

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 compliance, 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 EF 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.

Recommendation

12.1 The diagnosis of 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 should be considered 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.

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.

Diagnostic Utility of Natriuretic Peptides. Two forms of natriuretic peptide, 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.⁹

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 (BNP), provides important evidence supporting the clinical utility of plasma BNP in the assessment of patients presenting with possible HF.^{10,11} 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

1071-9164/\$ - see front matter
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doi:10.1016/j.cardfail.2005.11.017

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 LV function was depressed or preserved.¹² 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.^{13,14}

The clinical utility of NT-proBNP in the diagnosis of heart failure 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 congestive HF in 600 patients who presented with dyspnea.¹⁵ NT-proBNP results were correlated with a clinical diagnosis of acute CHF as determined by study physicians blinded to these measurements. The median NT-proBNP level among the 209 patients who had acute CHF (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.

Prognostic Role of BNP. Although baseline BNP levels may correlate only modestly with pulmonary capillary wedge pressure (PCWP), changes in PCWP do correlate directly with change in BNP concentration during hospitalization.^{16,17} The predischARGE BNP after treatment for acute HF appears to predict patients at risk of early readmission or death following hospitalization for HF.^{18,19} 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 acute heart failure.^{19,20}

Triage Value of BNP. 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, they do not suggest that triage using BNP resulted in the undertreatment of patients truly at risk. The readmission rate for heart failure was similar in the 2 study groups and the mortality rate, while not reduced statistically, was lower in those patients with BNP determined. Additional, larger randomized trials of this strategy are needed to assess the impact of this approach on adverse outcomes associated with admission for ADHF.

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.²¹ 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.²² 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.¹² In addition, the biologic variability of the assays for B-type natriuretic peptides is nearly 100%.²³ This variability makes interpretation of day-to-day measurements problematic.

Interpretation of natriuretic hormone levels can be problematic in patients with pulmonary disease. BNP and NT-Pro BNP may be increased in patients with pulmonary embolus or cor pulmonale resulting from right HF in the absence of congestion.²⁴ 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.²⁵

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 concerning 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,

Table 12.1. Recommendations for Hospitalizing Patients Presenting With ADHF

Recommendation	Clinical Circumstances
(a) Hospitalization Recommended	Evidence of severely decompensated HF, including: <ul style="list-style-type: none"> • Hypotension • Worsening renal function • Altered mentation Dyspnea at rest <ul style="list-style-type: none"> • Typically reflected by resting tachypnea • Less commonly reflected by oxygen saturation <90% Hemodynamically significant arrhythmia <ul style="list-style-type: none"> • Including new onset of rapid atrial fibrillation Acute coronary syndromes
(b) Hospitalization Should Be Considered	Worsened congestion <ul style="list-style-type: none"> • Even without dyspnea • Typically reflected by a weight gain of ≥5 kg Signs and symptoms of pulmonary or systemic congestion <ul style="list-style-type: none"> • Even in the absence of weight gain Major electrolyte disturbance Associated comorbid conditions <ul style="list-style-type: none"> • 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

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 overload manifested by signs and symptoms of either pulmonary or systemic congestion (Table 12.2).² Most patients with signs and symptoms of volume overload will present with weight gain. However, some will show no weight gain due to concomitant loss of lean body mass.

Table 12.2. Signs and Symptoms of Congestion in HF

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

*May occur without congestion.

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)

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

Table 12.3. Treatment Goals for Patients Admitted for ADHF

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

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.²⁶ 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.

Adverse Effects of Therapy. High-dose diuretic therapy is a marker for increased mortality during hospitalization for HF, as it is in chronic HF.^{27,28} 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, and volume depletion. Treatments that effectively relieve symptoms in patients with ADHF, such as diuretics, 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.²⁹ 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.³⁰ 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.³¹ One outcome study comparing dobutamine to levosimendan suggested greater risk in patients randomized to dobutamine.³²

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 compliance, 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 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.

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

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	Including orthostatic blood pressure
At least daily	Signs	Edema Ascites Pulmonary rales Hepatomegaly Increased JVP Hepatojugular reflux Liver tenderness
At least daily	Symptoms	Orthopnea Paroxysmal nocturnal dyspnea (PND) Nocturnal cough Dyspnea Fatigue
At least daily	Electrolytes	Potassium Sodium
At least daily	Renal function	BUN Serum creatinine*

*See background section for additional recommendations on laboratory evaluations.

