Present advancement in the diagnosis and treatment of typhoid fever
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Introduction
Although advances in public health and hygiene have led to the virtual disappearance of enteric fever (more commonly termed typhoid fever) from much of the developed world, the disease remains endemic in many developing countries. Typhoid fever is caused by Salmonella enterica serovar typhi (S. typhi), a gram negative bacterium. A similar but often less severe disease is caused by S. paratyphi A and less commonly, by S. paratyphi B (Schotmulleri) and S. paratyphi C (Hirschfeldil). The common mode of infection is by ingestion of an infecting dose of the organism, usually through contaminated water or food. Although the source of infection may vary, person to person transmission through poor hygiene and sewage contamination of water supply are the most important.

Epidemiology
Worldwide, 15 to 30 million cases of typhoid occur each year with half a million deaths. In affluent countries, typhoid is seen in travellers or when food or water safety measures fail, with antibiotic treatment death is rare.

Few established surveillance systems for typhoid exist in the developing world, especially in community settings, so the true burden is difficult to estimate. This is shown by recent revisions in the global estimates of the true burden of typhoid. In contrast to previous estimates, which were 60% higher, investigators estimate that there are average 21.6 million typhoid cases annually, with the annual incidence varying from 100 to 1000 cases per 100000 population. Preliminary results form recent studies conducted in Bangladesh by ICDDR,B show an incidence of approximately 2000 per 100000 per year. Typhoid fever also has a very high social and economic impact because of the hospitalization of patients with acute disease and the complications and loss of income attributable to the duration of the clinical illness. It is important to note that reports form some provinces in China and Pakistan have indicated more cases of paratyphoid fever caused by S. paratyphi A than by S. typhi. The global mortality estimates from typhoid have also been revised downwards from 600000 to 200000, largely on the basis of regional extrapolations. Recent population based studies from South Asia suggest that the incidence is highest in children aged less than 5 years, with higher rates of complications and hospitalization, and may indicate risk of early exposure to relatively large infecting doses of the organisms in these populations. These findings contrast with previous studies from Latin America and Africa, which suggested that S. typhi infection caused a mild disease in infancy and childhood.

There are may be other factors that affect the changing epidemiology of typhoid. Although the overall ratio of disease caused by S. typhi to that caused by S. paratyphi is about 10 to 1, the proportion of S. paratyphi infections are increasing in some parts of the world.

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Also, in contrast to the Asian situation, the HIV and AIDS epidemic in Africa has been associated with a concomitant increase in community acquired bacteraemia due to nontyphoidal Salmonella such as S. typhimurium, an illness that may be clinically indistinguishable from typhoid\textsuperscript{12,13}. The exact reasons for these differences in the epidemiology and spectrum of Salmonella infections between Asia and Africa remain unclear.

Antibiotics resistance, particularly emergence of multidrug, resistant (MDR) strains among Salmonella is also a rising concern and has recently been linked to antibiotic using livestock. After sporadic outbreaks of Chloramphenicol resistant typhoid between 1970 and 1985, many strains of S. typhi developed plasmid mediated multidrug resistance (PMMDR) to the three primary antimicrobials used (Ampicillin, Chloramphenicol, and Co-trimoxazole)\textsuperscript{14}. This was encountered by the advent of oral Quinolones. Resistance to Ciprofloxacin also called Nalidixic Acid-resistant S. typhi (NARST) strain either chromosomally or plasmids encoded has been observed in Asia. A significant number of strains from Africa and the Indian subcontinent are MDR type. A small percentage of strains from Vietnam and the Indian subcontinent are NARST strains\textsuperscript{4}.

**Diagnosis of typhoid fever**

Typhoid fever is among the most common febrile illness encountered by practitioners in developing countries. The advent of antibiotic treatment has led to a change in the presentation of typhoid, and the classic mode of presentation with a slow and "Stepladder" rise in fever and toxicity is rarely seen. However, rising antimicrobial resistance has been associated with increased severity of illness and related complications.

Many other factors influence the severity and overall clinical outcome of the infection. They include the duration of illness before the start of appropriate treatment, the choice of antimicrobial, the patient's age and exposure or vaccination history, the virulence of the bacterial strain, the quantity of inoculum ingested and several host factors affecting immune status. Recent data from South Asia indicate that the presentation of typhoid may be more dramatic in children younger than 5 years, with higher rates of complications and hospitalization\textsuperscript{5-10}. So typhoid is predominantly an infection of children and young adults, affecting both sexes equally. Diarrhoea, toxicity and complications such as disseminated intravascular coagulation are also more common in infancy, with higher mortality.

