Division of Cardiology Faculty Papers

Division of Cardiology

7-2015

Current Management of Heart Failure: When to Refer to Heart Failure Specialist and When Hospice is the Best Option.

Behnam Bozorgnia
Einstein Medical Center

Paul J. Mather
Thomas Jefferson University

Heart Failure (HF) is a common syndrome caused by different pathologies of the cardiovascular system that result in impairment of the ventricles to fill or eject blood. Heart failure is one of the most common causes of hospitalization in United States with a very high cost to the healthcare system. There are 880,000 new heart failure diagnoses per year in the United States and 5 million cases currently identified in the US. (1-2). In this chapter we will focus on the etiologies of the left ventricle (LV) dysfunction, presentation and, the acute and chronic management of heart failure.

Etiologies of Heart failure

There is a broad spectrum of pathologies that cause LV dysfunction. The etiologies of systolic and diastolic dysfunction include of coronary artery disease, hypertension, valvular heart disease, to more rare etiologies such as infiltrative disorders and parasitic infections. Table 1. lists the most common of the etiologies of HF encountered by clinicians

Table 1

Etiologies of Heart failure
Myocardial disease
1. Coronary artery disease
2. Hypertension
3. Cardiomyopathy
a. Familial
i. Hypertrophic
ii. Dilated
iii. Arrhythmogenic right ventricular cardiomyopathy
iv. Restrictive
v. Left ventricular non-compaction
b. Acquired
i. Myocarditis
Infective
• Bacterial
• Spirochaetal
• Fungal
• Protozoal
• Parasitic
• Rickettsial
• Viral
Immune-mediated
• Tetanus toxoid, vaccines, serum sickness
• Drugs
• Lymphocytic/giant cell myocarditis
• Sarcoidosis
• Autoimmune
• Eosinophilic (Churg-Strauss)

Toxic	
	• Drugs (Chemotherapy, cocaine)
	• Alcohol
	• Heavy metals (copper, iron, lead)
ii. Endocrine/nutritional	
	• Phaeochromocytoma
	• Vitamin deficiency (e.g. thiamine)
	• Selenium deficiency
	• Hypophosphataemia
	• Hypocalcaemia
iii. Pregnancy	
iv. Infiltration	
	• Amyloid
	• Malignancy
Valvular Heart Disease	
	• Mitral
	• Aortic
	• Tricuspid
	• Pulmonary
Pericardial Disease	
	• Constrictive pericarditis
	• Pericardial effusion
Congenital Heart Disease	
Arrhythmia	
	• Tachycardia (atrial, Ventricular)
	• Bradyarrhythmia (Sinus node dysfunction, Atrioventricular block)
High Output States	
	• Anemia
	• Sepsis
	• Thyrotoxicosis
	• Paget's disease
	• Arteriovenous fistula
Volume Overload	
	• Renal failure
	• Iatrogenic (post-operative fluid infusion)

Table 1. Etiologies of Heart Failure. Adapted from European Society of Cardiology Guidelines, European Heart Journal, 2012

Acute Heart Failure

Common presenting symptoms of HF can include mild shortness of breath, peripheral edema and fatigue, to more severe symptoms such as hypotension, syncope, shock and respiratory failure. A thorough history and physical exam is critical in diagnosis and treatment of patients with HF. The presence of risk factors for developing HF such as

coronary artery disease, hypertension, and diabetes and the presence of substance abuse or recent viral syndrome can provide clues for the etiology of HF. Exposure to chemotherapeutic agents, endocrine abnormalities, recent pregnancy, family history of HF or transplant are all subjects that should be addressed during the initial interview of the patient with HF. A comprehensive history will narrow down the extensive list of etiologies and allows the clinician to provide a more focused and tailored therapy.

Physical Exam

Vital Signs: Evaluation of the HF patient starts with the vital signs. An elevated temperature can be present in myocarditis, or acute valvular lesions in infective endocarditis. Heart rate and regularity is also an imperative parameter in evaluating a patient with HF. Presence of tachycardia is an important and often ominous finding in acutely decompensated HF. Blood pressure can vary significantly depending on the stage and severity of the disease. HF patient can present to Emergency Room with very high systolic and diastolic pressures and acute pulmonary edema. A narrow pulse pressure (less than 25%) is a sign of low cardiac output and severely decompensated HF patient.

