8.6.9 Typhoid and paratyphoid fevers 1044

8.6.9 Typhoid and paratyphoid fevers 1044

section 8 Infectious diseases 1044 There is good in vitro evidence that monotherapy is associated with a slower rate of bacterial killing and the emergence of resistance; however, for uncomplicated infections, therapy with a single agent is probably adequate. Decisions on empirical antimicrobial therapy should be taken in the light of local information on patterns of re- sistance. The reader is encouraged to study this section in conjunc- tion with other relevant chapters on the management of conditions including neutropenic sepsis, ventilator-associated pneumonia, cystic fibrosis, and urinary tract, ear, and eye infections. Prevention Groups of patients (e.g. neutropenic patients, or patients with severe burns) who are particularly susceptible to invasive pseudomonal in- fection may be housed in clean units. Such units are equipped with filtered air supplies, and incoming water is chlorinated and continu- ously heated to 60°C. Attention is paid to the regular maintenance of air conditioning, hydrotherapy units, and water coolers. Visitors and staff are required to wear protective gowns and gloves, and to re- move their shoes to avoid contaminating the hospital environment with bacteria brought in from outside the hospital. Fresh flowers and fruit are prohibited for the same reasons, and a rigorous regimen of hand washing is instituted for all visitors and staff. The emergence over the last decade of highly transmissible strains of multidrug-resistant P. aeruginosa in people with cystic fibrosis has necessitated the institution of measures to segregate affected patients. Several vaccine candidates have been evaluated for using in clinical trials, but none are currently recommended for clinical use. FURTHER READING Chenoweth CE, Gould CV, Saint S (2014). Diagnosis, management, and prevention of catheter-associated urinary tract infections. Infect Dis Clin North Am, 28, 105–19. Torres A, et al. (2017). International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquiredpneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneu- monia (VAP) of the EuropeanRespiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), EuropeanSociety of Clinical Microbiology and Infectious Diseases (ESCMID)
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Wainwright C, Smyth AR (2013). Bronchoscopy-guided anti- microbial therapy for cystic fibrosis. Cochrane Database Syst Rev, 12, CD009530. Kaushik V, Malik T, Saeed SR (2010). Interventions for acute otitis externa. Cochrane Database Syst Rev, 1, CD004740. Langton Hewer SC, Smyth AR (2014). Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis. Cochrane Database Syst Rev, 11, CD004197. Paul M, et al. (2013). Beta-lactam versus beta-lactam-aminoglycoside combination therapy in cancer patients with neutropenia. Cochrane Database Syst Rev, 6, CD003038. 8.6.9 Typhoid and paratyphoid fevers Christopher M. Parry and Buddha Basnyat ESSENTIALS Typhoid and paratyphoid fever (the enteric fevers) are caused by specific serovars of the Gram-negative bacillus, Salmonella enterica. Sources of typhoid transmission are excreting chronic or convales- cent carriers and the acutely infected, with transmission occurring through contamination by carriers of food or water by effluents containing infected faeces or urine. Global estimates have varied be- tween 12 and 27 million cases of enteric fever in the world each year, almost all in low- and middle-income countries, with about 200 000 deaths. Clinical features—the main symptom is fever (39–40°C); head- ache and malaise are common; constipation is a frequent early symptom, but most patients will experience diarrhoea; abdominal pain is usually diffuse and poorly localized. Physical examination is often unremarkable, apart from fever, but rose spots and relative bradycardia may be observed. In developing countries, patients may progress in the second to fourth week, with life-threatening manifestations including gastrointestinal bleeding, intestinal per- foration, and the syndrome of mental confusion. Diagnosis—the principal method for confirming the diagnosis is by isolating Salmonella Typhi or Salmonella Paratyphi from blood or bone marrow. The organisms may also be isolated from stool, urine, and bile aspirates, but such demonstration should be interpreted with caution in areas with many chronic carriers as the acute illness may be due to another cause. Treatment—aside from supportive care, antibiotic therapy reduces mortality and complications and shortens the illness. Antibiotic re- sistance is a common and increasing problem, hence the choice of antibiotic should be informed by knowledge of likely local suscep- tibility. Fluoroquinolones are often given as first-line treatment, al- though low and high level resistance to these agents is becoming widespread in Asia, with extended-spectrum cephalosporins and azithromycin as alternatives. Prevention—typhoid has been eliminated from industrialized countries by (1) the provision of safe drinking water and safe disposal of sewage; (2) legal enforcement of high standards of food hygiene, and programmes to detect, monitor, and treat chronic carriers; and (3) prompt investigation and intervention when these safeguards are breached. Measures for individual protection are to (1) kill the organism in water by heating to 57°C, iodination, or chlorination; (2) take care with uncooked or reheated food; and (3) immunization—three typhoid vaccines are available and widely used in travellers, but their role as a public health tool in endemic areas is undefined; there is no paratyphoid vaccine.
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8.6.9 Typhoid and paratyphoid fevers 1045 Introduction The organisms classically responsible for enteric fever are Salmonella Typhi and Salmonella Paratyphi A, with occasional infections due to Salmonella Paratyphi B and C. They commonly present as a pro- longed febrile illness with a paucity of physical signs. The spectrum of disease varies from a mild self-limiting febrile illness to severe dis- ease associated with gastrointestinal bleeding, intestinal perforation, or mental confusion with shock. In the 19th century, typhoid fever was a leading cause of death in Europe and America. The disease today is predominantly found in low- and middle-income countries. Aetiology The Gram-negative bacilli Salmonella enterica subspecies enterica serovar Typhi (S.

