Epidemiologic and clinical profiles of bacterial myocarditis. Report of two cases and data from a pooled analysis

P. Ferrero, I. Piazza, L.F. Lorini, M. Senni

*Corresponding author.
E-mail address: pferrero@asst-pg23.it (P. Ferrero).

ARTICLE INFO

Article history:
Received 3 January 2020
Accepted 19 April 2020
Available online 27 April 2020

Keywords:
Myocarditis
Bacterial
Sepsis
Diagnosis
Epidemiology

ABSTRACT

We aimed to characterize the epidemiology, diagnostic peculiarities and outcome determinants of bacterial myocarditis. Two cases from our institution and literature reports were collected ending up with a total of 66 cases. In 37 (56%) patients, the diagnosis was confirmed by magnetic resonance and histopathological criteria. The other patients were classified as having possible myocarditis. Only occurrence of rhythm disturbances was associated with the specific diagnosis of myocarditis (p = 0.04). Thirty-two (48%) patients presented with severe sepsis that was associated with a worse prognosis. At multivariate analysis, left ventricular ejection fraction (LVEF) at admission and heart rhythm disturbances were associated with incomplete recovery (odds ratio (OR) 1.1, 95% CI 1.03–1.2, p = 0.004 and OR 6.6, 95% CI 1.35–32.5, p = 0.02, respectively).

In summary, bacterial myocarditis is uncommon. Most commonly, it is secondary to septic dissemination of bacteria or to transient secondary myocardial toxicity.

1. Introduction

Myocarditis is an inflammatory disease of the myocardium diagnosed by established histological, immunological and immunohistochemical criteria. The most frequent cause of myocarditis, especially in Europe and North America, is viral infections such as enterovirus, adenovirus, influenza virus, human herpes virus and parvovirus. However, cases of bacterial myocarditis can also be found in clinical practice and reported in the literature. Bacterial etiology is uncommon, and the clinical presentation and course can overlap with aspecific left ventricular dysfunction secondary to sepsis.

In western countries, the most common bacterial causes of myocarditis are Staphylococcus aureus and Streptococcus spp. infection, although myocardial infections associated with a broad range of bacterial pathogens have been described. However, the actual etiology often remains undetermined because of the limited access to endomyocardial biopsy in clinical practice.

The primary objective of this study was to review the epidemiology of this uncommon condition, with a particular focus on the different bacterial species involved in myocardial injury and the respective typical clinical presentation. Overwhelming sepsis is usually associated with myocardial depression and heart failure, eventually leading to secondary cardiogenic shock, without specific diagnostic criteria suggesting the diagnosis of myocarditis. The secondary objective was to explore clinical phenotype differences among patients with suspected or proved myocarditis, presenting with or without severe sepsis and/or septic shock. We have included in the series two cases of acute bacterial myocarditis from our institution secondary to Streptococcus pyogenes and Escherichia coli infection, respectively.

2. Case description

2.1. Case A

A previously healthy 35-year-old male, with a 2-day history of fever (39 °C) after an accidental left knee trauma with swelling, presented to the emergency department due to severe chest pain and dizzy spells. His blood pressure was 80/50 mmHg, and his heart rate was 108 bpm. The echocardiography showed severe left ventricular dysfunction (LVEF 10–15%), and the first ECG revealed sinus tachycardia and infero-lateral ST-elevation. He entered the intensive care unit (ICU) for hemodynamic support and empirical antibiotics. The blood cultures showed growth of Streptococcus pyogenes. A myocardial biopsy was performed, and revealed bacterial myocarditis with focal nonsuppurative inflammation and interstitial edema. The patient was treated with intravenous beta-lactams and the clinical condition improved over the next few days.
was admitted to the cardiac intensive care unit due to progressive hemodynamic deterioration and lactic acidosis, requiring inotropic support with adrenaline uptitrated to 0.1 mcg/kg/min, fluid resuscitation and intravenous antibiotics (Ampicillin/Sulbactam). Peak C reactive protein (CRP), procalcitonin and troponin I levels were 38 mg/L (normal <1), 60 ng/mL (normal <0.05) and 49 ng/mL (normal <0.07 ng/mL), respectively. On the second day, the LVEF improved to 45%. After 4 days, left knee arthrocentesis was performed, and cultures were positive for *S. Pyogenes*. QRS fragmentation in DIII, aVI, aVL and V1 (Fig. 1A and C) appeared after 48 h, which was consistent with late gadolinium enhancement (LGE) on cardiac magnetic resonance (CMR) imaging involving the inferior/lateral area of the left ventricle (Fig. 1A). The patient clinical status progressively improved, and he was discharged on day 16. Treatment with low-dose angiotensin-converting enzyme inhibitor (ACE-I) was started. No beta-blockers were administered due to a tendency toward sinus bradycardia. At the 3-months follow-up, left ventricular function had normalized. CMR imaging after 12 months showed almost complete resolution of LGE.

