Editorial

Enteric Fever Still haunts us with New Challenges

Enteric fever is a disease produced by *Salmonella enterica* serotype typhi and paratyphi A, B and C and rarely, cholerasuis. Introduced in the 1800s, the term is used because of the involvement of Peyer's patches along with mesenteric lymph nodes, but it is in fact a systemic infection with involvement of the mononuclear phagocytes. The terms 'typhoid fever' and 'paratyphoid fever', which indicate the particular toxic mental state of the patient, are used synonymously with enteric fever.

The incidence of enteric fever is low in developed nations, but it is endemic in the Indian population and is more commonly seen in urban compared to rural areas.[1] Young children and adolescents are more likely to be affected compared to people of the older age group. The disease spreads via the faeco-oral route, through contaminated food and water. Bacteria reach the reticulo-endothelial system through the mesenteric lymph nodes. In this phase, Peyer's patches hypertrophy and may even undergo necrosis due to recruitment of monocytes and lymphocytes. Eventually, bacteria enter the thoracic duct and finally reach the bloodstream.[2] Bacilli are seeded into various organs—liver, gallbladder, spleen, bone marrow, lymph nodes, lungs and kidneys.

Although the classical clinical features of typhoid are seen sometimes, the textbook description is not sufficiently sensitive or specific for typhoid fever, as diseases do not 'read textbooks'. The teaching that 'every undifferentiated fever in the tropics must be considered as typhoid, unless proven otherwise' has generated a lot of diagnostic lethargy and prescribing vigour. Other tests that give a diagnostic clue towards enteric fever but lack both sensitivity and specificity are serological tests such as the Widal test,[3] rapid serological tests detecting Vi or O:9 antigens.[4] Although used commonly for diagnosis, they are unreliable as false-negative results can occur in the early weeks of the illness, false-positive test results can be obtained in case of past infections, previous exposures or vaccination. There is no universally defined standard cut-off for the Widal test, leaving it to the physician to interpret. Due to these reasons, it should never be used as the sole test for diagnosis. ELISA test against polysaccharide Vi Ag may be useful in detecting carriers, but should not be used for diagnosis.[5] Some rapid diagnostic tests available are Multi-Test Dipsticks, TUBEX and TyphiDot. PCR (polymerase chain reaction) can be performed, and the flagellin, somatic gene and Vi gene can be detected by the same. Simple haematological tests such as complete blood count show anaemia, leukopenia (leukocytosis can be present in children, perforation and secondary infection), eosinopenia and thrombocytopenia. Absolute eosinopenia, i.e. an eosinophil percentage of 0 on peripheral smear, could be an important marker for typhoid.[6] However, it is not specific for enteric fever and may occur in other bacterial infections.[7] It has a high negative predictive value; therefore, a high eosinophil count may help the clinician rule out enteric fever and think of another diagnosis. A positive culture is the only confirmative diagnostic test for enteric fever. Organisms can be isolated from blood, bone marrow, stools, rose spots, intestinal secretions, urine, cerebrospinal fluid, pus from suppurative lesions and sputum. Sensitivity of bone marrow culture is >80%, of blood 40%–80%, of stools ~30%. When intestinal secretions, blood and bone marrow, all are cultured the sensitivity of all three together is >90%. Bone marrow can yield bacteria even after 5 days of initiation of antimicrobial therapy.[8] Stool culture is more sensitive in the third week.[2] Once Salmonella has been identified on culture, antisera is needed to differentiate between the various species.

Up to 1972, chloramphenicol was a widely used drug due to its efficacy and intracellular penetration, but resistance developed in the 1970s.[9] Ampicillin and trimethoprim–sulphamethoxazole came to be used after that. Multidrug-resistant

(MDR) strains have resistance encoded by plasmids to chloramphenicol, ampicillin and trimethoprim–sulphamethoxazole.[10] These MDR isolates started appearing in South and Southeast Asia in the late 1980s and 1990s and the newly introduced fluoroquinolones became the drugs of choice. Although excellent drugs, they came to be used so often, sometimes to the extent of abuse, where they were used too widely for treating human disease as well as in animal husbandry. In the Indian subcontinent, South Asia and South Africa, decreased susceptibility to ciprofloxacin (DSC)/ ciprofloxacin-resistant strains have started to appear.[11] Nalidixic acid was initially used as a marker for fluoroquinolone resistance, but eventually the break-points for fluoroquinolones were reduced and rationalized by the Clinical and Laboratory Standards Institute (CLSI). These strains have to be tackled by drugs such as third-generation cephalosporins. It is important to remember that aminoglycosides, first- and second-generation cephalosporins and cephamycins may appear active *in vitro* but are not effective clinically and should not be reported as susceptible, according to the CLSI guidelines. A 15 μg disc is used for azithromycin, with a ≥13 mm zone of diffusion to interpret it as susceptible. Patients should be empirically started on injection ceftriaxone 2 g b.d. i.v. for 10–14 days, or tablet azithromycin 1 g/day orally for 5 days. It is essential to change the antibiotic according to the drug sensitivity pattern, as soon as it is available, to prevent further induction of antibiotic resistance.[12] If the strain is fully susceptible, the first-line antibiotics include ciprofloxacin or azithromycin for 5 days. Alternatives that can be used are amoxicillin, chloramphenicol or trimethoprim–sulphamethoxazole for 7–14 days. First-line drugs such as ceftriaxone or azithromycin for 10–14 days can be given for MDR. Quinolone-resistant isolates should be treated with ceftriaxone 2 g b.d. i.v. for 10–14 days or azithromycin 1 g/day orally for 5 days.

XDR (extensively drug-resistant) strains are exclusively seen in Pakistan and Iraq and are called the 'Sindh strain'. This strain is resistant to chloramphenicol, ampicillin, trimethoprim–sulphamethoxazole, ciprofloxacin and third-generation cephalosporins, and sensitive to carbapenems and azithromycin.[13]

In case of severe infections adjunctive steroids can be added—injection dexamethasone initial dose of 3 mg/kg i.v. followed by 8 doses of 1 mg/kg i.v. 6 hourly.[14] Chronic carriers must be treated with 4 weeks of ciprofloxacin or other fluoroquinolones.[15] In patients who relapse, infection is by the same strain with usually the same susceptibility pattern, therefore the same treatment should be initiated. Gastrointestinal bleeds or perforations require antibiotics as well as surgical interventions.[16]

Prevention, as with any type of disease, is always better than cure. Therefore, basic hygiene practices are a must to eliminate food- and water-borne transmission. Vaccines available for use are Ty21a and ViCPS vaccine.[17] Vaccination is not recommended for adults living in endemic areas but is to be used after being exposed in a common source outbreak.[18] It is also recommended for immunocompromised individuals.

The only known host for enteric fever is humans; so in theory, it should be eradicated by good hygiene. However, we in India are still grappling with the problem that produces much morbidity and mortality. A reliable, quick, inexpensive diagnostic test for typhoid, which is still elusive, will prove to be useful as it can avoid unnecessary investigations and prevent antibiotic abuse. On the other hand, the efficacy of currently used antibiotics may soon be eroded, forcing us to use the 'last resort' antibiotics even for enteric fever. We need to understand that it is never going to be a good strategy of making antibiotics 'work overtime' for deficiencies in provision of clean water and sanitation which need the highest priority.

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