

A Clinical Audit of Presentation and Outcome of Salmonella Septicaemia

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Abstract

Introduction: Enteric fever is imported to developed countries while non-typhoidal salmonella infections occur globally. Clinicians and trainees need to recognise the varied presentations of serious salmonella infections. **Materials and Methods:** We reviewed the clinical presentations, hospital course, complications and outcomes of 50 patients who were blood culture positive for *Salmonella* spp seen in 2 years. **Results:** Nineteen of 24 patients with enteric fever had recently travelled to Asian countries. All the enteric fever patients recovered fully. Out of 26 patients with non-typhoidal salmonellosis, 10 had malignancies, 7 had immune dysfunction states and 3 had aortic aneurysms. Five patients had recurrent episodes of salmonellosis. Eight of these patients who had cancer (4), diabetes mellitus with renal failure (2) and gastric diseases (2) died. Fatal cases were older with multiple admissions and co-morbidities (median, 3) and presentation followed immunosuppressive interventions, often with no fever (4). Onset was sudden with a short and fatally unresponsive course despite effective antimicrobial agents with microbiologic diagnosis made posthumously (4). Death resulted rapidly from overwhelming sepsis and aneurysmal complications. Antibiotic resistance to ampicillin, cotrimoxazole and chloramphenicol was noted. **Conclusion:** Enteric fever should be considered in travellers returning from Asian countries with fever, and third-generation cephalosporins or quinolones should be used for empiric treatment. Given the presentation of non-typhoidal salmonella septicaemias, clinicians need to have a high index of suspicion and to consider preemptive therapy in patients with prior infection who are likely to develop severe immunosuppression following interventions.

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Introduction

Salmonella infection occurs globally and has diverse presentations including enteric fever, gastroenteritis, localised infection, chronic enteric or urinary carrier state and bacteraemias. Enteric fever, caused by *Salmonella typhi* (*S. typhi*) and *Salmonella paratyphi* (*S. paratyphi*), occurs mostly in developing tropical countries but is increasingly seen as imported infections in developed countries. Non-typhoidal salmonellosis is universal and presents as sporadic food related outbreaks of gastroenteritis with or without extra-intestinal manifestations, especially in immunocompromised patients.¹ These manifestations are varied and if unrecognised can be important causes of morbidity and mortality.^{2,3} Here we report a clinical audit of salmonella septicaemic patients seen over a 2-year

period in order to describe the risk groups, presentations, complications and outcome of salmonella infections.

Materials and Methods

Details of all patients whose blood cultures tested positive for *Salmonella* spp were drawn from the microbiology and medical records of the National University Hospital, Singapore in the period April 2001 to March 2003. Clinical and laboratory data were obtained from the patients' records and analysed retrospectively. The clinical information utilised for the analysis included age, sex, date of onset, presenting symptoms, co-morbidities, recent admissions, interventions, hospital course, outcome and infection recurrences. The laboratory data included admission routine and blood investigations, radiologic and bacteriologic

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findings. Our laboratory uses the BACTEC automated blood culture system, and isolate identification and sensitivities were determined according to the National Committee for Clinical Laboratory Standards (NCCLS). STATA version 7.0 (Stata, College Station, Texas USA) was used for analyses and Student's *t*-test, Wilcoxon rank-sum or Fisher's exact test were used for comparison between groups, with $P < 0.05$ regarded as statistically significant.

Results

Fifty patients with *Salmonella* spp bacteraemia were identified in the period. Twenty-four had enteric fever: *S. typhi* (15) and *S. paratyphi* A (9). Nineteen of these patients (79%) had recently travelled to neighbouring

countries; Indonesia (11), India (4), Malaysia (2), China (1) and Thailand (1). Two *S. typhi* strains were resistant to multiple antibiotics (ampicillin, cotrimoxazole and chloramphenicol), but no resistance was encountered in *S. paratyphi* A. All the enteric fever patients recovered with no significant complications.