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, PND, 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 from 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 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. 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 mortality in patients with acute heart failure.^{21,22,24,25,27-35} 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, but these modest increases have been associated with long-term reductions in mortality and hospital admissions in chronic HF.^{36,37}

Routine and frequent laboratory tests recommended in ADHF are shown in Table 12.5.

Table 12.5. Laboratory Evaluation for Patients With ADHF

Routinely	Electrolytes BUN and creatinine Blood glucose Troponin Complete blood count INR if using Coumadin
Frequently	Oxygen saturation BNP or NT-proBNP Liver function tests Urinalysis D-dimer Arterial blood gases

Electrolytes, BUN, and creatinine and troponin have been discussed. A complete blood count will exclude anemia. An oxygen saturation test will determine the need for 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 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. D-dimer should be used as suggested in guidelines to exclude pulmonary embolus.

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)

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. Oral furosemide is only 40% biogradable under ideal circumstances. This rate is highly variable from patient to patient and even from day to day in the same patient and is often considerably lower in patients with severe HF. Furosemide, a commonly used loop diuretic, has a short duration 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 improve response to diuretics if the current dose is insufficient to achieve maximal delivery of drug to the 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.³⁸ In contrast, administration of intravenous furosemide has been associated with neurohormonal activation, which may result in worsening of hemodynamics secondary to vasoconstriction in the early stages of therapy.³⁹ However, as sodium excretion increases and diuresis ensues, volume loss leads to a reduction in PCWP and improvement in symptoms.³⁹

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 intravascular volume, which may result in symptomatic hypotension and/or worsening renal function. (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. (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, and symptomatic hypotension, 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)**

Serum potassium and magnesium levels should 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, which should be treated with potassium replacement if indicated. (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.⁴⁰ Patients treated with diuretics should be monitored carefully for excessive urine output, development of hypotension, and reductions in serum potassium, magnesium, and renal function. 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.

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.⁴¹ 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 cardiomyopathy 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. During therapy for ADHF, diuretics appear to increase activation of neurohormonal systems considered maladaptive in HF. Enhanced activity of the RAS and the sympathetic system may occur with diuretics, and can result in secondary increases in systemic vascular resistance.^{42,43} Whether these changes have long-term adverse effects in patients with ADHF or limit the effectiveness of these agents 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, in turn impeding restoration of euvoemia.^{43,44}

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. Clearly, congested patients with acute HF with evidence of renal insufficiency should be treated with diuretics even as they need careful monitoring of renal function to minimize risk.

Recommendation

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

- 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).

A fifth 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.

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. One randomized crossover study compared the efficacy of continuous infusion of furosemide versus an equivalent dose of the agent given in a single bolus injection.⁴⁵ This study enrolled patients who were in New York Heart Association class III or IV HF and on oral doses of at least 250 mg furosemide per day. Patients on continuous infusion (mean total daily dosage 690 mg, range 250 to 2000, approximately 10 to 83 mg/hour) had a greater urine output, lower maximal furosemide plasma concentration and fewer adverse effects than patients on an equivalent dose of bolus medication.

Ultrafiltration. Mechanical methods of fluid removal are being actively investigated as potential alternatives to pharmacologic diuresis.⁴⁶ Small uncontrolled studies have long suggested the utility of this approach using not only traditional dialysis but hemofiltration methods.⁴⁷ More recently, 2 studies examined the utility of a peripheral venovenous system.^{48,49} Randomized controlled clinical trials are underway to evaluate the potential use of this treatment modality in patients with acute HF.

Recommendation

12.12 A low sodium diet (2 g daily) is recommended, as is supplemental oxygen as needed for hypoxemia. (Strength of Evidence = C)

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

Background

Dietary sodium restriction is important, even short-term in the hospital setting, to help restore euvoemia. The level of sodium restriction prescribed during hospitalization may be greater than typically feasible in the outpatient setting.

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.⁵⁰ 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 compliance.

