Intensive Care Med
DOI 10.1007/s00134-015-4041-5

REVIEW

Acute heart failure and cardiogenic shock: a multidisciplinary practical guidance

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Received: 23 April 2015
Accepted: 26 August 2015

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Published online: 14 September 2015

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Abstract *Purpose:* Acute heart failure (AHF) causes high burden of mortality, morbidity, and repeated hospitalizations worldwide. This guidance paper describes the tailored treatment approaches of different clinical scenarios of AHF and CS, focusing on the needs of professionals working in intensive care settings. *Results:* Tissue congestion and hypoperfusion are the two leading mechanisms of end-organ injury and dysfunction, which are associated with worse outcome in AHF. Diagnosis of AHF is based on clinical assessment, measurement of natriuretic peptides, and imaging modalities. Simultaneously, emphasis should be given in rapidly identifying the underlying trigger of AHF and assessing severity of AHF, as well as in recognizing end-organ injuries. Early initiation of effective treatment is associated with superior outcomes. Oxygen, diuretics, and vasodilators are the key therapies for the initial treatment of AHF. In case of respiratory distress, non-invasive ventilation with pressure support should be promptly started. In patients with severe forms of AHF with cardiogenic shock (CS), inotropes are recommended to achieve hemodynamic stability and restore tissue perfusion. In refractory CS, when hemodynamic stabilization is not achieved, the use of mechanical support with assist devices should be considered early, before the development of irreversible end-organ injuries. *Conclusion:* A multidisciplinary approach along the entire patient journey from pre-hospital care to hospital discharge is needed to ensure early recognition, risk stratification, and the benefit of available therapies. Medical management should be planned according to the underlying mechanisms of various clinical scenarios of AHF.

Keywords Heart failure · Cardiogenic shock · Emergency · Treatment

Introduction

Acute heart failure (AHF) is the most frequent cause of unscheduled hospital admissions; however, the mechanisms of heart failure decompensation are still unclear, and trials on novel pharmacological agents have been consistently negative. As stated by recent guidelines, physicians in charge of AHF often manage patients based only on expert opinion with insufficient evidence [1]. Indeed, most AHF therapies, including diuretics, vasodilators, inotropes, and vasopressors, are used despite lack of evidence on their impact on dyspnea or on outcome. Furthermore, AHF is managed by a variety of health care professionals including emergency physicians, intensivists, cardiologists, internal medicine physicians, and nurses who each may have a different opinion on the management strategy. Cooperation and homogenisation of AHF management are, however, key in improving the outcome of these patients.

In the absence of evidence-based guidelines, this paper gives multidisciplinary guidance for the treatment of AHF and cardiogenic shock (CS) from pre-hospital to intensive care (ICU).

Acute heart failure syndromes: definitions

AHF means rapid onset of, or worsening in, symptoms and signs of heart failure. It can be a new-onset disease ("de novo") or acute decompensation of chronic heart failure. AHF may occur with impaired left ventricular (LV) function or with preserved ejection fraction. The clinical phenotypes of AHF include patients with acute pulmonary edema (APE), hypertensive heart failure, decompensated chronic heart failure, and CS. [1] Although primarily a cardiac disease, due to the inadequate blood circulation, AHF leads to a systemic disorder affecting all vital organs. The two predominant mechanisms of organ dysfunction are congestion and hypoperfusion. The presence of multiple organ involvement, e.g., cardiorenal and cardiohepatic syndrome, is

associated with increased mortality [2, 3]. CS is the most severe form of AHF. Its contemporary definition is clinical, with prolonged hypotension [systolic blood pressure (BP) usually <90 mmHg] or vasopressors needed to increase BP >90 mmHg in the absence of hypovolemia, and with signs of hypoperfusion (cold periphery or clammy skin, confusion, oliguria, elevated serum lactate). Without early and effective treatment, CS may initiate systemic inflammatory responses and develop into multiorgan failure, leading eventually to death.

Benefit of short time to treatment in AHF

The first hours of hospitalization for AHF are marked by a high risk for complications, including death, and represent a "golden moment" for intervention. Indeed, a high number of AHF patients die in the emergency department (ED) before ICU/cardiac care unit (CCU) admission [4]. Earlier diagnosis, triage, and initiation of specific treatment for AHF are associated with reduced mortality as well as shorter lengths of hospital stay [5–8]. Indeed, initiation of intravenous nitrates immediately after presentation has been shown to reduce the rate of mechanical ventilation needed and to reduce adverse events [7, 9]. Early initiation of non-invasive positive pressure ventilation improves dyspnea and respiratory distress [10] and may improve outcome [11]. Rapid identifying of the precipitating factor for AHF, especially if reversible (e.g., acute coronary syndrome, ACS), is essential for early initiation of specific treatments and thereby prevention of aggravating AHF and possibly avoidance of the development of recurrent heart failure.

Pre-hospital management

Acute heart failure patients should be managed along a specialized medical care pathway that is fully recognized by all professionals involved (emergency medical services, ED, ICU or CCU, cardiology and cardiac surgery units). In the emergency call center and pre-hospital care, emphasis should be given to the early and accurate recognition of patients with chest discomfort, dyspnea, signs of pulmonary or systemic congestion, or signs of hypoperfusion.

Vital signs such as BP, heart and respiratory rate, and peripheral capillary oxygen saturation (SpO_2), should be assessed at first contact and monitored during the hospital transport. A 12-lead ECG should be performed as early as possible and be analyzed by a physician in the ambulance or sent electronically to an on-call physician. Early therapy is symptom-based and guided by vital signs: non-invasive ventilation (NIV) should be considered as soon as possible in cases of respiratory distress or pulmonary edema, and oxygen therapy should be started in cases of SpO_2 <90 %; intravenous diuretics (furosemide 0.5 mg/kg or double the home dose of loop diuretic) in cases of congestion; intravenous/sublingual/spray nitrates in cases of normal or high BP. In rare cases, careful fluid challenge (i.e. 4 mL/kg or 250 mL) may be considered if hypotension and signs of hypoperfusion are present [12, 13].