### 2.2. Case B

A previously healthy 51-year-old female, admitted due to a right ureteral stone with hydronephrosis, underwent ureteropellography and stone removal. After a few hours, she developed a temperature up to 40 °C, hypotension (80/50 mmHg) and tachycardia (120 bpm), consistent with severe sepsis. Echocardiography revealed a LVEF of 40% with antero-septal hypokinesis, and the ECG showed anterolateral ST-elevation. The patient was admitted to the

![Fig. 1. Panel A: First case, cardiac magnetic resonance imaging showing late gadolinium enhancement. Panels B and C: ECG showing QRS fragmentation. Panel D: Second case, cardiac magnetic resonance imaging showing late gadolinium enhancement. Panel E: ECG showing QRS fragmentation.](image-url)

![Fig. 2. Flowchart summarizing the screening and inclusion of relevant papers.](image-url)
| Author                  | Ref Year | Bacterial                                       | Gender | Age (years) | Clinical presentation | Chest pain | CRP peak (mg/L) | ECG | Arrhythmias | RQRS | CMRI | EF at admission (%) | EMB/Autopsy | ICU | Complete recovery | Partial recovery | Death | Associated conditions | Diagnosis       |
|-------------------------|----------|-------------------------------------------------|--------|-------------|-----------------------|------------|----------------|-----|--------------|------|------|---------------------|-------------|------|-------------------|-----------------|--------|---------------------|-----------------|
| Case 1                  | 2019     | Streptococcus pyogenes                         | M      | 34          | Fever + + 38 700     | ST-elevation | 0 + + 15       | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Septic arthritis    | Probable        |
| Case 2                  | 2019     | *Escherichia coli*                             | F      | 51          | Fever + + 30 1614    | ST-elevation | 0 + + 30       | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Urinary tract infection | Probable        |
| Sikary et al.           | 2016     | Streptococcus pyogenes                         | F      | 7           | Fever, Resp 0 - - -  | VT          | - - -          | +   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Erysipelas           | Probable        |
| Ozkaya et al.           | 2005     | Streptococcus pyogenes                         | F      | 35          | Fever, Resp, Rash    | + + - -     | VT             | - - - | + + 0       | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Definite             |                |
| Dominguez et al.        | 2013     | *B-hemolytic streptococcus*                    | M      | 46          | Fever, Rash 0 - 550  | ST-elevation | AV block - +  | 60   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Pneumonia            | Probable        |
| Lee et al.              | 2004     | *Salmonella enteritidis*                       | M      | 41          | Fever, Resp + + 8    | ST-elevation | AV block + + | 45   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Definite             |                |
| Khan et al.             | 2007     | *MRSA*                                          | M      | 41          | Fever, Resp - - -    | ST-elevation | AV block + +  | 45   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Purpura               | Possible        |
| Elias et al.            | 2008     | *MSSA*                                          | M      | 45          | Fever + + 160        | ST-elevation | VT             | - - - | + + 0       | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Buoné et al.            | 2018     | Neisseria meningitidis                         | M      | 16          | Fever, Rash + + - 1071 | ST-elevation | 0 - + 35       | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Gawalkar et al.         | 2017     | Neisseria meningitidis                         | M      | 17          | Fever, Resp 0        | Ripolarization abn. | 0 - - 30 | 0 + + 0       | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Al Shamlkhani et al.    | 2015     | *Salmonella enteritidis*                       | M      | 28          | Fever, GE 287 225    | ST-elevation | 0 + - 55      | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Childs et al.           | 2012     | *Salmonella enteritidis*                       | F      | 16          | Fever, GE 206 1071   | Ripolarization abn. | 0 0 - 47  | 0 + + 0       | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Villalbanca et al.      | 2015     | *Salmonella berta*                              | M      | 19          | Fever, GE + + 556    | ST-elevation | 0 + + 40       | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Aqeeq et al.            | 2009     | *Salmonella typhi*                              | M      | 34          | Fever, GE + + 98     | Ripolarization abn. | 0 + - 23  | 0 + + 0       | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Türoff et al.           | 2008     | *Salmonella typhi*                              | F      | 42          | Fever, GE, Rash + + 39.27 | Ripolarization abn. | 0 - - 40  | 0 + + 0       | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Komuro et al.           | 2018     | *Escherichia coli*                              | F      | 69          | Fever + + 8          | ST-elevation | AV block 0 - 31 + + 0 | 0    | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Coronaropathy         | Definite        |
| Gentile et al.          | 2010     | *Escherichia coli*                              | M      | 65          | Fever + + - 170      | Ripolarization abn. | 0 + - 58  | 0 + + 0       | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Chen et al.             | 2010     | *Escherichia coli*                              | F      | 25          | Fever, GE + + 388    | ST-elevation | 0 - + + 40    | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| De Cock et al.          | 2012     | Campylobacter jejuni                           | M      | 42          | Fever, GE + + 116    | ST-elevation | 0 - + + 40    | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Pena et al.             | 2006     | Campylobacter jejuni                           | M      | 16          | Fever, GE + + 398    | ST-elevation | 0 - - + + 0    | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Aeromonas hydrophila  | Definite        |
| Kushawaha et al.        | 2013     | Rickettsia rickettsii                          | M      | 26          | Fever, Rash + + - 3  | Normal       | 0 - - 20       | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Wilson et al.           | 2012     | Rickettsia australis                           | F      | 52          | Fever, Rash + + - 990 | ST-elevation | 0 - - 20     | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Roch et al.             | 2008     | Rickettsia africae                            | F      | 74          | Fever, Rash + + -     | ST-elevation | 0 - - 35       | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Zou et al.              | 2016     | *Klebsiella pneumoniae*                        | M      | 66          | Fever + + 67         | ST-elevation | 0 + - 45       | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Liver abscess        | Probable        |
| Chuang et al.           | 2012     | *Klebsiella pneumoniae*                        | M      | 52          | Fever, Resp + + - 3  | Idioventricular rhythm | 0 - - 50  | 0 + + 0       | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable             |                |
| Ladani et al.           | 2015     | Listeria monocytogenes                         | M      | 47          | Fever, Resp + + - 24  | ST-elevation | VT + + 35      | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Probable implantation | Definite        |
| Haddad et al.           | 2007     | Listeria monocytogenes                         | F      | 49          | Fever + + 53         | -           | 0 - - 12       | 0   | 0           | 0    | 0    | 0                   | 0            | 0    | 0                 | 0               | 0      | Definite             |                |
cardiac intensive care unit and intubated; her clinical conditions improved after fluid administration and noradrenaline infusion. Her TnI peak was 113 ng/mL (normal < 0.07 ng/mL), CRP was 30 mg/dl (normal < 1), and white blood count was 18,000/mm³. Blood cultures were positive for E. coli, and treatment with intravenous Cefotaxime was started. After 2 days, her clinical status improved and she was extubated. Coronary angiography excluded significant pathology. CMR imaging (Day 5) revealed LGE enhancement involving the antero-septal and inferior regions of the left ventricle, that roughly correlated with ECG fragmentation in DIII and aVL (Fig. 1D and E). The patient was discharged on day 21 and instructed to take an ACE-I, beta-blocker and spironolactone. CMR performed 6 months later showed a partial reduction of the LGE areas and left ventricular function improvement (LVEF 45%). The ECG at the 6-months follow-up was not normalized, with persistence of QRS fragmentation and T inversion in the anterolateral leads.

