Nontyphoidal Salmonellosis

Elizabeth L. Hohmann
Infectious Diseases Division, Harvard Medical School, Massachusetts General Hospital, Boston

Nontyphoidal *Salmonella* are important foodborne pathogens that cause gastroenteritis, bacteremia, and subsequent focal infection. These hardy bacteria are especially problematic in a wide variety of immunocompromised individuals, including (but not limited to) patients with malignancy, human immunodeficiency virus, or diabetes, and those receiving corticosteroid therapy or treatment with other immunotherapy agents. Endovascular infection and deep bone or visceral abscesses are important complications that may be difficult to treat. The site of infection and the individual's immune status influence treatment choices. The harbingers of resistance of nontyphoidal *Salmonella* to both fluoroquinolones and third-generation cephalosporins have been reported recently, and such resistance is likely to be a therapeutic problem in the future. The current report presents a brief overview of the problems and trends associated with salmonellosis that are of interest to the infectious diseases clinician.

Nontyphoidal salmonellae are important causes of reportable foodborne infection. Salmonellae are problematic, even in modestly compromised hosts, as a result of bacteremic spread, focal infection, and persistence in deep or endovascular sites. Approximately 45,000 cases and 400–600 deaths have been reported annually to the Centers for Disease Control (CDC; Atlanta) over the past decade, the tip of a large iceberg representing an estimated 1–3 million total cases. Salmonellae have a wide range of hosts and are strongly associated with agricultural products [1]. The increasing centralization and industrialization of our food supply have enhanced the distribution of these hardy organisms.

BACTERIOLOGY AND NOMENCLATURE: NEW AND IMPROVED?

Classification and nomenclature of *Salmonella* species are confusing, even for the enthusiast [2, 3]. DNA hybridization studies show that medically important *Salmonella* organisms may be considered as a single species, known as *Salmonella cholerasuis*, that has ~2500 different serotypes, or serovars, which have familiar names (e.g., *Salmonella* serotypes Typhimurium, Typhi, or Heidelberg) [2]. The species name *S. choleraesuis* is confusing, because there is also a *Salmonella* serotype Choleraesuis, which is associated with bacteremia. The novel, never previously used name "*Salmonella enterica*" has therefore been proposed as a replacement for the name "*Salmonella choleraesuis.*" According to this system of nomenclature, "*Salmonella typhimurium*" would be renamed "*Salmonella enterica* serotype Typhimurium." Although this proposal was not formally adopted by the International Committee of Systematic Bacteriology, these names have become accepted for use by the World Health Organization and in publications of the American Society for Microbiology. Most medical laboratories continue to report clinically familiar names, such as *Salmonella typhimurium* or *Salmonella* serotype Typhimurium. Although *Salmonella typhi,* the most frequent causative agent of enteric fever, may be rapidly identified (serogroup D; Vi-antigen positive) by use of commercial agglutination tests in all laboratories, *Salmonella paratyphi* and the multitude of nontyphoidal salmonellae are, variably, members of serogroups B and D and, less frequently, of serogroups A and C. Final serotyping will often require a reference laboratory and not be immediately available. Fortunately, clinical decision-making is based primarily on the host, severity of illness, and antimicrobial susceptibilities, and not specific serotype.

Identification of *Salmonella* species in the bacteriology laboratory is not difficult [2]. The best recovery of such species from fecal samples can be achieved by the use of direct plating

Received 14 July 2000; revised 11 September 2000; electronically published 15 January 2001.

Reprints or correspondence: Dr. Elizabeth L. Hohmann, Infectious Diseases Division, Harvard Medical School, Massachusetts General Hospital, Gray/Jackson 504, 55 Fruit St., Boston MA 02114 (ehohmann@partners.org).

