EDITORIAL COMMENTARY

Presumptive Treatment of Acute Febrile Illness for Preventing Acute Encephalitis Syndrome: Does It Work?

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Scrub typhus is an important cause of fever without focus in Asia, and outbreaks have been reported from all over India. High case fatality is reported in patients of scrub typhus with central nervous system involvement [1]. The current gold standard, Indirect immunofluorescent assay (IFA), is neither perfect nor practical. The antibody based tests are not positive in early illness. Besides, in endemic areas where there is likely to be circulating antibodies, an appropriate cut-off is needed to reduce false positives.

Recurrent outbreaks of acute encephalitis syndrome (AES) during post-monsoon season have been reported from Gorakhpur for over three decades. After the introduction of the JE vaccine, the incidence of JE in the Gorakhpur division declined and currently it accounts for less than 10% of AES in that area [2]. Scrub typhus was incriminated as a major cause of AES in outbreaks reported in 2015 and 2016 [3]. Scrub typhus was also reported as an important cause of acute febrile illness (AFI) from the same area [4]. Considering the high mortality and lack of good diagnostic facilities in the area, Indian Council of Medical Research (ICMR) recom-mended empiric treatment with oral doxycycline in cases of acute febrile illness and intra-venous azithromycin to treat established AES [5]. The study by Thangaraj, *et al*. [6] in this issue of the journal shows that the intervention is effective in reducing the progression of AFI to AES.The authors did not look at the etiology of AFI in the present study but about 37% of the cases had undifferentiated febrile illness. However, it must be pointed out that in an earlier study from the same area, 18% of patients with acute febrile illness had IgM antibody positive for scrub typhus, most of these had mild illness and recovered without specific treatment [4].

Both doxycycline and azithromycin are equally effective as treatment for scrub typhus. While these antimicrobials appear to have reduced the progression to severe form of scrub typhus, the effects of this therapy on malaria or other bacterial infections, particularly typhoid fever, are not clear and have not been studied. Data on the burden of malaria and typhoid during the post monsoon season in this region during this period would have provided key insights into the possibility for the additional therapeutic benefits to the childhood population.

In the MORDOR trial [7], a 14% reduction in all-cause childhood mortality among under-5 children in Malawi, Niger and Tanzania was reported with mass adminis-tration of one dose of azithromycin given every six months for two years. This is postulated to be due to the prevention of deaths due to respiratory infection, diarrhea and malaria in treated children as well as their close contacts. However, presumptive treatment for acute febrile illness risks the development of antimicrobial resistance in microorganisms. There is also a risk of over-use of this presumptive treatment beyond the season of transmission by all categories of health providers.

Antimicrobial resistance is a global health threat that is estimated to cause at least 700000 deaths annually [8]. India has one of the steepest antibiotic resistance rates among bacteria that cause community and healthcare acquired infections [9]. Indiscriminate use of azithro-mycin beckons accelerated emergence of macrolide resistance.Treating patients empirically is justified as a quick response measure during the peak season of transmission but bears the risk of antimicrobial resistance and cannot be the mainstay of approach to control scrub typhus.

The common causes of fever besides scrub typhus in the community include acute respiratory infections (mostly viral), dengue fever, malaria, and typhoid fever. It has been seen that algorithms that use a combination of clinical and laboratory tests improve diagnosis and optimize treatment [10]. The National Essential Diagnostic List developed by ICMR reiterates use of ELISA at the level of the district hospital [11]. It is time for India to invest in strengthening the capacity of public health facilities to rapidly diagnose causes of febrile illnesses such as dengue fever, influenza and typhoid *etc*,

and develop a clinical algorithm incorporating point of care tests for management of AFI with rapid turnaround, which could be used at the level of primary health center. Use of rapid diagnostic tests has reduced the overuse of antimalarial drugs. Efforts are needed to expand the use of point of care tests for other common causes of febrile illness, which will optimize disease management. Future research efforts should focus on developing new antigen-based point of care tests to accurately diagnose scrub typhus in early phase, thereby reducing the number of patients treated empirically.

There is also a need for formative research into the modifiable risk factors for scrub typhus. Unlike adults who are at risk of scrub typhus due to their occupation, young children are likely to be at risk of exposure due to poverty-related poor sanitation practices and child rearing practices. Presence of vegetation or bushes near the house is a risk factor for scrub typhus. In Gorakhpur, children who had recent exposure to the outdoor environment (for defecation, playing or visiting agricultural fields), or engaged in storing firewood indoors, and handling fodder for cattle were found to be at a higher risk for acquiring scrub typhus [12]. Strategies for prevention of scrub typhus should therefore include providing sanitary toilets and focus on changing behaviors through policy initiatives like Swach Bharat Abhiyan.

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