Beyond Diuretics: Management of Volume Overload in Acute Heart Failure Syndromes

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ABSTRACT

Diuretics are an established foundation of therapy for patients with chronic heart failure (HF) as well as for those hospitalized for treatment of acute HF syndromes. Despite the accepted use of diuretics in acute HF syndromes, treatment patterns with diuretics vary widely, and there are no data from randomized studies on the benefit of diuretics on morbidity or mortality in patients hospitalized with acute HF syndromes. Additional pharmacologic therapies that complement or replace diuretics in this setting, especially in patients with diuretic resistance, include positive inotropes, nitrovasodilators, and natriuretic peptides, but data are likewise lacking on important clinical outcomes. Ultrafiltration has also been used as a nonpharmacologic strategy to treat patients with acute HF syndromes who exhibit resistance to diuretics. Effective monitoring of volume status with newer modalities may allow more selective use of diuretics and diuretic-like modalities, but additional randomized trial data are clearly needed to establish ideal strategies to promote volume removal in acute HF syndromes. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Diuretics; Heart failure; Inotropes; Treatment; Vasodilators

Diuretic therapy is a well-established treatment modality used in the management of advanced heart failure (HF). These agents are recommended by current American College of Cardiology/American Heart Association (ACC/AHA) guidelines as first-line therapies for the treatment of congestion in patients with chronic HF.[1] However, limited data exist on the management of patients hospitalized with an episode of acute decompensated heart failure (ADHF), and there is wide variation in the management strategies to facilitate volume removal in the treatment of these patients.

Intravenous (IV) diuretics are currently considered routine therapy for volume overload in patients with ADHF.[2–5] Diuretics relieve symptoms of congestion, reduce intracardiac pressures, and improve cardiac performance.[3,4] As a result, >80% of patients who are hospitalized for ADHF receive an IV diuretic.[6] However, despite a >50-year tradition of use, evidence-based data supporting this therapy are lacking.[2–4,7] Limited randomized, controlled trials of IV diuretic therapy have been performed with less than compelling outcomes data.

WHY LOOK BEYOND DIURETICS?

Diuretic therapy in the management of volume-overloaded patients with ADHF can be dramatically effective. Diuretic therapy is inexpensive, easily administered, and applicable in a variety of treatment settings including emergency departments, intensive care units, and monitored and unmonitored units. For the patient with normal blood pressure and intact renal function, diuretic therapy may be sufficient to relieve the acute symptoms of decompensated HF. However, there are important limitations associated with the utility and tolerability of diuretic use. The greatest concerns include additional activation of the neurohormonal cascade,[8–13] electrolyte depletion,[2,4,14–16] worsening prerenal azotemia despite ongoing ex-

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tracellular fluid volume excess, arrhythmias,[17] and, in a very worrisome way, renal injury.[2,15,16,18–22]

Excessive use of parenteral loop diuretics such as furosemide has been shown to generate substantial activation of the renin-angiotensin-aldosterone system (RAAS).[8–13] This neurohormonal RAAS activation leads to further systemic vasoconstriction and fluid retention,[9,12] which may further complicate the effective treatment of volume overload. This effect appears to be most pertinent when high doses of loop diuretics are given.

Diuretic therapy has also been associated with worsening renal function,[2,15,16,18–22] which is important because both morbidity and mortality risk increase with worsening renal function during hospitalization for HF.[23–25] Parenteral furosemide administration in volume-overloaded patients with HF has been demonstrated to acutely lower glomerular filtration rate (GFR) despite increasing urine output,[21] and to increase serum creatinine levels. As even small increases in serum creatinine are associated with increased postadmission mortality risk,[24] this risk of renal dysfunction should be carefully considered, and the patient receiving diuretic therapy should be followed very carefully for evidence of alterations in renal function.