Typhi) and S. Paratyphi A are the principal causa- tive agents of enteric fever. Three antigens are important for identi- fication: in Typhi the somatic oligosaccharide O antigen (9 and 12), the protein flagellar H-d antigen, and the polysaccharide envelope Vi antigen; in Paratyphi A the relevant O antigens are 1212 and H antigens a:[1,5]. Antibiotic resistance is conferred by R plasmids, usually of the incompatibility group IncH-1 (chloramphenicol, amoxicillin, co-trimoxazole), and by mutations in the chromosomal gyrA gene (fluoroquinolones). Whole genome sequencing of iso- lates of S. Typhi and S. Paratyphi A has shed light on the epidemi- ology and pathogenicity of these organisms. Evidence of a degraded genome compared with other Salmonella enterica serovars (deleted and inactivated genes) are consistent with its high level of adap- tion causing an invasive disease restricted to humans. The multiply antibiotic-resistant H58 lineage has emerged and spread throughout Asia and Africa. Transmission Sources of typhoid transmission are excreting chronic or convales- cent carriers and the acutely infected. Transmission occurs through contamination by carriers of food or water by effluents containing infected faeces or urine. ‘Typhoid Mary’ was a faecal carrier and cook who infected 53 people early last century, while the Aberdeen outbreak in 1964 was traced to a leaking corned beef tin which had been cooled with faecally contaminated river water. Transmission of typhoid has also been attributed to flies, laboratory mishaps, un- sterile instruments, and anal intercourse. Recent human challenge experiments have demonstrated that 103 organisms of Quailes strain of S. Typhi given orally in sodium bicarbonate solution infected 55% of experimental subjects. Susceptibility is increased by medi- cines which decrease the gastric acidic environment or by vagotomy. Infection may lead to acute disease, transient symptoms, or a symp- tomless carrier state. Multiplication and dissemination Bacteria are thought to pass from the gut through the cytoplasm of enterocytes and M cells overlying lymphoid tissue (Peyer’s patches) of the small intestine to reach the lamina propria from which they are conveyed to the mesenteric nodes before reaching the blood stream via the thoracic duct. During a transient primary bacter- aemia the organism is seeded to reticuloendothelial sites where intracellular multiplication occurs during a 7- to 14-day incuba- tion period. A second bacteraemia follows, accompanied by symp- toms as the infection spreads throughout liver, gallbladder, spleen, Peyer’s patches, and bone marrow. Multiplication occurs mainly in macrophages. Concentrated sites of infection in reticuloendothelial tissues, known as typhoid nodules, are characterized by infiltrates of lymphocytes and macrophages. At post-mortem examination, hypertrophy of lymphoid tissue is often visible within liver, spleen, mesenteric nodes, and Peyer’s patches. Ulceration of Peyer’s patches is seen where the inflammatory process has resulted in ischaemia and necrosis. Cytokines, such as tumour necrosis factor and interleukin-6, are elevated in the blood of patients with enteric fever but to a lesser de- gree than other Gram-negative septicaemias and the correlation be- tween cytokine levels and clinical outcome is less clear. The capacity of whole blood to produce proinflammatory cytokines following stimulation is reduced in patients with severe typhoid. HLA-DRB1 has been shown to be a major contributor to resistance against en- teric fever, presumably through an effect on antigen presentation Immune response There is a cell-mediated immune response lasting about 16 weeks, a mucosal immune response lasting for up to 48 weeks, and per- sistent circulating anti-O and anti-H agglutinins for up to 2 years. The predominance of clinical typhoid among children and young adults in endemic areas suggests a degree of acquired immunity. Only 25% of volunteers given a standard inoculum of S. enterica ser. Typhi 20 months after an initial infection developed clinical illness. Prolonged elevation of Vi antibody occurs in typhoid carriers. Immunodeficiency reduces the ability to clear salmonella infections. Epidemiology Worldwide, there are estimated to be between 12 and 27 million cases of enteric fever occur each year with about 200 000 deaths. In affluent countries, enteric fever is seen in returned travellers

