**Introduction: Acute Decompensated Heart Failure**

Acute decompensated heart failure (ADHF) refers to the new onset or worsening of signs and symptoms of heart failure, often resulting in hospitalization. It is a common and potentially life-threatening presentation in emergency departments and intensive care units. The pharmacist plays a pivotal role in assisting the medical team with prompt recognition, risk stratification, diagnosis, and evidence-based management of ADHF.

Epidemiology

* ADHF accounts for over 1 million hospitalizations annually in the United States.
* The incidence of ADHF increases with age, with the highest rates in patients over 85 years old.
* ADHF carries high morbidity and mortality. The 1-year mortality rate approaches 30% in some studies.

**Etiology and Pathophysiology**

ADHF can occur due to various etiologies:

* Acute myocardial infarction
* Uncontrolled hypertension
* Valvular disorders (e.g. mitral regurgitation)
* Arrhythmias (e.g. atrial fibrillation)
* Medication or dietary noncompliance
* Infection
* Endocrine disorders (e.g. hyperthyroidism, adrenal insufficiency)

**Pathophysiology**

The pathophysiology of ADHF involves a complex interplay of cardiac dysfunction, fluid overload, and neurohormonal activation. It typically begins with an insult that disrupts the equilibrium of chronic heart failure or triggers a new cardiac event. This can include factors such as dietary indiscretion, medication nonadherence, acute illness, or the development of a new cardiac condition like myocardial infarction or atrial fibrillation.

The underlying cardiac dysfunction, characterized by impaired contractility and ventricular remodeling, leads to reduced cardiac output and inadequate tissue perfusion. This triggers compensatory mechanisms, such as activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, resulting in vasoconstriction, sodium and water retention, and increased preload and afterload. These neurohormonal responses aim to maintain cardiac output, but they can contribute to further cardiac damage and exacerbate fluid overload.

In addition, the elevated ventricular filling pressures caused by fluid overload lead to pulmonary and systemic venous congestion. Symptoms like dyspnea and peripheral edema result from this backward failure. Impaired perfusion to vital organs caused by reduced cardiac output manifests as fatigue, altered mental status, and worsening renal function. Patients may present with signs and symptoms of both fluid overload and hypoperfusion.

Risk Factors

* Older age
* Male sex
* Reduced ejection fraction
* Ischemic heart disease
* Diabetes
* Chronic kidney disease
* Anemia
* High dietary sodium intake
* Lack of guidelinedirected medical therapy
* Low socioeconomic status

**Clinical Presentation Diagnostics**

Patients with ADHF may present in one of four hemodynamic subsets based on volume status (euvolemic or “dry” vs volume overloaded or “wet”) and cardiac output (adequate cardiac output or “warm” vs hypoperfusion or “cold”).

Volume overload: dyspnea, orthopnea, paroxysmal nocturnal dyspnea, ascites, gastrointestinal symptoms (poor appetite, nausea, early satiety), peripheral edema, weight gain.

Low output: altered mental status, fatigue, gastrointestinal symptoms (similar to volume overload), decreased urine output.

**Generalized Symptoms:**

* Dyspnea - Progressive exertional dyspnea is hallmark, can worsen to orthopnea and occur at rest
* Fatigue, weakness - Impaired cardiac output limits physical activity
* Peripheral edema - Systemic venous congestion causes bilateral lower extremity pitting edema
* Paroxysmal nocturnal dyspnea - Orthopnea with sudden awakening from sleep gasping for air
* Abdominal discomfort, nausea - Systemic and bowel wall venous congestion

**Signs:**

* Tachypnea - Respiratory rate >20 breaths/min suggests impaired gas exchange from pulmonary edema
* Tachycardia - Heart rate >100 bpm compensates for poor cardiac output
* Hypotension - Systolic BP <90 mmHg suggests impaired perfusion
* Hypertension - Systolic BP >180 mmHg from neurohormonal activation
* Jugular venous distension - Height >3 cm suggests elevated right heart pressures
* Pulmonary rales - Crackles on lung auscultation indicate extravascular lung water
* S3 heart sound - Third heart sound reflects increased left ventricular filling pressure
* Peripheral edema - Bilateral lower extremities, sacral edema in supine patients
* Hepatomegaly - Enlarged tender liver suggests passive venous congestion

**Laboratory Values**

Volume overload: B-type natriuretic peptide <100 pg/mL (ng/L; 29 pmol/L) and N-terminal B-type natriuretic peptide <300 pg/mL (ng/L; 35 pmol/L) are negatively predictive for congestive ADHF; serum sodium concentration <130 mEq/L (mmol/L); elevated alkaline phosphatase; elevated gamma-glutamyl transferase.