3. Materials and methods

We performed a systematic literature search for all reported cases of bacterial myocarditis from 2000 to 2018. A literature search in PubMed using “Bacterial” and “myocarditis” as keywords, limiting the results to humans and studies in the English language, was conducted.

Papers fulfilling the following criteria were included: case report or case series; inclusion of patients with at least one positive blood, stool and/or tissue culture; availability of information about ECG, serum cardiac markers (troponin) and ventricular function. The following variables were retrieved from each paper: bacterial etiology, gender, age, clinical presentation (fever with or without rush, respiratory or gastrointestinal syndrome and chest pain), CRP peak, troponin peak, ECG presentation, arrhythmias, presence of QRS fragmentation, LVEF at admission, presence of diagnostic criteria at the biopsy. We labelled as tachycardia any fast ventricular rhythm and bradycardia any heart rate lower than 60 bpm secondary to high degree AV block. The most significant and prognostically relevant heart rhythm disorder was considered in each case.

The whole population was dichotomized according to the presence or absence of septic shock and/or severe sepsis to investigate the association of this particular clinical presentation with the other variables. We assumed that, in the papers, the current definition of sepsis and septic shock was accepted, whenever not clearly stated. For analysis purposes severe sepsis and septic shock were considered as a single group gathering together patients with evidence of infection associated with organ dysfunction and circulatory failure.

Patients were categorized into three groups according to the diagnostic criteria of myocarditis: possible myocarditis, in the presence of LVEF depression in the context of systemic bacterial infection but without specific evidence of inflammatory myocardial involvement, probable myocarditis, in the presence of suggestive CMR findings, and definite myocarditis, according to histopathological criteria.

Patients with definite or probable myocarditis were grouped together and compared with those with the absence of specific diagnostic criteria (i.e. possible myocarditis).

For the analysis of outcomes, we considered overall mortality and complete recovery rate, defined as normalization of echocardiographic or CMR LVEF and/or resolution of LGE. All other patients with abnormal ventricular function of any degree were included in the group classified as having partial recovery.
Table 2
Overview of epidemiology and clinical characteristics of patients with bacterial myocarditis not presenting with severe sepsis.

