

# Problem pathogens: extra-intestinal complications of *Salmonella enterica* serotype Typhi infection

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Typhoid fever, caused by *Salmonella enterica* serotype Typhi (*S typhi*), has an estimated worldwide prevalence of 12–33 million cases. The pathogenesis of this disease depends on the ingested inoculum size of *S typhi*, the virulence of the strain, the host's immune response and previous exposure, and local protective factors. Numerous extra-intestinal complications can occur with *S typhi* infection, including the involvement of the central nervous system (3–35%), cardiovascular system (1–5%), pulmonary system (1–86%), bone and joints ( $\leq 1\%$ ), hepatobiliary system (1–26%), genitourinary system ( $< 1\%$ ), and others. Due to an increase in multidrug-resistant *S typhi*, fluoroquinolones and third-generation cephalosporins have been increasingly used for typhoid fever and its complications. We describe the epidemiology, clinical manifestations, pathogenesis, and treatment of extra-intestinal *S typhi* infections.

## Introduction

Typhoid fever, also called enteric fever, is caused by the facultative intracellular organisms *Salmonella enterica* serotype Typhi (*S typhi*) and *Salmonella paratyphi*. Typhoid fever is a disease occurring more commonly among people after travel to, or residence in, developing countries where sanitation is poor and where there is faecal contamination of food and water. Worldwide, the prevalence of typhoid fever is estimated at 12–33 million cases.<sup>1</sup> In the USA, less than 500 cases of typhoid fever are reported each year.<sup>2</sup> The morbidity of typhoid fever is more severe among infected patients with immunosuppression, biliary and urinary tract abnormalities, reticuloendothelial blockade, and infection with antimicrobial multidrug-resistant *S typhi* strains.<sup>3</sup> The mortality with severe typhoid fever is up to 32% depending on the country studied.<sup>4</sup>

Human beings become infected with *S typhi* through ingestion of faecal contaminated food, milk, or water. 1–5% of infected people become chronic carriers by harbouring *S typhi* in the gall bladder, despite antibiotic therapy.<sup>5</sup> Depending on the size of the inoculum ingested and the health and immune status of the person, the incubation period of *S typhi* ranges from 5 to 21 days.<sup>6,7</sup> Symptoms of typhoid fever are characterised by fever (30–100%), headache (43–90%), gastrointestinal symptoms (8–79%), relative bradycardia (17–50%), splenomegaly (23–65%), and leucopenia.<sup>6,8</sup> Less commonly, extra-intestinal infectious complications occur with *S typhi* infection. These complications can involve the central nervous system, cardiovascular system, pulmonary system, bone, joints, hepatobiliary system, genitourinary system, and others (table). Recognition of these complications, especially in patients returning from an endemic region, are important in preventing the delayed diagnosis of typhoid fever. Here, we review the epidemiology, pathogenesis, clinical manifestations by organ system, and management of extra-intestinal *S typhi* infections.

## Pathogenesis of extra-intestinal complications

The pathogenesis of extra-intestinal infectious complications of typhoid fever depends on the ingested inoculum size of *S typhi*, the virulence of the strain, the host's immune response and previous exposure, and local protective factors.<sup>43,44</sup> The inoculum size of *S typhi* determines the length of incubation period of this bacterium and the resulting threshold for initiating bacteraemia (attack rate) in causing extra-intestinal infections. However, the exact infectious dose and time to reach the threshold for bacteraemia for causing specific extra-intestinal infectious complications is unknown. The virulence of *S typhi* is dependent on its ability to invade cells, possession of a complete lipopolysaccharide coat, the presence of the Vi antigen, and the production and excretion of a protein known as invasins. Invasins allows non-phagocytic cells to take up the bacterium, where it is able to live and replicate intracellularly.