vis- iting friends and relatives abroad in areas of endemicity or when food or water safety measures fail. With appropriate antibiotic treat- ment, death is rare. In parts of the Indian subcontinent, Central and Southeast Asia, Indonesia, and sub-Saharan Africa, high rates of transmission are seen and annual incidence rates of 100 to 1600 cases per 100 000 population have been recorded. In these countries, transmission has been exacerbated by antibiotic resistance. Peaks of transmission occur in dry weather or at the onset of rains. Case fatality rates have exceeded 10% in some reports of hospitalized patients in Indonesia and Papua New Guinea. S. Paratyphi A was previously thought to cause less severe disease that S. Typhi; a study of 609 cases of bacteraemic enteric fever in Nepal (409 with S. Typhi and 200 with S. Paratyphi) found that the clinical syndromes were indistinguishable and of similar severity. Prevention The elimination of typhoid from industrialized countries can be attributed to the provision of safe drinking water, safe disposal of sewage, legal enforcement of high standards of food hygiene,

section 8 Infectious diseases 1046 programmes to detect, monitor, and treat chronic carriers, and prompt investigation and intervention when these safeguards are breached. Outbreaks were previously investigated using phage typing of isolates and pulsed-field gel electrophoresis but whole genome sequencing methods are now increasingly used. Registers are kept of known carriers. Bacterial cultures from sewer swabs have previously been used to trace isolates back to their source. This may be replaced by molecular detection of isolates in environmental samples in the future. Measures for individual protection are to kill the organism in water by heating to 57°C, iodination, or chlorination, care with un- cooked or reheated food, and immunization. Patients and conva- lescents with typhoid should be advised to wash their hands after using the toilet and before preparing food and to use separate towels. Western travellers visiting friends and relatives in areas of endemicity are vulnerable to acquiring enteric fever and counselling needs to be targeted on this group. The approach of travel medi- cine, which has evolved around the tourist industry, might miss this susceptible group. Clinical features Enteric fever is predominantly an infection of infants, children, and young adults, affecting both sexes equally. The incubation period ranges from 3 to 60 days, but most infections occur 7–14 days after exposure. The main focus of typhoid is in the small bowel, but sys- temic symptoms often overshadow abdominal symptoms. The predominant symptom is the fever which rises gradually to a high plateau of 39–40°C, and then shows little diurnal variation unless antipyretics are given. Rigors are uncommon, except in late or com- plicated typhoid or in patients treated with antipyretics. Patients usu- ally complain of headache and malaise, and constipation is a frequent early symptom. Most patients will experience diarrhoea, and typhoid can present as an acute gastroenteritis and occasionally bloody diar- rhoea. Severe diarrhoea or colitis have been reported in HIV-infected patients. The abdominal pain is usually diffuse and poorly localized but occasionally sufficiently intense in the right iliac fossa to sug- gest appendicitis. Nausea and vomiting are infrequent in uncompli- cated typhoid but are seen with abdominal distension in severe cases. Other early symptoms include cough, sore throat, and epistaxes. In developing countries, patients with typhoid in its second to fourth week present with accelerating weight loss, weakness, altered mental state, intestinal haemorrhage and perforation, refractory hypoten- sion, pneumonia, nephritis, and acute psychosis. Those infected with antibiotic-resistant infections may have more severe disease. Physical examination is often unremarkable apart from fever. A coated tongue might be observed. Rose spots appear at the end of the first week and form a sparse collection of maculopapular lesions on the abdominal skin, which blanch with pressure and fade after 2 or 3 days (Fig. 8.6.9.1). Osler found them in 90% of white-skinned patients and 20% of patients with black skin. The rash can extend on to the trunk and arms.