The duration of diuretic therapy during hospitalization can be a predictor of morbidity as measured by overall length of hospital stay.[26] Hospital length of stay can be related to the extent of congestion requiring treatment during hospitalization,[26] but several actions exerted by parenteral diuretics may independently contribute to inhospital complications. These actions include the activation of the RAAS,[9–12] as well as systemic volume contraction and electrolyte disturbances—particularly as potassium and magnesium depletion predispose to ventricular arrhythmias.[27]

Furthermore, certain patient populations may be predisposed to greater risk when treated with diuretic therapy. An analysis of hospitalized patients with acute renal failure found that diuretic use was associated with a 68% increase in mortality risk (95% confidence interval [CI], 6% to 164%) and a 77% increase in risk of death or nonrecovery of renal function (95% CI, 14% to 176%).[28] One of the greatest concerns is focused on patients treated with high doses of diuretics. Specifically, high-dose diuretic use, regardless of disease etiology, may increase morbidity and mortality because of either advanced disease resulting in resistance to diuretics or an independent effect of these agents.[28–31] However, it is important to recognize that the risk attributable to high-dose diuretic therapy may not be owing to diuretic agents per se, but rather to the underlying cardiorenal syndrome that the high dose implies.[32–34]

Diuretic resistance is of particular concern in patients with advanced HF because of the need for escalating doses of diuretics to achieve the same or lesser levels of diuresis.[4,5,35,36] As many as 33% of such patients experience some degree of diuretic resistance.[37] The group with the highest risk appears to be those patients with ADHF pre-

senting with hyponatremia and hypervolemia who are poorly responsive to conventional loop diuretics.[5,38]

Despite the routine use of IV diuretics in the treatment of ADHF, data from randomized, controlled studies that support their use in this setting are lacking.[3,4] Of note, to date, no parenterally administered therapies for ADHF, including diuretics, have been shown to improve morbidity, defined as rehospitalization or mortality. Clearly this represents a knowledge gap in our evidence-based literature.[3] In the absence of evidence-based data, careful clinical judgment should guide diuretic use, with particular concerns noted for patients with ADHF who present with diuretic resistance and certain comorbidities, including advanced age and the presence of renal dysfunction.

Alternatives to diuretics or adjunctive approaches that allow for lower doses of diuretic therapy may be reasonable to consider, especially in those patients at risk for harm due to diuretic therapy. These include nonpharmacologic strategies such as ultrafiltration (UF), as well as alternative therapies that include positive inotropes, vasodilators (nitrovasodilators and natriuretic peptides), vasopressor receptor antagonists, adenosine receptor A_1 antagonists, and calcium sensitizers.

ALTERNATIVES TO DIURETIC THERAPY

Ultrafiltration

Extracorporeal UF is a mechanical strategy that uses the convection-driven movement of water and non–protein-bound small and medium molecular weight solutes across a semipermeable membrane in an effort to reduce volume overload. Use of UF does not necessitate admission to an intensive care unit or specialized nursing care of technical oversight. Furthermore, UF does not seem to alter serum creatinine or blood (serum) urea nitrogen (BUN) concentrations. Extracellular fluid is removed while intravascular fluid volumes are maintained, resulting in decreased ventricular filling pressures without significant changes in renal function.[39] Because both water and electrolytes (e.g., sodium) are simultaneously moved across the membrane, the electrolyte concentration of the ultrafiltrate is similar to that of the overall blood plasma.[40] This avoids sudden shifts in electrolyte concentrations and results in more sodium removal than would be achieved with the use of diuretics (diuretics enhance excretion of urine, which has an intrinsically lower sodium concentration than blood plasma).[40]

Although originally developed for the treatment of renal dysfunction, UF is being evaluated for use in volume management of patients with ADHF.[5,40–44] Three recent studies examined the use of UF in patients with ADHF. Costanzo and coworkers[42] evaluated the use of early initiation of UF in 20 volume-overloaded patients with ADHF who had clinical evidence of renal insufficiency (RI) or diuretic resistance. An average of 8.6 ± 4.2 L of fluid was removed with UF. Mean patient weights decreased from 87 ± 23 kg (before UF) to 81 ± 22 kg (discharge) and remained lower than pre-UF weights at 30 days (84 ± 21 kg) and 90 days

