

Typhoid Fever and HIV Infection: A Rare Disease Association in Industrialized Countries

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Typhoid fever is still a global health problem, mainly in tropical and subtropical areas of the world and in developing countries, where relatively elevated morbidity and mortality rates still are present, mostly because of persisting poor hygienic conditions. In the majority of Mediterranean regions, including Italy, the disease is constantly present, though with a low prevalence rate, as a result of an endemic persistence of *Salmonella typhi* infection.¹⁻⁴ On the other hand, in industrialized countries, most cases of *S. typhi* infection are related to foreign travel or prior residence in endemic countries.⁴⁻⁶ In the United States, 2445 cases of typhoid fever have been reported in the decade 1985 to 1994, and the annual number of cases remained relatively stable over time: over 70% of episodes were acquired in endemic countries (mostly Mexico and India).⁶

The persisting morbidity of *S. typhi* also may be supported by the increasing resistance rate of this pathogen against a number of commonly used antimicrobial compounds. For instance, 6% of 331 evaluable *S. typhi* strains were resistant to ampicillin, chloramphenicol, and cotrimoxazole, and 22% of isolates were resistant to at least one of these three agents in a recent survey performed in the United States.⁶ The spread of antibiotic resistance among *S. typhi* isolates is emerging in many countries, and multidrug-resistant strains have been isolated, as well as isolates with poor susceptibility to fluoroquinolones,^{3-5,7-9} so that in vitro susceptibility should be determined for all cultured strains, and antimicrobial treatment should be adjusted accordingly. Nevertheless, fluoroquinolones (e.g., ciprofloxacin and pefloxacin) or third-generation cephalosporins, still represent the best choice for empirical treatment,^{2,4,6-8,10} and mortality remains rare in Western countries (less than 1% of episodes), although it is expected to be greater in developing areas of the world.

The aim of this report is to describe two cases of typhoid fever that occurred in patients with human immunodeficiency virus (HIV) infection, a rarely reported disease association in industrialized countries.

CASE REPORTS

Two male intravenous-drug users aged 34 and 41 years, with a prior diagnosis of acquired immunodeficiency syndrome (AIDS) due to *Pneumocystis carinii* pneumonia and extrapulmonary cryptococcosis, respectively, were hospitalized because of prolonged irregular hyperpyrexia (lasting more than 1 week) preceded by chills and followed by abundant sweating. Toxemia, malaise, headache, and abdominal pain were the associated complaints, although no diarrhea or constipation were present. The second patient also had a faint maculopapular exanthema on the abdominal wall. From an epidemiologic point of view, the first patient spent the 2 months preceding hospitalization on a long trip in Southeastern Asia; the second one was homeless, experiencing long-term abandonment, promiscuity, and poor hygienic conditions. A severe underlying immunodeficiency was documented by a CD4+ lymphocyte count of 34 and 7 cells/ μ L, and an absolute neutrophil count of 1200 and 1650 cells/ μ L, respectively. Neither patient had undergone treatment with zidovudine or cotrimoxazole, in the weeks preceding hospital admission. Repeated blood cultures yielded *S. typhi*; stool and urine cultures tested negative. Later, Widal's serum test proved positive in the first patient only (at a 1:160 dilution). On the basis of the in vitro susceptibility assay (showing a favorable activity of all tested compounds, including ampicillin, amoxicillin-clavulanate, piperacillin, cephalothin, ceftriaxone, ceftazidime, gentamicin, amikacin, netilmicin, chloramphenicol, ciprofloxacin, and cotrimoxazole), antimicrobial treatment was promptly started with intravenous cotrimoxazole (at 720 mg of trimethoprim) in the first case, and intravenous piperacillin (4 g/d) in the second patient. Antibiotic therapy was carried out for 10 and 12 days, respectively. Both patients showed a slowly progressive improvement of disease signs and symptoms, and complete clinical and

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microbiologic cure was obtained within 2 weeks, without complications or sequelae during the subsequent follow-up period.

DISCUSSION

Nontyphoid salmonellae are well recognized pathogens in the setting of HIV infection, and are mostly responsible for recurring bacteremia, which may represent up to 20% of episodes of bacterial septicemia in both adults and children with AIDS, with a particularly elevated incidence reported from Africa and other developing countries. *Salmonella enteritidis* and *Salmonella typhimurium* are the most common strains.¹¹⁻¹⁸ The authors have reported an association of severe immunodeficiency and full-blown AIDS with bacteremia; bacteremia may occur in 76% of cases, and relapsing disease in 38%.¹⁹ Because of its significant morbidity and relation with advanced HIV infection, nontyphoid salmonellosis has been included in the list of AIDS-defining diseases since 1987. The annual incidence of nontyphoid salmonellosis has been estimated to be 10- to 100-fold greater in HIV-infected individuals, compared with the general population.^{11,14} A low CD4+ lymphocyte count, concurrent opportunistic infections, alterations in intestinal mucosa, perianal ulcers, and prior use of broad-spectrum antibiotics, represent important risk factors.^{13-16,19} Disseminated disease sometimes leads to suppurative or focal complications (including endocarditis, meningitis, cellulitis, arthritis, myositis, pneumonia, and urinary tract infection),^{14,17,18,20-22} but gastrointestinal complaints are relatively infrequent, and *Salmonellae* may be isolated from stools in less than 20% of bacteremic patients. Even though antibiotic resistance of nontyphoid *Salmonellae* is increasing worldwide,^{8,14} quinolones, third-generation cephalosporins, as well as cotrimoxazole and ampicillin are still effective, and the mortality rate remains low.^{8,10,11,13-15,17-19} However, long-term suppressive chemotherapy is recommended to avoid recurrences. Cotrimoxazole (widely employed as a prophylactic agent for both AIDS-related pneumocystosis and toxoplasmosis) and zidovudine (which is effective against *Salmonella* spp) have been shown to significantly reduce both occurrence and relapse of nontyphoid salmonellosis in patients with HIV disease.²³⁻²⁵