The patient's state of mind and clarity can be determined during the interview. Low cardiac output can manifest itself as a confused and difficult to arouse patient. Evaluation of the jugular venous pressure (JVP) is probably the most important and challenging part of the exam of the HF patient. JVP will determine the volume status of the patient which will guide the HF therapy. JVP can also differentiate intravascular volume overload from extravascular edema present in other conditions. Presence of rales in an acute setting is common, although the absence of rales does not rule out HF especially in a patient with chronic HF. The cardiac exam includes the regularity of the rhythm, and the presence of murmurs and gallops. A displaced point of maximal impulse (PMI) is indicative of an enlarged heart. The abdominal exam includes the size of the liver and presence of edema. Ascites, sacral, scrotal, or lower extremity edema can be present in a volume overloaded patient with manifestations of right-sided heart failure. Cool extremities and low pulse volume can be another sign of the hypo-perfused patient with low cardiac output. Palpation of the peripheral pulses can also be helpful in assessing cardiac in assessing cardiac performance and stroke volume. A full and round pulse as compared to a short and pointed pulse can be the difference in a compensated HF patient or a sign of low cardiac output respectively.

Diagnostic Tests

Chest X-ray: CXR findings can be specific but not sensitive for diagnosing HF. Classically, presence of Kerley B lines, Peribronchial cuffing, pleural effusions, and cephalization of the pulmonary vasculature can be present in HF patients.

Electrocardiogram: ECG determines the presence of any arrhythmias that are common in HF patients. Presence of Q waves, or ischemic changes such as ST elevation or depressions vs. left ventricular hypertrophy or low voltage may guide the clinician towards the correct etiology of HF.

Laboratory Data: Patients with acute HF can present with low sodium levels. BUN/Creatinine can also be abnormal depending of the degree of decompensation and hypoperfusion. B-type natriuretic peptide (BNP), or N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurements are useful in an acutely decompensated patient (4-5). Although the absolute value of each lab value can be variable, both BNP and NT-proBNP can be useful in distinguishing HF from other common conditions when clinical picture is not clear (Class I indication). Of note, BNP levels can be falsely low in morbidly obese patients.

Other lab values to consider are as following:

- Troponin
- Thyroid stimulating hormone (TSH)
- Iron studies
- HIV
- Liver function test (LFT)

Troponin levels can be elevated in both ischemic and non ischemic HF patients. Persistent elevation of troponin levels does have a poor prognostic value in HF patients (6). Liver function can also be a marker of the level of congestion and chronicity of HF. In appropriate patients, HIV and Iron level are helpful to further narrow down the etiology of HF.

Acute Heart failure Therapy

Once the underlying cause of HF is identified, the HF therapy can be tailored to the individual patient. When evaluating a patient with acute HF, it is important to assess the level of congestion, i.e. "wet" vs. "dry" and also the level of perfusion, "warm" vs. "cold". The level of congestion and perfusion of the HF patient will guide the initial therapy. Figure 1. provides a quick assessment of the hemodynamic profile of the HF patient.
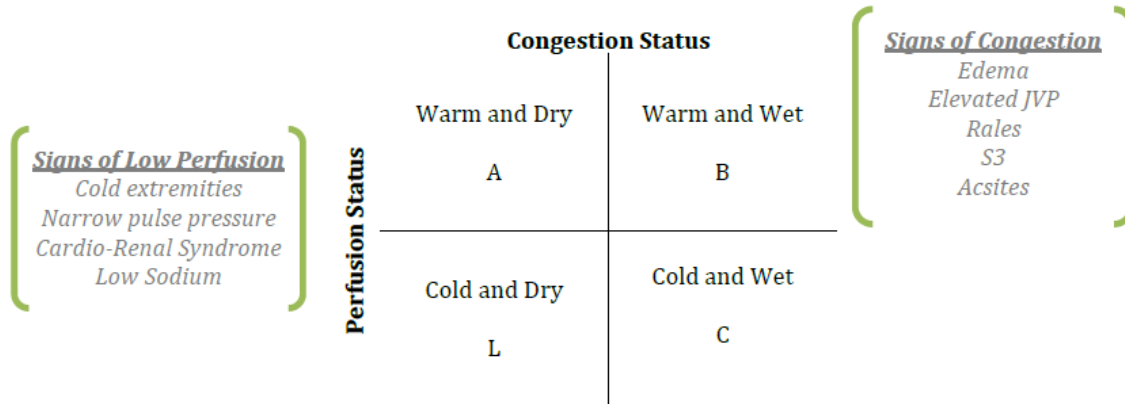
Figure 1. Hemodynamic Assessment of HF patient

Figure 1. Bedside hemodynamic assessment of HF patient to assist with tailoring therapy. Adapted from Dr. Lynne Warner Stevenson MD, JAMA. 2002;287(5):628-640 (doi:10.1001/jama.287.5.628)

A quick assessment of the hemodynamic profile is critical prior to initiation therapy since the spectrum of therapy can be variable and wide. Patient profile A (warm and dry) can be managed as outpatient, while patient profile C (cold/wet) will need inotrope or mechanical circulatory support.