The patients should be transported to a hospital by a 24/7 on-call service, preferably to a center with ED and CCU and/or ICU, all familiar with AHF. The patients with suspected CS should be transported to a recognized expert center that includes cardiac catheterization, assist device facilities and ideally cardiac surgery, with adequate experience and expertise in treating such patients [14]. In cases of AHF and acute myocardial infarction (AMI), the patient must be transported to the closest hospital with 24/7 on-call cardiac catheterization laboratory services.

Initial management of AHF without cardiogenic shock

Four consecutive steps should be rapidly performed (Fig. 1): (1) triage to assess initial severity, (2) confirm AHF diagnosis based on clinical signs and natriuretic peptides, (3) identify causes of AHF, and (4) assess organ injuries.

Confirm absence of respiratory distress and hemodynamic instability

The assessment of patient severity may be initiated in the pre-hospital setting or in the ED by a trained triage nurse, or junior or senior physician. Based on the physical examination, vital signs, and patient history, the patients with hemodynamic instability or respiratory distress not responsive to initial treatment should be quickly recognized and immediately transferred to an intensive care setting (CCU or ICU), the physician in charge being informed (Fig. 1). In the presence of ST segment elevation myocardial infarction (STEMI), or non-STEMI with hemodynamic instability or persistent chest pain, transfer to cardiac catheterization laboratory for primary revascularization is mandatory [15]. The large majority of AHF patients are, however, hemodynamically stable, and the primary diagnostic work-up and early treatment can therefore be initiated in the ED.

AHF diagnosis

The clinical presentation of patients with AHF is heterogeneous and challenging [16]. Acute respiratory

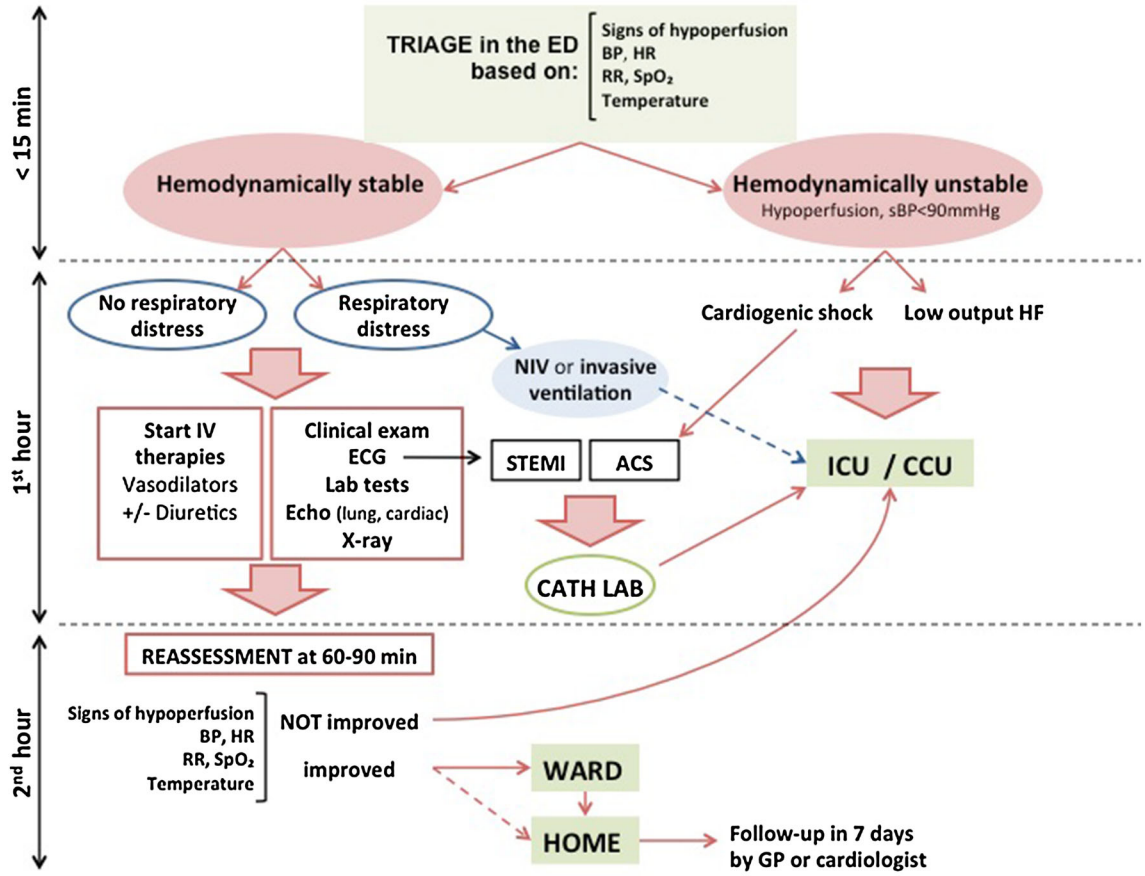

Fig. 1 The hospital management of patients with suspected acute heart failure. *ED* emergency department, *BP* blood pressure, *HR* heart rate, *RR* respiratory rate, SpO_2 peripheral capillary oxygen saturation, *Temp* body temperature, *NIV* non-invasive ventilation, *IV* intravenous, *ECG* electrocardiogram, *lab tests* laboratory tests, *echo* ultrasound (lung ± cardiac), *ACS* acute coronary syndrome, *STEMI* ST segment elevation myocardial infarction, *cath lab* cardiac catheterization laboratory, *ICU* intensive care unit, *CCU* cardiac care unit, *HF* heart failure, *GP* general practitioner. *Low output HF* systolic BP <90 mmHG without sighs of tissue hypoperfusion, usually in patients with end-stage heart disease

distress is considered the key symptom, although it is not specific [17]. Fatigue, dizziness, palpitations, and increasing body weight with peripheral edema, together with decreased diuresis, are also common manifestations. In the physical examination, special attention should be given to the signs of pulmonary (increased respiratory rate and effort, rales) and systemic (jugular vein distension, hepatomegaly, peripheral edema) congestion and organ hypoperfusion (cool extremities, altered mental status, decreased urine output, hyperlactatemia).