Once ingested, *S typhi* is able to survive exposure to gastric acid in the stomach before passage into the small intestine. *S typhi* possess a two-stage inducible acid tolerance system that allows the bacterium to survive in conditions of severe low pH stress (pH 3.3).<sup>45,46</sup> The first stage involves the production of an inducible pH homeostasis system functional at external pH values below 4.0, and the second stage involves the synthesis of acid shock proteins that are essential for pH 3.3 acid tolerance.

In the small intestine, *S typhi* penetrates the intestinal mucosa via M cells that overlie the ileal Peyer's patches.<sup>47</sup> *S typhi* are then taken up by mononuclear cells in the intestinal lymphoid tissue, which may lead to dissemination via the lymphatic system or the haematogenous route. This intracellular bacterium multiplies in reticuloendothelial cells and macrophages located in the lymph nodes, liver, spleen, and bone marrow during the asymptomatic incubation phase of typhoid fever.

Once a threshold level of *S typhi* is reached, the bacteria are released into the blood, initiating a

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Organ system involved	Prevalence	Risk factors	Complications
Central nervous system	3–35%	Residence in endemic region, <sup>9</sup> malignancy, <sup>10</sup> endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, trauma, surgery, and osteomyelitis of the skull	Encephalopathy, <sup>11</sup> cerebral oedema, <sup>9</sup> subdural empyema, <sup>12</sup> cerebral abscess, <sup>10,13</sup> meningitis, <sup>14</sup> ventriculitis, transient Parkinsonism, motor neuron disorders, ataxia, <sup>15</sup> seizures, Guillain-Barré syndrome, psychosis <sup>16</sup>
Cardiovascular system	1–5%	Cardiac abnormalities—eg, existing valvular abnormalities, rheumatic heart disease, or congenital heart defects <sup>17</sup>	Endocarditis, <sup>18–20</sup> myocarditis, <sup>16</sup> pericarditis, arteritis, congestive heart failure <sup>21</sup>
Pulmonary system	1–6%	Residence in endemic region, past pulmonary infection, sickle cell anaemia, alcohol abuse, diabetes, HIV infection <sup>7</sup>	Pneumonia, <sup>2,22</sup> empyema, bronchopleural fistula
Bone and joint	<1%	Sickle cell anaemia, diabetes, systemic lupus erythematosus, lymphoma, liver disease, previous surgery or trauma, those at extremes of age, and steroid use <sup>23</sup>	Osteomyelitis, <sup>16,24–27</sup> septic arthritis <sup>28</sup>
Hepatobiliary system	1–26%	Residence in endemic region, pyogenic infections, intravenous drug use, splenic trauma, HIV, haemoglobinopathy	Cholecystitis, hepatitis, <sup>16,29</sup> hepatic abscesses, <sup>30</sup> splenic abscess, <sup>31–33</sup> peritonitis, paralytic ileus <sup>16</sup>
Genitourinary system	<1%	Urinary tract, pelvic pathology, and systemic abnormalities	Urinary tract infection, <sup>34,35</sup> renal abscess, pelvic infections, <sup>36</sup> testicular abscess, prostatitis, epididymitis
Soft tissue infections	At least 17 cases reported in the English literature	Diabetes <sup>37</sup>	Psoas abscess, <sup>37,38</sup> gluteal abscess, <sup>39</sup> cutaneous vasculitis <sup>40</sup>
Haematological	At least five cases reported in the English literature		Haemophagocytosis syndrome <sup>41,42</sup>

**Table:** Extra-intestinal infectious complications of typhoid fever caused by *Salmonella enterica* serotype Typhi

continuous secondary bacteraemia with secretion of cytokines by macrophages during the symptomatic phase of typhoid fever.<sup>44</sup> This secondary, and persistent, bacteraemia seeds additional organs, which results in extra-intestinal infectious complications.

