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Management of Acute Decompensated Heart Failure

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A 63-year-old woman with a past history of coronary artery disease, diabetes mellitus, ischemic cardiomyopathy with chronic heart failure, hyperlipidemia, and hypertension presented to the emergency department in respiratory distress. She was noted to have a pulse of 100 bpm and a blood pressure of 195/110 mm Hg. Physical examination was significant for respiratory accessory muscle use, tachycardia, elevated jugular venous pulsation up to the mandible at 30 degrees along with a positive abdominojugular reflux, and bilateral rales over two thirds of the lungs. Lower extremities were warm with 2+ pitting edema. Chest radiograph confirmed the clinical diagnosis of heart failure, while electrocardiogram demonstrated old Q waves in the anterior leads. The patient was administered bolus intravenous furosemide (80 mg and then 160 mg), which resulted in minimal urine output. A nitroglycerin drip was initiated. Blood pressure was lowered to 150/70 mm Hg with resultant urine output of more than 500 mL over the ensuing 30 to 40 minutes and marked improvement in her respiratory status.

Heart failure (HF) affects 4 to 5 million people in the United States, and more than 500,000 new cases are diagnosed annually.[1,2] The prevalence of HF increases with age, occurring in up to 10% of patients over age 75 years. HF is the leading cause for hospitalizations in the United States, with over 1 million hospitalizations each year.[3] In fact, HF hospitalizations have increased approximately 150% over the last 20 years. Inpatient and postdischarge mortality rates approach 5% and 10%, respectively.[2,4–7] It is estimated that 50% of HF patients die within 5 years of diagnosis.

Frequent hospitalizations for acute decompensated heart failure (ADHF) are associated with an enormous economic burden, including disability, direct medical costs, and lost employment. Hospitalizations cost nearly $25 billion annually and account for approximately 60% of total costs for HF.[2,7] Hospital losses are an estimated $1300 per patient admitted for HF.[8] Superimposed upon the economic burden are great emotional and physical hardships for patients and their families.

Given these costs, effective management of ADHF is paramount in reducing length of stay, revisits, complications, and expenditures. Although proposed guidelines for the treatment of ADHF exist, they lack a clear consensus, and many are limited in regard to specific drug therapy. Thus, review of the available literature for recent studies that provide new information on diagnosis and management of ADHF can guide formulation of the most effective approach. This article focuses on the diagnosis and treatment of ADHF to achieve symptom relief based on current scientific evidence.

DIAGNOSIS

Assuring the correct diagnosis of ADHF can be a clinical challenge. A recent survey revealed that physicians were uncertain about the diagnosis in approximately 60% of cases, and another study showed that the misdiagnosis rate for ADHF may be as high as 10% to 20%.[9,10] A carefully completed history and physical examination is the cornerstone of diagnosis.

Clinical Assessment

Patients with ADHF often present with symptoms of worsening fluid retention and/or decreasing exercise tolerance. Although symptoms appear to occur acutely, patients often describe a progressive worsening of symptoms for which they compensate by decreasing activity levels. Symptoms are attributable to depressed cardiac output and elevated right-sided and left-sided filling pressures. The Framingham Heart Failure criteria are useful for identifying chronic HF but have

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TAKE HOME POINTS

- Acute decompensated heart failure (ADHF) is associated with prolonged hospitalizations, excessive costs, and increased inpatient and postdischarge mortality rates.
- Categorizing patients into ADHF types ("warm and wet" versus "cold and dry") based on clinical history and physical examination allows a rational approach to choosing appropriate therapy.
- Initial therapy for patients with ADHF manifested clinically as volume overload (orthopnea, dyspnea, weight gain, rales, abdominojugular reflux, pulmonary congestion on chest radiographs) should consist of stabilization of the airway, intravenous diuretics, and in more severe cases, intravenous vasodilators (as long as systolic blood pressure is > 90 mm Hg).
- Patients with hypotensive heart failure and/or signs of low cardiac output (decreased urine output, cool extremities, narrow pulse pressure, prerenal physiology, altered mental status) may require intravenous inotropic therapy. Milrinone should be used in patients treated chronically with β-blockers.