| Author          | Ref. Year | Bacterial                  | Gender | Age (years) | Clinical presentation | Chest pain | CRP peak (mg/L) | STN Troponin ratio | ECG | Arrhythmias | CMRI | LGE | EF at admission (%) | EMB/ Autopsy | ICU Complete recovery | Partial recovery | Death | Associated conditions | Diagnosis          |
|-----------------|-----------|----------------------------|--------|-------------|-----------------------|------------|-----------------|--------------------|-----|-------------|-----|-----|---------------------|--------------|----------------------|-----------------|-------|---------------------|------------------|
| Royston et al.  | 34 2018   | Streptococcus sanguinis     | M      | 39          | GE                    | +          | 580             |                    |     | 0           |     |     | 0                  | +            | 0                    | 0               |       | Endocarditis         | Probable        |
| Aguirre et al.  | 35 2015   | Streptococcus M3            | M      | 42          | Fever, Resp           | +          | 686             | ST-elevation       | 0   | + 46        |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Sundbom et al.  | 36 2018   | Salmonella enteritidis      | M      | 22          | Fever, GE             | +          | 209             | ST-elevation       | 0   | + 55        |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Hibbert et al.  | 37 2010   | Salmonella enteritidis      | M      | 25          | Fever, GE             | +          | 26              | ST-elevation VF    | 0   | 0          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Palombo et al.  | 38 2013   | Salmonella typhi            | M      | 27          | Fever, GE             | +          | 1.3             | ST-elevation VF    | 0   | 30          |     |     | 0                  | 0            | 0                    | 0               |       | ICD implantation     | Probable        |
| Williams et al. | 39 2004   | Salmonella typhi            | M      | 31          | GE                    | +          | 77              | ST-elevation       | 0   | 0          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Uribarri et al. | 40 2011   | Escherichia coli            | M      | 64          | Fever, GE             | +          | 3               | Normal             |     | 50          |     |     | 0                  | 0            | 0                    | 0               |       | Urinary tract infection | Probable        |
| Inayat et al.   | 41 2017   | Campylobacter jejuni        | M      | 20          | Fever, GE             | +          | 121             | 1300               | Ripolarization     | 0   | 41          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Hessulf et al.  | 42 2016   | Campylobacter jejuni        | M      | 24          | GE                    | +          | 89.1            | 72                 | ST-elevation       | 0   | 60          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Panikkath et al.| 43 2014   | Campylobacter jejuni        | M      | 43          | Fever, GE             | +          | 90.7            | 48                 | ST-elevation       | 0   | 65          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| De Cock et al.  | 20 2012   | Campylobacter spp           | M      | 21          | Fever, GE             | +          | 120             | Normal             | Ripolarization     | 0   | 41          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Fica et al.     | 44 2012   | Campylobacter jejuni        | M      | 17          | Fever, GE             | +          | 269             | 413                | ST-elevation       | 0   | 60          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Kratzer et al.  | 45 2010   | Campylobacter jejuni        | M      | 19          | Fever, GE             | +          | 15.05           | 7                  | ST-elevation       | 0   | 55          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Nevzorov et al. | 46 2010   | Campylobacter jejuni        | M      | 24          | Fever, GE             | 0          | 3               | Normal             | Ripolarization     | 0   | 45          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Heinzl et al.   | 47 2009   | Campylobacter jejuni        | M      | 16          | Fever, GE             | +          | 132             | 17                 | ST-elevation       | 0   | 45          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Williams et al. | 39 2004   | Campylobacter spp           | M      | 40          | GE                    | +          | 48              | 15                 | Ripolarization     | 0   | 50          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Cunningham et al.| 50 2003  | Campylobacter jejuni        | M      | 30          | Fever, GE             | +          | 125             | 604                | Ripolarization     | 0   | 45          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Hannu et al.    | 51 2002   | Campylobacter jejuni        | M      | 43          | GE                    | +          | 54              | Normal             | ST-elevation       | 0   | 45          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Cox et al.      | 52 2001   | Campylobacter jejuni        | M      | 32          | Fever, GE             | +          | 123             | Ripolarization     | 0   | 40          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Revilla-Marti et al. | 2017 | Rickettsia sibirica m. | M     | 39          | Fever, Rash           | +          | 41              | Ripolarization     | 0   | 55          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Silva et al.    | 54 2015   | Rickettsia slovaca          | M      | 28          | Rash                  | +          | 30              | ST-elevation       | 0   | 55          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
| Doyle et al.    | 55 2006   | Fever, Rash                | M      | 54          | Fever, Rash           | +          | 16              | ST-elevation       | 0   | 40          |     |     | 0                  | 0            | 0                    | 0               |       | Probable             |                 |
P. Ferrero et al. / Indian Heart Journal 72 (2020) 82–92

3.1. Statistical analysis

Continuous variables are expressed as medians and inter-quartile ranges and were compared by the Wilcoxon rank sum test (Mann–Whitney test). Comparisons between more than two groups were performed by the Kruskal–Wallis test. Categorical variables are reported as counts and percentages and were compared using the chi square test and Fisher’s exact test as appropriate. Multivariate association with categorical variables was determined by logistic regression analysis. A p value of 0.05 was assumed to indicate statistical significance.

4. Results

The search yielded 362 publications. A total of 59 papers and 64 case reports were deemed eligible for study inclusion, with a total of 66 patients (including ours), thirty-two of whom had a clinical course characterized by sepsis (Fig. 2).

Tables 1 and 2 summarize the demographic, clinical, bacterial etiology and diagnostic examination data for individuals in the publications presenting with or without severe sepsis, respectively. Fifteen different etiologies were recorded. Staphylococcus, Neisseria, Klebsiella, Listeria, Leptospira and Brucella species were more commonly found in patients presenting with severe sepsis. Blood culture were positive in 14 out of 32 (44%) and in 4 out of 34 (12%) patients presenting with or without severe sepsis respectively (Fig. 3; Table 3).

Table 4 presents general demographic, clinical, instrumental and laboratory data as well as differences between patients with and without sepsis. Males were more prevalent in the whole group, accounting for 51 patients (77%), while females more frequently presented with sepsis (13 out of 32 (41%) vs 2 out of 34 (6%); p = 0.001). Chest pain and fever were the most common clinical presentations, followed by gastrointestinal syndrome, skin rash and respiratory symptoms, with frequencies of 58 (88%), 57 (86%), 33 (50%), 13 (20%), and 11 (17%), respectively. Fever and respiratory symptoms were more frequently found in patients who developed severe sepsis (31 out of 32 (97%) vs 26 out of 34 (76%); p = 0.02, and 9 out of 32 (28%) vs 2 out of 34 (6%); p = 0.02, respectively). Symptoms at presentation correlated well with the involved organs, and are grouped as follows: gastrointestinal, 31 (47%); respiratory, 14 (21%); urogenital, 8 (12%); articular/soft tissue, 11 (17%); and central nervous system, 2 (3%) (Fig. 4).