Clinical Infectious Diseases 2001; 32:263–9

1058-4838/2001/3202-0013$03.00

and inoculation of standard enrichment broths. Rectal swabs are inferior to fecal specimens and are not recommended. Many selective agar plates are available for *Salmonella.* Most laboratories use one medium with low selectivity, such as MacConkey agar, and one with higher selectivity, such as Hektoen enteric agar or XLD agar; a medium with higher selectivity is also useful for the identification of *Shigella* species. Newer, more-selective chromogenic agars may be useful, but have not yet made their way into routine clinical use. Less than 1% of nontyphoidal *Salmonella* are lactose positive (pink on MacConkey agar plates, like *Escherichia coli*), but this is rarely a problem in the laboratory if one of the aforementioned plates that look for hydrogen sulfide production by *Salmonella* is also used. Salmonellae are facultative anaerobes that grow well both in bottles of standard, paired automated systems for culture of blood samples and on culture media routinely used for urine, tissue, and respiratory cultures.

EPIDEMIOLOGY: THE CHICKEN OR THE EGG OR ANYTHING ELSE

More than 95% of cases of *Salmonella* infection are foodborne, and salmonellosis accounts for ~30% of deaths resulting from foodborne illnesses in the United States [1]. After *Campylobacter, Salmonella* is the most commonly isolated bacterial pathogen when laboratory diagnosis of diarrhea is sought. Acquisition of *Salmonella* from pets (e.g., reptiles and birds), direct personal contact, nosocomial transmission, waterborne transmission, and contaminated drugs and solutions are less common modes of transmission. In the late 1990s, *S. typhimurium* serogroup B and *Salmonella enteritidis* serogroup D were the most frequently isolated serotypes, accounting for ~50% of isolates from patients in the United States. Notable recent outbreaks of *Salmonella* infection have been linked to eggs, cheese, dry cereal, ice cream premix, a variety of fresh sprouts, juice, cantaloupes, and other fresh vegetables. Undercooked eggs have been linked to sporadic transmission, because *Salmonella* infection may be passed transovarially from chickens to eggs that may appear normal to consumers. In 1999, there was a decrease in the number of *S. enteritidis* infections (Foodnet, available at www.cdc.gov/ncidod/dbmd/foodnet/), perhaps as a result of public awareness about food safety regarding poultry and eggs. Phage typing and restriction fragment length polymorphism analyses are useful tools for the study of *Salmonella* outbreaks.

HOST SUSCEPTIBILITY: INTRINSIC AND IATROGENIC

Gastrointestinal salmonellosis and its serious sequelae are linked to a wide variety of illnesses and therapies that affect the body's multiple defenses against enteric and intracellular pathogens. Gastric hypoacidity in infants, in pernicious anemia, or caused by antacids and H-2 blockers may predispose individuals to salmonellosis. Risk factors for salmonellosis include extremes of age, alteration of the endogenous bowel flora of the intestine (e.g., as a result of antimicrobial therapy or surgery), diabetes, malignancy, rheumatological disorders, reticuloendothelial blockade (e.g., as a result of malaria, sickle-cell disease, or bartonellosis), HIV infection, and therapeutic immunosuppression of all types. Anatomical disruptions, including kidney stones and other urinary tract abnormalities, gallstones, atherosclerotic endovascular lesions, schistosomiasis, and prosthetic devices, may all serve as foci for persistent *Salmonella* infection.

In a recent look at the past decades' 129 nonfecal isolates of *Salmonella* at the Massachusetts General Hospital, Boston (mostly adults; unpublished data), we found that the most common risk factors were corticosteroid use, malignancy, and diabetes (each ~15%), and HIV, prior antimicrobial agents, and other immunosuppressive drugs (each ~10%). Infants may have prolonged intestinal carriage of *Salmonella* species and are at risk of developing CNS infection after bacteremia. The occurrence of bacteremia without associated recent gastrointestinal symptoms is ominous and should prompt clinicians to consider whether an underlying immunosuppressive illness or anatomical risk factor is present.

GASTROENTERITIS TREATMENT: NO FREE LUNCH

Enteric infection with *Salmonella* cannot be reliably distinguished clinically from that caused by other enteric bacterial pathogens, although very bloody diarrhea suggests infection with *Shigella* or enterohemorrhagic *E. coli* (EHEC). Patients typically present with an acute onset of fever, diarrhea, and cramping; there is a wide spectrum of severity of illness. The incubation period is dependent upon the host and inoculum, but is generally 6–72 h.

