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Review Article

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

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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.[1] 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.[2] 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

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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, aVf, 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 uretheropielography 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

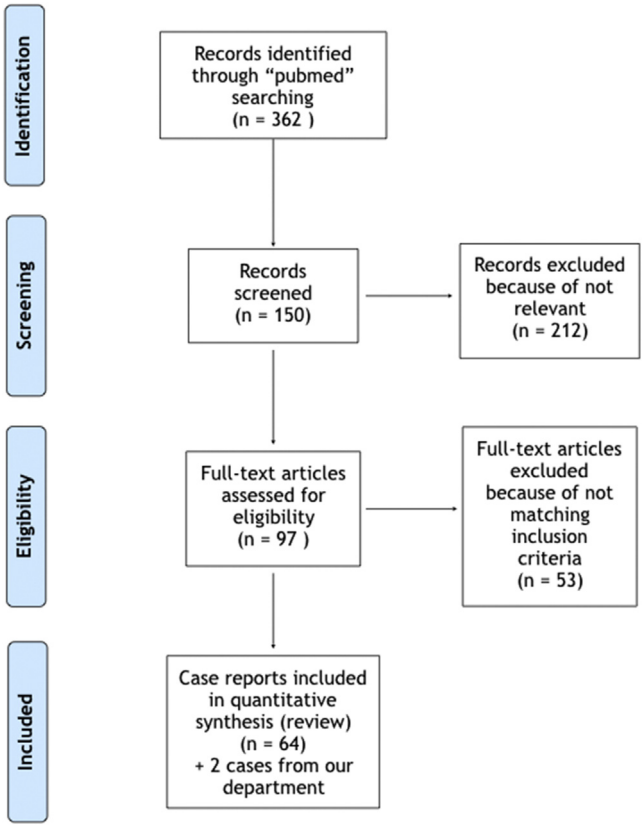

Fig. 2. Flowchart summarizing the screening and inclusion of relevant papers.

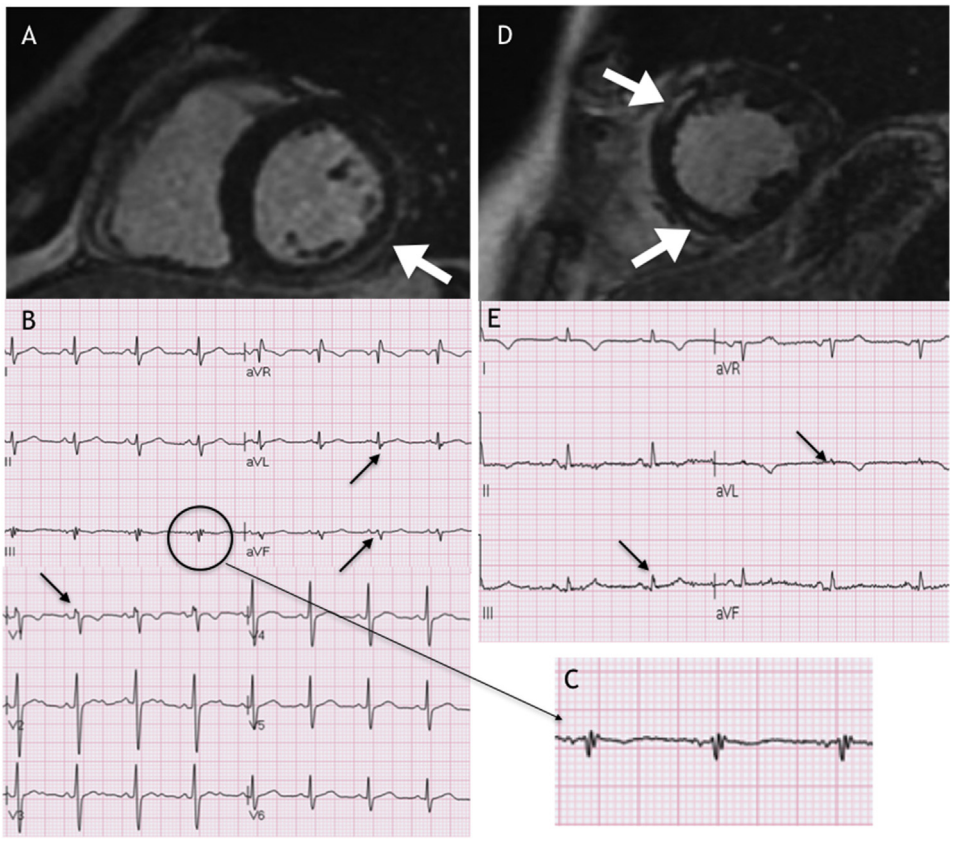

Fig. 1. Panel A: First case, cardiac magnetic resonance imaging showing late gadolinium enhancement. Panels B and C: ECG showing QRS fragmentation. Panel D: Second case, cardiac magnetic resonance imaging showing late gadolinium enhancement. Panel E: ECG showing QRS fragmentation.

