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BRIEF REPORT

A Turtle Disaster: *Salmonella enteritidis* Cardiovascular Implantable Electronic Device Infection

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Cardiovascular implantable electronic device (CIED) infections have high mortality and morbidity. CIED infections secondary to gram-negative pathogens are rare, and there are few data regarding their treatment. We report a case of a 60-year-old male who developed recurrent *Salmonella enteritidis* bacteremia leading to CIED infection and nonsusceptibility to ciprofloxacin.

Keywords. antibiotic resistance; combination antibiotic therapy; *Salmonella*.

The incidence of device infections has been increasing in parallel with the rising number of patients with cardiovascular implantable electronic devices (CIEDs) over the past 30 years [1]. The majority (60%–80%) of CIED infections are due to staphylococcal species, with only 5%–9% caused by gram-negative bacteria [1, 2]. There are few data related to the selection of antibiotics for gram-negative CIED infections [1]. In addition, a recent review of >1 million Medicare patients with a CIED found that only 18% of patients with CIED infections had guideline-directed treatment of device removal within 30 days of diagnosis [3]. We present a patient with 3 episodes of *Salmonella* bacteremia associated with CIED infection, review guideline-directed care for CIED infections, and discuss antibiotic selection in gram-negative CIED infections.

Patient Case

A 60-year-old male presented to an outside hospital with malaise, fever, chills, and abdominal pain of unclear origin. His medical history included atrial fibrillation (on warfarin), cirrhosis, diabetes mellitus (well controlled, hemoglobin A1C 6.6%), and an implanted pacemaker. The patient endorsed a distant smoking history but no illicit drug use. For his pacemaker, he had 1 right-sided right atrium (RA) lead implanted in 2014 and 3 abandoned left-sided RA leads implanted between 1998 and 2002. The last device intervention was 4–5 years before admission. The patient also reported living with 3 dogs, 6 ferrets, and 3 turtles.

Upon admission to the outside hospital, blood cultures were collected that grew *Salmonella enteritidis*. Treatment was initiated with ciprofloxacin 750 mg by mouth every 12 hours. An echocardiogram was negative for valve/device lead vegetation. The patient was discharged after 3 days to complete 2 weeks of therapy with ciprofloxacin. Two weeks after completing ciprofloxacin, the patient was readmitted to the same hospital with similar symptoms and again had positive blood cultures for *Salmonella enteritidis*. He was initiated on oral ciprofloxacin 500 mg twice per day and an unknown dose of ceftriaxone. After 6 days, he was discharged on both antibiotics for a planned duration of 8 weeks. Due to concern for drug reaction with eosinophilia and systemic symptoms (DRESS) hypersensitivity syndrome, ceftriaxone was stopped at 6 weeks. Ciprofloxacin was continued for the planned duration of 8 weeks. One day after completing the planned course, the patient was readmitted to the outside hospital with chills, abdominal pain, and a body temperature of 38.5°C. Blood cultures on admission grew *Salmonella enteritidis* resistant to ampicillin but sensitive to ciprofloxacin, meropenem, and cefotaxime. The patient was restarted on oral ciprofloxacin 500 mg twice per day and an unknown dose of meropenem. Repeat blood cultures on days 3 and 4 were negative. A transesophageal echocardiogram (TEE) showed "mobile echodensity attached to the atrial lead of pacemaker suggesting vegetation, vegetation reportedly slightly less than 1 cm." The patient was transferred to a tertiary care center for further management.

Upon admission to the tertiary care center, his body temperature was 36.4°C, blood pressure was 110/63 mmHg, respiratory rate was 20 breaths per minute, and heart rate was 73 beats per minute. The patient endorsed ongoing chills, night sweats, fatigue, and abdominal tenderness. Initial bloodwork revealed a normal white blood cell count of 9.8×10^9/L and other labs within normal limits. The patient was continued on oral ciprofloxacin 500 mg every 12 hours. The following day, infectious diseases (ID) consultation was obtained, and addition of ertapenem 1 g intravenous (IV) daily was recommended by ID consultants.

The patient successfully underwent complete device and lead laser extraction 5 days after admission to the tertiary care center

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and 13 weeks after the initial admission for *Salmonella enteritidis* bacteremia. A TEE during extraction did not demonstrate any valve vegetation. Lead tip cultures collected during extraction, as well as blood cultures collected upon admission, grew *Salmonella enteritidis* resistant to ampicillin, susceptible to meropenem, and now ciprofloxacin intermediate. After extraction, the patient was discharged to complete 6 weeks of ertapenem 1 g daily intravenously. He successfully completed 4 weeks of parenteral antibiotics, following which he was transferred to an outside health system.

DISCUSSION

In 2017, the Heart Rhythm Society (HRS) released guidelines for the management of CIED infections [1]. These guidelines recommend removal of the "device if recurrent or continued gram-negative bacteremia occurs despite appropriate antibiotics" [1]. The recommendation does not require definitive evidence of CIED infection, such as a positive TEE, to remove the device if recurrent bacteremia occurs. While CIED extraction is a significant procedure with rates of major complications around 1.7%, patients with CIED infections have a 7-fold increase in 30-day mortality if the device is not removed [1]. Mortality is further reduced if extraction is completed within 3 days of diagnosis [1]. Studies have found that the rate of relapse with CIED infection is near 100% in patients without device removal, compared with 0%–4.2% in patients who undergo device removal [3]. Device removal is essential but is not often done in a timely manner.

