

## Case Report

### **Salmonella-induced pericarditis**

I Wayan Suranadi<sup>1</sup>, I Komang Putra Adnyana<sup>2</sup>, Ni Made Adi Tarini<sup>2,3</sup>

<sup>1</sup> Department Anesthesiology, Pain Management, and Intensive Care, Faculty of Medicine, Universitas Udayana / Prof. dr. I.G.N.G. Ngoerah General Hospital, Denpasar, Indonesia

<sup>2</sup> Clinical Microbiology Department, Faculty of Medicine, Universitas Udayana, Denpasar, Indonesia

<sup>3</sup> Clinical Microbiology Laboratory, Prof. dr. N.G.N.G. Ngoerah Hospital, Denpasar, Indonesia

#### **Abstract**

**Introduction:** *Salmonella*-induced pericarditis (SIP) is a rare complication of *Salmonella* infection, with only 30 cases reported to date, and a mortality rate of 14.8%. It is mostly associated with immunosuppression and can result in complications such as pericardial effusion, cardiac tamponade, and myopericarditis.

**Case Presentation:** A 58-year-old man complained of chest pain, cold sweats, shortness of breath, cough, and a history of fever. Physical and supporting examinations including echocardiography and pericardial fluid culture were positive for *Salmonella* based on VITEK 2 Biomerieux. Based on antibiotic sensitivity testing for therapy selection, the patient received 2 grams of ceftriaxone via intravenous (IV) every 24 hours which was then maximized to 2 grams every 12 hours. Outpatient management was planned after confirming the amount of pericardial fluid, last culture results, and clinical improvement.

**Discussion:** SIP is very rare. These infections are caused by direct spread from intrathoracic foci or hematogenous spread from other sites of infection, including cross-reactivity of infectious antigens with the body's antigens, and/or the presence of infection stimulating host immune reactions. Antimicrobials such as fluoroquinolones and third-generation cephalosporins can be given for 4-6 weeks, especially in immunocompromised individuals or those with spread to extra-intestinal sites.

**Conclusions:** SIP in adult patients with comorbidities and immunocompromised are associated with high morbidity and mortality. Early diagnosis, rational antibiotic therapy, and appropriate surgery provide good prognosis for patients.

**Key words:** Pericardial fluid culture; pericarditis; *Salmonella*; salmonellosis.

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#### **Introduction**

*Salmonella* are gram-negative bacilli that measure 1 to 3µm, are facultatively anaerobic, do not form spores or capsules, and are widely distributed in nature. Various animal reservoirs such as chickens, birds, cats, dogs, pigs, cattle, reptiles, fish, shellfish, and rats can spread this bacterium to humans through contact or contamination. *Salmonella* are motile and infect a wide range of hosts through fecal-oral transmission [1,2]. The Centers for Disease Control and Prevention (CDC) estimates that *Salmonella* causes more than 1 million infections and more than 20,000 hospitalizations in the United States. There are more than 2,500 *Salmonella* serotypes, and about 20 of them are most commonly associated with human infections [3,4].

Salmonellosis is classified as typhoidal or nontyphoidal. Nontyphoidal *Salmonella* infections generally present as gastroenteritis after consuming contaminated food (usually poultry, eggs, and dairy products), and are the leading cause of diarrhea worldwide [5,6]. In the United States, nontyphoidal

salmonellosis is one of the leading causes of foodborne illness, with *Salmonella enteritidis*, *Salmonella newport*, and *Salmonella typhimurium* being the most commonly isolated serotypes from these cases as well as in Asia [7,8]. Extra-intestinal manifestations of *Salmonella* are known to occur, including endocarditis, mycotic aneurysms, visceral abscesses, and osteomyelitis. Although rare, purulent pericarditis associated with cardiac tamponade can be found in cases of this infection [9].

Pericarditis is an inflammatory disease of the pericardium, which can be caused by infectious or noninfectious causes. It is the most common pericardial disease worldwide with 27.7 cases per 100,000 people per year [10]. Classic clinical manifestations include sharp chest pain that feels like stabbing, pericardial friction noise, wide ST elevation and PR depression on electrocardiogram, and pericardial effusion seen on echocardiogram [11–13]. Tuberculosis as an etiology accounts for 70% of pericarditis cases in developing countries with a high prevalence of tuberculosis.