Table 1
Overview of epidemiology and clinical characteristics of patients with bacterial myocarditis presenting with severe sepsis.

Author	Ref	Year	Bacterial	Gender	Age (years)	Clinical presentation	Chest pain	CRP peak (mg/L)	STN Troponin ratio	ECG	Arrhythmias	fQRS	CMRI LGE	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	Septic arthritis	Probable
Case 2	–	2019	*Escherichia coli*	F	51	Fever	+	30	1614	ST-elevation	0	+	+	30	0	+	0	+	0	Urinary tract infection	Probable
Sikary et al.	4	2016	Streptococcus pyogenes	F	7	Fever, Resp	0	–	–	–	VT	–	–	–	+	0	0	0	+	–	Definite
Ozkaya et al.	5	2005	Streptococcus pyogenes	F	35	Fever, Resp, Rash	+	–	–	–	VT	–	–	–	+	+	0	0	+	–	Definite
Dominguez et al.	6	2013	Streptococcus B-hemolytic	M	46	Fever, Rash	0	–	550	ST-elevation	AV block	–	+	60	0	0	+	0	0	Erysipelas	Probable
Lee et al.	7	2008	MRSA	M	41	Fever, Resp	+	–	8	ST-elevation	0	+	–	20	0	+	0	+	0	Pneumonia	Possible
Khan et al.	8	2007	MRSA	M	41	Fever	+	–	–	ST-elevation, BBSx	AV block	–	–	45	+	+	0	0	+	AV Fistula Infection	Definite
Elias et al.	9	2008	MSSA	M	45	Fever	+	160	–	ST-elevation	VT	+	–	20	+	+	0	0	+	–	Definite
Buoneb et al.	10	2018	Neisseria meningitidis	M	16	Fever, Rash	+	–	1071	ST-elevation	0	–	+	35	0	+	+	0	0	–	Probable
Gawalkar et al.	11	2017	Neisseria meningitidis	M	17	Fever, Resp, Rash	0	–	–	Ripolarization abn.	0	–	–	30	0	+	+	0	0	Purpura fulminant	Possible
Al Shamkhani et al.	12	2015	Salmonella enteritidis	M	28	Fever, GE	+	287	225	ST-elevation	0	+	–	55	0	+	+	0	0	Rabdomyolysis	Possible
Childs et al.	13	2012	Salmonella enteritidis	F	16	Fever, GE	0	206	1071	Ripolarization abn.	0	0	–	47	0	+	+	0	0	–	Possible
Villablanca et al.	14	2015	Salmonella berta	M	19	Fever, GE	+	–	556	ST-elevation	0	+	+	40	0	0	+	0	0	–	Probable
Al-aqeedi et al.	15	2009	*Salmonella typhi*	M	34	Fever, GE	+	–	98	Ripolarization abn.	0	+	–	23	0	+	0	+	0	Rabdomyolysis	Possible
Türoff et al.	16	2008	*Salmonella typhi*	F	42	Fever, GE, Rash	+	39.27	–	Ripolarization abn.	VT	–	–	40	0	+	+	0	0	–	Possible
Komuro et al.	17	2018	*Escherichia coli*	F	69	Fever	+	8	–	ST-elevation, BBSx	AV block	0	–	31	+	+	0	0	+	Coronaropathy	Definite
Gentile et al.	18	2010	*Escherichia coli*	M	65	Fever	+	–	170	ST-elevation	0	+	–	58	0	+	+	0	0	Urinary tract infection	Possible
Chen et al.	19	2010	*Escherichia coli*	F	25	Fever, GE	+	–	882	ST-elevation	0	0	–	50	0	+	+	0	0	Urinary tract infection	Possible
De Cock et al.	20	2012	Campylobacter jejuni	M	42	Fever, GE	+	–	116	ST-elevation	0	–	+	40	0	0	+	0	0	–	Probable
Pena et al.	21	2006	Campylobacter jejuni	M	16	Fever, GE	+	–	398	ST-elevation	0	–	–	–	+	+	0	0	+	Aeromomas hydrophila	Definite
Kushawaha et al.	22	2013	Rickettsia rickettsii	M	26	Fever, Rash	+	–	3	Normal	0	+	–	20	0	+	0	+	0	–	Possible
Wilson et al.	23	2012	Rickettsia australis	F	52	Fever, Rash	+	–	990	ST-elevation	0	–	–	20	0	+	0	+	0	–	Possible
Roch et al.	24	2008	Rickettsia africae	F	74	Fever, Rash	+	–	–	ST-elevation	0	–	–	35	0	+	+	0	0	–	Possible
Zou et al.	25	2016	*Klebsiella pneumoniae*	M	66	Fever	+	–	67	ST-elevation	0	+	–	45	0	+	+	0	0	Liver abscess	Possible
Chuang et al.	26	2012	*Klebsiella pneumoniae*	M	52	Fever, Resp	+	–	3	Idioventricular rhythm	VT	–	–	50	0	+	0	0	+	–	Probable
Ladani et al.	27	2015	Listeria monocytogenes	M	47	Fever, Resp	+	–	24	ST-elevation	VT	+	+	35	0	+	0	+	0	ICD implantation	Probable
Haddad et al.	28	2007	Listeria monocytogenes	F	49	Fever	+	–	53	–	0	–	–	12	+	+	0	+	0	–	Definite

