

Sepsis-induced myocardial dysfunction: a global overview of a common disorder. case reports and a narrative review of the literature

Abstract

Sepsis-induced myocardial dysfunction (SIMD), often referred to as septic cardiomyopathy (SCM), is a frequent yet under-recognized complication of sepsis and septic shock, reported in 10–70% of critically ill patients and consistently associated with higher mortality. Despite having been described almost six decades ago, the condition still lacks a unified definition, validated diagnostic thresholds, and a disease-specific treatment. It is characterized by acute, generally reversible biventricular systolic and/or diastolic impairment that occurs in the absence of obstructive coronary disease and typically recovers within seven to ten days. We present three illustrative cases managed in our intensive care unit—a streptococcal toxic shock syndrome complicating Fournier gangrene, a biliary sepsis mimicking acute coronary syndrome, and a refractory septic shock requiring venoarterial extracorporeal membrane oxygenation—and review the current understanding of the epidemiology, pathophysiology, multimodal diagnosis, and therapeutic strategies for SIMD. Early recognition through bedside echocardiography and cardiac biomarkers, source control, individualized hemodynamic support, and management of multiorgan dysfunction remain the cornerstones of care.

Keywords: septic cardiomyopathy; sepsis-induced myocardial dysfunction; septic shock; echocardiography; methylene blue; vasoplegia; critical care.

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Abbreviations: ACS, acute coronary syndrome; AKI, acute kidney injury; BNP, B-type natriuretic peptide; CI, cardiac index; CO, cardiac output; CRP, C-reactive protein; CRRT, continuous renal replacement therapy; cTn, cardiac troponin; ECMO, extracorporeal membrane oxygenation; GLS, global longitudinal strain; IABP, intra-aortic balloon pump; ICM, ischemic cardiomyopathy; ICU, intensive care unit; IL-6, interleukin-6; IVIG, intravenous immunoglobulin; LAD, left anterior descending artery; LVEF, left ventricular ejection fraction; MAP, mean arterial pressure; MAPSE, mitral annular plane systolic excursion; MB, methylene blue; MODS, multiple organ dysfunction syndrome; NT-proBNP, N-terminal pro-B-type natriuretic peptide; pVAD, percutaneous ventricular assist device; RFR, resting full-cycle ratio; ROS, reactive oxygen species; SCM, septic cardiomyopathy; SIMD, sepsis-induced myocardial dysfunction; SIMI, sepsis-induced myocardial injury; TAPSE, tricuspid annular plane systolic excursion; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VTI, velocity-time integral; WSES, World Society of Emergency Surgery.

Introduction

Septic cardiomyopathy is one of the more common cardiac complications of sepsis, with a reported frequency that ranges widely from roughly 10% to 70% and that translates into a meaningful increase in mortality. Although clinicians first recognized the entity nearly six decades ago, its conceptual boundaries remain blurred: the definition is still debated, the underlying mechanisms are only partially understood, the diagnostic criteria have not been standardized, and no specific pharmacological therapy has been established. For these reasons, sepsis-induced myocardial injury continues to pose a clinical challenge that demands both a clearer working definition and

more effective management strategies. The purpose of this review is to provide a comprehensive overview of the literature, focusing on how the definition has evolved over time, on the hemodynamic phenotypes of the condition, on the multifactorial mechanisms that drive its development, on the diagnostic tools available—with particular attention to echocardiography as the reference standard and to its limitations—and on the therapeutic options currently under consideration.

Septic shock is a life-threatening state arising from a dysregulated host response to infection that culminates in profound circulatory failure and cellular injury. As the most severe expression of the sepsis continuum, it carries a mortality that exceeds 40% despite advances in supportive care.^{1,2} The myocardial damage that accompanies septic shock stems from several converging pathological processes, including inflammation, oxidative stress, and microcirculatory failure. Clinically, this injury becomes apparent through the release of cardiac biomarkers such as troponins and is consistently linked to worse outcomes.³

Identifying myocardial injury as a forerunner of multiorgan failure is essential for timely intervention and for prognostic stratification in patients with septic shock; the involvement of the heart in the systemic response to infection underscores its dual role as both a target and a predictor of organ dysfunction.⁴ The present review seeks to clarify the mechanisms responsible for myocardial injury in sepsis, to examine its diagnostic and prognostic implications, and to discuss therapeutic approaches that may attenuate its impact. By integrating the available evidence and pointing to remaining knowledge gaps, we aim to inform bedside practice and to stimulate further research in this critical area of intensive care medicine.

Case presentations

Case 1 — Streptococcal toxic shock syndrome and Fournier gangrene

A 52-year-old man with a recent history of internal and external hemorrhoidectomy and drainage of a transmural abscess (7 October) developed a rapidly progressive necrotizing perineal and gluteal infection with scrotal extension, consistent with Fournier gangrene. The process evolved into septic shock with features of streptococcal toxic shock syndrome, and *Streptococcus pyogenes* was confirmed on culture. During his intensive care unit (ICU) stay he developed global, sepsis-associated myocardial dysfunction—encompassing both systolic and diastolic impairment—together with catecholamine-refractory vasoplegia and multiorgan failure.

The initial hemodynamic and echocardiographic assessment showed a hypodynamic, low-output profile: cardiac output 3.16 L/min, cardiac index 1.85 L/min/m², diffuse ventricular hypokinesis, a reduced ejection fraction, an altered E/A ratio, an elevated E/e', a shortened deceleration time, TAPSE < 17 mm, tricuspid S' < 9.5 cm/s, fractional area change < 35%, and a left ventricular outflow tract velocity–time integral (LVOT VTI) of 8.1 cm. Biomarkers were markedly elevated: troponin I 866 ng/mL, CK-MB 786 ng/mL, procalcitonin 31.46 ng/mL, C-reactive protein 250 mg/L, and interleukin-6 1233 pg/mL.

