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REVIEW ARTICLE

Salmonella infective endocarditis



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Received 3 November 2014; received in revised form 2 February 2015; accepted 10 February 2015
Available online 24 March 2015

KEYWORDS

Bacteremia;
Infective
endocarditis;
Perivalvular abscess;
Salmonella

Objective: *Salmonella* endocarditis is so rarely reported that its clinical features, prognosis, and optimal treatment remain unclear. In this paper, we report a female with nontyphoid *Salmonella* endocarditis complicated with perivalvular abscess. We also review and summarize other cases reported in the English literature.

Methods: Using the key words “*Salmonella*”, “infective endocarditis”, and “mural endocarditis” to search the PubMed database, we reviewed case reports on *Salmonella* endocarditis published between 1976 and 2014 and case series of infective endocarditis that included at least 500 cases.

Results: *Salmonella* species were rare infective endocarditis pathogens. Among 16 large case series, they accounted for less than 0.01% and up to 2.9% of bacterial endocarditis cases. From 1976 to 2014, a total of 87 cases of typhoid and nontyphoid *Salmonella* endocarditis were reported, which included 42 cases in 1976–1984, 30 cases in 1986–2002, and 15 cases in 2003–2014. Men predominated among the cases (58.6%), and the mean age was approximately 50–60 years. The major affected valves were the mitral valves (33.3%). Mural endocarditis was common (26.4%). Perivalvular abscess was only reported in 10.5% (6 cases) of 57 cases. The overall mortality rate was 42.5% and decreased over time from 69.0% to 13.3% during the three study periods.

Conclusion: *Salmonella* endocarditis, although rare, may cause purulent infections in the perivalvular area or myocardium and lead to substantial mortality.

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Introduction

Salmonella species are important bacterial pathogens that cause foodborne diseases in developed and developing countries. It is estimated to cause more than 1.2 million illnesses each year in the United States with more than 23,000 hospitalizations and 450 deaths.¹ *Salmonella* isolates often cause human infections ranging from mild gastroenteritis to severe invasive infections, especially in infants, the elderly, and immunocompromised hosts.^{2,3} Any anatomical site may be seeded hematogenously by *Salmonella*; however, the involvement of the cardiovascular system is a rare but serious disease.^{4–6} Many studies have investigated a complication of *Salmonella* bacteremia, infected aortic aneurysm, because it is associated with a high mortality rate if not diagnosed and treated early.^{7–9} However, *Salmonella* endocarditis is uncommon, and its clinical characteristics and prognosis have not been fully defined. In this paper, we report a case of *Salmonella enteritidis* bacteremia and aortic valve endocarditis complicated with perivalvular abscess. In addition, to delineate the temporal evolution of *Salmonella* endocarditis, we summarized the clinical manifestations in 14 similar cases published in the past decade, and compared them with reports in two earlier reviews.

Case report

A 55-year-old female with chronic kidney disease and diabetes mellitus presented with fever, chills, productive cough, and chest tightness for 1 week. Two weeks before admission, she received an antibiotic for presumed acute

pyelonephritis. On admission, the chest film showed increasing infiltration in the right middle lung, and the abdominal ultrasound showed mild fluid accumulation in the perirenal area. She was treated for healthcare-associated pneumonia with cefepime and doxycycline. With the laboratory result of bacteremia due to *S. enteritidis*—which is susceptible to ampicillin, cefotaxime, ciprofloxacin, co-trimoxazole, and ertapenem—antimicrobial therapy was de-escalated to cefotaxime. An abdominal computed tomography (CT) scan showed no aortic aneurysm or renal abscess. Serum antibody against human immunodeficiency virus-1 was not present. On Day 6, a Grade I heart murmur was heard, and electrocardiography showed sinus tachycardia. An inflammation scan discovered inflammation around the upper heart (Fig. 1A). Transthoracic and transesophageal echocardiogram studies showed moderate pericardial effusion, a bicuspid aortic valve with a 6-mm diameter vegetation over the commissure, and a perivalvular abscess with a length of approximately two-thirds the aortic root diameter along the left coronary cusp, which communicated with the aortic root (Fig. 1B). A computed tomography (CT) scan showed a bicuspid aortic valve with vegetation and periaortic leakage or abscess beside the right ventricular outflow tract (Fig. 1C). Cardiac surgery was performed on Day 12. At surgery, a 1.5 cm × 1.5 cm perivalvular abscess underneath the left coronary orifice and a small vegetation over the commissure of the bicuspid aortic valve were present. A pathological study found Gram-negative bacilli in the valvular tissue. After 41 days of intravenous antibiotic therapy, she was discharged with oral levofloxacin for another 10 days. Six months later, she remains in a stable condition.