Pushpakumara et al.	29	2015	Leptospira spp	M	36	Fever	+	74	228	ST-elevation	VT	0	–	20	0	+	0	0	+	Respiratory distress	Possible
Morgan et al	30	2017	*Chlamydia trachomatis*	F	19	Fever	0	–	–	Ripolarization abn.	0	–	–	35	0	+	+	+	0	PID	Possible
Hoefer et al.	31	2005	Chlamydia pneumoniae	F	24	Fever, Resp	0	5	–	–	VT	–	–	10	+	+	+	0	0	BVAD	Definite
Suesaowalak et al.	32	2008	Chlamydia pneumoniae	M	11	Fever, Resp, GE, Rash	+	17	32	Ripolarization abn.	0	–	–	50	0	+	+	0	0	–	Possible
Efe et al.	33	2009	Brucella spp	F	51	Resp	+	55	140	Ripolarization abn.	0	–	–	15	0	+	0	+	0	Ascites	Possible

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 antero-lateral 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[1]: case report or case series[2]; inclusion of patients with at least one positive blood, stool and/or tissue culture[3]; 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 LGE, 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	fQRS	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	ST-elevation	0	–	+	–	0	+	0	+	0	Endocarditis	Probable
Aguirre et al.	35	2015	Streptococcus A	M	42	Fever, Resp	+	–	686	ST-elevation	0	+	+	55	0	0	+	0	0	–	Probable
Sundbom et al.	36	2018	Salmonella enteritidis	M	22	Fever, GE	+	200	209	ST-elevation	0	+	+	46	0	+	+	0	0	–	Probable
Hibbert et al.	37	2010	Salmonella enteritidis	M	25	Fever, GE	+	–	26	ST-elevation	VF	0	+	55	0	0	0	0	0	–	Probable
Palombo et al.	38	2013	*Salmonella typhi*	M	27	Fever, GE	+	–	1.3	ST-elevation	VF	–	+	30	0	+	0	+	0	ICD implantation	Probable
Williams et al.	39	2004	*Salmonella typhi*	M	31	GE	+	72	77	ST-elevation	0	+	–	45	0	0	+	0	0	–	Possible
Uribarri et al.	40	2011	*Escherichia coli*	M	64	Fever, GE	+	–	3	Normal	0	–	+	50	0	0	+	0	0	Urinary tract infection	Probable
Inayat et al.	41	2017	Campylobacter jejuni	M	20	Fever, GE	+	121	1300	Ripolarization abn.	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	–	Possible
		2016	Campylobacter jejuni	M	23	Fever, GE	+	46.5	18	Normal	0	+	–	60	0	0	+	0	0	–	Possible
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	0	–	+	50	0	0	0	+	0	–	Probable
		2012	Campylobacter jejuni	M	24	Fever, GE	+	–	89	ST-elevation	0	–	+	40	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 spp	M	24	Fever, GE	0	–	–	Ripolarization abn.	NSVT	+	–	45	0	0	+	0	0	–	Possible
Heinzl et al.	47	2009	Campylobacter jejuni	M	16	Fever, GE	+	132	17	ST-elevation	0	–	+	45	0	0	+	0	0	–	Probable
		2009	Campylobacter jejuni	M	17	Fever, GE	+	32	8	ST-elevation	0	–	+	60	0	0	+	0	0	–	Probable
Turley et al.	48	2008	Campylobacter jejuni	M	24	Fever, GE	+	125	140	ST-elevation	0	0	+	45	0	0	0	+	0	Noonan Syndrome	Probable
Kotilainen et al.	49	2006	Campylobacter spp	M	47	Fever, GE	+	73	–	Ripolarization abn.	0	–	–	50	0	0	+	0	0	Acute appendicitis	Possible
Williams et al.	39	2004	Campylobacter jejuni	M	40	GE	+	48	15	Normal	0	–	–	60	0	0	+	0	0	–	Possible
Cunningham et al.	50	2003	Campylobacter jejuni	M	30	Fever, GE	+	–	604	Ripolarization abn.	0	–	–	60	0	0	+	0	0	–	Possible
Hannu et al.	51	2002	Campylobacter jejuni	M	43	GE	+	54	–	ST-elevation	0	–	–	45	0	0	+	0	0	–	Possible
		2002	Campylobacter jejuni	M	30	Fever, GE	+	30	–	ST-elevation	0	–	–	50	0	0	+	0	0	–	Possible
Cox et al.	52	2001	Campylobacter jejuni	M	32	Fever, GE	+	123	–	Ripolarization abn.	0	–	+	40	0	0	+	0	0	–	Probable
Revilla-Marti et al.	53	2017	Rickettsia sibirica m.	M	39	Fever, Rash	+	–	41	ST-elevation	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		M	54	Fever, Rash	+	–	16	Normal	0	–	–	40	0	0	0	+	0	–	Possible

