

Review Article



Acute Heart Failure Management

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ABSTRACT

Acute heart failure (AHF) is a life-threatening medical condition, where urgent diagnostic and treatment methods are of key importance. However, there are few evidence-based treatment methods. Interestingly, despite relatively similar ways of management of AHF throughout the globe, mid-term outcome in East Asia, including South Korea is more favorable than in Europe. Yet, most of the treatment methods are symptomatic. The cornerstone of AHF management is identifying precipitating factors and specific phenotype. Multidisciplinary approach is important in AHF, which can be caused or aggravated by both cardiac and non-cardiac causes. The main pathophysiological mechanism in AHF is congestion, both systemic and inside the organs (lung, kidney, or liver). Cardiac output is often preserved in AHF except in a few cases of advanced heart failure. This paper provides guidance on AHF management in a time-based approach. Treatment strategies, criteria for triage, admission to hospital and discharge are described.

Keywords: Heart failure; Cardiogenic shock; Management; Treatment

INTRODUCTION

Recent guidelines from European Society of Cardiology (ESC) and American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and guidance papers from European Society of Emergency Medicine (EUSEM), European Society of Intensive Care Medicine (ESICM) have provided updated recommendations on acute heart failure (AHF) management.¹⁻⁴⁾ However, there is still a lack of evidence in the field and physicians frequently have to make decisions based on expert opinion consensus, rather than evidence-based recommendations. Management of AHF relies on rapid recognition of the symptoms, identifying the underlying or precipitant cause, assessing severity of AHF, recognizing complications and initiating specific treatment as soon as possible. Both ESC and ACCF/AHA guidelines underscore that, similarly to acute coronary syndrome (ACS), AHF patients might benefit from “time-to-therapy” concept.^{1,2)} Consequently, rapid diagnosis and immediate treatment can be potentially lifesaving in these patients, thus exact time-based algorithms must be in place in pre-hospital

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

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and hospital settings. Recently, an interest in acute right heart failure (HF) has developed, since it has distinct clinical features, its own diagnostic difficulties and treatment.⁵⁾

Although it is necessary to follow similar strategies of managing AHF throughout the world, one should keep in mind that there are regional differences. We recently showed that patients from East Asia had a better 1-year survival following an AHF admission than European patients in an analysis including more than 18,000 patients.⁶⁾

This paper summarizes recommendations from most recent ESC, ACCF/AHA guidelines and EUSEM, ESICM guidance papers and provides contemporary perspective based on state-of-art clinical trials.

DEFINITION

AHF is a rapid onset or acute worsening of symptoms and/or signs of HF, associated with elevated plasma levels of natriuretic peptides (NPs).¹⁾ It requires immediate medical management and, usually, urgent hospital admission. It can be a first occurrence of AHF (de novo) or, more frequently, acute decompensation of chronic heart failure (ADHF). De novo AHF is mainly caused by primary cardiac dysfunction (mainly ACS), while ADHF may be precipitated by infection, uncontrolled hypertension, rhythm disturbances or non-compliance with the prescribed drugs/diet.^{1,2)} AHF is a multifaceted syndrome with various clinical phenotypes, such as acute pulmonary edema (APE), hypertensive HF, cardiogenic shock (CS) and others.⁷⁾ It may present with impaired or preserved left ventricular ejection fraction, or disturbance of right ventricle function. Although considered as a primarily cardiac syndrome, AHF may lead to systemic disorders and affect all vital organs due to insufficient blood circulation⁴⁾ caused by high level of venous back-pressure and/or low cardiac output.

CLASSIFICATION

Nomenclature of AHF depends on the criteria used. Guidelines suggest that the most useful classifications in practice are those that rely on clinical presentation.^{1,2)} They help clinicians to identify the patients at high risk and initiate the necessary treatment rapidly. Most AHF patients present with normal or high blood pressure (BP) and symptoms/signs of congestion. Only 5–8% patients present with hypotension, which is associated with poor prognosis, especially if accompanied with hypoperfusion.¹⁾ Hypotension (systolic blood pressure [SBP] <90 mmHg or >90 mmHg maintained by vasopressors) with the absence of hypovolemia and signs of hypoperfusion (cold sweated extremities, oliguria, altered mental state, metabolic acidosis, etc.) is defined as CS. Although relatively rare, CS is the most severe form of AHF, treated in the coronary care unit (CCU)/intensive care unit (ICU). With delayed treatment, CS may initiate systemic inflammatory responses, leading to multiorgan failure and death.

