Section 12: Evaluation and Management of Patients with Acute Decompensated Heart Failure

Overview

Acute decompensated heart failure (ADHF) has emerged as a major public health problem over the past 2 decades.[1,2] Heart failure (HF) is the leading cause of hospitalization in patients older than 65 years of age. In-hospital mortality is excessive and readmission is disturbingly common, despite advances in pharmacotherapy and device therapy for HF.[3,4] The large direct costs associated with caring for the 5 million Americans who have chronic HF are largely attributable to hospitalization.[5]

Data from several studies have refined our understanding of the clinical characteristics of patients hospitalized with worsening HF.[2,4–6] These studies demonstrate that the majority of patients hospitalized with HF have evidence of systemic hypertension on admission and commonly have preserved left ventricular ejection fraction (LVEF). Most hospitalized patients have significant volume overload, and congestive symptoms predominate. Patients with severely impaired systolic function, reduced blood pressure, and symptoms from poor end-organ perfusion are in the distinct minority. Natural history studies have shown that ADHF represents a period of high risk for patients, during which their likelihood of death and rehospitalization is significantly greater than for a comparable period of chronic, but stable HF.[6]

The clinical classification of patients with ADHF continues to evolve and reflects ongoing changes in our understanding of the pathophysiology of this syndrome.[7] Worsening renal function, persistent neurohormonal activation, and progressive deterioration in myocardial function all seem to play a role. Decompensation also commonly occurs without a fundamental worsening of underlying cardiac structure or function. Failure to adhere to prescribed medications related to inadequate financial resources, poor adherence, and lack of education or an inadequate medical regimen may lead to hospitalization without a worsening of underlying circulatory function.

There is a paucity of controlled clinical trial data to define optimal treatment for patients with acute HF. The few trials have focused primarily on symptom relief, not outcomes, and have mainly enrolled patients with reduced LVEF who were not hypertensive. Clinical studies to determine the best care processes to achieve the multiple goals for patients admitted with ADHF are lacking. The recommendations in this section address the common therapeutic dilemmas associated with the broad group of patients with ADHF using the best available evidence from clinical research and consensus expert opinion.

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Diagnosis

Recommendation

12.1 The diagnosis of acute decompensated HF should be based primarily on signs and symptoms. (Strength of Evidence = C)

When the diagnosis is uncertain, determination of plasma B-type natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration is recommended in patients being evaluated for dyspnea who have signs and symptoms compatible with HF. (Strength of Evidence = A)

The natriuretic peptide concentration should not be interpreted in isolation, but in the context of all available clinical data bearing on the diagnosis of HF, and with the knowledge of cardiac and noncardiac factors that can raise or lower natriuretic peptide levels.

Background

Signs and Symptoms. The major symptoms of ADHF, shortness of breath, congestion, and fatigue, are not specific for cardiac and circulatory failure.[8] They may be caused by other conditions which mimic HF, complicating the identification of patients with this syndrome. Various forms of pulmonary disease, including pneumonia, reactive airway disease and pulmonary embolus, may be especially difficult to differentiate clinically from HF.[9]

Diagnostic Utility of Natriuretic Peptides. Two forms of natriuretic peptides, BNP and NT-proBNP, have been studied as aids to establish the diagnosis, estimate prognosis and monitor the response to therapy of patients with ADHF.[10]

Measurement of these peptides has been proposed in cases where the diagnosis of HF is uncertain. A large, multicenter investigation, The Breathing Not Properly Study provides important evidence supporting the clinical utility of plasma BNP in the assessment of patients presenting with possible HF.[11,12] This study evaluated 1586 patients seen in the emergency department with the complaint of acute dyspnea who had prospective determination of BNP by bedside assay. Patients were assigned a probability of HF by physicians in the emergency department who were blinded to the results of the BNP assay. The final determination of whether or not HF was present was based on a review of the clinical data by 2 cardiologists also blinded to the BNP assay results. The sensitivity and specificity of BNP measurements for the diagnosis of HF were compared with the accuracy of an assessment based on standard clinical examination.

The diagnostic accuracy of BNP, using a cutoff value of 100 pg/mL, was 83% relative to the assessment made by the independent cardiologists, whereas the negative predictive value of BNP for HF when levels were <50 pg/mL was 96%. As expected, measurement of BNP appeared to

be most useful in patients with an intermediate probability of HF. In these patients, a BNP cutoff value of 100 pg/mL resulted in the correct classification 74% of the time. BNP was found to be predictive of HF when left ventricular (LV) function was depressed or preserved.[13] Although BNP levels were lower in patients with HF associated with preserved LVEF, the cutoff value of 100 pg/mL still had a sensitivity of 86% and a negative predictive value of 96%. BNP levels increase with age, more so in older women, so that cutoff of 100 pg/mL may not provide the same degree of specificity for the diagnosis of HF, especially in elderly women with dyspnea.[14,15]

The clinical utility of NT-proBNP in the diagnosis of HF was reported in the N-terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study. This study used NT-proBNP measurements in the emergency department to rule out acute HF in 600 patients who presented with dyspnea.[16] NT-proBNP results were correlated with a clinical diagnosis of acute HF as determined by study physicians blinded to these measurements. The median NT-proBNP level among the 209 patients who had acute HF (35%) was 4054 versus 131 pg/mL among 390 patients who did not (65%, $P < .001$). NT-proBNP levels increase with age so that the study investigators recommend NT-proBNP cut points of >450 pg/mL for patients younger than 50 years of age and >900 pg/mL for patients age 50 years or older, both of which were highly sensitive and specific for HF in this study. For patients 75 years or older, 1800 pg/mL is the recommended cutpoint for NT-proBNP.[17,18]

Prognostic Role of Natriuretic Peptides. Although baseline BNP levels may correlate only modestly with pulmonary capillary wedge pressure (PCWP), changes in PCWP do correlate directly with changes in BNP concentration during hospitalization.[19,20] The predischarge BNP after treatment for acute HF appears to predict patients at risk of early readmission or death following hospitalization for HF.[21,22] Although specific discharge cutoff values are still being defined, patients whose BNP increases during hospitalization are at very high risk, as are patients with levels >700 pg/mL at discharge. Patients with levels <350 pg/mL at discharge appear to be at relatively low risk of readmission and death after discharge. Two recent studies have demonstrated that discharge BNP and change in BNP from admission to discharge provide independent predictive value for poor outcomes after an episode of ADHF.[22,23]

Triage Value of Natriuretic Peptides. The value of BNP determination in the triage of patients seen in the emergency department has been evaluated in a prospective, randomized, controlled, single-blind study in which 452 patients presenting with acute dyspnea were randomized to assessment with routine clinical evaluation or routine clinical evaluation plus the measurement of BNP. The diagnosis of HF was considered ruled out when BNP levels were <100 pg/mL, whereas levels of >500 pg/mL were considered diagnostic of ADHF.

Fewer patients were hospitalized or admitted to intensive care units in the BNP aided group compared with those evaluated by standard clinical evaluation alone. The median time to discharge was 8 days in the group with BNP measured versus 11 days in the control group ($P = .001$). Although the data on outcomes from this study are not definitive and the hospital lengths of stay are not reflective of practice patterns in the United States, making generalizability problematic, they do not suggest that triage using BNP resulted in the under-treatment of patients truly at risk. The readmission rate for HF was similar in the 2 study groups and the mortality rate, while not reduced statistically, was lower in those patients with BNP determined. Larger randomized trials of this strategy are needed to assess the impact of this approach on adverse outcomes associated with admission for ADHF.

Use of Natriuretic Peptides to Guide Therapy. A small number of studies have evaluated the use of BNP or NT-proBNP to guide HF therapy. In the initial study, Troughton et al[24] randomized 69 patients with symptomatic HF and LVEF <40% to a clinically guided treatment group and a group for whom therapy was increased to drive the aminoterminal portion of BNP (N-BNP) level to <200 pg/mL. In the N-BNP guided group there were fewer total cardiovascular events (death, hospital admission, or HF decompensation than in the clinical group (19 *vs* 54, p=0·02). At 6 months, 27% of patients in the N-BNP group and 53% in the clinical group had experienced a first cardiovascular event (p=0·034). Changes in LV function, quality of life, renal function, and adverse events were similar in both groups. In the Systolic Heart Failure Treatment Supported by BNP (STARS-BNP) study[25] 220 patients with New York Heart Association (NYHA) Class II-III HF symptoms on evidence-based medical therapy with angiotensin converting enzyme (ACE) inhibitors and beta blockers were randomized to a clinical care group and a group for whom the goal was a BNP of <100 pg/mL. The primary endpoint of HF hospitalization or HF death was significantly lower in the BNP group (24% vs 52%, p, 0.001). All-cause hospital stays were not different in the two groups (60 in the control group vs 52 in the BNP group) while HF hospital stays were significantly different favoring the BNP group (48 in control group vs 22 in BNP group, p< 0.0001) Thus there were 30 non-HF hospital stays in the BNP group vs only 12 in the control group raising the concern that targeting therapy to BNP might lead to hospitalizations for hypotension, renal insufficiency, or hyperkalemia although the specific reasons for non-HF hospitalizations were not mentioned.

The randomized controlled multicenter Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) enrolled 499 patients aged 60 years or older with systolic HF (LVEF ≤45%), NYHA class of II or greater, prior hospitalization

for HF within 1 year, and N-terminal BNP level of 2 or more times the upper limit of normal.[26] The primary endpoints were survival free of all cause hospitalizations and quality of life. There were similar rates of survival free of all-cause hospitalizations (41% vs 40%, respectively; hazard ratio [HR], 0.91 [95% CI, 0.72-1.14]; $P=.39$) in both groups over 18 months of follow-up. Quality-of life metrics improved but these improvements were similar in both the N-terminal BNP–guided and symptom-guided strategies. Survival free of hospitalization for HF, a secondary end point, was higher among those in the N-terminal BNP–guided group (72% vs 62%, respectively; HR, 0.68 [95% CI, 0.50-0.92]; $P=.01$).

