

# Medical management of decompensated heart failure in adult patients: Part 1: Definition and medical management

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## ABSTRACT

Acute decompensated heart failure (ADHF) is the leading cause of hospitalization in patients older than 65 years. It continues to increase in prevalence and is associated with significant mortality and morbidity including frequent hospitalizations. The American Heart Association is predicting that more than 8 million Americans will have heart failure by 2030 and that the total direct costs associated with the disease will rise from \$21 billion in 2012 to \$70 billion in 2030. The definition of ADHF has important limitations, and its management differs significantly from that of chronic heart failure. Although many large, randomized, controlled clinical trials have been conducted in patients with chronic heart failure, it was not until recently that more studies began to address the management of ADHF. The mainstay of ADHF management involves identification of precipitating factors, oxygen supplementation, sodium and fluid restriction, and diuresis. The phenomenon of diuretic resistance is a significant obstacle to relief of congestion and is a field of active investigation. Other important adjuncts to treatment include noninvasive ventilation, inotropes, vasopressors, nitrates, opiates, and vasopressin receptor antagonists. In this review, we will discuss the terminology and classification of ADHF, and review the multiple modalities and strategies available for the management of this disorder.

**Keywords:** heart failure, medical management, complications, devices, palliative care

## INTRODUCTION

### DEFINITION OF HEART FAILURE

Heart failure (HF) is a clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.<sup>1</sup> It may be due to dysfunction of either the right ventricle (RV) or left ventricle (LV). There is no widely accepted nomenclature for HF syndromes requiring hospitalization. Patients are described as having “acute HF,” “acute HF syndromes,” or “acute decompensated HF.” While the

third term has gained the widest acceptance, it too has limitations, for it does not make the important distinction between those with a *de novo* presentation of HF from those with worsening of previously chronic stable HF. In this paper, we will use the term *acute decompensated heart failure* (ADHF) to describe the clinical syndrome of new or worsening signs and symptoms of HF, often leading to hospitalization or a visit to the emergency department.

### CLASSIFICATION OF HEART FAILURE

During an index hospitalization the initial step in evaluating someone presenting with HF symptoms is to identify the subtype. Ejection fraction (EF) determination is considered important in classification of

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patients with HF due to LV dysfunction due to differing patient demographics, comorbid conditions, prognosis, and response to therapies.<sup>2</sup> Heart failure may be further classified according to EF into HF with reduced ejection fraction (HFrEF) or HF with preserved ejection fraction (HFpEF; LVEF  $\geq$ 50%). HFrEF and HFpEF are also recognized as systolic and diastolic heart failure, respectively. Patients with EF between 41–49% have also been classified as heart failure with borderline EF (HFbEF). There is also a subset of patients with HFpEF or HFbEF who previously had HFrEF. These patients should be considered as having recovery in EF and may be clinically distinct from those with persistently preserved or reduced EF.<sup>3</sup> Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines define patients who have LVEF  $>$ 40%, but who previously had LVEF  $\leq$ 40%, as heart failure with improved ejection fraction (HFief).

### **PRECIPITATING FACTORS**

During the process of identifying the type of HF the patient presents with, it is also important to identify potential precipitating factors. The Organized Program To Initiate Lifesaving Treatment In Hospitalized Patients With Heart Failure (OPTIMIZE-HF) study identified at least one exacerbating factor in most patients hospitalized with heart failure. Pneumonia/respiratory disease (15.3%), ischemia (14.7%), arrhythmia (13.5%), and uncontrolled hypertension (10.7%) were identified most frequently.<sup>4</sup> Nonadherence to medications was identified in 8.9% and nonadherence to diet in 5.2% of patients. Other studies have reported similar findings.<sup>5–7</sup>

### **INITIAL SYMPTOM MANAGEMENT**

To control the presenting symptoms from decompensated heart failure it is important to understand why they develop. The National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand have published specific recommendations for the medical management of congestive heart failure.<sup>8</sup> The diagnosis of decompensated HF starts with a focused history and physical examination to identify precipitating factors and rule out other diagnoses. Signs of congestion and hypoperfusion often