### Organ systems

Central nervous system involvement with *S typhi* infection occurs in 3–35% of patients. Central nervous system manifestations include encephalopathy, meningitis (12%),<sup>14,48</sup> transient Parkinsonism, motor neuron disorders, ataxia,<sup>15</sup> cerebral abscesses,<sup>13</sup> cerebral oedema,<sup>9</sup> seizures, and Guillain-Barré syndrome.<sup>49</sup> Risk factors for central nervous system involvement include endocarditis, congenital heart disease, paranasal sinus infections, pulmonary infections, meningitis, ventriculitis, trauma, surgery, and osteomyelitis of the skull;<sup>13</sup> however, many cases do not have any known risk factors. These patients often present with fever, headache, vomiting, seizures, altered states of consciousness, papilloedema, and focal neurological deficits within the first few days of fever.<sup>43,50</sup> Neuroimaging with magnetic resonance imaging (MRI), computed tomography (CT), angiography, and/or radionuclide scans may be helpful, especially with focal central nervous system lesions such as subdural empyemas, epidural empyemas,<sup>43</sup> and brain abscesses.<sup>12</sup> Electroencephalogram and cerebrospinal fluid studies, although usually abnormal, are often not diagnostic.<sup>11</sup> A lumbar puncture obtained in the setting of a brain abscess may result in brain herniation and therefore is not recommended in these patients.

Cardiac problems caused by *S typhi* infection, such as myocarditis and endocarditis, occur in 1–5% of cases.<sup>17,18,51,52</sup> Pericarditis and arteritis occur in less than 1% of cases. Persistent *S typhi* bacteraemia may lead to

an increased propensity for this bacterium to attach to endovascular compartments, including atherosclerotic aneurysms. Most patients with cardiac infectious complications have underlying cardiac abnormalities such as existing valvular abnormalities, rheumatic heart disease, or congenital heart defects.<sup>17</sup> These patients present with fever, chest pain, palpitations, a new murmur or a change in character of a previous murmur, embolic phenomenon, and cardiac arrhythmias. An electrocardiogram (ECG) and cardiac echocardiography are helpful tools for showing the involvement of the cardiovascular system with *S typhi* infection. In one study, cardiac arrhythmias occurred in 3% of patients.<sup>48</sup> ECG findings are not diagnostic but may show nodal tachycardia, A-V dissociation with narrow QRS complexes, and/or non-specific ST segment changes. Cardiac echocardiography may show evidence of vegetations. In general, a transoesophageal echocardiography has a higher sensitivity compared with a transthoracic two-dimensional echocardiography for detecting valvular dysfunction and vegetations (90% vs 50%, respectively).

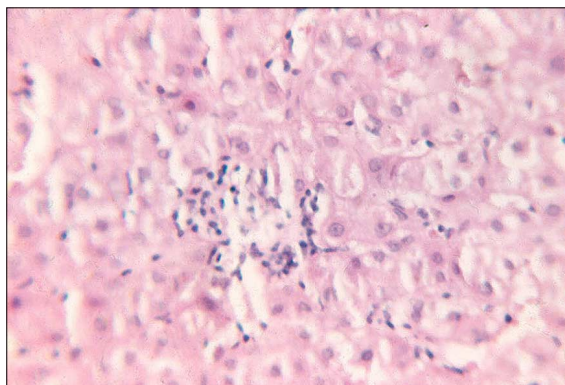
Respiratory symptoms of typhoid fever, such as cough, occur in 11–86% of cases.<sup>8</sup> Pneumonia, empyema, and bronchopleural fistulas caused by *S typhi* occur in 1–6% of cases.<sup>48</sup> A case of massive pulmonary embolism in the course of pneumonia due to *S typhi* has been reported.<sup>22</sup> Patients with pulmonary manifestations of typhoid fever often have underlying lung abnormalities, a previous history of lung infection, sickle cell anaemia, alcohol abuse, diabetes, or immunosuppression with HIV/AIDS. Patients may present with fever, chills, cough (with or without productive sputum), pleuritic pain, coarse crackles and bronchial breathing on auscultation, diarrhoea, and leucopenia.<sup>53</sup> Chest radiograph abnormalities occur in

