

# Management of acute heart failure—Is there a paradigm shift around the corner?

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## ABSTRACT

**It has become increasingly apparent that the looming epidemic of heart failure calls for systematic treatment approaches tailored to the needs of individual patient phenotypes. Although chronic heart failure (CHF) therapies are continuously evolving based on the increasing understanding of the involved etiology, acute heart failure (AHF) therapies are still based on hemodynamic improvements and symptom alleviation. Guidelines on AHF management have highlighted that the currently administered AHF therapies lack evidence and have raised concerns on the safety and efficacy of some of the hitherto accepted treatment modalities. Additionally, the high mortality and morbidity rates associated with the current AHF therapies also add to the imperative need to re-visit AHF management. The last decade has witnessed a paradigm shift in the way we define and diagnose AHF. Apart from it being recognized as a distinct clinical entity, research has also led to new data on the pathophysiological changes associated with AHF. These developments along with the limited short- and long-term effects of currently used therapies may herald a paradigm shift in the way we plan and deliver management strategies to treat the pathological progression of heart failure.**

**Keywords:** Acute Heart Failure; Hemodynamic; Clinical and Residual Congestion; Vasodilators; Diuretics; Management Strategies

## 1. EPIDEMIOLOGIC CONSIDERATIONS

Clinical and epidemiological evidence derived from studies carried out in the United States, Canada, Japan, Western and Eastern Europe indicate that presentation of the AHF patients to the emergency department (ED), their background etiologies, precipitating factors, and existing co-morbidities are marked by large heterogeneity.

This heterogeneity is also observed in the treatment strategies and the overall management of these patients from the time of ED admission to their long-term follow-up. Diuretics, vasodilators, and positive inotropes comprise the mainstay of AHF management, with wide variations noted in their usage. For example, nitroglycerine is used in 32.8% of patients in Eastern Europe, 24.4% in Western Europe, and 2.5% in the United States; on the other hand carperitide—a recombinant form of alpha-human atrial natriuretic peptide—is used in 69.4% of patients in Japan [1,2]. A common denominator, however, is the extensive use of loop diuretics in up to 90% of patients in all regions. In this respect, a one-size-fits-all pattern seems to be deeply embedded in the ED routines in an almost universal manner, assumedly, to the benefit of the patients receiving these. Apart from management therapies, resource utilization also varies dramatically amongst the regions, with the length of hospital stay varying from 21 days on an average in the Asia-Pacific region to 4 - 9 days in the United States and 8 - 12 days in Europe [1,3,4].

Of more concern is the increasing prevalence of heart failure in parallel with the increase in the aging population worldwide and the improving number of patients with coronary heart disease surviving acute events (there by running a greater risk for developing heart failure). The huge economic and public health burden resulting from heart failure-related morbidity and mortality is common to all healthcare systems. For example, in 2010 alone the total costs associated with heart failure was estimated to be about \$39.2 billion in the United States, £1.4 billion in United Kingdom, and €2.4 billion in France. The estimated projected cost for heart failure in 2030 for the United States alone is US \$97.0 billion [5-7]. In heart failure patients, the in-hospital mortality can vary from 4% - 11% [1,3,8-10], whereas the re-hospitalization rate at Day 30 post-discharge is about 25% [11]. Six-month readmission rates are even higher, trending near

50% in most reports [12]. Overall, hospitalizations account for 75% of the total cost for heart failure within the first 48 hours post-admission in the United States, whereas hospitalization in Europe constitute up to 70% of the total heart failure costs [13-17].

Notably, despite these alarming figures, general awareness about heart failure is far from the average knowledge in the general population compared to other cardiovascular entities like myocardial infarction and stroke. A survey in nine European countries (SHAPE, 2005) exploring general awareness about heart failure has shown that out of almost 8000 inhabitants only 3% could identify heart failure from a description of the symptoms and signs; although, 31% of subjects could identify angina and 51% stroke [18].

## 2. DIAGNOSTIC CHALLENGES

Data from two of the largest heart failure databases (ADHERE and OPTIMIZE) indicate that majority of AHF patients present with clinical picture of worsening of previously diagnosed HF and only 12% - 25% are *de novo* cases, whereas a minority of the total (1% - 2%) have cardiogenic shock. Furthermore, the most often encountered physical signs are dyspnea (61% - 89%), rales (62% - 68%), and peripheral edema (66%) [3,8]. Notably, in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE), rales were present in 20% and edema in 40% of AHF patients, suggesting again the great variability in the findings from different research sources [19].