Detailed patient history should be obtained, with special attention to earlier cardiac disorders (angina, myocardial infarctions, revascularization, previous diagnosis or episodes of decompensation of heart failure). Patient history is also important for differential diagnosis and for revealing the precipitating factors for the acute decompensation (previous angina, arrhythmias, infections, non-compliance with salt or water restriction, or inconstancy on medications). Comorbidities, such as chronic obstructive pulmonary disease (COPD), diabetes mellitus, and atrial fibrillation, are common especially in the elderly, and should be considered in the primary diagnostic work-up.

Plasma natriuretic peptides play an important role in the early diagnosis of AHF, as the sensitivity and specificity of clinical assessment alone may be insufficient. It was recently recommended to measure plasma natriuretic peptide concentration (BNP, NT-proBNP, or MR-proANP) in patients presenting with acute dyspnea to the ED or CCU/ICU to rule in, and more importantly to rule out, AHF [18]. Natriuretic peptides are quantitative markers of heart failure [19–22]: the higher their concentration, the higher the likelihood that AHF is the main cause of acute dyspnea. Higher natriuretic peptide concentrations are also associated with greater severity of heart failure and worse post-ICU outcome, including high readmission rate and high mortality [23, 24]. In the Breathing Not Properly study [25] a BNP concentration

above 100 pg/mL had a sensitivity of 90 % and specificity of 76 % for differentiating heart failure from other causes of dyspnea. The investigators of the PRIDE study [20] suggested age–specific cutpoints of NT-proBNP of 450–1800 pg/mL for supporting the diagnosis of AHF. The concentrations of natriuretic peptides do not differentiate among the different AHF phenotypes, however, and interpretation of their levels must always be accompanied by clinical assessment and cardiac imaging as a second step. False positive values may be present in comorbid conditions such as renal failure or severe infections, but low plasma levels of natriuretic peptides have a high negative predictive value.

Complementing exams

The following exams are suggested at admission: 12-lead ECG, laboratory tests including troponins, creatinine, urea, electrolytes, liver function tests, and blood glucose. In severe cases with hemodynamic instability or respiratory distress, blood gases and lactate are also needed. Cardiac troponin is a quantitative marker of cardiomyocyte injury, and, although closely associated with the severity of AHF, its role in detecting AMI as the trigger of the AHF episode is more limited [26].

Procalcitonin has recently been shown to help in diagnosis of respiratory infection in dyspneic patients and may help in guiding the initiation of antibiotic therapy [27, 28]. Kidney and liver function markers should be repeatedly checked in AHF patients. A rise in liver transaminases (ALT, AST) generally reflects liver cell ischemia/necrosis caused by hypoperfusion, whereas the rise in cholestatic markers (alkaline phosphatase) is associated with right heart congestion [3]. Circulatory or urinary biomarkers, such as NGAL, kidney injury marker-1 (KIM-1), and *N*-acetyl-beta-D-glucosaminidase (NAG), may be useful in predicting worsening renal function, but remain unvalidated in AHF [29].

The chest X-ray is important for the evaluation of patients with AHF because it can detect cardiomegaly, pulmonary congestion, pleural effusion, and pulmonary infection. Also alternative causes of the patient's symptoms may be identified, but X-ray cannot assess for pulmonary embolism. Due to its low sensitivity and specificity [30], the chest X-ray should not be the key diagnostic tool in identifying specific causes of heart failure. Thoracic computed tomography scan, as a very rapid diagnostic method, is essential for the diagnosis of pulmonary embolism in patients with intermediate to high clinical suspicion.

Lung and pleural ultrasound, due to its widespread availability and absence of ionizing radiation, is an elegant imaging modality in patients with heart failure. It may reveal pulmonary congestion and/or pleural effusion [31]. Multiple B-lines are considered as good indicators of alveolar interstitial edema, though not specific for AHF. The presence of at least three B-lines per field of scan seen longitudinally between two ribs using a phased array or sector probe, with a distance between two B-lines of $<7 \pm 1$ mm, is the current criteria for abnormality [32]. Bilateral B-lines in either anterior or lateral chest is considered the most specific finding. More importantly, the absence of multiple B-lines rules out AHF as an etiology of dyspnea [33]. Echocardiography evaluating the etiology of heart failure and the hemodynamic parameters (i.e. filling pressures) should be performed immediately in cases of hemodynamic instability but most often can be performed later, within 12–24 h.

Immediate treatment

Early therapeutic considerations in AHF should be based on the status of congestion ("wet" vs. "dry") and systemic perfusion ("warm" vs. "cold") based on clinical signs, laboratory tests, and ultrasound [34]. Indeed, in cases of warm/wet AHF, the management is based on diuretics, vasodilators, and oxygen, or on NIV in cases of APE [1]. The use of inotropes and vasopressors should be restricted to maintain perfusion pressure in those AHF patients with signs of hypoperfusion and/or shock (see "Cardiogenic shock").

Diuretics

For patients with congestion (systemic or pulmonary edema), a bolus dose of a loop diuretic (e.g., 0.5 mg/kg of furosemide or double the usual oral dose, intravenously) should be administered, if not given in the pre-hospital care. Furosemide acts as immediate venodilator and subsequent diuretic agent, usually rapidly relieving symptoms. If respiratory distress persists after 2 h and diuresis is active, the bolus dose should be repeated. If diuresis is not improved, new attempts should be made with greater doses. Some patients may benefit from a tailored initial approach of diuretic dosing [35], and a combination therapy of a loop diuretic with thiazide or other class of diuretics may improve the diuretic effect [36, 37]. In cases of APE associated with abrupt hypertension, diuretics are not recommended since systemic volume overload is usually absent; in contrast, vasodilators and NIV are the first-line therapy in that scenario.

