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Infection as an under-recognized precipitant of acute heart failure: prognostic and therapeutic implications

Sofia Bezati[1] · Maria Velliou[1] · Ioannis Ventoulis[2] · Panagiotis Simitsis[3] · John Parissis[1,4] · Effie Polyzogopoulou[1,4]

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Abstract
As the prevalence of heart failure (HF) continues to rise, prompt diagnosis and management of various medical conditions, which may lead to HF exacerbation and result in poor patient outcomes, are of paramount importance. Infection has been identified as a common, though under-recognized, precipitating factor of acute heart failure (AHF), which can cause rapid development or deterioration of HF signs and symptoms. Available evidence indicates that infection-related hospitalizations of patients with AHF are associated with higher mortality, protracted length of stay, and increased readmission rates. Understanding the intricate interaction of both clinical entities may provide further therapeutic strategies to prevent the occurrence of cardiac complications and improve prognosis of patients with AHF triggered by infection. The purpose of this review is to investigate the incidence of infection as a causative factor in AHF, explore its prognostic implications, elucidate the underlying pathophysiological mechanisms, and highlight the basic principles of the initial diagnostic and therapeutic interventions in the emergency department.

Keywords Infection · Acute heart failure · Pathophysiology · Management

Introduction

Acute heart failure (AHF) is a leading cause of unscheduled hospitalizations among patients > 65 years old in the western world, and despite recent therapeutic advances, it is still associated with increased mortality and high readmission rates. Infection is typically considered one of the most common medical conditions than can result in rapid development or deterioration of signs and symptoms of heart failure (HF) [1, 2].

AHF-related infections might be acquired during hospitalization or in the community setting. Their clinical presentation usually overlaps with other clinical entities, thus often leading to delayed diagnosis and management. Available data indicate that hospital admissions due to infection among patients with AHF are associated with a greater risk of death and recurrent hospitalizations. The need for rapid in-hospital identification and management of infection is firmly highlighted in the recently published guidelines (2021) from the European Society of Cardiology, whereby the acronym CHAMP (acute Coronary syndrome, Hypertension emergency, Arrhythmia, Mechanical cause, Pulmonary embolism) has been extended to the new acronym CHAMPIT, in order to include infections (represented by I) and tamponade (indicated by T) as potential etiological factors of AHF [2, 3]. However, infection is not only a causative factor of HF, but in the majority of cases, it is a precipitating factor for decompensation of existing HF, leading to multiple hospital admissions and worsening of cardiac function, thus promoting transition to advanced heart failure stage (Fig. 1).

The majority of AHF patients present with signs and symptoms related to systemic and/or pulmonary congestion, including dyspnea during exercise or at rest, orthopnea,

Sofia Bezati and Maria Velliou contributed equally to this work.

✉ Sofia Bezati
sofiabezati@gmail.com

1 Emergency Medicine Department, Attikon University Hospital, Rimini 1, Chaidari, 12462 Athens, Greece

2 Department of Occupational Therapy, University of Western Macedonia, Keptse Area, Ptolemaida 50200, Greece

3 National and Kapodistrian University of Athens, 2nd Department of Cardiology, Heart Failure Unit, Attikon University Hospital, Athens, Greece

4 Emergency Medicine Department, National and Kapodistrian University of Athens, Athens, Greece

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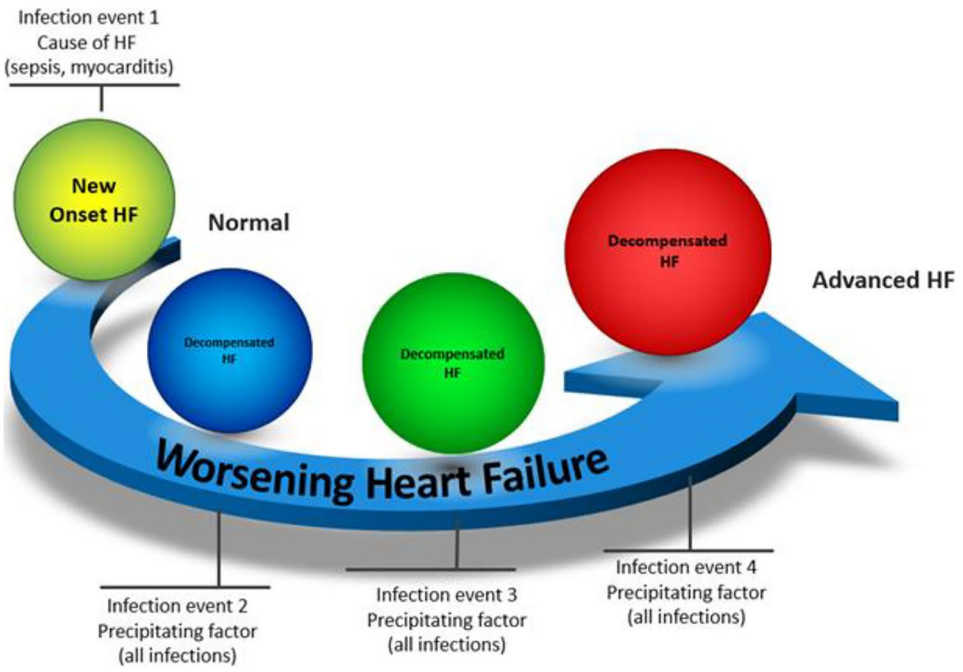