Twenty-six patients had non-typhoidal salmonella bacteraemias with varied manifestations (Table 1); 8 of the 26 patients (31%) died (Tables 2 and 3). Two of the surviving patients were on prophylactic therapy: the only HIV patient in the series who also had recurrent *S. enteritidis* bacteraemia was on cotrimoxazole and an elderly patient with *S. enteritidis* aortic aneurysm who was offered but declined surgery was on ciprofloxacin.

Table 1. Background and Manifestations of Non-typhoidal Salmonella Bacteraemias (n = 26)

Background or manifestation	Clinical cases
Malignancy (10*)	Solid cancers (7) [colon-2, ampulla of Vater-1, lungs-2, breast-1, ovary-1], acute myeloid leukaemia (1), chronic lymphocytic leukaemia (1), and HIV/Burkitt's lymphoma (1)
Recurrence (5)	Chronic lymphocytic leukaemia (1); SLE (1); aortic aneurysm (1); colon cancer (1); HIV/Burkitt's lymphoma (1)
Immune dysfunction† (7)	HIV/AIDS (1); SLE (2*); Immunoglobulin G deficiency (1); ? Interleukin 12 or Interleukin 12 receptor β 1 deficiency‡ (1); exclusive steroid use (2)
Aortic mycotic aneurysm (3‡)	Died (2; 1 with aorto-bronchial fistula); declined surgery (1)

BCG: Bacille Calmette Guerin; CSF: cerebrospinal fluid; SLE: systemic lupus erythematosus

§ Patient had concomitant tuberculosis and salmonella was additionally isolated in CSF (meningitis); twin sibling had disseminated BCG and *Rhodococcus equi* infections (not included here).

† Immune dysfunction excluding malignancies.

* Two cancer and both SLE patients were on steroids; 1 of the latter 2 had recurrent salmonella with salmonella calf muscle abscess.

‡ Excludes 1 fatal case with severe "shoulder pains" who died without autopsy.

Table 2. Comparison between Surviving and Fatal cases (n = 26)

Characteristic	Died (n = 8)	Survived (n = 18)	P value
Age (y)			
Mean [range]	65.88 [56-74]	43.36 [0.5-80]	$P = 0.0206^*$
Sex M:F	7:1	13:5	$P = 0.628^\dagger$
No. of co-morbidities			
Median [range]	3 [1-6]	1.5 [0-4]	$P = 0.0744^\ddagger$
No. of previous admissions in the last 12 months			
Median [range]	2 [0-12]	0 [0-3]	$P = 0.0108^\ddagger$
Effective antibiotic started empirically	7/8	18/18	$P = 0.3077^\ddagger$
Isolates			
<i>S. enteritidis</i>	7	16	
<i>S. typhimurium</i>	1	1	
Salmonella Group B	—	1	
Isolates resistant to:			
Ampicillin	2/8	3/17	$P = 0.8332^\ddagger$
Co-trimoxazole	0/6	3/18	$P = 0.4031^\ddagger$
Chloramphenicol	1/8	0/15	$P = 0.3478^\ddagger$

* Student's *t*-test

† Fisher's exact test

‡ Wilcoxon rank-sum test

All 50 *Salmonella* spp isolates were susceptible to ceftriaxone and ciprofloxacin and these agents, especially ceftriaxone, were used empirically routinely in our hospital.

Of the 8 fatal cases, 7 received effective empiric antibiotics: ceftriaxone (5), imipenem-cilastin (1) and intravenous augmentin (1). Patient 8 was treated with vancomycin initially as he had had an methicillin-resistant *Staphylococcus aureus* (MRSA) nosocomial infection in a preceding admission and ceftazidime was started just before death (Table 3). Resistance to antibiotics was similar in survivors and fatal cases (Table 2).

Discussion

Most patients with enteric fever had imported the infection from endemic neighbouring Asian countries.⁴ It is diagnosed

with an incidence rate of 0.03% per month among travellers to the Indian subcontinent⁵ and relevant history in returnees with fever should always be explored. Resistance to simpler antibiotics is widespread throughout Asia⁴ and we observed multidrug-resistant *S. typhi* in 2 out of 15 strains (13.3%), a slight reduction compared to the 17.4% reported in Singapore a decade earlier.⁶ Patients were treated with third-generation cephalosporins or fluoroquinolones and all recovered with no serious complications. These antibiotics or azithromycin should be used in the empiric treatment of returning travellers from Southeast Asia when typhoid fever is suspected.⁴ With emergence of low-level resistance to fluoroquinolones in Asia,⁴ typhoid vaccination should be considered for travellers at increased risk of infection.