The ''Can Pro-Brain-Natriuretic Peptide Guided Therapy of Chronic Heart Failure Improve Heart Failure Morbidity and Mortality?'' (PRIMA) study presented at the American College of Cardiology 2009 Scientific Sessions enrolled 345 HF patients who were hospitalized with elevated NT-proBNP levels ($\geq$1700 pg/mL).[27] After NT-proBNP levels dropped by more than 10% (to 850 pg/mL or less), patients were randomized to receive NT-proBNP-guided treatment (n=174) or clinically guided treatment (n=171). Serum levels of NT-proBNP were measured at discharge and again at the first follow-up period (two weeks post-discharge). The lesser of the two values was deemed the target value. If the NT-proBNP levels in patients in the guided-treatment group showed any increase at any subsequent follow-up, more intensive heart-failure therapy was immediately instituted. At a median follow-up of 702 days (range 488-730) there was a small but non-significant increase in the trial's primary end point—number of days alive outside the hospital—among patients in the NT-proBNP-guided group. Survival free of HF hospitalizations, a secondary endpoint, was significantly lower in the NT-proBNP group.

Based on all these results, it is not yet possible to recommend the use of natriuretic peptides to guide HF therapy, in either the outpatient or inpatient setting. Larger trials using HF hospitalization and mortality are being planned.

Limitations of Natriuretic Peptides. There are limitations concerning the utility of natriuretic peptides in the diagnosis of HF that need to be considered to gain maximum benefit from this testing.[28] Some patients with obvious ADHF by clinical criteria may not have BNP levels typically considered to be diagnostic. In contrast, there may be patients, especially those with chronic LV systolic function, who have persistently elevated BNP levels despite clinical compensation and adequate volume status.[29] Single measurements of BNP or NT-Pro BNP may not correlate well with measures of PCWP in patients in the intensive care unit, especially in patients with renal dysfunction.[13] In addition, the biologic variability of the assays for BNP is high making interpretation of day-to-day measurements problematic.[30]

Interpretation of natriuretic hormone levels can be problematic in patients with pulmonary disease. BNP and NT-proBNP may be increased in patients with pulmonary embolus or cor pulmonale resulting from right HF in the absence of congestion.[31] Some patients with HF without LV dysfunction may require treatment for peripheral edema despite having low BNP levels, indicating that BNP determination cannot always identify patients who need diuretic therapy. Patients with pulmonary disease may have concomitant LV dysfunction which may become more symptomatic during a primary respiratory illness, further complicating the interpretation of BNP levels.

The ranges of BNP for patients with and without a final diagnosis of HF overlap, which makes the test potentially less valuable in an individual patient with intermediate levels of BNP. Because many conditions can increase BNP levels, low values of BNP are most useful because they make the diagnosis of decompensated HF very unlikely as an explanation for dyspnea. Decision analysis indicates that BNP testing is generally most useful in patients who have an intermediate probability of HF. BNP levels rarely alter the diagnosis in patients who are very likely or unlikely to have HF based on usual clinical evaluation. ADHF remains a clinical phenomenon of symptoms due to circulatory dysfunction whose identification as yet cannot be reduced to a single laboratory measurement. Results of BNP testing must be interpreted in the context of the overall clinical evaluation, and such testing must augment rather than supersede careful clinical reasoning.[32]

Hospital Admission

Recommendation

12.2 Hospital admission is recommended for patients presenting with ADHF when the clinical circumstances listed in Table 12.1(a) are present. Patients presenting with ADHF should be considered for hospital admission when the clinical circumstances listed in Table 12.1(b) are present. (Strength of Evidence = C)

Background

The clinical characteristics detailed in this recommendation serve as a guide to determine which patients presenting with worsening HF require hospitalization. These criteria delineate severe symptoms that necessitate rapid relief; situations where outpatient therapy, typically with oral medications, is unlikely to be effective; and instances in which deterioration in the patient's clinical condition requires more intense monitoring than can be accomplished in an outpatient setting. In addition, some patients with decompensated HF require invasive diagnostic procedures, coronary intervention or surgical treatments that necessitate hospitalization. The application of these guidelines for admission should take into account the level of outpatient support and services available, the response to therapy in the emergency department, and the therapeutic goals for each patient. Most patients with ADHF have evidence of volume

Table 12.1. Recommendations for Hospitalizing Patients Presenting With ADHF

Recommendation	Clinical Circumstances
(a) Hospitalization Recommended	Evidence of severely decompensated HF, including: Hypotension Worsening renal function Altered mentation Dyspnea at rest Typically reflected by resting tachypnea Less commonly reflected by oxygen saturation <90% Hemodynamically significant arrhythmia Including new onset of rapid atrial fibrillation Acute coronary syndromes
(b) Hospitalization Should Be Considered	Worsened congestion Even without dyspnea Signs and symptoms of pulmonary or systemic congestion Even in the absence of weight gain Major electrolyte disturbance Associated comorbid conditions Pneumonia Pulmonary embolus Diabetic ketoacidosis Symptoms suggestive of transient ischemic accident or stroke Repeated ICD firings Previously undiagnosed HF with signs and symptoms of systemic or pulmonary congestion

overload manifested by signs and symptoms of either pulmonary or systemic congestion (Table 12.2).[2] Many patients with signs and symptoms of volume overload will present with weight gain, although in one recent study more than half of patients admitted with acute decompensated HF had less than a two pound weight gain.[33] However, some will show no weight gain due to concomitant loss of lean body mass.

Alternatively, those patients with ADHF without obvious high-risk features may benefit from further treatment and risk-stratification in an observation unit (OU).[34] OU management has been suggested to be a safe and cost-effective alternative to hospitalization in specific subsets of patients. The majority of patients are discharged within 24 hours of admission and subsequent adverse event rates are similar to those in hospitalized subjects.[35,36]

Treatment

Recommendation

12.3 It is recommended that patients admitted with ADHF be treated to achieve the goals listed in Table 12.3. (Strength of Evidence = C)

Table 12.2. Signs and Symptoms of Congestion in HF

	Pulmonary	Systemic
Symptoms	Dyspnea	Edema
	Orthopnea	Abdominal (or hepatic) swelling and pain
	PND	Anorexia
		Early satiety
Signs	Rales	Edema
	Wheezing	Elevated JVP
	Pleural effusion and tenderness	Hepatic enlargement
	Hypoxemia	Ascites
	Third heart sound (left-sided)*	Third heart sound (right-sided)*
	Worsening mitral regurgitation	Worsening tricuspid regurgitation
		Hepatojugular reflux

*May occur without congestion.

Background

Although improving signs and symptoms are the principal immediate goals, successful inpatient therapy for worsening HF involves a comprehensive care plan. Treatment to relieve symptoms should be applied in a way that limits side effects and reduces the risk of cardiac and renal injury. Precipitating factors must be identified and chronic oral therapy optimized during the patient's hospitalization. Patients who could potentially benefit from revascularization should be identified. Education must be provided concerning dietary sodium restriction, self-assessment of volume status and principal cardiac medications. Optimizing inpatient care is critical to achieve symptom relief and low readmission rates within an acceptable period of hospitalization.

Symptom Relief. Symptoms in patients hospitalized for HF typically arise from 2 distinct causes: pulmonary or systemic congestion and poor end-organ function from inadequate cardiac output. Data from several studies demonstrate that volume expansion and congestion are far more common than symptoms arising from low cardiac output.[37] Dyspnea often improves significantly within the first few hours from diuretic and vasodilator therapy even though volume loss may not be substantial. Several additional days of hospitalization are often necessary to return the patient to a volume status that makes discharge acceptable.

Table 12.3. Treatment Goals for Patients Admitted for ADHF

Improve symptoms, especially congestion and low-output symptoms
Restore normal oxygenation
Optimize volume status
Identify etiology (see Table 4.6)
Identify and address precipitating factors
Optimize chronic oral therapy
Minimize side effects
Identify patients who might benefit from revascularization
Identify patients who might benefit from device therapy
Identify risk of thromboembolism and need for anticoagulant therapy
Educate patients concerning medications and self management of HF
Consider and, where possible, initiate a disease management program

Adverse Effects of Therapy. High-dose diuretic therapy is a marker for increased mortality during hospitalization for HF, as it is in chronic HF.[38,39] Whether this is a direct adverse effect of diuretics or a reflection of the severity of the HF is unclear. However, complications of diuretic therapy that could result in poor outcomes include electrolyte disturbance, hypotension, volume depletion, and worsening renal function. Treatments that effectively relieve symptoms in patients with ADHF, such as diuretics, morphine, vasodilators, and inodilators, can be associated with significant short- and even long-term adverse effects on renal function.

Troponin release has been documented during hospitalization for ADHF.[40] These findings suggest that myocyte loss from necrosis and apoptosis may be accelerated in patients admitted with ADHF. Mechanisms potentially accounting for cell death are still being determined but may include neurohormonal activation and pharmacologic therapy. Medications that increase myocardial oxygen demand have the potential to induce ischemia and may damage hibernating but viable myocardium, especially in patients with ischemic heart disease. Experimental data indicate that dobutamine can cause necrosis in hibernating myocardium.[41] One outcome study comparing dobutamine to levosimendan suggested greater risk in patients randomized to dobutamine.[42]

Precipitating Factors. Many episodes of worsening HF requiring hospitalization are triggered by comorbid conditions and may not be due to progressive cardiac dysfunction. Poor medication adherence, inability to maintain a restricted sodium diet, or unwillingness to follow the care plan may be the primary cause of many admissions. Not surprisingly, these factors predispose to high rates of readmission following hospital discharge.

Optimization of Oral Pharmacologic Therapy. Hospitalization for ADHF presents an excellent opportunity to restructure the patient's chronic oral medication regimen. The inpatient period is especially useful in adjusting oral therapies in patients with low blood pressure, reduced heart rate and impaired renal function, circumstances which typically make dose adjustment problematic on an outpatient basis. The need for potassium and magnesium supplementation can also be addressed.

Device Therapy. Evaluate the patient for implantable cardioverter defibrillator (ICD) or biventricular pacing therapy (see Section 9).

Education. Hospitalization provides the opportunity to enhance patients' understanding of their HF. Although retention of knowledge imparted during an admission may be limited, introduction of key concepts, including the seriousness of HF, important aspects of therapy, and monitoring volume status, sets the stage for additional education in the follow-up period. See Section 8 for additional information on patient education.

