

SCRUB TYPHUS: COMBINATION THERAPY CAN SAVE MORE LIVES

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March 04, 2023 08:15 pm | Updated 11:27 pm IST

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Scrub typhus — a life-threatening infection caused by *Orientia tsutsugamushi* bacteria — is a major public health threat in South and Southeast Asia. As per estimates, nearly one million cases are reported from South and Southeast Asia with 10% mortality. India is one of the hotspots with at least 25% of the disease burden; in CMC Vellore alone, 500-1,000 patients are treated each year, of which 250-300 have severe disease.

A seroprevalence study undertaken about five years ago in Vellore, Tamil Nadu, by researchers at the CMC Vellore showed over 30% antibody positivity for the bacteria in the community, indicating that they were exposed to the pathogen.

What makes scrub typhus a major public health threat is the very high mortality rate in patients with severe disease despite diagnosis and treatment. In a study published by CMC Vellore researchers in 2014, the mortality in patients with severe scrub typhus disease with multi-organ dysfunction was 24%.

Till date, monotherapies using either doxycycline or azithromycin was the commonly used treatment. A trial carried out now in seven centres in India where patients were randomly assigned to receive a combination therapy of both doxycycline and azithromycin showed faster resolution of complications compared with two other arms where patients were given monotherapy of either doxycycline or azithromycin. The trial enrolled nearly 800 patients (265 in the doxycycline group, 263 in the azithromycin group, and 266 in the combination-therapy group). The results were published in *The New England Journal of Medicine*.

“The 28-day mortality was the same (12.1%) in all the three groups. But since we were able to achieve faster resolution of complications at day seven in the combination therapy group, we can potentially save thousands of lives,” says Dr. George M. Varghese, Professor at the department of infectious diseases, CMC Vellore, and the primary investigator and corresponding author of the paper.

The frequencies of respiratory, renal, hepatic, and central nervous system complications were lower in the combination-therapy group than in either of the monotherapy groups. “We need a larger number of patients enrolled in the trial to conclusively prove that faster resolution of complications will result in more lives saved. But it is unethical now to continue the trial as the benefit of the combination therapy over monotherapies has already been established,” says Dr.

Varghese.

Among the patients who died in the study, 50% died within 48 hours of arrival. This indicates that patients who arrive late with multiple organ dysfunction may have a higher risk of mortality as their condition may have progressed too far for effective treatment.

“This trial has shown that the combination therapy using both doxycycline and azithromycin is far more effective in treating severe scrub typhus than monotherapies of either drug by itself,” he says.

“Although mortality was similar in the combination-therapy and monotherapy groups, the reduced number of complications at day seven in the combination-therapy group may translate into important benefits in underdeveloped regions in which scrub typhus is endemic, where the capacity for advanced supportive care is limited,” says an accompanying editorial in the journal.

Until the results of this trial were published, there were no clear-cut treatment guidelines for severe scrub typhus. Though oral doxycycline was routinely used as a monotherapy, the drug has to be administered intravenously for severe disease. This made treatment with azithromycin attractive as the intravenous formulation of the drug was widely available. However, even the largest trial so far, comparing doxycycline and azithromycin, included only less than 100 patients with milder disease.

In contrast, the superiority of combination therapy for severe scrub typhus has been demonstrated by clinical evidence from the largest ever randomised, controlled trial. Second, the combination therapy was able to achieve faster clearance of the bacteria compared with monotherapies. The faster clearance in the combination therapy arm may be due to the complementary effect of the drugs.

While azithromycin concentration inside the cells where the bacteria proliferate can be 100 times that of the plasma, doxycycline has higher concentration in the plasma. The different sites where the two drugs stop the bacteria from producing proteins through different but complementary mechanisms may be the reason why the combination therapy has been able to clear the pathogen faster.

Scrub typhus is transmitted to humans by bites from tiny infected larvae of mites; mites breed during July-March. Only the larval stage of the mite requires a blood meal, which is usually from rodents.

“The larvae are invisible to the naked eye and the bite is not painful. So people don’t realise they have been bitten by an insect and possibly infected,” Dr. Varghese says. The infection does not cause typical symptoms, thus, making correct and early diagnosis difficult. Also, awareness about the infection and disease is very low despite high disease burden and mortality rate. Increasing the awareness can clearly bring down the mortality rate, as demonstrated by the CMC Vellore researchers.

“In 2005-2006, the mortality rate was 15% in patients presenting at our hospital. By building awareness and early diagnosis, we were able to more than halve the mortality from 15% to 6% in about 10 years even with monotherapy,” he recalls.

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