		Rickettsia rickettsii																
Bellini et al.	56	2005	Rickettsia africae	M	35	Fever, Rash	+	–	91	Ripolarization abn.	0	+	–	60	0	0	+	0	–	Possible
Silingardi et al.	57	2006	*Mycobacterium avium*	F	33	–	0	–	–	–	–	–	+	–	0	0	0	+	–	Definite
Dellegrottaglie et al.	58	2014	*Chlamydia trachomatis*	M	32	–	+	–	1600	ST-elevation	0	+	+	55	0	0	+	0	Epididymitis	Probable
Mavrogeni et al.	59	2008	*Chlamydia trachomatis*	M	49	Fever	+	–	23	–	0	–	+	47	+	0	+	0	Prostatitis	Possible
Carrascosa et al.	60	2012	Coxiella burnetii	M	23	Fever	+	–	655	ST-elevation	NSVT	–	+	55	0	0	+	0	Pneumonia and hepatitis	Probable
Paz et al.	61	2002	Mycoplasma pneumoniae	F	30	Fever, Resp	+	–	–	ST-elevation	0	–	–	50	0	0	+	0	–	Possible

3.1. Statistical analysis

Continuous variables are expressed as medians and interquartile 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*, *Klesiella*, *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[20–39] 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%,[20,35–53] and patients with sepsis had significantly lower values (35%[20–44] vs 50%[39,44–56]; ($p < 0.001$)).

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%), $p = 0.02$).