With the great majority of AHF patients actually being chronic heart failure patients (and thereby known to the local health care system) and with physical signs that are easily identifiable even by junior physicians, it may come as a surprise to often hear that accuracy of HF diagnosis overall is quite poor [20,21]. In one study, the combination of clinical signs had only a 58% rate of sensitivity in detecting patients with elevated pulmonary capillary wedge pressure (PCWP) [22], whereas radiographic pulmonary congestion was absent in 53% of patients with a PCWP of 16 to 29 mmHg and in 39% of patients with a PCWP of 30 mmHg [23]. Thus, the low diagnostic sensitivity of clinical assessments is recognized; on the other hand, the role of biomarkers (such as B-type natriuretic peptide [BNP] and N-terminal pro B-type natriuretic peptide [NT-proBNP]) in improving the same is also acknowledged [24,25]. In highly specialized and well-resourced tertiary centers, diagnostic accuracy can accordingly be close to 90% as well [24]. The guidelines for diagnosis and treatment of heart failure from American College of Cardiology Foundation/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) have delineated the current methodology to

be adopted to standardize the diagnostic workup. Clinical assessments are recommended for supplementation by objective evidence of cardiac dysfunction and, if doubt persists, by response to initial treatment. Objective assessments such as electrocardiogram (ECG), chest x-ray, biomarkers, and echocardiography are required for confirmation of diagnosis [12,26]. Diagnostic and monitoring aspects of AHF patient care continuum are further exquisitely covered in this issue by J. Cleland *et al.* [Acute Heart Failure: Initial Diagnosis and Subsequent Evaluation with Traditional and Novel Technologies].

At closer scrutiny, diagnostic challenges seem to be compounded by a universal inertia by which acute heart failure is a 2nd tier urgency for which a 50-year-old management pattern (including oxygen supplementation, furosemide, eventually nitrovasodilators, and morphine) is used to relieve dyspnea and to allow for patient's early discharge or transfer to a ward. As a matter of fact, a relatively large proportion of patients seem to be discharged within hours after the acute event subsided or the day after. In a study by Richter *et al.*, only 55% of 448 randomly selected patients presenting to an ED were admitted. Of those not admitted, nearly 20% were either re-hospitalized or died in the following 30 days [27]. Not to much surprise, the early discharged patients leave with a persistent high degree of pulmonary and/or systemic congestion. To make things even worse, data indicate that often congestion may not be adequately addressed during hospitalization, which results in patients being discharged with improved symptoms yet with persistently elevated left ventricular (LV) filling pressures. This ultimately leads to early readmission when symptoms of congestion recur [28].

## 3. THE CURRENT ER PARADIGM

Sequential pathophysiological changes, commonly triggered by patient-related factors such as excessive salt and water intake, nonadherence to medication regimens, concurrent medication, acute infection, etc., are leading to a number of successive events with recognizable pattern regardless of geographical location.

Gradually increasing LV filling pressure, present in a majority of patients with AHF, is more or less silent until a sudden increase in the PCWP causes an overt, dramatic clinical picture of acute pulmonary edema (or alike) that compels the patient to seek urgent care (**Figure 1**).

A variable dose of loop diuretic combined (or not) with peroral nitrate agent or low dose morphine and supplemental oxygen will be administered usually before a positive diagnostic is established and, for most part, before common investigations are even started. Early vasoactive treatment has been reported to improve heart failure outcome and reduce in-hospital mortality [29,30]. Such

