Specialty Conference

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Salmonellosis

THOMAS T. YOSHIKAWA, MD:* Salmonellosis, or infections caused by salmonellae, remains an important disease in the United States. In 1978 and 1979 more than 29,000 isolates of salmonellae from humans were reported to the Center for Disease Control.[1,2] Although salmonellosis is clinically associated with underdeveloped countries, lower socioeconomic populations, poor hygiene, and contaminated food and water, physicians must still be aware of this infection, even in our modern society. With international tourism a common activity, physicians should consider that *Salmonella* infections may be acquired outside the United States.[3] Studies have indicated that at least 33 percent of typhoid fever cases in the United States are acquired during travels outside the states.[4]

A review of salmonellosis would be useful for practicing physicians. This discussion will be divided into (1) a brief history of salmonellosis, (2) microbiology, epidemiology and pathogenesis of salmonellosis, (3) clinical spectrum and management of salmonellosis and (4) precautions and recommendations for travel.

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Historical Aspects of Salmonellosis

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TYPHOID FEVER has probably been prevalent since the age of Hippocrates, but the first clear description is that of Thomas Willis of Wiltshire, England, in 1659.[5] In modern times it has caused frequent epidemics in army camps and in crowded cities. No respecter of classes, it attacks rich and poor alike through the medium of contaminated water and food. Albert, Prince Consort of Queen Victoria, died of typhoid fever in 1861 at the age of 42.[6]

John Huxham of Devon, writing in 1739, distinguished two kinds of enteric fevers: putrid malignant (typhus) and slow nervous (typhoid).[7] French physicians in the first third of the 19th century described swelling and ulceration of Peyer patches and enlargement of mesenteric lymph nodes in patients dying of what Prost called in 1804 "mucous fever." In 1813 mucous fever was identified by Petit and Serres as the condition Huxham had described as slow nervous fever.[8]

It was a Frenchman, Pierre Bretonneau of Tours, who recognized that slow nervous fever was a distinct clinical entity caused by a specific, albeit unknown, agent. Until this time it was still

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considered possible that all fevers were one disease with symptoms and signs varying from patient to patient depending on the circumstances of the illness. Bretonneau showed that the pathological findings in slow nervous fever were unique, differentiating it from all other fevers, including typhus, in which lesions of Peyer patches were not found.[6,8] He was convinced that the disease was contagious and proposed a new name for it, dothienenteritis (Greek *dothien:* circumscribed skin lesion).[8]

This unwieldy name was superseded by the term "fièvre typhoïde" (resembling typhus), introduced by Pierre Louis in his famous and comprehensive book on the disease published in 1829.[7] The word typhus derives from a Greek combining form meaning stupor and had been used in connection with enteric fever since its introduction by de Sauvages in 1759.[9]

Typhus and typhoid continued to be confused, however, until William Gerhard of Philadelphia in 1837 and the English physician Sir William Jenner in 1849 each wrote eloquent monographs separating the two diseases.[7] Jenner spoke from personal experience; during the course of his researches, he had contracted both maladies.[8]

Studies of epidemics by Piedvache in France in 1849 and by Murchison in England in 1858 showed that typhoid fever was a contagious disease. Murchison thought that it arose from a nonspecific corruption of air and water that, once the disease was contracted, could be further spread by intake of air, water or food that had been in contact with a person ill with the fever.[7] The Englishman William Budd of Devon made a careful study of an outbreak in Cowbridge in 1853. Rejecting the spontaneous generation theory, he thought that typhoid was due to a "self-propagating" principle and that all cases arose from antecedent cases. He realized that "the contagious element by which it is mainly propagated is contained in the specific discharges from the diseased intestine." He added, "The sewer . . . is, so to speak, the direct continuation of the diseased intestine."[10]

In 1880 C. J. Eberth saw typhoid bacilli in sections of lymph nodes and spleen from patients dying of typhoid fever.[8] Georg Gaffky, a Prussian army surgeon, grew the organism in pure cultures in 1884.[5] Durham, Pfeiffer and Kolle in 1896 used a prepared antiserum to identify the organisms by specific agglutination and immobilization, and Fernand Widal in 1896 showed the agglutinating reaction of serum from typhoid patients for the Eberth bacillus.[8]