However, tuberculosis is much less common in developed countries, accounting for less than 5% of all cases. In developed countries, 80-90% of cases are idiopathic after extensive diagnostic workup, and most are believed to be viral in etiology [14,15]. Other identified etiologies include malignancy, systemic inflammatory disease, pericardial injury, and purulent/bacterial pericarditis. Of the small number of patients who developed pericarditis with purulent or bacterial etiology, *Salmonella* was responsible for only a few cases [8,13].

*Salmonella*-induced pericarditis (SIP) is a rare complication of *Salmonella* infection, with only about 30 cases reported to date, with a high mortality rate in these cases [8]. *Salmonella typhimurium* is the most common cause of SIP [7,8]. Pericarditis can manifest with pericardial effusion, tamponade, and myopericarditis, with most patients with *Salmonella* pericarditis being immunosuppressed [9,11]. If there is a high clinical index of suspicion for the disease, early diagnosis and appropriate surgical and medical treatment, as well as appropriate antimicrobial selection, are recommended, so that there is a high chance of achieving a good recovery. Treatment for pericarditis involves the use of anti-inflammatory drugs, and if the patient has bacterial pericarditis, then antibiotic therapy sensitive to the organism identified through culture and sensitivity testing is required. There are no definitive guidelines for the duration of therapy, but a duration of 2 to 4 weeks is considered [9,16,17].

Extra-intestinal manifestations of *Salmonella* are rare, so it is important to determine how the infection spreads outside the gut while considering individual risk factors. In this report, the authors present a rare case of pericarditis caused by *Salmonella* spp. A 58-year-old man presented with chest pain, cold sweats, shortness of breath, cough, and a history of fever. A thorough analysis of the patient's medical history, microbiological diagnosis procedures, drug sensitivity tests, and treatment process was conducted. In addition, relevant literature related to this topic was reviewed and discussed. Through this case presentation, it is hoped that future clinicians can more quickly recognize the possibility of pericarditis caused by *Salmonella* to promote appropriate, effective, and efficient management.

### Case Report

A 58-year-old male patient was referred to a tertiary hospital for further treatment, with diagnoses of circumferential pericardial effusion, acute decompensated heart failure profile B due to unstable

angina pectoris, acute kidney injury stage I, and community-acquired pneumonia. The patient complained of chest pain one day before admission, the pain was felt and worsened two hours before admission. Chest pain felt heavy and penetrated to the back and was accompanied by cold sweat, complaints of shortness of breath were also felt which improved with a sitting position. The cough was experienced two days before admission and a history of fever for one day before admission. During treatment at the previous hospital, the patient was given aspirin 160 mg per oral (PO) initial dose and 80 mg PO continuation, clopidogrel 300 mg initial dose and 75 mg oral continuation, atorvastatin 40 mg PO, lovenox 0.6 mL subcutaneously, bisoprolol 2.5 mg PO, isosorbide dinitrate 5 mg PO, levofloxacin 750 mg IV, acetylcysteine 200 mg PO, and nebulization with ipratropium bromide/albuterol and budesonide. Past medical history was unknown, and the patient smoked 3 packs of cigarettes per day.

