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Recommended Citation

Bhutta, Z. A. (2006). Current concepts in the diagnosis and treatment of typhoid fever. *BMJ*, 333(7558), 78-82. **Available at:** https://ecommons.aku.edu/pakistan_fhs_mc_women_childhealth_paediatr/450

Clinical review

Current concepts in the diagnosis and treatment of typhoid fever

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BMJ 2006;333:78-82

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 (Hirschfeldii). 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.

Have the epidemiology and burden estimates of typhoid changed?

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,¹ investigators from the US Centers for Disease Control and Prevention estimate that there are 21.6 million typhoid cases annually, with the annual incidence varying from 100 to 1000 cases per 100 000 population.² The global mortality estimates from typhoid have also been revised downwards from 600 000 to 200 000, largely on the basis of regional extrapolations.² 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 hospitalisation, and may indicate risk of early exposure to relatively large infecting doses of the organisms in these populations.³⁻⁵ These findings contrast with previous studies from Latin America^{w1} and Africa,^{w2} which suggested that S typhi infection caused a mild disease in infancy and childhood.

There 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 is increasing in some parts of the world (Dong Mei Tan, personal communication 2005).⁶ Also, in contrast to the Asian situation, the HIV and AIDS epidemic in Africa has been associated with a concomitant increase

Summary points

Despite advances in technology and public health strategies, typhoid fever remains a major cause of morbidity in the developing world

In some areas typhoid fever disproportionately affects young children and may reflect high rates of transmission through food and water

Recent emergence of drug resistance—especially to common, first line antibiotics and quinolones—has made it very difficult and expensive for health services to manage the disease

Rapid and appropriate diagnostics are key to the management of typhoid in terms of public health

Although effective vaccines are available, there are no plans for large scale vaccination programmes in infants and children

in community acquired bacteraemia due to nontyphoidal salmonellae such as *S typhimurium*,^{7 8} an illness that may be clinically indistinguishable from typhoid. The exact reasons for these differences in the epidemiology and spectrum of salmonella infections between Asia and Africa remain unclear.

Another worrying development has been the emergence of drug resistant typhoid. After sporadic outbreaks of chloramphenicol resistant typhoid between 1970 and 1985, many strains of *S typhi* developed plasmid mediated multidrug resistance to the three primary antimicrobials used (ampicillin, chloramphenicol, and co-trimoxazole).⁹ This was countered by the advent of oral quinolones, but chromosomally acquired quinolone resistance in *S typhi* and *S paratyphi*³⁵ has been recently described in various parts of Asia, possibly related to the widespread and indiscriminate use of quinolones.^{10 11}



Can typhoid be diagnosed clinically where it matters?

Typhoid fever is among the most common febrile illnesses 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 hospitalisation.³⁻⁵ Diarrhoea, toxicity, and complications such as disseminated intravascular coagulation are also more common in infancy, with higher mortality. Table 1 shows some of the common clinical features and complications of typhoid in children and adults based on our experience in Karachi of hospitalised children and those diagnosed and treated in a community setting,^{5 12} indicating the significantly higher morbidity and complications among children presenting to hospital.

The presentation of typhoid fever may be altered by coexisting morbidities and early administration of antibiotics. In areas where malaria is endemic and where schistosomiasis is common the presentation of typhoid may be atypical.^{13 14} Multidrug resistant

Sources and selection criteria

We evaluated all recent clinical reviews of typhoid fever in the electronic data bases (Medline, PubMed, Embase, and the Cochrane Library) for the past 10 years (1996-2006) in all languages to identify critical reviews and systematic reviews on the risk factors, diagnosis, treatment, and prevention of typhoid and paratyphoid fever. The focus was on clinical publications on epidemiology, diagnosis, and treatment, but we also studied other related reviews and publications.

Although several reviews of typhoid fever and treatment are available, there have been few systematic reviews and meta-analyses of treatment strategies, with only one Cochrane review of treatment options and none on appropriate diagnostics for typhoid.

The main search terms used were "typhoid fever," "paratyphoid fever," "enteric fever," "typhoidal salmonellosis," and "*Salmonella*" in combination with "Typhi" or "Paratyphi." We also perused relevant reports from the World Health Organization and Centers for Disease Control and Prevention and the abstracts from five international symposiums on typhoid fever and other salmonelloses (Bangkok 1994, Bali 1997, Taipei 1999, Karachi 2002, and Guilin 2005).