guide treatment decisions.<sup>9,10</sup> Congestion results from elevated ventricular filling pressures, which lead to common symptoms and signs, including dyspnea, cough, oxygen desaturation, extremity edema, weight gain, abdominal fullness, nausea, emesis, abdominal pain, and early satiety. Gheorghide has described acute heart failure syndromes as a continuum that evolves from hemodynamic congestion to clinical congestion.<sup>11,12</sup> He notes that most patients who develop acute cardiogenic pulmonary edema have elevated left ventricular end-diastolic pressures, also known as hemodynamic constriction. However, this may not cause changes on chest x-ray or clinical symptoms if it has developed slowly over a prolonged period. Patients then deteriorate if capillary pressures continue to increase, fluid overload develops, or high pressures cause either additional cardiac dysfunction, pulmonary alveolar capillary damage, or neurohormonal activation. Neurohormonal activation is recognized as a contributing factor to the retention of sodium and water. In addition, fluid overload in the lungs in acute HF may not represent additional fluid accumulation but rather redistribution of fluid to the lungs. This happens secondary to decreased venous capacitance resulting in increased preload, and the impaired ventricular emptying secondary to increased arterial vasoconstriction or afterload.<sup>13</sup> The following discussion will focus on reviewing accepted and studied approaches for the initial medical management of ADHF.

### **SODIUM AND FLUID RESTRICTION**

The ACC/AHA recommends sodium restriction in patients with acute or chronic HF, although there are insufficient data to support any specific level of sodium intake in patients with symptomatic HF, as noted in the 2013 ACC/AHA and 2012 European Society of Cardiology (ESC) guidelines. Given the available evidence, we suggest sodium restriction (e.g.,  $<$ 2 g/d) in patients with symptomatic HF. The ACC/AHA guidelines suggest some degree of fluid (1.5 to 2 L/day) and sodium restriction ( $<$ 3 g/d) in patients with ADHF.<sup>14</sup> Stricter fluid restriction is indicated in patients with severe (serum sodium  $<$ 125 meq/L) or worsening hyponatremia. Both the ACC/AHA and the ESC accept that there are insufficient data to support any

specific level of sodium intake in patients with symptomatic HF.<sup>14,15</sup> Aliti et al. randomly assigned 75 patients with severe systolic dysfunction to a maximum dietary sodium intake of 800 mg/day and a maximum fluid intake of 800 mL/day vs a more relaxed sodium intake of 3 to 5 g and a fluid intake of at least 2.5 L/day and found no effect on clinical stability or weight loss at three days of hospitalization.<sup>16</sup> Travers et al. found no difference in time to reach clinical stability in patients treated with fluid restriction compared to those on free fluid intake.<sup>17</sup> Perceived thirst was significantly worse in the group with stricter sodium and fluid intake in both studies. Although some studies have suggested a possible benefit from a regimen of hypertonic saline plus furosemide in patients with ADHF, this approach is controversial and is of uncertain safety and efficacy.

## DIURETICS

Loop diuretics are the only medications shown to reliably reduce fluid retention in heart failure.<sup>18</sup> The intravenous route is preferred for diuretic administration in patients with decompensated HF due to more consistent and predictable pharmacokinetics.<sup>15,19,20</sup> Furosemide, in particular, has limited bioavailability when given orally. A prospective observational study of 1291 patients with ADHF reported improved in-hospital mortality with intravenous furosemide started within 1 hour of presentation compared with later treatment (2.3 versus 6.0 percent).<sup>21</sup> For patients who are naïve to loop diuretic therapy, intravenous diuresis may be started at a low doses (furosemide 20 to 40 mg, bumetanide 1 mg, torsemide 10 to 20 mg). Patients on chronic diuretic therapy may be started at a higher dose; a good rule-of-thumb is up to 2.5 times the maintenance total daily oral dose. Depending on the diuretic response, the dose may be doubled every 2–4 hours up to the recommended maximum.<sup>22</sup> A randomized controlled trial with 308 patients with acute decompensated heart failure found no significant differences in reported symptoms or serum creatinine levels when comparing continuous versus bolus administration of furosemide.<sup>23</sup> However, the study did note non-significant improvement in dyspnea with high dose compared to low dose diuresis. Patients receiving high dose furosemide had more frequent

acute kidney injury events; however, there were no differences in clinical outcomes at 60 days between the two dose strategies.<sup>24</sup>

## DIURETIC RESISTANCE

A significant subgroup of heart failure patients has persistent volume overload requiring progressively higher doses of diuretics, a condition called “diuretic resistance.”<sup>25</sup> There is significant variation in the degree of diuretic resistance among patients, and characteristics that help predict poor diuretic responses include low diastolic blood pressures, the absence of edema, advanced heart failure, renal impairment, diabetes mellitus, and atherosclerosis.<sup>26,27</sup>

