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Acute Decompensated Heart Failure Update

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Abstract: Acute decompensated heart failure (ADHF) continues to increase in prevalence and is associated with substantial mortality and morbidity including frequent hospitalizations. The American Heart Association is predicting that more than eight 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 increase in the prevalence and cost of HF is primarily the result of shifting demographics and a growing population. Although many large, randomized, controlled clinical trials have been conducted in patients with chronic heart failure, it was not until recently that a growing number of studies began to address the management of ADHF. It is the intent of this review to update the clinician regarding the evaluation and optimal management of ADHF.

Keywords: Acute decompensated heart failure, diuretics, inotropes, vasodilators.

INTRODUCTION

Acute decompensated heart failure (ADHF) is the rapid onset of, or change in, symptoms and signs of HF. It can be a life-threatening condition that requires immediate medical attention and usually leads to hospitalization. Acute decompensated heart failure continues to rise in prevalence and is associated with substantial mortality and morbidity. In the US, over 1 million patients are hospitalized annually with HF as a primary diagnosis with an additional 3 million hospitalizations with HF listed as a secondary or tertiary diagnosis [1]. Heart failure is the leading cause of hospitalization in patients older than 65 years of age. The readmission rate is as high as 35% at 60 days [1]. The majority of the enormous cost (80%) of HF care is attributable to hospitalization [2].

Although many large, randomized, controlled clinical trials have been conducted in patients with chronic HF, it was not until recently that a growing number of studies began to address ADHF management. This article will review the evaluation and optimal management of ADHF and discuss the results of recent trials. It is important to note that the majority enrolled in ADHF trials are largely patients with HF due to reduced ejection fraction, and thus, this population is the primary focus of this review.

FROM PRESENTATION TO RISK STRATIFICATION

Clinical Presentation

The clinical syndrome of ADHF ranges from moderate volume overload to overt cardiogenic shock. While the great majority of patients have congestion, some patients present with low cardiac output and hypoperfusion with or without congestion, especially those presenting to tertiary care centers [3, 4]. In addition to the common symptoms of dyspnea, orthopnea, and paroxysmal dyspnea, chest pressure and nocturnal cough can be symptoms of volume overload. Patients can be classified as congested ("wet") or low output ("cold"). Table **1** provides an overview of common presenting ADHF signs and symptoms.

The majority (80%) of patients hospitalized with heart failure present as an acute decompensation of chronic HF [1]. These patients become refractory to oral therapies and decompensate following a relatively mild insult or develop new cardiac disease (e.g., ischemia or atrial fibrillation) that may result in decompensation. Newly diagnosed heart failure accounts for 15% of cases. Finally, end-stage patients refractory to therapy comprise fewer than 5% of hospitalizations. Table **2** reviews potential precipitating factors or etiologies for decompensation.

Evaluation and Differential Diagnosis

Physical examination and laboratory evaluation are typically sufficient to diagnose ADHF. Assessment of electrolytes (sodium, potassium, magnesium), renal function, hepatic enzymes are recommended. Natriuretic peptides (BNP, NT-proBNP) are sensitive biomarkers and should be assessed on admission and ideally upon discharge for prognosis; however, frequent monitoring of BNP during acute decompensation is not well established [5-7]. Pulmonary embolism may cause a rise in BNP. Elevated serum troponin, independent of acute coronary syndrome, is common in ADHF patients and is associated with more severe disease and worse prognosis [5]. Additional labs may

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Table 1. Clinical presentation of acute decompensated heart failure.

Signs	Symptoms
Pulmonary or Systemic Congestion ("wet")	
Weight gain	Dyspnea on exertion
Tachypnea	Dyspnea at rest
Jugular venous distension	Orthopnea
Rales	Paroxysmal nocturnal dyspnea
S3 or S4 gallop	Cough
Hepatojugular reflux	Chest pressure
Hepatomegaly/Splenomegaly	Abdominal distension/bloating
Peripheral edema	Early satiety
Ascites	Leg edema
Anasarca	
Low O_2 saturation	
Chest x-ray findings of congestion, pulmonary edema, pleural effusions	
Increased BNP or NT-proBNP	
Low Cardiac Output ("cold")	
Hypotension	Fatigue
Narrow pulse pressure	Decreased urine output
Tachycardia	Decreased mental acuity/ altered mental status
Altered mental status	Nausea/vomiting
Cool extremities	
Worsening renal and/or hepatic function	
Nonspecific	
Hyponatremia	Cachexia and anorexia

Table 2. Precipitating factors of heart failure exacerbation.

