Cardiac Involvement in Travelers with Enteric Fever

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Abstract. Data regarding cardiac involvement in enteric fever among travelers are scarce. In this retrospective study, 59 patients were hospitalized with enteric fever during 2004–2017 and 28 had cardiac workups. Among those, four had evidence of cardiac involvement, including clinical myocarditis, electrocardiogram changes, or troponin elevation. Cardiac involvement was higher among patients infected with *Salmonella* Typhi than with *Salmonella* Paratyphi A ($P = 0.08$), with a significant relative risk of 6 (95% CI: 1.15–31.22, $P = 0.03$). Time from symptoms onset to effective treatment was longer for patients with cardiac involvement (13 versus 7.15 days, $P < 0.05$). It seems that cardiac involvement in enteric fever is not uncommon in travelers. Such involvement seems to be more common in patients with delay of effective treatment to the second week of illness. Although fatal or complicated cases are rare in travelers, the cardiac complication may be an important contributor to morbidity and mortality in this group.

Enteric fever is a systemic disease caused by *Salmonella enterica* serovar Typhi or Paratyphi (*Salmonella* Typhi or *Salmonella* Paratyphi). The incidence of enteric fever in endemic regions, such as South Central Asia and southeast Asia, may rise to more than 270 per 100,000 persons/year, whereas the incidence in the industrialized world is very low, mostly acquired during travel.¹

Untreated disease can be fatal, mainly because of intestinal perforation, which can occur during the third week of the disease from necrosis of the Peyer's patches. Extraintestinal complications, including cardiovascular involvement, have also been described, mainly in endemic regions.^{2–5}

Data regarding myocardial involvement in returned travelers with enteric fever are scarce. We therefore conducted a retrospective analysis of all patients hospitalized in the Sheba Medical Center with culture-proven enteric fever during January 1, 2004, and October 19, 2017. Data regarding age, gender, travel history, medical history, electrocardiogram (ECG), troponin-I, and electrolytes were collected from patients' files. Every patient admitted to internal medicine ward from the emergency room undergoes an ECG as a routine. Electrocardiogram changes were defined as prolonged PR or QT intervals, abnormalities in ST intervals, any arrhythmia, or new bundle branch block. Corrected QT interval was calculated by the ECG machine and manually using Bazett and Framingham corrections. Any case with ECG changes or troponin elevation was considered having cardiac involvement. Clinical myocarditis was defined by the diagnostic criteria for clinically suspected myocarditis of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases.⁶

Only cases with ECG records were included for statistical analysis. Fisher's exact tests were used in intergroup comparisons of categorical variables, and categorical variables were expressed as numbers and percentages. Mann–Whitney U test was used for the comparison of medians, and P values lower than 0.05 were considered as statistically significant.

During the study period, 59 patients were culture positive for enteric fever (Table 1). Forty-six (78%) were infected with *S.*

Paratyphi A and 13 (22%) with *S. Typhi*. The patients were mostly young Israeli adults with a median age of 26 (range, 20–74) years, predominantly male (63%). Ninety-one percent of the patients acquired the disease in the Indian subcontinent (India and Nepal). Two patients were infected by exposure to contaminated laboratory disposal materials and two others were foreign workers. None had significant medical histories, with the exception of one who was an hepatitis B virus carrier and another who had hypothyroidism.

Electrocardiogram records were available in 28 (50%) cases; this group was not different from the whole study population (Table 1). Among them, four cases (a range of 6.8% from the all cases to 14.3% of patients with available ECG) had findings consistent with cardiac involvement. Two of the four in whom *S. Typhi* was isolated had clinical myocarditis, one of them had a life-threatening condition including ventricular fibrillation and sustained left ventricle ejection fraction reduction,⁷ the other had pulmonary congestion which needed diuretics treatment. The other two who were infected with *S. Paratyphi* A had either ECG changes or troponin elevations, without any cardiac symptoms (Table 2). All these four cases were susceptible to ceftriaxone and ampicillin and resistant to ciprofloxacin. The prevalence of cardiac involvement was higher in cases with serovar Typhi than with *S. Paratyphi* (50% versus 8.3%, $P = 0.08$), with a significant relative risk of 6 (95% CI: 1.15–31.23, $P = 0.03$). However, symptomatic cardiac cases were significantly higher among patients infected with *S. Typhi* ($P = 0.01$), with a relative risk of 25 (95% CI: 1.4025–445.6241, $P = 0.02$).

