RISK FACTORS FOR PRIMARY BACTEREMIA AND ENDOVASCULAR INFECTION IN PATIENTS WITHOUT ACQUIRED IMMUNODEFICIENCY SYNDROME WHO HAVE NON-TYPHOID SALMONELLOSIS

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Abstract

This study sought to find the risk factors for primary bacteremia, endovascular infection, and in-hospital death for patients without acquired immunodeficiency syndrome who have non-typhoid salmonellosis. From January 1995 through September 2011, 301 patients with non-typhoid salmonellosis were admitted to our hospital; of these patients, 121 had primary bacteremia, and 28 had endovascular infection. Of the 121 patients with primary bacteremia, 64 were aged >50 years, and 26 had endovascular infection. Overall, 90 patients (29.9%) had immunodeficiency. Predictors of primary bacteremia were age; presence of systemic lupus erythematosus; group B, group C, or group D Salmonella infection; and immunodeficiency. The positive predictor of endovascular infection in adult patients with primary bacteremia was group C Salmonella infection, and negative predictors were immunodeficiency and solid-organ cancer. The overall in-hospital mortality rate was 12%; for primary bacteremia, it was 24.8%; for endovascular infection, it was 14.3%. Predictors of in-hospital death were age, extraintestinal infection, and solid-organ malignancy.

Key words: salmonellosis, primary and secondary bacteremia, immunodeficiency

INTRODUCTION

Non-typhoid salmonellae are widely spread in nature and are commonly associated with certain animals (e.g., chickens and pigs). In humans, non-typhoid *Salmonella* infections are most often associated with contaminated food products (Hohmann EL et al., 2001; White DG et al., 2001, Tirado C et al., 2001) . The major risk factors for non-typhoid salmonellosis and bacteremia are certain immunocompromised conditions or periods, including extremes of age, alteration of the endogenous bowel flora of the intestine, diabetes, malignancy, autoimmune disorders, reticuloendothelial blockade, HIV infection, and therapeutic immunodeficiency (Brown M et al., 2000; Shimoni Z et al., 2000; Ramos JM et al., 2004). The occurrence of primary bacteremia (bacteremia without associated recent gastrointestinal symptoms) is ominous and should prompt clinicians to consider whether an immunodeficiency is present. In adults, non-typhoid *Salmonella* bacteremia is even more serious. *Salmonella* infection may manifest in 5 different clinical forms: asymptomatic chronic carrier state, gastroenteritis, enteric fever, bacteremia, and extraintestinal

localized complications (Cohen JI et al., 1997). A feared complication is the development of endovascular infection (e.g., infective endocarditis and infected aortic aneurysm), and the prognosis for patients with this condition is poor (Soravia-Dumond VA et al., 2010;Veraldi GF et al., 2010; Katz SG et al., 2002; Meerkin D et al., 2005; Oskoui R et al., 2003).

Endovascular infections are rare complications of salmonellosis. Frequently, the diagnosis is not established until the patient has an advanced stage of the disease. Anatomical disruptions, including atherosclerotic endovascular lesions and prosthetic devices, may all serve as foci for persistent *Salmonella* infection. Because of the insidious onset and poor prognosis of this condition, it is important to treat patients with non-typhoid salmonellosis during the early stage, before the development of endovascular infection (Oskoui R et al., 2003). Non-typhoid salmonellosis in compromised hosts can result in bacteremia and endovascular infection, leading to a high mortality rate. However, limited data from risk factor analysis for endovascular infection in patients with non-typhoid salmonellosis have been reported (Cohen PS et al., 1978). To ascertain which patients with known *Salmonella* infection are most likely to have primary bacteremia and endovascular infection, we retrospectively analyzed the medical records for patients with non-typhoid salmonellosis from a 16-year period.

MATERIAL AND METHOD

Patients. A retrospective analysis of the clinical and bacteriologic data for all patients with non-typhoid salmonellosis during the period of January 1995 through September 2011 was performed. Patients were included in this study if they had ?1 culture positive for non-typhoid salmonellae. Patients infected with Salmonella enterica serotype typhi and S. enterica serotype paratyphi were excluded from the study.

Data collection. The medical records were reviewed, and data on demographic characteristics (age and sex), underlying disease (systemic lupus erythematosus, hematologic malignancy, and solid-organ malignancy), clinical presentation (fever and diarrhea), bacteriology (*Salmonella* serogroups A–E and G), and in-hospital outcome (survival or death) were recorded. "Primary bacteremia" was defined as bacteremia without associated recent gastrointestinal symptoms. "Secondary bacteremia" was defined as bacteremia with recent gastrointestinal symptoms (diarrhea) or a positive stool culture result. "Immunodeficiency" was defined as suppression of the immune system that occurred with receipt of steroid therapy, chemotherapy for malignancy, and immunosuppressive therapy for organ transplantation.