Worsening chronic heart failure
- Dietary indiscretion (excess fluid or salt intake)
- Medication related
  - Medication nonadherence
  - Use of medications with negative inotropic properties (e.g. diltiazem, verapamil)
  - Use of medications prepared with sodium or with sodium-retaining therapies (e.g., piperacillin-tazobactam, nonsteriodal anti-inflammatory agents)
- Uncontrolled hypertension
- Substance abuse (e.g., alcohol, other)
- Concurrent non-cardiac illness (e.g., infection especially pneumonia, pulmonary embolus, thyroid disease, renal failure)

New or worsening cardiac processes - Ischemia/Myocardial infarction - Arrhythmias (e.g., atrial fibrillation, ventricular tachycardia, other) - Hypertensive urgency/emergency
De novo heart failure - Large myocardial infarction - Sudden elevation in blood pressure - Stress-induced (takotsubo) cardiomyopathy - Myocarditis - Peripartum cardiomyopathy - Acute valvular insufficiency – stenosis, regurgitation, endocarditis - Aortic dissection
End-stage HF with progressive worsening of cardiac output

include, serum glucose, glycosylated hemoglobin, fasting lipid panel, and thyroid stimulating hormone level in select patients [11].

A 12-lead ECG is recommended to evaluate rhythm and presence of ischemia. A chest x-ray can confirm pulmonary congestion, and may identify non-cardiac causes of symptoms (e.g., pneumonia). Echocardiography can evaluate cardiac structure and function, and valvuar disease.

Routine use of invasive hemodynamic monitoring in patients with ADHF does not impact survival and is not routinely recommended [12]. However, invasive monitoring should be considered in patients who are refractory to initial therapy, those in whom volume status is unclear, or who have hypotension or worsening renal function despite therapy. In addition, documentation of an adequate hemodynamic response to inotropic therapy is often necessary prior to initiating chronic outpatient therapy [13].

Differential diagnosis of ADHF includes acute coronary syndrome (ACS), exacerbation of chronic obstructive pulmonary disease, pneumonia, acute renal failure, and pulmonary embolism.

Decision to Admit and Risk Stratification

Hospitalization for ADHF is recommended when patients experience dyspnea at rest, typically reflected by resting tachypnea or less commonly oxygen saturation less than 90%. Patients should also be hospitalized if they demonstrate signs or symptoms of low cardiac output including hypotension, worsening renal function or altered mental status. Any patient with a hemodynamically significant arrhythmia (i.e., atrial fibrillation with rapid ventricular response) or acute coronary syndrome should be admitted. Hospitalization should be considered if patients have congestion without dyspnea, typically reflected by a weight gain of greater than 5 pounds or if patients have signs and symptoms of congestion despite a lack of weight gain. Any patient with major electrolyte disturbances or comorbid conditions (i.e., pneumonia) may also benefit from admission. Finally, patients with repeated implantable cardioverter-defibrillator firings or previously undiagnosed for heart failure but signs and symptoms of congestion should also be considered for admission [13].

Elevated blood urea nitrogen is the best predictor of in-hospital mortality followed by low systolic blood pressure and high serum creatinine. Patients presenting with all three high-risk parameters have an in-hospital mortality risk of 22% [14]. Hypotension and renal dysfunction at discharge are associated with increased mortality or readmission [15]. In contrast, patients with normal to high systolic blood pressure, low BUN and low serum troponin levels are at low risk and may often be discharged early [16].

GENERAL APPROACH TO TREATMENT

Goals of Therapy

The overall goals of therapy in ADHF include: identifying precipitating factors (Table **2**), relieving symptoms, directly improving short- and long-term outcomes, and initiation and optimization of long-term therapies.