Another possible approach is classifying patients based on precipitating factors or causes leading to decompensation, which have their specific treatments and need to be corrected urgently (**Table 1**).^{1,2)} Moreover, 2 main mechanisms causing organ dysfunction in AHF are congestion, which is very frequent, and hypoperfusion, which is rather rare. Classification based on bedside clinical examination evaluates the symptoms or signs of congestion (“dry”

Table 1. Precipitating factors of AHF⁽¹²⁾

ACS
Arrhythmias
Uncorrected hypertension
Concurrent infections
Non-compliance with the treatment plan, sodium and/or fluid restriction
Excessive use of toxic substances
Drugs exacerbating condition (e.g., calcium channel blockers, steroids, NSAIDs)
Exacerbation of COPD
PE
Metabolic or hormonal disorders
Cerebrovascular accident
Acute mechanical cause
Additional acute cardiovascular causes (e.g., pericardial effusion, myocarditis)

ACS = acute coronary syndrome; AHF = acute heart failure; COPD = chronic obstructive pulmonary disease; PE = pulmonary embolism.

vs. “wet”) and/or peripheral hypoperfusion (“warm” vs. “cold”).⁸⁾ This approach divides the patients into 4 groups, which helps guide the treatment in the initial phase and also has prognostic value (Table 2).⁸⁻¹⁰⁾ Classifications based on clinical presentation are intended to provide personalized care for the AHF patient.

MANAGEMENT OF ACUTE HEART FAILURE (EXCLUDING CARADIOGENIC SHOCK)

First hour management

Patients with AHF are at high risk of complications during the first hour of the onset of the disease.¹¹⁾ Therefore, it is increasingly acknowledged that “time-to-treatment” approach, which is highly established in ACS, should be considered in AHF to prevent adverse outcomes.¹²⁾¹³⁾ Indeed, early prehospital treatment is associated with lower mortality.¹⁴⁾ Urgent treatment is also important to prevent de novo AHF patients from developing chronic HF.⁴⁾ Patients should be rapidly transferred to the hospital, preferably to a center with a cardiology department and/or emergency department (ED) or CCU/ICU with AHF expertise.⁴⁾

Table 2. Clinical classification and appropriate treatment based on bedside clinical examination

Evidence of congestion		Pulmonary congestion, orthopnea/paroxysmal nocturnal dyspnea, peripheral edema, distended jugular veins, rales, hepatojugular reflux, ascites		
		Congestion (-)		Congestion (+)
Evidence of hypoperfusion: narrow pulse pressure, symptomatic hypotension, cool extremities, impaired mental status	Hypoperfusion (-)	Warm-dry (up to 25%) Compensated 1. Adjust oral therapy	Warm-wet (up to 50%) Predominant congestion 1. Diuretic 2. Vasodilator 3. Consider ultrafiltration if resistant to diuretics	Predominant hypertension 1. Vasodilator 2. Diuretic
	Hypoperfusion (+)	Cold-dry (up to 5%) Hypoperfused and hypovolemic 1. Consider fluid challenge 2. Consider inotropic agent if hypoperfusion persists	Cold-wet (up to 20%) SBP <90 mmHg 1. Inotropic agent 2. Vasopressor in refractory cases 3. Diuretic (when perfusion restored) 4. Consider mechanical circulatory support if unresponsive to drugs	SBP ≥90 mmHg 1. Vasodilator 2. Diuretic 3. Consider inotropic agent in refractory cases

Adapted from the 2016 ESC guidelines on acute and chronic HF.¹⁾ This approach was proposed by the analysis of Nohria et al.¹⁰⁾ Frequencies of the groups are given according to this analysis.
 ESC = European Society of Cardiology; HF = heart failure; SBP = systolic blood pressure.