The first practical typhoid vaccine was prepared from heat-killed bacteria by Sir Almroth Wright and was used to inoculate more than 3,000 soldiers in India in 1898. The admission rate there for typhoid fever dropped from 8.9 to 2.3 cases per 1,000, and there were fewer fatalities among these men, who nevertheless contracted the disease despite previous vaccination.[8]

Paratyphoid fever was first described by Achard and Bensaude in 1896. A severe outbreak occurred among British troops immunized against typhoid fever on the Gallipoli peninsula in 1915. Subsequent vaccines were fortified with *Salmonella paratyphi* A and B.[8]

Even before the development of specific vaccines, typhoid fever had begun to yield to improvements in sanitation. Following the passage of the Public Health Act in 1875 in Great Britain, the death rate from typhoid fever declined more than 50 percent during the next decade.[6]

The present name for the genus *Salmonella* was proposed by Lignières in 1900, for D. E. Salmon, who with Theobald Smith first isolated *Salmonella cholerae-suis.* This nomenclature was officially adopted in 1933.[11] Studies by White (1925) and Kauffman (1930) led to the Kauffman-White serological classification of salmonellae. Finally, the more contemporary work by Woodward and Hook provided a greater understanding of the pathogenesis and treatment of salmonellosis.[11]

Microbiology, Epidemiology and Pathogenesis of Salmonellosis

PHYLLIS A. OILL, MD*

Microbiology

Salmonella ORGANISMS are members of the family Enterobacteriaceae. They are nonspore-forming, aerobic, facultatively anaerobic, Gram-negative bacilli. *Salmonella* are motile by peritrichous flagella. Like that of all other enterobacteria, the cell wall of *Salmonella* is a complex structure composed of lipids, polysaccharides, protein and lipoproteins.[12] Endotoxin is the lipopolysaccharide portion of the cell wall (although some protein may also be present), with lipid A (lipid moiety

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of endotoxin) being responsible for the biological effects.[13] The common core monosaccharides and polysaccharides of endotoxin are also called somatic O antigens.[12] For *Salmonella* there are approximately 60 O antigens, which are designated by numbers. Additionally, there are several different flagella (H) antigens that are identified by numbers and letters. Based on a strongly reacting somatic antigen (major determinant) and one or more minor somatic antigens, salmonellae may be separated into major groups using specific antisera. Using the Kauffman-White schema, most salmonellae that cause human disease belong to groups A, B, C_1, C_2, D and E.[14] For specific serotype identification, the flagella antigens must be identified. Some serotypes of *Salmonella*—for example, *S typhi*—possess a capsular antigen called the virulence (Vi) antigen, which envelops the cell wall.

Using somatic and flagella agglutination reactions, more than 2,200 serotypes have been identified.[15] Previously, salmonellae were named according to the disease and animal from which they were isolated—such as *S cholerae-suis*. Later, the nomenclature was changed so the organisms got their names from the town, country or region in which they were first isolated—for example, *S saint-paul*. Traditionally, the various *Salmonella* serotypes have been treated as species (such as *S typhimurium*) and this practice is still common in the medical literature. However, Ewing has proposed only three primary species: *S typhi* (one serotype) and *S cholerae-suis* (one serotype), with *S enteritidis* encompassing all the remaining serotypes.[16] Hence, *S typhimurium* is designated *S enteritidis*, serotype Typhimurium. This latter nomenclatural approach is slowly being adopted by more and more microbiologists and infectious disease specialists.

Salmonella grow readily on most media including blood agar, MacConkey agar or eosin-methylene blue. Cultures of body fluids that are normally sterile (joint fluid, cerebrospinal fluid) can be grown on these media. However, with specimens such as feces, which contain many other organisms, highly selective media such as bismuth sulfate agar or desoxycholate agar should be used. The isolation of an aerobic Gram-negative bacillus that ferments glucose and mannose but not lactose or sucrose should alert the clinician that the laboratory is possibly dealing with a *Salmonella* isolate. *Salmonella* can readily be identified in most clinical laboratories by a variety of chemical tests. Moreover, a presumptive identification of *S typhi* and nontyphi *Salmonella* can be made by simple biochemical reactions. Gas production from glucose, ornithine reaction and rhamnose reaction are negative for *S typhi*, but are all positive for nontyphi *Salmonella*.