We carried out a manual search of the bibliographies of key articles and reviews. In all, we studied 156 recent articles in depth, of which 44 are cited in this review.

 Table 1
 Common clinical features of typhoid fever in childhood

 in hospital and community settings in Karachi, Pakistan. Values
 are numbers (percentages)

	Hospital based patients (n=1158)*	Community based cohort (n=340)†
High grade fever	1044 (95)	338 (99)
Anorexia	811 (70)	11 (3)
Vomiting	451 (39)	43 (13)
Hepatomegaly	471 (41)	68 (20)
Diarrhoea	406 (35)	26 (8)
Toxicity	377 (33)	1 (0.3)
Abdominal pain	320 (28)	65 (19)
Splenomegaly	226 (20)	17 (5)
Constipation	127 (11)	1 (0.3)
Headache	138 (12)	26 (8)
Jaundice	23 (2)	0
Obtundation	23 (2)	1 (0.3)
lleus	12 (1)	1 (0.3)
Intestinal perforation	58 (0.5)	1 (0.3)
Myalgia	174 (15)	15 (4.4)

*Data from Bhutta 1996.12

†Data from Siddiqui et al 2006.5

typhoid and paratyphoid infections are more severe with higher rates of toxicity, complications, and mortality than infections with sensitive strains.¹² This may be related to the increased virulence of multidrug resistant S typhi as well as a higher number of circulating bacteria.15 Although clinical diagnosis of typhoid may be difficult, there are indications that simple algorithms can be developed for diagnosis and patient triage in endemic areas.¹⁶ Such algorithms would have implications for diagnostic and treatment protocols in endemic areas: in particular, diagnosis and triage of typhoid among febrile children must be included among the protocols for integrated management of childhood illnesses in South Asia, which currently largely focus on malaria as a cause of fever without localising signs.

The challenge of appropriate diagnostics in typhoid

Although the mainstay of diagnosing typhoid fever is a positive blood culture, the test is positive in only 40-60% of cases,¹⁷ usually early in the course of the disease. Stool and 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 is 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 haematological investigations are nonspecific. Blood leucocyte counts are often low in relation to the fever and toxicity, but the range is wide; in younger children leucocytosis is a common association and may reach 20 000-25 000/mm^{3,12} ^{w4} Thrombocytopenia may be a marker of severe illness and accompany disseminated intravascular coagulation. Liver function test results may be deranged, but significant hepatic dysfunction is rare.

The classic Widal test measures antibodies against O and H antigens of *S typhi* and is more than 100 years old.^{w5} Although robust and simple to perform,

Table 2 Laboratory diagnosis of	typhoid		
Diagnostic test	Sensitivity range (%)	Specificity range (%)	Comments
Microbiological tests			
Blood culture	40-80	NA	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
Bone marrow cultures	55-67	30	Greater sensitivity but invasive and thus of limited clinical value, especially in ambulatory management
Urine culture	0-58	NA	Variable sensitivity
Stool culture	30	NA	Sensitivity lower in developing countries and not used routinely for follow-up
Molecular diagnostics			
Polymerase chain reaction	100	100	Promising, but initial reports indicated similar sensitivity to blood cultures and lower specificity
Nested polymerase chain reaction	100	100	Promising and may replace blood culture as the new "gold standard"
Serological diagnosis			
Widal test (tube dilution and slide agglutination)	47-77	50-92	Classic and inexpensive. Despite mixed results in endemic areas, still performs well for screening large volumes. May need standardisation and quality assurance of reagents
Typhidot	66-88	75-91	Lower sensitivity than Typhidot-M
Typhidot-M	73-95	68-95	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 in hospital
Tubex	65-88	63-89	Promising initial results but has yet to be evaluated in larger trials in community settings
Others			
Urine antigen detection	65-95	NA	Preliminary data only

NA=Not available.

this test lacks sensitivity and specificity, and reliance on it alone in areas where typhoid is endemic may lead to overdiagnosis.^{w6} Newer diagnostic tests have been developed—such as the Typhidot^{w7 w8} or Tubex,^{w9 w10} 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 evaluations in community settings. A nested polymerase chain reaction using *H1-d* 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.^{w11} Table 2 compares the performance of the various tests for typhoid.^{w12-w14}

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 localising signs. In children with multisystem features, the early 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, tularaemia, leptospirosis, and rickettsial diseases; and viral infections such as dengue fever, acute hepatitis, 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.^{w15}

How has drug resistance affected treatment?