Fig. 1 The impact of infection on the natural history of heart failure. HF, heart failure

fatigue, reduced exercise tolerance, rales, jugular venous distention, peripheral edema, and a third heart sound ("S3 gallop"). A subgroup of patients appears to have signs and symptoms suggestive of peripheral hypoperfusion, such as cold extremities, wet skin, oliguria, dizziness, mental confusion, weak pulse, and narrow pulse pressure. Hence, based on the presence/absence of congestion and/or hypoperfusion, four clinical profiles have been identified: (1) warm and wet (well perfused and congested), (2) cold and wet (hypoperfused and congested), (3) cold and dry (hypoperfused without congestion), and (4) warm and dry (compensated, well perfused without congestion). Finally, patients might also complain of fever, hematuria, dysuria, vomiting, abdominal pain, and altered mental status [4–6].

The aim of this article is to review and summarize current evidence regarding the incidence and outcomes of infection-related hospitalizations in patients with AHF, shed light on potential pathophysiological mechanisms, and underline the basic principles of a structured initial diagnostic and therapeutic approach in the emergency department (ED) setting.

Epidemiology

Infection as a frequent cause of hospitalization in patients with AHF seems to have independent prognostic implications. Several studies have demonstrated that admissions due to decompensated HF and concomitant infection are associated with higher mortality, prolonged hospitalization, and increased rehospitalization rates (Table 1).

The ALARM-HF (Acute Heart Failure Global Survey of Standard Treatment) registry showed that infection was one of the most frequent triggering factors of AHF. It was diagnosed in 18.7% of patients with pre-existing AHF episodes and in 12.1% of those with new onset HF [7]. Moreover, the Gulf CARE (Gulf Acute Heart Failure Registry) study, conducted in seven Middle Eastern countries, revealed that infection was more prevalent in patients with decompensated compared to those with new onset HF (17.5% versus 11.1%). In both groups, it was correlated with increased length of stay and higher in-hospital mortality. Remarkably, in patients with acute decompensated HF, the presence of infection as a precipitating factor incurred the highest rate of 1-year mortality (28.7%) [8]. EHFS II (EuroHeart Failure Survey II) also found that the prevalence of infection as a cause of hospitalization for AHF differed significantly between decompensated and new onset HF (19.2% versus 15%, respectively) [9].

EFICA (Etude Française de l'Insuffisance Cardiaque Aiguë) study revealed that 20% of the patients admitted to the intensive or coronary care unit (ICU/CCU) with acute decompensated HF had an underlying infection as the precipitating factor, while no statistically significant difference was observed between patients with and without cardiogenic shock and concomitant infection [10]. HFSIS (Heart Failure Survey in Israel) demonstrated that infection was independently correlated with a higher risk for short- and long-term mortality among patients with new onset AHF or acute exacerbation of chronic HF. Compared to ischemia, infection as a precipitating factor was associated with a 35% increased

Table 1 Data regarding the incidence of infection-related AHF hospitalizations and the associated clinical outcomes