TABLE 1.—*The Ten Serotypes of* Salmonella *Most Frequently Isolated From Human Sources in the United States in 1978-1979**

Serotype	Number of Isolates	Percent of Total	Rank in 1979/1978
typhimurium	10,153	32.6	1/1
enteritidis	2,633	8.5	2/3
heidelberg	2,490	8.0	3/2
newport	1,915	6.2	4/4
infantis	1,417	4.5	5/5
agona	1,103	3.5	6/6
saint-paul	856	2.8	7/9
typhi	647	2.1	8/8
montevideo	613	2.0	9/7
oranienburg	592	1.9	10/..
Subtotal	22,419	72.1	
Others	7,994	27.9	
TOTAL (all serotypes)	31,123	100.0	

*Adapted from the Center for Disease Control.[1,2]

Epidemiology

Salmonella infections occur worldwide. As mentioned in the opening remarks, salmonellosis is not uncommon in the United States. Although approximately 25,000 to 30,000 cases of salmonellosis are reported each year from the United States, these probably represent only 1 percent of the true incidence.[17] However, the incidence of *S typhi* infections appears to be declining.

Enteric fever caused by *S typhi* (typhoid fever) is acquired by ingesting the organism via contaminated food or drink. In contrast to the transmission pathway of other salmonellae, humans are the only true reservoir for *S typhi*. Hence, outbreaks of *S typhi* can usually be traced back to food or drink that has been contaminated by another infected person who is excreting the organism, usually in the feces. Occasionally, insects or flies have been implicated in carrying organisms from feces to food or drinks. In countries or areas of the United States where pure water supplies are scarce, and effective sewage disposal or other sanitation measures are suboptimal, the incidence of typhoid fever is high. The attack rate of *S typhi* is equal among males and females, but is slightly greater in children than in adults. There appears to be no seasonal variation for cases in the United States.[4] A chronic

biliary carrier state occurs more frequently in women than men, perhaps because older women have a higher prevalance of gallbladder disease.

Salmonellosis caused by *Salmonella* serotypes other than *S typhi* ("nontyphi" salmonellosis) are most frequently isolated from both human and nonhuman sources.[17] The ten most frequently isolated serotypes of *Salmonella* from humans in the United States in 1978 and 1979 are shown in Table 1.[2] Nontyphi salmonellae are primarily pathogens of animals, both warm- and cold-blooded species. *Salmonella* organisms have been isolated from virtually all animal species including chickens, turkeys, ducks, cows, pigs, sheep, seals, donkeys, dogs, cats, turtles, guinea pigs, lizards and snakes.[18] Human acquisition of nontyphi salmonellosis occurs from ingestion of contaminated poultry, poultry products, meats (beef or pork), dairy products and, less frequently, water. Animal infections can occur by animal-to-animal transmission or by ingestion of contaminated animal foods.

Nontyphi *Salmonella* infections occur with the greatest frequency during warm weather periods; in the United States, this is between July and November.[19] Children under the age of 5 years, particularly those in the first year of life, have the highest attack rate of salmonellosis. Although the largest number of outbreaks occur in the home environment, institutional outbreaks of salmonellosis are very common. Most institutional cases occur in acute care hospitals, pediatric wards and nurseries, followed in number of occurrences by nursing homes, psychiatric hospitals and institutions for the retarded.[20] Whereas contaminated food or drink is responsible for most outbreaks associated with restaurants, banquets, food stores and schools,[21] nosocomial outbreaks have not only been attributed to food or drink but also to blood products,[22] pharmacologic and diagnostic preparations derived from animals (for example, bile salts, carmine dye, liver extract, pepsin and thyroid extracts) and cross-infection.[20] Cross-infection occurs by person-to-person transmission[23,24] or by contact with contaminated fomites or diagnostic equipment.[25]

Pathogenesis

Several factors (inoculum, serotype and host) appear to play important roles in the development of disease following ingestion of *Salmonella* organisms. McCullough and co-workers[26,27] reported that a large quantity of organisms (10^6) was required in order to produce disease consistently in human volunteers. These findings were again confirmed by Hornick and associates.[28] In their investigations they showed that oral inocula of a strain of *S typhi* in quantities of 10^5, 10^7 and 10^9 produced disease in 28 percent, 50 percent and 95 percent of the volunteers, respectively.