Table 3. Characteristics and Presentations of Fatal Non-typhoidal Salmonella Bacteraemias

SN	Age (y)/ Sex	Comorbidity	Predisposing intervention	Presentation at admission	WBC*10 ⁹ /L [Abs lymph *10 ⁹ /L] (Abs neutrop *10 ⁹ /L)	Blood isolate	Hospital stay (days)	Comments/other new diagnoses
1	74/M	Ca colon	Radiotherapy; chemotherapy; post-surgery	4 day illness; 37.8°C	11.38 [1.43] (9.50)	<i>S. enteritidis</i>	5	Death due to overwhelming sepsis
2	72/M	Ca ampulla DM; HTN; IHD	Post Whipple's surgery	1 day illness; 36.0°C	8.3 [NA] (NA)	<i>S. enteritidis</i> (posthumous)	3	"shoulder pains"; ??aneurysmal dissection
3	57/M	Ca lung (+ brain metastasis)	Radiotherapy 5 day prior; on dexamethasone; post-chemotherapy	2 day illness; 37.5°C	15.48 [0.59] (14.21)	<i>S. typhimurium</i>	12	Sepsis with DIC
4	71/M	DM; HTN; chronic renal failure		3 day illness; 37.7°C	23.46 [0.28] (22.57)	<i>S. enteritidis</i> (and in urine)	10	Caecal mass and ascites noted on CT abdomen; ? Ca caecum
5	56/M	Old CVA; DM; focal glomerular sclerosis (chronic renal failure)	On prednisolone 60 mg daily for 3 wks prior to presentation	5 day illness; 37.1°C	11.53 [0.54] (10.48)	<i>S. enteritidis</i> (and in urine)	26	Was treated for <i>Salmonella enteritidis</i> 2 mth prior; MRA revealed infra-renal aneurysm
6	56/F	Ca lung (+ brain metastasis)	Radiotherapy 1 day prior; on dexamethasone	1 day illness; 35.0°C; septic shock (BP 60/40 mmHg)	5.58 [0.91] (4.43)	<i>S. enteritidis</i> (posthumous)	1	Overwhelming sepsis with shock
7	72/M	IHD; GERD; HTN; Lt TKR		14 day illness; haemoptysis; 38.7°C	12.03 [1.85] (9.19)	<i>S. enteritidis</i> (and in sputum; posthumous)	4	Ruptured thoracic aortic aneurysm + aorto-bronchial fistula on CT thorax
8	69/M	Eczema; asthma; chronic renal failure; PUD; gout; hyperlipidaemia		2 day illness; 38.0°C	19.85 [2.58] (13.74)	<i>S. enteritidis</i> (posthumous)	23	Was treated for salmonella bacteraemia 1 mth ago; had sepsis with arthritis

Ca: cancer; CT: computed tomography; CVA: cerebrovascular accident; DM: diabetes mellitus; DIC: disseminated intravascular coagulation; GERD: gastroesophageal reflux disease; HTN: hypertension; IHD: ischaemic heart disease; PUD: peptic ulcer disease; TKR: total knee replacement; WBC: white blood cells (normal range, 4.0 to 11.0*10⁹/L) [absolute lymphocytes (normal range, 1.5 to 4.0*10⁹/L); absolute neutrophils (normal range, 2.0 to 7.5*10⁹/L)]