A significant risk factor for developing cardiac involvement was the time from fever onset until initiation of appropriate antibiotic treatment. The four patients with cardiac involvement had a delay in effective treatment to the second week of illness, with a mean of 13 days compare with 7 days in patients in whom ECG was available, but without cardiac involvement ($P < 0.05$). The mean time for effective treatment of patients without available ECG (the data were available only for 21 patients) was 5 days and not significantly different from the latter group ($P = 0.14$).

Enteric fever is a systemic disease with varying severity and the potential for a dangerous outcome. In industrialized countries the disease is rare, and most cases are reported in returning travelers from developing regions.⁸ Acquisition of

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TABLE 1
Study population

Variables		All patients, n = 59	Patients with ECG record, n = 28	P-value
		n (%)	n (%)	
Gender	Male	37 (63%)	17 (61%)	1
	Female	22 (37%)	11 (39%)	
Age (median, range) years		26 (20–74)	25.5 (20–57)	0.79
Pathogen	<i>Salmonella</i> Typhi	13 (22%)	3 (11%)	0.25
	<i>Salmonella</i> Paratyphi	46 (78%)	25 (89%)	
Source	Indian subcontinent	54 (91%)	26 (93%)	1
	West Africa	1 (2%)	–	
	Multiple continents	1 (2%)	–	
	Laboratory/Israel	2 (3%)	1 (4%)	
	Unknown	1 (2%)	1 (4%)	
Total		59 (100%)	–	–

enteric fever due to travel to developed regions was reported as well.⁹ Mortality in travelers is rare although a case series from the United States demonstrated that death has occurred, although without details concerning the exact causes of death.¹⁰

The prevalence of cardiovascular complications, including myocarditis, endocarditis, pericarditis, and congestive heart failure, is reported as 1–5%.⁴ Yet, several studies from endemic regions show an even higher rate of cardiac involvement. In a series of 100 bacteriologically or serologically proven enteric fever in India, seven cases with clinical evidence of myocarditis and 46 cases with ECG evidence of myocarditis were found. The most common ECG abnormalities were QT prolongations in approximately a third of the patients, ST interval (ST or T wave deviations) changes in a fifth of the cases, followed by bundle branch block, first-degree A-V block, and arrhythmia.² Another study from Egypt, conducted in late 1940s, before the antibiotic era, reported ECG changes, other than tachycardia or bradycardia, in 60 of 106 patients during the infection, consisting of mostly flattened or inverted T waves or ST deviations.³ In both studies, ECG evidence for cardiac involvement was detected only because patients were intentionally monitored and the subclinical cases may explain the underestimated number of those with cardiac involvement.

Myocarditis could be a cause of death more often than appreciated. In the study mentioned from Egypt, seven patients died during the course of disease, with three cases attributed to myocarditis, two to intestinal perforation, and two others to toxic circulatory failure.³ In another series of autopsies on Soviet soldiers with fatal typhoid fever during the Afghanistan war in the 1980s, myocarditis was the most

frequent complication (84.6%). This was even higher than the hemorrhagic complications (50.8%) or intestinal perforations (49.2%).¹¹

Indeed, sepsis on its own may cause cardiac damage. Troponin elevation and ischemic-like ECG changes may occur.¹² Other ECG changes include a loss of QRS amplitude, increase in QT interval, and development of narrowed QRS intervals with deformed bundle branch blocks. Nevertheless, the ECG changes and cardiomechanical elevations were attributed to hypotension and vasoactive treatment, and appeared early during the disease.^{13,14} Moreover, these changes are not common in patients with normal coronaries.¹² In the case of enteric fever, it appears that the ECG changes are different and the cardiomechanical elevations occur late during the disease, in hemodynamic stable patients, even in those who are young without cardiovascular risk factors, as demonstrated in our series.

