

SALMONELLOSIS IN PERSONS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS: A REPORT OF SEVEN CASES FROM MALAYSIA

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Abstract. Persons infected with human immunodeficiency virus (HIV) have an increased risk of salmonellosis when compared to the general population. We describe seven such patients with *Salmonella* bacteremia, of whom two had recurrent salmonellosis. In the latter two cases the infection was unusually severe, characterized by widespread infection, bacteremia and relapse, despite standard antimicrobial therapy. HIV-infected individuals will benefit from education on the source of *Salmonella*, mode of acquisition and prevention through safe food handling and food preparation practices. Because of the difficulty of eradicating *Salmonella* infection in patients with acquired immunodeficiency syndrome, long-term suppressive treatment with antimicrobials is warranted.

INTRODUCTION

Non-typhoidal *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 (HIV) infection, or diabetes, and those receiving corticosteroid therapy or treatment with other immunosuppressive agents (Hohmann, 2001).

The progressive cellular immune defects associated with human immunodeficiency virus infections have led to an increased frequency of opportunistic infections with intracellular bacterial pathogens, such as non-typhoidal *Salmonella* species (Levine *et al*, 1991). *Salmonella* bacteremia is one manifestation of immunosuppression in patients with human immunodeficiency virus infection, and the development of bacteremia represents a frequent and severe complication in AIDS patients. Persons with HIV infections have an estimated 20- to 100- fold increased risk of salmonellosis compared with the general population (Celum *et al*, 1987; Tocalli *et al*, 1991). *Salmonella* is more likely to cause severe inva-

sive disease in persons with acquired immunodeficiency syndrome (AIDS) than in immunocompetent persons, including fulminant diarrhea, acute enterocolitis, rectal ulceration, recurrent bacteremia, meningitis, and death, despite antimicrobial therapy (Tocali *et al*, 1991; Angulo and Swerdlow, 1995).

Recurrent episodes are characteristic of non-typhoidal *Salmonella* septicemia in the AIDS population and are mainly associated with *Salmonella enterica* serotype Enteritidis or *Salmonella enterica* serotype Typhimurium. Indeed, since 1987, recurrent non-typhoidal *Salmonella* bacteremia has been included in the diagnostic criteria for AIDS. Recurrent infection apparently results from incomplete clearance of the primary infection because of impaired cell-mediated immunity, and without maintenance antimicrobial therapy, up to 45% of persons with HIV infection will have recurrent bacteremia (Sperber and Schlepner, 1987). However, in the developed countries, the incidence of recurrent non-typhoidal *Salmonella* bacteremia in persons with HIV has declined in recent years (Angulo and Swerdlow, 1995). This decline may be linked to the introduction of zidovudine in 1987 and to the use of trimethoprim-sulphamethoxazole for the prevention of *Pneumocystis pneumonia* (Salmon *et al*, 1991). Zidovudine is active against *Salmonella in vitro* at therapeutic serum concentrations and against *Salmonella*-infected macrophages (Keith *et al*, 1989; Hermann *et al*, 1990).

In Malaysia, the first HIV case was reported

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in December 1986 at the University of Malaya Medical Center. Since then, the number of HIV infections reported has continued to rise. As of 31 December 2000, a total of 38,340 HIV-positive cases (0.16% of the total population) were notified to the Ministry of Health, with a mortality of 9.30%. Five thousand, one hundred and seven new HIV infections and 1,168 new AIDS cases were reported in the year 2000. Males comprised 94.7%, and 81.5% were with an age range 20-39 years. The majority of the HIV-infected persons (76.1%) were intravenous drug users and 71.2% of them had shared needles (Juita and Osman, 1995; Department of Statistics Malaysia, 2001). The racial composition was 72.3% Malays, 15.4% Chinese, 8.8% Indians, others 0.9%, and 2.5% foreigners. Transmission by heterosexual route accounted for 10.8% of the HIV carriers, and the percentage has been on an upward trend in recent years. A retrospective analysis of a cohort of HIV-infected persons seen at UHKL from 1986-1996 showed that the proportion of heterosexually-acquired HIV infections had rapidly increased from 20% in 1994 to 38.9% in 1996. An increasing number of women were infected through sexual contact with their husbands (Ismail, 1998).

Human salmonellosis is initiated by the ingestion of food or water contaminated with one or other *Salmonella* strain. Non-typhoidal *Salmonella* infection is widely distributed among different animal species but is particularly prevalent in animals raised for food. *Salmonella* organisms may be cultured from approximately 50% of commercially available chickens, from 20% of frozen egg whites, from varying percentages of raw milk sources, and periodically, from ground beef used to make hamburgers (Wilder and MacCeady, 1966; Goldberg and Rubin, 1988).

This report is a retrospective review of seven cases of *Salmonella* bacteremia in HIV-infected or AIDS patients seen at the University Hospital, Kuala Lumpur, Malaysia over a period of 12 years. To the best of our knowledge there are no reports of such cases from Malaysia.