Table 1. Framingham Criteria for the Diagnosis of Chronic Heart Failure

Major criteria
Paroxysmal nocturnal dyspnea
Neck vein distension
Rales
Cardiomegaly on chest radiograph
Pulmonary edema on chest radiograph
S_3 gallop
Central venous pressure > 16 cm H_2O
Hepatojugular reflux
Weight loss > 4.5 kg in 5 days in response to treatment
Minor criteria
Bilateral ankle edema
Nighttime cough
Dyspnea on ordinary exertion
Hepatomegaly
Pleural effusion
Heart rate > 120 bpm
Decrease in vital capacity by one third from maximum recorded

Note: The diagnosis of heart failure requires the presence of 2 major or 1 major and 2 minor criteria.

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been less helpful for identifying ADHF (**Table 1**). Classic symptoms and signs of ADHF include weight gain, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, fatigue, cough, anorexia, nausea, bloating, ascites, peripheral edema, and cool extremities. Of these, orthopnea has the highest sensitivity (approximately 90%) for elevated pulmonary capillary wedge pressure (PCWP), but its specificity (< 60%) remains a problem.[11] History should include whether patients have a past diagnosis of HF or have previously used HF medications. Both of these facts have the best positive predictive value for the presence of HF. Potential precipitants should be investigated, such as ischemia, progressive left ventricular dysfunction, medical noncompliance, dietary indiscretions, and inadequate diuresis (**Table 2**). Identification of culprit etiologies can form the basis for a targeted approach to treatment. Past medical records should be reviewed for related comorbidities (lung disease, diabetes) and possible inciting medications.[12]

A carefully performed physical examination adds important clues to the diagnosis of ADHF. The examination relies on findings resulting from changes in filling pressures and perfusion and can be used for initial assessment as well as for monitoring response to treatment. Patients often present with rales and wheezing during ADHF, which are often absent in chronic HF because of compensatory increased lymphatic drainage.[11] An increase in the pulmonary component of the second heart sound (P_2) heard along the lower left sternal border reflects elevations in PCWP. The most specific signs of ADHF are elevated jugular venous (JV) pressures and a S_3 gallop (both with specificity of 95% and sensitivity of 20%).[13] Elevated JV pressures primarily reflect elevated right-sided filling pressures that are reliably associated with increased left-sided pressures and increased PCWP.[14] The abdominojugular reflux enhances the sensitivity and specificity of JV distension (> 80%).[15] The S_3 suggests left ventricular dysfunction, which is variably present depending on the degree of volume overload. Other findings of congestion (hepatomegaly, ascites, peripheral edema) and low perfusion states (hypotension, cool extremities) should be noted.

Adjunctive Tests

Although a thorough history and physical examination are key to diagnosis and are useful for providing prognostic information,[16] several clinical limitations may lead to misdiagnosis. Specifically, the history can be difficult to obtain in the acutely decompensated patient. With the exception of JV distension or an abnormal S_3, physical findings have similarly poor predictive abilities. Diagnostic studies, such as electrocardiograms (ECGs), chest radiographs, and laboratory tests (B-type natriuretic peptide [BNP] assay, cardiac enzymes), may aid in diagnosis. The ECG is usually abnormal but not specific for ADHF and may reveal Q waves, left ventricular hypertrophy, ST-T wave changes, and bundle branch block. Cardiomegaly, interstitial and alveolar edema, and pleural effusions may be demonstrable on chest radiograph. However, up to 20% of patients with ADHF may lack congestion on chest radiograph, especially those with end-stage HF.[17] Decreased arterial oxygen saturation is uncommon in HF patients, unless there is severe pulmonary edema. Increased wall stress due to overfilling can result in localized areas of ischemia and troponin elevations despite patent coronary arteries.[18]

Capitalizing on the known role of neurohormones in the pathophysiology of HF, recently developed assays for BNP are employed as an adjunct to clinical parameters in diagnosing ADHF. Pro-BNP is produced in response to increased ventricular wall stress. It is cleaved by a serine protease into an inactive N-terminal BNP (NT-pro BNP) fragment and the active C-terminal hormone, BNP.[19] Both peptides can serve as clinical markers of HF. BNP and NT-proBNP have similar diagnostic test characteristics and are best used when there is an intermediate pretest likelihood of disease.[20]