Management of Chronic HF Therapies during Acute Decompensation

During ADHF episodes, practitioners are challenged with how to manage standard HF therapies. If recent beta-blocker dose initiation or uptitration was responsible for decompensation and in the absence of cardiogenic shock, increased diuretic dose is often sufficient with continuation of the beta-blocker. Temporary discontinuation of angiotensin converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) or beta-blocker may be necessary in the setting of cardiogenic shock or symptomatic hypotension. ACE-I/ARB and mineralcorticoid receptor antagonists (MRAs) may also need to be temporarily held because of renal dysfunction, especially if oliguria and/or hyperkalemia exists. See Table **3** for additional details on home medication management.

The initiation of beta-blocker therapy during ADHF is contraindicated due to acute negative inotropic effects. However, when patients are euvolemic it is safe to start a low dose prior to discharge and improved outcomes have been reported in patients initiated on beta-blockers prior to discharge [17]. Observational data also suggests that the patients who are not discharged on a beta-blocker have the worst prognosis [15]. More recently, the Beta-blocker CONtinuation Vs. INterruption in patients with Congestive heart failure hospitalizED for a decompensation episode (B-CONVINCED) Trial randomized 147 patients who were hospitalized for ADHF to beta-blocker continuation versus discontinuation. The primary study endpoint, a composite of the dyspnea score and general well-being 3 days after admission, was improved in both treatment groups. Hospital length of stay and rehospitalization were similar between the two groups. More patients who continued beta-blocker therapy during hospitalization were receiving beta-blocker therapy at 3 months compared to those in whom therapy was at least temporarily discontinued (90% vs 76%, p=0.04). Thus, initiation of beta-blocker in euvolemic patients and continuing beta-blocker therapy during ADHF is safe and associated with increased long-term adherence to therapy [18].

Unless the risk of toxicity outweighs the benefit, discontinuation of digoxin is generally discouraged because an association between withdrawal of therapy and worsening HF has been well-documented [19, 20]. It is important not to withdraw digoxin in HF patients who were stable and tolerating digoxin, especially those experiencing frequent hospitalization [21].

THERAPY

Optimize Volume Status to Relieve Congestion

The majority of ADHF patients have congestion due to volume overload, vascular redistribution, or a combination of both (Fig. **1**). The goal is to reduce filling pressures and relieve symptoms through diuresis, vasodilation or both. Multiple recent trials have established the detrimental effect of hypotension in ADHF. The rate of diuresis should achieve a desirable volume status without causing a rapid reduction in intravascular volume, which may result in symptomatic hypotension or renal dysfunction.

Table 3. Management of chronic heart failure therapies during hospitalization.

Medication	Transition in Hospital	Monitoring
Diuretics	Continue or augment (if indicated), unless signs/symptoms of dehydration	Daily weight (standing) Strict intake and output Vital signs (BP, HR, RR, O_2 saturation) including orthostatic BP, HR BUN, serum creatinine Serum potassium and magnesium
Beta blockers	Continue unless decompensation due to recent addition or dose increase (in which case reduce dose). Discontinue if significant hypotension, bradycardia, or overt cardiogenic shock.	BP and HR including orthostatic BP, HR
ACE inhibitors and ARBs	Continue, unless hypotension or acutely worsening renal function	BP and HR including orthostatic BP, HR Strict intake and output BUN, serum creatinine Serum potassium
MRAs	Continue unless $K^+ > 5.5$ or CrCl < 30 mL/min	BP and HR including orthostatic BP, HR Strict intake and output BUN, serum creatinine Serum potassium
Digoxin	Continue unless acutely worsening renal function, significant bradycardia (HR < 45 bpm), or signs/symptoms of toxicity Note: half-life =36 hrs if normal renal function (minimum of 5-7 days to reach steady state post initiation or dose change)	HR Serum creatinine Serum potassium, magnesium, and calcium Serum digoxin concentration (at least 6 hrs post dose) if not recently obtained, change in renal function, or addition/removal of interacting medication
Hydralazine/ Isosorbide dinitrate	Continue unless significant hypotension	BP and HR including orthostatic BP, HR

ACE = angiotensin converting enzyme, ARBs = angiotensin receptor blockers, BP = blood pressure, BUN = blood urea nitrogen, CrCl = creatine clearance, HR = heart rate, K^+ = potassium, MRAs = mineralocorticoid receptor antagonists, O_2 = oxygen, RR = respiratory rate.