24% of patients with pulmonary findings such as bronchitis and pneumonia; however, *S typhi* is rarely found in the sputum.<sup>2</sup>

Osteomyelitis occurs in less than 1% of cases of typhoid fever.<sup>54-56</sup> Osteomyelitis caused by *S typhi* can arise in one of three possible ways: haematogenous spread, contiguous source, or as a result of vascular insufficiency. Of the three routes, haematogenous spread is the most common cause of *S typhi* osteomyelitis.<sup>57</sup> The sites most commonly infected are the diaphysis of long bones such as the proximal humerus, distal femur,<sup>58</sup> and distal tibia. Less common sites of infection include the spine, sternochondral junctions, radius,<sup>24</sup> ulna,<sup>57</sup> sternum, ribs, sternoclavicular joints, hand, foot,<sup>25</sup> and cranium. An association between *S typhi* osteomyelitis and sickle cell anaemia has been observed.<sup>23,54-56</sup> Other risk factors include diabetes, systemic lupus erythematosus, lymphoma, liver diseases, previous surgery or trauma, those at extremes of age, and steroid use.<sup>23</sup> Infections involving the spine most commonly involve the lower thoracic and lumbar vertebrae. These patients may present with fever of acute onset with local tenderness, rigidity, and a loss of function of the involved limb due to pain. Laboratory studies may show an anaemia and an elevated ESR or C-reactive protein (CRP). Radiographic images such as radiographs, CT, and MRI of bones are essential to the diagnosis of bone involvement. These imaging studies may show diaphyseal erosion with destruction of the bone, with or without sequestrum (ie, dead bone) formation. Nuclear medicine scans such as technetium methylene diphosphonate and indium-111 chloride may show increased radiotracer uptake in the involved areas due to increased osteoclast activity. Invasive tests such as CT-guided needle biopsy of affected bone are often needed to establish the microbiological diagnosis and to guide therapy in most cases of *S typhi* osteomyelitis.<sup>59</sup>

At least five cases of septic arthritis caused by *S typhi* have been reported.<sup>28,60-62</sup> One case involved the right hip, one case involved the elbow, and three cases involved the sacroiliac joint.<sup>62</sup> Patients may present with fever and an acutely swollen and painful joint with or without an effusion. Laboratory findings often show an increased peripheral leucocyte count. Imaging studies of the affected joint may be helpful. Aspiration of the affected joint is important in the diagnosis of *S typhi* arthritis. A leucocytosis (>50 000 leucocytes/mL) and low glucose (<50% of the plasma glucose concentration) in the joint fluid are suggestive of septic arthritis.

Hepatobiliary system and splenic infections caused by *S typhi* occur (figure 1).<sup>29,30</sup> Predisposing factors include pyogenic infections, intravenous drug use,<sup>63</sup> splenic trauma,<sup>63</sup> HIV, spread of a contiguous infectious process, and haemoglobinopathy.<sup>64,65</sup> Patients with cholecystitis due to *S typhi* present with



**Figure 1: A liver biopsy of a volunteer with experimental typhoid fever and hepatitis**

Note the granulomas and focal infiltration of lymphocytes.

fever, jaundice, nausea, vomiting, and abdominal pain. In patients with typhoid fever complicated by a hepatic abscess, pre-existing hepatobiliary diseases including hepatobiliary carcinoma may exist.<sup>3,30</sup> These patients present with fever, right upper quadrant pain, hepatomegaly with or without jaundice, and abnormal liver function tests. Before the antibiotic era, splenic abscess caused by salmonella infection occurred in about 2% of patients.<sup>31</sup> During the antibiotic era, less than 1% of typhoid fever cases are complicated by splenic abscess.<sup>66</sup> Patients with splenic abscess present with fever, anorexia, and left-sided abdominal discomfort worsened with walking and respiration. A plain radiograph, abdominal ultrasonography, or CT are helpful with the early diagnosis of this complication.<sup>64</sup>