Comparing our case series with the other studies from endemic areas, the rate of pathologic ECG changes in our case series was relatively low. This may be attributed to early diagnosis and treatment in the case of travelers. Two other cases of travelers with significant clinical myocardial involvement were published.⁷ In both cases, the isolated pathogen was *S. Typhi* and both received medical attention after the second week of the disease. In our case series, the severe cardiac involvement was also among those infected with *S. Typhi*. Clinical infection with *S. Typhi* or *S. Paratyphi* reported to be undistinguishable.^{15–17} However, in our case series, significant cardiac involvement was more common in *S. Typhi*. Whether it is only a sample error due to the small sample size or the time difference until appropriate treatment which was longer in our *S. Typhi* cases (mean time of 16 versus 10 days) should be determined by further case reports.

TABLE 2
Summary of cases with cardiac involvement

Gender/age/year	Pathogen	Days from symptoms onset*	Cardiac manifestation	Troponin I (μg/L) (N < 0.059)	ECG	Echo	Outcome
M/27/2011 ⁷	<i>Salmonella</i> Typhi	17	Myocarditis and ventricular fibrillation	0.088	Prolonged QT ICRBBB	LVEF 30%	LVEF returned normal in 2 years f/u
F/26/2017	<i>Salmonella</i> Typhi	15	Pulmonary congestion and peripheral edema	0.136	Normal ECG	Normal (5 days later)	Responded well to furosemide
M/24/2016	<i>Salmonella</i> Paratyphi A	12	ECG changes	Normal	New inferolateral T wave inversion followed by QT prolongation	Normal	ECG normalization a month later
M/38/2016	<i>Salmonella</i> Paratyphi A	8	Cardiomarkers elevation	0.127	Normal ECG	–	Troponin normalized

Age in years; ECG = electrocardiogram; Echo = echocardiography; F = female; ICRBBB = incomplete right bundle branch block; LVEF = left ventricle ejection fraction; M = male.

* Days from symptom onset mean days to the onset of fever till effective treatment.

Salmonella Paratyphi (mainly Paratyphi A) incidence is increasing in the endemic areas and among travelers.^{15,16,18} Strains of *S. Typhi* and *S. Paratyphi* as well are reported to have fluoroquinolone resistance.^{1,19} Azithromycin is highly effective in treating enteric fever, with this activity being attributable to the remarkable property of intracellular concentration of azithromycin in macrophages.²⁰ Hence, azithromycin has evolved as an important alternative in the treatment of enteric fever and found to be highly effective in combination with ceftriaxone.^{1,19,21} The standard protocol for treatment in our institute is co-treatment of ceftriaxone and azithromycin. In this series, two cases with cardiac involvement had QT prolongation while being treated with azithromycin. In our series, QT prolongation was evident, both around the third week of the disease and only in conjunction with other cardiac manifestations such as T wave inversion in one case and myocarditis in the other case. As azithromycin may cause QT prolongation mainly in patients with baseline cardiac disease, one may consider ECG tracking to assess QT interval while treating enteric fever with this drug.

There are limitations to this study. Not all the patients had cardiac workups, including ECG or cardiac biomarkers. Furthermore, not all the patients went through the same cardiac investigations, thus further prospective studies are needed.

To our knowledge, this is the first series describing cardiac involvement of enteric fever in travelers. In this series, cardiac involvement in travelers with typhoid was not uncommon (~14%), mostly affecting patients with a delay in appropriate antibiotic treatment.

The extent of this complication might be more prevalent in endemic areas where the diagnosis may be delayed and may contribute to morbidity and mortality; however, even among travelers, this complication is not uncommon. Therefore, the cause of death in severe typhoid cases might be cardiac related and not only gastrointestinal complications. Therefore, more vigilance to ECG changes and cardiac monitoring is crucial among returning travelers with typhoid fever.

Received September 24, 2018. Accepted for publication January 21, 2019.

Published online March 11, 2019.