Variable	Value
Cardiac output L/min)	3.16 L/min
Cardiac index (L/min/m ²)	1.85 L/min/m ²
E/A ratio	altered
E/e'	elevated
TAPSE (mm)	< 17 mm
S' Tricuspid (cm/s)	< 9.5 cm/s
FAC (%)	< 35 %
TSVI (cm)	8.1 cm
Troponin I (ng/mL)	866 ng/mL (normal < 0.04 ng/mL)
CK-Mb (ng/mL)	786 ng/mL (normal 0-5 ng/mL)
Procalcitonin (ng/mL)	31.46 ng/mL (normal 0.05- 0.1 ng/mL)
C-reactive protein (mg/L)	250 mg/L (normal 0.05- 0.1 ng/mL)
interleukin-6 (pg/mL)	1233 pg/mL (normal 5- 10 pg/mL)

Management. Etiological control was achieved with crystalline penicillin 5 million IU intravenously every 6 hours for 14 days (20 million IU/day) combined with the lincosamide clindamycin 900 mg intravenously every 8 hours for 14 days for its antitoxin effect against streptococci and clostridia, together with intravenous human immunoglobulin 200 g infused over four hours (2 g/kg). Hemodynamic support consisted of dual vasopressors—norepinephrine and vasopressin (peak doses 0.69 mcg/kg/min and 0.07 IU/kg/min, respectively)—and the inotrope dobutamine (peak dose 4 mcg/kg/min). Methylene blue was added for refractory vasoplegia at a loading dose of 2 mg/kg intravenously over 30 minutes, followed by a continuous infusion of 0.5 mg/kg/h for 24 hours. Surgical source control required repeated procedures: fasciotomy and abscess drainage, serial debridement of necrotic tissue, resection of skin, subcutaneous tissue and muscle, surgical washouts, and negative-pressure wound therapy. Multiorgan support included continuous renal replacement therapy delivered as continuous venovenous hemodiafiltration with oXiris/CytoSorb adsorptive membranes, temporary invasive mechanical ventilation, and management of liver injury and sepsis-associated coagulopathy. The patient improved progressively, with resolution of shock and partial recovery of myocardial function.

In this case two mechanisms of hemodynamic instability coexisted: distributive shock from nitric oxide-mediated vasoplegia and a relative cardiogenic component from septic myocardial depression. Streptococcal toxic shock syndrome amplifies the systemic inflammatory response through superantigens, which in turn promote endothelial dysfunction, myocardial depression, and coagulopathy. Methylene blue counteracts refractory vasodilation by inhibiting the nitric oxide–cyclic GMP pathway, allowing catecholamine requirements to be reduced, while beta-adrenergic inotropes such as dobutamine raise cardiac output in the setting of contractile depression. Early, aggressive surgical control of the infectious focus is fundamental in necrotizing infections and is decisive for survival, whereas continuous renal replacement therapy with adsorptive membranes may aid clearance of inflammatory mediators, although its definitive clinical benefit remains under investigation. The combination of sepsis-associated myocardial dysfunction and refractory vasoplegia represents a particularly severe form of septic shock whose successful management requires a multimodal strategy—source control, targeted antimicrobial therapy, individualized hemodynamic support, and treatment of multiorgan failure. The case illustrates why early recognition of myocardial depression in severe sepsis is essential to optimize treatment and improve prognosis.

Case 2 — Biliary sepsis mimicking acute coronary syndrome

A 51-year-old man without prior comorbidities was admitted with right upper-quadrant abdominal pain, fever, bilious vomiting, and malaise. He had previously undergone partial cholecystectomy and biliary stent placement for cholangitis. On admission he showed clinical signs of shock, including hypotension (mean arterial pressure 36 mmHg), a temperature of 39.9 °C, and altered mental status, and required norepinephrine (0.32 mcg/kg/min) and vasopressin (0.04 IU/kg/h).

Echocardiography documented significant biventricular dysfunction—fractional area change 15%, TAPSE 12 mm, tricuspid S' wave 9.6 cm/s, Tei (myocardial performance) index 0.7, global longitudinal strain (GLS) –9.6%, MAPSE 7 mm, left ventricular VTI 14 mm, RV/LV ratio 0.43, LVEF 40%, and cardiac output 2.94 L/min—accompanied by a marked rise in troponin I (3408 ng/L) and NT-proBNP (6098 pg/mL). The electrocardiogram revealed dynamic ST-segment elevation in the precordial leads.

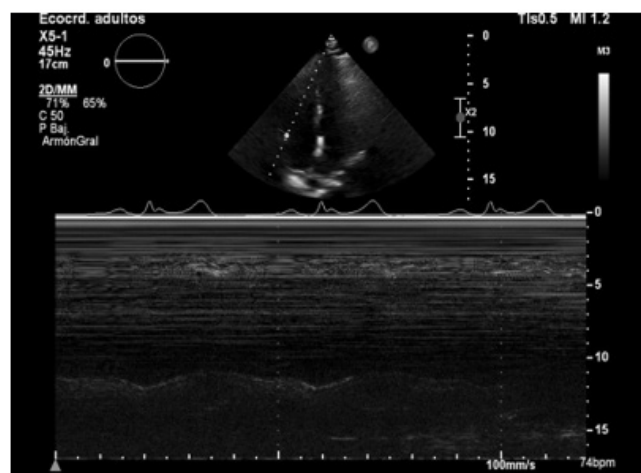


Figure 1 Right ventricle not dilated (basal diameter 31 mm), not hypertrophic (5 mm). Depressed right ventricular systolic function: TAPSE of 12 mm.