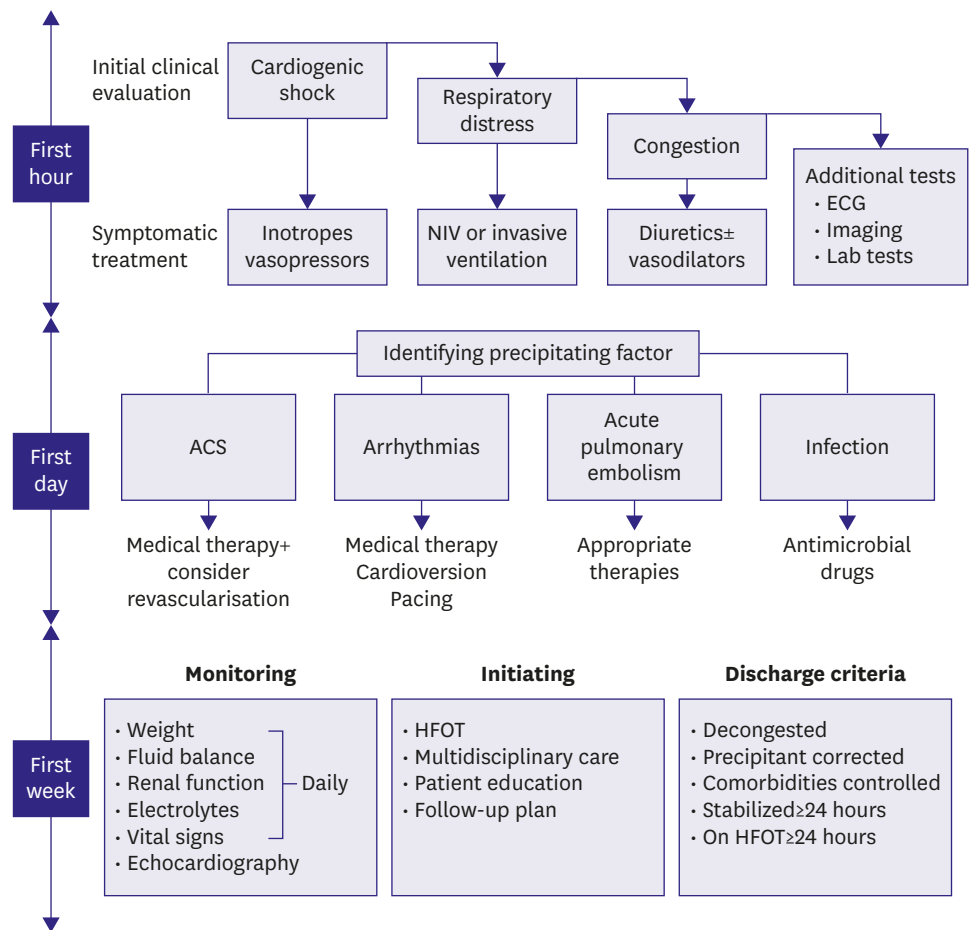


Figure 1. Time-based management in AHF.

ACS = acute coronary syndrome; AHF = acute heart failure; ECG = electrocardiogram; HFOT = heart failure oral therapy; NIV = non-invasive ventilation.

Immediate and concomitant investigation, diagnostic tests, pharmacologic and non-pharmacologic treatment should be initiated on the arrival (**Figure 1**).

Initial clinical evaluation

In the earliest stages of diagnostic workup, emphasis should be given to determination of cardiopulmonary stability based on dyspnea severity, hemodynamic status and heart rhythm.¹⁴⁾ This may be achieved by following assessments:

- Respiratory rate, orthopnea, accessory muscles use in respiration, visible cyanosis, pulse oximetry as objective measurements of respiratory distress
- Audible rales as sign of pulmonary congestion
- SBP and diastolic blood pressure (DBP)
- Heart rate and rhythm
- Objective determination of body temperature and signs/symptoms of hypoperfusion³⁾

Patients with respiratory failure or hemodynamic compromise should be transferred to a location where immediate respiratory and cardiovascular support is available. When AHF is caused by acute myocardial infarction, patient must be referred to the closest clinical

facility, where round-the-clock cardiac catheterization service is available.⁴⁾¹⁵⁾ If CS is present, patient should receive ventilation and hemodynamic support and be transferred directly to CCU/ICU.¹⁶⁾

Next, patient should be examined for signs of systemic congestion, such as peripheral edema, jugular venous dilatation and others (**Table 2**).

Additional tests used in patients with suspected AHF include:

1) Electrocardiogram (ECG)

Electrocardiogram (ECG) will exclude ST-segment elevation myocardial infarction (STEMI) and other high risk changes.¹⁾ Additional ECG value is limited, since it is rarely normal in those with suspected AHF and may reveal some chronic abnormality.³⁾

2) Imaging modalities

- Bedside thoracic ultrasound: With expertise, thoracic ultrasound can be a useful diagnostic tool for visualizing direct signs of interstitial edema.¹⁷⁾ Pulmonary congestion may be assessed by analyzing comet-like vertical reverberation artefacts, called B-lines.¹⁸⁾ The quantity and diffusion of B-lines provides a semi-quantitative estimation of extravascular lung water (≤ 5 , absent; 6–15, mild degree; 16–30, moderate degree; > 30 , severe pulmonary edema).¹⁸⁾ B-lines are useful in differential diagnosis between AHF and non-cardiac causes of dyspnea.¹⁹⁾
- Chest X-ray: It is one of the most used modalities in AHF settings. Most specific signs of AHF are pulmonary venous congestion, pleural effusion, interstitial or alveolar edema and cardiomegaly.¹⁾ However, sensitivity of chest radiography is limited, since it may be completely normal in almost 20% of the cases.²⁰⁾²¹⁾ If expertise is available, lung ultrasound may be more sensitive and timesaving modality in detecting interstitial edema.³⁾ Chest radiography can also identify alternative etiology of dyspnea, such as pneumonia or other pulmonary infections.
- Echocardiography: Immediate cardiac ultrasound is mandatory in all patients with CS and when acute life-threatening structural or functional cardiac abnormalities (mechanical complications, aortic dissection, etc.) are suspected.¹⁾³⁾ In other cases, it may be performed later during hospitalization, when expertise is available (preferably, during first 48 hours of admission). Early echocardiography should be pursued in de novo AHF patients and those, whose cardiac function is unknown.¹⁾
- Chest computed tomography (CT): Though not particularly relevant in diagnosing AHF, thoracic CT scan is essential, when pulmonary embolism (PE) is suspected as a precipitating factor of AHF.²²⁾

3) Laboratory tests

- NPs: Plasma NP level (B-type natriuretic peptide, N-terminal pro-B-type natriuretic peptide, or mid-regional pro-atrial natriuretic peptide) should be measured at presentation to the ED or CCU/ICU in all patients with acute dyspnea and suspected AHF. Due to their high sensitivity, NPs are very important in ruling out AHF as an etiology of acute dyspnea, since detecting normal levels makes AHF diagnosis improbable.³⁾²³⁾ However, there are numerous cardiac and non-cardiac causes, which may be associated with elevated plasma NP level. Therefore, a higher value of NP does not automatically confirm the diagnosis of AHF and interpretation of their levels must be combined with clinical assessment and cardiac imaging.⁴⁾ NPs have prognostic value in AHF: higher

concentrations mean more severe condition and increased risk for readmission and mortality.²⁴⁾