Diuretic resistance is common in patients with AHF but its mechanism(s) is uncertain. It may be associated with worsening renal function due to both renal hypoperfusion and congestion, as well as influenced by the neurohumoral activation and the effects of therapeutic interventions in AHF. There are few perspectives in the management of congestion in the case of diuretic resistance. Tolvaptan, a novel vasopressin v2 receptor

Table 1 Recommended dosing of intravenous vasodilators to treat acute heart failure

	Dosing	Main side effects	Other
Nitroglycerin	Start with 10–20 μg/min, increase up to 200 μg/min	Hypotension, headache	Tolerance after continuous use
Isosorbide dinitrate	Start with 1 mg/h, increase up to 10 mg/h	Hypotension, headache	Tolerance after continuous use
Nitroprusside	Start with 0.3 μg/kg/min and increase up to 5 μg//kg/min	Hypotension, Methemoglobinemia	Light sensitive
Nesiritide	Bolus 2 μg/kg + infusion 0.01 μg/kg/min	Hypotension	
Clevidipine	2.0 mg/h for 3 min, double every 3 min up to 32.0 mg/h	Hypotension	Made in fat emulsion

antagonist, when associated with natriuretic diuretics, has the potential to restore systemic and organ congestion [38, 39], although more evidence is needed. Ultrafiltration did not show a benefit compared to pharmacologic therapy in a randomized clinical trial of AHF patients with worsened renal function [40]. However, it has not been studied specifically in diuretic-resistant cases, and might be used in selected cases after failure of other options [37].

Vasodilators

The impact of vasodilators on outcome in AHF has recently been heavily challenged. Vasodilators are still underused (roughly 30 % of AHF [41]), likely due to the lack of trials showing benefits, as well as the potential harm in cases of excessive drop in BP [42]. Two large trials (NCT01661634 and NCT02064868) should assess whether agents with vasodilator properties (ularitide or serelaxine) improve outcome in AHF.

Until more evidence of novel treatments is gained, as stated in the recent European Society of Cardiology (ESC) and American guidelines [1, 43], we strongly recommend the use of nitrates as often as possible in AHF patients with normal or high BP. Nitrates may act as both venodilators and arteriodilators, reducing both preload and afterload. High dosing of nitrates has been shown, though in a small trial, to be safe and more effective compared to high-dose loop diuretics with low-dose nitrates in treating severe APE [9]. In a retrospective study [44], high-dose nitroglycerin treatment decreased the rates of endotracheal intubation and ICU admission. In cases of AHF with high BP, very early administration of clevidipine, a novel calcium-channel blocker, was associated with marked dyspnea improvement [45]. Although the use of vasodilators has only been indicated in patients with systolic BP >110 mmHg in the recent ESC guidelines [1], in a sub-analysis with propensity-based matched pairs, vasodilators were shown to be safe and effective on outcome in AHF patients with normal or low systolic BP [46]; this needs to be confirmed.

Vasodilators are indeed contraindicated in cases of shock and in those with history of significant mitral or aortic valvular stenosis, and should be used with caution in predominant right ventricular (RV) failure due to the risk of reducing coronary perfusion pressure. Table 1 shows the dosing schema and common side effects of the currently available vasodilators. The currently studied novel pharmacologic agents for the treatment of AHF are shown in Table 2.

Morphine

Opiates, such as morphine, may be offered to selected patients to relieve anxiety associated with acute respiratory distress [1]. However, their use has been associated with increased need of invasive mechanical ventilation, ICU admission, and even mortality [47, 48], and thus the routine use of opiates is not recommended.

Oxygen, non-invasive, and invasive ventilation in acute pulmonary edema

APE affects nearly 20 % of AHF patients [49] and is the most important indication for oxygen therapy and mechanical ventilation in patients with AHF. Mild hypoxemia usually responds to conventional oxygen therapy. However, patients with APE often show rapid progression of respiratory failure with mixed acidosis. The primary pathophysiological alteration is the flooding of the interstitium-alveoli, triggered by an abrupt increase in the hydrostatic lung capillary pressure. APE patients show increased work of breathing with severe dyspnea–orthopnea, tachypnea, and hypoxemia, which may lead to progressive respiratory failure. Systemic congestion may be absent in APE patients associated with abrupt