*S typhi* infection of the genitourinary system is a relatively rare event, even in endemic areas.<sup>67,68</sup> However, in endemic areas such as Egypt, some patients are chronic urinary *S typhi* carriers with intermittent bacteraemia and have either an active *Schistosoma haematobium* co-infection or have urinary tracts damaged by this parasite.<sup>69,70</sup> Risk factors for genitourinary involvement include underlying structural or functional abnormalities of the urinary tract, bladder, pelvic organs, and/or systemic symptoms. Predisposing aetiologies include congenital abnormalities, calculi or obstruction, pyelonephritis, chronic salpingitis, dermoid cyst, and renal transplant.<sup>34,36,69,70</sup> In a report of 18 patients with bacteruria culture-confirmed *S typhi*, 14 (79%) patients had symptoms of fever, dysuria, frequency, and suprapubic or pelvic discomfort. Urine analysis of these patients showed the presence of pyuria (94%) and proteinuria (91%).<sup>35</sup> The diagnosis of a urinary tract infection due to *S typhi* is made by confirming the presence of *S typhi* with detection of 10<sup>5</sup> colony forming units per millilitre of urine.

At least two cases of pelvic infections caused by *S typhi* have been reported.<sup>36</sup> These patients presented

with irregular menstrual cycles, discharge, and lower abdominal pain. Clinical examination may reveal adnexal tenderness and cervical involvement. Since the clinical features are often non-specific, laparoscopy and ultrasound have important roles in the diagnosis of pelvic involvement with *S typhi* infection.

At least 17 cases of soft tissue infections caused by *S typhi* have been reported—three cases involved the psoas,<sup>37,38,71</sup> one the gluteal muscle,<sup>39</sup> one the foot,<sup>72</sup> and 12 cases from other varying sites.<sup>73</sup> These patients presented with pain at the site of infection and laboratory findings of an increased peripheral leucocyte count and ESR.<sup>38</sup> Radiographic imaging with CT, MRI, ultrasound, and radiographs of soft tissues are helpful in better defining the area of involvement (figure 2).<sup>37</sup>

Cutaneous involvement with *S typhi* is common, including the characteristic skin lesion associated with typhoid fever described as rose spots (30%) (figure 3).<sup>3</sup> Rose spots are pink, blanchable, slightly raised macules on the chest and abdomen. One case of cutaneous vasculitis as a presentation of typhoid fever is reported.<sup>40</sup> Skin biopsy of this infected patient showed a histopathological finding of leucocytoclastic vasculitis with superficial and deep perivascular infiltrate of lymphocytes and neutrophils, and C3 deposits in the derma vessel walls. *S typhi* was not identified in the skin biopsy. In patients with cutaneous involvement with *S typhi*, blood cultures may be positive, skin swabs are useless, and skin biopsies may infrequently yield positive results.

Haemophagocytosis has been described in at least five cases of *S typhi* infection.<sup>41,42,74,75</sup> These patients

present with the syndrome of fever, lymphadenopathy, hepatosplenomegaly, pancytopenia, coagulopathy, evidence of hepatitis, hyperbilirubinaemia, and hyperferritinaemia.<sup>76</sup> A bone marrow examination is usually hypocellular with a marked reduction of megakaryocytes, myeloid precursors, and erythroid precursors. A Gram stain and culture of the bone marrow showing *S typhi* infection are required for the diagnosis of haemophagocytosis caused by this bacterium.

### Management

Selecting an appropriate antibiotic for the treatment of typhoid fever and its complications requires knowledge of the susceptibility of locally isolated strains and the complications caused by *S typhi*. Few studies exist concerning the antibiotic of choice for extra-intestinal infectious complications due to *S typhi*. Thus, the management section is based on studies of intestinal infectious complications caused by *S typhi* and the opinion of the authors.