- Cardiac troponins: They are useful for detection of ACS as the precipitator of AHF.¹⁾ Elevated troponin levels are also associated with poorer outcomes in AHF.²⁵⁾²⁶⁾
- The following laboratory assessments should be performed at admission in all patients with AHF: blood urea nitrogen (BUN)/urea, creatinine, electrolytes (sodium, potassium), liver function tests, glucose, and complete blood count.³⁾ Abnormal liver function tests reflect different clinical profiles in AHF. Elevated cholestasis markers are associated with signs of systemic congestion, right HF and higher concentration of creatinine and NPs, whereas increased levels of alanine aminotransferase, aspartate aminotransferase — with signs of hypoperfusion and consequent liver cell damage.²⁷⁾ Deteriorated kidney function is a frequent comorbidity of AHF, which worsens the prognosis.²⁸⁾ ESC guidelines also recommend performing thyroid-stimulating hormone (TSH), since both hypothyroidism and hyperthyroidism may precipitate AHF.¹⁾
- Although not needed in most cases, arterial blood gas may be useful in severe cases of hemodynamic instability and respiratory distress. Acid-base balance should be obtained on admission, especially in patients with APE or previous history of chronic obstructive pulmonary disease (COPD).³⁾ If respiratory distress persists despite initial therapy with oxygen and/or non-invasive ventilation (NIV), venous blood gas analysis is sufficient to detect respiratory or metabolic acidosis.²⁹⁾
- There are multiple novel biomarkers (sST2, Galectin-3, GDF-15, etc.) being investigated in AHF, but they have yet to be introduced to routine clinical practice.

Initial therapy

1) Oxygen therapy and/or ventilatory support

Oxygen saturation (SpO₂) should be monitored in all patients with dyspnea. Oxygen therapy should be initiated when SpO₂ is below 90% and fraction of inspired oxygen (FiO₂) should be increased up to 100%, if necessary, according to SpO₂ measurements. However, hyperoxia causes vasoconstriction and may decrease coronary and cerebral blood flow and thus should be avoided.³⁰⁾

NIV is indicated in patients with respiratory distress and should be initiated urgently, since it reduces respiratory distress and rate of mechanical endotracheal intubation.³¹⁾ In a randomized study comparing early versus delayed NIV, initiation of continuous positive airway pressure (CPAP) in pre-hospital settings in patients with cardiogenic APE significantly improved clinical dyspnea score, partial pressure of oxygen (PaO₂) levels and reduced tracheal intubation rates and in-hospital mortality.³²⁾ However, potential benefit of NIV on reducing mortality has only been shown in small-sample trials and larger trials are needed.³³⁾ Two main methods of NIV include CPAP and bi-level positive pressure ventilation (PPV).³⁴⁾ CPAP has a simpler technology and less expensive equipment than bi-level PPV. In turn, bi-level PPV devices consist of a higher inspiratory positive airway pressure and a lower expiratory pressure, providing inspiratory aid.³⁴⁾ The 2017 European Respiratory Society/American Thoracic Society guidelines recommend either of the NIV methods in acute respiratory failure due to cardiogenic APE and suggest initiating NIV in pre-hospital settings.³⁴⁾ In acidotic patients due to COPD exacerbation, bi-level PPV is recommended.³⁴⁾ NIV is contraindicated in patients with respiratory arrest, decreased conscious state or significant hemodynamic instability.³⁵⁾ Other contraindications include lack of staff expertise or patient's cooperation, vomiting and possible pneumothorax.⁴⁾ Patients with these conditions and those unresponsive to NIV should be intubated.

2) Diuretics

Intravenous loop diuretics are a key of symptomatic treatment in AHF patients with signs of significant fluid overload and congestion.^{1,2)} They increase renal salt and water excretion, have vasodilator properties and provide rapid decongestion and symptomatic relief.¹⁾ Intravenous furosemide is the first-line diuretic in most of the cases. ACCF/AHA guidelines recommend administering diuretics immediately upon presentation, as this approach may be associated with better outcomes.²⁾ However, there is little evidence defining optimal diuretic timing, dosage and method of delivery.¹⁾ In the Diuretic Optimization Strategies Evaluation (DOSE) trial, there were no statistically significant differences in symptom relief and creatinine levels in bolus vs. continuous diuretic infusion and in high-dose vs. low-dose groups.³⁶⁾ In the “high-dose” arm of the trial, patients were administered furosemide at 2.5 times their previous oral dose. This resulted in greater improvement in diuresis and dyspnea at the cost of transient worsening in renal function.³⁶⁾ It is therefore recommended to limit diuretic dose to the smallest amount needed to provide adequate symptomatic relief and modify the dose according to renal function and prior dose of diuretics.¹⁻⁴⁾ Hence, de novo AHF or diuretic naïve patients should receive initial intravenous furosemide bolus of 20–40 mg, while patients on chronic oral diuretic therapy should be administered intravenous bolus of at least equal to their oral dose.^{1,3)} If the patient is not hypotensive, combination with vasodilator agent for dyspnea relief may be used. In cases of diuretic resistance, dual nephron blockade by loop diuretics and thiazide diuretics or natriuretic doses of mineralocorticoid receptor antagonists (MRAs) may be administered for better effect.^{37,38)} However, these combinations may cause hypokalemia, renal dysfunction or hypovolemia, therefore cautious electrolyte, renal function, and fluid balance monitoring is required. If diuretic agents do not provide the expected effect, ultrafiltration may be considered,^{37,38)} but prognosis of this approach is poor.³⁹⁾ In patients with AHF and signs of hypoperfusion, clinicians should refrain from diuretics before adequate perfusion is restored.¹⁾