ADHF patients develop marked increases in BNP levels over previously recorded baseline levels. Increased BNP level correlates with New York Heart Association (NYHA) functional class (**Table 3**), implying that levels closely correlate with congestive HF severity. Changes in BNP levels are also correlated with changes in PCWP.[21] A BNP cutoff value of 100 pg/mL in patients presenting to the emergency department with dyspnea has a diagnostic sensitivity of 90% and a specificity of 76%.[22] Patients without HF secrete a low level of BNP (< 100 pg/mL). Levels in the range of 100 to 200 pg/mL are usually seen in patients with class I HF, whereas levels greater than 700 pg/mL may occur in patients with class IV HF. Levels over 400 to 500 pg/mL are highly sensitive for ADHF.[19]

Although rapid BNP assays can be invaluable in aiding the diagnosis of ADHF, certain caveats remain.

Table 2. Potential Precipitants of Acute Decompensated Heart Failure

Medical noncompliance (high salt intake, missed medication)
Initiation of β-blockers (especially high dose)
Nonsteroidal anti-inflammatory drugs
Arrhythmias (atrial fibrillation)
Ischemia/myocardial infarction
Alcohol
Inadequate medical regimen (suboptimal diuresis)
Hypoxemia (pulmonary embolus, chronic obstructive pulmonary disease)
Hypertension

Elevated BNP levels are seen in noncardiac conditions, including chronic kidney disease, acute pulmonary embolism, and pulmonary hypertension.[19] Furthermore, higher BNP levels are seen with older age and in women compared with men.[19] There is substantial interassay and intraindividual variation in BNP levels, and therefore only serial measurements revealing a 100% change is considered significant.[23] Notwithstanding these limitations, the BNP assay may be useful in patients with undifferentiated dyspnea.

THERAPEUTIC APPROACHES

As with any potentially life-threatening condition, attention should first be directed to the ABCs of airway, breathing, and circulation. Supplemental oxygen, noninvasive positive pressure ventilation, or endotracheal intubation should be considered for patients unable to maintain oxygen saturation (< 90%) or who are retaining CO_2. Positive pressure ventilation also decreases pulmonary edema because increases in intrathoracic pressure decrease cardiac preload.[24] Symptomatic treatment strategies to relieve dyspnea and exercise intolerance are the mainstay of acute therapy in the decompensated patient. Intravenous diuretics, vasodilators, and sometimes inotropes are used to achieve these goals. Morphine decreases sympathetically mediated vasoconstriction, leading to arteriolar and venous vasodilation and reduced cardiac filling pressures.[25] Possible reversible etiologies for decompensation should be rapidly addressed.

Diuretics

Because patients with ADHF usually present with signs of circulatory congestion, intravenous diuretic therapy serves as a first-line treatment strategy. These agents relieve volume overload by promoting a net diuresis and natriuresis by inhibiting the reabsorption of sodium in

Table 3. New York Heart Association Classification

Class	Description
I	No limitations of activities despite the presence of cardiac disease. Patient is asymptomatic during ordinary activities.
II	Presence of cardiac disease with slight limitation of physical activity; ordinary activity may result in some symptoms (fatigue, dyspnea, palpitations). Comfortable at rest or mild exertion.
III	Presence of cardiac disease with marked limitation of physical activity. Less than ordinary physical activity results in symptoms (fatigue, dyspnea, palpitations). Comfortable only at rest.
IV	Presence of cardiac disease with inability to carry out any physical activity without discomfort. Symptoms occur at rest—complete rest needed; confined to bed or chair.

the ascending limb of the loop of Henle.[26] Greater diuresis is achieved using loop diuretics as compared with thiazide or potassium-sparing diuretics because of their site of action in the kidney. Diuretics should be initially administered intravenously as a bolus to ensure maximal bioavailability and to circumvent possible decreases in oral absorption due to intestinal edema. High-dose or intravenous furosemide (180–360 mg) may be required, especially in patients with renal failure.[27] The efficacy of diuretic therapy is gauged by symptomatic improvement and urine output. Typically, more than 250 mL to 500 mL of urine output in the first several hours after administration is expected, depending upon the patient's renal function.[27] Escalating doses of furosemide (every 2–4 hours) are required if urine output is inadequate. Continuous infusion of furosemide, addition of a second diuretic (eg, metolazone [2.5–5 mg orally one half hour before the loop diuretic]) or addition of vasodilators or positive inotropic agents may be necessary to overcome diuretic resistance that develops in patients with advanced ADHF.[28]