Study	Patients	Age (years)	LVEF (%)	Infection		Comments/clinical outcomes
				Source	Incidence (%)	
ALARM-HF [7]	4953	> 18	40.0 ± 15.0: NOHF 37.0 ± 14.0: ADHF	NA	16.3	18.7% ADHF vs 12.1% NOHF
Gulf CARE [8]	5005	57.0 ± 14.7 NOHF 61.0 ± 15.0 ADHF	38.6 ± 12.7 NOHF 35.5 ± 14.1 ADHF	NA	14.6	Increased in-hospital and 1-year mortality, extended LOS
EHFS II [9]	3580	69.9 ± 12.5	NA	NA	17.6	19.2% ADHF vs 15% NOHF
EFICA [10]	581	73.0 ± 13.0	NA	NA	20	No difference in prevalence between subjects with and without cardiogenic shock
HFSIS [11]	2212	75.0 ± 10.0	NA	NA	21	Increased in-hospital and 10-year mortality
OPTIMIZE-HF [12]	48,612	73.1 ± 14.2	39.0 ± 17.6	Pulmonary tract	15.3	Increased in-hospital mortality
PAPRICA-2 [13]	3535	80.0 ± 10.0	52.0 ± 15.0	NA	39	Decreased readmissions
PAPRICA-4 [14]	9999	80.7 ± 9.9	51.7 ± 15.2	NA	32.7	No impact on 30-day mortality
GWTG-HF [15]	99,825	72.6 ± 14.2	39.3 ± 17.2	Pulmonary tract	28.2	Increased LOS and in-hospital mortality
CHARM [16]	1668	68.0 ± 11.0	37.0 ± 15.0	Pulmonary tract	10	No difference in mortality between CV and non CV precipitant factors
GREAT [17]	15,828	71 (61–80)	38 (27–50)	NA	14	Increased 90-day mortality with delayed peak at week 3
KCHF [18]	2399	77.1 ± 12.3	45.4 ± 16.3	Pulmonary tract, urinary tract, gastrointestinal tract, soft-tissue, catheters	9	Increased in-hospital and post-discharge mortality
BIOSTAT-CHF [19]	2465	68.4 ± 12.0	31.0 ± 10.5	NA	5.2	No impact on mortality
ELISABETH [20]	502	87 (81–91)	NA	NA	17.5	No impact on LOS and 30-day mortality
Opasich et al. [21]	304	53.0 ± 1.0	NA	Pulmonary tract, gastrointestinal tract, catheters	23	Unknown infection source in 6%
Chin et al. [22]	435	> 18	NA	Pulmonary tract	16	The most common cause of clinical deterioration prior admission
Dai et al. [23]	33,693	NA	NA	Pulmonary tract	2.5	Pneumonia in 2.5% of hospitalized HF patients vs HF in 4.9% of those hospitalized due to pneumonia
Alon et al. [24]	9335	76.0 ± 10.0	NA	Pulmonary tract, bacteremia, urinary tract, skin, soft-tissue	38	Increased 30-day mortality
Arrigo et al. [25]	755	64–84	NA	Pulmonary tract	20	Decreased readmissions and increased 1-year mortality
Cardoso et al. [26]	260	66.1 ± 12.7	25–45	Pulmonary tract, urinary tract	45.8	Increased in-hospital mortality
Ogbemudia et al. [27]	190	55.4 ± 17.4	40.2 ± 13.6	Pulmonary tract, urinary tract, endocardium	75	Pneumonia, arrhythmias, urinary tract infection and infective endocarditis were the most common precipitant factors
Drozd et al. [6]	711	71.6 ± 13.0	31.8 ± 9.9	Pulmonary tract, urinary tract, soft-tissue	25	Increased short- and long-term mortality and readmission rate

AHF acute heart failure, *ACS* acute coronary syndrome, *ADHF* acute decompensated heart failure, *CV* cardiovascular, *HF* heart failure, *LOS* length of stay, *LVEF* left ventricular ejection fraction, *NA* non-available, *NOHF* new onset heart failure

hazard for in-hospital mortality and a 24% higher risk for 10-year mortality [11].

In the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure) registry, pulmonary infection was considered one of the most common precipitants of AHF and was correlated with prolonged hospital stay and 1.6-fold rise in in-hospital mortality. The rates of post-discharge deaths and readmissions were also higher in AHF patients with pneumonia, but this finding was not statistically significant [12].

PAPRICA-2 (Papel de los Precipitantes de Episodios de Insuficiencia Cardiaca Aguda) study identified infection in 39% of the patients admitted to the ED with the diagnosis of AHF. Notably, infection was correlated with lower readmission rates compared to those without precipitating factors [13]. Four years later, PAPRICA-4 confirmed the aforementioned findings by demonstrating that infection constitutes the most prevalent precipitating factor of AHF and carries an intermediate risk (10%) of 30-day mortality. Nonetheless, the impact of infection on mortality showed a rather declining trend over time, when the investigators analyzed the temporal pattern of mortality along the course of the first 30 days after the acute event [14].

An analysis from the GWTG-HF (Get With The Guidelines-HF) program showed that pneumonia was the most frequent precipitating factor among patients hospitalized with AHF and was associated with prolonged hospital stay (> 4 days) and increased in-hospital mortality in all HF groups, irrespective of ejection fraction (EF) [15]. Along the same lines, a subanalysis of the CHARM (Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity) trial found that respiratory infections were unequivocally the leading non-cardiovascular cause of HF exacerbation and subsequent hospitalization, irrespective of EF [16]. Moreover, in the GREAT (Global Research on Acute Conditions Team) registry, infection was found to be independently associated with a 90-day mortality in AHF patients, especially those of Asian descent, while the 90-day risk of death incurred by infection remained persistently elevated even after adjustment for several prognostic factors. However, it was noted that the infection-related risk of death displayed a delayed peak at week 3 after AHF admission, probably owing to the fact that the attending physicians focused mainly on the symptomatic management of AHF and rather overlooked the underlying process of sepsis, thus failing to provide prompt and appropriate antibiotic treatment [17].