Melanesian typhoid patients develop purpuric macules that do not blanch (Fig. 8.6.9.2). Petechiae are sometimes visible on the conjunctivae (Fig. 8.6.9.3) Tachycardia is common although temperature–pulse dissociation (relative brady- cardia) is considered characteristic. Hypotension has important im- plications (see ‘Severe typhoid’, later in this chapter). Adventitious Fig. 8.6.9.1 Rose spots on the abdomen in typhoid fever. Copyright CM Parry. Fig. 8.6.9.2 Typhoid rash in a Melanesian child: sparse purpuric (non- blanching) macules. Copyright D. A. Warrell. Fig. 8.6.9.3 Conjunctival petechial haemorrhage in an African child with typhoid. Copyright D. A. Warrell.

 lung sounds, especially scattered wheezes, are common and might suggest pneumonia. These findings, with a normal chest radiograph and high fever, should prompt consideration of typhoid. Abdominal examination might reveal the typhoid rash, distension, or a diffuse tenderness, occasionally localized to the area of the terminal ileum. Intra-abdominal inflammation sometimes provokes retention of urine. A moderate soft tender hepatosplenomegaly eventually de- velops in most patients but it less likely to be found early. Patients with advanced illness may display the ‘typhoid’ facies (Fig. 8.6.9.4), a thin flushed face with a staring apathetic expression. Mental apathy may progress to an agitated delirium, frequently ac- companied by tremor of the hands, tremulous speech, and ataxic gait. If the patient’s condition deteriorates further, the features described in the writings of Louis and Osler make their appearance—muttering delirium, twitching of the fingers and wrists, agitated plucking at the bedclothes, and a staring unrousable stupor (coma vigil). Typhoid in children Community-based studies in highly endemic areas have shown that enteric fever can be common in children less than 5 years old. The main differences, compared to adults, are a greater frequency of diarrhoea and vomiting, jaundice, febrile convulsions, and nephritis or typhoid meningitis may occur. Relative bradycardia is of greater diagnostic significance for typhoid in febrile children. In some re- ports case fatality rates are high in the under-fives. The disease can also take a milder course in very young children, behaving like a nonspecific febrile illness or mild respiratory illness that is not clin- ically recognized as enteric fever. Typhoid may also occasionally de- velop in neonates born to infected mothers. Differential diagnosis Many viral, bacterial, and protozoal infections as well as noninfectious conditions characterized by fever, including lymphoproliferative disorders and vasculitides, resemble enteric fever. Typhoid should al- ways be considered when suspected malaria has not been confirmed or has not responded to antimalarial therapy. In areas of endemicity, typhus, leptospirosis, and dengue should be considered in the differ- ential diagnosis. Diagnosis Culture The definitive diagnosis of enteric fever rests on the isolation of S. Typhi or S. Paratyphi from blood, bone marrow, cerebrospinal fluid, or rose spots. In mild typhoid, the number of bacteria in blood may be less than 1 colony-forming unit/ml. The median number of bacteria in the blood of children is higher than adults and declines with increasing duration of illness. Successful culture from blood can be achieved in up to 80% of patients but depends on taking a generous volume of blood and using the correct volume of blood to broth (1:10). Although bone marrow generally gives a higher yield than blood, including those exposed to antibiotics, it is rarely per- formed. Rose spots, when present, can give a positive culture in 70% of patients. The organisms may also be isolated from stool, urine, and bile as- pirates. The number of organisms recoverable from faeces increases through the illness. The results should be interpreted with caution in areas with many carriers, as the acute illness may be due to another cause in chronic carriers. Isolation from urine is more common in areas endemic for schistosomiasis. Culture of bile obtained from an overnight duodenal string capsule gives a similar yield to blood and offers additional means to isolate S. Typhi and S. Paratyphi from children or from carriers. Serology The