Disease Management. Referral to a disease management program for HF can be facilitated by resources in the hospital and is often a key to reducing the risk of readmission. Patients with frequent hospitalization are readily identifiable as candidates for this approach. See Section 8 of this guideline for a full discussion of disease management approaches in HF.

Recommendation

12.4 Patients admitted with ADHF should be carefully monitored. It is recommended that the items listed in Table 12.4 be assessed at the stated frequencies. (Strength of Evidence = C)

Background

The value of specific clinical assessments to monitor the response of patients admitted with ADHF has not been evaluated in controlled studies. However, there is sufficient consensus of expert opinion to support the utility of serial evaluation of specific data obtained from the history, physical examination, and laboratory findings during hospitalization.

Tracking Volume Status. Evidence that congestion is resolving should be carefully documented during hospitalization by monitoring reduction in symptoms (orthopnea, dyspnea, paroxysmal nocturnal dyspnea [PND], abdominal bloating, and edema) and signs (jugular venous pressure [JVP], rales, peripheral edema, ascites) of volume overload. Daily weights and determination of intake and output are not always accurate indicators of volume status, but still are critical in this assessment, as long as they are correlated with changes in symptoms and physical signs of fluid overload.

Blood Pressure. Blood pressure may decline significantly during hospitalization due to multiple factors including diuretic and vasodilator therapy, bed rest, and a more limited sodium intake. Although declines in blood pressure are typically well tolerated, symptomatic hypotension is an important adverse event in patients admitted with decompensated HF. Excessive or overly rapid diuresis (or overly rapid fluid removal with ultrafiltration), or excessive vasodilator therapy, even when fluid overload is still present, may produce symptomatic hypotension. Documentation of orthostatic blood pressure change on admission and after therapy may help reduce the likelihood of this side effect.

Laboratory Assessment. Serial determinations of electrolytes (especially sodium, potassium, and magnesium) and renal function (blood urea nitrogen [BUN] and serum creatinine) are necessary during diuresis. Patients may become hypokalemic and require supplemental potassium.

Table 12.4. Monitoring Recommendations for Patients Hospitalized With ADHF

Frequency	Value	Specifics
At least daily	Weight	Determine after voiding in the morning Account for possible increased food intake due to improved appetite
At least daily	Fluid intake and output	
More than daily	Vital signs	Orthostatic blood pressure if indicated Oxygen saturation daily until stable
At least daily	Signs	Edema Ascites Pulmonary rales Hepatomegaly Increased JVP Hepatojugular reflux Liver tenderness
At least daily	Symptoms	Orthopnea PND or cough Nocturnal cough Dyspnea Fatigue, lightheadedness
At least daily	Electrolytes	Potassium Sodium
At least daily	Renal function	BUN Serum creatinine*

*See background section for additional recommendations on laboratory evaluations.

Measurement of serum potassium and renal function should be performed more frequently in patients experiencing substantial diuresis (more than 2 L/day) or in patients with abnormalities in serum potassium concentration or renal function before the initiation of diuretic therapy.

Deterioration of renal function during diuresis is a poor prognostic sign and may occur even before achieving euvolemic status. Studies indicate that increasing serum creatinine is associated with an increase in morbidity and mortality in patients with ADHF.[28,29,31,32,38–45] A major dilemma occurs when creatinine rises in the face of continued signs and symptoms of congestion. Few data are available to guide clinicians to the best response to a decline in renal function in this setting. Most physicians continue diuresis as long as the increase in creatinine is modest, since failure to relieve ongoing congestion often leaves the patient symptomatic and at risk for a poor outcome. If increasing creatinine is thought to reflect intravascular volume depletion, either relative or absolute, then reduction or temporary discontinuation of diuretic or vasodilator therapy should be considered, with a reduction in the rate of diuresis to prevent a rapid depletion of intravascular volume. Adjunctive use of inotropic therapy should be considered. If substantial fluid excess persists and diuresis cannot be achieved without an unacceptable degree of azotemia, then dialysis should be considered.

The prognostic significance of worsening renal function in the setting of drug therapy is more difficult to determine. Outpatient initiation of ACE inhibitor therapy commonly increases serum creatinine, especially in severe HF. In chronic HF, modest increases have been associated with long-term reductions in mortality and hospital admissions.[46,47] Routine and frequent laboratory tests recommended in ADHF are shown in Table 12.5.

Electrolytes, BUN, creatinine. and troponin have been discussed. A complete blood count will exclude anemia. Determination of oxygen saturation will define the need for supplemental oxygen. Arterial blood gases may detect unsuspected carbon dioxide retention and suggest a comorbid pulmonary problem. Liver function tests may be elevated when there is poor hepatic perfusion or congestion or may indicate a comorbid hepatic problem. Urinalysis will exclude urinary tract infections and will help exclude acute tubular necrosis if there has been a hypotensive episode and the creatinine is rising.

Fluid Overload

Recommendation

12.5 It is recommended that patients admitted with ADHF and evidence of fluid overload be treated initially with loop diuretics - usually given intravenously rather than orally. (Strength of Evidence = B)

Ultrafiltration may be considered in lieu of diuretics. (Strength of Evidence = B)

Background

Diuretic Therapy for Decompensated HF. Although their safety and efficacy have not been established in randomized, controlled trials, extensive observational experience has demonstrated that loop diuretics, generally alone but at times in combination with non-loop diuretics, effectively relieve congestive symptoms in patients admitted with volume overload. These agents remain first line therapy for the management of congested patients with ADHF (see Section 7 Tables 7.2 and 7.3).

Observational experience also suggests that loop diuretics should be administered intravenously for best effect in the setting of worsening HF. The bioavailability of oral furosemide is highly variable from patient to patient and even from day to day in the same patient and may be considerably lower in patients with decompensated HF. Furosemide, a commonly used loop diuretic, has a short duration

Table 12.5. Laboratory Evaluation for Patients With ADHF

Routinely	Electrolytes BUN and creatinine Blood glucose Troponin Complete blood count INR if using warfarin
Frequently	BNP or NT-proBNP Liver function tests Urinalysis
Occasionally	Arterial blood gases

of action, with a peak effect at 1 to 2 hours, which resolves approximately 6 hours after dosing. Administration 2 or more times a day may be necessary and is often the best approach when these agents are initially ineffective. Increasing the dose also improves response to diuretics if the current dose is insufficient to achieve maximal delivery of drug to the tubules. Alternatively, a continuous infusion of loop diuretic may help to maintain constant drug levels at target sites in the renal tubules.

Intravenous loop diuretics can produce significant acute reductions in left and right ventricular filling pressures as rapidly as 15 minutes after administration. This helps explain why some patients experience improvement in symptoms prior to the onset of the diuretic effect of these drugs.[48] In contrast, administration of intravenous furosemide has been associated with neurohormonal activation, which may result in worsening of hemodynamics secondary to systemic vasoconstriction in the early stages of therapy.[49] However, as sodium excretion increases and diuresis ensues, volume loss leads to a reduction in cardiac filling pressures and improvement in symptoms.[49]

Ultrafiltration. Mechanical methods of fluid removal are being actively investigated as potential alternatives to pharmacologic diuresis.[50] Small uncontrolled studies have long suggested the utility of this approach using not only traditional dialysis but hemofiltration methods.[51] Initial studies supporting the use of a venovenous system, or ultrafiltration, were small and had limited outcomes.[52,53] But they did provide evidence supporting ultrafiltration as an option that may be considered for the reduction of fluid overload in acute decompensated HF. In addition, a single session of ultrafiltration was shown to reduce neurohormones and increase subsequent diuretic responsiveness.

The most extensive study of 200 patients hospitalized with HF and hypervolemia showed no effect on dyspnea at 48 hours, but did show a significant reduction in weight compared to bolus or continuous diuretics at 48 hours and an improvement in rehospitalization rates at 90 days.[54] Despite its apparent effectiveness, cost, need for venous access, and nursing support are concerns, and more study is necessary.

Recommendations

12.6 It is recommended that diuretics be administered at doses needed to produce a rate of diuresis sufficient to achieve optimal volume status with relief of signs and symptoms of congestion (edema, elevated JVP, dyspnea), without inducing an excessively rapid reduction in 1) intravascular volume, which may result in symptomatic hypotension and/or worsening renal function, or 2) serum electrolytes, which may precipitate arrhythmias or muscle cramps. (Strength of Evidence = C)

12.7 Careful repeated assessment of signs and symptoms of congestion and changes in body weight is recommended, because clinical experience suggests it is difficult to determine that congestion has been adequately treated in many patients. (Strength of Evidence = C)

12.8 Monitoring of daily weights, intake, and output is recommended to assess clinical efficacy of diuretic therapy. Routine use of a Foley catheter is not recommended for monitoring volume status. However, placement of a catheter is recommended when close monitoring of urine output is needed or if a bladder outlet obstruction is suspected of contributing to worsening renal function. (Strength of Evidence = C)

Background

Relief of congestion is a self-evident goal of diuretic therapy in congested patients admitted with worsening HF. Achieving this result, while avoiding hypotension and worsening renal function, often requires close observation and careful titration of these agents. Excessively rapid diuresis may result in symptomatic declines in blood pressure and reduced renal function, even while some degree of congestion persists.

Clinical experience suggests it may be difficult to identify persistent congestion. In contrast, even modest relief of congestion may be associated with substantial improvement in dyspnea and sense of well being in many patients despite ongoing volume overload, which may result in premature discharge. The care of patients admitted with worsening HF requires careful physical and symptom assessment and monitoring of vital signs, body weight, and laboratory results to optimize fluid status. Reduction in body weight during hospitalization should be anticipated in patients presenting with significant congestion. Careful history will often document a clear weight gain and suggest a target weight that may be desirable to achieve before discharge. However, accurate determinations of body weight and, even more so, intake and output are not easy to achieve, even in the hospital environment. These measurements should be correlated with other evidence of resolving congestion to achieve the best assessment of an adequate therapeutic response.