Due to an increase in multidrug-resistant *S typhi*, fluoroquinolones (minimum inhibitory concentration [MIC]  $\geq 0.5$   $\mu\text{g/mL}$ ) and third-generation cephalosporins have been increasingly used, of which ceftriaxone has been the most widely given.<sup>77–79</sup> Fluoroquinolones are currently contraindicated in the US paediatric population because of their potential to damage cartilage and tendons based on animal studies. Other antibiotics used for typhoid fever and its complications include chloramphenicol (MIC 0.75–5  $\mu\text{g/mL}$ ), co-trimoxazole (trimethoprim-sulfamethoxazole),<sup>80,81</sup> ampicillin (0.25–5  $\mu\text{g/mL}$ ),<sup>82</sup> azithromycin,<sup>83–85</sup> furazolidone,<sup>86,87</sup> aztreonam,<sup>88</sup> and carbapenems. The use of chloramphenicol should be reserved for the treatment of serious infections caused by *S typhi* when less toxic antimicrobials are ineffective or contraindicated. The serious haematological complications of chloramphenicol are idiosyncratic, even with exposure to one dose. There is a dose-related and duration-related bone marrow depression among patients taking chloramphenicol. Chloramphenicol should be discontinued if blood dyscrasias such as aplastic anaemia (which occurs in approximately 1 in 25 000–40 000 patients), hypoplastic anaemia, thrombocytopenia, and granulocytopenia occur. Haematological studies are essential before, and frequently during, therapy with chloramphenicol.

In patients with central nervous system involvement caused by *S typhi*, surgical therapy when appropriate (ie, drainage of pus) and antibiotics that have good passage across the blood–brain barrier are the treatment of choice. Aspiration of purulent material can either be done at surgery or under stereotactic guidance by CT scan. The recommended therapy for central nervous system involvement is ceftriaxone for 14–28 days.<sup>12,13,89</sup> Alternative therapy for susceptible



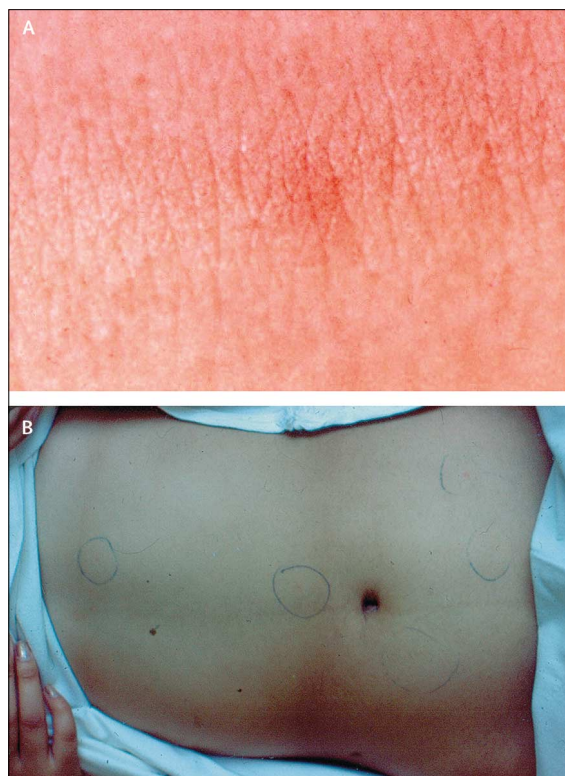
**Figure 2: A soft tissue infection with *S typhi***  
MRI with gadolinium diethylenetriaminepenta-acetic acid enhancement showing destruction of muscular architecture of the left distal psoas, iliopectus, adductor longus, and magnus and cystic lesions with air-fluid levels extending from the left pelvic cavity to the lower thigh of a patient with fatal septicaemia and pyomyositis caused by *S typhi*. Reproduced with permission from reference 37.