In enteric fever, bacteraemia is found in the early phase of most infections, as will be expected in recently returned infected travellers, and being a systemic disease bacteraemia is not necessarily related to severity. In contrast, in non-typhoidal salmonellosis, gastroenteritis is the usual presentation and bacteraemia is less common, suggesting invasiveness and severity. In that regard all the fatal cases were in patients with non-typhoidal salmonella septicaemia, who were often older, with more co-morbidities and recurrent hospital admissions as compared to survivors. Six patients had immunosuppressive states and or interventions, and 5/7 had lymphopenia without neutropenia. Those without lymphopenia had gastric lesions or surgical procedures known to predispose to salmonella gastroenteritis by altering gastric acidity, emptying times and host barrier defence mechanisms.^{7,8} These patients presented with short illnesses of sudden onset with no fever (temperature >37.6°C) in half of them. In some patients, the hospital course was equally short and fatal despite prompt institution of effective antibiotics. Indeed, microbiologic diagnosis was made posthumously in half of the fatal cases reported here.

The recorded mortality of 8/26 (31%) is slightly high partly because only bacteraemic patients were analysed; but a recent Danish study showed that even salmonella gastroenteritis is associated with increased short- and long-term (1 year) mortality compared to age and sex matched healthy controls after comorbidity was taken into account.⁹ Two of our patients were treated for *S. enteritidis* infection 1 to 2 months before presentation and one of them was started on high-dose steroid therapy a few weeks later, with ensuing immunosuppression and relapse of salmonella bacteraemia. Clinical guidelines in other immunosuppressive states such as advanced human immunodeficiency virus (HIV) infection, chemotherapy-related neutropenic fever and organ transplantation would have dictated a maintenance course or effective empiric chemoprophylaxis with either co-trimoxazole or a quinolone. However, these recommendations do not extend to immunosuppressive states resulting from co-morbidities, radiotherapy or steroid use, as described here. While antimicrobial therapy may increase duration of bacterial carriage and resistance in non-typhoidal *S. enteritidis*, clinicians need to treat elderly patients and to consider preemptive therapy or even chemoprophylaxis particularly in patients with prior salmonella infection who are likely to develop severe immunosuppression, especially if there is associated lymphopenia, given the rapid unresponsive fatal course typified by these patients despite effective antibiotics. This can be life saving and both our patients (with aneurysm and HIV) on prophylaxis are well at last follow-up. Indeed the use of chemoprophylaxis in HIV infection led to a decline in salmonella bacteraemias and

others have reported long-term suppression in salmonella aneurysm patients refusing surgery with antibiotic prophylaxis alone.^{10,11}

There is about 25% risk of aneurysm formation complicating salmonella bacteraemia in patients older than 50 years and this is most often associated with arteriosclerosis.¹² Three patients developed *S. enteritidis* radiologically confirmed aortic mycotic aneurysms, with unique adjoining organ complications and fatalities in 2; aorto-bronchial fistula from thoracic and renal involvement from infra-renal aneurysms respectively, with bacteria cultured in both blood and end organ secretion (Table 3). Only 6 cases of salmonella aorto-bronchial fistula have been reported in the literature previously.¹³⁻¹⁶ Exsanguination was the common mode of death and there is a need for a high index of suspicion, early recognition and surgical repair if fatal aneurysmal complications are to be avoided. Recurrent salmonella infections should suggest mycotic aneurysm, especially in the aged with bacteraemias,^{3,12-14} and or immune dysfunction states like HIV infection,¹⁰ systemic lupus erythematosus (SLE), especially in the young female, or other immunodeficiency states.^{17,18} With immune dysfunction infections often present without gastroenteritis¹⁹ in unusual locations (extra-intestinal, extra-vascular and non-contiguous), as seen here with *Salmonella* spp isolated from cerebrospinal (CSF) and calf muscle abscess. Another patient had *Salmonella* spp in blood and urine but ascitic fluid obtained by paracentesis did not show any bacteria although he was already on antibiotic therapy. Primary peritonitis due to non-enteric salmonellae has been reported²⁰ but it is likely that our patient had leakage with secondary peritonitis in view of the newly discovered caecal mass.

In conclusion, enteric fever encountered mostly in returning travellers was not associated with fatality but non-typhoidal salmonella septicaemia was found to be an important cause of death in elderly patients with immunosuppressive states or interventions. Illness was characterised by a sudden onset and rapidly fatal course despite effective antibiotics. Death resulted from overwhelming sepsis and aneurysmal complications. Given this presentation, clinicians need to have a high index of suspicion and to consider preemptive therapy, especially in elderly patients with prior salmonella infection who are likely to develop severe immunosuppression following interventions.