 Patients with gastrointestinal involvement were the youngest, with an average age of 25 years\textsuperscript{30–39} and always had negative blood cultures, while those with urogenital infection were the oldest, with an average age of 50 years (28.5–64.5) (p = 0.009).

Overall, 37 patients (56%) fulfilled the predefined criteria for probable or definite myocarditis, while the rest were deemed to have possible myocarditis according to the aforementioned criteria. A minority of reports (10; 15%) provided histopathological data, 9 of which were diagnostic for myocarditis, mostly within the subset presenting with sepsis (8 out of 32 (25%) vs 1 out of 34 (3%); p = 0.006).

The overall median LVEF at admission was 45%\textsuperscript{20,35–53} and patients with sepsis had significantly lower values (35%\textsuperscript{20–44} vs 50%\textsuperscript{44–56}; p < 0.001).

Accordingly, the percentage of patients admitted to the ICU and mortality rate were significantly higher in this subset of patients (27 (84%) vs 3 (9%); p < 0.001, and 8 (25%) vs 1 (3%); p = 0.01, respectively).

Similarly, patients who had severe sepsis demonstrated a lower percentage of complete recovery (16 (50%) vs 27 (79%); p = 0.02).
Overall 15 patients had rhythm disturbances, 11 among those presenting with severe sepsis/septic shock. In particular, 7 patients had sustained ventricular tachycardia (heart rate between 150 and 250), two patients complicated with ventricular fibrillation, in two patients not sustained ventricular tachycardia was recorded without mention of further details and 3 patients had complete AV block. In two cases AV block preceded progressive infra-hisian conduction impairment that eventually led to cardiac arrest.

In the univariate comparison between patients with and without a diagnosis of myocarditis, no differences were observed with respect to demographic, clinical presentation, LVEF and laboratory data, but rhythm disturbances were more prevalent in the former group 12 (32%) vs 3 (10%); p = 0.04 (Table 5).

Nine deaths occurred in the whole population. Almost all patients with an ominous prognosis presented with severe sepsis (8 out of 9 (88%) vs 24 out of 57 (42%); p = 0.01).

Furthermore, respiratory syndrome and occurrence of rhythm disturbances, either bradycardia or tachycardia, were associated with death based on the univariate analysis (p = 0.02 and < 0.001, respectively). (Table 6; Fig. 4).

Among the patients who survived, 43 (75%) had a complete recovery according to the aforementioned criteria. Older age, sepsis, respiratory involvement, lower LVEF and occurrence of arrhythmia were univariate predictors of incomplete recovery (p = 0.05, p = 0.02, p = 0.01, p = 0.0001 and p = 0.005, respectively). (Table 7; Fig. 5).

At the multivariate logistic regression analysis, LVEF at admission and heart rhythm disturbances remained independently associated with persistence of myocardial depression, odds ratio (OR) 1.1, for each percent unit of LVEF decrease, 95% confidence interval (CI) 1.03–1.2, p = 0.004 and OR 6.6, 95% CI 1.35–32.5, p = 0.02, respectively.

### Table 3

Prevalence of bacterial etiologies and culture positivity.

| Bacterial species | Overall, n 66 | Severe sepsis, n 32 | Blood cultures | Tissue cultures | Biological samples cultures | Not severe sepsis, n 34 | Blood cultures | Tissue cultures | Biological samples cultures |
|-------------------|---------------|---------------------|----------------|----------------|---------------------------|-------------------------|----------------|----------------|---------------------------|
| 1 Streptococcus spp, n (%) | 6 (9) | 4 (12) | 1 (25) | 1 (25) | 1 (25) | 2 (6) | 1 (50) | 0 | 0 |
| 2 Staphylococcus spp, n (%) | 3 (4.5) | 3 (9) | 3 (100) | 0 | 0 | 0 | NA | NA | NA |
| 3 Neisseria spp, n (%) | 2 (3) | 2 (6) | 2 (100) | 0 | 0 | 0 | NA | NA | NA |
| 4 Salmonella spp, n (%) | 9 (13.6) | 5 (16) | 3 (60) | 0 | 2 (40) | 4 (12) | 2 (50) | 0 | 2 (50) |
| 5 Escherichia spp, n (%) | 5 (7.6) | 4 (12) | 4 (100) | 0 | 1 (25) | 1 (3) | 0 | 0 | 1 (100) |
| 6 Campylobacter spp, n (%) | 20 (30) | 2 (6) | 0 | 0 | 2 (100) | 18 (53) | 0 | 0 | 18 (100) |
| 7 Rickettsia spp, n (%) | 7 (10.6) | 3 (9) | 0 | 1 (33) | 0 | 4 (12) | 0 | 1 (25) | 0 |
| 8 Klebsiella spp, n (%) | 2 (3) | 2 (6) | 1 (50) | 1 (50) | 1 (50) | 0 | NA | NA | NA |
| 9 Listeria spp, n (%) | 2 (3) | 2 (6) | 2 (100) | 0 | 0 | 0 | NA | NA | NA |
| 10 Mycobacterium spp, n (%) | 1 (1.5) | 0 | NA | NA | NA | 1 (3) | 0 | 1 (100) | 0 |
| 11 Leptospira spp, n (%) | 1 (1.5) | 1 (3) | 0 | 0 | 0 | 0 | NA | NA | NA |
| 12 Chlamydia spp, n (%) | 5 (7.6) | 3 (9) | 0 | 1 (33) | 1 (33) | 2 (6) | 1 (50) | 1 (50) | 1 (50) |
| 13 Coxiella spp, n (%) | 1 (1.5) | 0 | NA | NA | NA | 1 (3) | 0 | 0 | 0 |
| 14 Brucella spp, n (%) | 1 (1.5) | 1 (3) | 1 (100) | 0 | 0 | 0 | NA | NA | NA |
| 15 Mycoplasma spp, n (%) | 1 (1.5) | 0 | NA | NA | NA | 1 (3) | 0 | 0 | 0 |