Diuretics

Diuretic therapy is initiated in the acute setting to alleviate symptoms. Parenteral diuretic therapy should be initiated in an acute setting in a congested patient with adequate perfusion. The diuretic dose should be adjusted frequently until adequate response is obtained. Most commonly used loop diuretic is furosamide. Other diuretics such as bumetanide or torsemide are also utilized for their increased bioavailability in the oral form.

The diuretic effect of loop diuretics can be enhanced by addition of thiazide diuretics such as metolazone or spironolactone in a diuretic resistance patient (8). Renal function and electrolytes need to be monitored closely during aggressive parenteral diuresis.

When compared IV bolus vs. continuous infusion of loop diuretics, the data has not shown significant difference between the two strategies (9). The clinician however can choose either method if the patient is refractory to the initial therapy.

Parenteral Vasodilators

Parenteral vasodilators are used as adjuvant therapy to diuretics to relieve congestion and dyspnea in acute HF patient without hypotension. This class of medications increase systemic perfusion, including the renal system and therefore enhance the diuretic effect of loop diuretics.

Intravenous nitroglycerin can relieve congestion primarily through venodilation. This medication is mainly used in hypertensive patients with pulmonary edema. Intravenous nitroglycerin can also relieve symptoms of angina in patients with significant coronary disease. This medication is usually effective up to 24 hours. Patients can develop tachyphylaxis or resistance to nitroglycerin during this time (10).

Sodium Nitroprusside is another potent vasodilator used to treat acute HF. This medication relieves congestion by dilating the venous and arterial beds and reducing the systemic vascular resistance. Arterial line hemodynamic monitoring is usually needed during therapy as Nitroprusside can cause precipitous hypotension. Rare thiocyanate toxicity can occur with prolonged use particularly in patients with renal impairment (11).

Nesiritide can also be used to relieve symptoms of dyspnea and enhance diuresis in acute HF. As other vasodilators mentioned above, hypotension is a side effect during therapy. Brain natriuretic peptide (BNP) levels are not reliable during administration of Nesiritide. It is also important to note that the above vasodilators have not shown any mortality benefit for HF patient and are only utilized in the acute setting for symptomatic relief (12).

Beta Blockers

Beta Blockers (BB) are important class of drugs used in treatment of HF (13). In an acute presentation of HF however their use requires some clinical judgment and finesse. BB can be initiated at low dose, or continued if the patient is already on BB therapy as outpatient, in a well perfused patient. Titration of this class of drugs however should be avoided during the acute phase of HF. BB dose should be reduced or

stopped in more severe presentation of HF. It is imperative however that the patient be initiated on BB therapy prior to discharge to ensure use as transitions of care occur.

Sinus tachycardia is often present in acute HF presentation. One should refrain from titrating the BB dose in order to suppress sinus tachycardia in HF. In an acutely decompensated HF, sinus tachycardia is an appropriate and crucial physiological response to a low cardiac output state. Sinus tachycardia is usually resolved as the hemodynamic profile of the HF patient improves.

The literature on HF and BB is extensive. There are however mixed results with certain BB medications. For that reason, current recommendations encourage clinicians to use 1 of the 3 BBs that have showed benefit in clinical trials; Bisoprolol, Metoprolol Succinate, or Carvedilol. Table 2. Lists the target doses of the BBs in treatment of HF (13-16).

Angiotensin-Converting Enzyme Inhibitors

ACE inhibitors are the cornerstone of HF therapy (17-18). The vasodilation effects of ACE inhibitors are key in improving hemodynamics of HF in both acute and chronic state. Unlike BBs, ACE inhibitors do exhibit class effect. In acute HF patient without shock or significant renal dysfunction, ACE inhibitors should be initiated at low dose and titrated to the maximum tolerated dose. Short acting ACE inhibitors such as Captopril can be initiated in the acute setting if there is concern about hypotensive response. If tolerated, the short acting Captopril should be switched to a comparable dose of a long acting ACE inhibitor such as Lisinopril or Enalapril. Table 2. Lists the target doses of the ACE inhibitors in treatment of HF.

Angiotensin-receptor Blockers (ARBs)

ARBs are also vasodilators that can be utilized instead of ACE inhibitors in patients with acute HF (19-21). ARBs are used when patients exhibit ACE inhibitor intolerance such as cough. Table 2. Lists the target doses of the ARBs in treatment of HF.