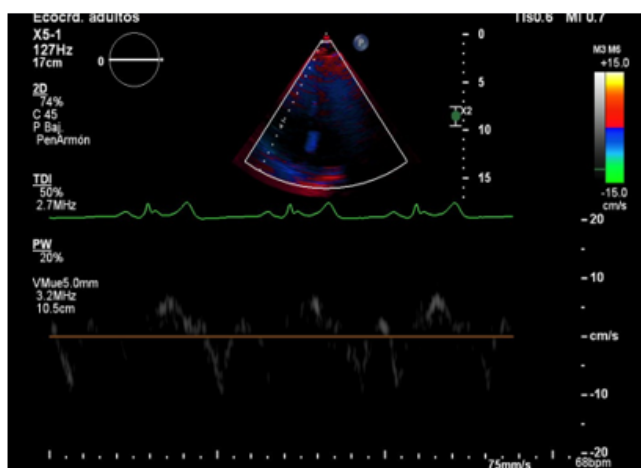


Figure 2 Right ventricle not dilated (basal diameter 31 mm), not hypertrophic (5 mm). Borderline right ventricular systolic function: RV free wall S wave of 9.6 cm/s.

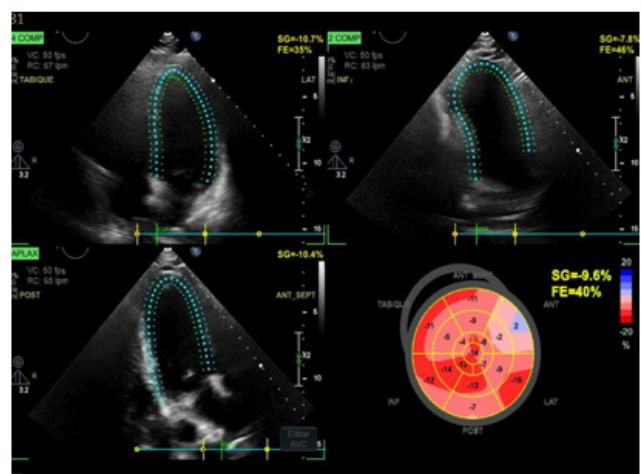


Figure 3 Left ventricle with generalized hypokinesis. Systolic function: ejection fraction 40% (VTD 70 ml and VTS 49 ml). Cardiac output 2.94 L/min.

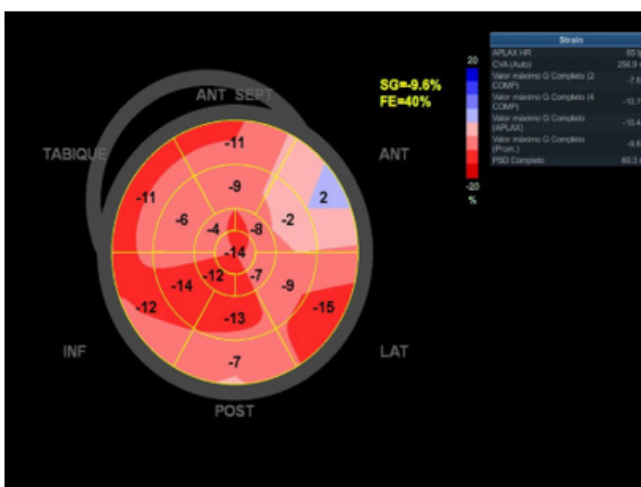
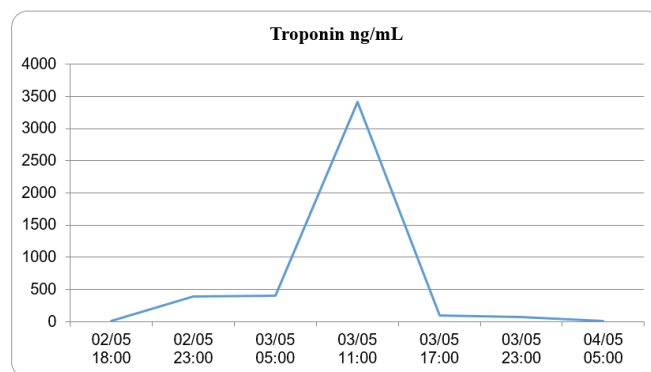


Figure 4 Systolic function: Decreased global longitudinal strain (-9.6%).



Graph 1 Behavior of high-sensitivity Troponin I levels.

Because acute coronary syndrome was suspected, cardiac catheterization was performed; it disclosed a 50% lesion in the proximal left anterior descending (LAD) artery without thrombosis. Resting full-cycle ratio (RFR) physiology was negative for ischemia, and obstructive coronary artery disease was therefore excluded. The working diagnosis was sepsis-induced myocardial injury progressing to septic cardiomyopathy in the context of grade III biliary cholangitis (WSES classification), with cultures positive for *Escherichia coli*, an interleukin-6 of 112,600 pg/mL (reference < 5–7 pg/mL), and criteria for multiorgan dysfunction that included cardiorenal syndrome, hyperlactatemia (lactate 6.7 mmol/L), KDIGO stage 2 acute kidney injury, and post-ERCP pancreatitis.

Treatment comprised ultrasound-guided volume resuscitation, vasoactive agents, the inodilator levosimendan, broad-spectrum antibiotics (meropenem), statins, and respiratory rehabilitation. Over the following days clinical and hemodynamic status improved, cardiac biomarkers fell progressively (troponin I 335 ng/mL; NT-proBNP 3772 pg/mL), and biventricular function recovered (fractional area change 35%, TAPSE 19 mm, S' 10 cm/s, Tei index 0.3, GLS 15%, MAPSE 12 mm, left ventricular VTI 21 mm, RV/LV ratio 0.8, LVEF 58%, cardiac output 4.94 L/min).

Criterion (Septic Cardiomyopathy)	Initial patient values	Final Patient Values
FAVD(%)	15% (Severe RV dysfunction)	35% (Improvement, within the low normal range)
TAPSE (mm)	12 mm (RV Dysfunction)	19 mm (Normal ≥ 17 mm)
Wave S(cm/s)	9.6 cm/s (RV longitudinal dysfunction)	10 cm/s (Normal lower limit)
Index TEI	0.7 (Altered, <0.55)	0.3 (Normal ≤ 0.55)
SGL(%)	14% (Low cardiac output)	15% (Persistent mild alteration)
MAPSE (mm)	7 mm (RV small compared to LV)	12 mm (Normal ≥ 10 mm)
ITV VI (mm)	14 mm (Low cardiac output)	21 mm (Normal)
Index RV/LV	0.43 (RV small compared to LV)	0.8 (Normal)
FEVI (%)	40% (Moderate LV Dysfunction)	58% (Normal)

Cardiac Output (L/min)	2.94 L/min (Low cardiac output)	4.94 L/min (Normal)
Electrocardiogram (EKG)	Dynamic ST elevation	No ischemic changes
Coronary angiography	Injury 50% proximal anterior descending, negative RFR	Without significant obstructive coronary artery disease

Graph 2 Evolution and behavior of echocardiographic, electrocardiographic variables, and coronary angiography findings.