The serotype of *Salmonella* may determine the clinical syndrome produced. Although *S typhi* is the classic serotype causing enteric fever (typhoid fever), other serotypes can cause this syndrome too (called paratyphoid fever). Gastroenteritis is most commonly caused by *S typhimurium*.[29] *Salmonella cholerae-suis* regularly invades the bloodstream producing bacteremic syndromes (but not enteric fever) and localized infections, especially in vascular structures.[29] *Salmonella* mycotic aneurysm and endocarditis are most commonly associated with *S cholerae-suis*.[30,31] *Salmonella typhimurium* and *S derby* appear to be most commonly isolated from patients with salmonellosis and neoplastic disease.[32,33]

Several host factors appear to be important in

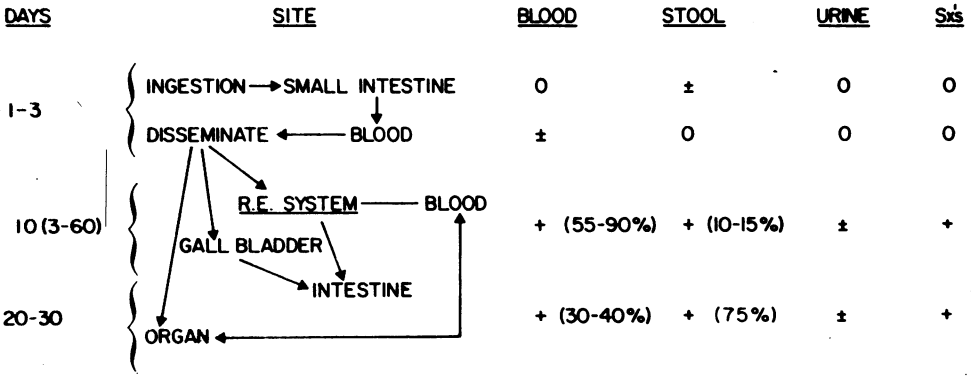

Figure 1.—Enteric fever: positive culture sites correlated with pathogenesis. R.E. = reticuloendothelial; Sx's = symptoms.

the acquisition of salmonellosis. Local gastrointestinal factors such as gastric acidity appear to influence the number of viable organisms; low pH will kill *Salmonella* organisms. Diseases of the stomach (or gastrectomy) that either decrease gastric acidity or enhance gastric emptying have been associated with *Salmonella* enteritis.[34,35] Alteration of the normal intestinal flora by administration of antibiotics may cause infection to occur with a small inoculum or possibly prolong the fecal shedding of nontyphi salmonellae.[36,37] As mentioned earlier, age is an important factor in the epidemiology of salmonellosis. The majority of nontyphi *Salmonella* infections occur in children younger than 5 years, particularly under the age of 1 year.[1,38] The specific mechanism for this age predisposition is not known although several factors could be operative, such as high frequency of fecal-oral contamination, decreased antibacterial activity of the normal intestinal microflora or immaturity of the immune systems.

Certainly, it appears that alteration of the cellular or humoral immune system, or both, may be important for predisposing to salmonellosis because several reports have shown the association of salmonellosis and malignancy.[32,33,39] Whether the underlying malignant conditions or the associated chemotherapy, radiotherapy, surgical treatment and hemolysis are the risk factors is not clear. Hemolysis is particularly important because sickle hemoglobinopathies, malaria and bartonellosis are associated with increased incidence of *Salmonella* infections.[18] Postulated mechanisms for hemolytic predisposition are defects in complement function, impairment of phagocytosis and abnormalities in killing of *Salmonella* following erythrophagocytosis, autosplenectomy or alteration in the immune system. Presence of *Schistosoma* infection leads to an increased incidence of *Salmonella* infection.[40] The *Salmonella* apparently localizes in the integument of a mature *Schistosoma* worm.[41] Elimination of schistosomiasis will eradicate the *Salmonella* infection.[18] Finally, the presence of chronic gallbladder disease, particularly cholelithiasis, favors the development of a chronic *Salmonella* carrier state, with persistent biliary excretion of the organism.

Development of salmonellosis occurs following ingestion of the organism. Viable bacteria pass to the small intestine where they multiply. Following multiplication, an infected individual may be totally asymptomatic and transiently shed the organisms in the feces. The pathogen then can disseminate hematogenously to the reticuloendothelial system, gallbladder or other organ sites. At these sites, the salmonellae may further replicate. From the reticuloendothelial sites, secondary bacteremia may occur causing an enteric fever syndrome, or organisms may again invade the small intestine. Gallbladder involvement leads to organisms localized to the intestinal tract via bile excretion. If salmonellae localize to an organ site (such as bone, meninges or heart), suppuration with secondary bacteremia may occur. These pathogenetic pathways are typical for enteric fever and are summarized on the left side of Figure 1. Alternatively, after intestinal multiplication, active infection may develop resulting in symptomatic acute *Salmonella* enterocolitis. Localization of the disease to the intestinal tract is usual; however, secondary bacteremia may occur with a clinical picture of Gram-negative sepsis, particularly in the immunocompromised host (malignancy group).

