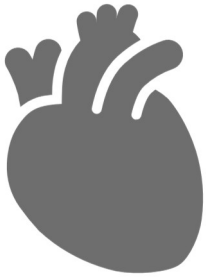

Acute Decompensated Heart Failure Pharmacotherapy

- Dr. Abdallah Abukhalil
- Pharmacotherapeutics I
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Reading:

- Pharmacotherapy: A Pathophysiologic Approach, 10th edition
  - Chapter 15: Acute Decompensated Heart Failure

2

Objectives

Identify factors that may lead to an acute decompensation of heart failure

Make appropriate recommendations to resolve or minimize factors that may lead to acute decompensation of heart failure

Stage patients based on the Forrester staging criteria and make appropriate recommendations for patients based upon their stage

Evaluate a home medication regimen and determine appropriate action upon hospital admission for treatment of acute decompensation

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Objectives

- Develop a diuretic regimen for treatment of acute decompensated heart failure and identify an appropriate strategy to overcome diuretic resistance
- Identify patients who are candidates for vasodilator, inotrope, and/or vasopressin antagonist therapy and select the most appropriate agent
- For each class of medications, be able to determine available agents and special considerations for each, mechanism of action, role in therapy, monitoring
- Develop and evidence-based regimen for hospital discharge and provide appropriate medication counseling

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Acute Decompensated Heart Failure (ADHF)

- Defined as sudden worsening of HF symptoms
- Generally requires hospitalization, intensive therapy, IV medications, intensive monitoring
- Terminology used to describe pts:
- Wet: fluid up, needs diuresis
- Dry: euvolemic
- Warm : well perfused
- Cold: poor perfusion

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NYHA Functional Classification

I – **No limitations** in physical activity due to HF symptoms

II - **Ordinary physical activity** will cause HF symptoms (slight limitation)

III - **Less-than-ordinary activity** will cause HF symptoms (marked limitation)

IV – HF symptoms are **present at rest**

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ACCF/AHA Heart Failure Staging

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ADHF Common causes

- ACS
- AFib/arrhythmias
- Infections
- Endocrine abnormalities (thyroid, DM
- Pulmonary embolus (PE)

. Other acute CV disorder (valve disease, endocarditis, etc.)

- Uncontrolled HTN

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History

Determine probable etiologies and precipitating/aggravating factors

Medications/medication history

Recent changes?

Symptoms

- Onset
- Duration
- Severity
- Ex - Orthopnea vs. SOB at rest vs. SOB on exertion

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Common causes

Meds

Non-compliance

Recent addition of negative inotropic agent

Na-retaining meds (NSAIDS, , steroids..)

Na/H2O retention

Excessive alcohol/drug use

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Diagnosis

Primarily based on signs, symptoms

- Congestion - fluid overload
- Hypoperfusion - decreased cardiac output

Natriuretic peptide monitoring

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Clinical Presentation

Most patients with a decompensation can be treated on a general medical floor

Admission to the ICU

- Hemodynamic instability requiring:
  - Frequent monitoring of vitals
  - Invasive hemodynamic monitoring
  - Rapid titration of IV medications with concurrent close monitoring

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ADHF
Signs and Symptoms

Congestion (fluid overload – "wet")	**Hypoperfusion (decreased CO – "cold")**

• Weight gain
• Ascites
• Pulmonary congestion
  • dyspnea, orthopnea, rales
• Systemic congestion
  • GI discomfort, ascites, peripheral edema, hepatomegaly, JVD
  • Increased BNP
	• **Altered mental status, fatigue, sleepiness**
	• **Cold extremities**
	• **Weak pulses**
	• **More severe**
	• **Hypotension**
	• **worsening renal function**
	• **Prerenal AKI (BUN:SCr > 20)**
	• Decreased urine output

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Natriuretic Peptide Monitoring

Neurohormones secreted from myocardium in response to increases in myocardial stretch (increases in ventricular volume and pressure)

Aid in differential diagnosis of dyspnea; interpret in context of clinical picture

BNP (B-type natriuretic peptide)

- BNP < 100 pg/mL: HF unlikely
- BNP 100 – 500 pg/mL: consider HF and other potential causes
- BNP > 500 pg/mL: HF very likely

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Monitoring

ECG monitoring

continuous pulse oximetry (oxygen saturation)

organ perfusion

- mental status, renal and hepatic function

urine flow monitoring; fluid intake/output (I/O's)

vitals and weight

- peripheral and femoral arterial catheters may be used for continuous monitoring of arterial pressure

electrolytes and serum creatinine

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Hemodynamic Monitoring

Pulmonary artery catheter – invasive hemodynamic monitoring helps evaluate volume and perfusion status