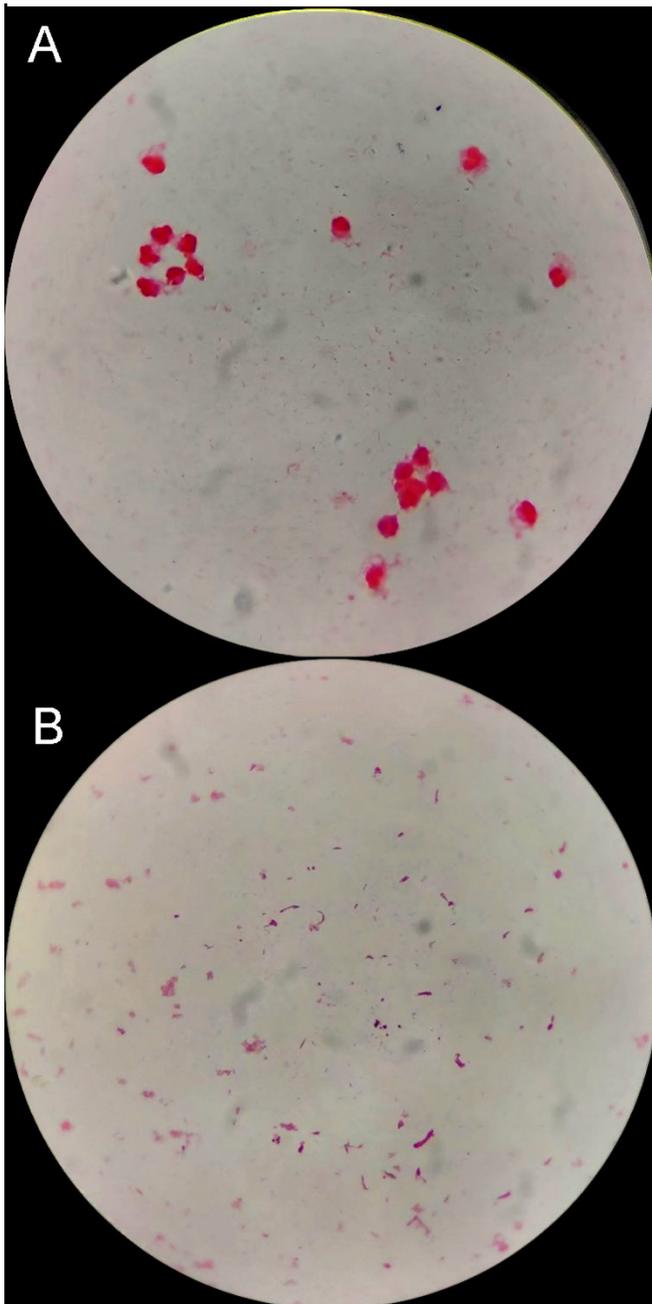
On physical examination, the patient appeared whimpering with the Glasgow Coma Scale (GCS) E4V5M6, looking weak. The patient's vital signs were obtained temperature 36.2°C, blood pressure 101/61 mmHg, respiration 22 times per minute, oxygen saturation 98% with nasal cannula 2 liters per minute. The general status examination found that the sound of both lung fields was vesicular, and minimal rhonchi and wheezing were found in both lung fields. Furthermore, venous blood was taken for complete blood examination, pericardial fluid analysis, and at the same time pericardial fluid culture examination. Complete

**Figure 1.** Anteroposterior thorax radiograph showing cardiomegaly with all chamber dilatation configuration with differential diagnosis of pericardial effusion, pulmonary edema, pneumonia, and bilateral pleural effusion.



blood laboratory results found a white blood cell count of  $17.81 \times 10^3/\mu\text{L}$  with neutrophils of 86.30%. Liver function was found within normal limits with SGOT 13 U/L and SGPT 18 U/L. Renal function was found to have increased with BUN 35.6 mg/dL and serum creatinine 2.27 mg/dL. Pleural fluid analysis results obtained large number of cells with 25,231 leukocytes/ $\text{mm}^3$  with 1.7% mononuclear leukocytes,

**Figure 2.** Direct gram examination results on pericardium fluid specimen L91 (A) showed leukocytes (3+) but no germs, while indirect gram examination results on pericardium fluid specimen L91 (B) showed the presence of gram-negative bacilli *Salmonella* spp. (Gram staining, 100 $\times$ ).



polymorphonuclear leukocytes domination 98.3%, positive Rivalta test, low total protein 6 g/dL, hypoalbuminemia 3.2 g/dL, and low glucose 51 mg/dL. The Procalcitonin examination was found to be elevated at 31.1 ng/mL.

Anteroposterior (AP) thorax photo examination revealed cardiomegaly with all chamber dilatation configurations with differential diagnosis of pericardial effusion, pulmonary edema, pneumonia, and bilateral pleural effusion (Figure 1). The Echocardiography examination showed moderate circumferential pericardial effusion with the largest diameter of 1.3 cm in the lateral LV, swinging heart (+). PCR examination of TB in pericardial fluid was performed on the second day of treatment, with negative results. On the first day of treatment, the patient was given empirical antibiotic therapy ceftriaxone 2 grams intravenously every 24 hours and azithromycin tablets 500 mg PO every 24 hours.