The presentation of typhoid fever may be altered by co-existing morbidities and early administration of antibiotics. In areas where malaria is endemic and where schistosomiasis is common the presentation of typhoid may be atypical\textsuperscript{15,16}. Multidrug resistant typhoid and paratyphoid infections are more severe with higher rates of toxicity, complications and mortality than infections with sensitive strains\textsuperscript{7}. This may be related to the increased virulence of multidrug resistant S. typhi as well as higher number of circulating bacteria\textsuperscript{17}.

The predominant symptom is the fever which rises gradually to a high plateau of 39 to 40\textdegree{}C, and shows little diurnal variation. Rigors are uncommon, except in late or complicated typhoid or in patients treated with antipyretics. Most patients will experience diarrhoea and typhoid can present as an acute gastroenteritis. Severe diarrhoea or colitis has been reported in HIV infected patients and bloody diarrhoea may be seen.

The abdominal pain is usually diffuse and poorly localized but occasionally sufficiently intense in the right iliac fossa to suggest appendicitis. Nausea and vomiting are infrequent in uncomplicated typhoid but are seen with abdominal distension in severe cases. Other early symptoms include cough, sore throat and epistaxis. In developing countries, patients with typhoid in its second to fourth weeks present with accelerating
weight loss, weakness, altered mental state, intestinal hemorrhage and perforation, refractory hypotension, pneumonia, nephritis and acute psychosis. Those infected with multidrug resistant S. typhi may suffer more severe disease. Physical examination is often unremarkable apart from fever. Careful examination may reveal splenomegaly, hepatomegaly or rose spots. Tachycardia is common although temperature pulse dissociation (relative bradycardia) is considered characteristic. Hypotension has important implications. A coated tongue is often observed. The lenticular rose spots, appear at the end of the first week. They form a sparse collection of maculopapular lesion on the abdominal skin, which blanch with pressure and fade after 2 or 3 days. The rash may extend on to the trunk and arms.

The challenge of appropriate diagnostics in typhoid
Although the main stay of diagnosing typhoid fever is a positive blood culture, the test is positive in only 40-60% of cases. Usually early in the course of the disease. Stool & urine cultures become positive after the first week of infection, but their sensitivity is much lower. In much of the developing world, widespread antibiotic availability and prescribing are another reason for the low sensitivity of blood cultures. Although bone marrow cultures are more sensitive, they are difficult to obtain, relatively invasive and of little use in public health settings.

Other hematological investigations are non-specific. Blood leukocyte counts are often low in relation to the fever and toxicity, but the range is wide, in younger children leukocytosis is a common association and may reach 20000-25000/mm³. Thrombocytopenia may be marker of servere illness and accompany disseminated intravascular coagulation. Liver function test results may be deranged, but significant hepatic dysfunction is rare.

The classic Widal test measures agglutinating antibody levels against O and H antigens of S. typhi and is more than 100 years old.

Although robust and simple to perform, this test lacks sensitivity and specificity and reliance on it alone in areas where typhoid is endemic may lead to overdiagnosis.

It may be negative in up to 30% of culture proven cases of typhoid ever. This may be because of prior antibiotic therapy that has blunted the antibody response. On the other hand S. typhi shares O and H antigens with other Salmonella serotypes and has cross-reacting epitopes with other Enterobacteriace and this can lead to false positive results. Such results may also occur in other clinical conditions, eg. malaria, typhus, bacteraemia caused by other organisms and cirrhosis. In areas of endemicity there is often a low background level of antibodies in the normal population. Determining an appropriate cut off value for a positive result can be difficult since it varies between areas and between times in given areas.

Despite these limitations the test may be useful, particularly in areas that cannot afford the more expensive diagnostic methods. The test is unnecessary if the diagnosis has already been confirmed by this isolation of S. typhi from a sterile site.

Newer diagnostic tests have been developed such as the Thyphidot or Tubex, which directly detect IgM antibodies against a host of specific S. typhi antigens but these have not proved to be sufficiently robust in large scale evaluation in community settings. A nested polymerase chain reaction using H1d primers has been used to amplify specific genes of S. typhi in the blood of patients and is a promising means of making a rapid diagnosis. Table-1 compares the performance of the various tests for typhoid.

Despite these new developments, the diagnosis of typhoid in much of the developing world is made on clinical criteria.
This poses problems since typhoid fever may mimic many common febrile illnesses without localizing signs. In children with multi system features, the every stages of enteric fever may be confused with conditions such as acute gastroenteritis, bronchitis and bronchopneumonia. 