Bacteriology. *Salmonella* isolates were initially identified using biochemical tests. Serogrouping was performed by agglutination testing with use of antisera specific to O antigen. Serotypes were not routinely determined.

Patients were classified into 4 groups: (1) those with intestinal salmonellosis, who had diarrhea and a stool culture positive for salmonellae; (2) those with extraintestinal salmonellosis, who had an extraintestinal focus of infection and salmonellae isolated from blood culture and culture of a sample other than a stool specimen; (3) those with primary bacteremia, who had no focus of infection and who had a blood culture positive for salmonellae; and (4) those with endovascular infection, who had infective endocarditis, infected aortic aneurysm, or infection in intravascular implants that was documented by an imaging study or a tissue culture.

Statistical analysis. Analysis was performed using the χ^2 test, Fisher's exact test, and the Mann-Whitney *U* test. Stepwise logistic regression was used to identify risk factors for primary bacteremia, endovascular infection, and in-hospital death.

RESULTS AND DISSCUSIONS

Patients. From January 1995 through September 2011, 301 patients with non-typhoid salmonellosis were admitted to our hospital. Of these patients, 175 had intestinal *Salmonella* infection, 39 of whom had secondary bacteremia; 5 had focal extraintestinal infection without bacteremia; and 121 had primary bacteremia, 28 of whom had endovascular infection. Among the 28 endovascular infections, there were 2 cases of infective endocarditis, 25 infected aortic aneurysms, and 1 infected vascular graft of arteriovenous fistula.

In total, there were 165 patients who had extraintestinal *Salmonella* infection, including 39 patients who had secondary bacteremia, 121 patients who had primary bacteremia, and 5 patients who had focal infection without bacteremia. There were 43 patients who had metastatic infection, including 28 patients with endovascular infection, 3 with infected pleural effusion, 3 with postoperative wound infection, 2 with urinary tract infection, 2 with osteomyelitis, 2 with bone marrow infection, 1 with arthritis, 1 with pneumonia, and 1 with soft-tissue infection.

Salmonella serogroups. Three cases (1.0%) of salmonellosis involved group A *Salmonella* organisms, 137 (45.5%) involved group B, 58 (19.3%) involved group C, 71 (23.6%) involved group D, 5 (1.7%) involved group E, and 1 (0.3%) involved group G. The serogroup was unidentified in 26 cases (8.6%). The distribution of serogroups did not change during the study period. Among 28 cases of endovascular infection, only 3 serotypes

were identified: *S. enterica* serotype typhi murium, in 2 cases, and *S. enterica* serotype cholerae suis, in 1 case.

Risk factor analysis. Overall, 90 patients (29.9%) had an immunodeficiency. Table 1 shows clinical data and infectious *Salmonella* serogroups for patients who had primary bacteremia and for those who did not. Table 1 also shows the clinical data and infectious *Salmonella* serogroups for bacteremic patients who had endovascular infection and for those who did not. Compared with bacteremic patients who did not have endovascular infection, bacteremic patients who had endovascular infection were older and were more likely to have underlying diseases or risk factors, including immunodeficiency, systemic lupus erythematosus, and solid-organ malignancy.

Table 1

Comparison between patients who have non-typhoid salmonellosis (NTS) but not primary bacteremie (PB), those who have NTS and PB but not endovascular infection (EVI), and those who have NTS, PB, and EVI

Characteristic	Patients with NTS but not PB (n=180)	Patients with NTS and PB but not EVI (n=93)	Patients with NTS, PB and EVI (n=28)
Male sex	101 (56)	55 (59)	22 (79)
Age, mean years +/- SD	15,7+/-22,8	44,4+/-22,8*	61,7+/-13,1**
Salmonella serogroup			
A	2 (1)	1 (1)	0 (0)
B	87 (48)	42 (45)	8 (29)
C	31 (17)	14 (15)	13 (46)**
D	32 (18)	34 (37)*	5 (18)
E	5 (3)	0 (0)	0 (0)
G	1 (1)	0 (0)	0 (0)
Not identified	22 (12)	2 (2)	2 (7)
Immunodeficiency	32 (18)	52 (56)*	6 (21)**
SLE	4 (2)	18 (19)*	1 (4)**
Hematological malignancy	23 (13)	16 (17)	1 (4)
Solid-organ malignancy	9 (5)	28 (30)*	2 (7)**
Fever	175 (97)	92 (99)	26 (93)