The KCHF (Kyoto Congestive Heart Failure) registry found that AHF patients, who were more prone to developing a newly diagnosed infection after admission, were those aged ≥ 80 years, who were not receiving loop diuretics as outpatients, were non-ambulatory, had an acute coronary syndrome, hyponatremia, or anemia, or required intubation. More importantly, patients diagnosed with infection after admission for AHF carried a significantly higher risk of in-hospital and 1-year mortality compared to those without infection. Nonetheless, the risk of HF rehospitalizations did not differ between these two groups (22% versus 24.7%) [18].

In BIOSTAT-CHF (A Systems Biology Study to Tailored Treatment in Chronic Heart Failure) study, infection was identified in about 5% of patients with symptoms of new onset or worsening HF. However, those with acute decompensated HF precipitated by infection did not have the worst clinical prognosis [19]. Likewise, ELISABETH trial concluded that a more comprehensive management of precipitating factors including infection, in the context of implementing an early guideline-based care bundle for elderly AHF patients presenting to the ED, did not significantly improve neither the length of hospital stay nor the 30-day mortality [20].

Pathophysiology: unravelling the tangle

Although infection has long been recognized as a precipitating factor of AHF, the underlying mechanisms which are responsible for the development of myocardial dysfunction have not been fully elucidated. Observational studies, regarding the prevalence of infections in patients with AHF, record respiratory infections, sepsis/bacteremia, urinary tract infections (UTI) as well as skin and soft tissue infections as the most frequent causes of HF exacerbation [24, 26]. The deleterious impact of any kind of infection on cardiac function seems to be related to their inherent ability to disseminate to several organ sites, other than the primary source, and activate the immune system at different levels and in varying degrees, thus establishing a state of generalized inflammation. In turn, inflammation plays a key role in the pathogenesis and progression of HF [28, 29]. Most evidence stems from studies concerning respiratory infections complicated by AHF and sepsis-induced cardiomyopathy. There seems to be a complex interplay between the infectious agent and the host's immune response, which results in the production of chemical mediators with direct and indirect effects on the myocardium [30, 31].

Both localized and systemic infections trigger the release of humoral factors and cell-mediated interactions, in an attempt to restrain the pathogen's proliferation [32]. In particular, the innate immune system is activated in response to the recognition of exogenous danger signals, termed pathogen-associated molecular patterns (PAMPs). Gram-negative lipopolysaccharides represent a typical example of PAMPs. PAMPS bind to pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs), and subsequently activate the host's defensive mechanisms, initiating an immune response. Meanwhile, necrotic or dying cells release endogenous molecules known as damage-associated molecular patterns (DAMPs), which are also detected by intracellular or extracellular PRRs and attach to them, eventually resulting in further activation of the innate immune system [28, 31, 33, 34].

Cytokines

Cytokines play a major role in the inflammatory cascade activated by an infectious insult. Homeostasis is maintained by the balanced production of pro-inflammatory and anti-inflammatory cytokines. However, during infection, an overwhelming inflammatory process, described as cytokine

storm, may initiate an inappropriate inflammatory response and lead to systemic dysfunction. The complex activation of signaling pathways mediated by pro-inflammatory cytokines may affect cardiac contractility in a time-dependent manner. As a matter of fact, immediate cytokine release, arising within minutes, results in a short-term cardiac adaptation to the insult through cardiostimulatory or cardiodepressant mechanisms, whereas delayed immune response, lasting hours or days, has a solely cardiodepressant effect. Predominance of the cardiodepressant effect, in combination with sustained cytokine release, may lead to myocardial injury, progressive left ventricular (LV) dysfunction and adverse LV remodeling [34–36].

Experimental studies have shown that most of the principal cytokines, like tumor necrosis factor-alpha (TNF-α) [37–39], interleukin-1 (IL-1) [40], interferon-γ (IFN-γ) [41], and interleukin-6 (IL-6) [42], act as dynamic mediators of cardiomyocyte depression, hypertrophy, fibrosis, ventricular dilation, and diastolic dysfunction. TNF-α is mainly derived from activated macrophages, but is also secreted by cardiac myocytes in response to sepsis [43]. It stimulates monocytes, macrophages, and neutrophils to synthesize and secrete IL-1, which depresses cardiac contractility through induction of nitric oxide (NO) synthase (NOS) [44]. Other cytokines implicated in the pathogenesis of HF and sepsis-induced cardiomyopathy are interleukin-8 (IL-8), interleukin-17 (IL-17), interleukin-18 (IL-18), and interleukin-33 (IL-33) [29].

Endothelial dysfunction and NO

Endothelial dysfunction in the setting of infection may also contribute to heart failure, through vascular tone alterations and thrombogenicity. Indeed, it has been shown that, in patients with AHF, endothelial derangement plays a pivotal role in systemic vasoconstriction and reduced peripheral perfusion [45–47]. Under normal circumstances, endothelial cells act as substantial contributors in the homeostasis of microcirculation through regulation of microvascular thrombosis, fibrinolysis, leukocyte adhesion and migration, vasomotor tone, trafficking of cells and nutrients, capillary permeability, and recruitment [48].