Low cardiac output: evidence of end-organ injury due to impaired perfusion, such as elevated liver transaminases and serum creatinine; mixed venous oxygen concentration <60% (0.60); elevated serum lactate.

**Hemodynamic Monitoring**

Volume overload: pulmonary capillary wedge pressure >18 mm Hg; other volumetric pressures (e.g. right atrial pressure, pulmonary artery diastolic pressure) are also commonly elevated.

Low cardiac output: cardiac index <2.2 L/min/m2 (0.037 L/s/m2), with or without systemic vascular resistance >1,400 dyne·sec·cm−5 (18 Wood units; 140 MPa·s/m3).

**Diagnostic Approach**

* Electrocardiogram: Evaluate for arrhythmias, ischemic changes, QRS morphology and duration
* Chest X-ray: Assess for pulmonary vascular redistribution, pleural effusions, cardiomegaly
* Echocardiography:
  + Ejection fraction: Differentiate HFrEF (<40%) vs HFpEF (≥50%)
  + Structural analysis: Valvular disorders, wall motion abnormalities
* Laboratory tests:
  + Complete blood count: Anemia, infection
  + Basic metabolic panel: Electrolytes, renal function
  + Troponin: Detect myocardial infarction as precipitant
  + Natriuretic peptides: BNP >400 pg/mL or NT-proBNP >2000 pg/mL supports ADHF diagnosis
  + Additional tests: Venous oxygen saturation, serum lactate, iron studies

* Consider right heart catheterization:
  + Warm and wet: PCWP >18 mmHg, CI >2.2 L/min/m2
  + Cold and wet: PCWP >18 mmHg, CI <2.2 L/min/m2
  + Cold and dry: PCWP <15 mmHg, CI <2.2 L/min/m2

Hemodynamic Profiles Patients can be classified into four hemodynamic profiles based on volume status and cardiac output:

1. Warm and Dry: Euvolemic, normal cardiac output
2. Warm and Wet: Hypervolemic, normal cardiac output
3. Cold and Dry: Hypovolemic, reduced cardiac output
4. Cold and Wet: Hypervolemic, reduced cardiac output

**Management Principles**

The priorities in management include:

* Respiratory support
* Hemodynamic stabilization
* Congestion relief
* Restoration of adequate perfusion
* Limiting organ injury
* Monitoring for arrhythmias
* Planning hospital discharge and follow-up

Desired Outcomes

* Relief of congestive symptoms
* Restoration of adequate end-organ perfusion
* Optimization of volume status and hemodynamic stability
* Minimization of further cardiac damage and adverse drug reactions
* Appropriate initiation/titration of guideline-directed medical therapies

General Approach

* Discontinue medications worsening heart failure (e.g. NSAIDs, thiazolidinediones)
* Initiate intravenous loop diuretics for congestion, using 1-2.5 times oral dose
* Continue beta-blockers and other guideline-directed medical therapies if possible
* Select additional therapies based on hemodynamic profile

**Pharmacologic Therapy**

* Diuretics: Loop diuretics (e.g. furosemide, bumetanide) are first-line for volume overload. May need combination with thiazide diuretics for diuretic resistance.
* Vasodilators: Nitroglycerin, nitroprusside - Used for rapid symptom relief in hypertensive ADHF with pulmonary edema.
  + Hemodynamic effects:  ↓ PCWP, ↓ SVR, ↓ MAP, ↑ CO
* Inotropes: Dobutamine, milrinone - Reserved for cardiogenic shock refractory to other measures. Increase contractility and cardiac output.
* Vasopressors: Norepinephrine, dopamine – Used in conjunction with inotropes for hypotensive shock with low blood pressure.
* Other agents: Morphine avoided due to risks. Vasopressin antagonists used for severe hyponatremia.