Aldosterone Antagonists

Utility of aldosterone antagonists such as Spironolactone, or Eplerenone are limited in acute HF setting. They are further discussed in the chronic HF section. Aldosterone antagonists do facilitate the diuretic effect of loop diuretics in a congested HF patient (22-23).

Hydralazine/Nitrates

In HF patients with significant renal dysfunction or uncontrolled hypertension despite maximum dose of ACE and BB, afterload reducers such as combination of hydralazine and nitrates can be used. While the benefit of hydralazine and nitrates combination has been shown mostly in African American population, this combination should be considered in non African Americans when ACE/ARB are not tolerated, or resistant hypertension is present (24).

Digoxin

Perhaps one of the oldest medications available, digoxin still has a role in treatment of HF patient. Digoxin is also the only safe and effective oral inotrope agent that has been identified so far. While this medication does not affect mortality, it has shown to reduce hospitalization in HF patient population (25). Digoxin's ideal use is in HFrEF patients with concomitant atrial fibrillation. This medication has a narrow therapeutic index and its serum levels should be kept at 0.5 to 0.9 ng/ml. The dose of this medication should be reduced in renally impaired patients.

Table 2. *Drugs Commonly Used in Stage C Heart Failure with Reduced Ejection Fraction.*

Drug	Initial Daily dose(s)	Maximum Dose(s)	Mean Doses Achieved in Clinical Trials
ACE inhibitors			
Captopril	6.25 mg 3 times	50 mg 3 times	122.7 mg/d (422)
Enalapril	2.5 mg twice	10 to 20 mg twice	16.6 mg/d (413)
Fosinopril	5 to 10 mg once	40 mg once	N/A
Lisinopril	2.5 to 5 mg once	20 to 40 once	32.5 to 35.0 mg/d (445)
Perindopril	2 mg once	8 to 16 mg once	N/A
Quinapril	5 mg twice	20 mg twice	N/A
Ramipril	1.25 to 2.5 mg once	10 mg once	N/A
Trandolapril	1 mg once	4 mg once	N/A
ARBs			
Candesartan	4 to 8 mg once	32 mg once	24 mg/d (420)
Losartan	25 to 50 mg once	50 to 150 mg once	129 mg/d (421)
Valsartan	20 to 40 mg twice	160 mg twice	254 mg/d (108)
Aldosterone antagonists			
Spironolactone	12.5 to 25 mg once	25 mg once or twice	26 mg/d (425)
Eplerenone	25 mg once	50 mg once	42.6 mg/d (446)
Beta blockers			
Bisoprolol	1.25 mg once	10 mg once	8.6 mg/d (117)
Carvedilol	3.125 mg twice	50 mg twice	37 mg/d (447)
Carvedilol CR	10 mg once	80 mg once	N/A
Metoprolol succinate extended release (metoprolol CR/XL)	12.5 to 25 mg once	200 mg once	159 mg/d (448)
Hydralazine and isosorbide dinitrate			
Fixed-dose combination (424)	37.5 mg hydralazine/ 20 mg isosorbide dinitrate 3 times daily	75 mg hydralazine/ 40 mg isosorbide dinitrate 3 times daily	~175 mg hydralazine/90 mg isosorbide dinitrate daily
Hydralazine and isosorbide dinitrate (449)	Hydralazine: 25 to 50 mg, 3 or 4 times daily and isosorbide dinitrate: 20 to 30 mg 3 or 4 times daily	Hydralazine: 300 mg daily in divided doses and isosorbide dinitrate: 120 mg in divided doses	N/A

ACE indicates angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CR, controlled release; CR/XL, controlled release/extended release; and N/A, not applicable.
Note: Adapted from ACCF/AHA Guideline for the Management of Heart Failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. By Yancy, CW et al. Circulation. 2013;128

Inotropes

Inotropic therapy is reserved for severely decompensated HF patient with signs of shock or hypo perfusion organ injury. Low cardiac output or shock can be obvious such as low pulse pressure, tachycardia, hypotension, and cool extremities. In some cases however, signs of low cardiac output can be subtle such as worsening of renal function with loop diuretics in a congested patient, changes in mental status, or abnormal liver function tests. Invasive hemodynamic monitoring is usually required to assess and manage patients with low cardiac output or shock. In this section, we will discuss some of the commonly used inotropic agents.