NO, a potent vasodilator, is normally produced from all cell types of the myocardium and regulates cardiac function through both vascular-dependent and vascular-independent mechanisms. The direct effect of NO on myocardial function is complex, as low levels of NO produce a positive inotropic effect, while higher levels lead to negative inotropy [47]. In inflammatory states, both NO dysregulation and functional impairment of endothelial cells lead to maldistribution of microvascular blood flow, eventually resulting in abnormal vascular tone, compromised tissue oxygen delivery, and tissue hypoxia. Moreover, increased oxidative stress, along with the excessive release of cytokines, may further impair endothelial function through the production of reactive oxygen species (ROS) and proinflammatory/vasoactive prostanoids [49, 50]. In parallel, decreased production of NO by endothelial NOS (eNOS), combined with increased NO inactivation due to the amplified ROS production and the decreased activity of antioxidant defense mechanisms, leads to attenuated endothelium-dependent vasodilation [45].

Thombogenicity

Dysfunctional endothelial cells may create a procoagulant milieu, by triggering fibrin formation as well as platelet adhesion and aggregation [51, 52]. Concomitant activation of adhesion molecules induced by functional abnormalities of red blood cells, leukocytes, and platelets, as well as by proinflammatory cytokines, may facilitate thrombogenicity [53].

Microcirculation and ischemia

Studies regarding the role of microcirculation and myocardial metabolism in sepsis have provided insight into various pathophysiological mechanisms responsible for myocardial dysfunction and ischemia. The earlier belief that myocardial depression may result from global ischemia and oxygen supply–demand imbalance has been refuted by the observation that septic patients exhibited high coronary blood flow and increased oxygen availability in the myocardium [54]. Nevertheless, in patients with preexisting and possibly undiagnosed coronary artery disease (CAD), regional myocardial ischemia or infraction may occur and eventually precipitate HF [55]. Later studies supported the concept of the hibernating myocardium acting as an adaptive and potentially protective mechanism during infection. Since coronary artery perfusion does not seem to be decreased, experimental studies have proposed that reversible cardiac dysfunction develops due to a metabolic deficit of cardiac cells experiencing cytopathic hypoxia [56, 57]. Notably, a study on septic shock patients revealed that EF is lower and end-diastolic volume is higher in survivors, compared to non-survivors. This suggests that ventricular dilation might be a compensatory mechanism to maintain adequate cardiac output and thus mitigate reversible myocardial depression [58].

Sympathetic nervous system

Sympathetic nervous system (SNS) activation is generally considered a physiologic stress response to a pathogen-related insult [59]. Specifically, in AHF, adrenergic upregulation is a valuable compensatory mechanism, since it induces a positive inotropic and chronotropic effect on cardiomyocytes, increases systemic vascular resistance in the circulatory system and recruits the endocrine system through the stimulation

of the renin–angiotensin–aldosterone axis [60]. However, the sustained stimulation of the catecholamine signaling pathway results in arteriolar vasoconstriction, elevated afterload, and high LV pressures. As a consequence, ventricular wall stress increases and may therefore provoke myocardial ischemia. Furthermore, systemic vasoconstriction, in conjunction with endothelial dysfunction and dynamic alterations in the vascular tone, may lead to volume redistribution and cause intravascular congestion and pulmonary edema [61].

The aforementioned pathophysiological pathways are summarized in Fig. 2 that depicts the complex interplay among various mechanisms triggered in the setting of an underlying infection, which eventually culminate in the development of AHF.

Below, the pathophysiology of the most common infections (respiratory and UTI) complicating AHF is discussed.

AHF and respiratory infections

The cardiovascular sequelae of community-acquired pneumonia (CAP) have been extensively studied. Evidence demonstrates that cardiac dysfunction, which presents in the form of non-ischemic myocardial injury, could be attributed to the combined effect of both the inflammatory mediators and the direct insult exerted by the infectious agent on the myocardium. In detail, it has been proven that pneumolysin, a pore-forming cytolysin excreted by *Streptococcus pneumoniae*, directly compromises contractility by interfering with calcium homeostasis [62, 63]. Furthermore, transient alterations of endothelial function and vascular tone may increase left ventricular afterload by aggravating peripheral microvascular resistance and arterial stiffness. Moreover, hypoxemia may increase pulmonary arterial pressure and right ventricular afterload and impair myocardial oxygen delivery [64, 65]. Concurrently, the exaggerated activity of the SNS may provoke myocardial ischemia by reducing cardiac output and coronary perfusion [30, 66]. In parallel, platelet and neutrophil activation may predispose to the development of intravascular thrombosis and instigate plaque instability, eventually leading to the manifestation of an acute coronary syndrome (ACS) [63, 67]. Finally, some bacteria possess the ability to survive intracellularly and thus maintain a reservoir of pathogens, by virtue of which the proinflammatory/procoagulant phenotype may be retained even after the resolution of the acute phase [62, 67].