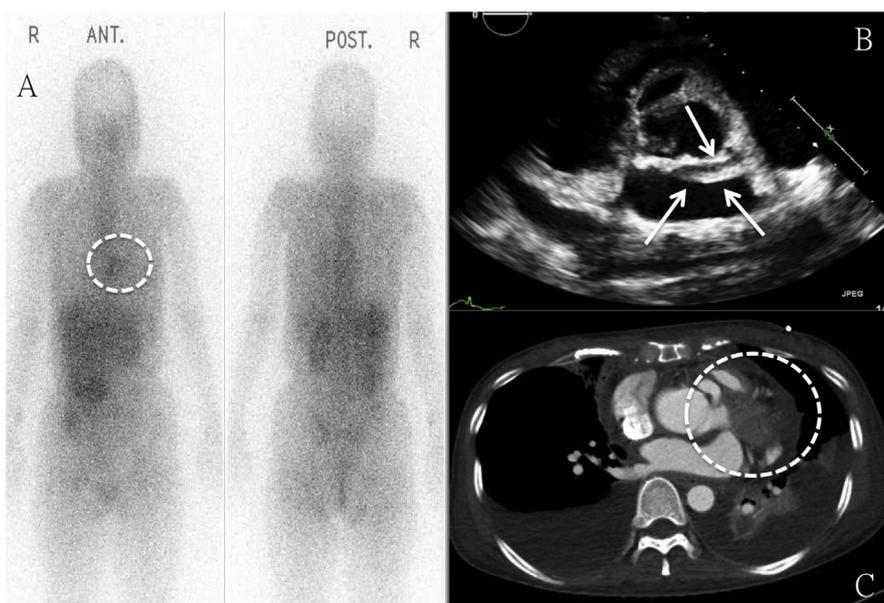


Figure 1. The image findings of a 55-year-old female with aortic valve endocarditis and perivalvular abscess due to nontyphoid *Salmonella*. (A) The inflammation scan shows inflammation around the upper heart (dotted circle). (B) The transesophageal echo shows the bicuspid aortic valve and a perivalvular abscess with a length of approximately two-thirds the aortic root diameter (arrows). (C) Cardiac computed tomography shows periaortic leakage or abscess near the right ventricular outflow tract (dotted circle).

Methods

We conducted a literature review of published cases of typhoid and nontyphoid *Salmonella* (NTS) endocarditis from 1976 onward by searching the PubMed database with the following keywords: “*Salmonella* endocarditis”, “nontyphoid *Salmonella* endocarditis”, and “mural endocarditis due to *Salmonella*”. The cases reported between 1976 and 2002 have been summarized in two review articles with 42 cases reported during 1976–1984,⁴ and 30 cases reported during 1986–2002.¹⁰ They were compared with the cases we reviewed and summarized during the latest period (2003–2014). Furthermore, to identify the role of *Salmonella* species among the causative pathogens of infective endocarditis, we used the keyword “infective endocarditis” to search for relevant articles. Because of the rarity of *Salmonella* species as the etiology of infective endocarditis, we arbitrarily included large case series that involved more than 500 cases in the past 10 years to identify the representative reports for further analysis.

Results

Including our case, we conducted a retrospective analysis of 14 cases (Table 1).^{7,11–22} The mean age was 48 years old, and 57% of patients were female. The NTS species were dominant in 10 cases, which included a case of mural endocarditis. Eight cases involved patients with recognized cardiovascular diseases, but three cases involved patients with no underlying medical disease. Nine patients (60%) received cardiac surgery, and included seven cases of prosthetic valve endocarditis. The overall mortality rate was 13.3%.