Milrinone

Phosphodiesterase (PD) inhibitors block the degradation of cyclic adenosine monophosphate leading to an increase in calcium influx into the myocardium and enhance contractility. PD inhibitors also have a vasodilatory effect on the pulmonary and peripheral circulation. Intravenous milrinone can be considered in HF patients with low cardiac output. This medication should be initiated at low dose and titrated to achieve acceptable hemodynamics. Since this class of drugs are also potent vasodilators, their use should be avoided in severely hypotensive patients. Concomitant use of low dose beta blockers is possible with this class of medications since they increase contractility independent of the beta adrenergic pathway (26).

Dobutamine

Beta adrenergic receptor agonists can also provide enhanced contractility and hemodynamic support in severely decompensated HF patients with low cardiac output. As compared to PD inhibitors, Dobutamine has a less vasodilatory effect on the periphery and is the preferred medication in hypotensive patients. Concomitant use of beta blockers, specially the non-selective class, should be avoided as they counteract utilizing the same receptor.

In general, use of intravenous inotropes is a temporary measure to provide hemodynamic support as a bridge to recovery or advance therapies (transplant or Left ventricular Assist Devices). Long term use of inotropes should be avoided except as palliative therapy in stage D HF patients, once all available therapies have been exhausted (27-28).

Use of agents with both inotropic and vasopressor property such as norepinephrine should only be used in profoundly hypotensive patients with hemodynamic collapse or sepsis. Pure vasopressors such as phenylephrine should generally be avoided in HF patients.

Mechanical Circulatory Support

In critically ill HF patients with severe hemodynamic compromise who are not responsive to medical therapy, Mechanical Circulatory Support (MCS) can be utilized to provide a bridge to recovery or advanced therapies. Intra-aortic balloon pumps are commonly used devices to provide support to an unstable HF patient. There are a number of newer MCS devices available for the end-stage patient. While they all provide hemodynamic support for unstable HF patients, one should recognize that each device has its challenges and side effects. These devices should only be utilized in highly skilled facilities with well trained support staff. Some of the more commonly used new devices are listed bellow:

- Extracorporeal Membrane Oxygenation (ECMO)
- TandemHeart
- Impella
- Centrimag

Chronic Heart Failure Management

In this section we will discuss management of chronic HF patient in an outpatient setting. Most of the initial work up of HF patient is usually done on the initial presentation in a hospital setting. It is important to obtain the comprehensive record of all the work up of the HF patient and start an individual profile for each patient. Outpatient management of HF serves as a checkpoint to address etiology, medication/device optimization, symptoms, advance therapies or palliative care.

Etiology

Management of HF patients in an outpatient setting begins with further narrowing down the differential diagnosis of HF etiologies. This step will ensure that all the reversible causes of HF have been investigated and either addressed, or ruled out. Presence of coronary disease, resistant hypertension, substance abuse, thyroid abnormalities, arrhythmias, and exposure to toxins are a few common and possibly reversible etiologies of HF. This information is key in tailoring the outpatient treatment to individual HF patients and improving outcomes.

Medication Optimization

Management of HF medications is a challenging, yet critical step in the outpatient setting. In patients with HFrEF, every effort should be made to include beta blockers, ACE inhibitors and aldosterone antagonists as part of medical therapy of chronic HF. The doses of these medications should be titrated up as tolerated by patients (Table 2.). Additional medical therapy such as Hydralazine/Nitrates combination, digoxin, and diuretics should also be initiated and maintained if HF patient continues to be

symptomatic or struggles with volume overload. ARBs should be utilized in HF patients who are ACE intolerant.

Volume Statue and Symptom Surveillance

Monitoring HF patient's volume status in an outpatient setting using physical exam (JVD, weight, edema) labs (BNP, sodium) and devices is crucial in maintaining the patient's overall quality of life and avoiding hospitalizations. HF patients should be advised to monitor their daily weights and report any sudden significant changes (> 2 lbs/day or 5 lb/week) to their HF care provider (29). The diuretic therapy can be adjusted accordingly.

New York Heart Association (NYHA) functional classification is a simple and robust way of monitoring patients' symptoms in an outpatient setting. The clinician's goal is to get the HF patient to Class I or II functional class, and escalate the level of care in functional classes III, and IV.

Device Optimization

Cardiac devices such as Implantable Cardioverter Defibrillator (ICD) or Cardiac Resynchronization Therapy (CRT) are now widely used in HFrEF patients who meet criteria. As part of the evaluation of HF patient in an outpatient setting, the clinicians should address the patient's candidacy for device therapy. In general, HFrEF patients with ejection fraction less than 35% who are optimized on medical therapy more than 3-6 months should be considered for ICD implantation. Patients with EF < 35% due to acute myocardial infarction should wait for 40 days prior to ICD implantation (30-32). ICDs should be reserved for patients with a reasonable expectation of survival in one year, and adequate quality of life.

