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Enteric fever

Buddha Basnyat

Farah Naz Qamar

Priscilla Rupali

Tahmeed Ahmed

Christopher M. Parry

CLINICAL UPDATE

Enteric fever

Buddha Basnyat, [1,2] Farah Naz Qamar, [3] Priscilla Rupali, [4] Tahmeed Ahmed, [5] Christopher M Parry[2,6]

1 Oxford University Clinical Research Unit-Patan Academy of Health Science Kathmandu, Nepal

2 Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, UK

3 Aga Khan University, Karachi, Pakistan

4 Christian Medical College, Vellore, India

5 icddr,b, Dacca, Bangladesh

6 Alder Hey Children' Hospital and Liverpool University Hospitals. Liverpool, UK

Correspondence to: B Basnyat
Buddha.Basnyat@ndm.ox.ac.uk

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What you need to know

- In endemic areas and in returning travellers, consider enteric fever in the differential diagnosis in patients with acute fever, particularly if they have abdominal symptoms
- Routine blood tests and blood culture can aid the diagnosis; serological tests, including the Widal test, are not recommended
- Antimicrobial resistance is common, so refer to national guidelines or formularies for choice of antibiotic
- In endemic areas, rule out other causes of acute fever such as malaria and dengue with tests and consider adding empirical treatment with doxycycline (or azithromycin) for scrub typhus and leptospirosis
- The Vi polysaccharide vaccine and Ty21a vaccine are available for use in travellers. The typhoid Vi conjugate vaccine is now recommended by the WHO in endemic areas

Enteric fever, also known as typhoid fever, is a common infectious disease in low and middle income countries.[1] It is the commonest bacterial cause of fever in returning travellers and migrants from these areas.[2,3] About 14 million people are affected annually with 136 000 deaths, mainly in low and middle income countries, according to estimates from the Global Burden of Disease Study in 2017.[1]

Diagnosis is complicated as symptoms overlap with other causes of fever and early investigations are inconclusive. Antimicrobial resistance is a growing concern. General practitioners have an important role in early diagnosis and management, prompt referral of patients with severe disease, and prevention including vaccination.

How is it caused?

Enteric fever encompasses typhoid fever, caused by infection with bacteria *Salmonella* Typhi (*S* Typhi), and paratyphoid fever, caused by *Salmonella* Paratyphi A and B. *S* Typhi is estimated to cause 76% of enteric fever globally.[1] Paratyphoid fever is mostly seen in parts of South Asia and China.[1,4] Ingestion of food or water contaminated by infected human faeces causes infection.[5]

Who gets enteric fever?

Poor access to clean drinking water and inadequate sanitation and hygiene increase the risk of transmission.[5,6] Enteric fever is most common in South Asia (incidence >500 per 100 000 population); South-East Asia, sub-Saharan Africa, and Oceania (>100 per 100 000 population); and Latin America and Caribbean (1-10 per 100 000 population).[1,7] Children and young adults are more commonly affected.[8-10] Among travellers, enteric fever is more common in adults after a visit to endemic areas.[2,3]

Use of proton pump inhibitors increases susceptibility to enteric fever by reducing gastric acidity, as per a systematic review.[11] The role of HIV infection as a risk factor is unclear, but it may contribute to disease severity.[12] A case series reported neonatal sepsis due to *S* Typhi and Paratyphi in babies born to infected mothers.[13]

How do patients present?

Patients present with a gradual onset of fever which typically rises to a plateau of 39-40°C (102-104°F) towards the end of a week.[8-10] This slow rise in fever contrasts with the intermittent high fever and rigors seen in malaria.

Abdominal symptoms such as diarrhoea, nausea, vomiting, and abdominal pain are common as per a systematic review on clinical profile of enteric fever (see supplementary table 1 on bmj.com).[9] Abdominal pain is diffuse and poorly localised but occasionally intense in the right iliac fossa, mimicking appendicitis. Patients may also have headache, cough, and malaise. Children under 5 years old frequently present with only fever, and the diagnosis may be missed unless they have complications.[9]

Symptoms start 7-14 days after exposure (range 3-60 days). Paratyphoid fever has a shorter incubation period (4-5 days), but symptoms are indistinguishable from those of typhoid fever.[4,14]

How is it diagnosed?