Early diagnosis of typhoid fever and prompt institution of appropriate antibiotic treatment are essential for optimal management, especially in children. Although most cases can be managed at home with oral antibiotics and regular follow-up, patients with severe illness, persistent vomiting, severe diarrhoea, and abdominal distension require hospitalisation and parenteral antibiotic treatment. In addition to antibiotics, supportive treatment and maintenance of appropriate nutrition and hydration are crucial (box 1).

Appropriate antibiotic treatment (the right drug, dose, and duration) is critical to curing typhoid with minimal complications.¹⁸ Standard treatment with chloramphenicol or amoxicillin is associated with a relapse rate of 5-15% or 4-8% respectively, whereas the newer quinolones and third generation cephalosporins are associated with higher cure rates.¹⁷ 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

Box 1: General principles for the management of typhoid

- Rapid diagnosis and institution of appropriate antibiotic treatment
- Adequate rest, hydration, and correction of
- fluid-electrolyte imbalance
- Antipyretic therapy as required (such as paracetamol 120-750 mg taken orally every 4-6 hours)
- Adequate nutrition: a soft, easily digestible diet should be continued unless the patient has abdominal distension or ileus
- Close attention to hand washing and limitation of close contact with susceptible individuals during acute phase of infection

• Regular follow-up and monitoring for complications and clinical relapse (this may include confirmation of stool clearance in non-endemic areas or in high risk groups such as food handlers) Table 3 Recommended antibiotic treatment for typhoid fever (adapted from WHO¹⁷ and Bhutta²⁰)

	Optimal treatment			Alternative effective treatment		
Susceptibility	Drug	Daily dose (mg/kg)	Course (days)	Drug	Daily dose (mg/kg)	Course (days)
Uncomplicated typ	hoid fever					
Fully sensitive	Fluoroquinolone (such as ofloxacin or ciprofloxacin)	15	5-7*	Chloramphenicol	50-75	14-21
				Amoxicillin	75-100	14
				TMP-SMX	8-40	14
Multidrug resistance	Fluoroquinolone or	15	5-7	Azithromycin	8-10	7
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone resistance†	Azithromycin or	8-10	7 Cefixime	00	7 1 4	
	Ceftriaxone	75	10-14		20	7-14
Severe typhoid fev	ver requiring parenteral treatment					
Fully sensitive	Fluoroquinolone (such as ofloxacin)	15	10-14	Chloramphenicol	100	14-21
				Ampicillin	100	14
				TMP-SMX	8/40	14
Multidrug resistant	Fluoroquinolone	15	10-14	Ceftriaxone or	60	- 10-14
				Cefotaxime	80	
Quinolone resistant	Ceftriaxone or	60	— 10-14	Fluoroquinolone	00	14
	Cefotaxime	80		10-14		20

*Three day courses 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.

endemic.¹⁹ 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.^{20 21}

Table 3 shows the World Health Organization's recommendations for treating uncomplicated and severe cases of typhoid fever.¹⁷ Studies of short course antibiotic treatment for multidrug resistant typhoid have shown that fluoroquinolones can achieve satisfactory cure rates,^{w16} w17 but parenteral ceftriaxone was associated with higher rates of relapse.^{w18} 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.22 Although some open studies have suggested that cure rates may be better with oral fluoroquinolones compared with chloramphenicol,23 these case series also include multidrug resistant cases. Given the signs of rapidly increasing resistance of S typhi to fluoroquinolones, it is imperative that the widespread use of these antibiotics for fever and their availability over the counter are restricted, although it may already be too late.24 However, treatment regimens must restrict as much as possible the use of further second and third line antibiotics for treating typhoid in primary care settings.25

The prognosis for a patient with enteric fever depends on the rapidity of diagnosis and treatment with an appropriate antibiotic. Other factors include the patient's age, general state of health, and nutrition; the causative *Salmonella* serotype; and the appearance of complications. Infants and children with underlying malnutrition and those infected with multidrug resistant isolates are at higher risk of adverse outcomes. Although additional treatment with dexamethasone (3 mg/kg for the initial dose, followed by 1 mg/kg every 6 hours for 48 hours) has been recommended among severely ill patients with shock, obtundation, stupor, or coma,^{w19} this must be done only under strictly controlled conditions and supervision, and signs of abdominal complications may be masked.