Consider for some patients:

refractory to therapy	volume status unclear	clinically significant hypotension (SBP < 80 mmHg)	worsening renal function despite treatment

From: 2013 ACCF/AHA Guideline for the Management of Heart Failure

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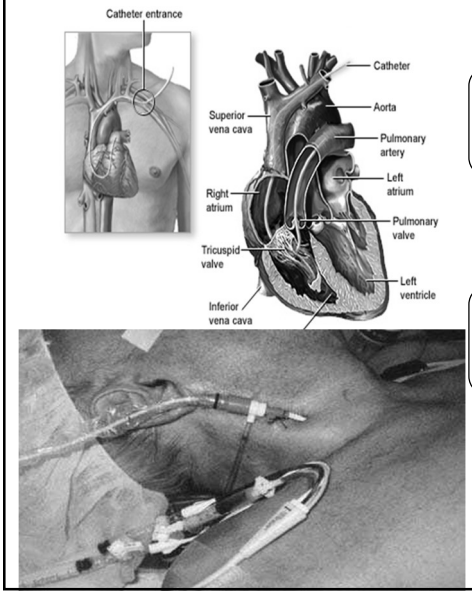
Invasive hemodynamic monitoring



Swan-Ganz catheter

- Inserted through a peripheral vein and advanced through right side of heart
- Inflated balloon in pulmonary artery

Pulmonary capillary wedge pressure (PCWP)

- Indicator of volume status
  - ↑PCWP = fluid overload
  - Normal PCWP = <12 mmHg

Cardiac output (CI)

- Cardiac output (CO) normalized for BSA
  - CO = volume of blood pumped in 1 minute
- CI = CO/BSA

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Hemodynamic Monitoring

Hemodynamic Parameter	Normal Value	Usual Value in ADHF	
Cardiac Index (CI) (contractility)	2.5 - 4.2 L/min/m^2	1.3 - 2 L/min/m^2 **(CI < 2.2 = "cold")**	↓
Pulmonary Artery Occlusion Pressure (PAOP) or Pulmonary Capillary Wedge Pressure (PCWP) (preload or LV filling pressure)	5 - 12 mm Hg in healthy patients **(15 - 18 mmHg necessary for HF patients to optimize CI)**	18 - 30 mm Hg **(PAOP > 18 = "wet")**	↑
Systemic Vascular Resistance (SVR) (afterload)	900 - 1,400 dyne.sec.cm^{-5}	1500 - 3000 dyne.sec.cm^{-5}	↑
Central Venous Pressure (CVP)	2 - 6 mm Hg	6 - 15 mm Hg	↑

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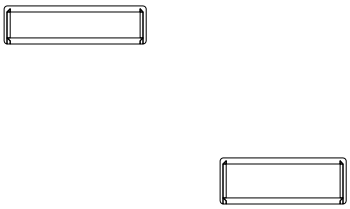
Hemodynamic Subsets

Forrester hemodynamic classification



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Management

Usually based on clinical presentation

- Is patient **wet** (congestion) or **dry** (no congestion)?
  - Majority of ADHF patients present as wet
- Is patient **cold** (low CO, hypoperfusion) or **warm**?

May be based on hemodynamic monitoring

- Hemodynamic subsets (I – IV)
- PAOP > 18 mmHg = **wet**
- CI < 2.2 L/min/m^2 = **cold**

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Clinical Presentation

Hypoperfusion (decreased CO – "cold")	(fluid overload – "wet") **Congestion**

• Altered mental status, fatigue, sleepiness
• Cold extremities
• Weak pulses
• More severe:
  • hypotension
  • worsening renal function
	• Weight gain
	• Pulmonary congestion
	  • dyspnea, orthopnea, rales
	• Systemic congestion
	  • GI discomfort, ascites, peripheral edema, hepatomegaly, JVD