Enteric fever is mainly a clinical diagnosis based on history and examination. A gradual onset of fever, particularly with one or more abdominal symptoms, should raise suspicion of enteric fever in endemic areas. Ask about travel to endemic regions.

Physical findings are often non-specific.[8-10] Soft tender hepatosplenomegaly, abdominal distension, mild ascites, and a diffuse or localised tenderness may be noticed on abdominal examination. Hepatitis and hepatomegaly are more common in children under 5 years old and are seen in 30-50% of children with enteric fever.[9] Scattered wheezes or crepitations in the chest might suggest bronchitis. A bradycardia relative to the height of the fever may be noted. Rose spots, blanching erythematous maculopapular lesions on the trunk, were considered characteristic of typhoid fever, but are now rarely reported (fig 1).[9] If the disease progresses beyond the first week the patient often becomes impassive and unresponsive.[10]

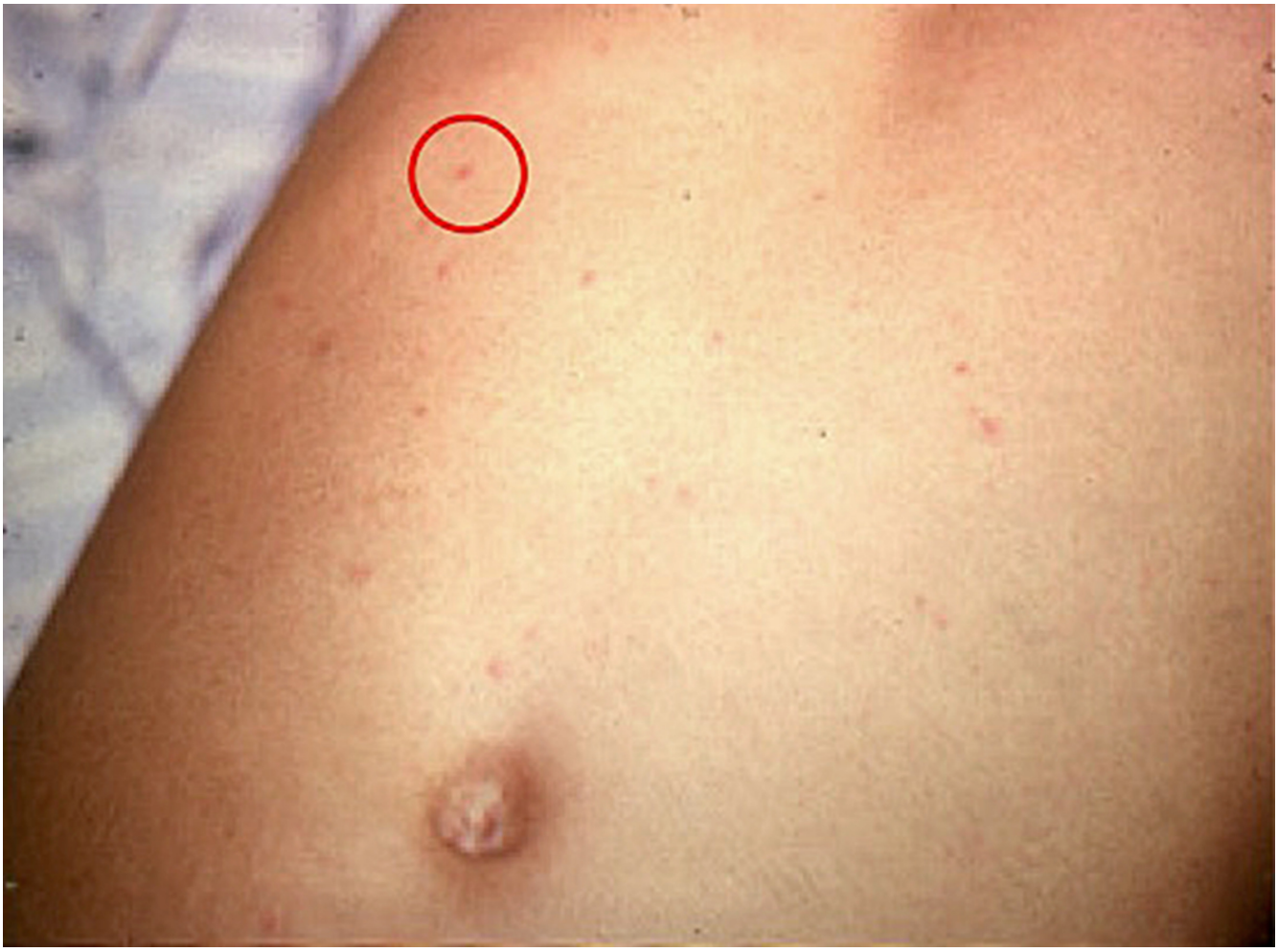

Fig 1 | Example of erythematous maculopapular lesions on the trunk characteristic of typhoid fever

What are the investigations?