Sepsis-induced myocardial dysfunction is an acute, generally reversible process unrelated to acute coronary syndrome, characterized by systolic and/or diastolic impairment with left ventricular dilation. Sepsis-induced myocardial injury, by contrast, denotes myocardial damage detected through elevated biomarkers even when overt echocardiographic dysfunction is absent; it may progress to septic cardiomyopathy, in which biventricular dysfunction, elevated troponin and NT-proBNP, and initial electrocardiographic changes that mimic acute myocardial infarction coincide, a presentation associated with a poorer prognosis. In this patient, coronary angiography ruled out significant obstructive disease, and the clear, sustained recovery of cardiac function after hemodynamic and inotropic support supported the diagnosis of septic cardiomyopathy.

Several findings favored this interpretation: biventricular functional recovery without coronary intervention; hemodynamic improvement with vasopressors and normalization of lactate; a 50% proximal LAD lesion shown by coronary physiology to be non-ischemic; an echocardiographic pattern of reversible dysfunction without necrotic segments; and severe systemic inflammation (IL-6 > 112,600 pg/mL, CRP > 160 mg/L, procalcitonin > 20 ng/mL). The slow pancoronary flow observed may reflect sepsis-induced microvascular vasoplegia, a phenomenon described in septic cardiomyopathy. Taken together, the combination of biventricular abnormalities, hypoperfusion, cardiorenal syndrome, and progressive organ dysfunction points to a low-output state secondary to systemic myocardial dysfunction rather than to a structural ischemic cause.

Case 3 — Refractory septic shock rescued with venoarterial ECMO

A 49-year-old woman with no known structural heart disease was admitted with an acute abdomen secondary to gastric perforation and presented with signs of hypovolemic shock. An emergency exploratory laparotomy confirmed the perforation, and an antrectomy with Roux-en-Y reconstruction was performed; she was then transferred to the ICU for close monitoring. During the first 24 hours she remained hypotensive despite crystalloid resuscitation and required norepinephrine. Septic shock from an intra-abdominal focus was diagnosed and broad-spectrum antibiotics were started. Over the next 48 hours her hemodynamics deteriorated, with rising lactate and signs of systemic hypoperfusion. A transthoracic echocardiogram revealed a left ventricular ejection fraction of 17% with global hypokinesis but no segmental ischemia, consistent with severe septic cardiomyopathy. Inotropic support was added for the resulting low cardiac output, producing a mixed distributive–cardiogenic shock state. Despite dual vasopressors and inotropes she developed refractory hypotension, anuria, and progressive metabolic acidosis.

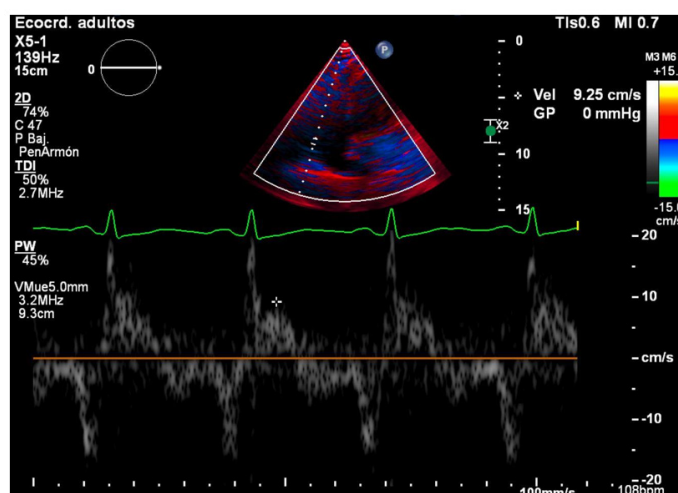


Figure 5 Pulsed tissue Doppler at the level of the tricuspid annulus in apical 4-chamber view. A decreased systolic velocity (S' wave) of 9.2 cm/s is evident, suggestive of right ventricular systolic dysfunction.

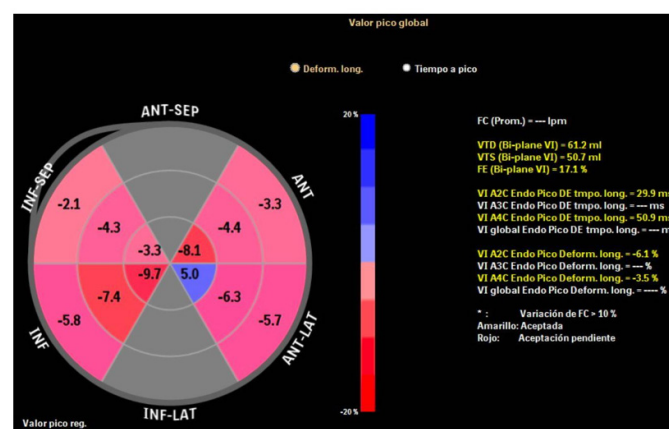


Figure 6 Polar map ("bull's-eye view") of left ventricular longitudinal strain (18 segments) obtained by speckle tracking from the apical window. Severe systolic dysfunction is observed with a marked reduction in global longitudinal strain estimated from the apical 4- and 3-chamber views (average -4.8%). The left ventricular ejection fraction by biplane (Simpson) method was 17%.