Patients with HFrEF and wide QRS morphology (ideally left bundle morphology with QRS >150 ms) should be referred for CRT evaluation. Persistent right ventricular pacing due to atrioventricular block or atrial fibrillation with slow ventricular response are also indications for CRT in HFrEF patients.

Referral to Advance Heart Failure Program

Despite optimal medical therapy, revascularization, and device therapies, a certain percentage of HF patients will progress to more advanced stages of the disease. The transition of a HF patient from stable on medical therapy, to an advanced stage requiring mechanical circulatory support (MCS) or heart transplantation can be subtle. Here are some clinical findings that should trigger a referral to an advanced heart failure program:

-Persistent NYHA class III-IV despite medical/device therapy
-Deteriorating renal or liver function (BUN>40 mg/dL or creatinine >1.8 mg/dL)
-Beta blocker or ACE inhibitor intolerance due to hypotension
-Increasing diuretic requirements (>120 mg/day or equivalent)
-Recurrent hospitalizations for HF (more than 1 in 6 months)

It is imperative to realize that once the patient develops irreversible organ damage, advanced therapies such as heart transplantation and Left Ventricular Assist Devices (LVADs) may no longer be options. Therefore, timely referral to heart failure program is important.

Hospice

As mentioned at the beginning of this chapter there are over 5 million patients who suffer from heart failure. Approximately, 5% of the HF patient population is classified as NYHA IV, stage D. A small portion of the NYHA IV patients will receive heart transplantation or LVAD therapy, however, majority of them will not be candidates for advanced therapies with very poor outcomes (Figure 2). Patients with end stage HF have recurrent hospitalizations, deteriorating renal function, and poor quality of life. The patients and their caregivers are also burdened with significant physical and emotional stress at the final moths of life (32). Since the trajectory of end stage heart failure is well known and documented, it is imperative for the physician to recognize and address such situations. Listed below are some of the signs that should prompt the clinician to start the end of life discussion with the patient and their family.

-NYHA IV symptoms despite optimal medical, surgical, and device therapies
-Deemed a poor candidate for transplant or LVAD
-Recurrent hospitalizations despite good compliance
-Persistent ventricular arrhythmias despite medical and surgical interventions
-Profound cardiac cachexia

End of life discussions are always difficult, both for the patient and clinicians. The primary physician's role is crucial in approaching the end stage patient, as they usually have a closer and longer bond with the patient and their family. Some of the common symptoms of end stage HF are dyspnea, fatigue, pain, anorexia and cachexia. Management of the HF patient in the palliative care and hospice stage focuses on patient's comfort and quality of life.

Dyspnea can be treated with continuous infusion of home inotropes. Nitrates, opioids and home oxygen are also effective in alleviating breathlessness. Caffeine and certain stimulants have been used to address fatigue in certain HF patients. Titrating down the

dosage of beta blockers and ACE inhibitors, or stopping a class of medication altogether can also be considered in hypotensive patients.

End stage HF patients are prone to tachyarrhythmias and recurrent ICD shocks. ICD therapy should also be discussed with the patient and the family. While discontinuing the defibrillating capability of the ICDs is a reasonable approach, the CRT portion of the devices should be continued as it may provide symptom relief.
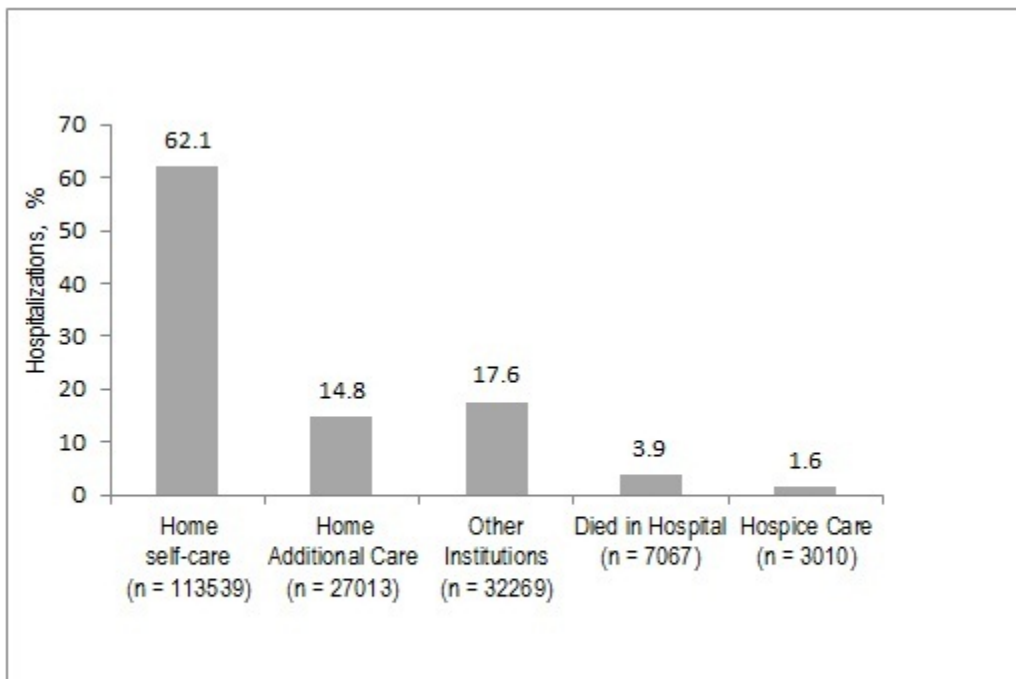