Treatment of patients with symptoms of infectious diarrhea with antimicrobial agents remains controversial. The decision is complicated by the fact that (1) presenting patients could have any one of a number of enteric pathogens, so treatment for severe illness "up front" is usually empiric; and (2) the long-appreciated but counterintuitive finding that antibiotic treatment of patients with nontyphoidal salmonellosis may actually prolong, rather than limit, fecal shedding of these organisms. It is worth noting that antibiotic treatment of EHEC may increase the risk of development of hemolytic uremic syndrome [4]. Nelson and colleagues' early study of children with salmonellosis showed that those who were treated with am-

picillin or amoxicillin were more likely to have both prolonged excretion and clinical relapse than were those who were given placebo [5]. Animal studies support the hypothesis that antibiotics do this by suppressing the "protective" effects of endogenous intestinal bacterial flora, which results in recrudescence of the hardy *Salmonella* species. Many clinicians are not aware that the median duration of fecal shedding of nontyphoidal salmonellae after intestinal infection is ~1 month in adults and 7 weeks in children <5 years of age [6].

It was hoped that the fluoroquinolones would prove ideal for both symptomatic relief and durable eradication of *Salmonella* species from the intestine; unfortunately, these robust microorganisms have not cooperated. Several double-blind studies have evaluated the use of oral quinolone therapy for patients with presumed bacterial gastroenteritis. Studies have used dosing regimens that vary from single oral doses to 7 days of therapy [7]. Both immediate treatment and treatment started after symptoms have been present for at least 3 days have been studied. In summary, these studies show that quinolone therapy may modestly decrease the duration of symptoms by <1–3 days in individuals found to have enteritis caused by *Salmonella* species [7]. The clinical significance of this improvement is uncertain; some studies show that the benefit is greatest for patients who are more severely ill. These studies also show that although quinolone therapy rapidly converts the results of stool cultures to negative immediately after therapy, if patients are followed longer, there is usually no difference in time to final stool clearance of *Salmonella* in placebo versus treated patients. Some studies have shown that the duration of fecal shedding is longer in treated patients. Although quinolones do not unequivocably prolong carriage of *Salmonella* organisms, they do not predictably or consistently shorten it either. Therefore, antibiotic therapy is *not* routinely recommended for the empiric treatment of mild to moderate presumed or proven *Salmonella* gastroenteritis in healthy individuals.

Antimicrobial therapy *should* be initiated for those who are severely ill and for patients with risk factors for extraintestinal spread of infection (see the risk factors mentioned in the "Host Susceptibility: Intrinsic and Iatrogenic" section, above), after appropriate blood and fecal cultures are obtained. Usually, 3–7 days of treatment is reasonable. Neonates <3 months of age should be treated, and some experts suggest that those <1 year of age should also be treated. A brief course of "preemptive" therapy (duration, 48–72 h or until the patient is afebrile) is also commonly given to patients >50 years of age who may have underlying atherosclerotic lesions that could be seeded by bacteremia. Antibiotics may also be useful when rapid interruption of fecal shedding is needed to control outbreaks of salmonellosis in institutions [8].

Good drugs for *Salmonella* infection include fluoroquinolones, trimethoprim-sulfamethoxazole (TMP-SMZ), ampicillin, or third-generation cephalosporins (e.g., ceftriaxone, or cefixime if oral drugs are possible). Because resistance to TMP-SMZ and ampicillin is common, use of a third-generation cephalosporin or quinolone is reasonable if susceptibilities are unknown. Fluoroquinolones are not approved by the US Food and Drug Administration for use in children because of concern about the adverse effects on cartilage that have been observed in juvenile animals [9]. However, there is increasing evidence that these agents may be safely given to children if needed for serious infections with resistant pathogens, if alternative antibiotics cannot be used. Fluoroquinolones are now routinely given to children for 5–7 days in areas of the world where multidrug-resistant *Salmonella typhi* is common [10]. Azithromycin and aztreonam are alternative agents that have been studied, in a limited fashion, for the treatment of both typhoidal and nontyphoidal salmonellosis, and these drugs may be useful for patients with multiple allergies or for organisms with unusual resistance patterns.