Diuretics

Table **4** reviews commonly used diuretic therapies in ADHF management. To date, diuretics have not improved survival in HF patients, but they remain necessary to maintain euvolemia. Current guidelines recommend intravenously administered diuretics as first line therapy for volume oveload [13]. Loop diuretics, furosemide, bumetanide, and torsemide, are initial diuretics of choice in ADHF. Although higher doses produce greater diuresis and perhaps more rapid dyspnea relief, these effects are not associated with improved long-term outcomes and must be weighed against the risk of worsening renal function [22]. Increased mortality has been associated with treatment with high loop diuretic doses [23]. However, it is not clear if the prognostic role of high diuretic doses reflects increased severity of HF or is a cause of HF progression.

In the multicenter Diuretic Optimization Strategies Evaluation (DOSE) Trial, 308 patients with ADHF were randomized to low-dose versus high-dose administered as continuous infusion or twice daily intravenous bolus. The co-primary endpoints, patient global assessment of symptoms and mean change in serum creatinine at 72 hours, were not significantly different between treatment groups. For secondary endpoints, higher doses were associated with significantly improved net urine output, weight loss, and dyspnea balanced by worsening renal function [22].

In patients who are refractory to high dose loop diuretics, combining a loop diuretic with a distal tubule acting agent such as oral metolazone or intravenous chlorothiazide produces a synergistic diuretic effect. However, use of this combination can result in profound diuresis with severe electrolyte and volume depletion; therefore, close monitoring is needed. In the setting of suboptimal renal perfusion, inotropes may improve diuresis. However, inotropic therapy should generally be reserved for patients with evidence of low cardiac output.

Administration of low dose dopamine to enhance diuresis has generally been abandoned as most studies indicate minimal if any improvement in diuresis [24]. A recent study comparing high-dose furosemide infusion to the

Fluid Overload	Low Cardiac Output
IV Bolus Loop Diuretic ± Venous Vasodilator* Diuretic Naive: furosemide 20-40 mg IV bolus Diuretic PTA: furosemide 2.5 x Dose PTA** (max 180 mg) If after 2 hours, UOP < 400 mL, consider: 1) Increase IV loop diuretic dose - OR - 2) Switch to IV loop diuretic continuous infusion (preceded by IV bolus at 2 x prior dose prior IV dose) - OR - 3) Add a diuretic with a different mechanism (metolazone PO, HCTZ PO, or CTZ IV) If above ineffective, consider PAC to guide therapy *Adjunct vasodilator (NTG, NTP, or NES) may be considered if hypoxia and SBP > 90 **Should consider < 2.5 x dose PTA (e.g., 1-2 x dose PTA) if poor or declining renal function, low albumin, SBP < 90, or other findings to suggest patient will not tolerate aggressive diuresis	Assess fluid status; if clinical or PAC findings suggest hypovolemia or PCWP < 15-18 mmHg, administer IV fluid cautious If SBP > 90 mmHg + chronic beta blocker – consider milrinone or arterial vasodilator (NTP, NES) If SBP < 90 mmHg or symptomatic hypotension – consider dobutamine If severe hypotension (MAP < 50 mmHg), consider dopamine

Fig. (1). Algorithm for managing acute decompensated heart failure.
CTZ = chlorothiazide, HCTZ = hydrochlorothiazide, IV = intravenous, MAP = mean arterial pressure, NES = nesiritide, NTG = nitroglycerin, NTP = nitroprusside, PAC = pulmonary artery catheter, PCWP = pulmonary capillary wedge pressure, PO = oral, PTA = prior to admission, SBP = systolic blood pressure, UOP = urine output.

combination of low-dose furosemide and dopamine infusion suggested a reduced rate of worsening renal function; however, limitations in the trial design preclude attributing this benefit to dopamine [25]. More recently, preliminary results from the Dopamine in Acute Decompensated heart failure II Trial (DAD II) suggested no difference between high-dose furosemide, low-dose furosemide, and low-dose furosemide plus dopamine, on mortality or readmission for ADHF [26].