Recommendation

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

Background

Supplemental oxygen therapy should be individualized. The congested dyspneic patient who presents with oxygen desaturation requires oxygen therapy. Patients with systemic fluid overload that does not compromise oxygenation do not require oxygen therapy.

Recommendation

12.15 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 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 reduces pulmonary congestion.⁵¹ 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 myocardial infarction. Nitroglycerin therapy results in neurohormonal activation; whether this has a detrimental effect in acute HF is uncertain.^{51,52} Based on physiologic considerations, it is not expected that the use of nitroglycerin in patients with ADHF would have a direct effect on renal function.

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.⁵³ 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.^{54,55} 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 and symptomatic hypotension. 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 400 mcg. Thiocyanate toxicity is rare when nitroprusside is used by an experienced care team.

Nesiritide. A number of cardiovascular, renal, and neurohormonal effects of BNP have been identified.^{56,57} Nesiritide, a peptide identical to human B-type natriuretic peptide, 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.⁵⁸⁻⁶¹ At the currently recommended dose (0.01 µg/kg), nesiritide significantly reduces LV filling pressure but has variable effects on cardiac output.⁶² A reduction in circulating aldosterone levels has been observed.⁶³

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.^{63,64} 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.⁶² Patients had evidence of elevated cardiac filling pressures, either by clinical examination or documented by a directly measured PCWP of ≥20 mm Hg. The study used a dose of nesiritide (bolus of 2 µg/kg followed by an infusion of 0.01 µg/kg/min) designed from pharmacokinetic and pharmacodynamic data to decrease the time to onset of initial hemodynamic effects and to reduce the blood pressure-lowering action of the drug over longer periods. Study treatment (either nesiritide or intravenous nitroglycerin) was to be continued for at least 24 hours as tolerated. 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 ($P = .03$). Although hemodynamic data was limited after 24 hours because of the nature of the protocol design, an effect of nesiritide on PCWP (change from baseline) was sustained throughout this period and appeared to be present up to 48 hours with few dose increases (ie, no apparent tachyphylaxis).

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. The risk of hypotension appears to be reduced in the absence of volume depletion, so correct assessment of fluid status will help to minimize this side effect. If rapid onset of hemodynamic effect is not needed, the bolus dose of nesiritide can be omitted, which may lessen the risk of symptomatic hypotension, although this strategy has not been tested in controlled trials. Headache is not a common side effect and only infrequently is severe enough to warrant discontinuation of the drug.

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 RAS 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 $> .5$ mg/dL during the study period.⁶⁵ 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.⁶⁵

Whether the worsening renal function induced by nesiritide is associated with adverse outcomes in patients with ADHF is uncertain. There is clear evidence from database studies that worsening renal function during an episode of ADHF is associated with increased mortality.^{33–35} However, worsening renal function induced by other neurohormonal antagonists, such as ACE inhibitors, is not predictive of worsened survival.³⁷ 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.

The current guideline has stressed the importance of careful monitoring of renal function in patients admitted with ADHF and this certainly applies to patients treated with nesiritide. Potential strategies to reduce the risk of renal dysfunction during nesiritide therapy include use of the drug at the recommended dose with titration dictated by clinical response as tolerated, adjustment of concomitant diuretic therapy and avoidance of hypotension.

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.⁶⁶ However, the data overall do not provide convincing evidence of an adverse effect of nesiritide on mortality in patients with ADHF. The potential for the drug to produce hypotension and worsening renal function, as well as lack of outcome data at the currently recommended dose, points to the need for more data concerning the effect of nesiritide on renal function and mortality in ADHF. Additional, well designed and adequately powered prospective studies are warranted to determine the effect of this drug on outcomes in patients with ADHF.

Recommendation

12.16 Intravenous vasodilators (intravenous 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 of 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

myocardial infarction, requirement for mechanical ventilation or death than those treated primarily with a more aggressive diuretic regimen.⁶⁷

Recommendations

12.17 Intravenous vasodilators (nitroprusside, nitroglycerin, or nesiritide) may be considered in patients with ADHF and advanced HF who have persistent severe HF despite aggressive treatment with diuretics and standard oral therapies. (Strength of Evidence = C)

12.18 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 = B)

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

Administration of intravenous inotropes (milrinone or dobutamine) in the setting of ADHF should 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 as severe LV systolic dysfunction with

ventricular dilation and marked chronic clinical symptoms, represent a major therapeutic challenge.^{68,69} 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. Although there are no randomized controlled trials comparing vasodilators in lieu of inotropes in this population. 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.