The clinical manifestations of enteric fever, primarily the pyrexia and toxemia, have been traditionally ascribed to continuous endotoxemia.[42] However, more recent studies in human volunteers showed that endotoxin tolerance can be induced but that challenges of *S typhi* still produced the febrile and toxic manifestations of enteric fever.[28] Moreover, one study investigating typhoid fever and disseminated intravascular coagulation suggested that neither endotoxemia nor bacteremia played a major pathogenic role in this disease.[43] Although the exact pathogenesis of enteric fever remains unclear, it is possible that endotoxin may still play a role, possibly at the local tissue level.[42]

Clinical Spectrum and Management of Salmonellosis

THOMAS T. YOSHIKAWA, MD

Salmonella INFECTION may appear to be one of several distinct clinical syndromes, or symptoms may overlap in its clinical presentation. The major disease states produced by salmonellosis are enterocolitis (gastroenteritis), enteric fever, bacteremia, focal infection and chronic carrier state.

Enterocolitis

Localized acute intestinal infection is the most common form of salmonellosis.[29,38] In the small

intestine, epithelial invasion occurs but without extensive destruction of intestinal mucosa.[44] The organisms reach the lamina propria where they multiply and elicit an inflammatory response. In *S typhi,* this response may trigger production of predominantly mononuclear cells, whereas nontyphi *Salmonella* infection generally evokes polymorphonuclear neutrophilic reaction. It is also now known that colonic involvement occurs with acute salmonellosis (hence the term "enterocolitis"); histological changes include edema, inflammation, erosion and microabscesses.[45]

Nontyphi *Salmonella* serotypes, particularly *S typhimurium,* are most commonly responsible for acute enterocolitis.[29,38] Although *S typhi* may produce enterocolitis and cause diarrhea, constipation may be an equally or a more common gastrointestinal symptom with this strain of *Salmonella.*[46,47] Clinical expression of acute enterocolitis may occur as soon as 8 hours or as late as 72 hours following ingestion of *Salmonella* organisms.[48] Symptoms may begin with transient nausea and vomiting followed by myalgia, headache, fevers, chills, diarrhea and abdominal cramps.[18] Generally, the stools are not bloody, are of moderate volume and loose in character. Occasionally, the disease may be severe, associated with fluid and electrolyte depletion leading to hypovolemic shock, blood loss, toxic dilatation of the colon[45] or bacteremia, particularly in those patients with increased susceptibility to salmonellosis. Symptoms of fever last less than 48 hours and diarrhea usually abates within one week, although patients with colonic involvement, intra-abdominal suppuration or other complications may have a prolonged course of fever, loose stools and abdominal complaints.

Diagnosis is made by isolating the pathogen by stool culture. Except for *S typhi* cases, blood cultures generally are nonrewarding. Serological tests for antibodies to O and H antigens are of limited value. Follow-up of these patients will show that stool cultures may remain positive in up to 65 percent of cases during the second or third week after onset of illness, even though most patients are asymptomatic.[36,37] In untreated patients, fecal excretion of nontyphi salmonellae beyond two months may occur in up to 25 percent of cases. By six months all stool cultures are generally negative for these organisms. Chronic carrier states of nontyphi salmonellae are uncommon but do occur.[18,49]

Management will depend on severity of illness and any associated complications. For severe cases of diarrhea, fluid and electrolyte replacement is the single most important modality of therapy. Antiperistaltic agents to decrease diarrhea are generally not recommended. Most cases of enterocolitis will not require antimicrobial therapy. In fact, chemotherapy prolongs excretion of nontyphi *Salmonella* organisms and symptoms remain unchanged when compared with untreated controls.[36,37] However, in severely ill patients in whom bacteremia, enteric fever or metastatic focal infections develop, or who have impaired host resistance (such as malignancy, immunosuppression, sickle cell disease), antimicrobial therapy should be initiated (specific drug therapy will be discussed in the section on enteric fever). Moreover, if gastroenteritis is caused by *S typhi,* it may be advisable to treat patients with even mild disease because (1) enteric fever is more likely to occur with *S typhi* than with other serotypes, (2) patients with prolonged fecal excretion of the organism related to antimicrobial therapy are almost always those infected with nontyphi *Salmonella* and not *S typhi* and (3) most chronic carriers of salmonellosis are found to be infected with *S typhi* serotype. However, the recommendation to treat mild *S typhi* gastroenteritis is not accepted by most clinicians.