(80 $\pm$ 18 kg) ($P = 0.006$). Mean Minnesota Living with Heart Failure Questionnaire (MLHFQ) scores ($P = 0.003$) and Global Assessment scores ($P = 0.00003$) also improved after UF and at 30 and 90 days. The use of loop diuretics remained high throughout the follow-up period. However, there was no apparent deterioration in renal function, hypotension, or hyperkalemia.[42] Bart and associates[41] assessed the safety and efficacy of usual care alone versus usual care plus a single 8-hour session of UF (UF group) in 40 patients with ADHF and volume overload. After 24 hours, fluid removal was 4.6 L in the UF group and 2.8 L in the usual-care group. Dyspnea and HF symptoms improved in both groups at 24 hours, with a slightly greater improvement at 48 hours in the UF group. Average weight loss after 24 hours was 2.5 kg and 1.86 kg in the UF and usual-care groups, respectively ($P = 0.240$). There was 1 death in the UF group during the 30-day follow-up. However, compared with usual care, UF was not associated with significant changes in heart rate, blood pressure, electrolytes, or renal function. Patients receiving UF had a slight decrease in hemoglobin compared with the usual-care group ($P = 0.004$).[41] In the Ultrafiltration Versus IV Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial, 200 patients with ADHF were randomized to peripheral UF or standard IV diuretic therapy and were evaluated at 48 hours and out to 90 days. The primary end point of mean weight loss was significantly better in patients receiving UF compared with IV diuretic therapy (5.0 kg vs. 3.1 kg; $P = 0.001$).[44] Fewer patients receiving UF required rescue therapy with vasoactive drugs, and UF was not associated with hypokalemia or adverse changes in serum creatinine.

There are several potential advantages to the use of UF as compared with diuretics. Unlike diuretics, UF therapy has demonstrated the ability to mitigate RAAS activation [40] and restore diuretic efficacy.[45] In a study of 24 patients with refractory, end-stage HF, UF improved respiratory function, relieved peripheral edema, and enhanced response to diuretics without notable side effects or changes in hemodynamics.[45] A similar study of 11 patients with refractory HF produced similar results.[46] Meanwhile, an analysis of the utility of UF in a population of 30 patients with refractory HF found that this therapy was most effective in a younger population, in which greater volume removal was achieved and markers of renal dysfunction (BUN and serum creatinine) did not increase.[47] However, it should be noted that UF is not a substitute for dialysis in patients with RI, metabolic abnormalities, or uremia.[39] As with any new treatment modality, there are several questions left unanswered. In clinical practice, caution must be exhibited to not overdiurese a patient, especially when UF is used in combination with IV diuretics. The utility of UF in the routine management of patients with ADHF and volume overload remains to be determined by large-scale randomized studies. Nevertheless, current data suggest that this regimen has the potential to offer an alternative treatment for patients resistant to diuretic therapy, especially in younger patients without evidence of substantial renal dysfunction.

Inotropes

Positive inotropic therapy is often used as an adjunct to diuretics in ADHF because of the favorable, rapid changes in hemodynamics and cardiac output achieved with this treatment. However, the routine use of inotropic therapy in the setting of ADHF has been questioned because of consistent data suggesting a lack of efficacy and an increased mortality risk. A randomized, placebo-controlled study found that milrinone therapy did not reduce hospitalization days and significantly increased the incidence of important adverse effects, including hypotension requiring intervention ($P < 0.001$) and new atrial arrhythmias ($P < 0.004$).[48] An analysis of data from the Flolan International Randomized Survival Trial (FIRST) found that continuous-infusion therapy with dobutamine was an independent predictor of 6-month mortality ($P = 0.0001$) and did not provide significant quality-of-life enhancement compared with the absence of dobutamine therapy.[49] An analysis of the recent Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE), which included 433 patients, likewise found an increased risk of death ($P = 0.032$) and of a composite end point of death plus hospitalization ($P < 0.001$) with inotropic therapy.[50] Also, a recent analysis of >150,000 Acute Decompensated Heart Failure National Registry (ADHERE) enrollees suggested that inhospital mortality was higher in patients receiving positive inotropes compared with those receiving other vasoactive therapies, including nitroglycerin and nesiritide ($P \leq 0.005$ for both).[51]