**Fig. 3.** Relative prevalence of bacteria and culture results.
5. Discussion

The prevalence of bacterial myocarditis is poorly defined owing to the lack of uniform diagnostic criteria. Furthermore, there is a recognized overlap between myocarditis and aspecific myocardial depression in the context of sepsis.

This pooled analysis confirmed the epidemiological data for the whole group of patients with myocarditis in terms of age at presentation and the significant prevalence of males. The presentation significantly correlated with age, providing the clinicians with an indication of the spectrum of possible bacteria involved. Histological diagnosis was available for only a minority of the patients, with...
most of these analyses performed from post-mortem examination and from the subset who presented with overt sepsis. Microscopic examination consistently revealed the presence of leucocyte infiltrates, microabscess and necrosis, which is consistent with bacterial dissemination. In the other two patients, without sepsis, tissue specimens showed localized mycobacterial infection and the absence of direct signs of infection respectively.

The occurrence of rhythm disturbances seems to be the unique variable that was more specifically associated with definite/probable diagnosis of myocarditis, while demographic, clinical and echocardiographic findings were not. In particular, electrocardiographic changes are usually considered to be non-specific findings. In our two cases, we observed the appearance of QRS fragmentation (Fig. 1B, C, E). This feature has been hypothesized to indicate the expression of localized slowing of electrical conduction and correlates with the presence of LGE on CMR.

Although this finding was not clearly mentioned in any of the reports, it was clearly visible in 22 published ECG (79%), suggesting its reproducible presence across a wide spectrum of etiologies.

### Table 5
Univariate comparison of patients with or without ascertained diagnosis of myocarditis.

| Diagnosis ascertained (n = 37) | Diagnosis not ascertained (n = 29) | P value |
|--------------------------------|-----------------------------------|---------|
| Age (years), median (25th-75th) | 32 (21–42)                         | 34 (25–47) | 0.2 |
| Male, n (%)                     | 30 (81)                            | 21 (72)   | 0.5 |
| EF at admission (%), median (25th-75th) | 45 (35–55) | 45 (35–50) | 0.9 |
| CRP peak (mg/L), median (25th-75th) | 106 (30–132) | 55 (46–74) | 0.8 |
| STN Troponin ratio, median (25th-75th) | 120 (26–580) | 84 (20–226) | 0.5 |
| Sepsis, n (%)                   | 16 (43)                            | 16 (55)   | 0.4 |
| Rhythm disturbances, n (%)     | 12 (32)                            | 3 (10)    | 0.04 |
| Organ involvement              |                                   |          |
| Gastroenteric syndrome, n (%)  | 17 (46)                            | 14 (48)   | 0.9 |
| Respiratory syndrome, n (%)    | 9 (24)                             | 5 (17)    | 0.5 |
| Articular/Soft tissue, n (%)   | 6 (16)                             | 5 (17)    | 0.9 |
| Urogenital, n (%)              | 4 (11)                             | 4 (14)    | 0.7 |
| Central nervous system, n (%)  | 1 (3)                              | 1 (3)     | 0.9 |

### Table 6
Univariate comparison of clinical variables according to survival.

| Diagnosis ascertained (n = 57) | Diagnosis not ascertained (n = 9) | P value |
|--------------------------------|-----------------------------------|---------|
| Age (years), median (25th-75th) | 30 (23–43)                         | 36 (33–45) | 0.5 |
| Male, n (%)                     | 46 (80)                            | 5 (56)   | 0.1 |
| EF at admission (%), median (25th-75th) | 45 (35–55) | 31 (20–45) | 0.1 |
| CRP peak (mg/L), median (25th-75th) | 63.5 (35–124) | 74 (8–160) | 0.9 |
| STN Troponin ratio, median (25th-75th) | 94.5 (24–580) | 228 (3–398) | 0.8 |
| Sepsis, n (%)                   | 24 (42)                            | 8 (89)    | 0.01 |
| Rhythm disturbances, n (%)     | 2 (22)                             | 7 (78)    | <0.001 |
| Organ involvement              |                                   |          |
| Gastroenteric syndrome, n (%)  | 30 (52)                            | 1 (11)    | 0.03 |
| Respiratory syndrome, n (%)    | 9 (16)                             | 5 (56)    | 0.02 |
| Articular/Soft tissue, n (%)   | 9 (16)                             | 2 (22)    | 0.6 |
| Urogenital, n (%)              | 7 (12)                             | 1 (11)    | 0.9 |
| Central nervous system, n (%)  | 2 (4)                              | 0         | 0.9 |