Recommendation

12.9 Careful observation for development of a variety of side effects, including renal dysfunction, electrolyte abnormalities, symptomatic hypotension, and gout is recommended in patients treated with diuretics, especially when used at high doses and in combination. Patients should undergo routine laboratory studies and clinical examination as dictated by their clinical response. (Strength of Evidence = C)

It is recommended that serum potassium and magnesium levels be monitored at least daily and maintained in the normal range. More frequent monitoring may be necessary when diuresis is rapid. (Strength of Evidence = C)

Overly rapid diuresis may be associated with severe muscle cramps. If indicated, treatment with potassium replacement is recommended. (Strength of Evidence = C)

Background

Overview of the Adverse Effects of Diuretics. Despite beneficial effects in acute HF, diuretics may be associated with a variety of adverse effects that often require alterations in their use or the use of concomitant medications.[55] Patients treated with diuretics should be monitored carefully for excessive urine output, development of hypotension, rise in serum BUN and creatinine levels and reductions in serum potassium, and magnesium levels. Serial determinations of creatinine and BUN are particularly important when these side effects are present or anticipated. Diuretic therapy must be highly individualized based on the degree of fluid overload present and the degree of volume loss produced to minimize these side effects.

Hypokalemia. Potassium must be monitored closely, especially during the period when diuresis is most pronounced, with supplementation given as needed. Patients with reduced serum potassium need immediate replacement before diuretic therapy for worsening HF. Aldosterone antagonists may be used cautiously in the setting of marked potassium wasting.

Hypotension. In patients with reduced LVEF and ventricular dilation, the effect of loop diuretics on cardiac output and blood pressure often seems counterintuitive. Despite decreasing filling pressures, loop diuretics usually do not produce clinically significant reductions in cardiac output or blood pressure in patients with worsening HF and LV systolic dysfunction. In patients with ventricular dilation and volume overload, total stroke volume is relatively independent of filling pressures.[56] Diuretic-induced reductions in left and right heart filling pressures are frequently accompanied by augmented forward stroke volume and cardiac output, related to (1) diminution in functional mitral regurgitation; (2) diminution in functional tricuspid regurgitation; and (3) reduction in right ventricular volume, associated with relief of ventricular-interdependent LV compression and improved effective LV distensibility.

In contrast, some patients do experience symptomatic hypotension with decreasing cardiac output and blood pressure during therapy. Intravascular volume must be maintained by reequilibration as interstitial fluid moves into the vascular bed to maintain blood pressure even as diuresis proceeds. The time course of this phenomenon varies among patients and, especially during periods of brisk diuresis, may lag behind the decline in intravascular volume, resulting in hypotension despite persistent total body fluid overload.

Diuresis accompanied by a reduction in filling pressure may make patients more sensitive to the hypotensive effects of drugs with vasodilator properties. Diuretics may significantly enhance the hypotensive effects of ACE inhibitors, even when volume overload is still present. Patients with HF with preserved LVEF or restrictive, hypertrophic, or infiltrative cardiomyopathies may be more sensitive to diuresis and may decrease their blood pressure during diuretic therapy despite continued volume expansion. All patients receiving diuretic therapy need careful monitoring to prevent adverse hemodynamic effects from excessive volume loss.

Neurohormonal Activation. Older studies demonstrated that increased activity of the renin-angiotensin and sympathetic nervous systems may occur with intravenous diuretics, and result in secondary increases in systemic vascular resistance.[57] It has been hypothesized that this acute vasoconstrictor response may play a role in the development of worsening renal function during treatment of ADHF. However, more recent studies in patients with ADHF have shown a reduction in plasma neurohormones, including norepinephrine, endothelin-1, and BNP, with parenteral diuretic and vasodilator therapy,[58] as well as following ultrafiltration.[54,59] Furthermore, the reduction in neurohormones appears to correlate with urine output and sodium excretion.[60] Whether changes in circulating neurohormones have beneficial or adverse long-term effects in patients with ADHF or alter the responsiveness to diuretic therapy requires further study.

Other Side Effects. Diuretic agents may increase the incidence of digitalis toxicity, either by decreasing glomerular filtration rate or by inducing hypokalemia and hypomagnesemia. Electrolyte disturbances induced by diuretics may result in arrhythmia. Hyponatremia may occur as a result of diuretic therapy, in part because of increases in circulating vasopressin, which can further reduce renal clearance of free water, plus an increase in free water intake in turn impeding restoration of euvolemia.[61,62] Diuretic therapy can also precipitate exacerbations of gout and at high doses cause reversible hearing loss.

Recommendation

12.10 Careful observation for the development of renal dysfunction is recommended in patients treated with diuretics. Patients with moderate to severe renal dysfunction and evidence of fluid retention should continue to be treated with diuretics. In the presence of severe fluid overload, renal dysfunction may improve with diuresis. (Strength of Evidence = C)

Background

Diuretic therapy may further worsen renal function in patients with baseline renal insufficiency. Loop diuretics may produce intrarenal regulatory changes, related in part to neurohormonal activation, which can compromise glomerular filtration rate. Excessive diuresis or overly rapid diuresis may lower preload so that systemic blood pressure is

compromised, especially in patients with marked HF with preserved LVEF and significant LV hypertrophy or restrictive physiology.

Despite these physiologic disadvantages, the net effect of diuretic therapy in individual patients with ADHF is difficult to predict. In some patients with reduced renal function at baseline, decongestion may improve serum creatinine and BUN, even as intravascular volume and filling pressures decline. Improved renal blood flow in response to relief of abdominal fluid overload is postulated as one physiologic mediator of this beneficial effect. Reduction of central venous pressure is another potential mechanism contributing to increases in glomerular filtration rate.

Recommendation

12.11 When congestion fails to improve in response to diuretic therapy, the following options should be considered:

- **Re-evaluating presence/absence of congestion**
- **Sodium and fluid restriction,**
- **Increasing doses of loop diuretic,**
- **Continuous infusion of a loop diuretic, or**
- **Addition of a second type of diuretic orally (metolazone or spironolactone) or intravenously (chlorothiazide).**

Another option, ultrafiltration, may be considered. (Strength of Evidence = C)

Background

Most patients admitted with worsened HF and congestion will respond adequately to loop diuretics with resolution of volume overload; however, a minority will experience some resistance to diuretic therapy. Increasing the frequency and then the dose of loop diuretic is recommended in these cases to restore volume status. Distal tubular diuretics augment the natriuretic effect of loop diuretics. These agents should be considered as adjunctive therapy in patients with diuretic resistance who do not respond to more frequent administration or escalating doses of loop diuretics. However, these agents can exacerbate adverse effects of loop diuretics, such as hyponatremia and hypokalemia.

Continuous infusion of a loop diuretic may produce higher and more sustained concentrations of furosemide within the renal tubule than repeated bolus injection. Continuous infusion may be associated with less prerenal azotemia and fewer other side effects compared with bolus administration, possibly because this method avoids the high peak concentrations associated with bolus dosing. [63]

Recommendation

12.12 A low sodium diet (2 g daily) is recommended for most hospitalized patients. (Strength of Evidence = C)

In patients with recurrent or refractory volume overload, stricter sodium restriction may be considered. (Strength of Evidence = C)

Background

Restricting fluid intake to 2 L/day is usually adequate for most hospitalized patients. Dietary sodium restriction is important, even short-term in the hospital setting, to help restore euvolemia. The level of sodium restriction prescribed during hospitalization may be greater than typically feasible in the outpatient setting. Education regarding sodium and fluid restriction may be initiated during an admission.[64]

Recommendation

12.13 Fluid restriction (<2 L/day) is recommended in patients with moderate hyponatremia (serum sodium <130 mEq/L) and should be considered to assist in treatment of fluid overload in other patients. (Strength of Evidence = C)

In patients with severe (serum sodium <125 mEq/L) or worsening hyponatremia, stricter fluid restriction may be considered. (Strength of Evidence = C)

Background

Severe hyponatremia is not a common manifestation of ADHF, but is an ominous sign. However, recent results suggest that even reductions in serum sodium traditionally considered mild (<137 mEq/L) are associated with prolonged hospitalization and increased in-hospital mortality.[65] Patients whose reduction in serum sodium is related to volume depletion as a result of diuretic therapy or environmental conditions will respond to administration of sodium and water. However, the great majority of hyponatremia in HF patients occurs in the setting of volume overload and cannot be corrected by the administration of sodium, which will only compound volume expansion.

Fluid restriction may produce some improvement in serum sodium concentration and may be transiently effective in mild hyponatremia. Fluid restriction can be difficult to maintain, because thirst is a common symptom in patients with HF. Patients may feel a certain amount of fluid ingestion is necessary for good health and that restriction will be harmful. Education concerning the benefits and lack of adverse effect of fluid restriction may help promote adherence. In patients with HF, hyponatremia is associated with a higher risk of clinical deterioration, including renal and hepatic dysfunction, longer hospital stays and high rehospitalization and mortality rates.[66–69] The degree of hyponatremia is inversely associated with mortality.[69] Hyponatremia in patients with HF is due to an inability to excrete free water, primarily due to neurohormonal activation. Increases in norepinephrine and angiotensin II result in decreased delivery of sodium to the distal tubule by causing decreased renal

perfusion, while arginine vasopressin increases water absorption from the distal tubule. In addition, angiotensin II directly promotes thirst. Thus serum sodium is a marker for poor cardiac output and neurohormonal activation.

Recently it has been suggested that hyponatremia may be associated with more neurocognitive symptoms than previously recognized. In a case-control study of 122 patients (none with HF) with hyponatremia (serum sodium 126 ±5 mEq/L), falls and attention deficits were far more common in the hyponatremic patients.[70] Treatment of hypervolemic hyponatremia with a V2-selective vasopressin antagonist (tolvaptan) was associated with a significant improvement in The Mental Component of the Medical Outcomes Study 12 item Short Form General Health Survey.[71]

Treatment of hyponatremia consists of water restriction and maximization of medical therapies such as ACE-inhibitors or angiotensin receptor blockers which block or decrease angiotensin II, resulting in improved renal perfusion and decreased thirst. Vasopressin antagonists have been shown to improve serum sodium in hypervolemic, hyponatremic states with either a V2-selective or a non-selective vasopressin antagonist.[71,72] Longer term therapy with a V2 selective vasopressin antagonist does not improve mortality but appears to be safe.[73,74] Currently two vasopressin antagonists are available for clinical use (conivaptan and tolvaptan) and only short-term studies are available. At present it may be reasonable to utilize a non-selective vasopressin antagonist to treat hyponatremia in patients with HF who are observed to have significant cognitive symptoms due to hyponatremia. However, the long-term safety and efficacy of this approach remains unproven. In patients with refractory hyponatremia, alternative causes (e.g., hypothyroidism, hypoaldosteronism, syndrome of inappropriate antidiuretic hormone) should be excluded.