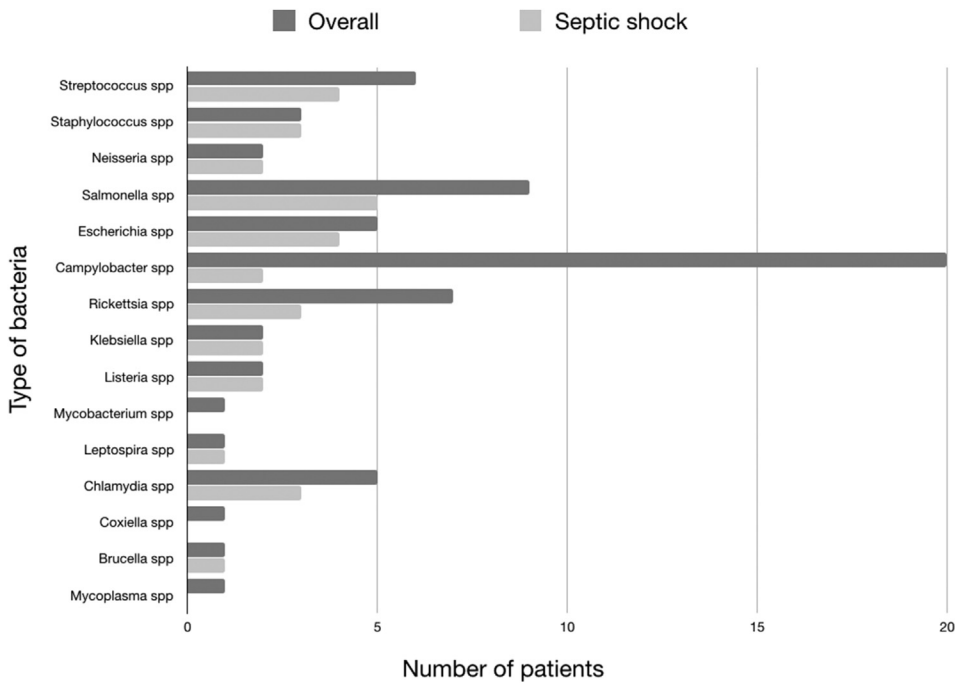

Fig. 3. Relative prevalence of bacteria and culture results.

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

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 tachicardia 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 4
Demographic clinical and instrumental characteristic.

	Overall, n 66	Severe sepsis, n 32	Not severe sepsis, n 34	P value
Age (years), median (25th-75th)	32 (23–43)	38.5 (21.5–50)	30 (23–39)	0.1
Males, n (%)	51 (77)	19 (59)	32 (94)	**0.001**
Diagnosis				
Possible, n (%)	29 (44)	16 (50)	13 (38)	
Probable, n (%)	28 (42)	8 (25)	20 (59)	
Definite, n (%)	9 (14)	8 (25)	1 (3)	**0.008**
Clinical presentation				
Fever, n (%)	57 (86)	31 (97)	26 (76)	**0.02**
Gastrointestinal symptoms, n (%)	33 (50)	9 (28)	24 (71)	**0.001**
Respiratory symptoms, n (%)	11 (17)	9 (28)	2 (6)	**0.02**
Skin rash, n (%)	13 (20)	9 (28)	4 (12)	0.08
Chest pain, n (%)	58 (88)	26 (81)	32 (94)	0.1
ECG				
Normal, n (%)	6 (9)	1 (3)	5 (15)	
ST-elevation, n (%)	40 (61)	19 (59)	21 (62)	
Ripolarization abnormalities, n (%)	14 (21)	8 (25)	6 (18)	
ECG informations not available, n (%)	6 (9)	4 (13)	2 (6)	0.3
fQRS, n (%)	22 (79)	11 (69)	11 (84)	0.4
Rhythm disturbance, n (%)	15 (23)	11 (34)	4 (12)	**0.04**
EF at admission (%), median (25th-75th)	45 (35–55)	35 (20–45)	50 (45–58)	**<0.001**
CMRI available, n (%)	28 (42)	7 (22)	21 (62)	–
Histopathology available, n (%)	10 (15)	8 (25)	2 (6)	**0.03**
ICU, n (%)	30 (45)	27 (84)	3 (9)	**<0.001**
PCR peak (mg/L), median (25th-75th)	72 (32–125)	39 (17–160)	81 (47–124)	0.3
Troponin peak (ratio), median (25th-75th)	98 (24–556)	197.5 (53–700)	72 (17–413)	0.1
Complete recovery, n (%)	43 (65)	16 (50)	27 (79)	**0.02**
Partial recovery, n (%)	14 (21)	9 (28)	5 (15)	0.2
Death, n (%)	9 (13)	8 (25)	1 (3)	**0.01**