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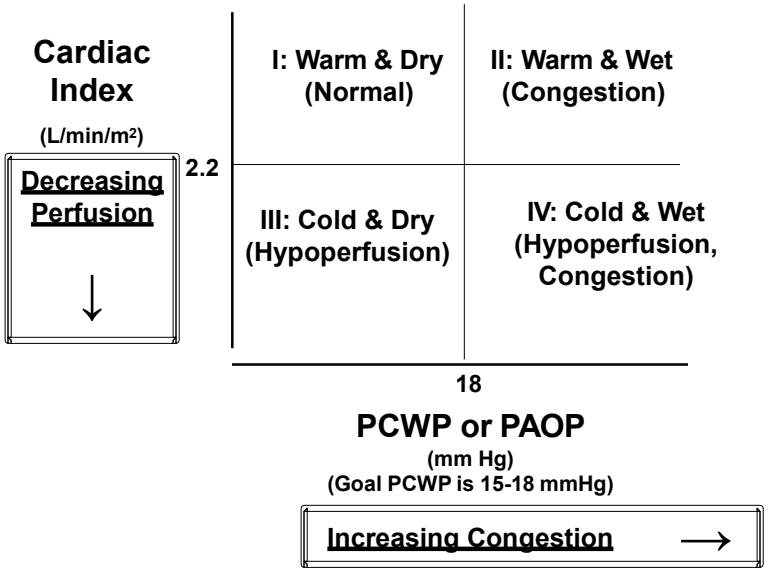
Forrester hemodynamic classification

Adapted from: 2013ACCF/AHA Guideline for the Management of Heart Failure



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Acute HF Subsets

Subset I (warm and dry)

- CI > 2.2, PCWP < 18
- Well perfused without congestion
- likely well compensated and only needs fine tunning oral meds and monitoring

Subset II (warm and wet)

- CL > 2.2, PCWP >18
- well perfused with congestion
- Needs reduction of preload with IV
- agents (loop diuretics, NTG, nesiritide)

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Acute HF Subsets

Subset III (cool and dry)

- CI <2.2 ,PCWP <18
- Inadequate perfusion without congestion
- High mortality
- Treatment focuses on increasing CO with
- a combination of positive inotropes, very
- cautious fluid replacement, and vasodilators
- Therapy will need to be tailored to each pt

Subset IV (cool and wet)

- CI < 2.2, PCWP >18
- inadequate perfusion with congestion
- most complicated presentation for ADHF with
- worst prognosis
- Therapy is highly individualized to diurese
- improve CO while maintaining adequate MAP
- AGENTS USED INCLUDE INOTROPES, VASODILATORS, AND DUIRETICS

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Treatment Goals

Goals:

- Relieve congestive symptoms
- Optimize volume status
- Treat symptoms of low CO
- Discharge patients on PO drug therapy
- Reduce recurrent hospitalization and mortality

Evaluate/correct potential etiologies and precipitating factors

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Treatment Consideration :Evaluate chronic therapy

Diuretic

- Increase PO dose vs. administer IV

Beta blocker

- Remember the three with mortality benefit in HFrEF
- ONLY STOP IF:
  - Initiation or up-titration led to decompensation
  - Hypotension or cardiogenic shock

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Treatment Consideration :Evaluate chronic therapy

ACE-I/ARB/Aldosterone Antagonist

- Discontinue if:
  - Acute Kidney Injury (increased SCr, BUN, or BUN:SCr ratio)
  - Hyperkalemia
  - Oliguria

Digoxin

- Only discontinue if:
  - Serum concentration increased (goal: 0.5-1.0 ng/mL)
  - Typically decrease the dose →→discontinuation = worsening HF

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Treatment Overview

Diet restriction: less than 2 grams sodium/day

Fluid restriction: less than 2 L fluid/day

Continuation of home HF medications if possible

Use of IV diuretics, vasodilators, positive inotropes

- balance medication benefit against potential toxicities:
  - electrolyte depletion, hypotension, renal dysfunction, myocardial ischemia, arrhythmias

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Treatment Overview

Discuss the appropriate use and monitoring of the following intravenous therapies in acute decompensated heart failure:

diuretics	vasodilators	inotropes

Devise a plan to produce an effective diuresis in a patient who is exhibiting diuretic resistance.

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IV Loop Diuretics

Improve congestion symptoms

Cautions/monitoring:

- Hypotension, dehydration, worsening renal function, electrolyte abnormalities
- Ototoxicity: hearing impairment (reversible or permanent) after rapid IV administration; tinnitus

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DIURETICS

Role: Decrease Volume

- First line in acute HF

IV loop diuretics

- Furosemide PO:IV = 2:1
- Bumetanide PO:IV = 1:1
- Torsemide PO:IV = 1:1

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DIURETICS

Need to initiate therapy ≥ home dose

- Typically increase home dose , double good starting point

Titrate to achieve desired diuresis

Goal urine output:

- > 500 mL in 1st 2 hours for SCr < 2.5 mg/dL
- > 250 mL in 1st 2 hours for SCr > 2.5 mg/dL

Monitor BP, electrolytes (Na, Mg, K), HF symptoms

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Diuretic Resistance Management

Use of larger, IV doses of loop diuretic

- Increase dose rather than frequency
- Initial IV dose should equal or exceed chronic PO dose

Continuous infusion of loop diuretic

- Maintain constant blockade and prevent rebound sodium and water retention between doses
- bumetanide: 1 mg IV load then 0.5 to 2 mg per hour
- furosemide: 40 mg IV load then 10 to 40 mg per hour
- torsemide: 20 mg IV load then 5 to 20 mg per hour

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Diuretic Resistance Management

Poor response to large doses of loop diuretic

Mechanism:

- Rate of PO absorption is longer →peak reduced
  - Drug concentrations unable to reach threshold for effective diuresis
- Distal tubule hypertrophy ? increased Na reabsorption in distal tubule

Treatment Options:

- Increase dose of loop diuretic
- Increase frequency of loop diuretic (continuous infusion?)
- Sequential blockade of nephron
  - Addition of thiazide/thiazide-like diuretic (typically metolazone)
  - Administer 30 minutes prior to loop diuretic

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Combination Diuretic Therapy

Higher risk for adverse reactions

- Volume depletion
- Electrolyte abnormalities
  - Na, K, Mg

Appropriate use

- Inpatient
- Outpatient
  - Lower doses/ Less frequent dosing (ie – 1-3x/week)
  - Close follow-up/frequent monitoring
  - Counseling : take thiazide/thiazide-like diuretic 30 minutes prior to administration of loop diuretic

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Loop Diuretics	Furosemide	Bumetanide	Torsemide
Equivalent dose	IV: 40 mg PO: variable (~ 80 mg)	IV: 1 mg PO: 1 mg	IV: 20 mg PO: 20 mg
Pharmacokinetics (Oral)			
Bioavailability	variable (average ~ 50%)	~ 80%	~ 80%

Adapted From: Pharmacotherapy 10th edition (Table 15-3, Diuretics Commonly Utilized for the Management of ADHF)

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Loop Diuretics	Furosemide	Bumetanide	Torsemide
Ceiling dose (intravenous) single dose above which additional response is unlikely to be observed			
normal renal function	40 – 80 mg	1–2 mg	10-20 mg
moderate renal impairment	80-160 mg	4-8 mg	20-50 mg
severe renal impairment	160-200 mg	8–10 mg	50-100 mg

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Drug	Dose	PAOP	CO	SVR
Dobutamine	usual range: 2.5-20 mcg/kg/min	–	+	–
Milrinone	loading dose (optional): 50 mcg/kg usual range: 0.1-0.75 mcg/kg/min	–	+	–
Nitroprusside	0.3-0.5 mcg/kg/min, increase by 0.5 mcg/kg/min up to 3 mcg/kg/min	–	+	–
Nitroglycerin	5 mcg/min, titrate by 5 mcg/min every 3-5 min up to 20 mcg/min. If no response at 20 mcg/min, titrate by 10 mcg/min every 3-5 min up to 200 mcg/min	–	0/+	0/–
Nesiritide	Bolus (may omit): 2 mcg/kg Infusion: 0.01 mcg/kg/min (limited experience with increasing the dose >0.01 mcg/kg/minute)	–	+	–
Furosemide	20–80 mg, repeated as needed (up to every 6 hours)	–	0	0

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Vasopressin Receptor Antagonists

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Vasopressin Antagonist

Tolvaptan, conivaptan – V_2 receptor antagonist

- Excretion of free water (without loss of sodium)
- Increases urine output and increases serum sodium

Indicated for hypervolemic hyponatremia (Na<125mmol/l

- May be considered short term if persistent severe hyponatremia
  - can improve cognitive symptoms of hyponatremia
- Must be initiated in hospital setting to avoid excessive fluid loss and rapid shifts in sodium

EVEREST Trial (NHYA III-IV) compared to placebo

- Improved hyponatremia, diuresis, congestion
- Did not improve mortality or rehospitalization

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Vasopressin Receptor Antagonists