During the three periods, there were 87 cases, which includes our case review (Table 2).^{4,10} The review by Fernández Guerrero et al¹⁰ included only NTS cases. The review by Cohen⁴ and our series included endocarditis due to NTS and *Salmonella typhi*/*Salmonella paratyphi*. In general, the mean age was 48–59 years and males predominated (58.6%). Preceding gastrointestinal symptoms were recalled in 27–42% of patients. The most commonly involved cardiac valve was the mitral valve (33.3%), and more than one-fourth (26.4%) of patients exhibited mural endocarditis. The available information on the complications of perivalvular abscess in 43 cases showed that this complication was more commonly found in cases of aortic valve endocarditis (19.0%) than in cases of mitral valve endocarditis (8.7%). The proportion of prosthetic valve endocarditis increased over time and was 46.7% in our review. Among 64 cases of valvular endocarditis, 25 patients (39.1%) required cardiac surgery, and the mortality rate was 39.1% (25/64). The mortality rate of 45 cases of native valve endocarditis was 43.4% (20 patients) and the mortality rate of 19 cases of prosthetic valve endocarditis was 31.6% (6 patients). The difference was not statistically significant ($p = 0.26$).

Among the cases of prosthetic valve endocarditis, patients with valvular surgery and antimicrobial therapy fared better than patients with antimicrobial therapy alone [15.4% (2/13 patients) vs. 66.7% (4/6 patients), respectively; $p = 0.046$]. In our latest case series, no native valve

endocarditis patients died. Excluding patients with incomplete clinical data, medical therapy tended to predict a worse outcome (36.3%, 4/11 patients), compared with cardiac surgery for the cases of valvular endocarditis (15%, 3/20 patients; $p = 0.38$). None of the 10 patients with mural endocarditis survived in the early series, but the mortality rate of later cases declined to 15.4% (2/13 patients). The overall mortality rate of 87 cases was 42.5% (37/87) and decreased over time.

In the past decade, the most common pathogen in 16 studies of infective endocarditis was the *Staphylococcus* species (Table 3).^{23–38} Five studies have listed this common Gram-negative bacillary pathogen rather than HACEK (*Haemophilus* species, *Actinobacillus actinomycesemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, or *Kingella* species).^{26,27,32,35,37} Three studies report the predominance of *Escherichia coli*, which accounted for 0.5–2.0% of all cases. By contrast, *Salmonella* endocarditis was rare, and accounted for less than 0.01% and up to 0.8% of cases in three studies,^{27,32,35} but accounted for 2.9% of 7240 cases in Taiwan.²⁶ Furthermore, the *Salmonella* spp. were the major Gram-negative bacillary pathogens, other than HACEK, that caused native endocarditis. The overall in-hospital mortality rate of these large case series did not vary greatly, and ranged from 10.4% to 24.5% (Table 3); however, no study specifically mentioned the mortality rate of *Salmonella* endocarditis.

Discussion

Based on our review of 1976 to 2014 in the English literature, only 87 cases of *Salmonella* endocarditis were reported, and among 16 large case series, *Salmonella* endocarditis accounted for less than 0.01% and up to 2.9% of bacterial endocarditis cases, which reflects the rarity of cardiac involvement by *Salmonella* species. Of note among the patients with available information, the mean age of disease presentation was in the sixth decade of life. The major affected valves were the mitral valves. Mural endocarditis and perivalvular abscess were noted in nearly one-fourth and one-tenth, respectively, of the cases. The overall prognosis of 87 reported cases of *Salmonella* endocarditis was grave with a mortality rate of 42.5%.

The patient in our reported case was younger than 60 years old, and had a bicuspid aortic valve and diabetes mellitus. These features were compatible with the study findings of the present review. We found *Salmonella* prosthetic valve endocarditis increased with advanced age, and most patients with *Salmonella* endocarditis had preexisting valvular abnormalities. Another common underlying disease of these patients was diabetes mellitus, especially in the NTS group. However, of the five cases of *S. typhi*/*S. paratyphi* endocarditis, three patients had no underlying disease, and their mean age was younger than patients with NTS endocarditis, which is suggestive of the invasiveness of *S. typhi*/*S. paratyphi* infections.