Enteric Fever

Enteric fever is clinically caused by *S typhi* and hence called typhoid fever. A clinical syndrome nearly identical to typhoid fever but caused by *S paratyphi* A, B or C was previously designated paratyphoid fever. However, because other serotypes may also cause enteric fever, it is more conventional now to ascribe paratyphoid fever to any serotype other than *S typhi* causing this syndrome.

Following ingestion of the organism, an incubation period of approximately ten days may be followed by bacteremia and the onset of the clinical features of enteric fever. The major clinical features of enteric fever are shown in Table 2. Four series of enteric fever reported in the literature were selected to illustrate similarities and differences in incidence of clinical findings. Series 1 represents an epidemic before the era of modern antimicrobial therapy[46]; series 2 represents an epidemic occurring in the United States in the modern chemotherapy period[50]; series 3 is made up of cases of enteric fever where the disease is endemic,[51] and series 4 illustrates features found in sporadic cases of enteric fever.[52] As noted in

TABLE 2.—*Clinical Features of Enteric Fever*

Clinical Features	Percent of Patients			
	Series 1*	Series 2†	Series 3‡	Series 4§
Symptoms				
Fever	100	93	98	100
Chills	37	37	NR	78
Headache	90	59	75	78
Diarrhea	43	57	37	44
Constipation	79	10	17	48
Nausea	54	23	NR	44
Vomiting	54	35	24	NR
Abdominal pain	19	39	52	37
Cough	86	28	53	56
Signs				
Rose spots	33	13	0	11
Hepatomegaly	25	52	NR	19
Splenomegaly	64	42	NR	30
Neurologic findings	12	5	33	NR

NR = not reported

*Stuart and Pullen: 1934-1944, epidemic of 360 cases.[46]
†Hoffman et al: 1973, epidemic of 105 cases.[50]
‡Wicks et al: 1966-1969, endemic outbreak of 265 cases.[51]
§Briedis and Robson: 1961-1977, 27 sporadic cases.[52]

Table 2, fever, chills, headache and gastrointestinal symptoms are the most important presenting complaints of patients with enteric fever. Interestingly, cough and bronchitic symptoms occur in more than half of the patients, but documented pneumonia is uncommon.[46,50] A variety of other nonspecific complaints such as myalgia, arthralgia, weakness or sore throat may also occur. Physical findings are primarily limited to the abdomen. Abdominal distention, tenderness and hypoperistalsis; hepatomegaly, and splenomegaly vary in frequency, but may be present. Classic rose spots (2- to 4-mm erythematous maculopapular lesions that blanch on pressure) may appear transiently on the upper abdomen but are infrequently observed in most reported series.[53] Relative bradycardia, another feature classic of typhoid fever, has been observed in only a third of cases.[51] Although paratyphoid fever is nearly identical to typhoid fever in its clinical features,[54,55] relative bradycardia has been reported in 50 percent to 100 percent of cases. Neuropsychiatric manifestations of enteric fever are nonspecific but may occur in up to 75 percent of patients.[56] Confusion, stupor and delirium are the most common findings, occurring in more than 50 percent of cases.[46,56] Other diffuse and focal neurological deficits and gross schizophrenic psychoses have also been reported.

Complications of enteric fever, other than death, can be classified as abdominal or extra-abdominal. In the era before antibiotics, mortality from enteric fever was 10 percent to 15 percent.[46] With antimicrobial therapy and supportive care, mortality should be nearly zero.[50] Abdominal complications that are most serious are intestinal perforation (1 percent to 5 percent) and intestinal hemorrhage (1 percent to 21 percent).[57] Complications occurring outside the abdomen include the previously mentioned neuropsychiatric features, localized infections (meningitis, endocarditis, arthritis, osteomyelitis, pneumonia), bone marrow suppression, parotitis, decubitus ulcer, renal failure and chronic carrier state.[51,58]

Diagnosis of enteric fever is primarily made by blood cultures. During the first week of illness, blood cultures are positive in 55 percent to over 80 percent of patients.[46,50] By the third week of illness, blood culture positivity diminishes to 30 percent to 40 percent. During this period, stool cultures are most rewarding, with a yield of nearly 75 percent (Figure 1). Late in the disease, bone marrow cultures may yield the pathogen.[59] Serological studies measuring fourfold or greater rises in agglutinins against the O and H antigens are unreliable[50] and are not recommended as a basis for diagnosis.[60] Management of enteric fever should be directed towards antimicrobial therapy, supportive care and the treatment of complications and extra-abdominal infections.