Practical strategies to counter diuretic resistance include intravenous diuretic administration and ‘sequential blockade’ with the addition of a thiazide or aldosterone antagonist to the loop diuretic. More controversial approaches include increasing the dosage or switching to a continuous infusion of diuretic, hypertonic saline boluses, and co-administration of albumin in hypoalbuminemic patients.<sup>23,28–33</sup> Dopaminergic agonists, such as fenoldopam, have not been found have not been shown to be effective. Intravenous vasodilators may improve the clinical status in some patients with diuretic resistance.<sup>8</sup> Nitrates are the most frequently used drug; they cause vasodilation (reduced afterload) and decrease pulmonary congestion by reducing preload if the patient has enough systemic arterial blood pressure to tolerate them.<sup>34</sup> Cotter et al. showed that high dose nitrates in combination with low dose furosemide was more effective than low dose nitrates in combination with high dose furosemide.<sup>35</sup>

## OPIATES

Opiates may be used in ADHF to reduce patient anxiety and decrease the work of breathing. This in turn decreases sympathetic tone, leading to vasodilatation and a fall in cardiac filling pressures.<sup>36,37</sup> However, evidence of the benefit of morphine therapy in ADHF is limited. The National Institute for Health and Care Excellence (NICE) study reviewed opiate use in (morphine or diamorphine) in ADHF and found no evidence of benefit and some evidence of harm,

but the available evidence was considered low quality.<sup>38</sup> The largest of the studies found that morphine was associated with increased rates of admission to the intensive care unit and mechanical ventilation.<sup>39</sup> Morphine remained an independent predictor of mortality (OR 4.8, 95% CI 4.52–5.18) even after risk adjustment and exclusion of ventilated patients. The 2012 ESC guidelines suggests considering morphine in some patients with acute pulmonary edema with the goal of reducing anxiety and distress associated with dyspnea.<sup>14</sup> The 2013 ACC/AHA guidelines do not mention morphine therapy as part of the management of ADHF.

### **VASODILATORS**

The routine use of vasodilators has not been shown to improve outcomes.<sup>38</sup> The use of vasodilator therapy in patients with ADHF is based largely on underlying hemodynamics and expert opinion,<sup>15,19</sup> since evidence on efficacy and safety of vasodilatory therapy in this setting is limited.<sup>40</sup> The A Study Testing the Effectiveness of Nesiritide in Patients With Acute Decompensated Heart Failure (ASCEND-HF) trial found an increase in hypotension and no change in the outcomes of death and 30-day rehospitalization with nesiritide, despite a borderline significant reduction in dyspnea.<sup>41</sup> The Registrational Study With Omecamtiv Mecarbil/AMG 423 to Treat Chronic Heart Failure With Reduced Ejection Fraction (GALACTIC) trial reported no improvement in a composite outcome of death and 180-day rehospitalization with early use of non-parenteral vasodilators (high-dose sublingual and transdermal nitrates, oral hydralazine, rapid up-titration of angiotensin converting enzyme inhibitor [ACEI], angiotensin II receptor blocker [ARB], or angiotensin-receptor neprilysin inhibitor [ARNI]), compared with usual care (slow up titration of ACEI, ARB, or ARNI).<sup>42</sup>

Nitrates are the most commonly used vasodilators in ADHF. They primarily produce venodilation and help reduce LV preload and pulmonary congestion. At high doses, however, nitrates also cause arteriolar vasodilation and reduce systemic vascular resistance and LV afterload, theoretically increasing stroke volume and cardiac output. Two small randomized trials of limited quality have suggested that treatment regimens for

acute HF that include high-dose nitrate therapy for ADHF and pulmonary edema may reduce the need for mechanical ventilation.<sup>35,40</sup> It has been proposed that high-dose nitrate therapy may be particularly helpful and well tolerated in patients presenting with hypertensive HF.<sup>43</sup> The National Institute for Health and Care Excellence (NICE) performed a systematic review comparing intravenous nitroglycerin with placebo in patients with ADHF in the UK, and found no good quality evidence of improvement in dyspnea with nitrates.<sup>38</sup> Potential adverse effects of nitroglycerin include hypotension and headache. Nitrates can precipitate hemodynamic collapse in settings in which ventricular filling is important, such as right ventricular infarction or aortic stenosis, or if administered concomitant to of PDE-5 inhibitors such as sildenafil.