Clinical management of the cardiovascular complications of *Salmonella* infections requires potent antimicrobial therapy with or without surgical intervention. The current standard of practice for a mycotic aneurysm is urgent surgical correction of the infected vessels because of the

Table 1 Clinical characteristics of 14 cases of typhoid and nontyphoid *Salmonella* endocarditis in the English literature between 2003 and 2014

First author/ published year ^{Ref.}	Age (y)/sex	Pathogen	Underlying disease	Involve valve/ prosthesis	Clinical symptoms	Antibiotic	Valvular surgery	In-hospital outcome
Nontyphoid <i>Salmonella</i> infective endocarditis (n = 10)								
Gönen/2004 ¹¹	51/Male	<i>S. enteritidis</i>	Rheumatic fever	MV + AV/Yes	Fever, confusion, diarrhea	PEN + GEN → SAM + CIP	Yes	Alive
Al-Sherbeeni/2009 ¹²	59/Female	<i>Salmonella</i> group B	Rheumatic heart disease, atrial fibrillation, DM	MV/Yes	Fever	CTX	Yes	Alive
Gorki/2009 ¹³	22/Female	<i>Salmonella</i> spp.	Systemic lupus erythematosus, DM	MV/Yes	Fever, heart failure, brain embolism	Yes	Yes	Alive
Kumar/2009 ⁷	69/Male	<i>Salmonella</i> spp.	Cancer, DM	AV/Yes	Fever	Yes	Yes	Dead
	62/Female	<i>S. enteritidis</i>	Rheumatic heart disease, abdominal aortic aneurysm	MV/No	Shock, spleen embolism	Yes	Yes	Alive
Mutlu/2009 ¹⁴	69/Female	<i>S. enteritidis</i>	DM, CAD, aortic stenosis	MV, TV, aortic root/Yes (AV)	Fever, chills	LEV → CRO	Yes	—
Tsugawa/2009 ¹⁵	68/Female	<i>S. enteritidis</i>	DM, end-stage renal disease	AV/Yes	Fever, diarrhea, brain embolism	CRO + CIP + CLN → CIP	Yes	Dead
Yu/2009 ¹⁶	45/male	<i>Salmonella</i> group D	Hypertension, CAD	Mural endocarditis (left ventricular pseudoaneurysm)	Fever, chest tightness	Yes	No	Alive
Clohessy/2012 ¹⁷	75/Female	<i>S. typhimurium</i>	AV block with pacemaker	AV/Yes	Fever, shock	CRO + GEN → CRO + CIP →	Yes	Alive
Our case/2014	55/Female	<i>S. enteritidis</i>	DM, chronic kidney disease	AV/No	Fever, shock	CFP → MER → ERT	Yes	Alive
<i>S. typhi</i> or <i>S. paratyphi</i> infective endocarditis (n = 5)								
Khan/2003 ¹⁸	25/Male	<i>S. typhi</i>	—	AV/No	Fever, palpitations, generalized aches	CRO + AMK → CRO	No	Alive
Wani/2004 ¹⁹	45/Female	<i>S. typhi</i>	—	MV/No	Fever, poor appetite, generalized weakness	AMP + GEN → CRO + AMK	No	Alive
Vaisbein/2006 ²⁰	24/Male	<i>S. paratyphi</i>	—	AV/No	Fever, diarrhea	CRO → GEN	No	Alive
Ozer/2009 ²¹	27/Female	<i>S. typhi</i>	Rheumatic heart disease, pregnancy	AV/No	Fever, anorexia	CTS	No	Alive
Khan/2011 ²²	21/Male	<i>S. typhi</i>	Mitral regurgitation, post repair	MV/No	Fever, diarrhea, dyspnea	PEN + GEN → CRO	No	Alive

AMK = amikacin; AMP = ampicillin; AV = aortic valve; CAD = coronary artery disease; CFP = cefepime; CIP = ciprofloxacin; CLN = clindamycin; CRO = ceftriaxone; DM = diabetes mellitus; ERT = ertapenem; GEN = gentamicin; LEV = levofloxacin; MER = meropenem; MV = mitral valve; PEN = penicillin; *S. enteritidis* = *Salmonella enteritidis*; *S. typhi* = *Salmonella typhi*; *S. typhimurium* = *Salmonella typhimurium*; SAM = ampicillin/sulbactam.