use of a tube or slide agglutination test (the Widal test) to diag- nose typhoid is cheaper and simpler than culture but fraught with pitfalls. The demonstration of a fourfold rise in titre of antibodies to S. Typhi or S. Paratyphi antigens suggests enteric fever but is too delayed to help clinical decision-making and is not observed in all patients. Single measurements of antibody titres have been found useful in populations where accurate up-to-date informa- tion about the predictive value of the test at specific cut-off points is available. False-positive serological tests are obtained from per- sons with previous infection, infection with cross-reacting organ- isms, or following vaccination. Several commercially available enzyme-linked immunosorbent assay (ELISA) and point-of-care rapid diagnostic tests perform somewhat better than the Widal test, but with sensitivities and specificities that are still not ad- equate for routine diagnostic use. An ELISA for antibodies to the Vi antigen can be useful for detecting carriers in the context of an outbreak.
Other tests for typhoid Many other tests for the detection of antibodies, antigens, and sal- monella DNA in body fluids have been described. Few have so far been adopted for routine use. The detection of IgA antibodies in the supernatant from blood lymphocytes and real-time polymerase chain reaction after short-term blood culture are two potentially promising new approaches.
Fig. 8.6.9.4 Typhoid facies: a man with the apathetic expression seen in severe typhoid. Copyright B Basnyat.

 Other laboratory findings in typhoid A mild normochromic anaemia, mild thrombocytopenia, and an increased erythrocyte sedimentation rate are common. Most pa- tients have a total white cell count within, or just below, the normal range. Leucocytosis suggests either perforation or another diag- nosis. Laboratory evidence of mild disseminated intravascular co- agulation is common but rarely of clinical significance. Common biochemical findings include hyponatraemia, hypokalaemia, and elevation of liver enzymes, which may mimic acute viral hepatitis. The urine often contains some protein and white cells. Examination of the cerebrospinal fluid may be normal or show a mild pleocytosis (<35 cells/mm3) in patients with central nervous system symptoms. Treatment The aims of management are to eliminate the infection swiftly with antibiotics, to restore fluid and nutritional deficits, and to monitor the patient for dangerous complications. In many parts of the world antibiotic treatment for typhoid fever is started empirically based on the syndrome of fever of 3 or 4 days and constitutional symptoms with no apparent source of infection and a negative malaria smear. Because there are no reliable clinical predictors, in areas of endem- icity concurrent treatment with doxycycline to cover for typhus and leptospirosis must be considered. Supportive care Cooling is preferred to antipyretics for relief of fever, and simple an- algesics may be used to relieve headache. Most patients can eat and drink normally; special diets do not protect the bowel from perfor- ation. Daily assessment of the patient’s mental and circulatory status is required plus examination of the abdomen for signs of impending perforation. Severely ill patients require intensive care with paren- teral fluids, intravenous steroids (see next), inotropic support, and sedation. Antibiotics Effective antibiotic therapy in typhoid reduces mortality and min- imizes complications and shortens the illness (see Table 8.6.9.1 for doses). Chloramphenicol was the first antibiotic found to be effective and the standard against which subsequent antibiotics have been measured. Symptom resolution occurs over a period of 3 to 6 days although it is generally suggested that the antimicrobial should be given for at least 2 weeks to prevent relapse. Ampicillin, amoxicillin, and co-trimoxazole have been shown to have comparable efficacy Table 8.6.9.1 Guidelines for the antibiotic treatment of enteric fever Antibiotic Daily dose Routea Doses/day Duration in nonsevere enteric fever (days) Duration in severe enteric feverb Acute infection Chloramphenicolc 50–100 mg/kg O/IM/IVd 4 14

