Enteric fever is an infectious disease of global distribution. It is a systemic infection caused by *Salmonella enterica*, remains an important worldwide cause of morbidity and mortality. According to the best global estimates, there are at least 16 million new cases of Enteric Fever each year, with 6,000,000 deaths.

Two features characterize enteric fever in industrialized countries. One is the general decline in the incidence of the disease and the second is the concomitant rise in the percentage of travel-related enteric fever.

Evidence of *Helicobacter pylori* infection also represents an increased risk of acquiring typhoid fever. Recurrent salmonellosis (usually *S. typhimurium*) is an AIDS defining criterion in HIV positive patients, though for reasons unknown this is rarely due to *S. typhi*. HIV positive patients are more prone to develop enteric fever and its frequent relapses.

**DIAGNOSIS**

Laboratory diagnosis of typhoid fever is based on three principles:

A. Isolation of organism
B. Detection of microbial antigen
C. Titration of antibody against causative organism

Blood cultures are the standard diagnostic method, and the results can be positive in 60 – 80% of patients, provided that a large volume of blood (typically 15 ml for adults) is cultured. Culture of the infectious agent may also be obtained from stool, urine, bone marrow or bile. Bone marrow is the most sensitive source (80-95%), but is not practical.

The role of the classic Widal test is controversial, with divergent views on the test’s utility in various areas of endemicity. Usually, O antibodies appear on days 6-8 and H antibodies on days 10-12 after the onset of the disease.

As per the one study from southeast Asia, patients tested positive for the Widal agglutination test with titers ranging from 1:80 to 1:320, no *Salmonella* organism was encountered in some cultures. The results suggest that serological investigations alone may not be a reliable index for the diagnosis of *Salmonella* infections. Malaria can interfere with serological diagnosis of typhoid and hence can lead to over diagnosis of typhoid.

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Recent advances include the IDL Tubex® test by a Swedish company, which reportedly can detect IgM O9 antibodies. The O9 antigen used in the test is extremely specific because its immunodominant epitope is a rare dideoxyhexose sugar in nature. This antigen has been found in serogroup D salmonellae but not in other microorganisms. A positive result given by Tubex® invariably suggests a *Salmonella* infection. Tubex® detects IgM antibodies but not IgG. This makes it invaluable as an aid in the diagnosis of current infections.

Another rapid serological test, Typhidot®, makes use of the 50 kD antigen to detect specific IgM and IgG antibodies to *S. Typhi* and takes three hours to perform. This dot enzyme immuno assay (EIA) test offers simplicity, speed, specificity (75%), economy, early diagnosis, sensitivity (95%) and high negative and positive predictive values. The detection of IgM reveals acute typhoid in the early phase of infection, while the detection of both IgG and IgM suggests acute typhoid in the middle phase of infection. Since IgG can persist for more than two years after typhoid infection, the detection of specific IgG cannot differentiate between acute and convalescent cases.

A newer version of the test, Typhidot-M®, was recently developed to detect specific IgM antibodies only. This test can replace the Widal test, when used in conjunction with the culture method, for the rapid and accurate diagnosis of typhoid fever. The high negative predictive value of the test suggests that Typhidot-M® would be useful in areas of high endemicity.

The typhoid IgM dipstick assay is also being designed for the serodiagnosis of typhoid fever, through the detection of *S. Typhi*-specific IgM antibodies in serum or whole blood samples. There has been study on validation of a PCR for diagnosis of typhoid fever and salmonellosis by amplification of the hilA gene in clinical samples from Colombian patients. But, it may not be cost-effective.

Salivary IgM test has also been used, though not yet available.

Mixed infection with multiple *Salmonella* serotypes in the same patient is an unusual finding; but there have been isolated such case reports.
Recent advances in molecular immunology have led to the identification of sensitive and specific markers. Currently, alternative methods for biological molecular analysis are enzyme immunoassay, surface plasmon resonance, and electrochemical immunoassay. In particular, the use of electrochemical immunoassay has attracted considerable interest for S. typhi determination because of its inherent simplicity, high sensitivity, inexpensive instrumentation, and miniaturization.

With the development of nanotechnology, various nanoparticles and nano-quantum dots have been used as labels to enhance the sensitivity of the electrochemical immunoassay technique.

The metal-enhanced colloidal gold electrochemical stripping metalloimmunoassay combines the high sensitivity of stripping metal analysis with the remarkable signal amplification resulting from the catalytic precipitation of metals onto the gold nanoparticles.

TREATMENT

More than 90% of patients are managed at home with oral antimicrobials, bed rest & close medical follow up.

Resistance to commonly used antibiotics such as chloramphenicol, ampicillin, amoxycillin and cotrimoxazole has been reported from different parts of India. Quinolones are being used as a first line therapy. Levofloxacin 750 mg administered orally once daily is an effective, safe, well-tolerated and cost-effective option in the treatment of typhoid fever in adult Indian males and non-pregnant females.

A recent Cochrane review of antimicrobial treatment of typhoid fever concludes that there is little evidence to support administration of fluoroquinolones to all cases of typhoid and that satisfactory cure rates can be achieved in drug sensitive cases with first line agents such as chloramphenicol. Although some open studies have suggested that cure rates may be better with oral fluoroquinolones compared with chloramphenicol; these case series also include multidrug resistant cases.

Third generation cephalosporins such as cefotaxime, ceftriaxone, and cefoperazone have been used successfully to treat typhoid fever, with courses as short as 3 days showing similar efficacy to the usual 10 to 14 days regimen, but it is recommended to treat with ceftriaxone for 10-14 days. Sensitivity of S. typhi isolates to cephalosporins have increased from 2001 – 2004 while that of S. paratyphi A showed a decline. Despite demonstrating in vitro killing of salmonellae, first- and second-generation cephalosporins and aminoglycosides are ineffective in treating enteric fever.

Resistance to third and fourth generation cephalosporins is emerging in India and will gain significance in the coming decade. Azithromycin has shown promise in a limited number of trials. The main advantage of aztreonam and azithromycin is that they can be used in children and in pregnant or nursing females.

Most laboratories use disk diffusion for evaluation, the sensitivity of which does not reflect true sensitivities. Nalidixic acid resistance is a marker for predicting low-level resistance to ciprofloxacin among S. typhi and also an indicator of treatment failure of ciprofloxacin. Clinical and Laboratory Standards Institute recommends testing for nalidixic acid resistance in all extraintestinal Salmonella isolates. Fluoroquinolone-susceptible, nalidixic acid-resistant isolates may not be eradicated by fluoroquinolone treatment. Typhoid fever caused by nalidixic acid-resistant S. typhi (NARST) infection is associated with poor clinical outcomes, probably due to delay in initiating appropriate antibiotic therapy.

Quinolones and zidovudine have a synergistic antibacterial effect against Salmonella, administration of both drugs may dramatically decrease the risk of recurrent infection.

CONCLUSION

Management of typhoid fever continues to pose a challenge. The absence of a reliable rapid diagnostic test, will test the diagnostic skills of the treating physician. With sufficient time and research, the promise of nanotechnology based disease diagnosis may become a reality. Therapeutic strategies will have to take into account the local antibiotic sensitivity patterns of S. typhi while defining treatment.

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