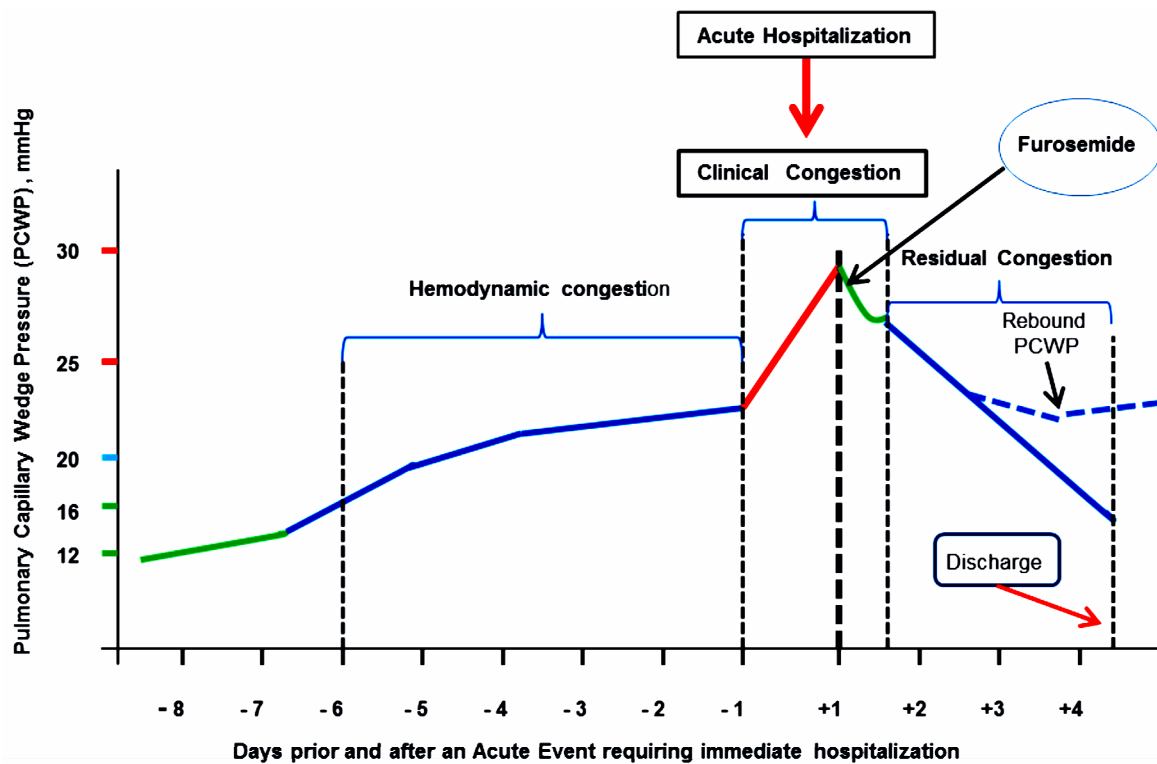


Figure 1. Hemodynamic, clinical and residual in AHF—An invisible continuum.

treatment is likely to relieve dyspnea and confer the patient with a relative general well-being within the next 15 - 60 minutes as a result of quick decrease in the PCWP (the green descending line in Figure 1).

This short-term improvement is very much in line with the prerogatives of an emergency department, *i.e.*, to stabilize the patient's hemodynamic and clinical status; it justifiably pleases the patient and the medical staff alike and may pave the path for the decision of early discharge.

Patients deemed to need more comprehensive investigations or who are having refractory heart failure or cardiogenic shock are transferred to an intensive or coronary care unit and may benefit from mechanical ventricular support, nowadays with good long-term prognosis.

The fate of the patients discharged should, however, attract particular attention, as in these patients the apparent clinical improvement leading to their early discharge may be masking residual high level LV filling pressure despite intensive diuretic treatment. A multitude of extraneous factors (e.g., excessive salt and water intake, nonadherence to medication regimens, etc.) may easily trigger a rebound of peak increase in the PCWP, acute re-admission and a down spiraling with disease progression, and further increased morbidity and mortality.

Figure 1 is a schematic representation of basic pathophysiological changes occurring as a result of fluid retention or fluid redistribution. Fluid redistribution is in-

duced by vascular mechanisms (vasoconstriction) as well as neurohormonal and inflammatory activation, renal dysfunction, and possibly inappropriate use of some medications. Fluid redistribution in particular causes elevated LV filling pressure with consequent gradual increase in the PCWP [31-33]. The resulting congestion is an obvious pathophysiological continuum consisting of three distinct stages: hemodynamic congestion [34], clinical congestion [34], and residual congestion. Calling this an "invisible continuum" would very much reflect the fact that clinically there is a typical discrepancy between the dyspnea severity and PCWP magnitude, especially during the hemodynamic and the residual congestion stage (adding up together to 90% of the time under observation) [34].

Overall, however, during the hemodynamic congestion stage [8] (1 - 2 weeks long), patients are minimally symptomatic. Quantifying congestion during this stage or at least qualitatively diagnosing it is a difficult task.

The clinical congestion, termed the "tip of the iceberg" by Gheorghiadu [32], usually lasts a few hours and culminates with dramatically worsened dyspnea, which compels the patient to seek acute care. This is when management in ED seems to be carried out according to old-fashion patterns, embedded in known routines, rather than aligned to current guidelines and applied to the particular individual needs.

The third stage, *residual congestion*, is probably the

most challenging one. Patients might be discharged early, which is highly advisable if reasonable decongestion has been attained. However, if substantial residual congestion persists at discharge, there is a great risk for short- and medium-term poor prognosis implying the need for sooner or later acute readmission.

Same logic applies to the patients who have been hospitalized for a while. If decongestion is inadequately assessed before discharge, as it may be the case when judgment is based mainly on body weight changes known nowadays to be neither sensitive nor specific to allow for identification or monitoring of patients with heart failure, the risk is again great that the patient will have to be readmitted within a short duration [28,35]. Data from the ADHERE registry indicate that up to 45% of patients have incomplete resolution of symptoms at the time of discharge [36,37].