	Tolvaptan	Conivaptan
Place in therapy	• Diuresis for treatment of severe hypervolemic hyponatremia, **when serum Na <125 mEq/L** • Acute setting ONLY	
Mechanism of effect	• Inhibits V_2 receptor in renal tubules → diuresis	NOT approved for use in HF
Dose	• 15 mg PO q day, then titrate at 24 h intervals to 30mg or 60mg daily for resolution of hyponatremia	
Considerations	• 3A4 substrate • MUST use fluid restriction and maximize medical therapy	
Monitoring	• Frequent serum Na (ie q6 hours) • Risk for damage to CNS tissue with rapid rise	

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Vasodilator Therapy

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IV Vasodilators

Vasodilator	arterial vasodilation (decrease afterload)	venous vasodilation (decrease preload)
Nitroglycerin	some arterial vasodilation at high doses	+
Nitroprusside	+	+
Nesiritide	+	+

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IV Vasodilators

Role:

- Decrease symptoms of volume overload (venous dilation)
  - Decrease in preload →decreased pulmonary congestion
- Increase in cardiac output (arterial dilation)
  - Decrease in vascular resistance →decrease afterload → increased CO

Agents:

- Nitroprusside → arterial and venous dilation
- Nitroglycerin → vasodilation > arterial dilation
- Nesiritide →arterial and venous dilation

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IV Vasodilators

Adjunct to diuretic therapy when:

- Symptoms persist OR
- Acute pulmonary edema OR
- Severe hypertension

Avoid vasodilators if systolic blood pressure is < 90 mmHg or symptomatic hypotension

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Vasodilators

	Nitroprusside	Nitroglycerin	Nesiritide
Administration	IV continuous infusion, titrate (↑ dose) as tolerated		
Initial Dose	• 0.1-0.2 mcg/kg/min	• 5-10mcg/min	• 0.01mcg/kg/min • LD 2mcg/kg
Adverse Effects	HYPOTENSION!!		
Considerations	• Requires invasive hemodynamic monitoring • Renal dysfunction – potential for cyanide toxicity • Can cause rebound phenomenon with abrupt withdrawal	• Tachyphylaxis	• Recombinant BNP → diuresis/natriuresis • Very expensive

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IV Vasodilators

Nitroglycerin

- Preferred for preload reduction
- Ideal agent for patients with hypertension, coronary ischemia, or mitral regurgitation

Nitroprusside

- Equally reduces preload and afterload

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Drug	Dose	PAOP	CO	SVR
Dobutamine	usual range: 2.5-20 mcg/kg/min	–	+	–
Milrinone	loading dose (optional): 50 mcg/kg usual range: 0.1-0.75 mcg/kg/min	–	+	–
Nitroprusside	0.3-0.5 mcg/kg/min, increase by 0.5 mcg/kg/min up to 3 mcg/kg/min	–	+	–
Nitroglycerin	5 mcg/min, titrate by 5 mcg/min every 3-5 min up to 20 mcg/min. If no response at 20 mcg/min, titrate by 10 mcg/min every 3-5 min up to 200 mcg/min	–	0/+ (at higher doses)	0/– (at higher doses)
Nesiritide	Bolus (may omit): 2 mcg/kg Infusion: 0.01 mcg/kg/min (limited experience with increasing the dose >0.01 mcg/kg/minute)	–	+	–
Furosemide	20–80 mg, repeated as needed (up to every 6 hours)	–	0	0

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Positive Inotropic Therapy

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Positive Inotropes

Role: Increase cardiac output → increased perfusion

Place in therapy:

- Cardiogenic shock, end organ dysfunction in stage D

Both are proarrhythmic!

Typically require ICU admission → both continuous IV infusions

Monitoring:

- Vitals Q15min until stable, then Q30min x 1 hr, then Q4H
- Urine output
- Symptoms

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Positive Inotropes

Dobutamine:

- Stimulation of β_1 → increased contractile force
  - May also cause tachycardia
  - Consider if hypotensive

Milrinone:

- Inhibits PDE_3 → increased contractile force
  - Also causes some vasodilation → hypotension
  - Consider if receiving beta-blocker therapy
  - Reduce dose in renal dysfunction

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Positive Inotropic Agents

Dobutamine, milrinone – most common

Dopamine

- may be preferable to dobutamine or milrinone in patient with marked systemic hypotension or cardiogenic shock
  - if MAP < ~65 mm Hg
  - dose dependent effects on beta and alpha receptors

Digoxin not routinely used

- delayed effect, long duration of action, limited inotropic effect and potential toxicity