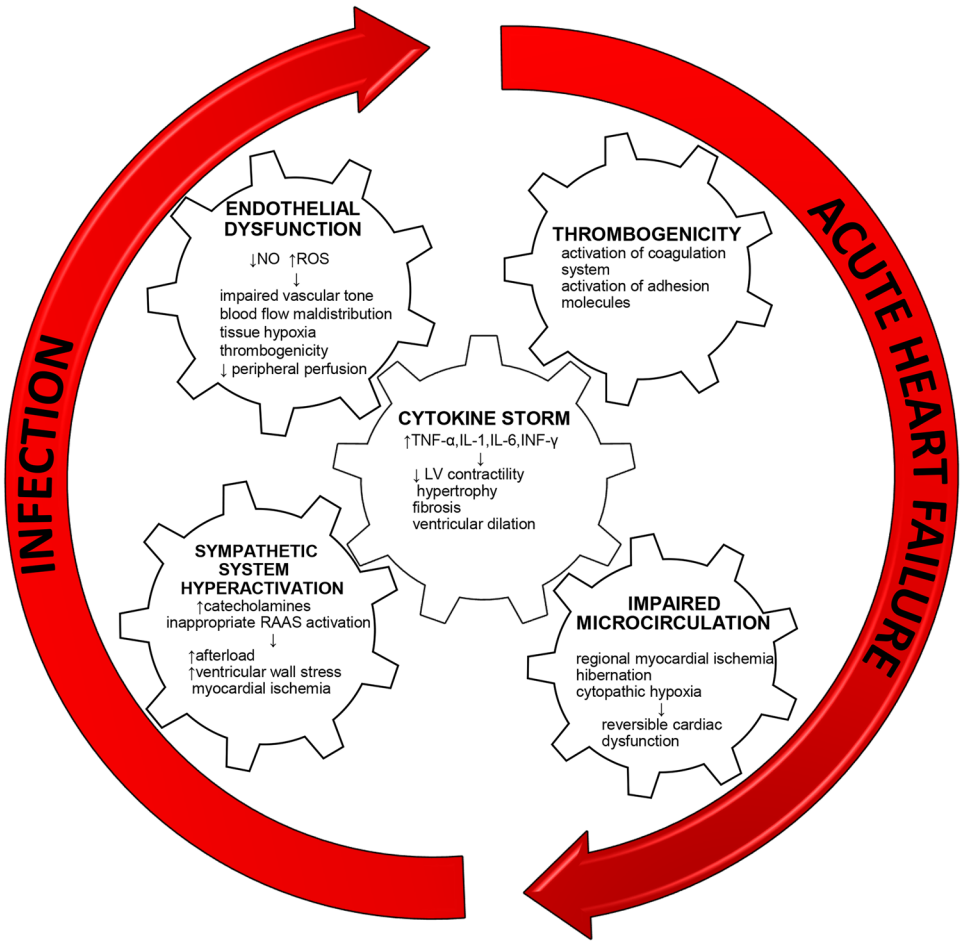

Fig. 2 The vicious cycle of infection-induced acute heart failure. *Abbreviations*: IL-1, interleukin-1; IL-6, interleukin-6; IFN-γ, interferon-gamma; LV, left ventricular; NO, nitric oxide; RAAS, renin angiotensin aldosterone system; ROS, radical oxygen species; TNF-α, tumor necrosis factor-alpha

Recently, specific attention has been drawn towards the pathogenesis of AHF during infection with severe acute respiratory syndrome *coronavirus 2 (SARS-CoV-2).* Principal pathophysiological mechanisms implicated in the course of the disease include the virus-induced infiltration of inflammatory cells and the subsequent burst of a cytokine storm, which may impair cardiac function and cause myocardial necrosis [68, 69]. In addition, endothelial injury may be responsible for the formation of thrombi and the development of microangiopathy and disseminated intravascular coagulation, all of which cumulatively cause indirect myocardial ischemia [70]. Besides, severe hypoxia due to acute respiratory distress syndrome, lung fibrosis, and respiratory failure may cause diminished oxygen supply to cardiomyocytes and increase pulmonary arterial pressure, ultimately compromising right ventricular function [71]. Lastly, the activation of the renin–angiotensin–aldosterone system, either by the virus itself [72] or through SNS stimulation [73], may incur volume overload and contribute to the establishment of the cardio-renal syndrome [74].