Recommendation

12.14 Routine administration of supplemental oxygen in the presence of hypoxia is recommended. (Strength of Evidence = C)

Routine administration of supplemental oxygen in the absence of hypoxia is not recommended. (Strength of Evidence = C)

Background

Routine oxygen administration in patients with acute HF is recommended to improve oxygen delivery to vital organs, including the myocardium. While there have been no randomized trials to support this, improving systemic and myocardial hypoxemia would be expected to improve the overall clinical status of patients with acute HF.

Supplemental oxygen therapy should be individualized. The congested dyspneic patient who presents with hypoxemia requires oxygen therapy. Patients with systemic fluid overload that does not compromise oxygenation do not require oxygen therapy. Supplemental oxygen in the setting of normal oxygen saturations on room air could be problematic if the patient also has a history of obstructive lung disease. In selected patients, oxygen may decrease elevated pulmonary vascular resistance and improve right heart function. Supplemental oxygen is also recommended in patients with acute myocardial infarction (MI) complicated by HF. The role of nocturnal oxygen in patients with central sleep apnea remains unproven.

Recommendation

12.15 Use of non-invasive positive pressure ventilation may be considered for severely dyspneic patients with clinical evidence of pulmonary edema. (Strength of Evidence = A)

Background

Previous small trials investigating the use of noninvasive ventilation (NIV) in emergency department patients with acute HF suggested it improved symptoms, decreased the need for subsequent intubation and reduced mortality.[75–77] There were some concerns from one of the early trials that bi-level positive pressure ventilation may have led to an increase in the number of patients with myocardial infraction.[78] However, a subsequent study did not encounter this association, and a review of data from the original trial suggests that a disproportionate number of patients with evolving MI may have been enrolled in the interventional arm.[79,80] Several subsequent meta-analyses based on these smaller NIV trials also suggested that both intubation rates and mortality were reduced with NIV.[81–83] However, results from a recent large randomized trial in the United Kingdom suggest while NIV improved patient's dyspnea and metabolic abnormalities, it did not significantly change mortality and intubation rates when compared to standard oxygen therapy.[84] Further, the authors found no significant differences in efficacy between continuous positive pressure ventilation and bi-level positive pressure ventilation. While this study has rather robust results and randomized over 1100 patients, it is worth noting that concomitant therapy was not standardized, opioids were used in over 50% of patients, and over 15% of patients on standard therapy crossed over to NIV. Further, the primary endpoint was measured at 7 days, a time far removed from the time frame of use of NIV. Despite those limitations, the preponderance of evidence suggests NIV is a useful temporizing measure that improves dyspnea but likely has no impact on intubation rates or mortality.

Prevention of Deep Venous Thrombosis and Pulmonary Embolism

Recommendation

12.16 Venous thromboembolism prophylaxis with low dose unfractionated heparin (UFH), low molecular weight heparin (LMWH), or fondaparinux

to prevent proximal deep venous thrombosis (DVT) and pulmonary embolism (PE) is recommended for patients who are admitted to the hospital with ADHF and who are not already anticoagulated and have no contraindication to anticoagulation. (Strength of Evidence = B)

Venous thromboembolism prophylaxis with a mechanical device (intermittent pneumatic compression devices or graded compression stockings) to prevent proximal DVT and PE should be considered for patients who are admitted to the hospital with ADHF and who are not already anticoagulated and who have a contraindication to anticoagulation. (Strength of Evidence = C)

Background

Prevention of DVT and PE remain important management issues in hospitalized patients. Ten percent of hospital deaths are considered to be due to PE and the prevention of DVT and PE is considered the most valuable of 79 preventative initiatives outlined by the Agency for Healthcare Research and Quality.[85,86] NYHA Class III and IV HF is a major risk factor for DVT and acute hospitalization increases the risk of DVT several-fold.[87,88] One million patients per year are admitted for acutely decompensated HF in both the US and Europe.[89] With an in-hospital mortality for decompensated HF of approximately 4%, as many as 4000 patients deaths due to PE are potentially preventable yearly in both the US and Europe.[90,91] Although no large randomized trial of DVT prophylaxis has been conducted solely in an acute decompensated HF population, several randomized trials conducted in hospitalized patients that have included a large percentage of patients admitted for decompensated HF.[92–98] Prophylaxis with low dose UFH, LMWH, and fondaparinux have been shown to decrease the incidence of asymptomatic DVT and in some cases symptomatic DVT.[92–98] Only one trial has independently demonstrated a benefit of anticoagulation prophylaxis on PE and that trial was conducted in patients with infectious diseases.[99] Two meta-analyses have reported a significant benefit of either low dose UFH or LMWH on DVT and PE without an effect on mortality and with a non-significant increase in the risk of major bleeding.[100,101] All but two of the studies in these meta-analyses included patients admitted with decompensated HF. The American College of Chest Physicians has given DVT prophylaxis with UFH or LMWH a 1A recommendation for acutely hospitalized patients with a high risk for DVT and NYHA Class III or IV HF is considered a high-risk category.[85] Although no single trial has been conducted in only hospitalized patients with HF, a subgroup analyses of two large randomized trials demonstrates a significant benefit of LMWH on DVT in HF patients.[102,103] No large study compares UFH to LMWH or fondaparinux, but a meta-analysis of all studies suggests a trend in favor of LMWH compared to low dose UFH for both reduction of DVT and PE with a trend for less bleeding.[104]

LMWH are renally excreted and should not be used in patients with a creatinine clearance <30 mL/min. LMWH should also be avoided in patients with HF who have undergone a recent surgical procedure, such as an ICD implantation.

Mechanical means of DVT prophylaxis, such as intermittent pneumatic compression devices or graded compression stockings, have not been subjected to randomized trials in medical patients and are reserved for patients with contraindications to anticoagulation.[85] Graded compression stockings may be preferable if intermittent pneumatic compression devices limit patient mobility.[104]

At the time of admission, screening for venous thromboembolism is indicated when patients present with unilateral or asymmetric lower extremity edema, chest pain, or presyncope. Worsening right HF and pulmonary hypertension may also be signs of chronic pulmonary emboli.

IV Vasodilators

Recommendation

12.17 In the absence of symptomatic hypotension, intravenous nitroglycerin, nitroprusside or nesiritide may be considered as an addition to diuretic therapy for rapid improvement of congestive symptoms in patients admitted with ADHF. (Strength of Evidence = B)

Frequent blood pressure monitoring is recommended with these agents. (Strength of Evidence = B)

These agents should be decreased in dosage or discontinued if symptomatic hypotension or worsening renal function develops. (Strength of Evidence = B).

Reintroduction in increasing doses may be considered once symptomatic hypotension is resolved. (Strength of Evidence = C)

Background

Nitroglycerin. Intravenous nitroglycerin acutely reduces LV filling pressure, primarily through its venodilator effects, which reduce pulmonary congestion.[106] At higher doses the drug may lower systemic afterload and increase stroke volume and cardiac output, but the extent of these effects is variable. Intravenous nitroglycerin may improve coronary blood flow, making it potentially more effective in patients with ADHF from acute ischemia or MI. Nitroglycerin therapy results in neurohormonal activation; whether this has a detrimental effect in acute HF is uncertain.[105,106]

Data demonstrating favorable hemodynamic effects of intravenous nitroglycerin in HF are derived primarily from small, uncontrolled studies of patients who were not usually hospitalized for acute decompensation.[107] These

studies demonstrate beneficial hemodynamic effects, but also document a relative resistance to nitroglycerin and significant tachyphylaxis to the vascular actions of this drug, changes that can occur within hours at high doses. The strategy of a nitrate-free interval, which may be an option to reduce tolerance during chronic therapy, could result in adverse hemodynamic effects that would be unacceptable in patients with acute HF.

Approximately 20% of patients with HF are resistant to the hemodynamic effects of any dose of nitroglycerin.[108,109] Patients who do not have hemodynamic benefit at doses of intravenous nitroglycerin in the range of 200 μg/kg can be considered non-responders for whom additional dosing is unwarranted.

The adverse effects of nitroglycerin therapy include headache, abdominal discontent, and symptomatic hypotension.[110] Hypotension is more likely when preload is low, which may occur as filling pressures decline in response to diuretic therapy. Symptomatic hypotension and headache respond to reduction in dose, but may require discontinuation of therapy.

Nitroprusside. This potent vasodilator has balanced effects on the venous and arteriolar tone. PCWP is reduced almost immediately, and there usually is a robust increase in cardiac output. The drug is used primarily in conjunction with hemodynamic monitoring. It can be easily titrated to an appropriate dose while maintaining a systolic blood pressure >90 mm Hg or mean arterial pressure >65 mm Hg. The dose range is between 5 and 300 mcg/minute. Thiocyanate toxicity may occur gradually in patients with renal dysfunction, but is rare when nitroprusside is used by an experienced care team.[111]

Nesiritide. A number of cardiovascular, renal, and neurohormonal effects of BNP have been identified.[112,113] Nesiritide, a peptide identical to human BNP, represents the form of BNP available for clinical use. Extensively evaluated in patients with HF from almost exclusively LV systolic dysfunction, nesiritide administration produces dose-dependent reductions in filling pressure, systemic and pulmonary vascular resistance, and an increase in cardiac output.[114–117] At the currently recommended dose (0.01 μg/kg), nesiritide significantly reduces LV filling pressure but has variable effects on cardiac output.[110] A reduction in circulating aldosterone levels has been observed.[118]

Studies of nesiritide in patients with HF from LV systolic dysfunction show no consistent effect on glomerular filtration rate and renal blood flow. Some studies have demonstrated enhanced urinary output and increased sodium excretion, while others have not.[118,119] A number of explanations have been proposed for these variable effects, including the dose of nesiritide studied, degree of concomitant diuretic therapy, and hemodynamic effects, which may include a reduction in blood pressure or an augmentation of cardiac output.