Request a complete blood count and blood culture. The total white cell count is usually within, or just below, the normal range in enteric fever. Leucocytosis (raised white cell count) may suggest intestinal perforation or another diagnosis such as a pyogenic infection or leptospirosis. A mild normochromic or hypochromic anaemia, mild thrombocytopenia, and mild elevation of liver transaminases with a normal bilirubin are common.[8-10] The C reactive protein (CRP) is usually elevated in enteric fever.

Blood culture is the optimum method to confirm the diagnosis by isolating the organism and testing antimicrobial sensitivity. It takes two to three days for a result, and empirical antimicrobial treatment is required in the interim. It has a sensitivity of 61% (95% CI 52 to 70) (see supplementary table 2 on bmj.com).[15 16] A negative blood culture does not exclude enteric fever. Antibiotic pre-treatment, low sample volume, and low circulating bacterial load in the blood result in this low sensitivity.[16 17] Bone marrow culture gives a higher yield, but it is rarely performed.[17] Faeces, urine, or bile aspirate may be cultured, but a positive result may indicate chronic faecal carriage rather than acute infection.[10]

Serological tests, including the Widal test and newer rapid diagnostic tests, are not confirmatory in the acute phase of illness. The Widal test measures antibodies against O and H antigens of *S* Typhi and *S* Paratyphi A. It is cheap and simple but lacks sensitivity and specificity.[18 19] A single measurement in the acute phase of the illness may be false negative or false positive.[10 19] Other commercially available, point-of-care rapid diagnostic tests detect IgM antibodies against *S* Typhi antigens. These are insufficiently accurate to be useful in diagnosis (see supplementary table 2).[20] In a diagnostic accuracy review, the TUBEX test (14 studies) had an average sensitivity of 78% (95% CI 71% to 85%) and specificity of 87% (82% to 91%). The Typhidot test had an average sensitivity of 66% (59% to 73%) with a specificity of 81% (58% to 93%)[20] across a number of versions. Novel assays to detect antibodies, antigens, and DNA in blood are being developed.[21 22]

In endemic areas and returning travellers, rule out malaria and dengue fever with testing. Consider other causes of acute fever based on local disease patterns—such as scrub and murine typhus, leptospirosis, brucellosis, influenza, chikungunya, and covid-19 and other viral conditions.[3 21 23]

What are the complications?

Severe disease usually manifests in the second or third week of illness with continuing fever, increasing weakness, anaemia, weight loss, persistent vomiting, or a clouded mental state. Delayed treatment, the virulence of the bacterial strain, and host factors contribute to disease severity.[24] In a pooled analysis (13 studies, 2554 patients), 27% (95% CI 21% to 32%) of patients with enteric fever experienced complications.[24] Encephalopathy, gastrointestinal

bleeding, nephritis, and hepatitis are common complications seen in 5-7% of hospitalised patients[24] (see supplementary table 3). Intestinal haemorrhage or colitis and intestinal perforation can occur. These present with signs of acute peritonitis or more insidiously with increasing restlessness, a diffusely tender abdomen, hypotension, tachycardia, and shock.[24 -26]

The mean case fatality rate with enteric fever is 2.49% (95% CI 1.65% to 3.75%), and 4.45% (2.85% to 6.88%) in hospitalised patients as per a recent systematic review (44 studies, 41 723 patients).[27] Between 5% and 10% of patients experience a relapse with a second episode of fever two to three weeks after initial recovery. This usually responds to the original treatment.[10]

How is it treated?

Initial treatment and referral

Patients can usually be managed at home if they have no complications. Referral to a hospital is necessary if the patient is vomiting and unable to take oral medication, is clinically unstable (see box for "red flags"), has developed complications, or if the diagnosis is uncertain.