However, 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 and ADHF and 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.

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. Afterload 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 a potent dilator of the pulmonary circulation and 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. Sodium nitroprusside has been noted to increase mortality rates when given to patients within 48 hours of an acute MI who are not in HF.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.⁷⁰

Sodium nitroprusside should be initiated at a rate dose of 5 to 10 $\mu\text{g}/\text{min}$. Doses exceeding 400 $\mu\text{g}/\text{min}$ 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.

Milrinone and Dobutamine. Milrinone, often termed an inodilator, causes, in the short term, increased myocardial contractility and decreased systemic and pulmonary vascular tone.⁷¹ 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, an important observation in patients being considered for cardiac transplantation.⁷² Because dobutamine does not act as a pulmonary artery vasodilator, it typically has little direct 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.⁷³

In contrast to dobutamine, the hemodynamic effects of milrinone are not mediated by stimulation of β -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 β -blocking drugs. To avoid discontinuation of β -blockade, some clinicians use this agent for hemodynamic support of patients who are hospitalized with worsening HF while on β -blocker therapy.

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 OPTIME-CHF trial, even though the initial dose was 0.5 $\mu\text{g}\cdot\text{kg}\cdot\text{min}$ 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.⁷⁴ An increase of approximately 50% in cardiac index occurs during this brief period. Initial doses of 0.1 $\mu\text{g}\cdot\text{kg}\cdot\text{min}$ and final doses of 0.2 to 0.3 $\mu\text{g}\cdot\text{kg}\cdot\text{min}$ 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 $\mu\text{g}\cdot\text{kg}\cdot\text{min}$.

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, not a low output state, as the major reason for admission.^{2,26} No clinical benefits and evidence of adverse effects were found from the administration of milrinone in the study Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHE). The trial, discussed in more detail below, enrolled patients presenting with congestion rather than poor perfusion with end-organ dysfunction (low output syndrome) who were not felt to need inotropic therapy. 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.^{50,75} It should be remembered that differences in outcomes across nonrandomized groups, such as are observed in the ADHERE study, may reflect, at least in part, a difference in HF severity across these groups. However these data support the potential for adverse effects of inotropes on outcomes—among patients *who do not meet the clinical criteria delineated in Recommendation 12.18*.

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 the broad population of patients admitted with ADHF and systolic dysfunction, but without “low-output syndrome”—a population not usually considered for inotropic therapy. OPTIME-CHF specifically evaluated the benefits of adding milrinone to standard therapy in patients hospitalized with ADHF. A total of 949 patients were randomized to a 48-hour infusion of milrinone ($0.50 \mu\text{g}\cdot\text{kg}\cdot\text{min}$) 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 non-significant 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. Retrospective analysis also showed that there was a 30% increase in mortality in patients randomized to milrinone versus placebo among those patients with ischemic heart disease assigned as their primary etiology of heart failure.⁷⁶ The study authors of the OPTIME-CHF study concluded that milrinone therapy was not indicated for routine use as an adjunct to standard therapy in patients with an exacerbation of HF.

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 12.18. 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 placement of an assist device. 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.

Recommendations

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

12.20 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
- 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.⁷⁷

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.⁷⁸ 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.⁷⁹

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.

Recommendation

12.21 It is recommended that patients admitted with ADHF undergo evaluation for the following precipitating factors: atrial fibrillation or other arrhythmias (eg, atrial flutter, other SVT or VT), 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 precipitating factors is an important part of the management of ADHF and a key to preventing recurrent episodes.

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	
Iatrogenic volume expansion	
Progressive cardiac dysfunction	
Progression of underlying cardiac dysfunction	
Physical, emotional, and environmental stress	
Cardiac toxins: alcohol, cocaine	
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	
Acute myocardial infarction	
Myocardial ischemia	
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	
Thyroid disorders	
Adverse cardiovascular effects of medications	
Cardiac depressant medications	
Nondihydropyridine calcium antagonists	
Type Ia and Ic antiarrhythmic agents;	
Sodium retaining medications	
steroids;	
nonsteroidal anti-inflammatory drugs,	
Medications that reduce contractility	
anthracyclines and other chemotherapeutic agents	

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

Iatrogenic 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.

