SCRUB TYPHUS EMERGING THREAT

CLINICAL VIEW POINT

Scrub Typhus: Clinical Approach

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Scrub typhus is an acute, febrile, infectious illness caused by *Orientia* (formerly Rickettsia) *tsutsugamushi*, an obligate intracellular gram-negative bacterium. Humans are accidental hosts in this zoonotic disease (1-3).

Clinical Presentation

Suspected cases of scrub typhus, elicit history of travel to endemic areas. The incubation period from the mite bite is 5-20 days following inoculation (4). There is great variation in the severity of illness produced by each organism. Infection most commonly begins with a papule forming at the site of the bite where the infection was introduced. This usually becomes necrotic and forms a typical black eschar (scab). It is usually painless and 3-6 mm in diameter. Four days to two weeks after the bite, symptoms begin with fever and malaise followed by adenitis in the lymph glands draining the bite site (5). As the organisms spread throughout the body, fever, malaise and headache increase and general lymphadenopathy occurs in most cases.About a week after onset the main features are continuous fever (104-105°F), cough and signs of bronchitis or pneumonia, photophobia, conjunctivitis, generalised adenopathy, delirium, deafness and a centrifugal maculopapular rash most commonly over the trunk & proximal limb parts, approximately 35% of patients Splenomegaly occurs in some cases (5).A small number of patients have CNS involvement with tremors, nervousness, slurred speech, nuchal rigidity, or deafness during, the second week of the disease. More virulent strains of O. tsutsugamushi can cause hemorrhage and intravascular coagulation. Children with scrub typhus may develop serious complications and may even die if appropriate treatment is not given (6).Fever may persist for 14 days without antibiotic treatment. The fatality rate in untreated cases is 1-40%. This increases with age and depends on the infection site, the type of Rickettsiae involved and previous exposure. More virulent strains of *O. tsutsugamushi* can cause hemorrhage and intravascular coagulation.

Differential Diagnosis

Differential diagnosis of eschar include viral infections (herpes simplex virus), bacterial conditions (anthrax, tularemia, ecthyma, other rickettsioses according to endemicity) and fungal diseases (aspergillosis, fusariosis, mucormycosis) and other rickettsial infections like murine typhus, mediterranean spotted fevers. Lymphadenopathy adds leptospirosis, typhoid, dengue, malaria, HIV, EBV, CMV, T. gondii to the differentials (5). Classical eschar will be seen in cases of scrub typhus only. Both enteric and scrub typhus will present most of the times with low or normal WBC counts

Laboratory Tests

Routine laboratory studies in patients with scrub typhus reveal early lymphopenia with late lymphocytosis. Albuminuria is a common laboratory finding. Abnormal hepatic function tests may be seen during the illness. Results from the cerebrospinal fluid examination either are normal or indicate a low number of monocytes.The confirmatory tests are the indirect immunoperoxidase test and the immunofluorescent assay. An infection is confirmed by a 4-fold increase in antibody titers between acute and convalescent serum specimens. A single high titer with classic clinical features is considered a probable case. A dot immunoassay has also been used in the serodiagnosis of scrub typhus. The organism has been identified by the polymerase chain reaction (PCR) technique in clinical specimens. The Weil-Felix OX-K strain agglutination reaction may be the only serologic test available in our primary care settings, but it is not a very sensitive assay (7). Non-specific radiological findings varying from ground glass opacities, mediastinal lymphadenopathy, pleural effusion, pulmonary consolidation may be seen on chest radiography (8).

Preventive Measures

There is no vaccine available. People who enter infected areas can be protected by impregnating their clothing with dimethyl phthalate and renewing the repellent frequently. Topical DEET (N,N-diethyl-m-toluamide) applied to exposed skin will prevent tick, flea, and chigger bite. Bites may also be limited by wearing long trousers that are tucked into boots (9). Chemoprophylaxis can be successfully used short term and for this a consultation with an infectious diseases specialist is recommended. Weekly doses of 200 mg of doxycycline can prevent scrub typhus, but the

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efficacy of the daily 100 mg doxycycline dose regimens for malaria chemoprophylaxis against O. tsutsugamushi or Rickettsia spp infection is untested and unknown (9)

Management of Scrub Typhus

Without treatment, fever subsides within 2 weeks spontaneously but the mortality rate may be 10-30%. Treatment of scrub typhus must be initiated early in the course of the disease, based on presumptive diagnosis, to reduce morbidity and mortality (2).Broad spectrum antibiotics effective against rickettsiae are the only agents which can be used for treatment. Antibiotic treatment is thought to shorten the illness and reduce mortality. It is usually presumptive, being given to cases who are febrile in an area where the disease is endemic. Chloramphenicol was the first drug described in a series of studies to reduce the morbidity and mortality associated with the disease. Other drugs which can be used for managing the illness include tetracycline, doxycyline and rifampicin.Doxycycline remains the treatment of choice for all patients, including young children. In general, the risk of dental staining by doxycycline is negligible when a single, relatively short (eg, 5-10 days) course of therapy is administered. Parenteral doxycycline should be given to patients who cannot swallow tablets or who are severely ill. The recommended duration of doxycycline in scrub typhus should be not less than 7 days (10). Scrub typhus cases from northern Thailand with a diminished response to conventional therapy of doxycycline have been described although neither the geographic distribution of resistance nor its mechanism has been defined (2). Rifampicin seem to be more effective than doxycycline in areas where scrub typhus appears to respond poorly to standard doxycycline therapy (11). In patients with severe hypersensitivity to the tetracyclines, 50 to 75 mg/kg per day of chloramphenicol has been considered an alternate therapy but its use is limited by side effects. In general, use of this drug as therapy for rickettsioses should be considered as empirical treatment of severe cases only if no other drugs are available. Azithromycin has also been evaluated in clinical trials, but is not yet approved for this condition (12).

Although scrub typhus is uncommon in pregnant women, when present, it can have serious repercussions for the mother and developing fetus. Azithromycin has been found to be effective against scrub typhus and had favorable pregnancy outcomes (13). The fluoroquinolones may have efficacy against scrub typhus in clinical practice, but as yet, there are insufficient data and reports are largely anecdotal. New antibiotics are required to have the antibacterial activity against doxycycline-resistant Orientia tsutsugamushi (14). The efficacy and safety of a 5-day once-a-day regimen of 800 mg telithromycin was equivalent to those of a 5-day twice-a-day regimen of 100 mg doxycycline in patients with mild-to-moderate scrub typhus. Telithromycin could be considered a promising new antibacterial agent for patients with scrub typhus.The current research aims mainly to characterise the appropriate length of antibiotic treatment to minimize recrudescence and to confirm the potential advantage of alternative drugs (azithromycin, clarithromycin,and ciprofloxacin).

Conclusion

Little is known about the scrub typhus in the tropics.Heightened awareness of rickettsial illnesses, careful history taking, and thorough physical and laboratory examinations by primary physicians have been crucial. Presumptive treatment with doxycycline should be instituted on clinical suspicion. Increasing awareness of rickettsial illness is need of hour.

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