The antimicrobial chemotherapy that has been used to treat enteric fever has been primarily chloramphenicol, ampicillin or trimethoprim-sulfamethoxazole. Although other antimicrobial agents such as aminoglycosides may be active in vitro against *Salmonella* organisms,[61] clinical experience is too limited to recommend these agents for treatment of salmonellosis. Cephalosporins, such as cefazolin, have been used in a small number of patients with promising results.[62] At present, chloramphenicol remains the drug of choice for enteric fever.[63] The recommended dosage is 50 mg per kg of body weight per day in four divided doses for at least 14 days, taken orally. However, if patients are ill enough to be admitted to hospital, chloramphenicol should be administered intravenously. One study states that orally given chloramphenicol provides higher blood levels than parenteral chloramphenicol and therefore is more effective in treating typhoid fever.[64] These investigators, however, administered chloramphenicol succinate intramuscularly. It is now known that the succinate form of this drug produces only half the blood level of drug compared with orally given chloramphenicol because of the failure of the suc-

cinate to hydrolyze.[65] Chloramphenicol succinate, therefore, is not recommended by the manufacturer for intramuscular administration.[66] Moreover, the fatal aplastic anemia associated with chloramphenicol appears to be seen almost exclusively with oral administration of the drug.[67,68] At this institution, it is our recommendation to administer chloramphenicol only by the intravenous route. The response rate of salmonellosis to this drug has been excellent (unpublished data).

Ampicillin in a dose of 100 mg per kg of body weight per day (up to 200 mg per kg per day given parenterally in severely ill patients) in four divided doses either orally or intravenously for two weeks is also effective for treating enteric fever. The clinical response appears to be somewhat slower than with chloramphenicol[50,59,69]; however, the relapse rate may be lower with ampicillin (5 percent) than with chloramphenicol (10 percent). Amoxicillin, an ampicillin analogue, also appears to be effective in treating enteric fever.[70,71,72] Trimethoprim-sulfamethoxazole has been shown to be effective in treating typhoid fever, provided that the dosage is sufficient.[70,73,74] The recommended dose is 320 to 640 mg of trimethoprim with 1,600 to 3,200 mg of sulfamethoxazole in two to four divided doses (four to eight tablets of 80 mg of trimethoprim and 400 mg of sulfamethoxazole) for two weeks.

Salmonella typhi resistance to antimicrobial agents, especially chloramphenicol, has been reported from Mexico,[75] Vietnam,[76] Korea[77] and parts of the United States.[78,79] The mechanism of drug resistance appears to be primarily R-factor mediated, which is transferable[80] and often associated with multiple drug-resistance patterns.[75,77,78] Resistance to ampicillin may also occur, but less often than to chloramphenicol. Trimethoprim-sulfamethoxazole resistance of *S typhi* and other *Salmonella* species is uncommon even though resistance to sulfonamides alone may be present.[81] In patients with enteric fever from areas where chloramphenicol resistance is endemic, initial therapy before data are available about organism susceptibility should be carried out with ampicillin or amoxicillin. If a strain of *S typhi* resistant to both chloramphenicol and ampicillin is isolated, trimethoprim-sulfamethoxazole should be administered.

Supportive care for enteric fever includes proper hydration, maintenance of adequate perfusion and observation for complications. In very sick patients, a short course of corticosteroids may be lifesaving. Prednisone in a dose of 40 mg to 60 mg per day for *not more than three days* is recommended.[57] Intestinal perforation is a complication that is associated with high mortality. Controversy exists over whether medical or surgical therapy is the best approach to managing this problem. Those who advocate medical therapy recommend antibiotics, general supportive care and nasogastric suction.[57] Surgical treatment is reserved for deterioration of a patient's condition while on medical therapy or for development of abscess or adhesions. Proponents of immediate surgical intervention for all cases of typhoid intestinal perforation justify these recommendations by operative findings of open perforation or gangrene in 96 percent of cases.[82] Moreover, intestinal flora other than *Salmonella* will have contaminated the peritoneum following perforation and may lead to peritonitis and sepsis. Under these conditions, such additional antimicrobial therapy as aminoglycosides and clindamycin (if chloramphenicol is not already being administered) may be essential.