strains is chloramphenicol, ampicillin, or cotrimoxazole for 14–28 days.<sup>86</sup> In a review of the world literature from 1884–1984, eight cases of *S typhi* focal intracranial infections were documented.<sup>43</sup> Five of these cases had surgical drainage and three of the eight patients with *S typhi* received antibiotics (ie, ampicillin or chloramphenicol). The three patients who received antibiotics recovered, compared with two of five patients not receiving antibiotics.<sup>43</sup> In general, the use of corticosteroids as adjunctive therapy has been recommended for children with meningitis because corticosteroids have been shown to reduce long-term neurological sequelae. Such additional therapy is controversial in adults with meningitis.

In patients with cardiac involvement caused by *S typhi*, most commonly endocarditis, the recommended therapy is ceftriaxone or a fluoroquinolone intravenously for 4–6 weeks.<sup>19,20</sup> Alternate therapy for susceptible strains is chloramphenicol,<sup>21</sup> ampicillin, or co-trimoxazole for 4–6 weeks. In one patient with endocarditis caused by *S typhi*, a combination of ceftriaxone 3 g/day and amikacin 15 mg/kg per day for 14 days, followed by ceftriaxone 3 g/day for an additional 14 days was used with success.<sup>18</sup> Although there are inadequate data, cardiac surgery, including valve replacement, may be required in rare cases of typhoid fever involving the heart. Criteria for cardiac surgery include progressive heart failure, persistent bacteraemia despite antibiotics, relapse after the second course of antibiotics, and extension of infection into the conducting system or pericardium.

The recommended therapy for pulmonary manifestations caused by *S typhi* is ceftriaxone and fluoroquinolones for 14–21 days.<sup>90</sup> Alternate therapy for susceptible strains is co-trimoxazole, ampicillin, or chloramphenicol for 14–21 days.<sup>2</sup> In cases of empyema, this fluid should be drained either percutaneously or by an open surgical procedure. Ongoing trials are being conducted to evaluate the use of percutaneous instillation of thrombolytic agents into the pleural space in aiding in drainage and resolution of empyemas.

Osteomyelitis caused by *S typhi* requires thorough surgical debridement combined with a prolonged course ( $\geq 4$  weeks) of intravenous antibiotics that allow concentrations of the antibiotics to rise to therapeutic levels in bone and soft tissue. Some surgeons believe surgical debridement is inadequate and thus recommend radical debridement of lesions, which includes removal of soft tissue, bone, sequestra, and infected prosthetic material that may serve as a nidus for continued infection.<sup>91</sup> Paravertebral abscesses may co-exist with osteomyelitis and require CT-guided drainage along with prolonged courses of intravenous antibiotics. The recommended therapy for bone infections caused by *S typhi* is ceftriaxone or a



**Figure 3:** (A) A rose spot in a volunteer with experimental typhoid fever. (B) Small clusters of rose spots are usually located on the abdomen. These lesions may be difficult to identify, especially in dark skinned people.

fluoroquinolone for 4–6 weeks.<sup>26,57</sup> Alternate therapy for susceptible strains is co-trimoxazole, ampicillin,<sup>24</sup> or chloramphenicol for 4–6 weeks.<sup>27,57,58,92</sup> The progress of treated osteomyelitis should be monitored clinically, and by follow-up radiographic imaging.

Therapy for septic arthritis caused by *S typhi* includes adequate joint drainage, antibiotic therapy, and analgesics.<sup>62</sup> Adequate joint drainage may include repeated joint aspiration, arthroscopic washout, or open surgical drainage. The recommended therapy is ceftriaxone and fluoroquinolones for 4–6 weeks.<sup>28,62</sup> Alternate therapy for susceptible strains is co-trimoxazole, ampicillin, or chloramphenicol for 4–6 weeks.<sup>27,62,92</sup> Analgesics, rest splints, and subsequent active physiotherapy often aid the recovery of patients with septic arthritis caused by *S typhi*. Prosthetic joints infected with *S typhi* often require removal for cure. Reimplantation of a prosthetic joint can occur once the infection has been cured with adequate joint drainage and antibiotics.