Figure 1. Adapted from Characteristics of Patients Hospitalized With Acute Decompensated Heart Failure Who Are Referred for Hospice Care. Hauptman, PJ et al. Arch Intern Med. 2005;165(13):1469-1477
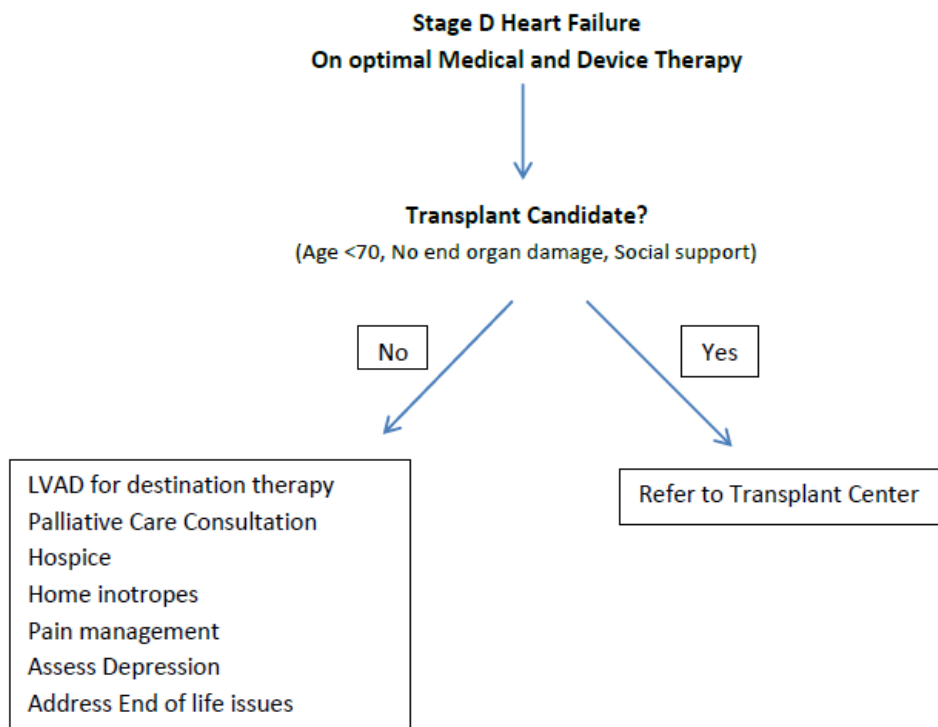
Figure 2. Algorithm for treatment of end-stage HF patient. Adapted from Eric D. Adler, Circulation. 2009;120:2597-2606

References

1. Giamouzis G, Kalogeropoulos A, Georgiopoulou V, et al. Hospitalization epidemic in patients with heart failure: risk factors, risk prediction, knowledge gaps, and future directions. J Card Fail. 2011;17:54-75.

2. Fang J, Mensah GA, Croft JB, et al. Heart failure-related hospitalization in the U.S., 1979 to 2004. J Am Coll Cardiol. 2008;52:428-34.

3. Nohria, A., Mielniczuk, L.M., Stevenson, L.W. Evaluation and monitoring of patients with acute heart failure syndromes. Am J Cardiol. 2005 Sep 19;96(6A):32G-40G.

4. Januzzi JL, Jr., Sakhuja R, O'donoghue M, et al. Utility of amino-terminal pro-brain natriuretic peptide testing for prediction of 1-year mortality in patients with dyspnea treated in the emergency department. Arch Intern Med. 2006;166:315-20.