Red flags for referral of patients

Adults

- Two or more of the following the Quick Sepsis-related Organ Failure Assessment (qSOFA) criteria on initial examination:
  - Altered mental status
  - Respiratory rate ≥22 breaths/min
  - Systolic blood pressure ≤100 mm Hg
- The patient may be at risk of severe sepsis and needs higher level of care

Children

- Looking sick and toxic
- Unable to take oral medication
- Persistent vomiting
- Signs of severe dehydration
- Abdominal distension with or without tenderness
- Jaundice
- Drowsy or altered consciousness
- Signs of gastrointestinal bleeding (such as passing fresh blood in stools or melaena)
- Signs of haemodynamic shock, including mottled skin and reduced capillary return
- Seizures
- Any sign of severe disease as per the Integrated Management of Childhood Illness Algorithm (IMCI)[47]

Effective antimicrobial therapy shortens the illness and reduces mortality from complications.[10] As there is no simple confirmatory test for enteric fever, empirical treatment is advised in endemic areas at the time of presentation. Oral antimicrobials may be started in patients with fever for three to four days and suggestive symptoms with no apparent focus of infection identified and, where relevant, a negative malaria smear. Although such empirical use may lead to antimicrobial overuse, the absence of a simple diagnostic test leaves no alternative.

Ensure adequate hydration, antipyretics for fever, and careful follow-up.[10] Concurrent treatment with doxycycline (or azithromycin in children) is advised to cover for scrub typhus and leptospirosis where these infections are endemic.[23 28] High dose corticosteroids may be considered in patients with severe disease or complications (see table 1).[32]

Table 1 | Antimicrobial treatment options for enteric fever[10 29 -31]

Susceptibility*	First-line treatment: Antimicrobial	First-line treatment: Total daily dose (mg/kg)	First-line treatment: Duration (days)	Alternative treatment: Antimicrobial	Alternative treatment: Total daily dose (mg/kg)	Alternative treatment: Duration (days)
Uncomplicated enteric fever						
Unkown susceptibility*	Azithromycin	20	7	—		
Fully susceptible	Ciprofloxacin†	20	7	Chloramphenicol‡	50-75	14
				Amoxicillin	75-100	14
				TMP-SMX§	8-40¶	14
				Cefixime	20	7-14
Multidrug resistant**	Ciprofloxacin†	20	7	Cefixime	20	7-14
				Azithromycin	20	7
Quinolone resistant††	Azithromycin	20	7	—		
Extensively drug resistant‡‡	Azithromycin	20	7	—		
Severe enteric fever requiring parenteral treatment§§						
Unkown susceptibilty*	Ceftriaxone	50-75	10-14			
Fully susceptible	Ciprofloxacin†	20	10-14	Ceftriaxone	50-75	10-14
Multidrug resistant**	Ciprofloxacin†	20	10-14	Ceftriaxone	50-75	10-14
Quinolone resistant††	Ceftriaxone	50-75	10-14	Azithromycin	20	10-14
Extensively drug resistant‡‡	Meropenem	60	10-14	Azithromycin	20	10-14
Regimens proposed for eradication of chronic carriage (dependent on susceptibility of the isolate)						
Amoxycilllin susceptible	Ampicillin	100	90	—		
	Amoxycillin with probenecid	30				
TMP-SMX§ susceptible	TMP-SMX§	8-40¶	90	—		
Ciprofloxacin susceptible	Ciprofloaxacin	20	28	—		

* Culture and susceptibility results often unavailable. Empirical treatment should be based on regional knowledge of susceptibility patterns.

† Ofloxacin and levofloxacin are effective alternatives.

‡ Chloramphenicol may cause bone marrow suppression; oral route preferred.

§ TMP-SMX = trimethoprim-sulphamethoxazole. Inexpensive; may cause allergic reactions and nephrotoxicity, not suitable for children <2 years old or during pregnancy.

¶ 8 mg/kg trimethoprim–40 mg/kg sulphamethoxazole.

** Multidrug resistant: resistant to chloramphenicol, amoxycillin, trimethoprim-sulphamethoxazole

†† Quinolone resistant: non-susceptible to ciprofloxacin (pefloxacin resistant/ciprofloxacin resistant by disk testing)

‡‡ Extensively drug resistant: resistant to chloramphenicol, amoxycillin, trimethoprim-sulphamethoxazole, ciprofloxacin, and ceftriaxone

§§ In severe enteric fever (characterised by delirium, obtundation, coma, or shock) dexamethasone may be beneficial (dose 3 mg/kg infused intravenously over 30 min, followed by 8 doses of 1 mg/kg every 6 hours). In severe enteric fever with intestinal perforation and peritonitis, a laparotomy is recommended to identify and close the perforation(s) and to perform cleaning of the peritoneal cavity.