14–21 Co-trimoxazolee Trimethoprim 6.5–10 mg/kg O/IM/IV 2–3 14 14 Sulfamethoxazole 40 mg/kg Amoxicillin 75–100 mg/kg O/IM/IV 3 14 14 Ceftriaxone 50–60 mg/kg IM/IV 1–2 7–14 14 Cefixime 20 mg/kg O 2 7–14 Ciprofloxacinf 20–25 mg/kg O/IV 2 7–14 14 Ofloxacinf 15–20 mg/kg O/IV 2 7–14 Pefloxacinf 800 mg O/IV 2 7–14 Fleroxacinf 400 mg O/IV 1 7–14 Gatifloxacin 10 mg/kg O 1 7 Azithromycin 10–20 mg/kg O 1 7 Treatment of carriers Ampicillin or amoxicillin with probenecid 100 mg/kg O 3–4 90g 30 mg/kg Co-trimoxazole 6.5–10 mg trimethoprim O 2 90 Ciprofloxacin 1500 mg O 2 28 O, oral; IM, intramuscular; IV, intravenous. a Oral therapy is satisfactory for most patients. Parenteral therapy is generally reserved for severely ill patients. b In intestinal perforation, the antibiotic therapy should also cover other aerobic and anaerobic gastrointestinal bacteria contaminating the peritoneum. In severe typhoid (characterized by delirium, obtundation, coma, or shock) dexamethasone is beneficial (see text). c May cause bone marrow suppression. d The oral route is preferred; there are reports of lower blood levels of chloramphenicol in patients given parenteral therapy. e May cause allergic reactions and nephrotoxicity. Not suitable for children younger than 2 years or during pregnancy. f Infection with isolates that have low-level fluoroquinolone resistance (nalidixic acid resistance) may not respond. g The duration of treatment can be shortened if parenteral therapy is given (e.g. 8-hourly intravenous ampicillin for 2 weeks).

8.6.9 Typhoid and paratyphoid fevers 1049 to chloramphenicol while having less toxicity; they are also recom- mended to be given for at least 2 weeks. In many areas these drugs are no longer used because of the spread of multidrug-resistant strains of S. Typhi and S. Paratyphi A. Alternative antibiotics active against multidrug-resistant infec- tions include the fluoroquinolones, although resistance has, in turn, emerged to these agents, the extended-spectrum cephalosporins (e.g. parenteral ceftriaxone), and azithromycin. In recent years many physicians have given a fluoroquinolone, ciprofloxacin, or ofloxacin as first-line therapy. Treatment can be completed in a week or less with minimal toxicity. In controlled trials in endemic areas, infections with fully susceptible isolates have resulted in a rapid resolution of symptoms with high cure rates and low levels of relapse and faecal carriage. Response rates in endemic areas may be better than those of nonimmune travellers. There have been questions about the safety of fluoroquinolones in children and during pregnancy. Careful follow-up studies of children in Asia fol- lowing fluoroquinolone therapy have not shown toxicity and there has been a growing consensus that where alternatives are limited the advantages of therapy outweigh the potential dangers. Strains of S. Typhi and S. Paratyphi A with low-level resistance (or intermediate susceptibility) to the commonly used fluoroquinolones (ciprofloxacin and ofloxacin) are common in Asia and sporadic- ally reported in sub-Saharan Africa. These strains are usually nali- dixic acid, or pefloxacin, resistant and this can be a useful, although not a completely sensitive, laboratory marker. Where possible ciprofloxacin and ofloxacin should be avoided in patients infected with these strains. The newer fluoroquinolone gatifloxacin is effective but safety concerns mean it is unavailable in some countries. These infections can be treated with extended-spectrum cephalosporins (ceftriaxone) or, in nonsevere cases, with azithromycin. Another alternative is cefixime, an oral third-generation cephalosporin, al- though there have been concerns about its efficacy in some studies. Many areas in the Indian subcontinent now report isolates that are fully resistant to all the fluoroquinolones including gatifloxacin. A recent outbreak in Pakistan of MDR typhoid that is also resistant to ceftriaxone and fluorquinolones is giving cause for concern. In some places there has been an increase in isolates that have regained sus- ceptibility to the old first-line drugs, chloramphenicol, ampicillin, and co-trimoxazole. In such circumstances these older drugs may be appropriate. Some antibiotics such as gentamicin appear sensi- tive in vitro but are ineffective in vivo and should not be used in