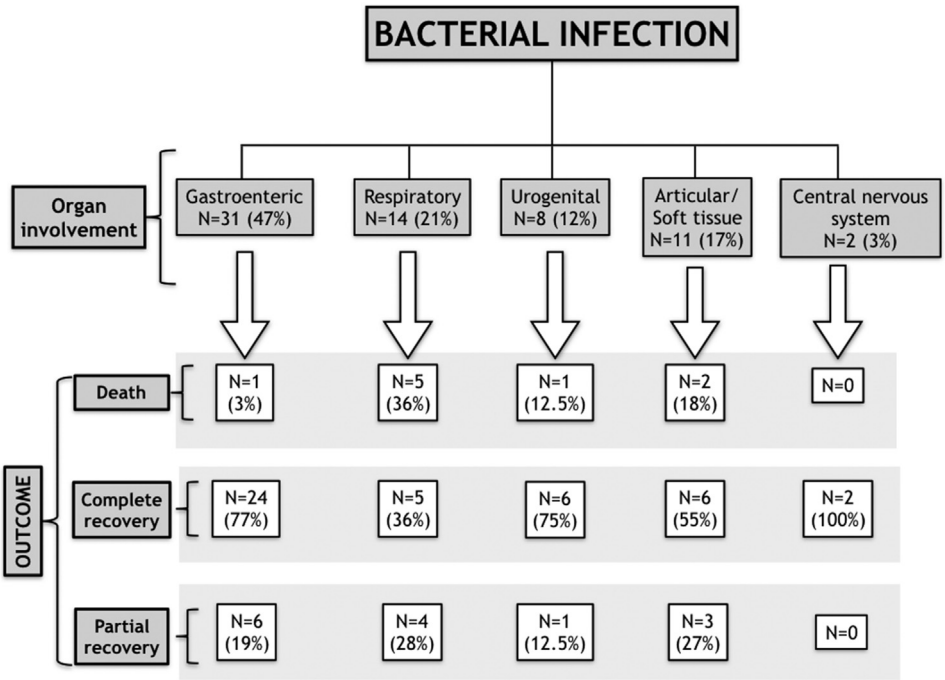

Fig. 4. Flowchart summarizing the outcomes of patients with bacterial myocarditis according to the syndrome at presentation.

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

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.

	Survivors (n = 57)	Not survivors (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.

	Complete recovery (n = 43)	Uncomplete recovery (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

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.

Patients with severe sepsis displayed a cluster of bacterial etiology, among which *Staphylococcus* and *Streptococcus* spp were relatively more prevalent, and respiratory symptoms were the most frequent at presentation. This subset of patients was characterized by a higher mortality, a lower recovery rate, a lower LVEF at admission and a higher rate of rhythm disturbances. We hypothesize that pathological myocardial involvement during bacterial sepsis is secondary to metastatic spread of infection from the primary focus, leading to architectural disruption of the myocardium. This concept may be confirmed by the histopathological data, which showed that eight of the ten patients for whom tissue samples were available, presented with sepsis, 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.[57,59]

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.[3]

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.

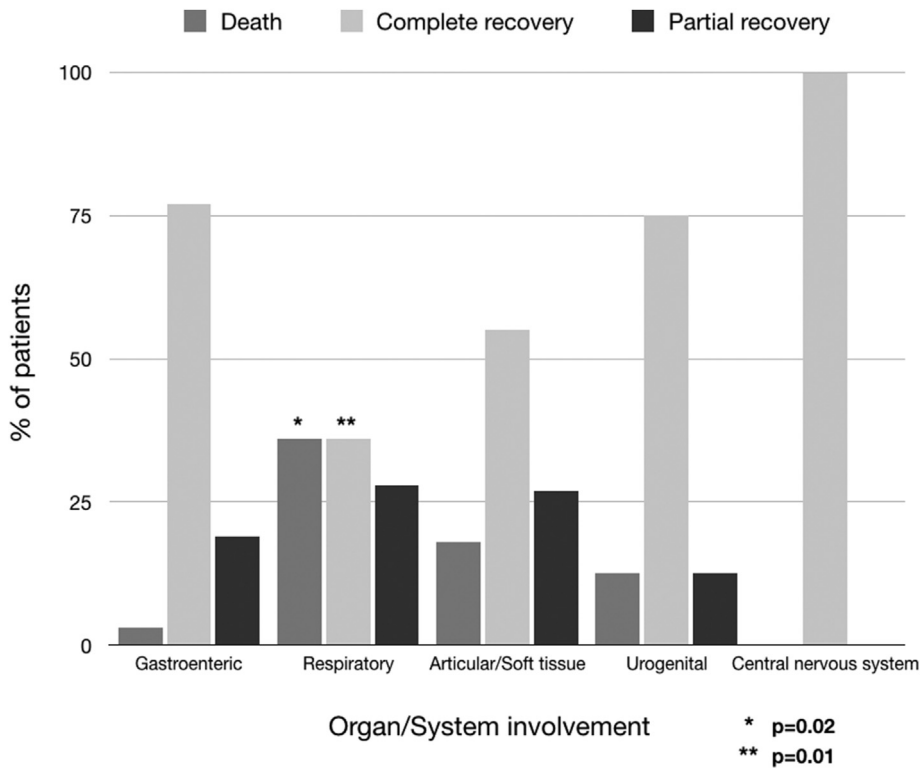

Fig. 5. Histogram depicting mortality and recovery rates according to the syndrome at presentation.

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.

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Declaration of Competing Interest

All authors have none to declare.

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