Because of the important limitations and risks associated with inotropic therapy, current ACC/AHA guidelines do not recommend the use of intermittent IV inotropic therapy and suggest that chronic inotropic infusions be limited to palliative use in patients with advanced HF.[1] Nevertheless, positive inotropic support is still considered a viable treatment option for volume overload management in patients with ADHF exhibiting low cardiac index, although it should be reserved for only the sickest patients.[3] Most patients presenting with ADHF, however, do not exhibit a low-output state.[52,53]

Nitrovasodilators

Vasodilator therapy is commonly used in the management of ADHF because of the ability of these agents to rapidly improve resting hemodynamics, which is so often disturbed by volume overload. Traditional nitrovasodilator agents include nitroprusside and nitroglycerin, both of which can significantly reduce pulmonary capillary wedge pressure (PCWP) and preload.[54-57] As discussed previously, an analysis of ADHERE recently found a significantly lower inhospital mortality rate with the use of nitroglycerin compared with positive inotropes ($P < 0.005$).[51] IV nitroprusside has been proved to provide significant hemody-

namic benefits in patients with severe left ventricular systolic dysfunction and aortic stenosis, without an apparent increased risk of adverse effects.[57] Nitrovasodilators may be particularly suited to use as combination therapy with a low-dose diuretic in the treatment of ADHF. A study of 104 patients presenting with ADHF reported that high-dose isosorbide dinitrate in combination with low-dose furosemide was more effective than high-dose diuretics plus low-dose nitrates in improving pulmonary edema.[56] The authors theorized that this effect was owing to the substantial, rapid improvements in preload and afterload conferred with nitrovasodilators, leading to improved cardiac output and relief of congestion.[56] In a highly selective analysis of the long-term effects of hemodynamically tailored therapy—including ACE inhibitors, diuretics, and nitrates, but not more contemporary therapies for HF—the investigators found a sustained hemodynamic response at 8 months of follow-up evaluation, resulting in symptomatic improvements and maintenance of filling pressures in patients with advanced HF.[54] However, these findings may not be duplicated in other settings and may not be pertinent in the context of contemporary therapy. The ability of nitrovasodilators to alleviate elevated filling pressures also results in a rapid reduction in neurohormonal activation, as demonstrated by a trial of nitroprusside and diuretic therapy that reported improved hemodynamics and reductions in neurohormone levels, including endothelin and norepinephrine.[55]

Important limitations nevertheless exist with the use of nitrovasodilators because they cause early tachyphylaxis in many patients,[58,59] leading to frequent dose titrations and the requirement for careful monitoring.[3] A subgroup analysis of the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial found that all patients receiving nitroglycerin required dose titration during the study period.[60] Dose-dependent hypotension is also common with nitroglycerin, which can further contribute to the need for intensive care unit monitoring and invasive hemodynamic monitoring.[3] Nitrovasodilators are considered a mainstay of current therapy for ADHF, but important treatment considerations should be taken into account when choosing these agents.

Natriuretic Peptide Vasodilators

Natriuretic peptides are a family of structurally similar hormones with different physiologic effects.[61] Currently identified natriuretic peptides include atrial natriuretic peptide (ANP), human B-type natriuretic peptide (hBNP), C-type natriuretic peptide, dendroaspis natriuretic peptide,[61] and urodilatin. ANP is released by cardiac atria in response to atrial stress, whereas hBNP is released by both atrial and ventricular myocardial cells in response to wall stress.[61] Levels of hBNP in particular are elevated in patients with HF in response to pressure and volume overload, and it has been theorized that hBNP acts as a counterregulatory physiologic response to the RAAS activation that occurs in HF[62]; hBNP also enhances natriuresis and diuresis.[63,64]

These effects are quickly overwhelmed in the HF milieu, however, making hBNP a target of therapeutic interest.