#### 4. MANAGEMENT PRINCIPLES

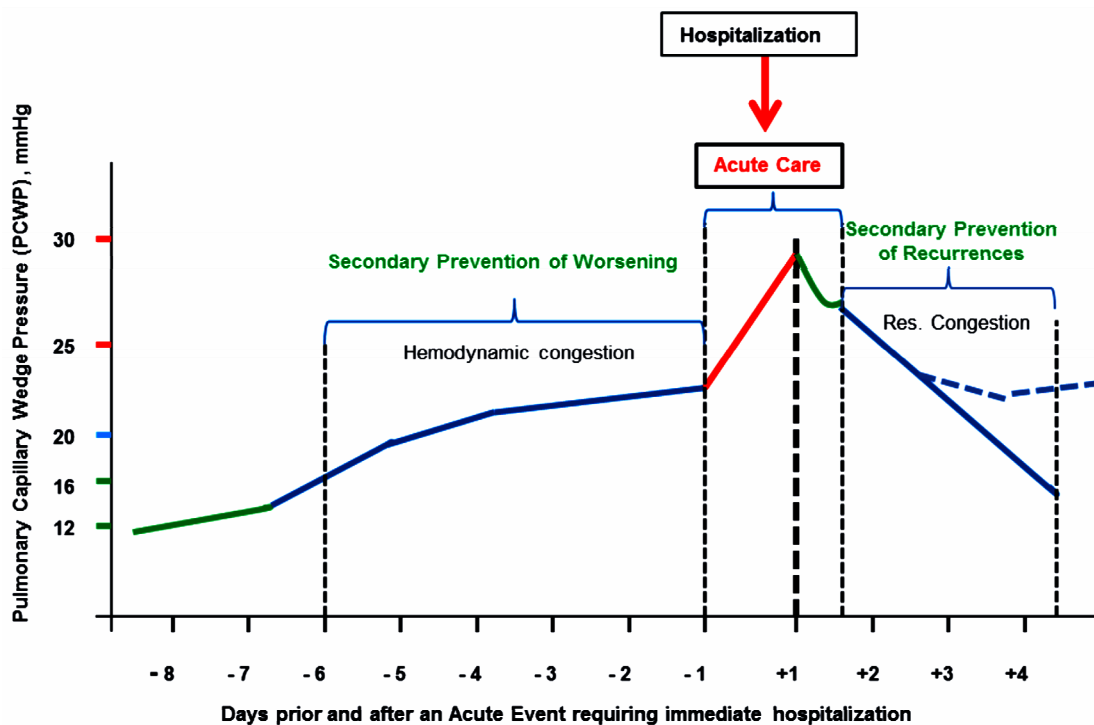
**Figure 2** suggests that overall management of patients with AHF might be structured around three distinct pathophysiological processes occurring sequentially during the course of 3 - 4 weeks.

The ability to identify hemodynamic congestion before its symptoms arise forms a secondary prevention step for a heart failure worsening episode and may help to avoid hospitalizations and reduce disease progression in heart failure patients. Device-based fluid status monitoring (covered in this issue by Cleland *et al.*) including

invasive alternatives (e.g., CRT-D or IDS) or noninvasive impedance monitoring (ICG) appear to develop into novel and innovative modalities for management of heart failure patients [38].

Management of heart failure in the ED might need to be refined; albeit, a simple but thorough bedside evaluation can provide key information about the degree of decompensation and overall prognosis. A simple strategy suggested by Nohria *et al.* classifies patients into four specific hemodynamic profiles based on the absence or presence of congestion (wet or dry) and the adequacy of perfusion (warm or cold), where congestion is defined by a Pulmonary Capillary Wedge Pressure (PCWP) > 18 mmHg [39]. These bedside hemodynamic profiles can be used successfully to guide therapy in most patients who are perfusing well and displaying different degrees of volume overload (includes approximately 70% of AHF patients). These patients are typical candidates for combined early diuretic and vasodilator therapy, with the caveat that therapy should be adjusted to maintain a blood pressure adequate for cerebral perfusion and to avoid postural hypotension [40]. Likewise, special attention should be paid with regard to the risk of some treatments inducing or worsening previous renal dysfunction, as this contributes to a prolonged length of hospital stay as well as increased mortality [26,41,42].

Management of heart failure in the ward (whether cardiology or internal medicine profiled) is multifactorial by definition. Frequently, coexistence of concomitant dis-



**Figure 2.** A holistic approach to management strategies in acute heart failure.

eases like diabetes, asthma, COPD, renal dysfunction, and variable level of cognitive impairment complicate both diagnosis as well as the management strategy. Obviously, particular attention is given to the underlying precipitants such as acute infections, ischemia, arrhythmia, etc. [43].

Evidence-based therapies should be instituted prior to discharge to improve long-term outcomes. Patients should receive education regarding healthy lifestyles, dietary discretion, medication adherence, and monitoring for and response to changes in fluid status. This can be facilitated by an early follow-up, possibly within 1 - 2 weeks after discharge to ensure adherence and clinical stability. Lastly, heart failure disease management programs have consistently been shown to reduce heart failure hospitalizations and should be optimally utilized, especially for high-risk patients [44,45].

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