Table 2 Potential future therapies of acute heart failure

Agent	Example	Mechanism of action	State of development	Study population	Study identifier
Vasodilators					
Vasodilator, vascular endothelial growth factor and angiogenesis	Serelaxin	Binding to the cognate receptor, (RXFP1), a G-protein coupled receptor	Phase III	Acute dyspnea due to acute heart failure	NCT02064868; NCT01870778
Natriuretic peptide	Ularitide	Renal-tubular isoform of ANP	Phase III	Acute dyspnea due to acute heart failure	NCT01661634
Natriuretic peptide	Carperitide	Recombinant atrial natriuretic peptide	launched	Acute heart failure	NCT00259038
Natriuretic peptide	PL-3994 (NPRA)	Natriuretic peptide receptor-A (NPR-A) agonist	Pre-clinical	Evaluated in hypertension	NCT00686803
Relaxin	BMS-986046	Binding to the cognate receptor, (RXFP1), a G-protein coupled receptor	Pre-clinical	Not available	Not available
sGC activators	Cinaciguat, riociguat	Activation of soluble guanylate cyclase, endothelial independent vasodilation	Development stopped for cinaciguat, use in pulmonary hypertension for riociguat	Chronic thrombembolic pulmonary hypertension, idiopathic pulmonary hypertension, information about use in acute heart failure scant	NCT02117791
Dihydropyridine calcium-channel blocker	Clevidipine	Dihydropyridine calcium channel antagonist	Phase III	Acute heart failure	PRONTO2 in preparation
Angiotensin II typ 1 receptor antagonist	TRV1200027 (Trevena)	β-Arrestin biased ligand of the angiotensin II type 1 receptor	Phase III	Acute heart faiure in hospitalized patients	NCT01966601
Vasopressin V2 receptor antagonists					
	Tolvaptan, conivaptan	Blockade of renal vasopressin V2 receptor	Launched	Worsening heart failure and difficult volume management	NCT01584557
	Lixivaptan	Blockade of renal vasopressin V2 receptor	Phase III	Congestive heart failure	NCT01055912
Inotropic drugs					
Cardiac myosin activator	Omecamtiv mercarbil	Increasing the probability of the transition of a weakly actin-bound to a strongly actin-bound force-producing state	Phase IIb	Hospitalized for acute heart failure and reduced LV function	NCT01300013
Na^+/K^+-inhibitors	Istaroxime	Inhibition of Na^+/K^+-ATPase and SERCA2 activation	Phase II (development stopped)	Worsening heart failure	NCT00616161
Ca^+ release channel stabilizers	JTV-519 (K201), S107, S44121	Stabilization of RyR2 by improving binding of calstabin2 to RyR2	n/a	Information about use in acute heart failure scant	e.g. ISRCTN14227980
	Urocortin		Phase II	Not available	NCT01599728
Others					
	ONO-4232	EP4 agonist: involved in prostaglandin E induced vasodilation	Pre-clinical	Not available	Not available
	CXL-1427, (CXL-1020, CXL 1036; developed by Cardioxyl)	Nitroxyl (HNO) Donors, enhances sarcoplasmic reticular Ca(2+) uptake and myofilament Ca(2+) sensitivity, improving cardiac contractility	Phase I	Possible use in acute decompensated heart failure, information scant	NCT02157506
	MST-188 (Mast)	Poloxamer 188, multiple clinical indications for diseases and conditions characterized by microcirculatory insufficiency	Preclinical for acute heart failure, phase III for sickle cell disease	Not available	

hypertension (flash edema) and often with preserved LV function [50]. These patients differ from those with APE and decompensated chronic heart failure, in whom congestion is always present.

Oxygen therapy, diuretics, and vasodilators are the baseline treatment for APE [1, 9]. NIV techniques are indicated to improve the respiratory distress more quickly, and to reduce the intubation rate compared to conventional oxygen therapy [10, 11, 51, 52], although the impact in mortality is less conclusive [10]. There are two main modalities of NIV: continuous positive airway pressure (CPAP), and non-invasive pressure support ventilation (NIPSV) used with positive end-expiratory pressure (PEEP). The CPAP is a simple technique that may be applied without a ventilator, which may be advantageous in low-equipped or low-training areas. The NIPSV is equally effective and in addition provides inspiratory aid that may be beneficial in hypercapnic or fatigued patients. However, NIPSV requires a ventilator, some expertise, and occasionally mild sedation to improve patients' adaptation [51]. NIV should be started early, probably in the pre-hospital setting through CPAP [53]. Acid–base balance may be monitored through serial arterial or venous samples [54]. According to SpO_2, F_IO_2 may be increased, but hyperoxia should be avoided since it may decrease coronary blood flow [55]. After improvement, no special weaning protocol is necessary in APE. Conversely, obtunded patients and those who fail with NIV should be intubated. Although the positive intrathoracic pressure reduces both LV preload and afterload and may increase cardiac output, persisting hypotension after initiation of mechanical ventilation may require inotropic or vasopressor medication, especially in patients with depressed LV function. PEEP is mandatory, but high levels may not be tolerated in patients with low systolic BP. The contraindications for NIV in AHF patients include significantly altered mental status, poor co-operation, apnea, hypotension, and vomiting, as well as possible pneumothorax. Moreover, due to increasing the RV afterload, mechanical ventilation should be used with caution in isolated RV failure.

Cardiogenic shock

Cardiogenic shock is the most severe manifestation of AHF, accounting for <5 % of AHF cases in the western world [49]. It is characterized by severe circulatory failure of cardiac cause, with hypotension and sings of organ hypoperfusion. The most common etiology of CS is ACS with or without mechanical complication (80 %), the other causes of CS include severe decompensation of chronic heart failure, valvular disease, myocarditis, or even Tako-Tsubo syndrome [56]. Although still associated with poor prognosis, survival in CS has improved markedly during the last 30–40 years, and short-term mortality is around 40 % in contemporary cohorts of CS