Exogenous BNP is administered in the form of nesiritide, a recombinant analog of hBNP that has been approved for patients with ADHF experiencing dyspnea at rest or with minimal activity. Recombinant hBNP has demonstrated the ability to counteract the deleterious effects of RAAS activation by reducing levels of renin, angiotensin, aldosterone, endothelin, and norepinephrine.[62–65] Furthermore, recombinant hBNP causes substantial arterial and venous dilation, decreasing both preload and afterload.[62] These effects reduce PCWP and systemic vascular resistance, improving cardiac hemodynamics in patients with HF.[62,64] A recent preclinical study reported that the addition of recombinant hBNP to loop diuretic therapy enhanced natriuresis and diuresis while inhibiting RAAS activation and maintaining GFR, which is suppressed as a result of diuretic administration.[66]

As previously discussed, a recent analysis of the AD-HERE database suggested lower inhospital mortality rates when either nitroglycerin or nesiritide was administered instead of a positive inotrope.[51] Earlier studies reported beneficial reductions in PCWP and systemic vascular resistance [67,68] and consequent improvements in clinical status with nesiritide treatment.[68] The VMAC trial found significantly greater reductions in PCWP with nesiritide therapy than with placebo, in addition to standard therapy, over a 24-hour period, and an adverse effect profile for nesiritide similar to that of nitroglycerin.[69] Dose-related hypotension is the most commonly reported adverse effect associated with nesiritide, and the duration of activity may be longer than that of nitroglycerin. As early initiation of vasodilator therapy is likely to enhance outcomes,[70,71] the use of either nitrovasodilators or nesiritide should be considered when choosing an initial therapeutic regimen for volume management in ADHF.

Concerns have been raised regarding the safety profile of nesiritide. A selective post hoc analysis of data submitted by the US Food and Drug Administration (FDA) suggested that nesiritide was associated with an increase in renal function indices.[72] These changes are noted at doses greater than the standard dose of 0.01 μg/kg per min. Another retrospective meta-analysis demonstrated a non–statistically significant trend toward increased 30-day mortality ($P = 0.059$).[73] These data were not adjusted for known important variables that predict mortality in the setting of ADHF,[25] including measures of BUN, serum creatinine, and blood pressure. It is important to have these questions resolved because the benefit of natriuretic peptides is intriguing, but the clinical efficacy on important outcomes remains unknown.