3) Vasodilators

Intravenous vasodilators, predominantly nitrates, provide additional symptomatic relief to diuretics and are the second most used drugs in AHF.³⁾ Nitrates have a dual mechanism of action as they act as both venodilators and arteriodilators, reducing both preload and afterload and as a result increasing stroke volume.^{1,4)} Intravenous vasodilators are especially indicated in hypertensive AHF.¹⁾ Previous ESC guidelines restricted vasodilators use in patients with SBP <110 mmHg;⁴⁰⁾ this has been changed — 2016 ESC guidelines recommends avoiding vasodilators when SBP is <90 mmHg or hypotension in symptomatic.¹⁾ ESICM guidance recommends initiating vasodilators as soon as possible in patients with normal to high BP;⁴⁾ a delay of vasoactive drugs administration has been associated with higher mortality.¹³⁾ Furthermore, initiation of intravenous vasodilators urgently after presentation has been shown to reduce the rates of mechanical ventilation and risk of adverse events (AEs).^{13,41)}

Recent randomized controlled trials have challenged the use of agents with vasodilator properties in AHF. In Trial of Ularitide Efficacy and Safety in Acute Heart Failure (TRUE-AHF) study, patients were randomly assigned to receive continuous intravenous infusion of either ularitide or matching placebo for 48 hours, in addition to adequate AHF therapy.⁴²⁾ There were no differences in co-primary outcomes (cardiovascular mortality over the 15 months of the trial and the clinical course during the initial 48 hours evaluated by hierarchical clinical composite outcome) between the 2 trial arms. Ularitide did not show benefit in any of the clinical secondary outcome measures either. In a post hoc analysis, which excluded

the patients, which had been randomized despite being ineligible for the trial, ularitide was shown to improve hierarchical clinical composite outcome but still did not reduce the risk of cardiovascular mortality.⁴²⁾ Although RELAXin in Acute Heart Failure (RELAX-AHF) trial findings were promising for another vasodilator agent serelaxin,⁴³⁾ a subsequent larger RELAX-AHF-2 trial (NCT01870778) did not meet either of its primary endpoints, which were 180-day cardiovascular mortality and worsening HF in the first 5 days.⁴⁴⁾⁴⁵⁾ A novel calcium channel blocker with vasodilator properties clevidipine safely and rapidly reduced BP and improved dyspnea more effectively than standard-of-care intravenous antihypertensive therapy in patients with hypertensive AHF in a pilot Prioritising Responses of Nurses to Deteriorating Patient Observations (PRONTO) study.⁴⁶⁾ Nonetheless, due to relatively small sample size, open-label design, and short follow-up time, these findings have to be confirmed in larger randomized controlled trials.⁴⁷⁾

Vasodilators are contraindicated in shock and should be used cautiously when significant mitral or aortic valvular stenosis is suspected or in predominant right ventricular (RV) failure.⁴⁾

4) Other agents

Even though they relieve dyspnea and anxiety, routine use of opiates is not recommended in AHF.¹⁾ In the Acute Decompensated Heart Failure National Registry (ADHERE), morphine use was associated with higher rates of mechanical ventilation, ICU admission and death.⁴⁸⁾

As noted in the ESC guidelines, administration of vasopressor in AHF (excluding CS) should be restricted to patients with hypotension and administration of sympathomimetic — to patients with signs of low cardiac output.¹⁾ In the recent international European Society of Cardiology Heart Failure Long-Term Registry (ESC-HF-LT) registry⁴⁹⁾ the use of inotropes and/or vasopressors was lower than in previous registries (12% vs. 20% in Italian Italian Network on Heart Failure [IN-HF] Outcome registry⁵⁰⁾ and 33% in global Acute Heart Failure Global Registry of Standard Treatment [ALARM-HF] registry⁵¹⁾). Nonetheless, the use of these drugs was still inappropriate as only a small number of the treated patients had CS and less than half had signs of peripheral hypoperfusion.⁴⁹⁾ In analysis with propensity-based matched pairs from this registry, patients receiving intravenous inotrope and/or vasopressor had a higher long-term mortality risk compared to those who did not. The findings also showed that dopamine had the greatest negative association with mortality among studied inotropes (dobutamine, levosimendan), but the study was not powered to prove such results.⁴⁹⁾