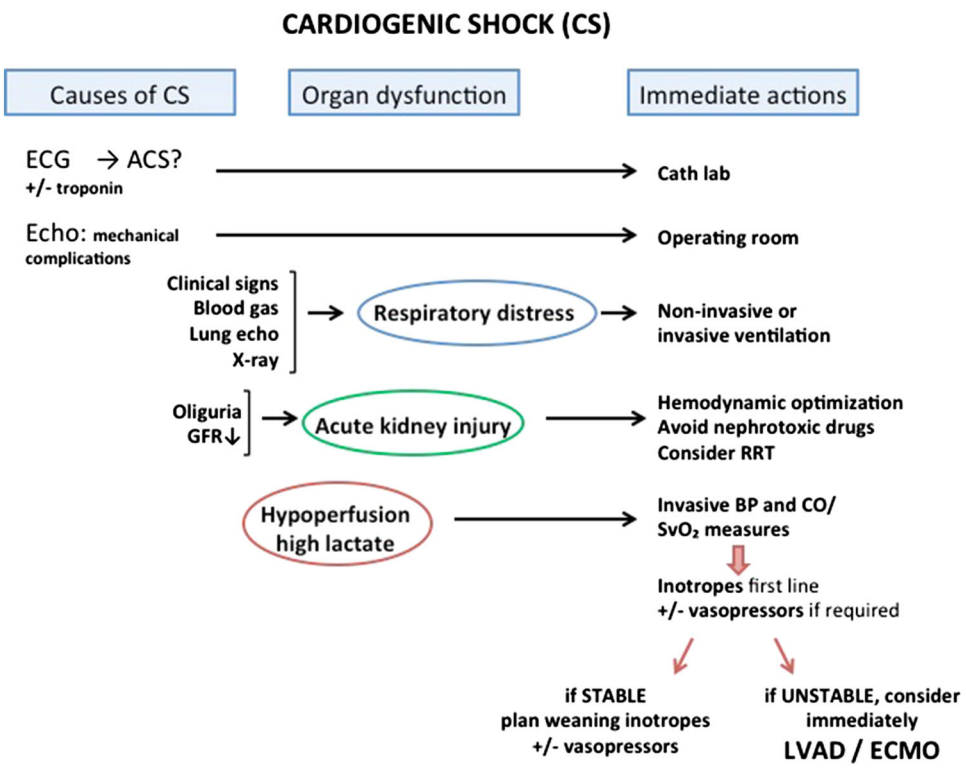

Fig. 2 Treatment schema for patients with cardiogenic shock. *ECG* electrocardiogram, *echo* echocardiography, *ACS* acute coronary syndrome, *cath lab* cardiac catheterization laboratory, *BP* blood pressure, *CO* cardiac output, SvO_2 mixed venous oxygen saturation, *LVAD* left ventricular assist device, *ECMO* extracorporeal membrane oxygenation

[56, 57]. Despite active use of early revascularization, development of systemic inflammatory response syndrome and multi-organ dysfunction are believed to be major contributors to the high early mortality.

In all shock patients, a coronary cause should be routinely sought with ECG and troponin assay, and coronary angiogram should be considered (Fig. 2). The Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock (SHOCK) trial showed the benefit of an early revascularization strategy in patients with CS due to AMI [58]. Recent ESC guidelines [15] recommend urgent revascularization by percutaneous coronary intervention, or rarely by coronary artery bypass surgery, in all CS patients in the setting of ACS, independent of the time delay from the onset of the pain (I/B recommendation). Although still a matter of uncertainty [57], complete revascularization by multivessel PCI, in addition to the culprit coronary lesion, is encouraged by the European guidelines (IIa/B recommendation) [15]. The ongoing CULPRIT-SHOCK trial (NCT01927549) will hopefully bring clarity to this issue. Apart from revascularization, there is a lack of data on management strategies with outcome benefit [57]. Moreover, controlled normothermia in patients with CS after cardiac arrest is not inferior to therapeutic hypothermia [59].

Hemodynamic monitoring

Echocardiography should be performed immediately after presentation to rule out mechanical complications, to evaluate the etiology of CS, and to assess cardiac function. Repetitive echocardiography should be used to monitor hemodynamic evolution. An arterial catheter should be placed in all patients to monitor BP and to guide the use of inotropic agents and vasopressors, if needed. Arterial catheters also allow repetitive blood gas analyses to monitor respiratory support therapy [13]. In addition, repeated serum lactate measurements, which are required to assess improving or worsening organ hypoperfusion [12], can be obtained through arterial catheter. In hypotensive patients requiring vasoactive support, a central venous catheter (superior vena cava) should be inserted [13]. This can be used to monitor central venous pressure and for measurement of central venous oxygen saturation ($ScvO_2$) to estimate the global oxygen supply–demand ratio, and therefore to evaluate the variation of cardiac output in response to therapy. Pulmonary artery catheter (PAC) should be considered in CS not responding to initial treatment [1]. PAC can be of particular benefit in RV failure to determine pulmonary artery pressures, right atrial pressure, stroke volume, and mixed venous oxygen saturation (SvO_2), and the effects of therapies. As recently recommended by the European Society of Intensive Care Medicine (ESICM) guidelines [12], transpulmonary thermodilution monitor/pulse wave analysis can serve as an alternative to PAC in shock patients with acute respiratory distress syndrome.

Inotropes and vasopressors

Inotropes and/or vasopressors are used to improve cardiac performance and restore BP levels in patients with CS. The use of these agents should, however, be restricted to the shortest possible duration and lowest possible dose to maintain perfusion pressure [57]. It is advisable to first start with inotropic support, and, if necessary, add a vasopressor as short-term combination treatment [60]. The first line inotropic agent in CS should be dobutamine [61, 62], or the calcium sensitizer levosimendan that might be favored in patients with history of chronic heart failure and in those with post-operative cardiac stunning [63]. Small studies have found that levosimendan is superior to milrinone in refractory CS, and potentially useful in patients on beta-blockers [64, 65]. Levosimendan and milrinone may cause less pronounced tachycardia but more profound hypotension than dobutamine; in addition, they reduce cardiac filling pressures and pulmonary vascular resistance, where they might be particularly beneficial for patients with concomitant pulmonary artery hypertension [63]. Epinephrine has more deleterious effects (e.g., lactic asidosis, arrhythmia) compared to norepinephrine and dobutamine [61]. If needed, norepinephrine is the vasopressor of choice in CS [60, 62].

Device therapy

Mechanical circulatory support in CS is reviewed in detail elsewhere [57, 66]. Intra-aortic balloon pump (IABP) has been widely used in CS patients, but a recent randomized trial did not show any mortality benefit with IABP treatment in patients with AMI complicated by CS compared to medical treatment alone [67, 68]. If temporary circulatory support is needed, ESC and American guidelines [15, 69] recommend the use of a left ventricular assist device (LVAD) or extracorporeal membrane oxygenation (ECMO) without any preference (IIa/C recommendation). The currently available LVAD options are Impella (2.5, 3.5, or 5.0), Tandem Heart, and iVAC 2L (Table 3) [57, 66]. IABP may still be considered in the case of mechanical