Other Parenteral Agents

Several additional parenteral agents are currently being evaluated as alternatives to diuretics for use in ADHF. Vasopressin receptor antagonists may provide benefit by preventing electrolyte disturbances and renal dysfunction associated with diuretics. A recent trial reported that coad-
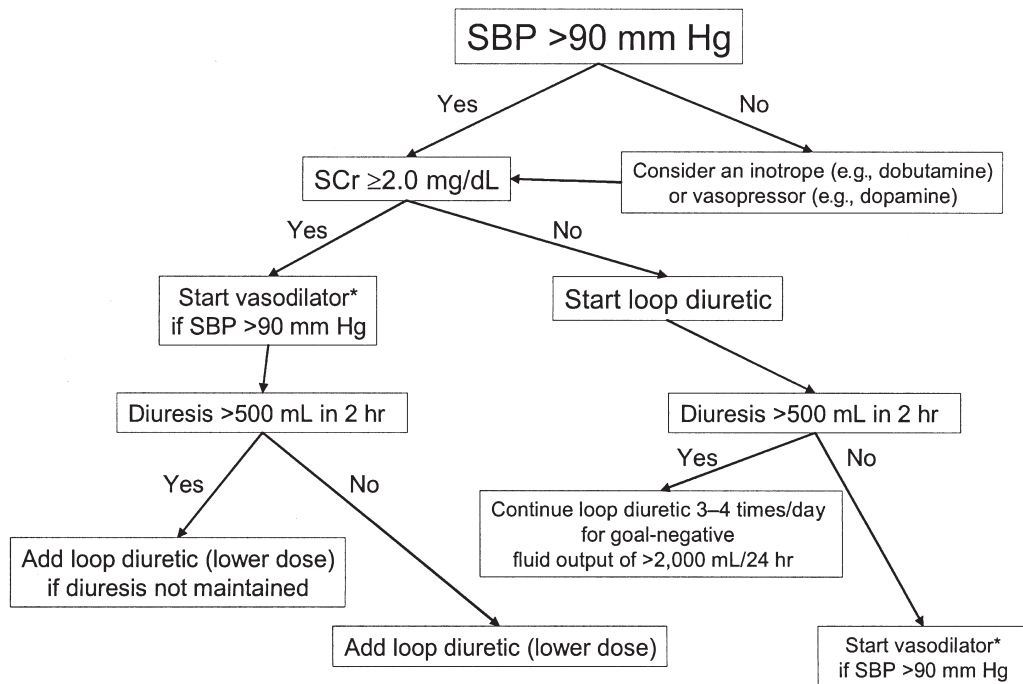
Figure 1   Treatment algorithm for the management of volume overload in patients with heart failure. To achieve serum creatinine (SCr) in micromoles per liter, multiply by 76.25. *Vasodilator therapy includes nitrovasodilators or natriuretic peptides. SBP = systolic blood pressure.

ministration of the selective vasopressin receptor antagonist tolvaptan with standard therapy, including diuretics, resulted in a greater net volume loss than does standard therapy alone.[74] Median (interquartile range) body weight at 24 hours after randomization decreased by −1.80 kg (−3.85 to −0.50 kg), −2.10 kg (−3.10 to −0.85 kg), −2.05 kg (−2.80 to −0.60 kg), and −0.60 kg (−1.60 to 0.00 kg) in the groups receiving tolvaptan 30, 60, and 90 mg/day, and placebo, respectively ($P \leq 0.008$ for all tolvaptan groups vs. placebo). The decrease in body weight with tolvaptan was not associated with changes in heart rate or blood pressure, and did not result in hypokalemia or worsening renal function. Furthermore, in a post hoc analysis, 60-day mortality was lower in tolvaptan-treated patients with renal dysfunction or severe systemic congestion.[74] Adenosine receptor A_1 antagonists have also been investigated for use in ADHF. A recent trial compared an investigational A_1 antagonist (BG9719) plus furosemide to furosemide therapy alone in patients with HF who were receiving standard therapy that included angiotensin-converting enzyme (ACE) inhibitors. Patients receiving the A_1 antagonist in addition to furosemide exhibited greater urine output and sodium excretion compared with those receiving furosemide alone.[21] Serum creatinine was maintained in patients receiving combination therapy, whereas it worsened in those receiving furosemide alone.[21] Calcium-sensitizing agents have also been proposed for the treatment of ADHF. Levosimendan, a novel calcium sensitizer of myocardial contractile proteins, has been investigated in the setting of ADHF.[75–77] Two recent trials, the Randomized Multicenter Evaluation of Intravenous Levosimendan Effi-

cacy (REVIVE) II and the Survival of Patients With Acute Heart Failure in Need of Intravenous Inotropic Support (SURVIVE-W), reported modest improvements in the relief of symptoms but a mortality signal similar to dobutamine.[78,79] How levosimendan will factor in the management of ADHF remains to be seen.

Although additional data will be needed before the routine adoption of these newer therapies, all of them currently represent future treatment options beyond diuretic therapy in the management of ADHF.