First day management

After initial diagnostic tests and symptomatic treatment of the urgent symptoms, clinicians should seek to rapidly identify the etiology or precipitating factor for AHF and initiate the specific treatment (**Figure 1**). This is extremely important to prevent worsening of AHF and avoid adverse outcomes and should be achieved within the initial few hours of AHF management.¹⁾²⁾

Precipitating factors and their specific treatment

- ACS: It is a frequent cause of both acutely decompensated HF and de novo AHF.⁵²⁾ ECG may rapidly reveal STEMI, however, diagnosis of other ACS cases may be more complicated.²⁾ Troponin levels are elevated in many patients with AHF with or without ACS as the sensitivity of troponin assays increases.⁵³⁾ ACCF/AHA guidelines recommend considering coronary angiography in all patients with newly diagnosed HF.²⁾ We

recommend to consider this when patient is stabilized. Patients with coexistent ACS (both non-ST elevation ACS and STEMI) and AHF are at a very-high risk group and immediate revascularization is indicated, regardless of other findings.¹⁾¹⁵⁾⁵⁴⁾

- Severe arrhythmias/rhythm disturbances. Tachyarrhythmia, bradyarrhythmia or conduction disturbances may precipitate AHF. Several ESC guidelines address the management of severe rhythm disturbances.⁵⁵⁻⁵⁷⁾ Urgent electrical cardioversion is recommended if arrhythmia is related to hemodynamic instability. In AHF patients with atrial fibrillation (AF) and rapid ventricular rate (>110 bpm), intravenous boluses (0.25–0.5 mg intravenously, smaller doses of 0.0625–0.125 mg in patients with moderate to severe renal dysfunction) of digoxin should be considered for rapid control of the ventricular rate.¹⁾ In other patients with HF and AF, beta blockers are preferred to control the ventricular rate.³⁾
- Acute mechanical causes: They include complications of ACS (e.g., free wall or ventricular septal rupture, acute mitral insufficiency), chest trauma, cardiac intervention, endocarditis (acute native or prosthetic valve lesion), aortic dissection and rarer causes of obstruction (e.g., cardiac tumors). Immediate echocardiography is crucial to confirm the diagnosis when acute mechanical cause is suspected and treatment comprises of urgent surgical or percutaneous repair.¹⁾¹⁵⁾
- Acute PE: Pulmonary embolus should be considered as a precipitant of AHF since patients with HF are more likely to be in a hypercoagulable state.²⁾ Chest CT is a gold standard in the diagnostic process.²²⁾ When acute PE is confirmed, immediate primary reperfusion is recommended. This may be achieved by thrombolysis, catheter-based approach or surgical embolectomy.²²⁾
- Infection: Respiratory infections are frequent precipitants for HF.⁵⁸⁾ They cause hypoxia and are associated with higher in-hospital and long-term mortality.⁵⁸⁾⁵⁹⁾ Sepsis is associated with reversible left ventricle hypokinesia.⁶⁰⁾ Procalcitonin is useful in diagnosis of primary or coexisting respiratory infection in dyspneic patients and guiding the initiation of antibiotic treatment.⁶¹⁾⁶²⁾ Significantly elevated procalcitonin levels predict worse in-hospital outcomes and increased 30-day mortality, irrespective of HF severity.⁶³⁾ Rapid detection of bacterial infections and initiation of specific antibiotic treatment is essential to prevent adverse outcomes in patients with AHF.

Determining necessary level of care for acute heart failure patient

AHF patients need different levels of care (discharge, observation, ward, ICU, etc.) depending on the severity of their condition. Algorithms and risk scores aimed at predicting in-hospital mortality may provide additional value to clinical judgment in the decision process. The ADHERE registry including more than 65,000 patients developed an algorithm predicting in-hospital mortality in patients with HF.⁶⁴⁾ It consists of measurements of BUN, SBP, and creatinine and helps identify high risk population that should be referred to ICU. Moreover, low risk population may be identified by the absence of high risk features (high plasma NP levels, hypotension, positive troponin, deteriorated renal function, etc.). These patients can be treated in the observation unit to evaluate the response to the initial therapy.³⁾ EUSEM guidance provides a list of indicators of good response to therapy to consider in ED:

- Subjective improvement noted by patient
- Resting heart rate <100 bpm
- No orthostatic hypotension
- Adequate urinary output
- SpO₂ >95% in room air
- No or moderate worsening of renal function (chronic renal disease might be present)³⁾

The following criteria are recommended for admitting the patient to ICU/CCU:

- Need for intubation (or already intubated)
- Evidence of organ hypoperfusion
- SpO₂ <90% on oxygen therapy
- Increased breathing effort, respiratory rate >25/min
- Heart rate <40 or >130 bpm, SBP <90 mmHg^{1,3)}

ESC guidelines recommend that patients with AHF without the criteria for intensive care be hospitalized in ward with only a small part of the patients discharged home from the ED with arranged follow-up in an outpatient clinic.¹⁾ Transferring the patient out of ICU/CCU is determined by stabilization of the condition.¹⁾