Choice of antimicrobial

Antimicrobial choice (table 1) is complicated by resistance to commonly used drugs. Culture and susceptibility results are crucial to guide treatment for individual patients and to monitor regional resistance rates, but these are often unavailable in endemic areas because of the lack of microbiology capacity. Consult national guidelines or local formularies for choice of antimicrobial based on regional susceptibility patterns.[28 33]

Chloramphenicol, amoxicillin, and trimethoprim-sulphamethoxazole were first-line choices before the 1990s. Multidrug resistance, defined as resistance to these three antimicrobials, led to use of fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin) for enteric fever.[33] High rates of fluoroquinolone resistance are now reported in South Asia and increasingly in Africa.[33 34] Extended spectrum cephalosporins, oral cefixime and parenteral ceftriaxone, and oral azithromycin[28 -31 33] are now recommended options. Cefixime and ceftriaxone are associated with higher rates of relapse. Resistance to all three agents is appearing.[35 36] Since a large outbreak of extensively drug resistant typhoid (resistant to ciprofloxacin, ceftriaxone, amoxycillin, chloramphenicol, and trimethoprim-sulphamethoxazole) in Pakistan in 2016, the treatment choice for such infections has shifted to oral azithromycin or parenteral meropenem.[37 38]

Follow-up

Fever resolves in five to 10 days, but patients often feel better sooner as fever intervals and intensity improve. Antibiotic treatment durations of 7-14 days or five days after fever resolution, whichever is longer, have traditionally been used. In clinical trials, shorter durations of between three and five days of ceftriaxone and ofloxacin have proved effective in uncomplicated

disease.[29 30] Patients commenced on parenteral antimicrobials can be switched to oral medications once they are clinically stable. If the susceptibility pattern is known, de-escalate from a broad spectrum to a narrow spectrum drug.

Re-evaluate patients with persistent high fever and symptoms after 7-10 days of treatment. Blood culture can be repeated to detect antimicrobial resistance or another diagnosis.

What about chronic carriage?

Carriers are asymptomatic but can transmit infection. About 10% of patients who have had an episode of enteric fever intermittently shed bacteria in faeces for several weeks after infection.[39] If shedding continues beyond one year, it is called chronic carriage.[5 39] The focus of infection in chronic carriage is thought to be the gall bladder, and carriage is more common in individuals with gall bladder disease and in women over 40 years old.[39] There is an increased risk of cholecystitis and carcinoma of the gallbladder in chronic carriers. A meta-analysis reported an odds ratio of of 4.28 for gall bladder malignancy in *S* Typhi carriers.[40] Kidney stones, as well as schistosomal infection in African studies, increase the risk of persistent typhoid urinary tract infection and chronic urinary carriage.[41]

Public health authorities, such as Public Health England, recommend three negative faecal culture samples a minimum of 48 hours apart after an acute episode of enteric fever to exclude carriage.[42] This is particularly important in food handlers and staff working in healthcare or day care facilities. An elevated Vi antibody titre (antibody to the Vi antigen of *S* Typhi) is helpful in detecting carriers in low incidence settings but not in endemic areas or areas with widespread use of vaccine. Eradication requires prolonged treatment with high dose antibiotics (table 1), and, rarely, cholecystectomy to surgically remove the focus of infection.[10]

How can enteric fever be prevented?

Improving access to clean drinking water, hygienic sanitation, and safe sewage disposal is critical to reduce the burden of disease in endemic areas. There is a need for high food hygiene standards and for prompt management of acute illness and chronic carriers.[5] For travellers, regular hand washing; using bottled water; avoiding contaminated water, salads, ice, and street food; and pre-travel vaccination can prevent infection.

Typhoid vaccination can potentially reduce disease burden among infants, children, young adults, and professional food handlers in endemic areas. The World Health Organization has approved three typhoid vaccines. These are not yet part of routine immunisation programmes in countries. There are no paratyphoid fever vaccines.