Indirect gram staining of the pericardium fluid specimen showed gram-negative bacilli, with a positive time of 19 hours and 4 minutes (Figure 2). Then the specimen was incubated in an  $\text{O}_2$  incubator from 35°C to 37°C and showed positive results before 24 hours of incubation. The specimen was then inoculated onto MacConkey and blood agar culture media. There was growth of one type of bacterial colony on blood agar culture media and MacConkey media after the plate was incubated in an  $\text{O}_2$  incubator at 35°C to 37°C 5% for 24 hours. On blood agar media, one type of round white non-hemolytic colony was obtained up to quadrant III, while on MacConkey media, one type of round non-lactose fermenter colony was obtained up to quadrant I (Figure 3). The colonies were each subjected to indirect gram examination. The colonies were each subjected to indirect gram examination and the results consistently showed the findings of gram-negative rod bacteria (Figure 4). The L91 pericardium fluid culture results concluded the presence of *Salmonella* spp.

Identification and antibiotic sensitivity tests were performed using the VITEK 2 Biomerieux automated bacteriology identification system, using the GN 93 cassette. *Salmonella* spp. identified with 96% probability showed sensitivity to ampicillin, ampicillin/sulbactam, piperacillin/tazobactam, cefixime, cefoperazone, ceftazidime, ceftriaxone, cefoperazone/sulbactam, cefepime, aztreonam, ertapenem, meropenem, tigecycline, trimethoprim/sulfamethoxazole. and resistant to cefazolin, cefuroxime, amikacin, and gentamicin.

Based on the results of the antibiotic susceptibility test, the patient was then advised to continue definitive

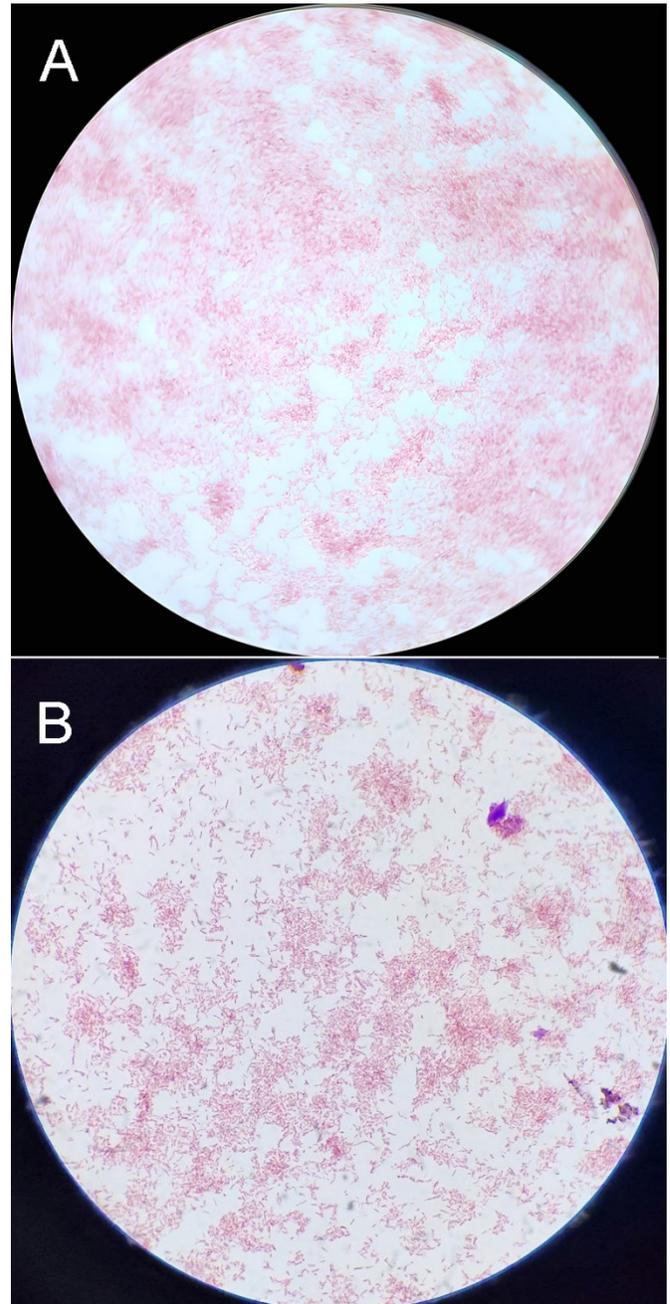
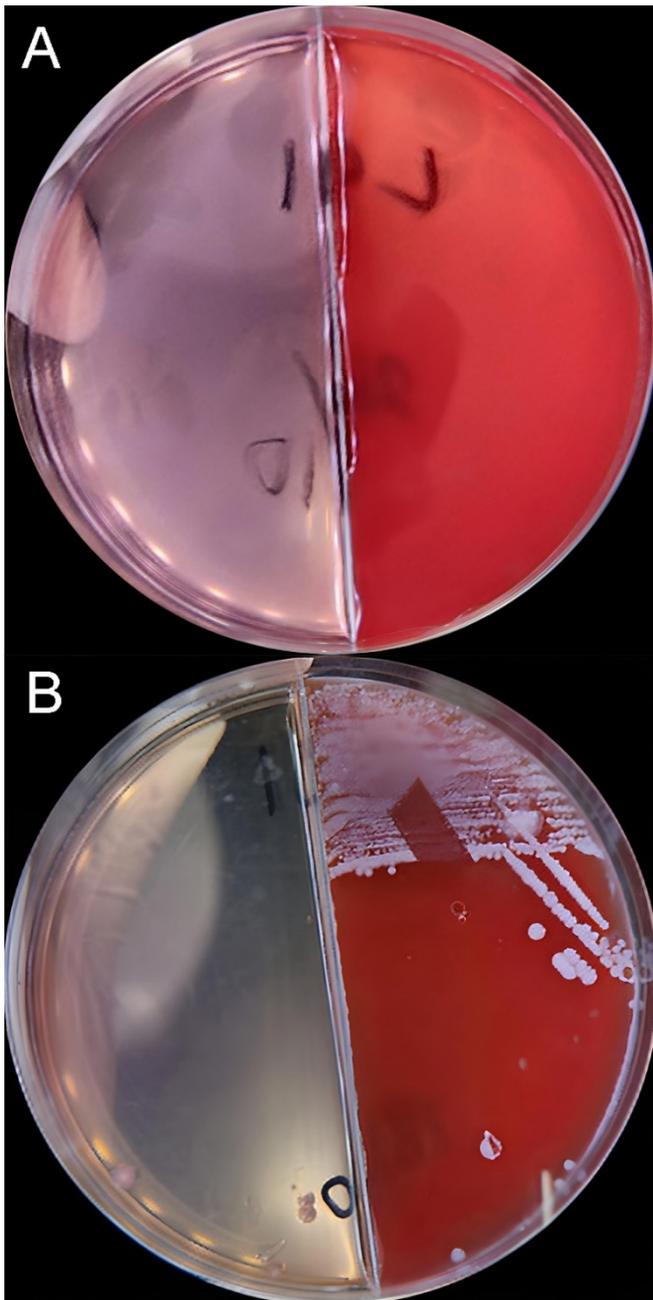
antibiotic therapy ceftriaxone injection and discontinue the use of azithromycin antibiotics. Then the clinician who treated the patient continued to give ceftriaxone antibiotic injection of 2 grams every 24 hours, but after giving antibiotic therapy with this dose for one week, the amount of pericardial fluid production increased to