Given refractory shock with severe but potentially reversible myocardial dysfunction, venoarterial extracorporeal membrane oxygenation (VA-ECMO) was instituted as rescue therapy. Systemic perfusion improved progressively thereafter, lactate fell, and vasoactive requirements declined. The course was complicated by acute arterial ischemia of the right lower limb during ECMO support, managed with angiography and balloon angioplasty; the event was attributed to the prothrombotic state of sepsis, intense vasopressor-induced vasoconstriction, and the hemodynamic alterations inherent to extracorporeal support. In the following days ventricular function recovered—consistent with the reversible nature of septic cardiomyopathy—and the patient was successfully weaned from ECMO with complete withdrawal of vasoactive support.

Definition and classification of myocardial injury

Myocardial injury can arise from a variety of cardiac and non-cardiac conditions and may be acute or chronic. When sepsis is the primary cause, myocardial injury becomes a frequent complication that is independently associated with early mortality. The pathophysiology

of sepsis-induced myocardial injury (SIMI) is heterogeneous and involves multiple mechanisms, including the cardiac dysfunction that drives high rates of morbidity and mortality. Importantly, sepsis-induced myocardial dysfunction is reversible and is characterized by left ventricular depression, with most patients recovering completely within a few days.⁵⁻⁷ Appropriate classification and assessment of myocardial injury—whether it occurs in the context of acute coronary syndrome (ACS) or of sepsis—are essential for sound clinical management and improved outcomes, and further work is needed to refine our understanding of these mechanisms and to design more effective therapies.

Toward a working definition

No universally accepted definition of sepsis-induced cardiomyopathy yet exists, owing to the wide variability in diagnostic criteria. Drawing on the features most consistently described, a practical working definition can nonetheless be assembled around the following elements: (1) acute cardiac dysfunction; (2) the absence of acute atherosclerotic coronary disease as the cause of that dysfunction; (3) ventricular dilation with increased compliance and filling pressures that may be normal or even low; (4) a reduced ejection fraction without a fall in stroke volume; (5) dysfunction that may be left- or right-sided, systolic or diastolic, biventricular, or global; (6) a diminished or absent response to fluid resuscitation and catecholamines; and (7) reversibility of the condition within 7 to 10 days.⁸⁻¹²

Incidence and clinical significance (epidemiology)

The reported incidence of septic cardiomyopathy (SCM) varies considerably, with prevalence estimates spanning 10% to 70%.^{13,14} SCM denotes a reversible myocardial dysfunction triggered by sepsis that reduces myocardial contractility and left ventricular ejection fraction (LVEF) and that generally returns to baseline within seven to ten days.¹³ Its full clinical significance is still being clarified, and the specific implications and long-term consequences of SCM remain incompletely defined.¹⁴ Even so, it is recognized as a serious condition capable of markedly worsening the prognosis of sepsis and septic shock.¹⁵ Additional studies are warranted to characterize the epidemiology and clinical impact of SCM more precisely and to develop standardized diagnostic and treatment protocols.¹⁴

Pathophysiology: mechanisms of myocardial injury in septic shock

Inflammatory response

The inflammatory response in septic shock is a complex process involving the activation of leukocytes, endothelial cells, and the coagulation system. In severe sepsis, the release of bacteria, their toxins, and a range of inflammatory mediators sets off a systemic inflammatory cascade that produces a hyperinflammatory state, compromises innate immune function, and ultimately drives septic shock and multiorgan failure.¹⁶⁻¹⁸ The intensity of this response varies from moderate to severe, and both human and rodent studies indicate that the systemic inflammatory response syndrome of sepsis is accompanied by a disturbed redox balance, heightened inflammation, and impaired innate immunity.^{17,18} Across the onset, resolution, and longer-term course of sepsis, the immune system displays a persistent and simultaneous mix of inflammatory and anti-inflammatory activity, reflecting dysfunction of both innate and adaptive immunity.¹⁹ Although the inflammatory response initially

alerts the host to infection, it becomes dysregulated as the disease evolves, yielding a paradoxical combination of hyperinflammation and immunosuppression.¹⁸

Microcirculatory dysfunction

Microcirculatory failure is a hallmark of sepsis and plays a central role in its pathophysiology. The characteristic disturbances—impaired nitric oxide-dependent arteriolar vasodilation together with heightened perfusion heterogeneity from inadequate vasoconstriction—reduce oxygen delivery, produce tissue hypoxia, and promote organ dysfunction.²⁰⁻²² These changes appear early in the disease course, and the degree of microvascular impairment correlates with severity and prognosis in ICU patients.^{21,22} Microcirculatory assessment, however, is difficult at the bedside and is often inferred from macrohemodynamic surrogates such as blood pressure, cardiac output, and heart rate.²¹ Importantly, microcirculatory recovery after early resuscitation is associated with lower mortality,²¹ so restoring microvascular flow is emerging as a promising resuscitation target, even though further data are required to confirm its benefit.^{21,22} Recognizing the pivotal role of the microcirculation encourages clinicians to look beyond systemic hemodynamic parameters and toward more targeted resuscitation strategies.²²

Cellular and metabolic alterations

Sepsis provokes substantial metabolic derangement, with mitochondrial dysfunction acting as a principal driver of cellular metabolic dysregulation. These disturbances affect the handling of all macronutrients, favoring intensified glycolysis, increased lactate production, and enhanced lipolysis in adipose tissue.²² The hyperinflammatory state of sepsis deepens the cellular energy deficit, forcing adaptive shifts in metabolism and a reallocation of energy expenditure.²⁴ Because mitochondrial dysfunction reduces respiratory capacity and impairs metabolic function, it is closely tied to prognosis.²⁴ Overall, the cellular and metabolic disturbances of sepsis arise from an interconnected network of pathways encompassing altered carbohydrate and lipid metabolism and the downstream consequences of mitochondrial dysfunction on cellular homeostasis.^{21,22}

Oxidative stress and mitochondrial dysfunction

Oxidative stress and mitochondrial dysfunction are tightly interrelated and feature in the pathogenesis of many diseases. Mitochondria are a major source of intracellular reactive oxygen species (ROS) and are themselves highly vulnerable to oxidative injury. Excessive ROS production combined with failing antioxidant defenses can damage the mitochondrial respiratory chain, disrupt membrane permeability, and destabilize cellular homeostasis.²³⁻²⁵ The resulting surge of free radicals inflicts oxidative damage on key cellular constituents, including DNA, proteins, and lipids.^{25,26} Mitochondrial dysfunction and oxidative stress have been implicated in a broad spectrum of disorders—metabolic, neurodegenerative, and cardiac²⁴⁻²⁷—which has fueled interest in mitochondria-targeted antioxidant therapies as potential treatments.²⁵ Clarifying the interplay between oxidative stress and mitochondrial dysfunction therefore remains a research priority with wide implications for interventions that could slow disease progression and improve outcomes.