Table 3 Technical features of the currently available percutaneous circulatory support devices for patients with cardiogenic shock

	iVAC 2L®	TandemHeart™	Impella®5.0	Impella® 2.5	Impella® CP	ECLS (multiple systems)
Catheter size (F)	11 (expandable)	–	9	9	9	
Cannula size (F)	17	21 venous 12–19 arterial	21	12		17–21 venous 16–19 arterial
Flow (L/min)	Max 2.8	Max. 4.0	Max. 5.0	Max. 2.5	3.7–4.0	Max. 7.0
Pump speed (rpm)	Pulsatile, 40 mL/beat	Max. 7500	Max. 33 000	Max. 51 000	Max. 51 000	Max. 5000
Insertion/placement	Percutaneous (femoral artery)	Percutaneous (femoral artery + vein for left atrium)	Peripheral surgical (femoral artery)	Percutaneous (femoral artery)	Percutaneous (femoral artery)	Percutaneous (femoral artery + vein)
LV unloading	+	++	++	+	+	−
Anticoagulation	+	+	+	+	+	+
Recommended duration of use	−21 days	−14 days	10 days	10 days	10 days	−7 days
CE-certification	+	+	+	+	+	+
FDA	−	+	+	+	+	+
Relative costs	++	+++++	++++	+++	++++	+(+)

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complications (IIa/C recommendation) [15]. Veno-arterial ECMO has the advantage of delivering both circulatory and oxygenation support for patients with both hypoperfusion and ventilatory failure. The goal for device therapy is to bridge to recovery or alternatively to LVAD and/or to cardiac transplantation, which makes the patient selection crucial; risk stratification accounting for global risk (age and comorbidities), as well as neurological and other end-organ damage should be carefully assessed. While device therapy has been shown to improve hemodynamics, no adequately powered trial has so far been able to demonstrate outcome benefit in patients with CS.

Other clinical scenarios of AHF seen in the ICU

AHF in acute coronary syndrome

Acute coronary syndrome is one of the main precipitating factors of AHF and may lead to deterioration in patients with pre-existing heart failure or may be the cause of de novo AHF. Approximately 15–20 % of patients with ACS have signs and symptoms of AHF [70]. AHF is usually the consequence of large ischemia and myocardial dysfunction, but may also result from arrhythmia. AHF in the setting of ACS may deteriorate into CS, as described above. Patients with ACS complicated by AHF have markedly increased mortality rates [71–74] and the majority develop recurrent heart failure [75].

The clinical presentation of ACS and AHF are often overlapping. AHF may mask the signs and symptoms of ACS, and, conversely, minor elevations in cardiac troponin levels are associated with AHF itself. Repeated ECG and cardiac troponin measurements may show alterations indicating the diagnosis of ACS and supporting the pharmacological management approach of AMI [76]. The indications of emergency invasive evaluation and revascularization are AHF with STEMI or with other high-risk ECG signs (such as ST segment elevation in lead aVR, or persistent deep precordial T-waves or ST segment depression), ACS associated with persistent chest pain, and ACS with unstable AHF or with CS [15]. Of note, antithrombotic drugs should be used in their usual indications and doses.

Myocarditis

Myocarditis is an inflammatory disease of the myocardium, often resulting from viral infection or post-viral immune-mediated responses. It may cause sudden death or lead to dilated cardiomyopathy [77]. The clinical presentation varies from asymptomatic and self-limiting disease to myocardial injury (mimicking AMI), AHF, and CS. High cardiac troponin values are common, and

related to worse prognosis. In addition to ventricular dysfunction and dilated cavities, increased wall thickness and altered myocardial texture appearance, as well as pericardial effusion (perimyocarditis) may be seen in echocardiography [78]. Cardiac magnetic resonance imaging (CMR) with gadolinium also helps in differential diagnostics [79].

Patients with fulminant myocarditis or hemodynamically unstable AHF with suspected myocarditis should be transferred to an expert center. The hemodynamic treatment in fulminant myocarditis with signs of CS is supportive and symptomatic, including assist devices if needed, as described above. Urgent referral for evaluation for cardiac transplantation should be considered in cases refractory to treatment [80]. Endomyocardial biopsy remains the gold standard of diagnosis, and should be performed in hemodynamically compromised AHF with normal-sized or dilated ventricles, or when clinical suspicion of specific myocarditis with potential therapeutic consequences is high, after exclusion of ACS and without signs of rapid recovery [81]. Routine use of general or specific immunological therapies directed toward myocarditis is not recommended, but may be beneficial in certain specific etiologies [80, 82].

Predominant right ventricular failure

Some AHF patients have predominant signs of RV failure, including distended jugular veins and enlarged liver. Predominant RV failure may be caused by pulmonary embolism, pericardial tamponade, RV infarction, or other deterioration in a patient with pre-existing pulmonary vascular disease. Urgent echocardiography is needed in RV failure to confirm diagnosis, to estimate pulmonary pressures and to assess associated valvular disease. Alteration of liver function tests (especially cholestasis [3]) and kidney markers may be associated with a notable increase in serum lactate (as a sign of liver congestion), though systemic hemodynamics, especially BP, blood flow, and stroke volume, may remain stable. The first therapeutic action should be the correction of the precipitating factor, if possible, such as urgent revascularization in RV infarction or thrombolytic therapy in massive pulmonary embolism and hemodynamic instability.

For the acute hemodynamic treatment of RV failure, the following should be corrected: BP, RV preload, RV afterload (i.e. pulmonary resistance) and, if needed, RV contractility. In case of hypotension, vasopressors, usually norepirephine, are needed to maintain coronary and other organs' perfusion pressure. The optimization of RV preload is essential; the action needed depends on the level of RV afterload. Thus, in case of increased RV afterload, such as in pulmonary artery hypertension, volume loading may impair LV filling by further displacement of interventricular septum into the LV cavity, as well as decrease coronary perfusion by increasing RV wall stress [83].