Salmonella endocarditis and CIED infections are rare, with only an estimated 1.8% of endocarditis cases being attributable to non-HACEK gram-negative bacteria with a 1-year mortality of 20%–40% [4, 5]. While *Salmonella* outbreaks have primarily been associated with poultry, eggs, and dietary supplements, transmission can occur from contact with reptiles, amphibians, live poultry, other pets, and pet foods [6]. Turtle-related *Salmonella* outbreaks are a re-emerging public health issue, especially in children [7]. At the time of our patient presentation, the Centers for Disease Control and Prevention (CDC) was investigating a multistate outbreak of *Salmonella* infections related to pet turtles [8]. Eighty-two percent of the patients reported to the CDC in the outbreak had pet turtles with shell lengths <4 inches [8]. It is illegal in the United States to commercially distribute turtles <4 inches long to prevent *Salmonella* outbreaks, as they are the most likely to harbor *Salmonella* [8]. Our patient revealed that one of his turtles was the size of "a silver dollar" and that he had had close physical contact with all the turtles, which were likely the source of his infection.

The 2017 HRS make no specific recommendation for treatment of gram-negative CIED infections beyond selecting therapy from susceptibility testing results [1]. However, for non-HACEK gram-negative endocarditis, the Infectious Diseases Society of America (IDSA) 2015 endocarditis guidelines state that "combination antibiotic therapy with a beta-lactam (penicillins, cephalosporins, or carbapenems) and either an aminoglycoside or fluoroquinolone for 6 weeks is reasonable" [4]. The rationale for initiating combination antibiotics in these patients is to provide appropriate coverage even with the development of drug resistance during prolonged treatment and the possible synergistic effects of antibiotics. The high mortality of disease also suggests that appropriate empiric coverage is critical.

Salmonella species utilize plasmid-mediated resistance mechanisms and have a high proclivity for antibiotic resistance [9]. *Salmonella* CIED infections have been reported twice in the literature [10, 11]. One case reported a *Salmonella* Blockley CIED infection in a 76-year-old man that was ciprofloxacin intermediate [10]. The patient had prompt device removal and was treated with 1 month of beta-lactam monotherapy without incident. The other case described a patient treated with ciprofloxacin monotherapy empirically for a CIED infection due to *Salmonella enteritidis* without device removal [11]. After 4 weeks, the patient had ongoing pocket site symptoms and had device extraction complicated by septic shower. Blood cultures revealed *Salmonella enteritidis,* now resistant to ciprofloxacin. Our patient received prolonged durations of antibiotics, including at least 2 weeks of ciprofloxacin monotherapy without source control, and the *Salmonella enteritidis* became nonsusceptible to ciprofloxacin. This case highlights the ability of *Salmonella* to quickly develop antibiotic resistance and the importance of combination coverage before source control to provide appropriate coverage.

High-quality randomized trials are difficult to conduct given the rarity of this infection. Parra et al. published a prospective observational study of 104 patients with non-HACEK gram-negative endocarditis. They found that treatment with a beta-lactam and fluoroquinolone lowered in-hospital mortality compared with a beta-lactam alone or beta-lactam plus aminoglycoside (odds ratio [OR], 0.29; 95% CI, 0.09–0.96; $P = .043$) [12]. This study did not demonstrate benefit of combination therapy with a beta-lactam and aminoglycoside, which is consistent with other studies [13]. A study by Morpeth et al. found no difference in mortality between patients who received combination antibiotic therapy vs monotherapy [5]. However, a majority of patients were treated with a beta-lactam and aminoglycoside [6]. A single-center retrospective cohort study by Lorenz et al. evaluated a composite outcome of 60-day all-cause mortality, readmission, or recurrence of bacteremia comparing combination and monotherapy in 60 patients with non-HACEK gram-negative endocarditis [14]. There was no difference in the primary composite outcome between the monotherapy and combination therapy groups (62% vs 50%; $P = .36$) [14]. A small retrospective review of 20 patients with

non-HACEK gram-negative endocarditis demonstrated higher 90-day mortality and infection-related readmission in patients who received combination beta-lactam and fluoroquinolone therapy (OR, 4.2; 95% CI, 1.1–15.7; $P = .03$) [15]. While data do not demonstrate the strong benefit of combination therapy, it may be reasonable to initiate in patients with endocarditis infections, especially in those without source control and in those with organisms with higher risk for antibiotic resistance such as *Salmonella*.

Patients with a CIED and bacteremia should be thoroughly assessed for CIED infection. Recurrent gram-negative bacteremia requires device removal, even with a negative TEE for vegetation. For patients with non-HACEK gram-negative endocarditis and CIED infections, combination therapy with a fluoroquinolone and a beta-lactam should be considered before source control.

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