PATIENTS AND METHODS

All patients with positive blood cultures for *Salmonella* species and serologically positive for HIV infection, from 1991 to 2003, were included

in the study. Patients' records were reviewed for demographic data, *ie* age, sex, ethnic group, occupation, sexual preference, history of intravenous drug usage, dietary habits, and for the presence of other risk and comorbid factors.

The *Salmonella* isolates were identified by standard biochemical reactions. *Salmonella enterica* Typhi isolates were differentiated from other *Salmonella* species by their inability to produce gas on fermentation of carbohydrates. Serotyping of the strains was performed at the Institute for Medical Research, Kuala Lumpur, the National Reference Laboratory for *Salmonella*. Antibiotic susceptibility testing was carried out using standard disc diffusion procedures.

Screening for HIV antibodies was carried out using Abbott AxySm microparticle enzyme immunoassay (MEIA) HIV 1/2 (Abbott Laboratories Diagnostics Division, Abbott Park, USA). All samples negative for anti-HIV 1/2 antibodies were considered negative. A particle agglutination (PA) assay (Serodia HIV-1/2, Fujirebio Inc, Japan) was used as a supplementary test to confirm samples that were repeatedly MEIA anti-HIV 1/2 antibody reactive. Inno-Lia HIV (Innogenetics NV, Belgium) carried out according to the manufacturer's recommendations, was used as a confirmatory assay. Only samples repeatedly reactive with MEIA, PA positive and with specific bands present on the nylon strip of Inno-Lia HIV, were considered positive for HIV infection.

Case histories

Table 1 summarizes the relevant data of the seven HIV/AIDS cases with *Salmonella* bacteremia. All were adult patients between the ages of 30 and 61 years and all, except one, were males. Five patients were Chinese, one was Malay, and one Indian, the only female, was admitted for a lung infection and a recent history of diarrhea and vomiting. Her blood culture grew *Streptococcus pneumoniae* and *Salmonella enterica* Enteritidis and then only was she diagnosed as HIV-positive. She gave a history of blood transfusion one and a half years ago. Of the remaining six males, three were intravenous drug users and one admitted to smoking marijuana. None of them were involved in homosexual activity. Promiscuity was admitted by two. *Salmonella* was isolated from the blood cultures of all of them and two had recurrent cultures positive over a period of time. All except one were treated with ceftriaxone in

Table 1
Salmonella septicemia in HIV-infected patients.

Case No.	Age (yr)/ Sex	Risk / Comorbid factors	Source of organism	<i>Salmonella</i> serovar	Antimicrobial therapy	Duration of HIV infection
1	34 M	IVDU Heterosexual Promiscuity <i>Pneumocystis carinii</i> Oral thrush	Blood x 5 Stool x 1 Urine x 4	Typhimurium	Chloramphenicol Ampicillin Co-T Ceftriaxone Ciprofloxacin Ketoconazole	4 years
2	61 F	Blood transfusion Lobar pneumonia	Blood x 1	Enteritidis	C. Penicillin Ceftriaxone	Post- <i>Salmonella</i> septicemia 3 years
3	52 M	IVDU Mycotic aneurysm	Blood x 1 Tissue from aneurysm	Group D	Ampicillin-sulbactam	
4	34 M	IVDU Heterosexual Oral thrush Bronchopneumonia	Blood x 1	Enteritidis	Ceftriaxone Co-T Itraconazole	2 weeks
5	41 M	Heterosexual Promiscuity Pulmonary TB - 2 years Oral thrush	Blood x 1	Enteritidis	Co-T Ceftriaxone Itraconazole	2 months
6	30 M	Marijuana smoker Heterosexual Cerebral toxoplasmosis	Blood x 1	Enteritidis	Co-T Ceftriaxone Metronidazole Itraconazole	Known history-?yrs
7	40 M	Heterosexual No history of drug abuse, pulmonary TB Diarrhea, pleural effusion	Blood x 1 Stool x 1 Pus x 5	Typhimurium	Ceftriaxone Ciprofloxacin Co-T	13 years

IVUD - intravenous drug user; Co-T - trimethoprim-sulphamethoxazole

combination with other drugs, such as cotrimoxazole, ciprofloxacin, or an antifungal agent. The following is a more detailed report of cases number one and seven; both had recurrent salmonellosis.

Case 1. A 34-year-old Chinese man was admitted in November 1990 with a history of fever for one month associated with chills and rigors. He had been diagnosed HIV-positive in 1987, and had a previous history of admission for fever and oral thrush. Blood culture grew *Salmonella enterica* Typhimurium and he was given chloramphenicol. He had recurrent episodes of salmonellosis and had five blood cul-

tures, one stool and one urine specimen positive over a period of one year, until December 1991. He was not homosexual and was briefly married and traveled extensively in Europe. He was an artist and painter by profession and admitted to intravenous drug abuse and promiscuity.