Follow-up fecal cultures are generally not indicated for the typical patient with uncomplicated intestinal salmonellosis, regardless of the treatment given. Results will frequently be positive, and they may be intermittently positive (for a detailed review, see [6]). Therefore, the information is neither completely reassuring nor of clear utility if the patient is asymptomatic. Because of this, meticulous personal hygiene may be rationally viewed as the most important part of prevention of secondary infections. Cessation of diarrhea and good hand washing practices are appropriate criteria for return of health care workers to their duties [11]. Follow-up of health care workers and, more frequently, of food handlers may be problematic. Local health departments must be consulted, because local laws must be followed and because such laws may vary (e.g., a health care worker or food handler may be required to have 1, or sometimes, 2 negative stool culture results before being allowed to return to work; these results usually must be obtained at least 48 h after cessation of antibiotic treatment, if given). Requirements may differ in an outbreak situation. I would not routinely treat health care workers or food handlers differently than other healthy adults, because studies do not show that routine antimicrobial treatment shortens the duration of carriage of *Salmonella* species. Individualized approaches may occasionally be needed for economic reasons if an individual is found to be a prolonged asymptomatic excreter who cannot meet local requirements for return to work. Chronic fecal carriage of nontyphoidal *Salmonella* species (duration, >1 year) is rare and occurs less frequently than does chronic fecal carriage of *S. typhi.* Management is generalized from experience with *S. typhi,* and includes the long-term use of oral antibiotics and consideration of cholecystectomy.

BACTEREMIA AND ENDOVASCULAR INFECTION: SERIOUS COMPLICATIONS

Approximately 5% of individuals with gastrointestinal illness caused by nontyphoidal *Salmonella* will develop bacteremia, a serious and potentially fatal problem. Bacteremia is more likely to occur in immunologically compromised patients, and these hosts are also more likely to develop focal infection. A recent retrospective review of cases of nontyphoidal *Salmonella* bacteremia seen at Children's Hospital, Boston [12], showed that approximately 1 in 6 patients had obvious risk factors for salmonellosis; it was also noted that 7 of 25 immunocompromised children developed a focal infection, compared with 5 of 132 children who were not immunocompromised ($P < .01$). Focal infections included meningitis, septic arthritis, osteomyelitis, cholangitis, and pneumonia. There were 5 fatalities, 2 of which (1.4% of the total number of bacteremias) were directly attributed to *Salmonella* infection. On the basis of these data, the authors recommended careful clinical assessment for septic foci, additional blood cultures, and antimicrobial therapy for all children with bacteremia caused by nontyphoidal *Salmonella.*

In adults, nontyphoidal *Salmonella* bacteremia is even more serious. This reflects both the tenacity of the organism and the comorbidities of people who develop bacteremia; these bacteremic patients represent a small percentage of the large number of people with both overt and subclinical intestinal infection. In a study from Spain of 172 cases of *Salmonella* bacteremia (70% *S. enteritidis* and 17% *S. typhimurium* [1982–1992]), 16% of patients developed septic metastases, and 16% died [13]. Approximately 17% had a relapse after therapy, and nearly 60% of those who had a relapse also had AIDS. In the 1990s, at Massachusetts General Hospital, 18% of 45 patients with nontyphoidal *Salmonella* bacteremia died.

A feared complication of *Salmonella* bacteremia in adults is the development of infectious endarteritis, especially that which involves the abdominal aorta (the arteritis formerly known as mycotic). Previously, this was almost uniformly fatal, but a review of 148 evaluable cases seen from 1948 through 1999 found a 62% survival rate for all patients treated with combined surgical and medical therapy, and a 77% survival rate for 30 patients who were able to undergo extra-anatomical bypass with construction of an axillobifemoral graft [14]. Although data are limited, the prognosis with medical therapy alone is grim, even with use of "today's antibiotics." Use of medical therapy alone was fatal in all 3 patients described in a Taiwanese series of 16 patients with pathologically documented *Salmonella* aortitis, most of whom received ceftriaxone [15]. A classic study published in l978 found that 25% of bacteremic adults >50 years of age, identified on the basis of positive results of blood cultures, developed arteritis or endocarditis [16], complications not found in younger subjects. The Taiwanese study published in l996 found that 35% of bacteremic adults >65 years of age had aortitis [15]. In the Spanish study noted above, only 1 infected aneurysm (0.6%) was documented, but endocarditis was not specifically mentioned, and the overall mortality rate was high. Although advances in diagnostic techniques, surgical care, and antimicrobial therapy appear to have improved the survival of patients with the worst complications of nontyphoidal *Salmonella* bacteremia, a cautious approach is still warranted, especially in older patients with comorbidities.