5. Januzzi JL, Jr., Rehman S, Mueller T, et al. Importance of biomarkers for long-term mortality prediction in acutely dyspneic patients. Clin Chem. 2010;56:1814-21.

6. Horwich TB, Patel J, MacLellan WR, et al. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. Circulation. 2003;108:833-8.

7. Stevenson LW, Nohria, A, et al. Medical Management of Advanced Heart Failure, Journal of the American Medical Association. 2002;287(5):628-640.

8. Rosenberg J, Gustafsson F, Galatius S, et al. Combination therapy with metolazone and loop diuretics in outpatients with refractory heart failure: an observational study and review of the literature. Cardiovasc Drugs Ther. 2005;19:301-6.

9. Salvador DR, Rey NR, Ramos GC, et al. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev. 2005;CD003178.

10. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. JAMA. 2002;287:1531-40.

11. Cioffi G, Stefenelli C, Tarantini L, et al. Hemodynamic response to intensive unloading therapy (furosemide and nitroprusside) in patients >70 years of age with left ventricular systolic dysfunction and decompensated chronic heart failure. Am J Cardiol. 2003;92:1050-6.

12. Colucci WS, Elkayam U, Horton DP, 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.

13. Butler J, Young JB, Abraham WT, et al. Beta-blocker use and outcomes among hospitalized heart failure patients. J Am Coll Cardiol. 2006;47:2462-9.

14. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. N Engl J Med. 2001;344:1659-67.

15. Effects of carvedilol, a vasodilator-beta-blocker, in patients with congestive heart failure due to ischemic heart disease. Australia-New Zealand Heart Failure Research Collaborative Group. Circulation. 1995;92:212-8.

16. Fonarow GC, Abraham WT, Albert NM, et al. Influence of beta-blocker continuation or withdrawal on outcomes in patients hospitalized with heart failure: findings from the OPTIMIZE-HF program. J Am Coll Cardiol. 2008;52:190-9.

17. 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.

18. Kober L, Torp-Pedersen C, Carlsen JE, et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. Trandolapril Cardiac Evaluation (TRACE) Study Group. N Engl J Med. 1995;333:1670-6.

19. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med. 2001;345:1667-75.

20. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003;362:767-71.

21. Granger CB, McMurray JJ, Yusuf S, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet. 2003;362:772-6.

22. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003;348:1309-21.

23. Butler J, Ezekowitz JA, Collins SP, et al. Update on aldosterone antagonists use in heart failure with reduced left ventricular ejection fraction heart failure society of america guidelines committee. J Card Fail. 2012;18:265-81.

24. Taylor AL, Ziesche S, Yancy C, et al. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med. 2004;351:2049-57.

25. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. N Engl J Med. 1997;336:525-33.

26. Klein L, O'Connor CM, Leimberger JD, 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.

27. Aranda JM, Jr., Schofield RS, Pauly DF, et al. Comparison of dobutamine versus milrinone therapy in hospitalized patients awaiting cardiac transplantation: a prospective, randomized trial. Am Heart J. 2003;145:324-9.

28. Gorodeski EZ, Chu EC, Reese JR, et al. Prognosis on chronic dobutamine or milrinone infusions for stage D heart failure. Circ Heart Fail. 2009;2:320-4.

29. Abraham WT, Compton S, Haas G, et al. Intrathoracic impedance vs daily weight monitoring for predicting worsening heart failure events: results of the Fluid Accumulation Status Trial (FAST). Congest Heart Fail. 2011;17:51-5.

30. Zareba W, Piotrowicz K, McNitt S, et al. Implantable cardioverter-defibrillator efficacy in patients with heart failure and left ventricular dysfunction (from the MADIT II population). Am J Cardiol. 2005;95:1487-91.

31. Barsheshet A, Wang PJ, Moss AJ, et al. Reverse remodeling and the risk of ventricular tachyarrhythmias in the MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy). J Am Coll Cardiol. 2011;57:2416-23.

32. Cleland JG, Ghosh J, Freemantle N, et al. Clinical trials update and cumulative meta-analyses from the American College of Cardiology: WATCH, SCD-HeFT, DINAMIT, CASINO, INSPIRE, STRATUS-US, RIO-Lipids and cardiac resynchronisation therapy in heart failure. Eur J Heart Fail. 2004;6:501-8.

33. Adler ED, Goldfinger JZ, Kalman J, et al. Palliative care in the treatment of advanced heart failure. Circulation. 2009;120:2597-606.