AHF and UTI

There is scarce data on how UTI may predispose to the development of AHF. An observational study in patients admitted for UTI reported an association between history of congestive HF and the development of sepsis-induced myocardial dysfunction [75]. A presumed mechanism could be the attachment of bacteria to the uroepithelial cells, which in turn gives rise to the activation of the immune system through the release of cytokines (IL-1, IL-6, and IL-8) and the recruitment of neutrophils and other inflammatory cells [76, 77]. Besides the systemic activation of the immune system, some virulence factors, like α-hemolysin, P-fimbriae, and lipopolysaccharide, which are produced by uropathogenic bacteria (most commonly *Escherichia coli*) and facilitate their invasion, have been found to determine the severity of UTI [78, 79]. In addition, the host's immune response may also lead to tissue damage and permanent scarring, hence contributing to the development of acute kidney injury [80]. This latter observation may provide a potentially important link between tissue injury, renal dysfunction, and subsequent volume overload, eventually leading to AHF.

Management of AHF patients with an underlying infection

The management of patients with AHF in the ED necessitates early identification and treatment of precipitating factors, as well as vigorous resuscitation, in order to reduce the risk of progression and prevent clinical deterioration. Although infection may be a reversible cause of cardiac decompensation, oftentimes, its diagnosis may be delayed or its severity may be underestimated even when promptly recognized. Diagnostic uncertainty may arise from the fact that infections and AHF share overlapping clinical presentations and radiologic findings, often making the differential diagnosis between these two clinical entities challenging. In addition, patients may not present with characteristic symptoms and signs of infection, thus further perplexing the situation.

Initial diagnostic approach

An initial systematic Airway, Breathing, Circulation, Disability, Exposure (ABCDE) approach guarantees a holistic and focused evaluation of critically ill patients [81]. Focus should then be directed towards identifying the clinical phenotype of AHF by determining hemodynamic status and congestion. Simultaneously, potential signs of an underlying infection should be meticulously and systematically sought for and duly addressed. Screening and management of sepsis or septic shock should be carried out according to usual care sepsis bundles [82, 83].

Biomarkers and laboratory studies

Laboratory studies are useful for the confirmation of AHF (natriuretic peptides), as well as for the recognition of precipitating factors. Indeed, troponin serves for the detection of an ACS, D-dimers may indicate pulmonary embolism, thyroid stimulating hormone (TSH) may point towards hypo- or hyper-thyroidism, while procalcitonin (PCT) is particularly useful when infection is suspected [3]. PCT is a novel inflammatory biomarker of particular diagnostic and prognostic value [89], which is principally elevated in the setting of bacterial infections afflicting various organ sites [84]. When implemented in the management of patients with infection, PCT has been shown to detect systemic bacterial infections with high specificity, guide antibiotic therapy, and dictate effective antibiotic stewardship by decreasing their inappropriate use and obviating the risk of antibiotic-associated adverse effects [85, 86]. Even in cases where slight increases of PCT are observed in patients with AHF [87–89], a cut-off value of 0.21 ng/ml or 0.20 ng/ml has been proposed to aid the diagnosis and mandate immediate treatment of superimposed [90] and/or undiagnosed [91] infections, respectively. Nonetheless, strict PCT-guided initiation of antibiotics has not been proven to be superior to standard clinical decision making [92].

High-sensitivity C-reactive protein (hsCRP) has been traditionally used for the diagnosis of bacterial infections. Due to its low specificity in various inflammatory states, like AHF [93–95], its clinical utility is limited. Considering its confounding effect, a randomized clinical trial suggested a cut-off value of 25 mg/l beyond which an infection should

be sought as a triggering factor of AHF, a finding that necessitates further research [96].

White blood cell count is highly nonspecific and of minor importance in the diagnostic workup of infections complicating AHF. Indeed, leukocyte count showed limited accuracy compared to PCT or hsCRP [97, 98].

Interpretation of troponin levels in the setting of AHF should be done with caution, since elevated levels are a common finding in patients with AHF [99, 100]. Based on the clinical context, ACS should be appropriately excluded, and further investigation of other alternative etiologies should ensue.

Lactate levels and blood cultures should be obtained to assess the degree of hypoperfusion and the probability of underlying bacteremia, respectively [101]. Depending on the presumed infectious source, urine, cerebrospinal fluid, or soft tissue cultures should also be acquired to guide antibiotic therapy.

Imaging

Chest X-ray and lung ultrasound are the initial imaging techniques in the recommended diagnostic assessment of patients with AHF [3]. Although chest X-ray is widely available, and findings like interstitial edema, cardiomegaly, and pleural effusion may facilitate the diagnostic workup; it may be normal in up to 20% of patients with AHF [102]. Lung ultrasound possesses a major advantage; it can be performed and interpreted by clinicians at the bedside. It is considered a more accurate method for the detection of pulmonary congestion, while it can rule in or rule out other pulmonary causes through the implementation of the BLUE protocol, with a diagnostic accuracy of 90.4% [103–105]. Focused echocardiography in the acute setting is of paramount diagnostic importance, since it can provide a global assessment of the cardiac function and at the same time an estimation of inferior vena cava (IVC) diameter and its respiratory variation [106–108]. A proposed systematic sonographic approach in patients with AHF and infection comprises the estimation of left ventricular contractility combined with IVC and lung scanning, in order to evaluate cardiac function, volume status and fluid responsiveness.