Treatment of *Salmonella* bacteremia is generally undertaken with a single bactericidal drug, e.g., ampicillin or a third-generation cephalosporin, or a quinolone in 2001. Given the resistance trends (see below), life-threatening infections should be treated with both a third-generation cephalosporin and a fluoroquinolone until the susceptibilities of antimicrobial agents are known. If the results of blood cultures are not persistently positive, and if there is no suspicion of endovascular focus, bacteremia that complicates gastroenteritis can usually be successfully treated with 10–14 days of therapy. If there is suspicion of an endovascular focus, additional blood cultures should be performed, and appropriate imaging forays should be made (e.g. echocardiography, CT scanning, or arteriography in some form). Today, arteritis is usually diagnosed preoperatively on the basis of CT evidence of inflammation in the appropriate clinical setting (persistent bacteremia, pain, fever, and clinical findings suggestive of an expanding or leaking aortic aneurysm). If endocarditis or infectious arteritis is documented, surgery should be undertaken as soon as possible for the best chance of achieving a cure.

The often destructive and aggressive course of *Salmonella* endocarditis usually requires valve replacement. However, there are a number of case reports of long-term survival with medical therapy alone for both native and prosthetic-valve *Salmonella* endocarditis [17]. This may be considered for the relatively unusual, hemodynamically stable patient for whom surgery is not otherwise reasonable or possible. Antimicrobial therapy for endovascular infections should be continued for a minimum of 6 weeks if surgical intervention is successful; many consultants would prescribe some months of suppressive therapy, even for patients who do well. Years of therapy or even lifelong suppressive antimicrobial therapy is usually given in cases where residual organisms may be expected (e.g., when surgery is not possible, when prosthetic devices or grafts cannot be removed, or for chronic bone and joint infections).

The choice between a fluoroquinolone and a β-lactam antibiotic for serious endovascular infection is an issue over which reasonable infectious diseases consultants might disagree, and one that is not likely to be resolved by head-to-head clinical studies. There is a longer track record of successful use of high-dose parenteral ampicillin or third-generation cephalosporins

[15]. First- and second-generation cephalosporins may appear to be effective in vitro, but they are not clinically effective and should not be used. For any suggestion of meningitic or deep CNS involvement, high-dose ceftriaxone would be the best choice for optimal penetration of the blood-brain barrier. The National Committee for Clinical Laboratory Standards defines "sensitive" *Salmonella* species as those for which MICs of fluoroquinolone are <1–2 μg/mL and those for which MICs of ceftriaxone are <8 μg/mL, although most susceptible *Salmonella* species have MICs that are much lower (usually 20–100-fold lower). Serum levels of fluoroquinolones that are typically achieved are 4–6 μg/mL, and those for ceftriaxone (2-g dose) are 200–250 μg/mL. By extrapolation of data from animal models of infectious endocarditis, the higher serum levels of cephalosporins relative to minimum bacterial concentrations may favor the use of cephalosporins for penetration and killing within vegetations or devitalized tissue. By extrapolation from studies of *Salmonella typhi* infection, for which fluoroquinolones result in more-rapid and durable clinical responses than do cephalosporins [18], and from in vitro data, which show greater penetration of fluoroquinolones into phagocytic cells where salmonellae persist [19], one might reasonably choose a fluoroquinolone. The daily or twice-daily oral dosing of the fluoroquinolones and their safety/tolerability make them ideal for suppressive therapy in many instances. Many clinicians might use β-lactams initially, followed by a longer "tail" of oral fluoroquinolone therapy, when indicated. There are no clinical data that suggest that combination therapy (e.g., a fluoroquinolone plus a third-generation cephalosporin) is more effective than either single agent.