Vasopressin levels are elevated in HF and may result in myocardial fibrosis, hypertrophy and vasoconstriction (V_{1a} receptor activation), and water retention and hyponatremia (V_2 receptor activation). The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Trial randomized 4133 patients with ADHF (LVEF ≤40%) to tolvaptan or placebo [27, 28]. The primary outcome (composite change in patient-assessed global clinical status and body weight at day 7 of inpatient hospital stay or discharge if earlier than 7 days) was significantly improved with tolvaptan; however, this benefit was driven primarily by reduction in weight loss. Unfortunately, there was no significant benefit in other clinical outcomes.

Ultrafiltration

Ultrafiltration reduces pulmonary artery pressure and increases diuresis. Complications of ultrafiltration include those associated with central venous access and intravascular depletion.

The Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure (UNLOAD) Trial demonstrated significantly greater weight loss at 48 hours and net fluid loss with ultrafiltration compared to intravenous diuretics in ADHF patients, but no difference in dyspnea relief at 72 hours. A marked reduction in HF-related urgent medical care visits was reported [29]. More recently, the CARdiorenal REScue Study in Acute Decompensated Heart Failure (CARRESS) Trial randomized 188 patients with ADHF, worsened renal function, and persistent congestion to ultrafiltration or stepped pharmacologic therapy. For the primary end point, bivariate change from baseline in serum creatinine and body weight at 96 hours, ultrafiltration was inferior primarily due to an increase in creatinine (p=0.003). Unlike the UNLOAD Trial, weight loss was not significantly different and more patients in the ultrafiltration group experienced a serious adverse

Table 4. Diuretic therapies.

	Furosemide	Bumetanide	Torsemide	Metolazone	Chlorothiazide
Mechanism of action	Loop Diuretic	Loop diuretic	Loop diuretic	Thiazide-like diuretic	Thiazide diuretic
Bioavailability	40%–70%	80%–95%	80%–90%	65%	N/A
Dose Equivalents	PO: 40 mg, IV: 20 mg	1 mg	20 mg	N/A	N/A
Usual oral dosing	40-80 mg one or twice daily, max 600 mg/d	1-2 mg once or twice daily, max 10 mg/d	20-40 mg once or twice daily max 200 mg/d	2.5-5 mg once daily, max 10 mg/d	N/A
Usual intravenous bolus dosing	Diuretic naïve: 40-80 mg q8-24h Diuretic PTA: 1-2.5 x PO dose PTA*, May repeat in 2-3 hours, max 600 mg/d	Diuretic naïve: 0.5-1 mg q8-24h Diuretic PTA: 1-2.5 x PO dose PTA*, May repeat in 2-3 hours, max 10 mg/d	Diuretic naïve: 10-20 mg q8-24h Diuretic PTA: 1-2.5 x PO dose PTA*, May repeat in 2-3 hours, max 200 mg/d	N/A	250 mg-500 mg q12-24h, max 2 gm/day
Usual intravenous continuous infusion dosing	40-80 mg IVB load, then 5-10 mg/hr, max 40 mg/hr	1-2 mg IVB load, then 0.5-2 mg/hr, max 2 mg/hr	20-40 mg IVB load, then 5-20 mg/hour, max 20 mg/hour	N/A	N/A
Duration of action	4–6 hours	6–8 hours	12–16 hours	12-24 hours	6-12 hours

IVB =intravenous bolus, PO = oral, PTA = prior to admission.
*See text regarding selection of 1, 2, or 2.5 x PO dose PTA

event [30]. Therefore, the role of ultrafiltration in patients with ADHF needs to be clarified through additional clinical trials.

Vasodilators

Intravenous vasodilators often provide rapid symptom resolution, especially in patients with acute pulmonary edema or severe hypertension. Such therapy may also be considered in patients who fail to respond to aggressive diuretic treatment. Vasodilators should be avoided in patients with reduced filling pressures or symptomatic hypotension. Although vasodilators improve hemodynamic parameters and can relieve congestion, there is little evidence for improved outcome. The three available intravenous vasodilators are summarized in Table **5**.