The VMAC Trial. The Vasodilator in the Management of Acute Heart Failure (VMAC) study was a complex multicenter, randomized, double-blinded controlled trial of nesiritide, nitroglycerin, and standard therapy in 489 patients hospitalized for worsening HF.[110] The study used a dose of nesiritide (bolus of 2 μg/kg followed by an infusion of 0.01 μg/kg/min) .The primary endpoints of the VMAC trial were change in PCWP from baseline (catheterized stratum only) and change in dyspnea score from baseline. The primary study comparison of these endpoints was between nesiritide on top of standard therapy versus standard therapy alone at 3 hours.

Trial results showed that the combination of nesiritide plus standard therapy significantly decreased PCWP ($P < .001$) and dyspnea score ($P = .03$) at 3 hours compared with standard therapy alone. Nesiritide did not improve dyspnea compared to nitroglycerin, but did lower the PCWP more than nitroglycerin ($P = .03$). However, the nitroglycerin doses used in VMAC were relatively small and may account for the observed differences in PCWP.

Adverse Effects. The potential side effects of nesiritide include hypotension, headache, and worsening renal function. The risk of hypotension appears to be dose dependent and was less frequent in the VMAC study than in earlier trials that used higher maintenance doses. The incidence of symptomatic hypotension in the VMAC trial was similar in patients treated with nitroglycerin versus nesiritide. Because of the longer effective half-life of nesiritide, hypotension may last longer with nesiritide than with nitroglycerin. Headache is not a common or severe side effect of nesiritide.

Worsening Renal Function. Worsening of renal function has been observed in clinical trials with nesiritide. The mechanisms for this adverse effect on renal function are unknown but physiologic considerations suggest interaction with diuretic therapy, reductions in blood pressure and inhibition of the renin angiotensin aldosterone system may play a role. Only limited data are available from clinical trials to assess the frequency and severity of this adverse effect. Analysis of available data from the VMAC study and other nesiritide trials demonstrated that nesiritide plus standard therapy was more likely than standard therapy alone to be associated with a rise in creatinine of >0.5 mg/dL during the study period.[120] This analysis was retrospective and used data from studies that were not prospectively designed to assess serial changes in renal function. The cut point of serum creatinine used to indicate worsening renal function was dictated by the data available to the investigators and has been employed in other studies. Whether there is a general relationship between nesiritide and worsening renal function or whether other cut points of creatinine increase would show a similar adverse effect is unknown. Although most of the clinical trials of nesiritide were not designed to monitor effects on renal function for a 30-day period, analysis of any additional data available is needed.

The dose of nesiritide may be a significant factor related to the risk of worsening renal function. In the VMAC study worsening renal function, as defined by the 0.5 mg/dL endpoint, occurred in 21% of patients randomized to standard therapy plus nitroglycerin versus 27% in the patients randomized to nesiritide.[120]

Whether the worsening renal function induced by nesiritide is associated with adverse outcomes in patients with ADHF is uncertain. Additional mechanistic studies are needed to better understand the effects of nesiritide on renal function, both regarding glomerular filtration rate and urinary sodium excretion, and how this may vary with diuretic use and volume status in patients with ADHF.

Outcome Data. The current guideline has specified that nesiritide may be considered for symptom relief in patients with symptomatic congestion. A recent meta-analysis has suggested that use of nesiritide in patients with ADHF is associated with increased mortality.[121] However, the data overall do not provide convincing evidence of an adverse effect. Similar evaluations for intravenous nitroglycerin and nitroprusside in patients with ADHF are not available. Well designed and adequately powered prospective studies are warranted to determine the effect of this drug on outcomes in patients with ADHF.

Morphine

Morphine has been used as adjunctive therapy in acute HF for several decades. Though its beneficial mechanism of action in acute HF is unclear, it is thought to produce mild venodilation and preload reduction.[122,123] Further, it may impart a beneficial effect through relief of anxiety and a diminished catecholamine response. However, prospective data supporting its use is limited. Retrospective data suggest an association between morphine use and adverse outcomes such as endotracheal intubation, intensive care unit admission and prolonged hospital length of stay.[124,125] A recent Acute Decompensated Heart Failure National Registry (ADHERE) analysis suggests the use of morphine was also associated with increased in-hospital mortality.[126] Much of this data is confounded by the possibility that those patients who were ''sicker'' received morphine. Prospective study is necessary to determine the risks and benefits of morphine use. If used at all in acute HF, it should be used with caution, especially in those patients with abnormal mental status and impaired respiratory drive.

Recommendation

12.18 Intravenous vasodilators (nitroglycerin or nitroprusside) and diuretics are recommended for rapid symptom relief in patients with acute pulmonary edema or severe hypertension. (Strength of Evidence = C)

Background

Diuretics remain an important treatment for acute pulmonary edema, although randomized controlled trial data to establish the best strategy for the use of these agents (eg, duration and dose of this therapy) are not available. Data from contemporary randomized controlled clinical trials demonstrating the benefit of vasodilator therapy plus standard therapy compared with standard therapy alone are also lacking. Support for the use of these agents comes from extensive clinical experience in patients admitted with this syndrome, which suggests benefit is common. In addition, one study has suggested that intravenous isosorbide dinitrate and low-dose diuretics might be more effective than high-dose diuretics in patients with this condition. In this trial, 110 patients were randomized to treatment with (1) repeated high-dose boluses of intravenous isosorbide dinitrate plus a single 40-mg bolus of intravenous furosemide or (2) repeated high-dose furosemide. These regimens were administered until oxygen saturation was above 96% or mean arterial blood pressure decreased by 30% or to below 90 mm Hg. Patients randomized to repeated high doses of isosorbide dinitrate and a low-dose diuretic had a significantly lower combined risk of MI, requirement for mechanical ventilation or death than those treated primarily with a more aggressive diuretic regimen.[127] Similar results were also seen in an ED-based non-randomized trial of high dose nitroglycerin in the treatment of severe decompensated HF.[128]

Recommendations

12.19 Intravenous vasodilators (nitroprusside, nitroglycerin, or nesiritide) may be considered in patients with ADHF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies.

- **Nitroprusside (Strength of Evidence = B)**
- **Nitroglycerine, Nesiritide (Strength of Evidence = C)**

12.20 Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced HF characterized by LV dilation, reduced LVEF, and diminished peripheral perfusion or end-organ dysfunction (low output syndrome), particularly if these patients have marginal systolic blood pressure (< 90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators. (Strength of Evidence = C)

These agents may be considered in similar patients with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function. (Strength of Evidence = C)

When adjunctive therapy is needed in other patients with ADHF, administration of vasodilators should be considered instead of intravenous inotropes (milrinone or dobutamine). (Strength of Evidence = C)

Intravenous inotropes (milrinone or dobutamine) are not recommended unless left heart filling pressures are known to be elevated or cardiac index is severely impaired based on direct measurement or clear clinical signs. (Strength of Evidence = C)

It is recommended that administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm. (Strength of Evidence = C)

If symptomatic hypotension or worsening tachyarrhythmias develop during administration of these agents, discontinuation or dose reduction should be considered. (Strength of Evidence = C)

Background

Introduction. Although they account for only a small percentage of ADHF, patients with advanced HF, which may be defined by severe LV systolic dysfunction with ventricular dilation and marked chronic clinical symptoms, represent a major therapeutic challenge.[129,130] Treatment options are limited and there is little evidence from randomized trials to guide management. Marked resting hemodynamic derangements, such as reduced cardiac output and increased PCWP, are characteristic in these patients. Available clinical studies have assessed the effect of treatment almost exclusively on hemodynamic endpoints. These studies provide convincing evidence that administration of vasodilators and inotropic agents, alone or in combination, usually results in significant short-term hemodynamic improvement in most patients. Many patients with advanced HF and ADHF will have moderate to severe vasoconstriction and substantially elevated filling pressures, a hemodynamic pattern that may improve with vasodilators alone.

Intravenous inotropes (milrinone or dobutamine) may be considered to relieve symptoms and improve end-organ function in patients with advanced HF and diminished peripheral perfusion or end-organ dysfunction (low output syndrome). Inotropic therapy is often used if these patients have marginal systolic blood pressure (<90 mm Hg), have symptomatic hypotension despite adequate filling pressure, or are unresponsive to, or intolerant of, intravenous vasodilators. Patients with advanced HF and reduced blood pressure and normal or low systemic vascular resistance often will not tolerate or derive sufficient hemodynamic benefit from vasodilator therapy. Inotropic agents may be necessary to maintain circulatory function in these patients. Even patients with advanced HF may present with ''low cardiac output'' syndrome due to volume depletion. Elevation of left heart filling pressures based on classical signs and symptoms or direct measurement should be documented prior to use of vasodilators or inotropic agents in patients with advanced HF. Vasodilators and inotropic agents may be considered in patients with advanced HF with evidence of fluid overload if they respond poorly to intravenous diuretics or manifest diminished or worsening renal function.

Administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF and advanced HF should be accompanied by continuous or frequent blood pressure monitoring and continuous monitoring of cardiac rhythm. Discontinuation or dose reduction is often necessary if the use of vasodilators or inotropic agents is accompanied by symptomatic hypotension. Inotropic agents may promote or aggravate tachyarrhythmias and discontinuation or reduction in dose may be necessary when these side effects occur. The effects of dobutamine may wane with time (tachyphylaxis) or be negated by development of hypersensitivity myocarditis.

Data concerning the hemodynamic effects of intravenous nitroglycerin and nesiritide are reported elsewhere; this background section will focus on the use of sodium nitroprusside and inotropic agents in patients with advanced HF.

Sodium Nitroprusside. Sodium nitroprusside exerts a significant effect on both ventricular preload and afterload, resulting in both a decrease in LV filling pressures and typically an increase in LV stroke volume. After-load reduction may be of particular benefit in patients with acute HF complicated by significant mitral regurgitation, making sodium nitroprusside effective in these patients. This drug can be used to establish reversibility of pulmonary hypertension in patients being evaluated for cardiac transplantation. Sodium nitroprusside may prove useful in patients with ADHF associated with LV dysfunction and severe aortic stenosis.