Table 2 Comparisons of clinical cases of *Salmonella* infective endocarditis in the English literature in three periods

Characters	Case number/total case number (%)			
	1976–1984 ⁴ (n = 42)	1986–2002 ^{10,a} (n = 30)	2003–2014 (n = 15) (Present review)	Overall (n = 87)
Mean age (y)	49	59	48	—
Sex, male/total (%)	24/42 (57.1)	21/30 (70.0)	6/15 (40.0)	51/87 (58.6)
Mural endocarditis	10/42 (23.8)	12/30 (40.0)	1/15 (6.7)	23/87 (26.4)
Valvular endocarditis	32/42 (76.2)	18/30 (60.0)	14/15 (93.3)	64/87 (73.6)
Mitral valve	17/42 (40.5)	7/30 (23.3)	5/15 (33.3)	29/87 (33.3)
Ring/perivalvular abscess	1	—	1	2
Aortic valve	14/42 (33.3)	5/30 (16.7)	7/15 (46.7)	26/87 (29.9)
Ring/perivalvular abscess	1	—	3	4
Tricuspid valve	1/42 (2.4)	1/30 (3.3)	0/15 (0)	2/87 (2.3)
≥2 valves	0/42 (0)	5/30 (16.7)	2/15 (13.3)	7/87 (8.0)
Prosthetic valve	3/42 (7.1)	9/30 (30.0)	7/15 (46.7)	19/87 (21.8)
Preceding diarrhea	18/42 (42.9)	9/30 (30.0)	4/15 (26.7)	31/87 (35.6)
Cardiac surgery				
Mural endocarditis	4/10 (40.0)	10/12 (83.3)	0/1 (0)	14/23 (60.9)
Valvular endocarditis	5/32 (15.6)	11/18 (61.1)	9/14 (64.3)	25/64 (39.1)
Mortality rate				
Prosthetic valve endocarditis	1/3 (33.3)	2/9 (22.2)	2/7 (28.6)	5/19 (26.3)
Native valve endocarditis	18/29 (62.1)	2/9 (22.2)	0/7 (0)	20/45 (44.4)
Mural endocarditis	10/10 (100)	2/12 (16.7)	0/1 (0)	12/23 (52.2)
Overall	29/42 (69.0)	6/30 (20.0)	2/15 (13.3)	37/87 (42.5)

^a Only nontyphoid *Salmonella* infective endocarditis is included.

substantial risk of aneurysm rupture and sudden death.⁷ However, the optimal treatment for *Salmonella* valvular or mural endocarditis is not clearly defined. The mortality rate of patients with valvular endocarditis managed by medical therapy alone was higher (27.2%) than patients managed by surgery and medical therapy (15.0%), based on the summary of our case review and the Fernández Guerrero review.¹⁰ In the subgroup with prosthetic valve endocarditis in our review, patients often received surgical interventions and had a better prognosis, which is indicative of a possible survival benefit of surgical intervention. However, we cannot exclude the likelihood that patients with medical therapy alone were too ill to receive cardiac surgery. The role of valvular surgery to treat cases of *Salmonella* endocarditis remains to be confirmed in future case studies with more clinical details of disease severity, comorbidity, and hemodynamic status.

It is noteworthy that more than one-fourth (26.4%) of our cases of infective endocarditis had mural endocarditis with a mortality rate of 52%. By contrast, intracardiac abscess caused by *Staphylococcus aureus* was only noted in 6.9% of 566 episodes of *S. aureus* endocarditis.³⁹ This finding may be related to the avidity of the *Salmonella* spp. to the damaged endothelium, as in the condition of infected aortitis. Such a mural infection may cause ventricular wall rupture, peripheral embolism, and (not surprisingly) high mortality and morbidity.⁴⁰ Therefore, clinicians should be aware of this rare and potentially fatal endovascular complication of *Salmonella* bacteremia.

Concerning the clinical outcome of the published cases, *Salmonella* endocarditis generally exhibits a poor outcome

with an overall mortality rate of 42.5%. However, the mortality rate of *Salmonella* endocarditis decreased over time. Of the recent cases, the overall mortality rate of 13.3% in Table 2 was similar to the mortality rate of 16 clinical studies of bacterial endocarditis in Table 3. The improved outcome may be attributable, at least partially, to the advent of diagnostic modalities, potent antimicrobial therapy, and sophisticated surgical techniques. Of note in Taiwan, NTS isolates were the major Gram-negative bacillary pathogens, other than HACEK, that caused native valve endocarditis. In our previous work, the incidence of NTS-associated hospitalizations in Taiwan was close to that of Spain or Denmark.⁴¹ There are no descriptive epidemiology data of the bacterial endocarditis pathogen distribution in the former two countries, although our review suggests that NTS strains in Taiwan have a more significant role in infective endocarditis. For clinicians in Taiwan, the possibility of infective endocarditis as a complication of NTS bacteremia should be considered.