FOCAL INFECTIONS: PROTEAN AND PROBLEMATIC

Virtually any anatomical site may be seeded hematogenously by nontyphoidal salmonellae and may evolve into local infection, even if the bacteremia is successfully treated. Information on focal infections and their treatment has been extensively reviewed and nicely tabulated by Miller and Pegues [11]. Focal infections should be drained or débrided whenever possible. A *minimum* of 2 weeks of antimicrobial therapy is suggested for the treatment of a surgically eradicated soft-tissue focus in a normal host. Therapy for 4–6 weeks most often is advisable, given the known persistence of *Salmonella* species at compromised sites. Several specific complications merit comment. Osteomyelitis and joint infections, which are common in patients with sickle-cell anemia, are difficult to treat. Failure of fluoroquinolones and emergence of quinolone resistance have been demonstrated in patients with osteomyelitis [20]. Severe, prolonged polyarticular reactive joint disease can occur after intestinal salmonellosis and is not altered by long-term antibiotic therapy [21]. Splenectomy may be required for splenic abscesses. CNS infection is fatal in ~50% of cases. Urinary isolates of *Salmonella* are common (they accounted for 50 of 129 extraintestinal isolates found in patients at our hospital in the l990s). Positive urine culture results may erroneously be attributed to fecal contamination or "urinary tract colonization," but they frequently reflect bacteremic seeding and secondary infection of the urinary tract. Especially in the case of functionally or structurally abnormal urinary tracts, it may be necessary to use longer courses of antimicrobial agents excreted in the urine (e.g., TMP/SMZ or quinolones) to eradicate these infections.

HIV INFECTION AND SALMONELLOSIS

In the developing world, HIV infection is a prominent risk factor for nontyphoidal salmonellosis and bacteremia. In recent series of HIV-infected African adults with documented bloodstream infections, nontyphoidal *Salmonella* were isolated from up to 35% of adults (mycobacteria were most commonly isolated). Of interest, despite the prominence of bacteremic infection with nontyphoidal *Salmonella* species in such patients, there are few series that describe such infection with *S. typhi* or *S. paratyphi,* which are endemic in some areas. This could be related to (1) the fact that there are many different serotypes of nontyphoidal *Salmonella* species, and immunity is at least partially serotype specific; and (2) the fact that nontyphoidal *Salmonella* more vigorously and durably colonize the intestinal tract than do typhoidal strains, thereby providing more prolonged opportunity for dissemination. Dissemination might also be enhanced by intestinal inflammation resulting from chronic diarrheal disease, parasitic infection, or suboptimal nutrition. It is believed, but it is not well documented, that prolonged therapy (duration, 4–6 weeks) of HIV-infected individuals with an initial diagnosis of *Salmonella* bacteremia may be helpful in eradicating the organism and preventing relapse. Zidovudine has documented anti-*Salmonella* activity in vitro, and this appears to be clinically useful in the prevention of relapse of infection [22].

ANTIMICROBIAL RESISTANCE: BAD NEWS

In the 1980s, nontyphoidal *Salmonella* species were fairly "sensitive" organisms. In the l990s, clinical isolates studied at the CDC showed increasing resistance to ampicillin, chloramphenicol, and TMP-SMZ. A remarkable bacterial "success story" of the l990s was the emergence and worldwide spread of *S. typhimurium* definitive phage type 104 (DT104), which carries chromosomally based resistance to the aforementioned drugs plus streptomycin and tetracycline (resistance type, ACSSuT [23]). A l998 report described the US debut of DT104 [24], which

accounts for ~8%–9% of *Salmonella* isolates in the United States today. As DT104 "took over" in the United Kingdom, isolates with decreased susceptibility to the fluoroquinolones (MICs, >0.25 μg/mL) were found. This was linked to the approval and use of enrofloxacin for veterinary use in Europe.