Moreover, ultrasound is a readily available tool, which can be proven valuable in different clinical settings. It can aid in the detection of biliary or hepatic sepsis, intra-abdominal fluid collections, and urological complications, including renal abscess or pyonephrosis or conditions that predispose to renal infection, such as structural malformations. However, computed tomography (CT) has a higher sensitivity and remains the method of choice for the diagnosis of intra-abdominal or retroperitoneal abscesses, pancreatitis, and intra-biliary stones, as well as in cases where ultrasound findings are inconclusive [109, 110].

Therapeutic interventions

Antibiotics

Prompt and appropriate antibiotic therapy is the cornerstone in the management of patients with infection complicated by AHF [32, 101]. Optimal treatment involves early control of the source along with optimization of the patient's hemodynamic profile. The proper antibiotic regimen should be selected with caution, as some common antibiotic agents carry special contraindications. For instance, some beta-lactam antibiotics, like benzylpenicillin or piperacillin-tazobactam, contain substantial amounts of sodium, which definitely needs to be taken into account when treating patients with pre-existing HF. Moreover, macrolides and fluoroquinolones may cause QT prolongation and increase the risk of polymorphic ventricular tachyarrhythmia. Thus, careful ECG assessment and monitoring are advisable for patients receiving these agents [30].

Respiratory support

In patients with AHF oxygen therapy should be administered when SpO2 is < 90% or PaO2 < 60 mmHg, while noninvasive positive pressure ventilation should be commenced as soon as possible once respiratory distress develops (respiratory rate > 25 breaths/min, SpO2 < 90%) [3]. Although in septic patients with hypoxemic respiratory failure without hypercapnia, high flow oxygen is preferred over noninvasive ventilation, escalation of respiratory support is required when conventional interfaces fail to deliver sufficient amount of oxygen [101].

Circulatory support

In patients presenting with acute decompensated HF or pulmonary edema without signs of hypoperfusion, initial supportive treatment should include intravenous diuretics and vasodilators. In patients with hemodynamic instability or an elevated lactate level, fluid resuscitation is the mainstay of treatment in order to restore hypovolemia. However, there may be a reasonable concern regarding the potential risk of volume overload in patients with cardiac dysfunction [111]. Therefore, fluid resuscitation should be guided by physical exam, follow-up of vital signs, lactate, dynamic, and ultrasonographic measurements. A focused review regarding the management of septic patients with AHF suggests a relatively liberal administration of fluids, that is, > 200 ml in 15–30 min and up to 500 ml in the first hour followed by a reduced infusion rate until the total fluid administered reaches 2 L in the first 24 h upon admission [112]. Vasopressors, in particular norepinephrine, should be applied in case

hemodynamic stability is not achieved after fluid resuscitation. Vasopressin is recommended as a second-line agent if hemodynamic status does not improve. Patients with persistent hypotension and cardiac dysfunction should be supported with intravenous inotropes, preferably dobutamine [3, 112]. Otherwise, administration of epinephrine alone has a weak recommendation, reserved only for cases of refractory shock despite therapy with vasopressors and dobutamine, with close monitoring for adverse effects [113]. The use of levosimendan is not supported by the current survival sepsis campaign guidelines due to lack of benefit [101, 114], though its use might be considered in certain patient categories (β-blockade, elevated right ventricular pressures, Takotsubo cardiomyopathy) [112].

Conclusion

Infection is a common, yet often under-recognized, precipitant of AHF inflicting immense perturbations along the time course of HF patients and accounting for a considerable portion of their related morbidity and mortality. In parallel, patients with HF are usually frail, of advanced age, with comorbidities that render them more vulnerable to infections due to their impaired immune system and diminished homeostatic mechanisms. Given that infection constitutes a reversible cause of AHF in most cases, its prompt identification and management in the ED is of major importance. Currently, the intricate interactions between infection and AHF continue to pose many scientific challenges and await to be extensively clarified. Accordingly, it is anticipated that the full elucidation of the exact pathophysiological mechanisms that come into play will provide the basis for further therapeutic strategies to be implemented for the prevention of cardiac complications in patients with infection and the attenuation of the associated adverse outcomes.

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Data availability No new data was created or analyzed in this study.

Declarations

Ethics approval Not applicable.

Conflict of interest Dr. Bezati, Velliou, Ventoulis, Simitsis, and Polyzogopoulou have no conflicts of interest or financial ties to disclose. Professor Parissis received honoraria for lectures from Orion Pharma, Pfizer, Servier, Astra, AO Orphan, and Roche Diagnostics.

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