more than 300 cc per 24 hours, and the color was increasingly cloudy and clinically the patient was still complaining of shortness, chest pain and still accompanied by coughing.

After a team meeting, it was agreed that the patient would be given ceftriaxone 2 grams of antibiotics intravenously every 12 hours. The patient was planned to have a procalcitonin recheck, and a pericardiectomy was planned if the amount of pericardial fluid increased. After being given therapy, pericardial fluid

**Figure 3.** Examination results on blood agar and MacConkey media; pericardium fluid specimen L91 direct (A) showed no colony growth, while pericardium fluid specimen L91 indirect (B) showed growth of round, non-lactose fermenter colonies up to quadrant I on MacConkey media, as well as round, white, non-hemolytic colonies up to quadrant III on blood agar media, this corresponds to *Salmonella* spp.

**Figure 4.** The results of indirect gram examination on colonies growing on blood agar (A) and MacConkey (B) media consistently show the findings of gram-negative rod bacteria.



production became 13 cc per 24 hours and progressively decreased to nothing, with the results of L2 pericardial fluid culture still containing *Salmonella* spp. Antibiotic therapy was continued until day 21 when the patient experienced clinical improvement, the last L50 pericardial fluid culture showed no colonies, and then the patient was declared cured and allowed to go home, and advised to control back to the polyclinic.