Nitroglycerin exhibits primarily venodilation at low doses and mild arterial vasodilation at higher doses; thus, it is the preferred agent for preload reduction [31]. At higher doses, nitroglycerin is a potent coronary vasodilator and an optimal agent in patients with active myocardial ischemia. Without implementation of a nitrate-free interval, tolerance to the hemodynamic effects of nitroglycerin commonly develops. Hypotension can be potentiated by rapid diuresis with volume depletion. Concomitant use of phosphodiesterase-5 inhibitors (e.g., sildenafil) is contraindicated due to the risk of profound hypotension.

Nitroprusside is a balanced arterial and venous vasodilator which results in augmentation of cardiac output and reduction in filling pressure (similar to dobutamine and milrinone), but with greater reduction in pulmonary artery pressure, systemic vascular resistance, and blood pressure. Although nitroprusside has a short half-life, profound hypotension can occur. Thus, it is used primarily in patients with high systemic vascular resistance and often requires invasive hemodynamic monitoring. The primary disadvantages of nitroprusside beyond hypotension and tachyphylaxis include the risk of cyanide and thiocyanate accumulation and toxicity, which is extremely rare in the absence of prolonged or high dose administration. In patients with substantial hepatic or renal impairment, this agent should be avoided or dose and duration of therapy should be minimized.

Nesiritide or human B-type natriuretic peptide produces dose-dependent venous and arterial vasodilation with a reflexive increase in cardiac output and natriuresis. Compared to nitroglycerin, nesiritide significantly reduces pulmonary capillary wedge pressure and dyspnea at 3 hours [32]. While nesiritide was FDA-approved based upon these endpoints, two meta-analyses suggested worsened renal function and increased 30-day mortality [33]. Subsequently, the Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (ASCEND-HF) Trial demonstrated that although nesiritide did not cause worsening renal function (defined by more than a 25% decrease in

Table 5. Vasodilator therapies.

	Nitroglycerin	Nitroprusside	Nesiritide
Mechanism	Increase NO synthesis and cGMP	Increase NO synthesis and cGMP	Activate guanylate cyclase–linked NP receptor A to increase cGMP
Clinical effects	Vasodilator (venous > arterial)	Vasodilator (venous = arterial)	Vasodilator (venous = arterial)
Indication	Warm & wet, Cold & wet, HTN Crises, ACS	Warm & wet, Cold and wet, HTN Crises	Warm & wet, Cold & wet
Usual dosing	10–30 mcg/minute and titrate by 10–20 mcg/ minute every 10–20 minutes, to max 200 mcg/kg/min	0.1–0.2 mcg/ kg/minute and titrate by 0.1–0.2 mcg/kg/minute every 10–20 minutes, to max 2 mcg/kg/min	0.01 mcg/kg/minute and titrate by 0.005 mcg/kg/minute every 3 hours, to max 0.03 mcg/kg/min
Onset, Half-life	1-5 minutes, 1-4 minutes	< 1 minute, < 10 minutes	15-30 minutes, 20 minutes
Elimination	Inactive metabolites in urine (no renal/hepatic adjustment)	Cyanide (hepatic), thiocyanate (renal)	NP receptor C (no renal/hepatic adjustment)

ACS = acute coronary syndrome, cGMP = cyclic guanosine monophosphate, HTN = hypertensive, NO = nitric oxide, NP = natriuretic peptide.

the estimated glomerular filtration rate), self-reported symptoms of dyspnea and 30-day readmission and mortality were not improved in patients receiving nesiritide compared to placebo [34]. Given the high cost of nesiritide and limited benefit noted in the ASCEND-HF trial, use of this agent should be limited to select patients.

Treat Hypoperfusion to Improve Low Output

Regardless of fluid status, low cardiac output results in signs and symptoms of peripheral hypoperfusion (i.e., decreased urine output, weakness, peripheral vasoconstriction, weak pulses). Inotropes can be administered to patients with low systolic blood pressure in the setting of adequate filling pressures or in patients with congestion and low output who do not respond to diuretic therapy. Patients with heart failure with preserved ejection fraction do not benefit from inotrope therapy. Two commonly used positive inotropic agents are dobutamine and milrinone (Table **6**). Dopamine may be useful in select patients. Since these agents have not been shown to improve outcomes, they should be used short-term to aid diuresis and improve organ perfusion as well as long-term as a bridge to cardiac transplantation or for palliation of symptoms in end-stage patients [35-37]. Table **6** differentiates the available inotropic therapies.

