endemic areas with an annual incidence of approximately one million cases.^[4] In India, the disease was first noted among troops during World War II in Assam and West Bengal, and during Indo-Pak war in 1965.^[5] Though specific data is not available from our country, but outbreaks have been reported from the Sub-Himalayan belt, from Jammu to Nagaland,^[6] Haryana,^[7] and in 2012 from Rajasthan. Keeping in view the morbidity and mortality associated with undiagnosed cases (due to both lack of specific diagnostic tests and ignorance about the disease), the disease deserves a special mention.

In past, characteristic eschar (blistered ulcer covered with black crust and surrounded by reddish erythema) at the bite site was considered to be pathognomic of scrub typhus. However, eschar is reported in only up to

50% cases,^[2] is uncommon in patients living in South East Asian countries and indigenous persons of typhus endemic areas.^[8] Virulent strains of *O. tsutsugamushi* are associated with hemorrhagic and intravascular coagulation, purpura fulminans, atypical pneumonia, acute respiratory distress syndrome, myocarditis, jaundice, and meningoencephalitis in addition to skin rash.

The mortality rate in pre-antibiotic era had varied from 3% in Taiwan to 60% on the North coast of Japan. Despite effective and cheaply available treatment modality, this disease still carries a huge burden in terms of mortality owing to misdiagnosis and delayed treatment.

Diagnosis of the disease still remains an enigma in resource-limited settings like India. The confirmation of diagnosis is usually by serological tests such as Weil Felix. The test is highly specific and cheap, but less sensitive. The test detects antibodies cross reactive to antigens of the OX-K strain of unrelated bacteria proteus mirabilis. A 4-fold rise in agglutinin titre in paired sera or a single titre of $\geq 1:160$ is considered diagnostic of recent infection. The gold standard diagnostic tests include immunofluorescent assay and immunoperoxidase assay, based on cell culture-derived *O. tsutsugamushi* antigen. Molecular methods like polymerase chain reaction (PCR) for detection of 47 kDa and 56 kDa protein gene of *O. tsutsugamushi* are reliable and quantitative. Rapid diagnostic tests include anti *O. tsutsugamushi* IgG and IgM antibodies detection with commercially available ELISA kits. The drawbacks include poor availability and cost.

Management includes the early and prompt use of antibiotics on suspicion of scrub typhus. Unless contraindicated, Doxycycline is the drug of choice (100 mg q12h for 7 days after a loading dose of 200 mg).^[9] Chloramphenicol or tetracyclines are also useful. Alternative drugs include rifampicin (600-900 mg) and azithromycin (500 mg on 1st day and 250 mg/day later on),^[10] later being useful in pregnancy.

Intensivists often come across the febrile illness cases with features of multi-organ dysfunction syndrome (MODS), ARDS, and bleeding diathesis. 17% of ARDS cases in our intensive care in 2010 were due to scrub typhus with only 40% of them having an eschar, however, MODS was universal (unpublished data). This resulted in doxycycline

(azithromycin in pregnancy) being made a standard part of initial treatment of fever having MODS/ARDS reporting to our institution.

These cases are increasingly seen all over and are treated as either enteric/Gram-negative sepsis or malaria. Rampant misuse of antibiotics, which have activity against typhus, has also added to the confusion. Absence of eschar or rash should not lead to its exclusion from differential diagnosis. A high index of suspicion, effective and prompt treatment can save lives.

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