## Discussion

*Salmonella* is a fecal-oral zoonosis spread through water and food and belongs to a genus of gram-negative bacteria in the *Enterobacteriaceae* family related to *Escherichia* and *Shigella* [1,2]. Salmonellosis is classified as typhoidal or nontyphoidal. Nontyphoidal *salmonella* is a major cause of gastroenteritis that is generally self-limited but can have extra-intestinal manifestations, including septicemia, acute endocarditis, osteomyelitis, meningitis, vascular infections, and rarely pericarditis [9]. A review of previous literature found only one case of *Salmonella* Dublin pericarditis, diagnosed in 1990, suggesting that *Salmonella* pericarditis is a very rare condition [8]. The transmission mode of this bacterium starts from the ingestion of contaminated water or undercooked food products, meat, and vegetables. In addition, cookware used to process contaminated meat can spread the bacteria to other foods. Transmission can also occur directly from one individual to another via the fecal-oral route, or from direct contact with infected animals [1,3,4].

The pathogenesis of pericarditis caused by *Salmonella* remains unclear. Infection of the pericardium by this bacterial organism is caused by direct spread from intrathoracic foci or hematogenous spread from other sites of infection. It has been generally described that infection with bacteria, fungi, parasites, viruses, or other unknown causes can lead to two pathophysiologic pathways, namely cross-reactivity of infectious antigens with the body's antigens as well as the presence of infection stimulating host immune reactions [8,10,13]. Then these two mechanisms cause inflammation of the tissue sac surrounding the heart called pericarditis. In this condition, there can be an increase in inflammatory acute phase reactants, including ESR, CRP, and WBC. The inflamed/irritated visceral and parietal pericardium rub against each other, and then the chest wall comes into contact with the inflamed pericardium when lying down or from chest volume expansion during inspiration, resulting in clinical manifestations of pleuritic chest pain (pain during inspiration and when

supine). The inflammation also causes the pericardial tissue with abrasive texture to make audible sounds when the heart beats and friction occurs, giving rise to the triphasic friction rub heard during auscultation (i.e. during atrial contraction, ventricular contraction, and diastolic filling). Inflammation of the pericardium may extend to the myocardium causing extensive inflamed myocardium, resulting in elevated cardiac markers (elevated troponin I and T), as well as altered ventricular repolarization in the form of diffuse ST elevation in multiple ECG leads. Inflammatory cells and serum accumulate in the pericardial space causing an increase in pericardial fluid in the space (pericardial effusion), further fluid may accumulate due to pressure (rare), putting pressure on the underlying heart resulting in cardiac tamponade. The pericardium may also thicken or scar with fibrosis after inflammation resulting in constrictive pericarditis [13,18,19].

Cardiovascular salmonellosis is a very rare extra-intestinal manifestation that can present as endocarditis, myopericarditis, or endovascular infection. Patients with nontyphoidal *Salmonella* pericarditis generally have immunosuppressive conditions, and patients who develop endovascular infection with bacteremia are generally older and have underlying conditions similar to the patient in this case report [8]. Previous studies have studied important risk factors that predispose individuals to *Salmonella* bacteremia in sub-Saharan Africa, namely patients with HIV, infants, and young children with malaria, anemia, and severe malnutrition leading to an immunocompromised state [20,21]. Studies have also largely suggested that an immunosuppressed state with relative underlying disease or immunotherapy may predispose to some of these disease-related comorbid conditions [8,20,21]. Other risk factors include individuals in frequent contact with poultry (farmers) known to contain *Salmonella* species, as well as alcohol and tobacco abuse including smoking [9]. Other important predisposing factors for the development of pericarditis include pre-existing pericardial effusion with uremia or a history of thoracic surgery [8,20,21]. The patient in this case report was elderly and had underlying illnesses of heart failure and community-acquired pneumonia, thus possible risk factors were the patient's immunosuppressed/immunocompromised state, as well as a history of smoking.

*Salmonella* pericarditis often presents with cardiovascular or pulmonic symptoms similar to other etiologies of pericarditis, such as sharp chest pain, and pleuritis, and may have pericardial friction rub on examination, although not always as in this case report.