enteric fever. Ampicillin, amoxicillin, or ceftriaxone are considered safe in pregnancy with enteric fever. There are limited data on the manage- ment of immunocompromised patients with enteric fever, but data from patients with nontyphoidal salmonella infections suggest that they may need extended treatment to prevent relapse. Complications Box 8.6.9.1 lists the complications of typhoid. Most are rare and only likely to be encountered in patients who present with untreated dis- ease lasting 2 weeks or more. Occasionally, a complication domin- ates the clinical picture and deflects attention from the underlying diagnosis of typhoid. Box 8.6.9.1 Complications of typhoid Abdominal • Intestinal perforation • Intestinal haemorrhage • Hepatitis • Cholecystitis (usually subclinical) • Spontaneous splenic rupture • Rupture and haemorrhage from mesenteric nodes • Pancreatitis Genitourinary • Retention of urine • Glomerulonephritis • Pyelonephritis • Cystitis • Orchitis Cardiovascular • Asymptomatic electrocardiogram changes • Myocarditis • Pericarditis • Endocarditis • Phlebitis and arteritis • Deep venous thrombosis • Gangrene • Haemodynamic shock • Sudden death Respiratory • Bronchitis • Laryngeal ulceration • Glottal oedema • Pneumonia (S. enterica ser. Typhi, Streptococcus pneumoniae) Neuropsychiatric • Delirium • Psychotic states • Depression • Deafness • Meningitis • Encephalomyelitis • Transverse myelitis • Signs of upper motor neuron lesions • Signs of extrapyramidal disorder • Impairment of coordination • Optic neuritis • Peripheral and cranial neuropathy • Guillain–Barré syndrome • Pseudotumour cerebri Haematological • Disseminated intravascular coagulation (usually subclinical) • Anaemia • Haemolysis • Haemolytic uraemic syndrome Focal infections • Abscesses of brain, liver, spleen, breast, thyroid, muscles, lymph nodes • Parotitis • Pharyngitis • Osteitis, especially tibia, ribs, spine • Arthritis (continued)