**Non-pharmacologic Therapy**

* Oxygenation/ventilation support
* Ultrafiltration for diuretic resistance
* Mechanical circulatory support devices in refractory shock
* Cardiac transplantation or left ventricular assist devices in advanced heart failure

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| **Subset** | **Primary Treatment** |
| **Subset I:  “Warm and Dry”:**  **Optimize PO heart failure regimen** | **GOAL** |
| **Subset II:  “Warm and Wet”:**  **Provide symptomatic relief from congestion** | **DIURETIC** |
| **Subset III:  “Cold and Dry”:**  **Increase perfusion to vital organs to alleviate symptoms** | **FLUIDS** |
| **Subset IV:  “Cold and Wet”:**  **Alleviate congestion and hypoperfusion** | **INOTROPE OR VASOPRESSOR + DIURETIC** |

**Pharmacologic Therapy**

The choice of pharmacologic agents depends on the patient's hemodynamic profile:

Warm and Dry: (CI greater than 2.2 L + PCWP less than 18 mm Hg)

* Focus on optimizing chronic oral heart failure therapies
  + Initiate/uptitrate beta-blockers (e.g. carvedilol, metoprolol succinate) and ACE inhibitors or ARBs (e.g. lisinopril, losartan) as tolerated
  + Add hydralazine and nitrates (e.g. isosorbide dinitrate) in African American patients
  + Consider adding angiotensin receptor-neprilysin inhibitor (sacubitril/valsartan) for HFrEF if tolerated
  + Continue other oral therapies (digoxin, loop diuretics) if previously prescribed

Warm and Wet: Without Flash Pulmonary Edema (CI> 2.2 L + PCWP greater than 18 mm Hg)

* Intravenous loop diuretics (furosemide 20-40 mg IV or bumetanide 1-2 mg IV)
* Double patients' oral daily loop diuretic dose for initial IV dose
* If oral loop diuretic naive, start furosemide 40 mg IV daily or bumetanide 2 mg IV daily
* Monitor urine output, symptoms, weight loss
* Repeat doses every 2 hours as needed
* For diuretic resistance:
  + Increase loop diuretic dose
  + Add metolazone 2.5-10 mg oral daily
  + Switch to continuous infusion loop diuretic
  + Consider ultrafiltration
* Add intravenous nitroglycerin infusion if persistent symptoms, start at 5-10 mcg/min, titrate by 5-10 mcg/min every 5 minutes, max 200 mcg/min
* For hypertensive patients, sodium nitroprusside 0.3-5 mcg/kg/min IV is an alternative to nitroglycerin

Warm and Wet: Flash Pulmonary Edema (CI> 2.2 L + PCWP greater than 18 mm Hg)

A subset of warm and wet profile patients present with flash pulmonary edema, characterized by:

* Abrupt onset dyspnea and hypoxemia
* Pink, frothy sputum
* Hypertensive crisis (SBP > 180 mmHg)
* Bilateral pulmonary rales

Management should focus on rapid symptom relief:

* High dose intravenous nitroglycerin
  + Options:
    - Intravenous bolus of 2000 mcg every 3-5 minutes as needed
    - Intravenous infusion at 100-200 mcg/min
  + Titrate to relief of dyspnea and oxygenation improvement
  + Wean infusion as symptoms and blood pressure improve
* Non-invasive positive pressure ventilation
* Consider intravenous enalaprilat 0.625-1.25 mg if blood pressure remains elevated after nitroglycerin
* Cautious use of intravenous furosemide 20-40 mg to relieve fluid overload after stabilization with above measures

Cold and Dry:(CI less than 2.2 L + PCWP less than 18 mm Hg)

* Assess PCWP
  + If <15 mm Hg, administer IVF
  + If 15-18 mm Hg, assess for systemic hypotension
    - Mean arterial pressure (MAP):  2/3 DBP + 1/3 SBP
* Cautious intravenous fluids 250-500 mL to increase preload
* Consider holding loop diuretics temporarily
* Inotropes if fluid bolus insufficient:
  + Dobutamine 2-20 mcg/kg/min IV
  + Milrinone 0.375-0.75 mcg/kg/min IV
    - Small trials directly comparing these agents in ADHF have resulted in no difference in clinical outcomes

* Titrate to target CI > 2.2 L/min/m2 and MAP > 65 mmHg
* Add norepinephrine if MAP remains low after inotrope initiation

Cold and Wet: (CI less than 2.2 L + PCWP greater than 18 mm Hg)