According to previous studies, the perivalvular abscess in our patient, which is a rare complication of infective endocarditis, may predispose patients to severe valvular dysfunction.^{42,43} The causative pathogens of perivalvular abscess, not surprisingly, were similar to those of infective endocarditis.⁴⁴ Most experts often recommended an early operation to treat perivalvular abscess and prevent complications.^{44,45} To date, no studies have validated the survival benefits of early surgery.⁴⁶ However, physicians should be cautious about the relevant complications of perivalvular abscess such as uncontrolled infection, fistula formation, or circumferential abscess.

Table 3 Summary of 16 clinical studies, which include more than 500 cases of infective endocarditis during the period 2004–2014

First author/ publishing year ^{Ref.}	Study period	Episode number	Methods	Population	Country	Major pathogen (%)	Major non-HACEK GNB pathogen (%)	<i>Salmonella</i> spp. (%)	In-hospital mortality rate, %
Cabell/2005 ²³	—	1516	Database	Native valve	ICE-MD	<i>S. aureus</i> (23.5)	—	—	15.3
Kourany/2006 ²⁴	—	1055	Database	DM/non-DM	ICE-MD	<i>S. aureus</i> (22.9)	—	—	20.3
Delahaye/2007 ²⁵	1998–2000	559	Mail	—	France	<i>Streptococci</i> (46)	—	—	17
Lee/2007 ²⁶	1997–2002	7240	NHI ICD-9	Native valve	Taiwan	<i>Staphylococci</i> (32)	<i>Salmonella</i> spp.	2.9	18
Morpeth/2007 ²⁷	2000–2005	2761	Database	—	ICE-PCS	—	<i>E. coli</i> (0.5)	0.04	17.4 ^a
Durante-Mangoni/2008 ²⁸	2000–2005	2759	Database	—	ICE-PCS	<i>S. aureus</i> (31.4)	—	—	17.4
Shroff GR/2008 ²⁹	1995–2003	831	USRDS database ICD-9	Renal transplanted waiting list	USA	<i>S. aureus</i> (40.9)	—	—	Transplant, 16 Waiting list 18.6
Benito/2009 ³⁰	2000–2005	1622	Database	Healthcare/ Nonhealth care	ICE-PCS	<i>S. aureus</i> (28.2)	—	—	17.3
Murdoch/2009 ³¹	2000–2005	2781	Database	—	ICE-PCS	<i>S. aureus</i> (31.2)	—	—	17.7
Krcmery/2010 ³²	—	606	Database	—	Slovakia	—	<i>P. aeruginosa</i> (1.3)	0.8	15
Fedeli/2011 ³³	2000–2008	1863	Hospital discharge records/ICD9	—	Italy	<i>Staphylococci</i> (42)	—	—	14.3
Leone/2012 ³⁴	2004–2009	1082	Database	—	Italy	<i>S. aureus</i> (21.9)	—	—	15.1
Bor/2013 ³⁵	1998–2009	382153	ICD9	—	USA	<i>S. aureus</i> (28.7)	<i>E. coli</i> (1.7)	<0.01 <i>S. typhi</i>	14.5
Lalani/2013 ³⁶	2000–2006	1025	Database	Prosthetic valve	ICE-PCS	<i>S. aureus</i> (22.3)	—	—	24.5
Ohara/2013 ³⁷	2007–2009	513	CADRE	—	Japan	Viridans streptococci (33.1)	<i>E. coli</i> (2.0)	—	11
Ternhag/2013 ³⁸	1997–2007	7817	Hospital discharge register/ICD10	—	Sweden	—	—	—	10.4 (crude 30-day)

^a 49 patients with non-HACEK Gram-negative bacillary (GNB) infective endocarditis.

CADRE = Cardiac Disease Registration; DM = diabetes mellitus; *E. coli* = *Escherichia coli*; HACEK = *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, or *Kingella* species; ICD9/10 = *International Classification of Diseases-9/10*; ICE-MD = International Collaboration of Infectious Endocarditis Merged Database; ICE-PCS = International Collaboration on Endocarditis Prospective Cohort Study; NHI = National Health Insurance; *S. aureus* = *Staphylococcus aureus*; USRDS = United States Renal Data System.

In conclusion, *Salmonella* endocarditis, although rare, may involve the mitral or aortic valve (i.e., valvular endocarditis) and the cardiac walls (i.e., mural endocarditis) and is associated with a high mortality rate.

Conflicts of interest

None of the authors has any conflicts of interest to declare.

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