First week management

Monitoring in the hospital

AHF patients should be carefully monitored in the hospital. Daily weight, supine and standing vital signs (pulse, respiratory rate, BP) measurements and accurate daily fluid balance monitoring should be maintained throughout the hospital stay. Daily assessment of BUN/urea, creatinine and electrolytes is preferred to monitor renal function, especially in patients on diuretics or when HF medications are titrated.^{1,2)} Worsening renal function has been associated with worse prognosis in AHF patients.⁶⁵⁾ Multidisciplinary care is essential to AHF/ADHF patients, since they generally have multiple comorbidities and up to two-thirds of their readmissions are due to causes other than HF.⁶⁶⁾ The team should consist of different specialists to assess comorbidities and possible causes of non-HF readmissions to reduce post-discharge event rate.⁶⁷⁾ Routine measurements of NPs may help with discharge planning.¹⁾ If not performed in the urgent phase, echocardiography should be performed during hospitalization or if condition deteriorates.

Evidence based oral heart failure therapies

The patient's compliance with HF medications should be reviewed at admission and adjustments should be made, if needed.²⁾ In most of the patients hospitalized due to AHF, evidence-based heart failure oral therapy (HFOT) should be continued or even uptitrated.^{1,3)} In particular, discontinuing beta-blockers has been shown to significantly increase the risk of AEs.⁶⁸⁾ Beta-blockers should be withheld when patient is hospitalized after recent initiation or increase of the dosage and in cases of CS.²⁾ Dosage of ACE inhibitors, ARBs, MRAs should be reduced or temporarily discontinued in patients with hyperkalemia and significant worsening of renal function.^{1,3)} Oral HF therapy should be discontinued in all patients with severe hypotension until condition is resolved. In new-onset AHF, clinicians should initiate evidence based oral therapies promptly after stabilization.³⁾

Discharge phase and early follow-up

In the discharge phase, clinicians should assess functional capacity of patient and potential exacerbating factors, optimize pharmacologic therapy and establish post-discharge plans together with the patient.⁶⁹⁾ Transition to oral diuretic therapy should be initiated and evaluated to verify its effectiveness.²⁾ ACCF/AHA guidelines suggests that hospitalization presents an opportunity to properly educate the patient and family and develop adequate strategy for chronic treatment.²⁾ Patient should be hemodynamically stable, decongested and on evidence-based HF therapy at least 24 hours before discharge.¹⁾ Guidelines underline that

follow-up plans must be implemented before discharge and communicated to primary care team.^{1,2)} It is recommended that the patients be:

- Provided with self-care education
- Enrolled in a disease management program
- Seen by their general practitioners within 1 week of discharge and by the hospital based cardiologist within 2 weeks
- Followed-up within a multidisciplinary HF service^{1,3)}

Noncompliance is one of the most important factors precipitating exacerbation of HF. Recognizing and assessing compliance problems and other potential precipitating factors is a critical step towards optimal management of AHF. Every patient should have an appropriately detailed evidence-based plan, preferably in writing. Staff should communicate the plan clearly ensuring patient's comprehension and evaluating potential issues of following the plan. In a randomized, controlled trial of acute HF with reduced ejection fraction patients the addition of a 1-hour individual teaching session with a nurse educator to the standard discharge process, decreased the risk of readmission or death, increased compliance, and reduced costs of care.⁷⁰⁾ This or similar approaches have to be studied in larger trials, but the findings are indeed suggesting that patient education should be an important part of the discharge phase.

OTHER CLINICAL SCENARIOS

Cardiogenic shock

CS is defined as hypotension (SBP <90 mmHg) >30 minutes despite adequate volume status (fluid challenge) with signs of organ hypoperfusion. It is a rare but severe phenotype of AHF.⁷⁾ STEMI with or without mechanical complications is the most common etiology of the CS (80% of the cases). Non-ACS causes include worsening of congestive HF, valvular disease and other mechanical causes, myocarditis and stress-induced cardiomyopathy.⁷¹⁾ ACS is associated with increased in-hospital mortality comparing to non-ACS causes.⁷¹⁾ Due to high early mortality, CS requires urgent diagnosis of the cause, recognition of organ dysfunction and immediate actions. ECG and troponin are used to diagnose coronary cause of CS; coronary angiogram should also be considered. Early revascularization strategy is strongly recommended in these patients.¹⁵⁾⁵⁴⁾ There has been an uncertainty whether complete revascularization should be performed in addition to the culprit coronary lesion in cases of multi-vessel disease. This issue was addressed in the recent international Culprit Lesion Only percutaneous coronary intervention (PCI) versus Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial, in which the 30-day risk of a composite of death or severe renal failure was lower in CS patients who underwent PCI on culprit lesion only than among those who underwent immediate multi-vessel PCI.⁷²⁾