Reduction of RV afterload is also important: mechanical ventilation, especially with PEEP, increases pulmonary pressures and may therefore aggravate RV dysfunction. However, the correction of hypercapnia, acidosis, and alveolar hypoxia, all aiming at decreasing hypoxic pulmonary artery vasoconstriction is important, and is the first action required to lower RV afterload. Indeed, using a low level of pressure support oxygenation may be useful. To further decrease pulmonary pressures, inhalation with nitric oxide or prostanoids are effective options. In cases of pulmonary hypertension, consultation with a specialized center, particularly prior the initiation of specific treatment for pulmonary arterial hypertension, is mandatory. To increase RV contractility and restore cardiac output, especially in cases of hemodynamic compromise, several inotropic drugs can be used [84]. Milrinone and levosimendan, which both also reduce pulmonary resistance, may be particularly beneficial in this scenario [63]. If pharmacologic therapy fails, veno-atrial ECMO may be used to ensure systemic oxygenation and to unload the RV [18].

Discharge criteria and post-discharge follow-up

The mean duration of hospitalization for AHF varies from 5 days in the US to 12 days in some European countries [85]. The more severe cases are admitted in ICU/CCUs with a usual stay of 2–6 days. In many countries, there is increasing financial pressure for shortening hospital stays and reducing rehospitalizations of heart failure patients [86]. It is difficult, however, to

Table 4 Example of a checklist that may be used to optimize patient's condition before discharge

Clinical parameters
Dyspnea/edema improved Y/N
Body weight decrease >3 kg Y/N
HR slowed Y/N
BP normalized Y/N
Biology
Natriuretic peptide low Y/N
GFR stable and >60 Y/N
Precipitating factor found and controlled Y/N
Comorbidities controlled Y/N
Drug prescription
A CE-I/ARB Y/N
Betablockers Y/N
MRA Y/N
Diuretics Y/N
Anti-thrombotics Y/N
Diet prescription Y/N
Post-discharge work-up organized Y/N

Y yes, *N* no, *HR* heart rate, *BP* blood pressure, *GFR* glomerular filtration rate, *ACE-I* angiotensin converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *MRA* mineralocorticoid receptor antagonists

state concrete discharge criteria to optimize the time of discharge. We propose a check list of items that will help to ensure the stabilization of patient condition, including reduction of clinical and biological signs of congestion via natriuretic peptide measure, before discharge (Table 4) [87–89].

Prevention of rehospitalization for heart failure includes: (1) continuation or initiation of long-lasting therapies of heart failure: beta-blockers, angiotensin converting enzyme (ACE) inhibitors [or angiotensin receptor blockers (ARBs)], and mineralocorticoid receptor antagonists (MRAs) before discharge; (2) optimal management of underlying heart diseases (e.g., coronary artery disease, control of arrhythmias); (3) optimal management of comorbidities, such as COPD, sleep apnea, anemia, depression, and memory disorders; (4) patient education on water and salt restrictions; (5) nutritional support, though supporting data are lacking; and (6) careful patient education on all items of the program. Those items should be part of a tight post-discharge program including scheduled follow-ups starting within 7 days after discharge, as recently described [90–92]. Post-discharge programs are especially beneficial for reducing adverse outcomes in high-risk patients, such as those over 65 years of age, with advanced heart disease, multiple prior hospitalizations, multiple co-morbidities, or poor cognitive capacity or social support network [93], though cost/effectiveness is still debatable [94].

In summary, the key messages of the present paper are:

- AHF mostly corresponds to organ congestion.
- Early treatment initiation is associated with superior outcomes in AHF.
- Lung ultrasound is an easy and efficient diagnostic tool to rule out pulmonary congestion.
- The use of vasodilators is strongly recommended in most AHF patients.
- NIV techniques improve respiratory rate faster compared to conventional oxygen therapy in APE patients.
- Inotropes and vasopressors are restricted to patients with cardiogenic shock, and should be used for the shortest possible period and with the lowest possible dose to restore perfusion pressure.
- Patients with hemodynamic instability or cardiogenic shock should be treated in a specialized center with facilities of assist devices for circulatory support.
- Mechanical support with assist devices should be considered early in the treatment of patients with cardiogenic shock, before the development of irreversible end-organ injuries.
- AHF patients should benefit from a tight multidisciplinary post-discharge program to avoid rehospitalizations and other adverse outcome.

Acknowledgments The work of G. Baksyte was supported by the grant MIP-049/2015 from the Research Council of Lithuania.

Compliance with ethical standards

Conflicts of interest A. Mebazaa received speaker's honoraria from The Medicines Company, Novartis, Orion, Servier, Vifor Pharma, and fee as member of advisory board and/or Steering Committee from Cardiorentis, The Medicine Company, Adrenomed and Critical Diagnostics.J. Lassus has received consulting and speaker's honoraria from Bayer, Boeringer Ingelheim, Novartis, Orion Pharma, Pfizer, ResMed, Roche Diagnostics, Servier and Vifor Pharma.W.F. Peacock received research grants from Abbott, Alere, Banyan, Cardiorentis, Janssen, Portola, Pfizer, Roche, The Medicine's Company and consultant fees from Alere, Cardiorentis, Janssen, Alere, Cardiorentis, and Janssen. W.F. Peacock has Ownerships in Comprehensive Research Associates LLC, Emergencies in Medicine LLC.M.B. Yilmaz received research fee from Novartis and Cardiorentis.A. Cohen Solal received speaker and consulting fees from Actelion, Ipsen, Sorin, Abbott, Novartis, Thermofisher, Alere, Pfizer, Vifor, Amgen, Servier, Bayer, Sanofi, and Boehringer Ingelheim.M. Christ has received grants for clinical studies and speaking honoraria by Novartis GmbH, Alere GmbH and Roche Diagnostics, Germany.J. Januzzi has received grants from ThermoFisher, Prevencio, Siemens, and Singulex; consulting fees from Novartis, Critical Diagnostics, Radiometer, diaDexus.CEC; and fees for data and safety monitoring board (DSMB): Novartis, Amgen, Boeringer-Ingelheim.Other co-authors have no conflict of interests.

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