Note: Data are no. (%) of patients, unless otherwise indicated. SLE=systemic lupus erythematosus
*P< .05 for patients who have NTS and PB but not have EVI vs. patients who have NTS but not PB
**P< .05 for patients who have NTS, PB, and EVI vs. patients who have NTS and PB but not EVI

Table 2 shows clinical data, infectious Salmonella serogroups, and outcomes for adults (age ≥18 years) and children with non-typhoid salmonellosis. Adult patients had more group D and fewer group B infections than did children. Adult patients had more underlying diseases, including immunodeficiency, systemic lupus erythematosus, and solid-organ malignancy; more clinical presentations of primary bacteremia, extraintestinal infection, and endovascular infection; and a higher mortality rate.

Table 2

Comparison between adults (age ≥ 18 years) and children with non-typhoid salmonellosis (NTS)

Characteristics or outcome	No. (%) of adults with NTS (n=160)	No. (%) of children with NTS (n=141)	P
Male sex	97 (61)	81 (57)	.329
Salmonella serogroup			
A	2 (1)	1 (1)	.999
B	64 (40)	73 (52)	.049
C	34 (21)	24 (17)	.382
D	48 (30)	23 (16)	.382
E	2 (1)	3 (2)	.668
G	0 (0)	1 (1)	.468
Not identified	10 (6)	16 (11)	.150
Immunodeficiency	64 (40)	26 (18)	< .001
SLE	20 (13)	3 (2)	.001
Hematological malignancy	21 (13)	19 (13)	.999
Solid-organ malignancy	36 (23)	3 (2)	< .001
Fever	156 (98)	137 (97)	.999
Primary bacteremia	105 (66)	16 (11)	< .001
Extraintestinal infection	122 (76)	43 (31)	< .001
Endovascular infection	28 (18)	0 (0)	< .001
Death	33 (21)	3 (2)	< .001

Note: SLE=systemic lupus erythematosus

Table 3 shows the predictors of primary bacteremia, as determined by stepwise logistic regression. Predictors of primary bacteremia were older age; presence of systemic lupus erythematosus; infection with group B, group C, or group D *Salmonella* organisms; and immunodeficiency. Table 4 shows the predictors of endovascular infection in adult patients, as determined by stepwise logistic regression. The positive predictor of endovascular infection was infection with group C *Salmonella* organisms, and negative predictors were immunodeficiency and solid-organ malignancy.

Table 3

Predictors of primary bacteremia as determined by stepwise logistic regression

Predictor	OR (95% CI)	SEM	Z	P > |Z|
Age	1.055657	0.00688	8.31	.000
SLE	4.440189	2.943173	2.25	.025
Salmonella				
Serogroup B	3.633744	2.27459	2.06	.039
C	3.834823	2.562609	2.01	.044
D	5.453769	3.56788	2.59	.010
Immunodeficiency	3.086655	1.114255	3.12.002	

Note: SLE=systemic lupus erythematosus

Table 4

Predictors of endovascular infection in adults (age ≥ 18 years) with non-typhoid salmonellosis and primary bacteremia as determined by stepwise logistic regression

Predictor	OR (95% CI)	SEM	Z	P > |Z|
Salmonella serogroup C	3.766619	2.040494	2.45	.014
Immunodeficiency	0.2999848	0.1640051	-2.20	.028
Solid-organ malignancy	0.1605884	0.1290742	-2.28	.023

In-hospital outcome. Overall, 36 patients (12%) died in hospital. The in-hospital mortality rate was 2.2% (3 of 136 patients) for intestinal salmonellosis without secondary bacteremia, 7.7% (3 of 39 patients) for intestinal salmonellosis with secondary bacteremia, 20% (33 of 165 patients) for extraintestinal salmonellosis, 24.8% (30 of 121 patients) for primary bacteremia, and 14.3% (4 of 28 patients) for endovascular infection. Table 5 shows the predictors of in-hospital death for patients with non-typhoid salmonellosis. Predictors of in-hospital death were older age, extraintestinal infection, and solid-organ malignancy.

Table 5

Predictors of in-hospital death as determined by stepwise logistic regression

Predictor	OR (95% CI)	SEM	Z	P > |Z|
Age	1.032214	0.0095759	3.42	.001
Extraintestinal infection	4.49189	2.986901	2.26	.024
Solid-organ malignancy	5.503254	2.37318	3.95	< .0001

CONCLUSIONS

In conclusion, nontyphoid *Salmonella* bacteremia was associated with old age, systemic lupus erythematosus, and immunodeficiency. The incidence of endovascular infection among adult patients with *Salmonella* bacteremia was high in Taiwan. Serogroup C salmonellae, but not systemic lupus erythematosus or immunodeficiency, predisposed patients to endovascular infection.