MANAGEMENT ALGORITHM: VOLUME OVERLOAD IN HEART FAILURE

There is a lack of clinical guidelines regarding the concomitant use of diuretics and vasodilators for the treatment of volume overload in ADHF. The algorithm in **Figure 1** represents an attempt to prioritize the use of these agents based on clinical experience. The benefits of such an algorithm are that it uses a simple clinical measure to make a treatment plan, and an effective course of therapy is identified in a relatively short time.

Institution of this algorithm generally does not require intensive care unit–level care, but it presumes that the patient is relatively stable both from a hemodynamic and a respiratory standpoint. Although the use of vasoactive agents is generally safe, many patients with ADHF have relatively low blood pressure. To ensure a modest increase in blood pressure, an infusion of low-dose dopamine can be prescribed. The serum creatinine level chosen in the algorithm is arbitrary, but it is based on the clinical experience that the dose of loop diuretic

ADHF Assessment: Physical Findings

	Improved	Worsened
Orthopnea	☐	☐
Shortness of breath/DOE	☐	☐
Pulmonary edema evidence by CXR	☐	☐
Recent weight gain	☐	☐
Increased JVD	☐	☐
S3 and/or S4 heart sounds	☐	☐
Rales	☐	☐
HJR/AJR	☐	☐
Increased BNP levels	☐	☐

Figure 2   Checklist for patients hospitalized with acute decompensated heart failure (ADHF). AJR = abdominal jugular reflux; BNP = B-type natriuretic peptide; CXR = chest x-ray; DOE = dyspnea on exertion; HJR = hepatojugular reflux; JVD = jugular venous distention.

is often problematic and potential changes in renal function are unpredictable in patients with HF who have RI. The dose of loop diuretic is deliberately left out because of its many determining factors, including preexisting chronic dose, preexisting duration of therapy, and history of response. In our experience, however, infusions of loop diuretics are more effective than is bolus therapy. The specific amount of urine output that triggers a change in therapy is arbitrary and may be higher or lower depending on the specific circumstance. The key is the development of short-term treatment goals for volume loss. The advantage of IV loop diuretics is that they work quickly so that rapid dose-titration is possible. ADHF management strategies must always be selected with the careful consideration of several other important patient factors that include age, extent of volume overload, presenting hemodynamics, and the use of long-term therapies for HF management.

MONITORING VOLUME STATUS

Current strategies to monitor volume status in ADHF rely on the use of diagnostic tools as well as on traditional clinical assessment of signs and symptoms associated with volume overload. Unfortunately, congestion due to volume overload does not always translate easily into traditional signs and symptoms. The use of a checklist might be useful during hospitalization for ADHF in an effort to accurately assess volume status. Because 20% of ADHERE enrollees exhibited no weight loss or a net weight gain during hospitalization for ADHF, weight monitoring alone may be insufficient in tracking effective volume normalization. **Figure 2** is a sample checklist of major parameters used to assess euvolemia in hospitalized patients with ADHF, making it clear that that no single parameter is sufficient.

SUMMARY

The management of volume overload in ADHF remains a pressing clinical challenge owing to the lack of consistent data from randomized studies in this clinical setting and the resulting lack of formal, evidence-based treatment guidelines. Patients with ADHF are routinely discharged without achieving a clinically ideal volume state, but treatment goals are poorly defined and no clear criteria exist to direct clinicians in determining when the appropriate volume status has been reached. Diuretic therapy remains necessary for ADHF, but mounting evidence suggests that diuretic therapy may not be entirely benign, and either adjunctive strategies that permit lower doses of diuretic therapy or alternative strategies that obviate the need for diuretic therapy represent important new directions for research. Nondiuretic therapies, especially vasodilators, play a role in volume management and should be considered as adjunct therapies in this setting, especially in patients exhibiting diuretic resistance. Nonpharmacologic mechanical volume removal strategies may become important in certain clinical circumstances. All volume removal strategies may be more easily administered with more effective monitoring of volume status. Ultimately, new treatments for ADHF must clearly demonstrate the achievement of symptom benefit and a favorable effect on morbidity.

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