### **VASOPRESSIN RECEPTOR ANTAGONISTS**

Vasopressin receptor antagonists have been investigated as an adjunct to diuretics and other standard therapies in patients with ADHF as a means of countering arterial vasoconstriction, hyponatremia, and water retention. However, the long-term safety and benefit of these drugs are unknown. The Efficacy of Vasopressin Antagonism in hEart failuRE: Outcome Study With Tolvaptan (Everest) trial randomized 4133 patients with ADHF to tolvaptan vs placebo, and found no differences between the groups for the composite of cardiovascular death or hospitalization for heart failure as well as the secondary end points of cardiovascular mortality, cardiovascular death or hospitalization, and worsening heart failure.<sup>44</sup> Tolvaptan significantly improved serum sodium levels in patients with hyponatremia but was associated with increased thirst and dry mouth. The ACC/AHA classify as 'reasonable' the short-term use of vasopressin antagonists in hospitalized patients with volume overload who have persistent severe hyponatremia and are at risk for cognitive symptoms despite water restriction and maximization of guideline-directed medical therapy, although the long-term safety and benefit of this approach are unknown.<sup>15</sup> The 2012 ESC guidelines suggest consideration of tolvaptan for HF patients with hyponatremia in an ungraded recommendation.<sup>14</sup> The potential for hepatotoxicity with

tolvaptan is a significant concern; the United States Food and Drug Administration recommends that tolvaptan use be limited to 30 days and cautions against its use in patients with liver disease.

### **INOTROPIC AGENTS**

Addition of an inotrope is suggested for patients with ADHF who develop signs of hemodynamic compromise (hypotension, oliguria, confusion).<sup>14</sup> Both the ACC/AHA and the ESC support the use of these drugs as a temporizing measure in the setting of severe LV systolic dysfunction with diminished peripheral perfusion and end-organ dysfunction until definitive therapy (coronary revascularization, mechanical circulatory support, or heart transplantation) or resolution of the underlying pathology.<sup>14,15</sup> Continuous intravenous inotrope infusion is reasonable as a “bridging therapy” in advanced heart failure refractory to guideline-directed medical therapy and qualifying for mechanical circulatory support or cardiac transplantation. In addition, inotropic therapy may be utilized for clinical palliation in end-stage heart failure that remains symptomatic despite optimal medical/device therapy. The administration of intravenous inotropes requires continuous telemetry with frequent monitoring of blood pressure.<sup>19</sup> Inotropes are not indicated for treatment of ADHF in the setting of preserved systolic function.

Inotropic drugs increase myocardial oxygen consumption and may provoke ischemia, particularly in patients with ischemic heart disease, and may precipitate atrial and ventricular tachyarrhythmias,<sup>45,46</sup> in the absence of systemic hypoperfusion, inotropes may negatively impact outcomes in patients with ADHF.<sup>45,47</sup> A systematic review of randomized controlled trials of inotropes found insufficient evidence to convincingly support the efficacy and safety of these agents in ADHF.<sup>38</sup> The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure—OPTIME-CHF (OPTIME-CHF) trial studied milrinone and placebo in 949 patients presenting with acute exacerbation of CHF.<sup>45</sup> Milrinone therapy was associated with significant increases in hypotension and arrhythmias and a nonsignificant increases in mortality during the hospital stay (3.8 versus 2.3 percent) and at 60 days (10.3 versus 8.9 percent).

### **VASOPRESSORS**

Vasopressor therapy can be considered in patients with ADHF and marked hypotension on inotropic therapy in order to maintain systemic blood pressure and vital end-organ perfusion, although at the cost of increasing afterload and decreasing cardiac output.<sup>14</sup> A systematic review found no evidence to determine the clinical efficacy and safety of vasopressor therapy in ADHF.<sup>38</sup> Vasopressors used in this setting include norepinephrine, high-dose dopamine (>5 micrograms/kg/min), vasopressin, and these should be carefully titrated to achieve adequate perfusion of vital organs. Dopamine and norepinephrine have both beta inotropic and vasopressor activity. Phenylephrine should generally be avoided, since this drug increases afterload markedly without a positive inotropic effect.