Diagnosis and clinical characteristics of septic cardiomyopathy

Septic cardiomyopathy is a non-ischemic cardiac dysfunction that develops in patients with sepsis. Although no firm diagnostic criteria exist, most reviews and experts converge on a recognizable

set of features,¹⁵ foremost among them an acute, reversible course with gradual recovery to normal within 7 to 10 days of onset. In their early work, Parker et al.^{21,22} used continuous radionuclide angiography and thermodilution to study cardiac output in 20 patients with septic shock (13 survivors and 7 non-survivors) and showed that survivors characteristically developed a fall in ejection fraction and a rise in end-diastolic volume during the initial phase.

Echocardiographic findings

Echocardiography is a cornerstone of the diagnosis of septic cardiomyopathy, and there is broad agreement that every patient with hemodynamic instability in the ICU should undergo it.^{29,30} Goal-directed bedside assessment in patients with sepsis frequently provides the first evidence of the condition.³¹ Even so, no single echocardiographic parameter is diagnostic on its own.²¹

Global and biventricular dysfunction. Early echocardiographic studies demonstrated that some septic patients exhibit left ventricular systolic and diastolic dysfunction with reduced contractility.^{29,30} Right ventricular dysfunction in sepsis is closely linked to left ventricular dysfunction,^{32–34} and a growing body of work suggests the right ventricle may play a key role in septic cardiomyopathy.³⁵

Left ventricular dilation. According to the 1984 study by Parker et al.²¹, left ventricular dilation may reflect increased ventricular compliance. The higher left ventricular end-diastolic dimension seen in septic shock can stem from initial fluid resuscitation or from abnormal dilation induced by sepsis itself, suggesting that a greater initial end-diastolic dimension probably represents dilation caused by the myocardial changes intrinsic to septic shock.³⁶

Limited response to fluids and catecholamines. With regard to fluid management, it has become increasingly clear that excessive resuscitation harms septic patients, and a positive fluid balance has been identified as a factor that worsens prognosis.³⁸ Current sepsis survival guidelines endorse catecholamines to augment vascular tone within appropriate regimens,³⁸ although potential risks—such as increased myocardial oxygen consumption—remain.⁷ Stress-induced (Takotsubo) cardiomyopathy. Distinct from other myocardial dysfunctions, stress-induced (Takotsubo) cardiomyopathy is a dysfunction of the apical left ventricle characterized by mid-segment narrowing or dyskinesia, with or without apical involvement, that crosses single coronary territories.³⁹ Sepsis is the most common trigger of Takotsubo cardiomyopathy,⁴⁰ and stress-induced cardiomyopathy has been reported to raise mortality in septic patients by more than 20%.^{41,42} Although both septic and Takotsubo cardiomyopathy are associated with sepsis, their pathogenesis differs.

Echocardiographic indices of cardiac function

Left ventricular ejection fraction (LVEF). LVEF is one of the earliest indices used to describe septic cardiomyopathy and provides a measure of systolic dysfunction.²² Despite its advantages, LVEF is not the optimal marker of left ventricular function because it is strongly load-dependent;⁴³ used in isolation, it can lead to misdiagnosis of septic cardiomyopathy. The vasopressor dose and the depth of shock must therefore be considered when interpreting LVEF, which captures systolic function only partially and carries inherent limitations.

Myocardial performance (Tei) index. The myocardial performance index, or Tei index, is a Doppler-derived measure that integrates systolic and diastolic function as a proportion of the cardiac work cycle.⁴⁴ An impaired index has been associated with increased 90-day mortality over a 24-hour study window;⁴⁵ accordingly, a lower (better) index correlates with a more favorable prognosis.

Mitral annular plane systolic excursion (MAPSE). MAPSE measures the linear displacement of the mitral annulus toward the apex during contraction⁴⁶ and serves as an index of global and regional left ventricular systolic function.²¹ It has been shown to be an independent predictor of mortality in sepsis.⁴⁷ Global longitudinal strain (GLS). Strain imaging quantifies regional myocardial deformation and can detect subtle declines in left ventricular systolic function before LVEF falls.^{48,49} Ehrman et al.^{49,50} proposed GLS as the preferred parameter for studying the relationship between systolic function and prognosis in septic cardiomyopathy. Its main limitation is a dependence on good image quality and susceptibility to artifact and noise.^{50,51} e' and E/e' . Many septic patients display diastolic dysfunction.²³ Early diastolic mitral annular velocity (e') and the E/e' ratio are key indices of left ventricular diastolic function,⁴⁴ with e' serving as a first-line measure. Although e' can refine prognostic prediction in sepsis,⁵² it is influenced by age, mitral valve disease, and mechanical ventilation.⁵³

Tricuspid annular plane systolic excursion (TAPSE). Right ventricular dysfunction increases morbidity and mortality across several conditions, including heart failure and pulmonary hypertension.^{54,55} TAPSE is a readily obtained and reproducible index of right ventricular function, although further studies are needed to define its relationship with sepsis and septic cardiomyopathy.^{56,57}