Several lines of evidence that link antimicrobial resistance of human isolates with agricultural use of antibiotics are summarized in a recent paper from the CDC [25]. A study from Denmark in l999 described an outbreak of salmonellosis caused by multidrug- and quinolone-resistant DT104 linked to a Danish swine herd. Eleven of 25 patients were hospitalized, and 2 died [26]. The identified strains were resistant to nalidixic acid. Although they were formally susceptible to ciprofloxacin by routine clinical testing, the isolates had increased MICs of ciprofloxacin (0.064–0.124 μg/mL), compared with strains that were fully susceptible to nalidixic acid. Clinical data suggested reduced effectiveness of quinolone therapy in patients with nalidixic acid–resistant strains. A study of >1000 stored *Salmonella* isolates from Finland has confirmed earlier data that show that resistance to nalidixic acid by means of disk diffusion is a sensitive and specific way of screening *Salmonella* isolates for reduced susceptibility to fluoroquinolones [27]. Resistance to nalidixic acid appears to be a predictor of clinical "quinolone hyporesponsiveness," and it is a harbinger of bona fide resistance to the clinically useful fluoroquinolones.

The latest bad news is the emergence of *Salmonella* species that are resistant to extended-spectrum cephalosporins. The first US clinical case report described a child with gastroenteritis caused by *S. typhimurium* resistant to ceftriaxone and other extended-spectrum cephalosporins, ACSSuT, aminoglycosides, and aztreonam [28]. All but one of the resistances to 13 antimicrobial agents were carried on a conjugative plasmid (a genetic element capable of rapid movement into other strains of Enterobacteriaceae). The child lived on a Nebraska farm, and the clinical strain was indistinguishable from one that was isolated from the family's cattle. Resistance to third-generation cephalosporins reasonably can be predicted to be an increasing clinical problem, especially among children, for whom these agents are the current drugs of choice.

CONCLUSIONS

Salmonellosis in compromised hosts may be severe and can result in bacteremia and focal infection. Routine antibiotic treatment of healthy younger adults with mild to moderate gastroenteritis is not indicated. *Salmonella* bacteremia, especially that without gastrointestinal symptoms, merits careful clinical and microbiological evaluation. Antimicrobial resistance to clinically essential "first-line" drugs is increasing among *Salmonella* worldwide. This trend is alarming and is linked to agricultural uses of antimicrobial agents. These findings highlight the need for judicious use of antimicrobial agents in all venues, and they strongly argue for continued worldwide surveillance programs for antimicrobial resistance in important foodborne pathogens.

Acknowledgments

Clinical data from the Massachusetts General Hospital were kindly provided by Dr. Katharina Loock. I thank Dr. Fred Angulo for his thoughts on antimicrobial resistance trends.

References

1. Mead P, Slutsker L, Dietz V, et al. Food-related illness and death in the United States. Emerg Infect Dis **1999**; 5:607–25.
2. Bopp CA, Brenner FW, Wells JG, et al. *Escherichia, Shigella,* and *Salmonella.* In: Murray P, Baron EJ, Pfaller MA, Tenover F, Yolken R, eds. Manual of clinical microbiology. Washington DC: ASM Press, **1999**: 467–74.
3. Brenner F, Villar R, Angulo F, et al. *Salmonella* nomenclature. J Clin Microbiol **2000**; 38:2465–7.
4. Wong C, Jelacic S, Habeeb R, et al. The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. N Engl J Med **2000**; 342:1930–6.
5. Nelson JD, Kusmiesz H, Jackson LH, et al. Treatment of *Salmonella* gastroenteritis with ampicillin, amoxicillin or placebo. Pediatrics **1980**; 65:1125–30.
6. Buchwald D, Blaser M. A review of human salmonellosis: II. Duration of excretion following infection with non-typhi *Salmonella.* Rev Infect Dis **1984**; 6:345–6.
7. Dryden M, Gabb R, Wright S. Empirical treatment of severe acute community-acquired gastroenteritis with ciprofloxacin. Clin Infect Dis **1996**; 22:1019–25.
8. Lightfoot NF, Ahmad F, Cowden J. Management of institutional outbreaks of *Salmonella* gastroenteritis. J Antimicrob Chemother **1990**; 26(Suppl F):37–46.
9. Burkhardt J, Walterspiel J, Schaad U. Quinolone arthropathy in animals vs. children. Clin Infect Dis **1997**; 25:1196–1204.
10. Wain J, Hoa N, Chinh N, et al. Quinolone-resistant *Salmonella typhi* in Viet Nam: molecular basis of resistance and clinical response to treatment. Clin Infect Dis **1997**; 25:1404–10.
11. Miller S, Pegues D. *Salmonella species,* including *Salmonella typhi.* In: Mandell G, Bennett J, Dolin R, eds. Principles and practice of infectious diseases. Philadelphia: Churchill Livingstone, **2000**:2344–62.
12. Zaidi E, Bachur R, Harper M. Non-typhi *Salmonella* bacteremia in children. Pediatr Infect Dis J **1999**; 18:1073–7.
13. Galofre J, Moreno A, Mensa J, et al. Analysis of factors influencing the outcome and development of septic metastasis or relapse in *Salmonella* bacteremia. Clin Infect Dis **1994**; 18:873–8.
14. Oskoui R, Davis W, Gomes M. *Salmonella* aortitis: a report of a successfully treated case with a comprehensive review of the literature. Arch Intern Med **1993**; 153:517–25.
15. Wang J-H, Liu Y-C, Yen M-Y, et al. Mycotic aneurysm due to non-typhi *Salmonella*: report of 16 cases. Clin Infect Dis **1996**;23:743–7.
16. Cohen P, O'Brien T, Schoenbaum S, et al. The risk of endothelial infection in adults with *Salmonella* bacteremia. Ann Intern Med **1978**; 89:931–2.
17. Fernandez-Guerrero ML, Torres-Pera R, Gomez-Rodrigo J, et al. Infectious endocarditis due to non-typhi *Salmonella* in patients infected