Despite appropriate treatment, some 2-4% of infected children relapse after initial clinical response to treatment.¹⁷ 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.¹⁷

In summary, many challenges remain for the effective control and management of typhoid in endemic countries. Although these include establishing rapid clinical diagnosis and confirmation, the fact that both *S typhi* and *S paratyphi* are rapidly becoming resistant

Box 2: Advice for travellers to areas where typhoid is endemic

• Avoid undue exposure to possible infection through food and water (contaminated water, salads, street foods). Use bottled water whenever possible, otherwise use only boiled water

- Two typhoid vaccines are available, both with proved efficacy of 60-80%, and should be taken at least two weeks before travel
- *Oral Ty21a vaccine*—Enteric coated capsules taken on alternate days for four doses. The vaccine is contraindicated in pregnant women, children under the age of 6 years, and immunocompromised patients. A booster may be required every five years *Vi polysaccharide vaccine*—0.5 ml as a single intramuscular dose for travellers older than 2 years. A booster may be required every two years
- Further advice on typhoid prevention and
- vaccination can be obtained from
 - Centers for Disease Control and Prevention (www.cdc.gov/travel)
- World Health Organization (www.who.int/ith) International Society of Travel Medicine (www.istm.org)
- Travel Doctor (www.traveldoctor.co.uk/diseases.htm)

to commonly used antibiotics is of great concern. Addressing this issue would require a host of measures, including adequate investments in safe water and sanitation services, community education, control over antimicrobial prescribing and over the counter sales, and large scale vaccination strategies. Box 2 details some of the preventive strategies and advice for travellers to areas where typhoid is endemic.

Competing interests: None declared.

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(Accepted 5 June 2006)

Separating a septum sandwich

A 7 year old boy had inquisitively removed two small circular magnets attached to the bottom of his toy car. He then inserted one up each nostril. The magnets were immediately drawn to each other, clamping firmly on to either side of his nasal septum.

On his arrival in the accident and emergency department, various manual manoeuvres with metal instruments were attempted, but these were attracted to each magnet with a resounding "clunk," provoking squeals of pain from the child as doctors grappled to remove the adherent instruments. Plastic instruments failed to provide sufficient grip on the slippery edges of the magnets. Doctors and patient were becoming more frustrated, with the latter increasingly reluctant to let anyone near his nose. A powerful pacemaker resetting magnet was brought down from the coronary care unit, but this attracted both small magnets, pulling the septum forward. Vaseline was applied to both sides of his septum in the hope of slipping the magnets off, but it only made a sticky situation even stickier.

Three hours after the provoking event, I was called to see the patient. The likelihood of septal necrosis with perforation and infection was increasing each minute, just as the child's faith in the medical profession was diminishing. Understandably, he was anxious to prevent any further attempts to remove the magnets and cupped both hands protectively over his nose, turning away to sob despairingly into his mother's bosom.

After much coaxing, I had to promise the boy that my attempt would be successful. I then obtained a pair of Blakesley forceps, usually used to perform functional endoscopic sinus surgery, from theatre. A nurse grasped his head firmly, his distraught mother held his left hand, and the senior house officer held his right. He shut his eyes and braced himself at the sight of the approaching forceps. With a deep breath from the patient and myself, a quick lateral tug dislodged the magnet from the septum, such that it stuck to the Blakesley forceps. The remaining magnet was easily retrieved as it had fallen off the septum.

Separating the septum sandwich had taken a long time, not to perform the actual procedure itself but to comfort and gently persuade the boy into allowing me one final attempt. Crucially, the promise I made him meant that there was no room for error. Children, even more so than adults, take promises very seriously, and broken promises are difficult to understand and accept. Fortunately, I managed to keep my word and was rewarded with the beaming smile of a relieved child.

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We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. Please submit the article on http://submit.bmj.com Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.