Biochemical diagnosis

Troponins. Troponin is a fundamental cardiac biomarker widely used to diagnose myocardial injury in settings such as acute coronary syndrome and ischemic cardiomyopathy. The protein complex comprises three subunits (troponin T, C, and I), of which the cardiac T and I isoforms (cTn) show high specificity and sensitivity for cardiac myocytes, making their appearance in the bloodstream a useful marker of myocardial damage. Troponin levels typically peak 12 to 48 hours after injury and remain elevated for four to ten days, and the sensitivity for detecting cardiac troponin T and I approaches 100% when sampling is performed 6 to 12 hours after the onset of acute chest pain. Consequently, to reliably exclude acute coronary syndrome, troponin should be repeated 6 to 12 hours after the initial measurement. Because conditions such as myocarditis, Takotsubo cardiomyopathy, and shock can also raise troponin, results must always be interpreted within the clinical context.^{58–62}

Natriuretic peptides. B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are established biomarkers for the diagnosis and prognosis of heart failure, and both US and European guidelines recommend their measurement for diagnosis and risk stratification. Elevated levels, particularly of BNP, are strongly associated with adverse outcomes—worse prognosis, higher mortality, and greater risk of readmission—and they help differentiate heart failure from other conditions when the clinical picture is uncertain. Despite the concurrent rise of troponins in heart failure, natriuretic peptides remain the preferred biomarkers because of their specificity and clinical utility.^{63–66} Their central role, especially that of BNP and NT-proBNP, underscores their importance in everyday practice.

Inflammatory markers. Inflammatory biomarkers form a further subset used in the diagnosis of myocardial injury and reflect the role of inflammation in its pathogenesis. Several have been identified, including C-reactive protein (CRP), interleukin-6 (IL-6), and S100A9. CRP levels correlate with plaque rupture in acute myocardial infarction; IL-6, a proinflammatory cytokine released after tissue injury, is consistently elevated in patients with myocardial injury; and S100A9, released by neutrophils and monocytes, is linked to myocardial inflammation. Although useful, these markers

lack specificity for septic cardiomyopathy and may rise in other conditions, so a multimodal approach that combines biomarkers with echocardiography, magnetic resonance imaging, and ventriculography is often required for accurate diagnosis.^{61–70} Inflammatory markers thus provide valuable information about myocardial injury, but their broad applicability reinforces the need for a multifaceted diagnostic strategy to distinguish septic cardiomyopathy from other entities.

Association with multiple organ failure

Relationship between myocardial injury and organ dysfunction

Myocardial injury in sepsis is intrinsically connected to multiorgan failure, with sepsis-induced cardiomyopathy acting as a critical factor. Sepsis-induced myocardial dysfunction—a reversible decline in contractility accompanied by left ventricular cavity dilation and a reduced LVEF—is closely associated with cardiac dysfunction, multiorgan failure, and increased mortality in septic patients.^{71–73} Its pathophysiology involves impaired myocardial perfusion, direct myocardial depression, and mitochondrial dysfunction;^{71,72} together these substantially worsen sepsis-related cardiac dysfunction and correspond to markedly higher mortality.⁷² Management is challenging, and current strategies center on infection control, mitigation of organ damage, and hemodynamic support; further research is needed to deepen our understanding of the pathophysiology of sepsis-induced cardiomyopathy and to design more effective therapies.^{71,72}

Myocardial injury as a prognostic marker of multiorgan failure

Myocardial injury is an important prognostic indicator for the development of multiorgan failure. In acute heart failure, dysfunction or injury across multiple organs—including the heart—identifies patients at the highest risk of adverse outcomes, in whom worsening heart failure is more frequent.⁷⁶ In severe COVID-19, the unfavorable prognosis associated with myocardial injury is driven primarily by multi-system involvement and disease severity.⁷⁷ More broadly, myocardial injury is associated with higher mortality among septic patients and represents the most frequent complication of organ dysfunction in this population;^{75,77} research has consistently linked it to an increased risk of both long-term and in-hospital mortality, underscoring its role as a prognostic marker of multiorgan failure.⁷⁵

Implications for patient management and prognosis

The implications of septic cardiomyopathy (SCM) for management and prognosis are substantial. Characterized by a reversible decrease in contractility, left ventricular dilation, and a reduced LVEF, the condition can precipitate cardiac dysfunction, multiorgan failure, and increased mortality in septic patients.^{78–80} Although the prognostic weight of septic left ventricular dysfunction is still debated, its treatment likewise remains a matter of discussion.¹³ At present, management rests chiefly on supportive measures—infection control, mitigation of organ damage, and hemodynamic support.⁷⁸ Interventions intended to strengthen cardiac function, such as heart-rate reduction with ivabradine or beta-blockers, have been proposed and may prove beneficial, though their use remains experimental.⁸⁰ Because the pathophysiology of sepsis-induced cardiomyopathy spans impaired myocardial perfusion, direct myocardial depression, and mitochondrial dysfunction,¹² continued research is essential to improve understanding of the condition and to design more effective therapeutic strategies.

Therapeutic interventions

Pharmacological approaches

Several pharmacological options beyond conventional amine-based therapy have been proposed for septic shock, including beta-blockers, hormone replacement therapy, levosimendan, and angiotensin II.⁸¹ Melatonin, a hormone with diverse physiological roles, has emerged as a candidate treatment for septic cardiomyopathy because of its anti-inflammatory, antioxidant, and anti-apoptotic properties.⁸² Among inotropes, levosimendan has shown efficacy in reducing mortality in severe sepsis and septic shock. Dobutamine, a beta-1 adrenergic agonist, stimulates myocardial beta-1 receptors to increase contractility without provoking vasoconstriction or tachycardia and has long been used to counter the downregulation of beta-adrenergic receptors in patients with persistent cardiogenic shock in the ICU. Levosimendan, acting as a calcium sensitizer, enhances the effect of calcium on the myofilaments during contraction.⁷⁹ Whether levosimendan is superior to dobutamine remains a contentious question.