Continuous monitoring of organ perfusion and hemodynamic status is crucial to guide the treatment for CS. Echocardiography should be performed immediately at admission to rule out mechanical complications and assess cardiac function.¹⁾³⁾⁴⁾ Repetitive echocardiography should be used for monitoring hemodynamic changes.¹⁾ Invasive monitoring with an arterial line is strongly recommended.⁷³⁾ Central venous catheter should be inserted for intermittent or continuous measurement of central venous oxygen saturation (ScvO₂).⁷³⁾ A pulmonary artery catheter may be considered, in patients with refractory CS and RV dysfunction.⁷³⁾

After fluid challenge of up to 250 milliliters, the treatment consists of inotropes, in cases of low cardiac output, and vasopressor, when mean arterial pressure need pharmacologic support.¹⁾⁷³⁾ Dobutamine should be a first-line inotropic agent.⁷³⁾ As an alternative, levosimendan may be used, especially in patients on beta-blockers at admission.⁷³⁾ Norepinephrine is the recommended vasopressor.⁷³⁾ The use of these agents should be restricted to the shortest possible duration and lowest possible dose.⁷⁴⁾ By contrast, increasing evidence shows that dopamine and epinephrine should not be used routinely in CS patients.⁷³⁾⁷⁵⁾⁷⁶⁾

When there is an inadequate response to pharmacologic treatment, device therapy has to be considered.¹⁾ Intra-aortic balloon pump (IABP) is the most widely used left ventricular assist device (LVAD) for hemodynamic support. However, results of the recent IABP-SHOCK II trial did not show any mortality benefit of IABP over medical treatment in patients suffering from acute myocardial infarction and CS.⁷⁷⁾⁷⁸⁾ There are several percutaneous LVADs (Impella [2.5, 3.5, or 5.0], Tandem Heart, and iVAC 2L) and peripheral extracorporeal membrane oxygenation (ECMO), which seems to be preferred by some recommendations.⁷³⁾ ESC guidelines recommend short-term mechanical circulatory support in refractory cases with IIb class of recommendation and C level of evidence.¹⁾ The goal for device therapy is to stabilize patients not responding to standard therapy, preserve organ perfusion and bridge to recovery or to surgical LVAD and/or to heart transplantation. Therefore, patient selection based on their global risk, neurological and end-organ damage is very important.⁴⁾ Although more evidence is needed to support the use of device therapy, their use is increasing.⁷⁹⁾

PREDOMINANT RIGHT HEART FAILURE

Rather unappreciated before, right HF has gained more recognition recently as a distinct clinical entity.⁵⁾ AHF patients may present with predominant signs of RV failure, including distended jugular veins and enlarged liver. Causes of RV failure include left-sided HF, acute PE, RV infarction, pericardial tamponade or other deterioration in patients with pre-existing pulmonary vascular disease. This condition must be recognized early since it may require specific treatment methods and conventional management strategies may sometimes result in adverse outcomes.⁵⁾ Urgent echocardiography is a first-line test in RV failure. It assesses RV size, function and load, associated valvular diseases and pulmonary pressures. Quantitative assessment of global RV function should be achieved by at least one of the following parameters: tricuspid annular plane systolic excursion (TAPSE), RV fractional area change (FAC), Doppler tissue imaging-derived systolic S' velocity of the tricuspid annulus or RV index of myocardial performance (RIMP). Changes in biomarkers include alteration in cholestasis (alkaline phosphatase)²⁷⁾ markers, creatinine, increase in serum lactate, NPs and cardiac troponins.⁵⁾ Precipitating factor must be corrected by urgent measures, if possible, such as urgent revascularization in cases of RV infarction or thrombolytic therapy in PE.⁵⁾

When treating RV failure, careful attention to RV preload is essential and excess volume should be avoided. Indeed, when RV afterload is increased (e.g., in pulmonary artery hypertension), volume loading may further overdilate the ventricles, worsen ventricular interdependence, and reduce cardiac output, as well as decrease coronary perfusion by increasing RV wall stress.⁵⁾ Diuretics are often the first option to reduce RV overload for most patients with RV failure who present with signs of venous congestion and maintained BP. On the other hand, nitrates and diuretics may compromise RV preload and be deleterious. In

order to prevent hemodynamic compromise, volume optimization must be done cautiously.⁵⁾ In hypotensive patients, norepinephrine is highly recommended to restore organ perfusion.⁵⁾

Hypercapnia, acidosis and alveolar hypoxia cause pulmonary artery vasoconstriction and further increase RV afterload.⁵⁾ Correction of these conditions may be achieved by low level of pressure support oxygenation.⁴⁾⁵⁾ Inhalation of nitric oxide²²⁾ or prostanoids⁸⁰⁾ are also effective options. Milrinone and levosimendan both reduce pulmonary resistance and increase RV contractility, which may be particularly beneficial in cases of hemodynamic compromise.⁵⁾⁸¹⁾

GAPS IN KNOWLEDGE AND PERSPECTIVES

There are several areas in AHF, which require further investigation. More extensive studies are needed in biomarker-guided risk stratification and treatment. “Time-to-treatment” concept should be investigated prospectively. There is a need in determining causes of readmissions and establishing appropriate strategies to prevent early readmissions after discharge. Many uncertainties remain in the field of acute RV failure and more evidence is needed regarding RV-specific treatment approaches.

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