Dobutamine

Dobutamine, a synthetic β1- and β2-receptor agonist, is an inotrope with vasodilatory effects at higher doses. Dobutamine should be considered in patients with borderline low blood pressures when a significant decrease in mean arterial pressure might further compromise hemodynamic function. The hemodynamic effects of dobutamine are blunted in patients receiving nonselective beta-blockers. However, hemodynamic effects may persist in the presence of beta- 1 selective agents as a result of beta-receptor upregulation or selective activation of beta-2 receptors [38]. Higher doses may be necessary if beta-blockers are continued. Adverse effects of dobutamine include tachycardia, tachyarrhythmias, myocardial ischemia. In addition, short-term survival was reduced in ADHF patients treated with inotropes [39].

Milrinone

Milrinone is a phosphodiesterase-III inhibitor that blocks the degradation of cyclic adenosine monophosphate. It is an inotrope with systemic and pulmonary vasodilating effects. Given its vasodilatory properties, milrinone should be administered cautiously in patients with hypotension. Despite a rise in cardiac index, mean arterial pressure often remains constant due to a concomitant decrease in arteriolar resistance. However, the vasodilating effects of milrinone may outweigh the rise in cardiac index, leading to a fall in blood pressure and reflex tachycardia. Milrinone will also reduce pulmonary pressure.

Milrinone is the drug of choice in patients receiving chronic beta-blocker therapy because its inotropic effects do not involve stimulation of beta-receptors. Continued beta-blocker therapy may even augment the hemodynamic effects of milrinone, a phenomenon observed in studies of an agent with similar structure [40]. Although, milrinone is theoretically associated with less tachycardia and arrhythmias, it has a longer elimination half-life (one hour if normal renal function, three hours if renal dysfunction). Milrinone has also been associated with hypotension, ventricular and atrial arrhythmias, myocardial ischemia and decreased survival [35].

Table 6. Inotrope therapies.

	Dobutamine	Milrinone
Mechanism	Beta agonist, increases AC to convert cATP to cAMP	PDE-III inhibitor, blocks degradation of cAMP
Clinical effects	Positive inotropic effect, slight peripheral vasodilation	Positive inotropic effect, moderate peripheral and pulmonary vasodilation
Indication	Cold and wet Cold and dry	Cold and wet Cold and dry
Usual intravenous dosing	2.5–5 mcg/ kg/minute and titrate by 2.5 mcg/kg/minute every 10–20 minutes, to max 20 mcg/kg/min	0.1–0.375 mcg/ kg/minute and titrate by 0.125–0.25 mcg/ kg/minute every 6–12 hours (intravenous bolus dose generally avoided)
Onset, Half-life	5-10 minutes, 2 minutes	90 minutes, 1 hour, prolonged 2-3 hours if CrCl < 50 ml/min
Other comments	-Recommend if hypotensive - May cause hypotension and tachyarrhythmias	-Recommend if receiving a beta-blocker and SBP > 90 mmHg -May cause hypotension -Elimination prolonged with renal dysfunction

AC = adenyl cyclase, cAMP = cyclic adenosine monophospate, cATP = cyclic adenosine triphosphate, CrCl = creatinine clearance, PDE = phosphodiesterase, SBP = systolic blood pressure.

Investigational Therapies

Several recombinant neurohormones are currently under investigation. Serelaxin is a novel recombinant form of human relaxin-2, a hormone that modulates the cardiovascular response during pregnancy including increased arterial compliance, cardiac output, and renal blood flow. The Recombinant Human Relaxin-2 for Treatment of Acute Heart Failure (RELAX-AHF) Trial randomized 1160 patients with ADHF to serelaxin or placebo. Serelaxin-treatment resulted in significant improvement in the change in 5-day dyspnea. Although there was no significant difference in 24-hour dyspnea, length of hospital stay was significantly reduced. There was no effect on cardiovascular death or HF/renal failure hospitalizations up to 60 days. However, serelaxin significantly reduced death at 180 days (HR 0.63, 95% CI 0.42–0.93; p=0.019)**.** Serelaxin significantly improves HF signs and symptoms [41], and markers of congestion and end organ damage [42].