Subsequently, the differential diagnosis includes malaria, sepsis with other bacterial pathogens, infections caused by intracellular organisms such as tuberculosis, brucellosis and infectious mononucleosis. There is thus an urgent need to develop a multipurpose “fever stick” that may allow the rapid and specific diagnosis of common febrile illnesses, especially malaria, dengue fever and typhoid.

Definitive diagnosis of enteric fever requires the isolation of S. typhi or S. paratyphi. Cultures of blood, stool, urine, rose spots, the blood mononuclear cell platelet fraction, bone marrow and gastric or intestinal secretions may each be useful in establishing the diagnosis. The duodenal string test is especially useful as a noninvasive technique to sample duodenal secretion. A positive culture for a S. typhi or S. paratyphi is obtained in more than 90% of patients; if blood, bone marrow and intestinal secretions are all performed. The sensitivity sensitivity of blood culture alone is only 50 to 70% probably because small quantity of S. typhi (i.e <.15organisms/ml) are typically present in the blood of patients with typhoid fever. The sensitivity of bone marrow culture is 90% and unlike blood culture is not reduced by up to 5 days of prior antimicrobial therapy. In some patients with negative results on bone marrow cultures, the duodenal string cultures have been positive.

One study found that in children the combination of blood and duodenal string culture was as sensitive as bone marrow culture. Children also have a higher incidence of positive stool cultures than adults do (60% versus 27%). Therefore, ideally in adults and children blood, bone marrow,

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Sensitivity range (%)</th>
<th>Specificity range (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microbiological tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood culture</td>
<td>40-80</td>
<td>NA</td>
<td>Widely regarded as the gold standard, but sensitivity may be low in endemic areas with high rates of antibiotic use; hence true specificity is difficult to estimate.</td>
</tr>
<tr>
<td>Bone Marrow culture</td>
<td>55-67</td>
<td>30</td>
<td>Greater sensitivity but invasive and thus of limited clinical value, especially in ambulatory management.</td>
</tr>
<tr>
<td>Urine culture</td>
<td>0-58</td>
<td>NA</td>
<td>Variable specificity</td>
</tr>
<tr>
<td>Stool culture</td>
<td>30</td>
<td>NA</td>
<td>Sensitivity lower in developing countries and not used routinely for follow-up.</td>
</tr>
<tr>
<td><strong>Molecular diagnostics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymerase chain reaction</td>
<td>100</td>
<td>100</td>
<td>Promising, but initial reports indicated similar sensitivity to blood cultures and lower specificity.</td>
</tr>
<tr>
<td>Nested polymerase chain reaction</td>
<td>100</td>
<td>100</td>
<td>Promising and may replace blood culture as the new “gold standard”.</td>
</tr>
<tr>
<td><strong>Serological diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Widal test (tube dilution and slide agglutination)</td>
<td>47-77</td>
<td>50-92</td>
<td>Classic and inexpensive. Despite mixed results in endemic areas, still performs well for screening large volumes. May need standardization and quality assurance of reagents.</td>
</tr>
<tr>
<td>Typhidot</td>
<td>66-88</td>
<td>75-91</td>
<td>Lower sensitivity than Typhidot-M.</td>
</tr>
<tr>
<td>Typhidot-M</td>
<td>73-95</td>
<td>68-95</td>
<td>Higher sensitivity and specificity than classic Typhidot in some series, but other evaluations suggest that the performance may not be as robust in community settings as hospital.</td>
</tr>
<tr>
<td>Tubex</td>
<td>65-88</td>
<td>83-89</td>
<td>Promising initial results but has yet to be evaluated in larger trials in community settings.</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine antigen detection</td>
<td>65-95</td>
<td>NA</td>
<td>Preliminary data only.</td>
</tr>
</tbody>
</table>
stool, and duodenal string cultures should all be performed. DNA probes for S. typhi and other Salmonellae have been developed, but these tests are not commercially available.

**Treatment of typhoid fever**

Azithromycin, a new macrolide antibiotic administered in a dose of 1 gm. once daily for 5 days is also useful for the treatment of typhoid fever, although the disease takes longer period to defervesce. The main advantage of Aztreonam and Azithromycin is that they can be used in children and in pregnant or nursing females.

These drugs should be reserved for Quinolone resistant cases. It is recommended to treat with Ceftriaxone for 10-14 days. Several small studies have reported successful treatment of typhoid fever with Aztreonam, a Monobactam antibiotic. This antibiotic has been shown to be more effective than Chloramphenicol in clearing the organism from the blood and was associated with fewer adverse reactions. However a prospective clinical trial in children in Malaysia was discontinued because of a high failure rate with Aztreonam.