Ty21a is a live attenuated oral vaccine. A three-dose schedule has a cumulative efficacy at 2.5-3 years of 50% (95% CI 35% to 61%, 4 trials, 235 239 participants aged 3-44 years; moderate certainty evidence). Fever was more common following Ty21a vaccination compared with placebo. The Vi capsular polysacchride vaccine (ViPS) is given as a single injection and has an efficacy of 59% (45% to 69%; 4 trials, 194 969 participants aged 2-55 years; moderate certainty evidence) after two years.[43] Re-vaccination is recommended after three years with both these vaccines. Swelling and pain at the injection site were more common in the vaccine group. Both these vaccines are of limited value in preschool children because of difficulties of administration (Ty21a oral capsules) or inferior immune response (ViPS).

In 2018 the WHO recommended a new typhoid Vi conjugate vaccine (TCV) for use in children above 6 months of age.[44 45] The vaccine has Vi polysaccharide antigen conjugated to tetanus toxoid (Vi-TT) and is given as a single injection. It had an efficacy of 81.6% (58.8% to 91.8%) in a randomised controlled trial (20 0019 participants) in Nepal.[44] Low but similar rates of adverse events such as local pain, swelling, redness, or fever were noted in the two trial groups. The need for booster injections with TCV is unresolved. In 2018, Pakistan recently used the TCV vaccine in children aged 9 months to 15 years in an effort to control the outbreak of extensively drug resistant typhoid in Sindh province.[46] Further trials of this and other typhoid conjugate vaccines are in progress.

Sources and selection criteria

We searched PubMed, Embase, and the Cochrane Library for studies published in English between January 1990 and May 2020 using the MeSH terms: "(epidemiology, diagnosis, treatment, guideline) and (enteric fever, typhoid fever, paratyphoid fever)." Key references identified in review articles and textbooks and from the authors own collections were hand searched. We focused our selection on relevant papers published between January 2017 and June 2020. We also examined relevant reports from the World Health Organization.

Questions for future research

- What are reliable rapid diagnostic tests for undifferentiated febrile illness, including enteric fever, in low and middle income countries?
- What is the optimal antimicrobial therapy for antimicrobial-resistant enteric fever including extensively drug resistant typhoid?
- What antimicrobial combinations are effective for treatment of enteric fever, and how do they compare with monotherapy?
- What is the cost effectiveness of including typhoid vaccines in the routine immunisation programme in countries with high burden of enteric fever?

How patients were involved in the creation of this article

We asked a patient with enteric fever to share her story. She was initially diagnosed as having a viral fever. When high fever persisted, she returned to the clinic. She was suspected to have typhoid fever, and lab investigations were done. She was started on antibiotics, and her fever improved in a few days. Her blood culture came out to be negative. Her experience highlights the challenges with diagnosis of enteric fever. We have attempted to reflect on these in the article. We are grateful for the patient's input.

Additional educational resources

- European Centre for Disease Prevention and Control. Typhoid and paratyphoid fever. https://www.ecdc.europa.eu/en/typhoid-and-paratyphoid-fever
  - Includes a toolkit for outbreak response to food and waterborne diseases
- Indian Council of Medical Research. ICMR guidelines on management of acute fever. https://speciality.medicaldialogues.in/icmr-guidelines-on-management-of-acute-fever
  - Useful for treatment of acute febrile illness, of which enteric fever is the commonest bacterial cause in South Asia
- Medical Microbiology and Infectious Diseases Society of Pakistan. Typhoid management guidelines 2019. https://www.mmidsp.com/typhoid-management-guidelines-2019/
  - Useful guideline from an area with extensively drug resistant typhoid

Information resources for patients

- Centers for Disease Control and Prevention. Typhoid fever and paratyphoid fever. https://www.cdc.gov/typhoid-fever/resources.html
  - Free website with information for travellers and local language factsheets for patients (including Hindi, Bengali, and Urdu)
- Coalition against Typhoid and Typhoid Vaccine Acceleration Consortium. Take on typhoid. https://www.coalitionagainstty-phoid.org/
  - Free website with blogs and stories about patients who had typhoid
- The Conversation. Decades neglecting an ancient disease has triggered a health emergency around the world. https://theconversa-tion.com/decades-neglecting-an-ancient-disease-has-triggered-a-health-emergency-around-the-world-121282
  - History of typhoid fever including the spread by asymptomatic carriers and administration of the typhoid vaccine in willing military personnel as early as 1898. Free

Competing interests: We have read and understood BMJ policy on declaration of interests and have no relevant interests to declare.

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