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REFERENCES

1. Meltzer E, Stienlauf S, Leshem E, Sidi Y, Schwartz E, 2014. A large outbreak of *Salmonella* Paratyphi A infection among Israeli travelers to Nepal. *Clin Infect Dis* 58: 359–364.
2. Prabha A, Mohanan, Pereira P, Raghuveer CV, 1995. Myocarditis in enteric fever. *Indian J Med Sci* 49: 28–31.
3. Mainzer F, 1947. Electrocardiographic study of typhoid myocarditis. *Br Heart J* 9: 145–153.
4. Huang DB, DuPont HL, 2005. Problem pathogens: extra-intestinal complications of *Salmonella enterica* serotype Typhi infection. *Lancet Infect Dis* 5: 341–348.
5. Mellon G, Erme AL, Rohaut B, Brossier F, Epelboin L, Caumes E, 2017. Encephalitis in a traveller with typhoid fever: efficacy of corticosteroids. *J Travel Med* 24.
6. Caforio AL et al., 2013. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 34: 2636–2648, 2648a–2648d.
7. Palombo M, Margalit-Yehuda R, Leshem E, Sidi Y, Schwartz E, 2013. Near-fatal myocarditis complicating typhoid fever in a traveler returning from Nepal. *J Travel Med* 20: 329–332.
8. Connor BA, Schwartz E, 2005. Typhoid and paratyphoid fever in travellers. *Lancet Infect Dis* 5: 623–628.
9. Drewett G, Leder K, 2016. Infectious disease following travel to developed regions: a snapshot of presentations to an Australian travel medicine clinic. *J Travel Med* 23.
10. Ackers ML, Puhr ND, Tauxe RV, Mintz ED, 2000. Laboratory-based surveillance of *Salmonella* serotype Typhi infections in the United States: antimicrobial resistance on the rise. *JAMA* 283: 2668–2673.
11. Bobin AN, Klochov ND, Bogomolova NV, 1993. Complications and the proximate causes of death in typhoid [in Russian]. *Voen Med Zh*: 49–52.
12. Lv X, Wang H, 2016. Pathophysiology of sepsis-induced myocardial dysfunction. *Mil Med Res* 3: 30.
13. Maeder M, Fehr T, Rickli H, Ammann P, 2006. Sepsis-associated myocardial dysfunction: diagnostic and prognostic impact of cardiac troponins and natriuretic peptides. *Chest* 129: 1349–1366.
14. Spies C, Haude V, Fitzner R, Schroder K, Overbeck M, Runkel N, Schaffartzik W, 1998. Serum cardiac troponin T as a prognostic marker in early sepsis. *Chest* 113: 1055–1063.
15. Shlim DR, Schwartz E, Eaton M, 1995. Clinical importance of *Salmonella* Paratyphi A infection to enteric fever in Nepal. *J Travel Med* 2: 165–168.
16. Meltzer E, Sadik C, Schwartz E, 2005. Enteric fever in Israeli travelers: a nationwide study. *J Travel Med* 12: 275–281.
17. Vollaard AM, Ali S, Widjaja S, Asten HA, Visser LG, Surjadi C, van Dissel JT, 2005. Identification of typhoid fever and paratyphoid fever cases at presentation in outpatient clinics in Jakarta, Indonesia. *Trans R Soc Trop Med Hyg* 99: 440–450.
18. Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL, 2015. Typhoid fever. *Lancet* 385: 1136–1145.
19. Zmora N, Shrestha S, Neuberger A, Paran Y, Tamrakar R, Shrestha A, Madhup SK, Bedi TRS, Koju R, Schwartz E, 2018. Open label comparative trial of mono versus dual antibiotic therapy for typhoid fever in adults. *PLoS Negl Trop Dis* 12: e0006380.
20. Butler T, Girard AE, 1993. Comparative efficacies of azithromycin and ciprofloxacin against experimental *Salmonella typhimurium* infection in mice. *J Antimicrob Chemother* 31: 313–319.
21. Oey M, Malhotra P, 2016. Azithromycin and ceftriaxone combination treatment for relapsed *Salmonella* Paratyphi A bacteraemia. *J Travel Med* 23: tav032.