with HIV: report of two cases and review. Clin Infect Dis **1996**; 22: 853–5.
18. Cao X, Kneen R, Nguyen T, et al. A comparative study of ofloxacin and cefixime for treatment of typhoid fever in children. The Dong Nai Pediatric Center Typhoid Study Group. Pediatr Infect Dis J **1999**; 18: 245–8.
19. Chiu C, Lin T, Ou J. In vitro evaluation of intracellular activity of antibiotics against non-typhoid *Salmonella.* Int J Antimicrob Agents **1999**; 12:47–52.
20. Workman M, Philpott-Howard J, Bragman S, et al. Emergence of ciprofloxacin resistance during treatment of *Salmonella* osteomyelitis in three patients with sickle cell disease. J Infect **1996**; 32:27–32.
21. Sieper J, Fendler C, Laitko S, et al. No benefit of long-term ciprofloxacin treatment in patients with reactive arthritis and undifferentiated oligoarthritis: a three-month, multicenter, double-blind, randomized, placebo-controlled trial. Arthritis Rheum **1999**; 42:1386–96.
22. Casado J, Valdezate S, Caleron C, et al. Sidovudine therapy protects against *Salmonella* bacteremia recurrence in HIV-infected patients. J Infect Dis **1999**; 179:1553–6.
23. Threlfall EJ, Frost J, Ward L, et al. Increasing spectrum of resistance in multi-resistant *Salmonella typhimurium.* Lancet **1996**; 347(9007): 1053–4.
24. Glynn M, Bopp C, Dewitt W, et al. Emergence of multidrug-resistant *Salmonella enterica* serotype Typhimurium DT104 infections in the United States. N Engl J Med **1998**; 338:1333–8.
25. Angulo FJ, Johnson KR, Tauxe RV, et al. Origins and consequences of antimicrobial-resistant nontyphoidal *Salmonella:* implications for the use of fluoroquinolones in food animals. Microb Drug Resist **2000**; 6: 77–83.
26. Molbak K, Baggesen D, Aarestrup F, et al. An outbreak of multidrug-resistant, quinolone-resistant *Salmonella enterica* serotype *Typhimurium* DT104. N Engl J Med **1999**; 341:1420–5.
27. Hakanen A, Kotilanien P, Jalava J, et al. Detection of decreased fluoroquinolone susceptibility in *Salmonella* and validation of nalidixic acid screening test. J Clin Microbiol **1999**; 37:3572–77.
28. Fey P, Safranek T, Rupp M, et al. Ceftriaxone-resistant *Salmonella* infection acquired by a child from cattle. N Engl J Med **2000**; 342: 1242–9.