Renal function should be monitored during diuresis because prerenal azotemia and orthostatic hypotension may complicate therapy. Renal failure in this setting predicts worsening outcomes.[29] Diuresis can also cause hypokalemia, hypocalcemia, hypomagnesemia, and metabolic alkalosis, resulting in potentially life-threatening arrhythmias. Frequent electrolyte monitoring is required. By decreasing plasma volume, loop diuretics also increase neurohormonal activation, which may worsen HF. In fact, studies have linked use of diuretics to increased mortality.[30,31] Data from the Acute Decompensated Heart Failure National Registry (ADHERE) revealed an association between intravenous diuretic use and higher in-hospital mortality and lengthened hospital stays.[32] The propensity to use higher diuretic doses in more severely ill patients likely affected these analyses. Further research is required before definitive conclusions can be made about the safety of diuretics.

Although diuretic therapy is highly effective in the initial management of mild volume overload states, patients with moderate-severe volume overload or with low cardiac output may not adequately respond to diuretic management. These situations necessitate more aggressive pharmacologic regimens.

Vasodilators

Patients demonstrating an inadequate response to diuretic therapy as evidenced by suboptimal urine output or continued symptomatic deterioration, cardiac congestion, and preserved perfusion are characterized as "warm and wet."[33] Such patients have moderate-severe volume overload and require vasodilator therapy provided that they have adequate systolic blood pressure (> 90 mm Hg). Those with hypertension represent another subset that might benefit from vasodilator use.

Nitroglycerin and nitroprusside. The nitrates, nitroglycerin and nitroprusside, act on arterial and venous smooth muscle to increase levels of guanosine 3′5′-cyclic monophosphate (cGMP), resulting in vasodilation. Vasodilation in turn reduces PCWP, myocardial oxygen consumption, systemic vascular resistance (SVR), and the workload of the ventricles, thereby increasing the efficiency of cardiac function as well as reducing the production of harmful neurohormones.[34] Nitroglycerin's higher venous selectivity at low doses increases venous capacity and decreases ventricular-filling pressures and volume. Nitroglycerin also decreases coronary vascular resistance, augmenting perfusion to a failing heart. At higher doses, nitroglycerin reduces afterload by lowering arterial resistance. Nitroglycerin is very effective in treating ADHF and is the preferred nitrate given its low toxicity profile; however, it is limited by the rapid emergence of tachyphylaxis, which requires frequent dose titration.[35] Headache (20%) and dose-dependent hypotension (5%) are side effects. Because of these characteristics, nitroglycerin infusions should be administered in an intensive care setting.

Although it is infrequently used, nitroprusside is a very efficacious vasodilator and rapidly reduces SVR. Regardless of dose, it dilates both venous and arterial vessels. Nitroprusside increases cardiac output, improves renal function, and, in conjunction with diuretics, decreases neurohormonal activation.[36] In patients with left ventricular failure after an acute myocardial

infarction, however, nitroprusside reduced survival at 13 weeks when initiated less than 9 hours after the onset of pain.[37] The truncated survival noted was likely due to the shunting of blood away from ischemic areas.[38] Another concern is its potential to induce cyanide and thiocyanate toxicity in patients with renal or hepatic dysfunction. Nitroprusside is best used in an intensive care unit with pulmonary artery catheter and arterial blood pressure monitoring.