Appropriate antibiotic treatment (the right drug, dose and duration) is critical to curing typhoid with minimal complications. Standard treatment with Chloramphenicol or Amoxicillin is associated with a relapse rate of 5-15% or 4-8% respectively, where as the newer Quinolones and third generation Cephalosporins are associated with higher cure rates. The emergence of multidrug resistant typhoid in the 1990s led to widespread use of Fluoroquinolones as the treatment of choice for suspected typhoid especially in South Asia and South East Asia where the disease was endemic. In recent years however, the emergence of resistance to Quinolones has placed tremendous pressure on public health systems in developing countries as treatment options are limited.

Table 2 shows the World Health Organization's recommendations for treating uncomplicated and severe cases of typhoid fever. Studies of short course antibiotic treatment for multidrug resistant typhoid have shown that Fluoroquinolones can achieve satisfactory cure rates, but parenteral Ceftriaxone was associated with higher rates of relapse. A recent 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 included multidrug resistant cases.

**Table 2: Recommended antibiotic treatment for typhoid fever**

<table>
<thead>
<tr>
<th>Susceptibility</th>
<th>Optimal treatment</th>
<th>Alternative effective treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Drug</td>
<td>Dose (mg/kg)</td>
</tr>
<tr>
<td>Uncomplicated</td>
<td>Typhoid fever</td>
<td></td>
</tr>
<tr>
<td>Fully sensitive</td>
<td>Fluoroquinolone</td>
<td>10-13</td>
</tr>
<tr>
<td></td>
<td>(such as</td>
<td></td>
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<tr>
<td></td>
<td>Ciprofloxacin,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SMZ-TMP</td>
<td>8.40</td>
</tr>
<tr>
<td>Multidrug</td>
<td>Fluoroquinolone</td>
<td>15-20</td>
</tr>
<tr>
<td>resistant</td>
<td>(such as</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ciprofloxacin,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SMZ-TMP</td>
<td>8.40</td>
</tr>
<tr>
<td>Severe typhoid</td>
<td>Fluoroquinolone</td>
<td>15-30</td>
</tr>
<tr>
<td>fever requiring</td>
<td>(such as</td>
<td></td>
</tr>
<tr>
<td>parenteral</td>
<td>Ciprofloxacin,</td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td>SMZ-TMP</td>
<td>8.40</td>
</tr>
</tbody>
</table>

* Three days course also effective, particularly so in epidemic containment.† Optimum treatment for Quinolone resistant typhoid fever has not been determined. Azithromycin, third generation Cephalosporins, or a 10-14 day course of high dose Fluoroquinolone is effective. Combinations of these are now being evaluated.

The use of glucocorticoid has been advocated for the treatment of severe typhoid fever based on a randomized, double blind, placebo controlled trial carried out in Indonesia. This study showed a significant reduction in mortality in patients with severe typhoid fever.
(ie. associated delirium, obtundation, stupor, coma, or shock) treated with Chloramphenicol and Dexamethasone as compared with Chloramphenicol treated control patients (case fatality rate 10% versus 56%)\textsuperscript{30}. Although the case fatality rate in the control group was high and the study has never been repeated on the basis of this study Dexamethasone, 3 mg/kg. intravenously, followed by eight doses of 1 mg/kg every 6 hours for 48 hours, should be considered for the treatment of severe typhoid with altered mental status or shock. This must be done only under strictly controlled conditions and supervision, and signs of abdominal complications may be masked. Steroid treatment beyond 48 hours may increase the relapse rate\textsuperscript{31}.

Despite appropriate treatment, some 2-4% of infected patients relapse after initial clinical response to treatment. Individuals who excrete S. typhi for more than three months after infection are regarded as chronic carriers. However, the risk of becoming a carrier is low in children and increases with age but in general it occurs in less than 2% of all infected children\textsuperscript{6}.

**Conclusion**

In summary, management of typhoid fever remains a challenge, even one hundred years after the micro organism was first isolated by Gaffkey a German in 1884. Although these include establishing rapid clinical diagnosis and confirmation, the fact that both S. typhi and S. paratyphi are rapidly becoming resistant to commonly used antibiotics is of great concern. A concerted effort involving clean water supply, sanitary faeces disposal, effective vaccination and early diagnosis and prompt treatment of cases and carriers will be required to control the disease. Therapeutic strategies will have to take in to account the local antibiotic sensitivity patterns of S. typhi while defining treatment.

**Reference**