Progressive Cardiac Dysfunction. Progression of underlying cardiac dysfunction with worsening of myocardial muscle function with ventricular remodeling and enlargement 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.

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.

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 admission for HF.

Right Ventricular Pacing. If the underlying heart rate slows over time in response to β -blockers or for other reasons, patients with right ventricular 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.⁸⁰

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. Obstructive sleep apnea 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.

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. Nonsteroidal anti-inflammatory drugs 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 β -agonist bronchodilators may exacerbate HF by inducing tachyarrhythmias, including atrial fibrillation and flutter and ventricular arrhythmia. 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

12.22 It is recommended that every effort be made to use the hospital stay for assessment and

improvement of patient compliance via patient and family education and social support services (see Section 8). (Strength of Evidence = C)

Background

Hospital admission provides the opportunity to educate patients concerning their HF and to reinforce both pharmacologic and nonpharmacologic 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.

Recommendation

12.23 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 acceptable 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

Table 12.7. Discharge Criteria for Patients With HF

Recommended for all HF patients	<ul style="list-style-type: none"> • Exacerbating factors addressed. • At least near optimal volume status achieved. • Transition from intravenous to oral diuretic successfully completed. • Patient and family education completed. • At least near optimal pharmacologic therapy achieved (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	<ul style="list-style-type: none"> • 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

released prematurely. Patients who require several days of intravenous 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, 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

12.24 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 compliance**
- **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, presents 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.

References

1. U.S. Department of Health and Human Services, Health Care Finance Organization. MEDPAR Inpatient Hospital Datafile, Fiscal Year 1998. Washington DC: Bureau of Data Management and Strategy; 1999: June Update.
2. Adams KF Jr, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (AD-HERE). *Am Heart J* 2005;149:209–16.
3. Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA* 2005; 293:572–80.
4. Krumholz HM, Parent EM, Tu N, Vaccarino V, Wang Y, Radford MJ, et al. Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997; 157:99–104.
5. American Heart Association. Heart disease and stroke statistics—2004 update. Dallas TX: American Heart Association; 2004.
6. Blackledge HM, Tomlinson J, Squire IB. Prognosis for patients newly admitted to hospital with heart failure: survival trends in 12 220 index admissions in Leicestershire 1993–2001. *Heart* 2003;89:615–20.
7. Felker GM, Adams KF Jr, Konstam MA, O'Connor CM, Gheorghade M. The problem of decompensated heart failure: nomenclature, classification, and risk stratification. *Am Heart J* 2003; 145(Suppl):S18–25.
8. Baig MK, Mahon N, McKenna WJ, Caforio AL, Bonow RO, Francis GS, et al. The pathophysiology of advanced heart failure. *Am Heart J* 1998;135:S216–30.
9. Maisel AS, McCullough PA. Cardiac natriuretic peptides: a proteomic window to cardiac function and clinical management. *Rev Cardiovasc Med* 2003;(Suppl 4):S3–S12.
10. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002;347:161–7.
11. Baughman KL. B-type natriuretic peptide—a window to the heart. *N Engl J Med* 2002;347:158–9.
12. Maisel AS, McCord J, Nowak RM, Hollander JE, Wu AH, Duc P, et al. Bedside B-type natriuretic peptide in the emergency diagnosis of heart failure with reduced or preserved ejection fraction. Results from the Breathing Not Properly Multinational Study. *J Am Coll Cardiol* 2003;41:2010–7.
13. Maisel AS, Clopton P, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, et al. Impact of age, race, and sex on the ability of B-type natriuretic peptide to aid in the emergency diagnosis of heart failure: results from the Breathing Not Properly (BNP) multinational study. *Am Heart J* 2004;147:1078–84.
14. Redfield MM, Rodeheffer RJ, Jacobsen SJ, Mahoney DW, Bailey KR, Burnett JC Jr. Plasma brain natriuretic peptide concentration: impact of age and gender. *J Am Coll Cardiol* 2002;40:976–82.
15. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department (PRIDE) study. *Am J Cardiol* 2005;95: 948–54.
16. Forfia PR, Watkins SP, Rame JE, Stewart KJ, Shapiro EP. Relationship between B-type natriuretic peptides and pulmonary capillary wedge pressure in the intensive care unit. *J Am Coll Cardiol* 2005;45: 1667–71.
17. Kazanegra R, Cheng V, Garcia A, Krishnaswamy P, Gardetto N, Clopton P, et al. A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. *J Card Fail* 2001;7:21–9.
18. Cheng V, Kazanegra R, Garcia A, Lenert L, Krishnaswamy P, Gardetto N, et al. A rapid bedside test for B-type peptide predicts treatment outcomes in patients admitted for decompensated heart failure: a pilot study. *J Am Coll Cardiol* 2001;37:386–91.
19. Logeart D, Thabut G, Jourdain P, Chavelas C, Beyne P, Beauvais F, et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol* 2004;43:635–41.
20. Gackowski A, Isnard R, Golmard JL, Pousset F, Carayon A, Montalescot G, et al. Comparison of echocardiography and plasma B-type natriuretic peptide for monitoring the response to treatment in acute heart failure. *Eur Heart J* 2004;25:1788–96.