REFERENCES

1. Benenson S., Raveh D., Schlesinger Y., 2001, The risk of vascular infection in adult patients with non-typhi Salmonella bacteremia, Am J Med, 110:60-3;
2. Blaser MJ., Feldman RA., 2001, Salmonella bacteremia: reports to the Centers for Disease Control, J Infect Dis, 143:743-6;
3. Brown M., Eykyn SJ., 2000, Non-typhoidal Salmonella bacteremia without gastroenteritis: a marker of underlying immunosupression, 41:256-9;
4. Chiu CH., Lin TY., Ou JT., 1999, Predictors for extraintestinal infection of non-typhoidal Salmonella in patients without AIDS, Int J Clin Pract, 53:161-4;
5. Chiu CH., Wu TL., Su LH., 2002, The emergence in Taiwan of fluoroquinolone resistance in Salmonella enteric serotype cholerae suis, N Engl J Med, 346:413-9;
6. Cohen PS, O'Brien TF, Schoenbaum SC, Medeiros AA, 1978, The risk of endothelial infection in adults with Salmonella bacteremia, Ann Intern Med, 89:931-2;
7. Cohen JI., Bartlett JA., Corey GR., 1997, Extraintestinal manifestations of Salmonella infections, Medicine, 66:349-88;
8. Fernandez Guerrero ML., Ramos JM, Nunez A., 2007, Focal infections due to non-typhi Salmonella in patients with AIDS: report of 10 cases and review, Clin Inf Dis, 25:690-7;
9. Hohmann EL., 2001, Non-typhoidal Salmonellosis, Clin Inf Dis, 32:263-9;
10. Hsu RB., Wang SS., Chu SH., 2002, Surgical treatment for primary infected aneurysm of descending thoracic aorta, abdominal aorta and iliac arteries, J Vas Sur, 36:746-50'
11. Katz RB., Andros G., Kohl., 2002, Slamonella infections of the abdominal aorta, Surg Gynecol Obstet, 175:102-6;
12. Le Bacq F., Louwagie B., Verhaegen J., 2004, Salmonella typhi murium and Salmonella enteritidis: changing epidemiology, Eur J Epidemiol, 10:367-71;
13. Lim E., Koh SF., Lam MS., Howe HS., 2001, Non-typhoidal salmonellosis in patients with systemic lupus erythematosus: a study of fifty patients and a review of the literature, Lupus, 10:87-92;
14. Meerkin D., Yinnon AM., Munter RG., Shemech O., 2005, Salmonella mycotic aneurysm of the aortic arch: case report and review, Clin Inf Dis, 21:523-8;
15. Oskoui R., davis WA., Gomes MN., 2003, Salmonella aortitis: a report of a successfully treated case with a comprehensive review of the literature, Arch Intern Med, 158:517-25;
16. Ramos JM., Garcia-Corbeira P., Aguado JM., Arjona R., 2004, Clinical significance of primary vs. secondary bacteremia due to non-typhoidal Salmonella in patients without AIDS, Clin Inf dis, 19:777-80;
17. Shimoni Z., Pitlik S., Leibovici L., 2000, Non-typhoidal Salmonella bacteremia: age-related differences in clinical presentation, bacteriology, and outcome, Clin Inf Dis, 28:822-7;
18. Soravia-Dunand VA., Loo VG., Salit IE., 2009, Aortitis due to Salmonella: report of 10 cases and comprehensive review of the literature, Clin Infect Dis, 29:862-8;
19. Taylor G., Goodfield MJ., 2005, Fatal salmonellosis in systemic lupus erythematosus, Clin Exp dermatol, 20:255-7;
20. Tirado C., Schmidt K., 2001, WHO surveillance program for control of food-borne infections and intoxications: preliminary results and trends across greater Europe, World Health Organization J Inf, 43:80-4;
21. Torrey S., Fleisher G., Jaffe D., 2006, Incidence of Salmonella bacteremia in infants with Salmonella gastroenteritis, J Pediatr, 108:718-21;
22. Veraldi GF., De Manzoni G., Laterza E., 2010, Extraintestinal infection by group C Salmonella: a case report and review of literature, Hepatogastroenterology, 48:471-4;
23. Wang JH., Liu YC., Yen MY., 2006, Mycotic aneurysm due to non-typhi Salmonella: report of 16 cases, Clin Inf Dis, 23:743-7;
24. White DG., Zhao S., Sudler R., 2001, The isolation of antibiotic-resistant Salmonella from retail ground meats, N Engl J Med, 345:1147-54.