 Severe typhoid Studies from Indonesia and Papua New Guinea have revealed an im- portant subgroup of patients with mental confusion or shock (de- fined as a systolic blood pressure of less than 90 mm Hg in adults or less than 80 mm Hg in children), with evidence of decreased skin, cerebral, or renal perfusion, who have a 50% fatality rate and account for many typhoid deaths. In a small study in Jakarta, high doses of dexamethasone substantially reduced the mortality of such severe cases. The criteria for severe typhoid were marked mental confusion or shock. In adults treated with chloramphenicol, 3 mg/ kg dexamethasone infused intravenously over 30 min, followed by eight doses of 1 mg/kg every 6 h, resulted in a 10% case fatality rate compared to 55.6% in controls. This study has not been repeated. Intestinal haemorrhage and perforation Perforation of ileal ulcers occurs in less than 5% of typhoid patients (Fig. 8.6.9.5). The development of acute abdominal signs is often gradual, making diagnosis difficult. Severely ill patients display only restlessness, hypotension, and tachycardia. A chest radiograph may show free gas under the diaphragm. Ultrasonography is useful for demonstrating and aspirating faeculent fluid in the peritoneal cavity. Management includes nasogastric suction, administration of fluids to correct hypotension, and prompt surgery. Although simple closure of perforations can be adequate, experienced surgeons use procedures to bypass the worst-affected sections of the ileum in order to reduce postoperative morbidity. Closure of perforations should be accom- panied by vigorous peritoneal toilet. Metronidazole or clindamycin should be added to the therapy of ceftriaxone or fluoroquinolone- treated patients. Metronidazole and aminoglycosides are recom- mended for patients receiving chloramphenicol, ampicillin, or co-trimoxazole. In a recent systematic review, the mean case fatality rate of patients with intestinal perforation was 15.4%, reaching less than 5% in the best series, but postoperative complications were common. This compares with historical case fatality rates of around 70% in patients managed without surgery. Evidence for silent gastrointestinal bleeding may be sudden col- lapse of a patient or a steadily falling haematocrit. Most bleeding episodes are self-limiting. Severe bleeding is sometimes seen in

ad- vanced typhoid but is rarely fatal. A few require transfusion. In ex- ceptional circumstances surgery or intra-arterial vasopressin have been used to halt haemorrhage. Relapse Relapse in typhoid is a second episode of fever, usually milder than the first, occurring a week or two after recovery from the first epi- sode. Isolates from relapsing patients usually have identical anti- biotic susceptibility to those identified during the first episode. Relapse rates of 10% have been described in untreated typhoid and chloramphenicol-treated patients. Relapse is managed with a similar or abbreviated course of the same therapy used in the initial episode. Reinfection may also occur but can only be distinguished by differ- ences in the sensitivity pattern or molecular typing of isolates. Carriers Many patients will continue to excrete S. Typhi or S. Paratyphi in faeces, and occasionally urine, for several days or weeks after starting antibiotic treatment. For most patients this eventually stops but if they are still excreting at 3 months, they are unlikely to cease and at 1 year meet the formal definition of ‘chronic carrier’. Among carriers detected by screening, 25% give no history of acute typhoid. Faecal carriage is more frequent in individuals with gallbladder disease and is most common in women over 40; in the Far East there is an as- sociation with opisthorchiasis. Urinary carriage is associated with schistosomiasis and nephrolithiasis. Chronic carriage is occasion- ally complicated by acute typhoid and there is a long-term increased risk of carcinoma of the gallbladder. Patients discharged after treatment for typhoid with six negative faeces and three negative urine specimens and negative Vi serology are considered free of infection. Many public health authorities aim for the pragmatic requirement of three negative faeces samples. Most patients with positive faeces at the completion of treatment excrete temporarily and can be safely followed up. Antibiotic eradication of carriage is advised in those still excreting at 3 months, or earlier in those at particular risk of communicating infection to others. The pa- tient with a persistently elevated or rising Vi antibody titre is likely to be a carrier. Repeated checks of urine and faeces should be made and consideration given to obtaining bile cultures if these are negative. Eradication of carriage requires prolonged, high-dose anti- biotics (Table 8.6.9.1). Ampicillin, amoxicillin, co-trimoxazole, and fluoroquinolones have been used with some reported success. The choice depends on the antibiotic susceptibility of the organism. Cholecystectomy and nephrectomy, once used to eliminate carriage (and not without operative mortality), are hard to justify on public health grounds alone, but can be considered if antibiotic methods fail and there are additional indications for operation. The success rates of surgery are increased by giving antibiotics as well. Box 8.6.9.1 Continued Other • Myopathy • Hypercalcaemia • Decubitus ulceration • Abortion • Relapse Fig. 8.6.9.5 Typhoid perforation of the distal ileum at operation.

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