Hepatic abscesses caused by *S typhi* require drainage by open or percutaneous methods,<sup>30</sup> in addition to prolonged courses of antibiotics. Open surgical drainage is being replaced by ultrasound and CT-guided aspiration and drainage. The recommended therapy is ceftriaxone or fluoroquinolones for 14–21 days.<sup>30</sup> Alternate therapy for susceptible strains is

### Search strategy and selection criteria

Articles, limited to the English language, concerning the extra-intestinal complications caused by *S typhi* infection were identified using searches of PubMed and Medline without restrictions on study design, location, or publication date. The key words employed were “*Salmonella typhi*”, “extra-intestinal infections”, “central nervous system”, “cardiovascular”, “pulmonary”, “bone”, “joints”, “hepatobiliary”, “genitourinary”, “soft tissue infections”, “cutaneous”, and “hematologic”. Reference lists of relevant publications were reviewed to identify additional articles.

co-trimoxazole, ampicillin, or chloramphenicol for 14–21 days.<sup>29</sup> In the pre-antibiotic era, splenic abscesses caused by *S typhi* required splenectomy.<sup>66</sup> More recently, the drainage of splenic abscesses along with first-line therapy of ceftriaxone or fluoroquinolones have been used.<sup>30,40,64</sup> Alternate therapy for susceptible strains is co-trimoxazole, ampicillin, or chloramphenicol for 14–21 days. One patient with a splenic abscess caused by a multidrug-resistant strain of *S typhi* required treatment with imipenem.<sup>31</sup>

Genitourinary infections caused by *S typhi* should be treated with antibiotics. Patients with pelvic infections may require laparoscopic drainage of abscesses. Patients with symptomatic urinary tract infections caused by *S typhi* should maintain a good fluid intake and receive antibiotics. First-line therapy for genitourinary infections caused by susceptible *S typhi* strains consists of ceftriaxone, ampicillin, co-trimoxazole, or fluoroquinolones for 7–14 days. Alternate therapy is chloramphenicol for 7–14 days.<sup>69,70</sup> Patients with underlying abnormalities such as urolithiasis and perinephric abscess often require surgical removal of calculi and some form of drainage procedure in addition to antibiotics for cure. In these cases, and other complicated urinary tract infections, 14 days of treatment or longer may be needed in the treatment of *S typhi* urinary tract infections.

Subcutaneous abscesses caused by *S typhi* require drainage for both a microbiological diagnosis and for treatment. Additionally, antibiotics and intensive supportive care are required.<sup>38</sup> The recommended therapy is ceftriaxone<sup>37</sup> or fluoroquinolones for 14–21 days. Alternate therapy for susceptible strains is ampicillin, co-trimoxazole, or chloramphenicol for 14–21 days.

The recommended therapy for haematological complications such as haemophagocytosis caused by *S typhi* is ceftriaxone<sup>42</sup> or fluoroquinolones. Alternate therapy for susceptible strains is co-trimoxazole,<sup>22</sup> chloramphenicol, or ampicillin.

### Conclusion

Extra-intestinal infectious complications caused by *S typhi* are uncommon. However, when *S typhi* bacteraemia

occurs virtually any organ system may be potentially involved. Typhoid fever including extra-intestinal complications should be considered in a person with compatible illness returning from a typhoid-endemic region. Therapy of involved infected organ systems is dependent on local resistance patterns of these bacteria, and duration of therapy is dependent on the organ system involved and the nature of its complication. In general, excluding central nervous system involvement, fluorquinolones and third-generation cephalosporins are the first-line therapy for infections with *S typhi*. Alternative therapy for susceptible strains consists of ampicillin, chloramphenicol, and co-trimoxazole.

### Conflicts of interest

We have any conflicts of interest to declare. There were no funding sources for this review.

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