Salmonella typhi complications infrequently have been reported in HIV-infected patients, mostly in industrialized countries. In fact, most cases of HIV-associated typhoid fever have been described in the developing regions of the world, where both *S. typhi* and HIV infection are endemic.^{12,16,26-29} In Africa, the frequency and clinical features of HIV-associated *S. typhi* infection do not differ from those encountered in the general population, when a possible higher rate of focal complications is excluded.^{12,16,26-28} In particular, two cases have been

reported in a comprehensive series of HIV-related bacteremia from Kenya, where the estimated frequency of typhoid fever among patients with HIV disease was similar to that observed in a control group of non-HIV-infected subjects with septicemia; both isolated *S. typhi* strains appeared sensitive to all tested antibiotics, and both patients were cured.²⁶ In a series from Ivory Coast, only one case of typhoid fever was reported, caused by a strain that tested sensitive to all antibiotics. The global prevalence of HIV-associated disease is lower than that observed among patients without HIV infection.¹² Another case of *S. typhi* bacteremia involved an HIV-infected woman from Zimbabwe, and was complicated by common iliac artery occlusion.²⁷ In a second report, from Ivory Coast, a patient was described, and a similar prevalence of typhoid fever among HIV-positive and HIV-negative subjects was confirmed.¹⁶ The largest clinical series recently described from South Africa reported 10 cases of typhoid fever among subjects with asymptomatic HIV infection.²⁸ Fever, toxemia, and relative bradycardia were the most common clinical features; diarrhea was reported in four cases; and there was a lethal outcome in two. When compared with a control group of non-HIV-infected individuals, patients with underlying HIV disease did not show different epidemiologic or clinical features, when an increased risk of liver and kidney involvement was excluded.²⁸ Finally, an early report from Gotuzzo et al,²⁹ describing six cases of typhoid fever and two additional patients with *Salmonella paratyphi* infection complicating HIV disease in Peru, pointed out a typical clinical presentation and favorable therapeutic response in the four patients with asymptomatic or mildly symptomatic HIV disease, whereas the remaining four individuals with full-blown AIDS experienced severe intestinal complications (fulminant diarrhea, enterocolitis, or rectal ulcerations) and frequent relapses, despite therapeutic attempts with chloramphenicol, amoxicillin, norfloxacin, and ceftriaxone.²⁹ Only this last clinical report showed a significantly increased risk of typhoid fever among HIV-infected patients, associated with an apparently increased disease severity and mortality.²⁹ The estimated overall incidence was about 60 times greater than in the general population.

To the authors' knowledge, only five cases of HIV-associated *S. typhi* infection have been reported to date from developed countries.^{11,30-33} The first one from London, was described in 1986 in an homosexual male with a CD4+ lymphocyte count of 200 cells/ μ L and no history of travel in endemic regions; despite disseminated infection (with positive blood, stools, and bone marrow cultures) and one relapse, typhoid fever was successfully treated with chloramphenicol, later combined with amoxicillin.³⁰ A second case was reported 5 years later, in a series from Italy, and involved an adult patient with diffuse HIV-related lymphadenopathy; details regarding clinical picture, treatment, and outcome are lacking.¹¹ In 1992, one case of *S. typhi* bacteremic pneumonia was

reported from the United States in a Hispanic patient with AIDS with prior lung tuberculosis and concurrent Kaposi's sarcoma and disseminated mycobacteriosis and without a recent history of travel abroad.³¹ However, *S. typhi* was not isolated from respiratory secretions, and Widal's serology tested negative.³¹ In the same year (1992), in the United States one case of *S. typhi* post-traumatic splenic abscess was described in an HIV-infected intravenous-drug user who underwent splenorrhaphy; ampicillin administration and splenectomy led to complete remission.³² The last known case was reported, again from the United States, in 1995, and described an intrapartum chorioamnionitis caused by *S. typhi* in a pregnant HIV-infected woman. Maternal blood, cervical, uterine, and placental cultures grew the pathogen, but response to antibiotic therapy was favorable, without relapse, or involvement of the infant.³³

Both clinicians and microbiologists should be aware of the possible occurrence of *S. typhi* complications among immunocompromised patients with HIV disease, even in developed countries. According to the authors' experience, in the United States, the clinical picture and outcome of AIDS-associated typhoid fever do not show significant differences from those reported from non-HIV-infected patients. However, an association with far-advanced HIV disease and full-blown AIDS was demonstrated, as well as failure of specific serodiagnosis, as in a previously reported patient,³¹ possibly owing to the concurrent severe immunodeficiency. A careful evaluation of medical history and epidemiologic features may play a key role in prompting search for a *S. typhi* infection, especially in patients coming from endemic regions or living with poor hygiene and promiscuity, since the majority of signs and symptoms of typhoid fever mimic those of any sepsis, or other AIDS-related complications. In fact, international travel has been reported as a risk factor for exotic or imported infectious complications in patients with HIV disease,³⁴ so that information, precautions in handling food and beverages, and immunization should be recommended to anyone planning to travel in endemic countries. Because of the increasing frequency of antimicrobial resistance of *S. typhi* strains worldwide, *in vitro* susceptibility testing should be performed to guide antimicrobial treatment. The authors found all tested compounds to be active against cultured organisms, and cotrimoxazole or piperacillin administration proved clinically effective.

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