* Intravenous loop diuretics as above to relieve congestion
* Inotropes as above to improve cardiac output
* Vasopressors if inotropes cause hypotension:
  + Norepinephrine 0.2-1 mcg/kg/min IV
  + Dopamine 2-10 mcg/kg/min IV
* Target CI > 2.2 L/min/m2, MAP > 65 mmHg, PCWP 15-18 mmHg
* Consider mechanical circulatory support if refractory

Loop Diuretics

* Furosemide, bumetanide are first-line
* Initiate with IV bolus or infusion at 1-2.5 times oral dose
* Adjust dose based on urine output, weight loss, symptoms
* Monitor electrolytes, renal function
* Overcoming Resistance
  + Increase loop diuretic dose
  + Add thiazide diuretic (e.g. metolazone, chlorothiazide)
  + Switch to continuous infusion
  + Consider ultrafiltration

Nonpharmacologic Therapies

* Sodium restriction
* Ultrafiltration for diuretic resistance
* Temporary mechanical circulatory support (MCS) for refractory ADHF
* Durable MCS or cardiac transplantation in advanced heart failure

Evaluation of Therapeutic Outcomes

* Monitor symptoms, vital signs, orthostasis, weights, electrolytes, renal function
* Assess response to intravenous therapies
* Prepare for discharge once euvolemic and stable on oral agents
* Initiate/optimize guideline-directed medical therapies prior to discharge
* Schedule prompt follow-up appointment and testing after discharge

**Key Guidelines and Evidence**

* Evaluate and diagnose ADHF promptly based on clinical
* Guidelines for assessment and imaging studies ((ACC/AHA Guideline, ESC Guideline)
* Loop diuretics (furosemide, bumetanide) are first-line agents for relief of congestion in volume overload (ACC/AHA Guideline, ESC Guideline).
* Intravenous nitroglycerin or nitroprusside should be used for rapid improvement of congestive symptoms and blood pressure reduction in hypertensive acute pulmonary edema (ESC Guideline).
* Inotropic agents like dobutamine or milrinone should be reserved for patients with refractory congestion and evidence of low cardiac output with organ hypoperfusion (ACC/AHA Guideline).
* Individualize therapy based on patient-specific factors and closely monitor response.

Landmark Trials:

* OPTIME-CHF Trial (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure): This trial evaluated the use of intravenous milrinone in ADHF and found no significant improvement in clinical outcomes, including length of stay, compared to placebo. It highlighted the need for cautious use of inotropic agents in ADHF.

* ESCAPE Trial (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness): This trial assessed the impact of pulmonary artery catheter-guided therapy on outcomes in ADHF. It concluded that the routine use of pulmonary artery catheterization did not improve outcomes in a broad population of ADHF patients.

* DOSE Trial (Diuretic Optimization Strategies Evaluation): The DOSE trial compared diuretic strategies (high-dose versus low-dose, continuous infusion versus bolus) in ADHF. It demonstrated that high-dose diuretics resulted in better symptom improvement but increased renal impairment compared to low-dose diuretics. Continuous infusion diuretics were not superior to intermittent bolus administration.

* LIDO Trial (Levosimendan Infusion versus Dobutamine): The LIDO trial compared levosimendan, a calcium sensitizer, with dobutamine in ADHF patients with low cardiac output. It showed that levosimendan was associated with a greater improvement in hemodynamics and a lower mortality rate compared to dobutamine.

It is important for clinical pharmacists to stay updated with the latest guidelines, clinical trials, and evidence-based practices in ADHF. These resources provide a foundation for delivering optimal care to patients with ADHF.

**Clinical Scenarios**

Here are a couple of clinical scenarios that highlight key learning points or common pitfalls in the management of Acute Decompensated Heart Failure (ADHF):

**Clinical Scenario 1:**

A 68-year-old African American male with ischemic cardiomyopathy (ejection fraction 30%) presents with acute decompensated heart failure after stopping his medications due to cost, including furosemide 40 mg PO BID, lisinopril 10 mg daily, and metoprolol succinate 50 mg daily. He reports a 10 lb weight gain in 2 weeks. On exam, he has jugular venous distension, bilateral crackles, and 3+ pitting edema. His blood pressure is normal.

What is the appropriate initial diuretic therapy?