Patients may present with fever; however the absence of fever does not exclude a bacterial source. All patients should undergo history taking, physical examination, and supporting investigations including electrocardiogram (ECG), thorax photograph, complete blood count, troponin level, erythrocyte sedimentation rate, C-reactive protein level, and echocardiography. ECG changes characteristic of pericarditis are rare in *Salmonella* pericarditis [12,13]. Laboratory examinations are generally characterized by exudate, polymorphonuclear leukocyte predominance, and lactate dehydrogenase, as well as low glucose from pericardial effusion [8,10,13], which are similar results in this case report. Follow-up ECG and hemodynamic assessment are essential to suspect pericardial effusion in patients presenting with nonspecific symptoms and *Salmonella* bacteremia. In addition, the diagnosis was based on an echocardiogram, which helped to rule out vegetation, effusion, and cardiac tamponade. TB PCR was also performed in this patient to rule out the differential diagnosis of tuberculosis, as *Mycobacterium tuberculosis* is still high in developing countries and should be suspected as another etiology in this case [8,13,16].

Clinical recovery involves aggressive therapy, including immediate pericardiectomy and appropriate antibiotic treatment according to culture results and antibiotic sensitivity testing. Culture examination of this bacterium generally results in pale colonies that do not ferment lactose on MacConkey agar, and black nucleated pale colonies on tellurite-containing media (e.g. on *Salmonella*-Shigella agar) due to H<sub>2</sub>S production [6,22]. These results are consistent with the findings of the culture examination in the case. Antimicrobial therapy for *Salmonella* involves fluoroquinolones and third-generation cephalosporins. Guidelines suggest the first-line antibiotics for these cases are ampicillin ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, cefotaxime, or ceftriaxone [23]. Previous studies suggest third-generation cephalosporins are the most commonly prescribed antimicrobial therapy, with 92% of cases surviving on antimicrobials alone or with additional surgical intervention [9]. The recommended dose of ceftriaxone is 2 grams intravenously every 24 hours, with the duration of therapy varying from 14 days in healthy patients without extra-intestinal focal infections to 4-6 weeks in individuals who are immunocompromised or have spread to extra-intestinal sites (e.g., grafts, hardware, abscesses, endocarditis, bone infections) [8,24]. However, the therapy for one week did not make a difference, even causing the

amount of pericardial fluid production to increase, the color became cloudy and the patient's clinical condition did not improve. So based on clinical considerations, therapeutic doses in previous similar studies [9], and through team meetings, the patient's antibiotic therapy was continued with a maximized dose, namely ceftriaxone 2 grams intravenously every 12 hours for 21 days. This therapy gave good results judging from the patient's clinical and the last pericardial fluid culture results which showed no colonies, so the patient was declared cured.

A recent systematic review and meta-analysis showed complications are common in individuals with invasive nontyphoidal *Salmonella* disease, and approximately 15% of patients die. Previous case reports of *Salmonella* pericarditis showed a high mortality rate. A review in 2020 conducted a comparative analysis of *Salmonella* pericarditis cases and found a mortality rate of 14.8% [25]. Rapid diagnosis and management decisions, including empirical antimicrobial therapy, can improve patient outcomes. In addition, investment in improved clinical microbiology facilities to identify nontyphoidal *salmonella* and research efforts towards vaccine development and other preventive measures will prevent nontyphoidal *salmonella* invasive disease and consequent mortality [9,26].

## Conclusions

This case report discussed pericarditis caused by *Salmonella spp.* in a 58-year-old man, which is a rare case. However, morbidity and mortality are significant, and early recognition and efficient treatment of this bacterial infection are important. The diagnosis was made through history taking, physical and supporting examination, including the results of pericardial fluid culture, antibiotic sensitivity test, and echocardiography. The selection of appropriate and wise antibiotic therapy should be carried out according to the guidelines and adjusted to the culture results, besides that routine monitoring is still needed to determine the response of the therapy given to the patient. By presenting this case, it is hoped that clinicians will gain more insight into the clinical presentation, diagnosis, and management of pericarditis caused by *Salmonella spp.* so that they can provide appropriate, effective, and efficient management for patients with similar conditions in the future.

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### Ethical Clearance

The authors have secured informed consent from patient regarding this case report.

### Authors' contributions

I Wayan Suranadi contributed to the study conception and design and drafted the manuscript; I Komang Putra Adnyana and Ni Made Adi Tarini revised the manuscript critically for important intellectual content.

### Corresponding author

DR. dr. I Wayan Suranadi, Sp.An-TI, Subsp.TI (K)  
Department of Anesthesiology, Pain Management, and Intensive Care, Faculty of Medicine  
Universitas Udayana/Prof. dr. I.G.N.G. Ngoerah General Hospital  
Email: wayan.suranadi@unud.ac.id

### Conflict of interests

No conflict of interests is declared.

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