21. Cowie MR, Jourdain P, Maisel A, Dahlstrom U, Follath F, Isnard R, et al. Clinical applications of B-type natriuretic peptide (BNP) testing. *Eur Heart J* 2003;24:1710–8.
22. Tang WH, Girod JP, Lee MJ, Starling RC, Young JB, Van Lente F, et al. Plasma B-type natriuretic peptide levels in ambulatory patients with established chronic symptomatic systolic heart failure. *Circulation* 2003;108:2964–6.
23. Wu AH, Smith A. Biological variation of the natriuretic peptides and their role in monitoring patients with heart failure. *Eur J Heart Fail* 2004;6:355–8.
24. Yap LB, Mukerjee D, Timms PM, Ashrafian H, Coghlan JG. Natriuretic peptides, respiratory disease, and the right heart. *Chest* 2004;126:1330–6.
25. Mark DB, Felker GM. B-type natriuretic peptide—a biomarker for all seasons? *N Engl J Med* 2004;350:718–20.
26. Nohria A, Tsang SW, Fang JC, Lewis EF, Jarcho JA, Mudge GH, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 2003;41:1797–804.
27. Gupta S, Neyses L. Diuretic usage in heart failure: a continuing conundrum in 2005. *Eur Heart J* 2005;26:644–9.
28. Neuberg GW, Miller AB, O'Connor CM, Belkin RN, Carson PE, Cropp AB, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. *Am Heart J* 2002;144:31–8.
29. Gheorghiane M, Gattis WA, Adams KF Jr, Jaffe AS, O'Connor CM. A prospective randomized study of nesiritide versus dobutamine in decompensated heart failure (PRESERVED-HF): Design and preliminary data. *J Card Fail* 2003;9:S63.
30. Eichhorn EJ, Bristow MR. Medical therapy can improve the biological properties of the chronically failing heart. A new era in the treatment of heart failure. *Circulation* 1996;94:2285–96.
31. Schulz R, Rose J, Martin C, Brodde OE, Heusch G. Development of short-term myocardial hibernation. Its limitation by the severity of ischemia and inotropic stimulation. *Circulation* 1993;88:684–95.
32. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002;360:196–202.
33. Forman DE, Butler J, Wang Y, Abraham WT, O'Connor CM, Gottlieb SS, et al. Incidence, predictors at admission, and impact of worsening renal function among patients hospitalized with heart failure. *J Am Coll Cardiol* 2004;43:61–7.
34. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J* 2004;147:331–8.
35. Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, et al. The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail* 2002;8:136–41.
36. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;316:1429–35.
37. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000;160:685–93.
38. Verma SP, Silke B, Hussain M, Nelson GI, Reynolds GW, Richmond A, et al. First-line treatment of left ventricular failure complicating acute myocardial infarction: a randomised evaluation of immediate effects of diuretic, venodilator, arteriodilator, and positive inotropic drugs on left ventricular function. *J Cardiovasc Pharmacol* 1987;10:38–46.
39. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med* 1985;103:1–6.
40. Brater DC. Diuretic therapy. *N Engl J Med* 1998;339:387–95.
41. Stevenson LW, Tillisch JH. Maintenance of cardiac output with normal filling pressures in patients with dilated heart failure. *Circulation* 1986;74:1303–8.
42. Ikram H, Chan W, Espiner EA, Nicholls MG. Haemodynamic and hormone responses to acute and chronic frusemide therapy in congestive heart failure. *Clin Sci (Lond)* 1980;59:443–9.