Nesiritide. Nesiritide is a 32 amino acid synthetic BNP that induces beneficial hemodynamic, natriuretic, and neurohormonal effects in HF patients. Unlike traditional nitrates, nesiritide administration does not require intensive monitoring and it is not associated with tachyphylaxis. Receptor engagement by nesiritide increases cGMP, which results in dilation of arterial and venous beds. This serves to unload the heart by decreasing PCWP, right atrial pressure, and SVR, leading to reflex increases in cardiac output and cardiac index.[39] Additionally, nesiritide also decreases the levels of harmful neurohormones in HF patients.[40] Based on these effects, nesiritide improves patient symptoms in ADHF when compared with either nitroglycerin or placebo.[41,42] In a randomized, double-blind, placebo-controlled pilot study, nesiritide improved patient-assessed dyspnea and exhibited a trend in reducing 30-day rehospitalization rates compared with placebo.[43] Six-month mortality or rehospitalization rates were similar to those of nitroglycerin.[44] More patients experience adverse effects, especially headaches, with nitroglycerin therapy as compared with nesiritide, but hypotension is similar between the 2 drugs.[44] Nesiritide decreases mortality rates when compared with dobutamine in ADHF.[45] Limitations to nesiritide therapy include its cost and hypotension.[46,47] Large prospective trials are needed to further assess nesiritide's effect on outcomes.

Inotropic Therapy

Patients with ADHF presenting with decreased urine output, cool extremities, narrow pulse pressure, prerenal physiology, and altered mental status are suffering from low cardiac output; these patients represent less than 1% of ADHF presentations.[48] Inotropic therapy, including dobutamine and milrinone, should be considered in patients characterized by this "cool and dry" type of HF. Therapy with these agents usually produces short-term symptomatic and hemodynamic improvement.[49] Dobutamine stimulates cardiac β-receptors, thereby increasing cardiac output and improving hemodynamics in ADHF patients.[50] This increases pulse and blood pressure without significantly lowering PCWP but also increases myocardial oxygen demand and may induce arrhythmias. Milrinone increases intracellular concentrations of cAMP through its ability to inhibit phosphodiesterase activity. It also lowers PCWP by its vasodilating effects, which may cause hypotension, thus limiting bolus administration.

ADHF patients with low cardiac output and systolic blood pressure below 90 mm Hg should be started on either dobutamine or milrinone. However, initial use of a peripheral vasoconstrictor may be necessary to prevent severe reductions in blood pressure. Patients on chronic β-blocker therapy with low cardiac output and systolic blood pressure greater than 90 mm Hg should receive milrinone, as its effect would not be abrogated by β-blocker therapy.[51] In contrast, β-blocker therapy would offset any increases in cardiac output caused by dobutamine. Either milrinone or dobutamine could be used in patients not receiving β-blocker therapy.

Although the short-term benefits of inotrope therapy in ADHF seem obvious, adverse patient outcomes have been reported.[52] Milrinone therapy has been shown to increase the incidence of sustained hypotension as well as new atrial and ventricular arrhythmias and cause worsening of HF[53,54]; a trend towards an increase in hospital deaths at 60 days (10.3% milrinone versus 8.9% placebo; $P = 0.41$) in ADHF patients was also observed. Dobutamine increases the risk of untoward clinical events and is an independent predictor of death.[55,56] Dobutamine also increases ventricular ectopy and tachycardia when compared with nesiritide.[57]

Because the risks of inotropic therapy appear to outweigh the benefits, it is not routinely recommended for ADHF. Inotropic therapy may, however, provide short-term benefit in ADHF with low cardiac output states or where there is associated cardiogenic shock or hypotension. These agents are also approved as a bridge to cardiac transplantation and for palliation in stage IV HF.

CONCLUSION

ADHF presents a challenge to the clinician and usually requires complex decision making. The diagnosis is multifaceted and requires a thorough clinical assessment with adjunctive tests. The immediate management goals include improvement of symptoms and hemodynamic parameters. Current treatment standards demonstrate beneficial effects on both parameters, although effects on long-term mortality are lacking. Some agents provide short-term benefit but not without potential for adverse effects. It appears that effective neurohormonal antagonism might prevent cardiac and renal deterioration during ADHF. Future studies need

to better address how to decrease overall mortality in these patients. Finally, newer investigational agents, including calcium sensitizers, vasopressin antagonists, and adenosine agonists, may prove to be useful adjuncts in the treatment of ADHF and may have a positive effect on the striking morbidity and mortality currently seen in these patients. **HP**

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