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REFERENCES

1. Cohen JI, Bartlett JA, Corey GR. Extra-intestinal manifestations of salmonella infections. *Medicine (Baltimore)* 1987;66:349-88.
2. Lester A, Eriksen NH, Nielsen H, Nielsen PB, Friis-Moller A, Bruun B, et al. Non-typhoid Salmonella bacteraemia in Greater Copenhagen 1984 to 1988. *Eur J Clin Microbiol Infect Dis* 1991;10:486-90.
3. Salzberger LA, Cavuoti D, Barnard J. Fatal Salmonella aortitis with mycotic aneurysm rupture. *Am J Forensic Med Pathol* 2002;23:382-5.
4. Parry CM, Hien TT, Dougan G, White NJ, Farrar JJ. Typhoid fever. *N Engl J Med* 2002;347:1770-82.
5. Steffen R, Banos A, deBernardis C. Vaccination priorities. *Int J Antimicrob Agents* 2003;21:175-80.
6. Oh HM, Chew SK, Monteiro EH. Multidrug-resistant typhoid fever in Singapore. *Singapore Med J* 1994;35:599-601.
7. Waddell WR, Kunz LJ. Association of Salmonella enteritis with operations of stomach. *N Engl J Med* 1956;255:555-9.
8. Gorden J, Small PL. Acid resistance in enteric bacteria. *Infect Immun* 1993;61:364-7.
9. Helms M, Vastrup P, Gerner-Smidt P, Molbak K. Short and long term mortality associated with foodborne bacterial gastrointestinal infections: registry based study. *BMJ* 2003;326:357-60.
10. Angulo FJ, Swerdlow DL. Bacterial enteric infections in persons infected with human immunodeficiency virus. *Clin Infect Dis* 1995;21 (suppl 1):S84-93.
11. Donabedian H. Long-term suppression of Salmonella aortitis with an oral antibiotic. *Arch Intern Med* 1989;149:1452.
12. Cohen PS, O'Brien TF, Schoenbaum SC, Medeiros AA. The risk of endothelial infection in adults with Salmonella bacteremia. *Ann Intern Med* 1978;89:931-2.
13. Oskoui R, Davis WA, Gomes MN. Salmonella aortitis. A report of a successfully treated case with a comprehensive review of the literature. *Arch Intern Med* 1993;153:517-25.
14. Soravia-Dunand VA, Loo VG, Salit IE. Aortitis due to Salmonella: report of 10 cases and comprehensive review of the literature. *Clin Infect Dis* 1999;29:862-8.
15. Tan HC, Chan RKT, Tan WC. Fatal haemoptysis in Salmonella typhimurium septicaemia – A cautionary tale. *Singapore Med J* 1994;35:525-6.
16. Chung SL, Ding YA. Fatal hemoptysis in dissecting aortic aneurysm and salmonellosis: a case report. *Zhonghua Yi Xue Za Zhi (Taipei)* 1999;62:817-22.
17. Lim E, Koh WH, Loh SF, Lam MS, Howe HS. Non-typhoidal salmonellosis in patients with systemic lupus erythematosus. A study of fifty patients and a review of the literature. *Lupus* 2001;10:87-92.
18. Abel L, Casanova JL. Immunogenetics of the host response to bacteria and parasites in humans. In: Kaufman SHE, Sher A, Rafi A, editors. *Immunology of Infectious Diseases*. Washington: American Society for Microbiology (ASM) Press, 2002:395-406.
19. Brown M, Eykyn SJ. Non-typhoidal Salmonella bacteraemia without gastroenteritis: marker of underlying immunosuppression. Review of cases at St Thomas' Hospital 1970-1999. *J Infect* 2000;41:256-9.
20. McConkey SJ, McCarthy ND, Keane CT. Primary peritonitis due to nonenteric Salmonellae. *Clin Infect Dis* 1999;29:211-2.