43. Schrier RW, Martin PY. Recent advances in the understanding of water metabolism in heart failure. *Adv Exp Med Biol* 1998;449:415–26.
44. Channer KS, McLean KA, Lawson-Matthew P, Richardson M. Combination diuretic treatment in severe heart failure: a randomised controlled trial. *Br Heart J* 1994;71:146–50.
45. Dormans TP, van Meyel JJ, Gerlag PG, Tan Y, Russel FG, Smits P. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol* 1996;28:376–82.
46. Marenzi G, Agostoni P. Hemofiltration in heart failure. *Int J Artif Organs* 2004;27:1070–6.
47. Jaski BE, Ha J, Denys BG, Lamba S, Trupp RJ, Abraham WT. Peripherally inserted veno-venous ultrafiltration for rapid treatment of volume overloaded patients. *J Card Fail* 2003;9:227–31.
48. Costanzo MR, Saltzberg M, O'Sullivan J, Kotsos T. EUPHORIA trial: Early ultrafiltration therapy in patients with decompensated heart failure and observed resistance to intervention with diuretic agents. *J Card Fail* 2004;10(Suppl):S78.
49. Bart BA, Boyle A, Bank AJ, Anand I, Olivari MT, Kraemer M, et al. Randomized controlled trial of ultrafiltration versus usual care for hospitalized patients with heart failure: preliminary report of the Rapid Trial. *J Card Fail* 2004;10(Suppl):S23.
50. Klein L, O'Connor CM, Leimberger JD, Gattis-Stough W, Pina IL, Felker GM, et al. Lower serum sodium is associated with increased short-term mortality in hospitalized patients with worsening heart failure: results from the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) study. *Circulation* 2005;111:2454–60.
51. Elkayam U, Bitar F, Akhter MW, Khan S, Patrus S, Derakhshani M. Intravenous nitroglycerin in the treatment of decompensated heart failure: potential benefits and limitations. *J Cardiovasc Pharmacol Ther* 2004;9:227–41.
52. Parker JD. Counterregulatory responses: sustained-release isosorbide-5-monomonitrate versus transdermal nitroglycerin. *J Cardiovasc Pharmacol* 1996;28:631–8.
53. Dupuis J, Lalonde G, Lemieux R, Rouleau JL. Tolerance to intravenous nitroglycerin in patients with congestive heart failure: role of increased intravascular volume, neurohumoral activation and lack of prevention with N-acetylcysteine. *J Am Coll Cardiol* 1990;16:923–31.
54. Elkayam U, Group VS. Superior hemodynamic effect of nesiritide (B-type natriuretic peptide) compared to high dose nitroglycerine (NTG) in patients with decompensated heart failure. In: NAIP Fifth Annual Meeting; 2002. p. 7.
55. Fung HL, Bauer JA. Mechanisms of nitrate tolerance. *Cardiovasc Drugs Ther* 1994;8:489–99.
56. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. *N Engl J Med* 1998;339:321–8.
57. Johnston GD. Use of organic nitrates in the treatment of heart failure. *Fund Cardiovasc Pharm* 1999;6:140–2.
58. Abraham WT, Lowes BD, Ferguson DA, Odom J, Kim JK, Robertson AD, et al. Systemic hemodynamic, neurohormonal, and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. *J Card Fail* 1998;4:37–44.
59. Hobbs RE, Miller LW, Bott-Silverman C, James KB, Rincon G, Grossbard EB. Hemodynamic effects of a single intravenous injection of synthetic human brain natriuretic peptide in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1996;78:896–901.
60. Marcus LS, Hart D, Packer M, Yushak M, Medina N, Danziger RS, et al. Hemodynamic and renal excretory effects of human brain