Despite these favorable hemodynamic effects, sodium nitroprusside has not been widely adopted as a treatment modality for acute HF. There are a number of aspects related to the pharmacologic effects of the drug and its practical application that have limited its use in ADHF. In most centers, this drug is not administered without invasive monitoring of blood pressure and typically central hemodynamics. In the absence of HF, sodium nitroprusside has been noted to increase mortality rates when given within 48 hours of an acute MI.[70] One explanation for this adverse effect centers on the significant effects the drug may have on coronary blood flow. Coronary artery disease may limit the vasodilatory response to nitroprusside and thus create a circumstance of coronary steal with improved perfusion through normal vessels and reduced blood flow through diseased arteries. However, when pump dysfunction persists for greater than 48 hours after acute MI, nitroprusside may improve survival.[131]

Sodium nitroprusside should be initiated at a rate dose of 5-10 μg/min. Doses exceeding 400 μg/min generally do not produce added benefit and may increase the risk of thiocyanate toxicity. The drug may be titrated rapidly (up to every 5 minutes) until hemodynamic goals are reached. Caution is advised when discontinuing nitroprusside and monitoring for rebound vasoconstriction is warranted.[132]

Milrinone and Dobutamine. Milrinone, often termed an inodilator, causes, in the short term, increased myocardial contractility and decreased systemic and pulmonary vascular tone.[133] Heart rate typically is augmented to a lesser degree with milrinone than dobutamine, but both drugs may cause unwanted tachycardia. Milrinone typically produces significant vasodilation of the pulmonary arterial system, which may be important in supporting patients with marked pulmonary hypertension and poor cardiac output. Milrinone administration may demonstrate that increased pulmonary resistance is reversible,[134] an important observation in patients being considered for cardiac transplantation. Because dobutamine does not act as a direct pulmonary vasodilator, it typically has little effect on pulmonary vascular resistance. There is always concern that inotropic agents may increase myocardial oxygen consumption. In a small study of 10 patients, the use of milrinone was not associated with increased myocardial oxygen consumption from baseline.[135]

In contrast to dobutamine, the hemodynamic effects of milrinone are not mediated by stimulation of beta receptors. Thus the pharmacologic actions of milrinone do not appear to be diminished to the same extent as those of dobutamine by concomitant administration of beta blocking drugs. To avoid discontinuation of beta blockade, some clinicians use this agent for hemodynamic support of patients who are hospitalized with worsening HF while on beta blocker therapy. In patients with advanced dilated cardiomyopathy, the positive inotropic effects of dobutamine or milrinone may be highly variable and it is critical to titrate doses to desired clinical and hemodynamic effect.

Dosing. Bolus administration of milrinone definitely produces rapid hemodynamic improvement, but is associated with increased risk of symptomatic hypotension. Symptomatic hypotension occurred in more than 10% of patients in the milrinone arm of the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF), even though the initial dose was 0.5 μg/kg/min without a bolus.[50] However, recent work has shown that by 2 hours, the hemodynamic improvement from this infusion rate is similar with or without a loading dose.[136] An increase of approximately 50% in cardiac index occurs during this brief period. Initial doses of 0.1 μg/kg/min and final doses of 0.2 to 0.3 μg/kg/min should be considered, as they appear to be associated with symptomatic improvement and may be better tolerated, but the recommended dose range goes up to 0.75 μg/kg/min.

Risks of Inotropic Agents. Data from at least 2 studies confirm that there is no rationale for the use of inotropic agents in the great majority of patients admitted with acute HF with congestion who are not in a low output state.[2,37] No clinical benefits and evidence of adverse effects were found from the administration of milrinone in the OPTIME-CHF study. In addition, results from an observational analysis of the patients enrolled in the ADHERE registry suggest that this class of drugs is associated with an adverse effect on mortality among patients currently hospitalized with acute HF, the great majority of whom have elevated or normal blood pressure and congestion.[65,137]

Acute HF appears to represent a period during which the myocardium is at risk of additional damage, especially in patients with advanced HF, who are more likely to be treated with inotropic support. In this setting, there is concern that inotropic agents may: (1) increase heart rate, (2) adversely affect coronary flow to ischemic segments, (3) augment myocardial oxygen consumption, and (4) produce symptom relief with less reduction in filling pressure. These factors may all contribute to loss of additional cardiomyocytes and promote progressive HF.

Consideration of the OPTIME-CHF trial may further illustrate the limitations of inotropic therapy in broad populations of patients with ADHF. This study was a randomized, controlled, double-blind trial that tested the potential benefit of inotropic agents in patients admitted with ADHF and systolic dysfunction, but without "low-output syndrome"—a population not usually considered for inotropic therapy. A total of 949 patients were randomized to a 48-hour infusion of milrinone (0.5 μg/kg/min) or placebo within 48 hours of admission. Patients were excluded if, in the opinion of the investigator, they had an absolute requirement for inotropic therapy. Also excluded were those with a history of poor rate control of atrial fibrillation, a history of ventricular arrhythmia, or myocardial ischemia in the past 3 months. The primary end point of the study was rehospitalization for a cardiovascular cause within 60 days.

OPTIME-CHF demonstrated that the median number of days patients were hospitalized for cardiovascular causes did not differ significantly between patients given milrinone and those given placebo. Milrinone therapy showed early treatment failure and was associated with a nonsignificant higher number of deaths in hospital and within 60 days. The use of milrinone resulted in significantly higher incidence of new atrial arrhythmias and of sustained systolic BP of <80 for 30 minutes, requiring intervention. The study authors concluded that milrinone therapy was not indicated for routine use as an adjunct to standard therapy in patients with an exacerbation of HF.[138]

Potential Role for Inotropic Therapy. Careful patient selection is required to achieve a favorable risk-benefit ratio for inotropic therapy. Although ongoing clinical studies strongly suggest that inotropic therapy is not effective in broad populations of patients with ADHF, there are instances in which these drugs are necessary to maintain cardiac

output and may be more effective in the short-term for this purpose than vasodilators. Inotropic drugs may be considered in the highly selected patients described in recommendation 12.20. These patients often present with hypotension and may face an increased risk of further hypotension from vasodilator agents. Clinical experience indicates that patients with ''low cardiac output'' syndrome and reduced renal function may respond to inotropic support with diuresis and improved renal function. Patients presenting with cardiogenic shock may need inotropes to maintain the minimal cardiac output necessary for survival. In these cases, inotropes can be a ''bridge'' to more definitive therapy, such as revascularization, cardiac transplantation, or mechanical circulatory support. The use of inotropic agents as palliative care in patients who are not candidates for more definitive therapy recognizes that improvement in quality of life and clinical status may be all that is possible in certain patients and may be achieved at the expense of increased mortality during therapy. However, morbidity, such as non-related infection from central venous catheters used to administer the drugs, should also be considered.

Hemodynamic Monitoring

Recommendations

12.21 The routine use of invasive hemodynamic monitoring in patients with ADHF is not recommended. (Strength of Evidence = A)

12.22 Invasive hemodynamic monitoring should be considered in a patient:
- **who is refractory to initial therapy,**
- **whose volume status and cardiac filling pressures are unclear,**
- **who has clinically significant hypotension (typically SBP < 80 mm Hg) or worsening renal function during therapy, or**
- **who is being considered for cardiac transplant and needs assessment of degree and reversibility of pulmonary hypertension, or**
- **in whom documentation of an adequate hemodynamic response to the inotropic agent is necessary when chronic outpatient infusion is being considered. (Strength of Evidence = C)**

Background

Treating symptoms and improving the hemodynamic profile of patients admitted with HF generally can be guided by skilled clinical assessment and laboratory evaluation. Direct hemodynamic monitoring by right heart catheterization has been advocated in the management of hospitalized patients with advanced HF to (1) guide therapy by permitting direct tracking of filling pressures and systemic vascular resistance until certain specific hemodynamic goals are reached and (2) assist in understanding volume status and tissue perfusion by direct determination of the extent and type of hemodynamic abnormalities present.[139]

The first concept, that treatment to a specific hemodynamic goal through the use of invasive hemodynamic monitoring may be of value in patients admitted with advanced HF, has been evaluated recently in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial.[140] Hemodynamically guided therapy did not increase the number of days alive and out of hospital over the course of 6 months compared with standard management alone.[141]

Given the neutral results of ESCAPE, it is reasonable to ask whether or not there are patients admitted with ADHF who still need invasive hemodynamic monitoring. Patients with a clear clinical need for right heart catheterization were excluded from ESCAPE. Examples would include patients with cardiogenic shock. Uncertainty concerning the hemodynamic state of individual patients following careful clinical evaluation and initial therapy remains a reasonable indication for direct determination of hemodynamics. Invasive monitoring may benefit patients who are hypotensive, fail to respond to diuretic therapy, or have worsening renal function but unknown filling pressures and cardiac output. The need for invasive hemodynamics often becomes apparent as treatment progresses.

Clinical estimation or measurement of right atrial pressure usually correlates with left-sided filling pressures both at a single time point and during changes induced by medications. However, pulmonary disease or disproportionate right HF may alter this relationship. Right heart catheterization can assess LV filling pressures as long as accurate PCWP tracings can be obtained and there is no significant stenosis of the pulmonary veins or mitral valve. Complications associated with use of intra-cardiac catheters include ventricular arrhythmias and line-related infection. Incorrect interpretation of hemodynamic data or overtreatment based on data may also lead to adverse outcomes.[142,143]

Precipitating Factors

Recommendation

12.23 It is recommended that patients admitted with ADHF undergo evaluation for the following precipitating factors: atrial fibrillation or other arrhythmias (eg, atrial flutter, other supraventricular tachycardia or ventricular tachycardia), exacerbation of hypertension, myocardial ischemia/infarction, exacerbation of pulmonary congestion, anemia, thyroid disease, significant drug interactions, and other less common factors. (Strength of Evidence = C)

Background

A number of precipitating factors (see Table 12.6) may worsen cardiac function and volume status, resulting in an episode of ADHF. Proper detection and treatment of

Table 12.6. Common and Uncommon Precipitating Factors Associated With Hospitalization for ADHF

Dietary and medication related causes
Dietary indiscretion - excessive salt or water intake
Nonadherence to medications
latrogenic volume expansion
Progressive cardiac dysfunction
Progression of underlying cardiac dysfunction
Physical, emotional, and environmental stress
Cardiac toxins: alcohol, cocaine, chemotherapy
Right ventricular pacing
Cardiac causes not primarily myocardial in origin
Cardiac arrhythmias: atrial fibrillation with a rapid ventricular response, ventricular tachycardia, marked bradycardia, and conduction abnormalities
Uncontrolled hypertension
Myocardial ischemia or infarction
Valvular disease: progressive mitral regurgitation
Non-cardiac causes
Pulmonary disease - pulmonary embolus, COPD
Anemia, from bleeding or relative lack of erythropoietin or bone marrow suppression
Systemic infection; especially pulmonary infection, urinary tract infection, viral illness
Thyroid disorders
Adverse cardiovascular effects of medications
Cardiac depressant medications
Nondihydropyridine calcium antagonists
Type la and Ic antiarrhythmic agents
Sodium retaining medications
Steroids
Nonsteroidal anti-inflammatory drugs, COX-2 inhibitors, thiazolidinediones, pregabalin

precipitating factors is an important part of the management of ADHF and a key to preventing recurrent episodes.