Case 7. A 40-year-old Chinese businessman was admitted in January 2002 with persistent pussy discharge from the right loin, progressive lower limb swelling, abdominal distension for two weeks, and loss of appetite. A past history of being treated for pulmonary tuberculosis and abscess on his pelvis was elicited. He was di-

agnosed HIV-positive in 1990, but denied homosexuality or drug abuse. On clinical examination, he was found to be cachexic with moderate dehydration. Edema of both legs, abscesses on the posterior abdominal wall and in the right loin, pleural effusion, right lung consolidation, cardiomegaly, abscesses in the liver, ascites and shotty nodes in the para-aortic areas were present. He also suffered from persistent watery diarrhea. Over a period of several months, *S. enterica* Typhimurium was isolated from several pus aspirates including lymph nodes, psoas abscess, as well as from blood culture and peritoneal fluid. He was treated with ceftriaxone and ciprofloxacin.

DISCUSSION

Human immunodeficiency virus infection produces complex and progressive immunological deterioration that leads to a marked susceptibility to infections caused not only by typically opportunistic pathogens but also by microorganisms that cause common infections in the general population (Brettle, 1997), and the invasion of the blood stream is a critical clinical circumstance in any bacterial infection.

The most commonly recognized clinical syndrome caused by non-typhoidal *Salmonella* is gastroenteritis. But in AIDS patients, due to defective macrophage killing of these intracellular organisms, bacteremia occurs in as many as 70% of them. In contrast, bacteremic complications of *Salmonella* gastroenteritis occur only in 1%-4% of patients without underlying disease. Surprisingly, results of stool cultures are often negative, even when diarrhea is present (Celum *et al*, 1987), as only two patients in our series had positive stool cultures.

Salmonella enterica Typhimurium and *Salmonella enterica* Enteritidis have been the two most common serovars associated with infections in HIV/AIDS patients (Levine *et al*, 1991) and this is reflected in our small series. But these two serovars are also most commonly isolated from gastroenteritis as well as nontyphoidal *Salmonella* bacteremic cases in Malaysia, (Lee *et al*, 2000; 2003). Unfortunately, the organism from case number three was not available for speciation but was identified as group D and highly likely to have been *S. enterica* Enteritidis.

The virulence of any microorganism involves a complex interaction between the microorganism and the host's ability to limit infection. In *Salmonella* infection, host specificity is extremely important to disease and an intact cell-mediated immunity is vital in controlling this intracellular pathogen. Persons deficient in the interleukin-12 receptor are extremely susceptible to *Salmonella* infections, because interleukin-12 induces type 1 helper T-cell responses and interferon- γ production, and this innate immune pathway is necessary in resistance to salmonellosis (Angulo and Swerdlow, 1995; de Jong *et al*, 1998).

None of the seven patients was known to be homosexual and this is consistent with studies suggesting that Salmonellae do not occur commonly among gay men as pathogens or as colonizing organisms. On the other hand, a relatively high proportion of heterosexual intravenous drug users with HIV/AIDS infection had recurrent nontyphoidal *Salmonella* septicemia (Levine *et al*, 1991). In the present series of seven cases, three were intravenous drug users.

A study by Gordon *et al* (2002) found that non-typhoidal *Salmonella* bacteremia had a high recurrence rate (43%) in HIV-infected African adults and suggested that recurrence is caused by recrudescence rather than re-infection. As focal infections were rarely found, recrudescence may often have been a consequence of intracellular tissue sequestration.

In humans, non-typhoidal *Salmonella* infections are most often associated with food products. Foods of animal origin, including meat, poultry, eggs, or dairy products, can become contaminated with *Salmonella*. Eating uncooked or inadequately cooked food, or food cross-contaminated with these products, may lead to infection. Salmonellosis can also be associated with domestic and exotic pets, such as snakes, iguanas, turtles, birds, rodents, dogs and cats (Glaser *et al*, 1994). We were unable to ascertain the sources of the organism in our patients.

In HIV/AIDS-infected persons, the first episode of *Salmonella* bacteremia should be treated with one to two weeks of intravenous antimicrobial therapy followed by four weeks of oral quinolone therapy in an attempt to eradicate the organism and decrease the risk of recurrent bacteremia (Jacobson *et al*, 1989). Persons who re-

lapse after six weeks of antimicrobial therapy should receive long-term suppressive therapy with a quinolone or trimethoprim-sulphamethoxazole. Although data are lacking, because of its efficacy in the prevention of *Pneumocystis carinii* infection, trimethoprim-sulphamethoxazole may be a good choice for long-term suppressive therapy for salmonellosis if the organism is susceptible (Centers for Disease Control and Prevention, 1992). Two of our patients had recurrent episodes of *Salmonella* infection in spite of being on suppressive therapy and we suspect non-compliance was the cause.

The control and prevention of salmonellosis requires coordinated efforts on multiple levels, including the farm, food processors, and food handlers. Effort must be made to educate HIV-infected persons on the epidemiology of salmonellosis and food counseling for such persons, aimed at prevention of infection, should be undertaken. Such patients may benefit from education in safe food handling and preparation practices (Levine *et al*, 1991).

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