- natriuretic peptide infusion in patients with congestive heart failure. A double-blind, placebo-controlled, randomized crossover trial. *Circulation* 1996;94:3184–9.
61. Mills RM, LeJemtel TH, Horton DP, Liang C, Lang R, Silver MA, et al. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure: a randomized, double-blind, placebo-controlled clinical trial. Natrecor Study Group. *J Am Coll Cardiol* 1999;34:155–62.
 62. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA* 2002; 287:1531–40.
 63. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. *N Engl J Med* 2000;343:246–53.
 64. Wang DJ, Dowling TC, Meadows D, Ayala T, Marshall J, Minshall S, et al. Nesiritide does not improve renal function in patients with chronic heart failure and worsening serum creatinine. *Circulation* 2004;110:1620–5.
 65. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005;111:1487–91.
 66. Sackner-Bernstein JD, Kowalski M, Fox M, Aaronson K. Short-term risk of death after treatment with nesiritide for decompensated heart failure: a pooled analysis of randomized controlled trials. *JAMA* 2005;293:1900–5.
 67. Cotter G, Metzko E, Kaluski E, Faigenberg Z, Miller R, Simovitz A, et al. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* 1998;351:389–93.
 68. Adams KF Jr, Zannad F. Clinical definition and epidemiology of advanced heart failure. *Am Heart J* 1998;135:S204–15.
 69. Gheorghiade M, Cody RJ, Francis GS, McKenna WJ, Young JB, Bonow RO. Current medical therapy for advanced heart failure. *Heart Lung* 2000;29:16–32.
 70. Cohn JN, Francis JA, Francis GS, Archibald D, Tristani F, Fletcher R, et al. Effect of short-term infusion of sodium nitroprusside on mortality rate in acute myocardial infarction complicated by left ventricular failure: results of a Veterans Administration cooperative study. *N Engl J Med* 1982;306:1129–35.
 71. Baim DS, McDowell AV, Cherniles J, Monrad ES, Parker JA, Edelson J, et al. Evaluation of a new bipyridine inotropic agent—milrinone—in patients with severe congestive heart failure. *N Engl J Med* 1983;309:748–56.
 72. Chen EP, Bittner HB, Davis RD, Van Trigt P. Hemodynamic and inotropic effects of milrinone after heart transplantation in the setting of recipient pulmonary hypertension. *J Heart Lung Transplant* 1998;17: 669–78.
 73. Monrad ES, Baim DS, Smith HS, Lanoue AS. Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. *Circulation* 1986;73:III168–74.
 74. Baruch L, Patacsil P, Hameed A, Pina I, Loh E. Pharmacodynamic effects of milrinone with and without a bolus loading infusion. *Am Heart J* 2001;141:266–73.
 75. Fonarow GC, Adams KF Jr, Strausser BP, for the ADHERE Scientific Advisory Committee and Investigators. ADHERE (Acute Decompensate Heart Failure National Registry): Rationale, design, and subject population. *J Card Fail* 2002;8(Suppl):S49.
 76. Felker GM, Benza RL, Chandler AB, Leimberger JD, Cuffe MS, Califf RM, et al. Heart failure etiology and response to milrinone in decompensated heart failure: results from the OPTIME-CHF study. *J Am Coll Cardiol* 2003;41:997–1003.
 77. Steimle AE, Stevenson LW, Chelimsky-Fallick C, Fonarow GC, Hamilton MA, Moriguchi JD, et al. Sustained hemodynamic efficacy of therapy tailored to reduce filling pressures in survivors with advanced heart failure. *Circulation* 1997;96:1165–72.
 78. Shah MR, O'Connor CM, Sopko G, Hasselblad V, Califf RM, Stevenson LW. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE): design and rationale. *Am Heart J* 2001;141:528–35.
 79. Binanay C, Califf RM, Hasselblad V, O'Connor CME, Shah MR, Sopko G, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. *JAMA* 2005;294:1625–33.
 80. Wilkoff BL, Cook JR, Epstein AE, Greene HL, Hallstrom AP, Hsia H, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. *JAMA* 2002;288:3115–23.