### Table 7
Univariate comparison of clinical variables according to recovery rate.

| Diagnosis ascertained (n = 43) | Diagnosis not ascertained (n = 23) | P value |
|--------------------------------|-----------------------------------|---------|
| Age (years), median (25th-75th) | 30 (20–42)                         | 39 (26–51) | 0.05 |
| Male, n (%)                     | 36 (83)                            | 15 (65)  | 0.1 |
| EF at admission (%), median (25th-75th) | 50 (40–55) | 30 (20–45) | 0.0001 |
| CRP peak (mg/L), median (25th-75th) | 72 (38–123) | 64 (30–125) | 0.8 |
| STN Troponin ratio, median (25th-75th) | 103 (31–629) | 98 (16–228) | 0.3 |
| Sepsis, n (%)                   | 16 (37)                            | 16 (70)  | 0.02 |
| Rhythm disturbances, n (%)     | 5 (12)                             | 10 (43)  | 0.005 |
| Organ involvement              |                                   |          |
| Gastroenteric syndrome, n (%)  | 24 (56)                            | 7 (30)   | 0.07 |
| Respiratory syndrome, n (%)    | 5 (12)                             | 9 (39)   | 0.01 |
| Articular/Soft tissue, n (%)   | 6 (14)                             | 5 (22)   | 0.5 |
| Urogenital, n (%)              | 6 (14)                             | 2 (9)    | 0.7 |
| Central nervous system, n (%)  | 2 (5)                              | 0        | 0.5 |
6. Conclusion

Bacterial infection is a poorly reported etiologic cause of myocarditis. Diagnosis can be particularly challenging as it can be misled by aspecific transiently depressed myocardial contractility. Within this wide spectrum, apart from the occurrence of brady/tachyarrhythmias, no non-invasive diagnostic modalities appeared to support the specific diagnosis of myocarditis. Bacterial myocarditis may present in the context of severe sepsis. According to this pooled cohort, it is likely the consequence of dissemination of bacteria from the primary infection site to the heart and portend a poorer prognosis in terms of survival and recovery rate.

7. Limitations

This paper has several limitations. Firstly, data were pooled from a limited number of case reports displaying significant heterogeneity in terms of diagnostic criteria, which did not allow for the use of formal quantitative meta-analysis techniques. Secondly, the relatively small number of patients limits the reproducibility and generalizability of the inferences about the prognostic determinants. Furthermore, the diagnosis was based on histopathological criteria in only a few patients.

Funding

No funding was received.

Declaration of Competing Interest

All authors have none to declare.

References

1. Caforio ALP, Pankuweit S, Arbustini E, et al. 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*. 2013;34:2636.
2. Wasi F, Shuter J. Primary bacterial infection of the myocardium. *Front Biosci*. 2003;8:228–231.
3. Ferrero P, Piazza I, Grosu A, Brambilla P, Sironi S, Senni M. QRS fragmentation as possible new marker of fibrosis in patients with myocarditis. Preliminary validation with cardiac magnetic resonance. *Eur J Heart Fail*. 2019;21:1160–1161.
4. Sikary AK, Mridha AR, Behera C. Sudden death of a child due to pyogenic bacterial myocarditis. *Med Leg J*. 2017;85:105–107.
5. Ozkaya G, Shorbagi A, Ulger Z, et al. Invasive group A streptococcal infection with pancarditis caused by a new emm-type 12 allele of Streptococcus pyogenes. *J Infect*. 2006;53:1–4.
6. Dominguez F, Cobo-Marcos M, Guzzo G, et al. Erysipelas and acute myocarditis: an unusual combination. *Can J Cardiol*. 2013;29:1138.
7. Lee YP, Hoi WH, Wong RC. A case of myopericarditis in a patient with methicillin-resistant Staphylococcus aureus community-acquired pneumonia. *Ann Acad Med Singapore*. 2008;37:242–244.
8. Khan S, Strate RW, Helinsan R. Myocardial abscess and fatal cardiac arrhythmia in a hemodialysis patient with an arterio-venous fistula infection. *Semin Dial*. 2007;20:452–454.
9. Elias T, Roberts I, Jones N, Saha S, Leeson P. Suppurative bacterial myocarditis: echocardiographic and pathological findings. *Eur Heart J*. 2008;29:489.
10. Bouneb R, Mellouli M, Regaieg H, Majdoub S, Chouchene I, Boussarsar M. Meningococcemia complicated by myocarditis in a 16-year-old young man: a case report. *Pan Afr Med J*. 2018;29:149.
11. Gawalkar AA, Tale S, Chhabria RA, Bhalla A. Myocarditis and purpura fulminans in meningococcaemia. *QJM*. 2011;107:755–756.
12. Al Shamkhani W, Ajaz Y, Saud Jalal N, Roy Narayanan S. Myocarditis and rhabdomyolysis in a healthy young man caused by Salmonella gastroenteritis. *Case Rep Infect Dis*. 2015;2015, 954905.
13. Childs L, Gupta S. Salmonella enteritidis induced myocarditis in a 16-year-old girl. *BMJ Case Rep*. 2012;2012:bcr-2012-007628.
14. Villablanca P, Mohananey D, Meier G, Yap JE, Choudsey S, Abegunde AT. Salmonella Berta myocarditis: case report and systematic review of non-typhoid Salmonella myocarditis. *World J Cardiol*. 2015;7:931–937.
15. Al-aqeedi RF, Kamba A, Al-ani FK, Al-ani AA. Salmonella myocarditis in a young adult patient presenting with acute pulmonary edema, rhabdomyolysis, and multi-organ failure. *J Cardiol*. 2009;54:475–479.
16. Türoff A, Vollnberg H, Kohler BM. Acute myocarditis after visiting Pakistan. Disch Med Wochenschr. 2008;133:1493–1496.