Although crystalloids are generally recommended as the initial resuscitation fluid in sepsis, experimental data suggest that albumin and hypertonic saline may offer greater benefit for cardiac function in septic animals.⁷⁹ Norepinephrine is the vasopressor of choice for septic patients with low cardiac output because it augments preload and cardiac output in life-threatening states.⁸⁰ Additional pharmacological avenues that have been explored for sepsis-induced cardiomyopathy include dexmedetomidine, 3,3'-diindolylmethane, and traditional Chinese medicine.^{13,78,79} Nonetheless, treating sepsis-induced cardiomyopathy remains a considerable challenge, which highlights the urgent need for more research into effective therapeutic strategies.⁷⁹

Hemodynamic support

Hemodynamic support is a pivotal component of the management of septic cardiomyopathy. Although uncertainties persist, initial treatment rests on early recognition, fluid resuscitation, and vasopressor administration.¹³ The Surviving Sepsis Campaign and the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) strongly recommend norepinephrine as the first-line vasopressor in septic shock.¹³ Inotropic agents such as levosimendan have, in addition, demonstrated efficacy in reducing mortality in severe sepsis and septic shock.⁸⁰ Mechanical support devices—intra-aortic balloon pumps (IABP), percutaneous ventricular assist devices (pVAD), and extracorporeal membrane oxygenation (ECMO)—have also been considered for sepsis-induced cardiomyopathy, although conclusive evidence from randomized controlled trials is lacking.⁸³ Given the complexity of the condition, a personalized approach guided by each patient's hemodynamic status and response to treatment is essential.

Targeted therapies for myocardial protection

Therapies aimed specifically at myocardial protection are an active research focus. Strategies under investigation include heart-rate reduction with agents such as ivabradine and beta-blockers and inotropic support with drugs such as levosimendan; fluid resuscitation with albumin and hypertonic saline together with norepinephrine support are likewise considered important components, complemented by comprehensive supportive care and continuous monitoring. Nanocarrier-based approaches, including antibody-modified liposomes, have yielded promising preclinical results in the treatment of myocardial infarction,⁸⁴ and other avenues—protein-based drugs, gene-editing technologies, nucleic-acid drugs, and cell therapy—are

being explored.⁸⁵ Further research is nonetheless required to refine and optimize these modalities for eventual clinical use.

Methylene blue

Prolonged exposure to high-dose catecholamines causes adrenergic receptor downregulation and desensitization, so that some patients respond inadequately.^{86,90,91} In this setting, decatecholaminization strategies have been advocated for septic shock; because alternative vasopressors such as vasopressin, terlipressin, and angiotensin II also carry a higher likelihood of tachyarrhythmias, organ ischemia, and immune dysfunction,^{87,88} methylene blue (MB) has been investigated as a means of reaching hemodynamic targets.⁹¹ MB blocks soluble guanylate cyclase, curbing the excessive production of nitric oxide and attenuating its vasorelaxant effect on vascular smooth muscle, thereby restoring vascular tone and raising blood pressure.^{88,93}

Ibarra-Estrada et al.⁸⁶ conducted the largest randomized controlled trial of MB in septic shock, randomizing 91 patients to an intravenous infusion of 500 mL of 0.9% sodium chloride with or without 100 mg of MB over 6 hours, once daily, for three doses. MB improved hemodynamic status, shortened ICU length of stay, and reduced the number of days on mechanical ventilation, with no effect on methemoglobin levels—suggesting that the intervention is safe. Differences in patient populations, methods, dosing, and timing of MB administration probably account for the divergent results across studies. Early initiation of MB, within the first 8 hours of sepsis, combined with prolonged continuous infusion (given its 5- to 6-hour half-life), is likely to be more effective.^{90,98} Although further studies are needed, the available evidence suggests that MB may be a promising vasopressor-sparing agent in sepsis and septic shock.

Methylene blue is a versatile agent acting on multiple pathways. It restores vascular tone by inhibiting endothelial and inducible nitric oxide synthase and their downstream effector, soluble guanylate cyclase,⁸⁹ and re-establishes vascular regulation in vasoplegic states such as septic shock.^{89,90} MB also appears to have neuroprotective effects, and it has been hypothesized to limit brain damage and ischemia.⁹¹ As an oxygen-reducing agent, MB donates electrons to oxygen and accelerates the conversion of methemoglobin to hemoglobin, lowering the disease burden in methemoglobinemia.⁸⁴ With a short terminal half-life of about 5.25 hours, MB may require repeated dosing or continuous infusion to maintain its effect;⁹⁴ the lowest documented effective dose ranges from 0.25 to 2 mg/kg/h.⁸⁶ Starting MB together with vasopressors at the onset of sepsis (within 8 hours) is more beneficial than delayed initiation,⁹⁶ and MB is best used as adjunctive—rather than rescue—therapy in shock.⁹² In vasoplegic syndrome, early administration in the operating room has been associated with better outcomes than postoperative ICU administration, including fewer major adverse events such as renal failure and operative mortality.⁸⁸ No adverse events were observed with continuous infusion of MB for 48 hours;⁸⁹ skin and urine discoloration are the predominant non-fatal side effects.⁹⁷

Conclusion

This review has emphasized the central role of myocardial injury in septic shock, its intricate relationship with multiorgan failure, and its prognostic weight. By outlining the mechanisms that underlie myocardial injury— inflammation, mitochondrial dysfunction and oxidative stress, calcium dysregulation, microcirculatory failure, and myocardial hibernation—it has reinforced the value of early recognition and biomarker-guided monitoring in clinical decision-making. It has also highlighted the potential therapeutic implications

of addressing myocardial injury, from anti-inflammatory agents to supportive measures, with the goal of mitigating the adverse outcomes of septic shock. Future work should focus on clarifying the underlying pathophysiology, identifying novel therapeutic targets, and advancing personalized-medicine approaches to optimize care. Two questions in particular deserve attention: are our current definitions the best way to characterize sepsis-induced myocardial dysfunction, and could identifying cardiac subphenotypes to guide resuscitation improve outcomes? A better understanding of individual patient responses in the septic state holds considerable promise for personalized, targeted care.

Declarations

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