Various novel neurohormonal antagonists have been investigated for ADHF. The oral direct renin inhibitor, aliskiren recently demonstrated no beneficial effect on cardiovascular death or HF rehospitalization but increased adverse effects [43].

Multiple novel approaches to improving cardiac performance are also under investigation [44]. Omecamtiv mecarbil is a cardiac specific small molecule activator of myosin that has been shown to increase cardiac performance in healthy volunteers [45], and patients with chronic heart failure [46].

Table **7** provides an overview of current investigational therapies for ADHF.

PREPARATION FOR DISCHARGE

Optimize Chronic Oral Therapies

Prior to discharge, oral therapies should be optimized in a stable patient. Patients with reduced ejection fraction heart failure (HFrEF) should receive an ACE inhibitor (or ARB if intolerant), beta-blocker, and a MRA. Up-titration to target doses should be considered. Close follow-up post-discharge is necessary [47].

Patient Counseling

Patient education is essential and should involve a variety of disciplines, including dietitians, pharmacists, and other healthcare providers. Teaching should focus on identifying signs and symptoms of worsening HF, daily weight monitoring, and medications and dietary adherence [13]. Educate patients on only essential topics and reinforce and supplement education as an outpatient. Discharge instructions should be provided verbally and in writing. Patients and caregivers should be involved in discussing disease prognosis and quality of life [48].

CONCLUSIONS

Identifying precipitating factors for ADHF is instrumental in preventing readmission. Prior to discharge, optimize volume status and relieve congestion using intravenous diuretics. Continue beta-blocker unless cardiogenic shock or symptomatic hypotension presents. If beta-blocker is discontinued or dose reduced, such therapy should be restarted or up-titrated prior to discharge once the patient is euvolemic. Intravenous vasodilators may be used in conjunction with

Table 7. Investigational therapies for acute decompensated heart failure.

Therapy	Mechanism of Action
Aliskiren	Direct renin inhibitor with favorable neurohormonal and hemodynamic effects
Caperitide	Recombinant atrial natriuretic peptide; diuretic, natriuretic, and vasodilatory activity
Cenderitide (CD-NP)	Chimeric protein which causes cGMP-mediated venodilation
Cinaciguat	Vasodilator that activates soluble guanylyl cyclase, leading to increased cGMP and venous and arterial vasodilation
Clevidipine	Calcium channel blocker that selectively dilates arteries with no significant effect on myocardial contractility
Istaroxime	Inhibits sodium-potassium ATP activity and stimulates SERCA2a, thereby increasing lusitropy and inotropy
Omecamtiv mecarbil	Cardiac-specific activator of myosin, improves myocardial efficiency and performance
Serelaxin	Recombinant human relaxin 2, modulates cardiovascular and renal adaptations during pregnancy
Ularitide	Recombinate atrial natriuretic peptide hormone; natriuretic and diuretic activity

ATP = cyclic adenosine triphosphate, cGMP = cyclic guanosine monophosphate, SERCA2a = sarco/endoplasmic reticulum Ca^{2+} ATPase.

diuretics for rapid symptom resolution and may be considered in patients who fail to respond to diuretics alone. Intravenous inotropes may be utilized to relieve symptoms and improve end-organ function in patients with ADHF characterized by decreased peripheral perfusion or end-organ dysfunction.

Prior to discharge, chronic HF therapies should be optimized as tolerated with a stable oral medication regimen, ideally for 24 hours prior to discharge. Close follow-up is recommended by telephone within 72 hours in select patients and an outpatient visit within 7-10 days.

CONFLICT OF INTEREST

Rodgers – Novartis

Alburikan – Nothing to disclose

Metra - Amgen, Bayer, Novartis

Teerlink - Amgen, Corthera, Cytokinetics, Merck, Novartis, Scios/ Johnson and Johnson, Trevena

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