17. Komuro J, Ueda K, Kaneko M, Nitta S, Kasa M, Yokoyama M. Various cardiac abnormalities caused by bacterial myocardialitis. Int Heart J. 2018;59:229–232.

18. Gentile D, Meles E, Carbone C, Gantù E, Maggionni S. Unusual case of myocardial injury induced by Escherichia coli sepsis. Monaldi Arch Chest Dis. 2010;74:40–43.

19. Chen TC, Liu PL, Lin CY, Lin WR, Chen YH. Escherichia coli urosepsis complicated by myocarditis complicating typhoid fever in a traveler returning from Nepal. J Trav Med. 2013;20:329–332.

20. Pena LA, Fishbein MC. Fatal myocarditis related to Campylobacter jejuni enterocolitis causing myocarditis in a previously healthy 22-year-old male. Pediatr Cardiol. 2018;39:533–535.

21. Morgan AM, Roden RC, Matson SC, Wallace GM, Lange HLH, Bonny AE. Severe bacterial liver abscess mimicking acute myocardial infarction. Am J Case Rep. 2016;17:81.

22. Türoff A, Vollnberg H, Kohler BM. Acute myocarditis after visiting Pakistan. J Trav Med. 2013;20:329–332.

23. Pena LA, Fishbein MC. Fatal myocarditis related to Campylobacter jejuni enterocolitis causing myocarditis in a traveler returning from Nepal. Intern Med. 2013;20:329–332.

24. Hoefer D, Poelzl G, Kilo J, et al. Early detection and successful therapy of myocarditis associated with Campylobacter jejuni infection: a case report. Cardiovasc Pathol. 2007;16:119–121.

25. Wissahawa H, Brown M, Martin I, Evenhuis W. Hitch-hiker taken for a ride: an unusual cause of myocarditis, septic shock and adult respiratory distress syndrome. BMJ Case Rep. 2013;2012:bcr-2012-007155.

26. Wilson PA, Tierney L, Lai K, Graves S. Queensland tick typhus: three cases with unusual clinical features. Int J Med. 2013;43:823–825.

27. Koch N, Epaulard O, Pelloux I, et al. African tick bite fever in elderly patients: 8 cases in French tourists returning from South Africa. Clin Infect Dis. 2008;47:28–35.

28. Zou Y, Lin L, Xiao H, Xiang D. A rare case of toxic myocarditis caused by bacterial liver abscess mimicking acute myocardial infarction. Am J Case Rep. 2016;17:1–5.

29. Chuang TY, Lio GJ, Lee SW, et al. Rapidly fatal community-acquired pneumonia due to Klebsiella pneumoniae complicated with acute myocarditis and accelerated idioventricular rhythm. J Microbiol Immunol Infect. 2012;45:321–323.

30. Ladani AP, Biswas A, Vaghasia N, Generalovitch T. Unusual presentation of listerial myocarditis and the diagnostic value of cardiac magnetic resonance. Tex Heart Inst J. 2010;37:255–258.

31. Haddad F, Berry G, Doyle RL, Martineau P, Leung TK, Racine N. Active bacterial myocarditis: a case report and review of the literature. J Heart Lung Transplant. 2007;26:745–749.

32. Pushpakumara J, Prasath T, Samarawewa G, Priyadarshani S, Perera N, Indrakumara J. Myocarditis causing severe heart failure: an unusual early manifestation of leptospirosis: a case report. BMC Res Notes. 2015;8:80.

33. Morgan AM, Roden RC, Matson SC, Wallace GM, Lange HLH, Bonny AE. Severe sepsis and acute myocardial dysfunction in an adolescent with Chlamydia trachomatis pelvic inflammatory disease: a case report. J Pediatr Adolesc Gynecol. 2018;31:143–145.

34. Hoofer D, Poelzl G, Kilo J, et al. Early detection and successful therapy of fulminant chlamydiaemia pneumonieae myocarditis. Am Soc Artif Intern Organs J. 51:481–480.

35. Suesaowalak M, Cheung MM, Tucker D, Chang AC, Chu J, Arrieta A. Chlamydia trachomatis pelvic infection. Can J Cardiol. 2010;26:323–325.

36. Palombo M, Margalit-Yehuda R, Leshem E, Sidi Y, Schwartz E. Near-fatal myocarditis complicating typhoid fever in a traveler returning from Nepal. J Trav Med. 2013;20:329–332.