Intestinal hemorrhage generally is not massive and will respond to medical therapy. Occasionally, surgical intervention may be required. Such extra-abdominal complications as meningitis, endocarditis, osteomyelitis or arthritis should be managed in the standard manner appropriate for these infections.

Bacteremia and Focal Infection

Bacteremia from nontyphi *Salmonella* organisms occurs most commonly in patients with sickle cell disease, hemolytic anemia, malignancy, and liver and gallbladder disease.[32,33,83] The frequency of bacteremia or sepsis is 5 percent to 10 percent.[29,38] The clinical manifestations of bacteremia are identical to the classic Gram-negative bacillemia seen with other enteric organisms. Bacteremia can follow enterocolitis and lead to focal infections or be associated with extraintestinal sites of infection. Focal infections associated with nontyphi *Salmonella* include endocarditis, pericarditis, appendicitis, cholecystitis, salpingitis, intra-abdominal abscess, pneumonia, urinary tract infection, bone and joint infection, meningitis and mycotic aneurysm.[29,31,84,85] Such unusual infections as empyema, myocardial abscess and Reiter syndrome have been reported with salmonellosis.[86-88] Diagnosis of *Salmonella* bacteremia or

local infection, or both, can be made by isolation of the pathogen from blood or infected focal site(s).

Antimicrobial therapy for bacteremia and focal infections is the same as for enteric fever. However, with endocarditis and mycotic aneurysm secondary to salmonellae, a bactericidal agent such as ampicillin is preferred to chloramphenicol. Focal infections such as abscesses should be drained. Duration of therapy will depend on the site of the infection involved and on clinical response. Bacteremia alone without focal infection should be treated with antimicrobial drugs for 10 to 12 days.

Chronic Carrier State

The chronic carrier state is defined as the excretion of *Salmonella* for more than one year. Chronic enteric carriers who excrete organisms in the feces are the most common, although occasionally chronic urinary carriers are found. Chronic carriers are asymptomatic.

The chronic carrier state occurs more frequently following *S typhi* infection; the incidence is 2 percent to 4 percent.[89,90] Chronic carriers following nontyphi salmonellosis is uncommon.[49] The chronic enteric carrier state of *Salmonella* increases with age and is associated with biliary tract disease. A chronic urinary carrier state is more commonly associated with schistosomiasis of the urinary tract.

Diagnosis of a chronic carrier state is made by repetitive isolation of the organism for over one year. Management should be directed first toward determining the presence or absence of biliary tract disease. The antimicrobial drug of choice is ampicillin (not chloramphenicol, which has a poor success rate). In the presence of gallbladder disease, ampicillin in dosages of 6 to 8 grams per day plus 2 grams of probenecid (both drugs given in four divided doses) is started two to three days before operation. The diseased gallbladder is surgically removed and ampicillin is continued for two weeks postoperatively.[90] If biliary tract disease cannot be detected by roentgenogram (biliary tract carrier with normal cholecystogram or possibly hepatic carrier) or if fecal excretion of organisms continues postcholecystectomy (hepatic carrier), long-term administration of ampicillin is recommended.[91] Two effective regimens are 6 grams of ampicillin per day given orally plus 2 grams of probenecid in four divided doses for six weeks[91] or 3 grams per day given intravenously in three divided doses for two weeks.[92] Trimethoprim-sulfamethoxazole, 320 mg of trimethoprim and 1,600 mg of sulfamethoxazole in two divided doses for three months, also appears promising.[93]

Precautions and Recommendations for Travel

Because food and water are the major vehicles for transmitting salmonellae, proper sanitation and hygiene are extremely important in prevention of this disease. In countries where salmonellosis is endemic, all food should be properly cooked (particularly fowl, egg products and foods containing unpasteurized milk), and water should be boiled.[17] If travel to foreign countries is contemplated, the nearest United States Public Health Service office should be contacted to determine if typhoid vaccine (and other immunoprophylaxis) is recommended. The vaccine is given as two injections (0.5 ml) a month apart, or three injections at weekly intervals if time does not allow a four-week schedule. The vaccine is effective for three years and a single booster is recommended after this period.[94]

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