### **VENOUS THROMBOEMBOLISM PROPHYLAXIS**

Prophylaxis against venous thromboembolism (deep vein thrombosis and pulmonary embolism) with low-dose unfractionated heparin or low molecular weight heparin, or fondaparinux is indicated in patients admitted with ADHF who are not already anticoagulated and have no contraindication to anticoagulation. In patients admitted with ADHF who have a contraindication to anticoagulation, prophylaxis with a mechanical device (e.g., intermittent pneumatic compression device) is suggested.<sup>19</sup>

### **NON-INVASIVE VENTILATION**

Established guidelines for treatment of pulmonary edema include non-invasive ventilation (NIV), which has an important effect on gas exchange and patient support but a limited effect on the rate of patient improvement.<sup>48</sup> After pulmonary edema develops, changes in ventilatory management do little to change these patients' clinical courses. Whether it is basolaterally-directed fluid transfer or apically-applied positive pressure, the pooled alveolar fluid is very difficult to remove secondary to the disruption of alveolar-capillary units and maladaptive changes to the collagen barrier during healing. Pulmonary edema persists well past the acute illness because these membranes need to be repaired and, over time, replaced with

an physiologically normal functioning barrier, before alveolar fluid clearance mechanisms can be restored.

Non-invasive ventilation improves ventilation by recruiting alveoli and reduces airway resistance by opening airways. Lung inflation can decrease perivascular interstitial hydrostatic pressure.<sup>49,50</sup> Therefore, positive airway pressure can theoretically redistribute edema fluid from alveoli to the interstitium<sup>51</sup> where fluid has less of an impact on gas exchange and compliance than alveolar fluid.<sup>52,53</sup> Respiratory work and respiratory acidosis are reduced by the increased compliance and reduced airway resistance provided by NIV.<sup>52</sup> However, NIV can have important complications, especially in lungs with a heterogeneous distribution of edema and varying regional lung volumes. Positive-pressure ventilation has been associated with increased permeability of pulmonary capillaries.<sup>54</sup> Animal studies have found that stress failure of the alveolar membrane can be caused by high lung volumes secondary to over-inflation.<sup>55</sup> Mechanical ventilation can produce alterations in surfactant, and high tidal volumes may cause atelectasis by increasing surface tension and elastic recoil.<sup>56,57</sup> Wyszogrodski suggested that over-inflation inactivated surfactant rather than depleting it,<sup>58</sup> since larger tidal volumes cause large aggregates of surfactant to break down into smaller components which have less surface tension lowering activity.<sup>59</sup>

Non-invasive ventilation also has significant hemodynamic effects. Positive airway pressure increases intrathoracic pressure, which impairs right ventricular (RV) filling.<sup>60–62</sup> It increases pulmonary vascular resistance by compressing intra-alveolar vessels, which increases RV afterload.<sup>63</sup> Consequently, RV function is impaired with NIV, leading to decreased left ventricular (LV) filling and preload. However, increased intrathoracic pressures decrease LV afterload by creating a positive pressure difference between intrathoracic and extrathoracic circulation.<sup>64</sup> In a failing heart, which may be sensitive to changes in afterload, positive airway pressure can improve cardiac output by facilitating LV emptying. Consequently, the hemodynamic effect of NIV are uncertain and may be overlooked as long as gas exchange (i.e., PaO<sub>2</sub>) improves.

Several RCTs have demonstrated that NIV improves respiratory rate, oxygenation, and respiratory acidosis

in cardiogenic pulmonary edema<sup>52,65–73</sup> and reduces the rates of endotracheal intubation.<sup>52,74</sup> A large, multicenter RCT failed to demonstrate any improvement in short-term mortality with NIV compared to standard oxygen therapy,<sup>73</sup> but several systemic reviews and meta-analyses have reported important benefits.<sup>75–77</sup> A meta-analysis of 15 trials concluded that NIV reduced mortality rate by approximately 45%,<sup>75</sup> and Vital et al. found that NIV reduced in hospital mortality by 34%.<sup>76</sup>

## CONCLUSIONS-PART 1

Acute decompensated heart failure is characterized by the development of acute dyspnea associated with elevated intracardiac filling pressures with or without pulmonary edema. Appropriate management for ADHF requires identification of the precipitating factors. Intravenous loop diuretics are the initial therapy for patients with ADHF and volume overload. It is important for generalists and cardiologists to be familiar with the different strategies available to counter diuretic resistance. Timely use of noninvasive ventilation is an important adjunct to oxygen supplementation and can prevent intubations. Judicious use of vasodilators, opiates, inotropes and vasopressors can help relieve congestion but have not been shown to reliably improve outcomes and are often associated with significant adverse effects. There is a need for a universally accepted terminology for classifying heart failure syndromes to aid further investigation.

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