Process of Care and Adherence Issues. A number of factors not directly related to the circulatory pathophysiology of HF often contribute in a substantial way to hospitalization for ADHF. These precipitating factors are the target of disease management programs which are a critical factor in limiting recurrent admission for HF in many patients.

Dietary Indiscretion. Excessive sodium intake is a well recognized precipitating factor for admission for ADHF. Less well understood is the role of excessive water intake. A careful review of the patient's dietary history is a critical part of the assessment of patients admitted with ADHF.

Medication Nonadherence. Lack of access to medication for financial reasons or from access to care problems is a major cause of nonadherence which may be addressed during hospital admission.

Latrogenic Volume Overload. ADHF may be precipitated by inappropriate administration of fluid related to surgical or other procedures. Volume status may be difficult to assess in certain clinical conditions (eg, pulmonary infection) and inaccurate assessment of volume status may yield to unwarranted volume replacement. Patients with chronic HF and symptomatic hypotension do not require fluid resuscitation, and those with mild orthostatic hypotension may improve with liberalization of oral fluid intake.

Progressive Cardiac Dysfunction. Progression of underlying cardiac dysfunction with ventricular remodeling is an important cause of ADHF and if present will necessitate changes in chronic therapy. Progressive cardiac dysfunction is not always a consequence of worsening underlying disease, but may reflect adverse concomitant problems, such as pneumonia, uncontrolled diabetes, alcohol withdrawal, or cocaine use.

Atrial Fibrillation. The onset of atrial fibrillation is accompanied by the loss of coordinated atrial contraction, which may have detrimental hemodynamic effects. Uncontrolled atrial fibrillation with rapid heart rate is particularly troublesome to patients with HF. Ventricular filling may be compromised further, myocardial oxygenation adversely affected and myocardial contractility diminished. Atrial flutter or tachycardia with a 2:1 AV block may masquerade as or be mistaken for sinus tachycardia.

Uncontrolled Hypertension. Uncontrolled hypertension is a very common finding in patients admitted with ADHF. Data from the ADHERE registry indicate that approximately 50% of patients admitted with this syndrome have blood pressure $>140/90$ mm Hg.[2] Hospitalization for ADHF provides another opportunity to add medication aimed at improving long-term control of hypertension. However, excessive dosing of antihypertensive medication during concomitant diuresis may result in symptomatic orthostasis.

Myocardial Ischemia/Infarction. The occurrence of myocardial ischemia and infarction are significant, potentially treatable precipitants of acute exacerbation of HF. Use of coronary angiography and noninvasive imaging to determine the presence and extent of myocardial ischemia is important in the evaluation of patients with acute as well as chronic HF. Patients with HF complicating acute coronary syndrome often require rapid coronary angiography and intervention in the catheterization laboratory. Considerations that determine the diagnostic approach toward ischemic heart disease are often similar in patients with acute and chronic HF (see Section 13).

Other Precipitants of Acute HF. A number of other factors, many of which are preventable or avoidable, may be primary or secondary causes of hospital admission for HF.

Right Ventricular (RV) Pacing. If the underlying heart rate slows over time in response to beta blockers or for other reasons, patients with RV pacemakers may pace more frequently. In some patients, the increase in RV pacing may lead to myocardial dysfunction, presumably from the dyssynchrony produced by the pacing.[144]

Pulmonary Disease. Even minor congestion may be poorly tolerated in the presence of chronic obstructive pulmonary disease (COPD) because volume expansion easily impairs the already limited pulmonary function in these patients. Both HF and COPD increase the risk of pulmonary infections, which can cause ADHF. Sleep disordered breathing may exacerbate HF through adverse hemodynamic changes, hypoxia and fluid retention.

Anemia. The presence of anemia has been associated with increased risk of admission for ADHF. The reduction in hemoglobin may be profound in cases where bleeding, especially gastrointestinal, is a cause, or end-stage renal disease is the principal mechanism.

Thyroid Diseases. Hypo- or hyperthyroidism may exacerbate the signs and symptoms of HF. Up to 20% of patients hospitalized for ADHF are already being treated for thyroid disease. Therefore, evaluation of patients' thyroid therapy is recommended. For patients taking amiodarone, worsening HF with emergence of tachyarrhythmias may be due to amiodarone-induced thyrotoxicosis.

Noncardiac Medications. A number of medications, both cardiac and noncardiac, can precipitate or contribute to an episode of worsening HF. Medications for diabetes, including pioglitazone or rosiglitazone, may lead to peripheral edema, which can be associated with adverse clinical and hemodynamic effects. Similar effects are seen with pregabalin, which is frequently used to treat diabetic neuropathy.[146] Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors can promote sodium and fluid retention, interfere with the pharmacologic mechanism of ACE inhibitors, worsen renal function, and decrease the effectiveness of loop diuretics. Tricyclic antidepressants, whether used to treat depression or neuropathy, may cause cardiac conduction delays and increase the risk for ventricular arrhythmia. Theophylline and beta agonist bronchodilators may exacerbate HF by inducing tachyarrhythmias, including atrial fibrillation and flutter and ventricular arrhythmias. Over-the-counter drugs containing pseudoephedrine can aggravate hypertension, worsen HF by enhancing the activation of the sympathetic nervous system, and predispose to arrhythmias. Certain calcium antagonists and anti-arrhythmics may impair cardiac function and result in worsening HF.

Recommendation

12.24 It is recommended that every effort be made to use the hospital stay for assessment and improvement of patient adherence via patient and family education and social support services (see Section 8). (Strength of Evidence = B)

Background

Hospital admission provides the opportunity to educate patients concerning their HF and to reinforce both pharmacologic and non-pharmacologic approaches to management. Education in the hospital should be focused, because retention may be limited. Particular attention should be paid to the basic facts of HF, monitoring of fluid status, and medications. Identifying patients with limited social and family support before discharge may promote the development of a support system. Establishing support systems for patients with financial constraints is critical to their ability to obtain prescribed medications and access follow-up care. In a randomized, controlled trial of 233 hospitalized HF patients, a 1-hour pre-discharge teaching session directed by a nurse educator improved clinical outcomes and reduced cost of care.[64]

Hospital Discharge

Recommendation

12.25 It is recommended that criteria in Table 12.7 be met before a patient with HF is discharged from the hospital. (Strength of Evidence = C)

In patients with advanced HF or recurrent admissions for HF, additional criteria listed in Table 12.7 should be considered. (Strength of Evidence = C)

Background

Criteria for determining the optimal length of stay for individual patients admitted with ADHF remains to be established by rigorous clinical studies. Care must be taken to avoid premature discharge of patients with decompensated HF. The discharge criteria recommended here balance the need for adequate symptom relief and acceptably low readmission rates against the need for economical care.

Timing of discharge is further complicated by the fact that assessment of volume status can be difficult. As a result, patients with persistent volume overload are sometimes released prematurely. Patients who require several days of intravenous

Table 12.7. Discharge Criteria for Patients With HF

Recommended for all HF patients	• Exacerbating factors addressed. • Near optimal volume status observed. • Transition from intravenous to oral diuretic successfully completed. • Patient and family education completed, including clear discharge instructions • LVEF documented • Smoking cessation counseling initiated • Near optimal pharmacologic therapy achieved, including ACE inhibitor and beta blocker (for patients with reduced LVEF), or intolerance documented (Sections 7 and 11) • Follow-up clinic visit scheduled, usually for 7-10 days
Should be considered for patients with advanced HF or recurrent admissions for HF	• Oral medication regimen stable for 24 hours • No intravenous vasodilator or inotropic agent for 24 hours • Ambulation before discharge to assess functional capacity after therapy • Plans for postdischarge management (scale present in home, visiting nurse or telephone follow up generally no longer than 3 days after discharge) • Referral for disease management, if available

medications need a period of observation free of such support before discharge. In most cases, stability for 24 hours after discontinuation of intravenous therapy is sufficient to assess the likelihood that the patient will continue symptomatic improvement on oral medications alone. Meeting all criteria for discharge should be more stringently enforced in patients with advanced HF, especially the elderly, because they are at highest risk for readmission. Observation for a period of 24 hours after discontinuation of vasoactive or inotropic support is ideal, but shorter periods may suffice for patients whose symptoms have significantly improved and who tolerate weaning of intravenous support well.

Patients likely to need home care should have these plans developed and implemented before discharge. The hospital setting generally provides more resources for establishing this type of care plan than are available in outpatient settings.

Recommendation

12.26 Discharge planning is recommended as part of the management of patients with ADHF. Discharge planning should address the following issues:

- **Details regarding medication, dietary sodium restriction, and recommended activity level**
- **Follow-up by phone or clinic visit early after discharge to reassess volume status**
- **Medication and dietary adherence**
- **Alcohol moderation and smoking cessation**
- **Monitoring of body weight, electrolytes and renal function**
- **Consideration of referral for formal disease management. (Strength of Evidence = C)**

Background

The risk of readmission is highest just after hospitalization. Careful monitoring of patients soon after discharge may be useful in limiting the likelihood of readmission. Some patients have a tendency to become rapidly congested following discharge. Follow-up soon after discharge, either by phone or clinic visit, provides the opportunity to rapidly reevaluate the patient's volume status and to modify therapy to maintain control of congestion. It may be difficult to discharge patients on the dose of diuretic they probably need to maintain a euvolemic state after discharge when they have experienced a significant loss of fluid and have been maintained on a low sodium diet while in the hospital.

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