* What pharmacologic therapy should be initiated first in this volume overloaded patient?
  + Intravenous furosemide 40-80 mg is appropriate. For patients on oral loop diuretics, the intravenous dose should be 1-2.5 times the oral dose. This patient was on oral furosemide 80 mg daily, so an intravenous dose of 40-160 mg would be reasonable. Intravenous therapy is preferred over oral for reliability and efficacy.

**Clinical Scenario 2:**

A 79-year-old female with ischemic cardiomyopathy and ejection fraction 20% presents with acute decompensated heart failure. She was discharged from the hospital 5 days ago. She is now brought in by ambulance with severe dyspnea at rest. Her blood pressure is 82/60 mmHg, heart rate 115 bpm, and oxygen saturation 82% on room air. Lung exam reveals coarse crackles throughout all lung fields. S3 gallop and jugular venous distension 10 cm are noted. Labs show serum creatinine 2.4 mg/dL (baseline 1.7 mg/dL). NT-proBNP is 12,800 pg/mL.

* What hemodynamic profile does this patient most likely represent?
  + Cold and wet
    - Intravenous furosemide 40-80 mg is appropriate. For patients on oral loop diuretics, the intravenous dose should be 1-2.5 times the oral dose. This patient was on oral furosemide 80 mg daily, so an intravenous dose of 40-160 mg would be reasonable. Intravenous therapy is preferred over oral for reliability and efficacy.

* What is the most appropriate next pharmacotherapy step?
  + Initiate dobutamine infusion at 3 mcg/kg/min IV
    - Intravenous furosemide 40-80 mg is appropriate. For patients on oral loop diuretics, the intravenous dose should be 1-2.5 times the oral dose. This patient was on oral furosemide 80 mg daily, so an intravenous dose of 40-160 mg would be reasonable. Intravenous therapy is preferred over oral for reliability and efficacy.

* What parameters should be monitored closely?
  + Urine output, electrolytes, serum creatinine
  + Continuous cardiac monitoring for arrhythmias
  + Blood pressure, heart rate
  + Signs/symptoms of perfusion (mentation, skin temperature)

These clinical scenarios highlight the importance of individualized patient assessment, medication adherence, and appropriate selection of therapies in the management of ADHF.

**Tips for Board Exam Questions:**

1. Remember the 4 hemodynamic subsets - Categorizing patients into warm/dry, warm/wet, cold/dry, and cold/wet is essential for selecting appropriate therapies. Know the typical signs, symptoms, and hemodynamic parameters for each subset.
2. Understand diuretic strategies - High-dose IV loop diuretics are first-line, but be prepared for questions on overcoming resistance with increased doses, alternate diuretics, and ultrafiltration. Avoid over-diuresis.
3. Know vasoactive medications - Vasodilators are preferred for volume overload without hypotension. Inotropes are for low output with tissue hypoperfusion. Be familiar with drug classes, dosing, adverse effects, and special considerations like concomitant beta-blocker use.

**Summary: Acute Decompensated Heart Failure**

* In summary, Acute Decompensated Heart Failure (ADHF) is a clinical syndrome characterized by worsening signs and symptoms of heart failure requiring hospitalization or unscheduled medical care. Clinical pharmacists play a critical role in the management of ADHF, ensuring optimal medication therapy, monitoring, and patient education. Key aspects of ADHF management include relieving congestion, optimizing volume status, treating symptoms of low cardiac output, preventing further decompensation, and preparing patients for discharge.

* Pharmacotherapy is a cornerstone of ADHF management, with diuretics being the mainstay for relieving congestion. Vasodilators, inotropic agents, and vasopressorsare used based on individual patient characteristics and hemodynamic status. Close monitoring of clinical response, hemodynamic parameters, and electrolyte levels is essential.

* Guidelines, such as those provided by the American College of Cardiology (ACC) and the Heart Failure Society of America (HFSA), offer evidence-based recommendations for the evaluation, diagnosis, and treatment of ADHF. Landmark trials, including the OPTIME-CHF and ESCAPE trials, have contributed valuable insights into the management of ADHF.

* Overall, a comprehensive understanding of the clinical presentation, pathophysiology, diagnostic approach, pharmacotherapy, guidelines, and evidence-based practices in ADHF equips clinical pharmacists with the knowledge and skills necessary to provide high-quality care to patients with this complex condition.

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