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Drug	Dose	PAOP	CO	SVR
Dobutamine	usual range: 2.5-20 mcg/kg/min	–	+	–
Milrinone	loading dose (optional): 50 mcg/kg usual range: 0.1-0.75 mcg/kg/min	–	+	–
Nitroprusside	0.3-0.5 mcg/kg/min, increase by 0.5 mcg/kg/min up to 3 mcg/kg/min	–	+	–
Nitroglycerin	5 mcg/min, titrate by 5 mcg/min every 3-5 min up to 20 mcg/min. If no response at 20 mcg/min, titrate by 10 mcg/min every 3-5 min up to 200 mcg/min	–	0/+	0/–
Nesiritide	Bolus (may omit): 2 mcg/kg Infusion: 0.01 mcg/kg/min (limited experience with increasing the dose >0.01 mcg/kg/minute)	–	+	–
Furosemide	20–80 mg, repeated as needed (up to every 6 hours)	–	0	0

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Develop an appropriate pharmacotherapy regimen and monitoring plan for a patient with acute decompensated heart failure based on the patient's clinical presentation and hemodynamic parameters.

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Management Strategy

- **Subset I (dry and warm):**
  - PAOP within acceptable range, normal CI
  - Patients won't be admitted for decompensation if subset I
  - May be admitted for other reasons
  - maximize oral therapy and monitor
    - ACE-I/ARB, beta blocker, aldosterone antagonist, etc
    - Increase to target doses

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Treatment Approach/Subset II – Warm and Wet

Majority of HF decompensations that you will see

Fluid overloaded with adequate cardiac output

- Signs and symptoms of fluid overload
  - JVD, Crackles/rales, Edema
  - S3
  - Difficulty of breathing
  - Recent weight gain
- No signs/symptoms of low cardiac output
  - Responding to diuretic therapy
  - Adequate urine output
  - Extremities warm

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Treatment Approach/Subset II – Warm and Wet

Goal of therapy: reduce congestion

Avoid reductions in cardiac output or increases in HR

Diuresis

- IV loop diuretic
- Usually provides some relief of symptoms within a few hours

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Treatment Approach/Subset II – Warm and Wet

Venodilation

- Nitroglycerin, nitroprusside, nesiritide
- Relief of symptoms much quicker
- Reserved for patients with acute pulmonary congestion, severe hypertension, persistent symptoms despite diuresis

Sodium restriction (< 2 gm/day)

Fluid restriction (< 2 L/day)

- For patients presenting with moderate hyponatremia (< 130 mEq/L)

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Management Strategy

Subset III (dry and cold):

- Decreased CI, acceptable (or low) PAOP
- If PAOP < 15 mmHg: IV fluids needed to optimize CO (remove fluid restriction or administer fluids until PAOP 15-18 mmHg)
- If CI is low despite acceptable PAOP:
  - Use **arterial** vasodilator to decrease SVR and increase CO
  - Use inotrope if hypotension and/or worsening renal function
  - Add inotrope to vasodilator if no improvement in CI/symptoms
  - Dopamine may be needed if MAP < ~ 65 mm Hg

Guidelines recommend vasodilators prior to inotropes

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Management Strategy

Subset IV (wet and cold):

- Elevated PAOP, decreased CI
- Cannot maintain adequate CI despite elevated left ventricular filling pressure
  - Use diuretics +/-vasodilators (**venous and/or arterial**)
  - Use inotrope if hypotension and/or worsening renal function (may use diuretics with inotrope as tolerated)
  - Dopamine may be needed if MAP < ~65 mm Hg

Guidelines recommend vasodilators prior to inotropes

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Management Strategy

Use of Inotropes

Guidelines recommend using vasodilators prior to inotropes for cold patients

Reserve inotropes for cold patients with:

- **reduced perfusion (organ hypoperfusion – worsening renal function)**
- **low systolic blood pressure (less than 90 mmHg) or symptomatic hypotension**
- **Unresponsive to (or cannot tolerate) vasodilators**
- **Inotropes may also be considered in wet patients who are not responding to IV diuretics or develop worsening renal function on diuretics**

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Summary

Determine potential causes to the patient's decompensation

- Medications, compliance, comorbidities, etc.
- Correct or remove

Determine if the patient is congested, hypoperfusion or both

- Determination of how to treat

If a patient is not responding adequately to diuresis, increase dose/frequency, or addition of thiazide-like diuretic (metolazone)

- Addition of venodilators if rapid resolution of symptoms necessary
- If unresponsive to the above, can consider hemodialysis to remove fluid

Vasodilators and inotropic agents may need to be used for patients with significant hypoperfusion unresponsive to, or who are unable to tolerate fluid resuscitation

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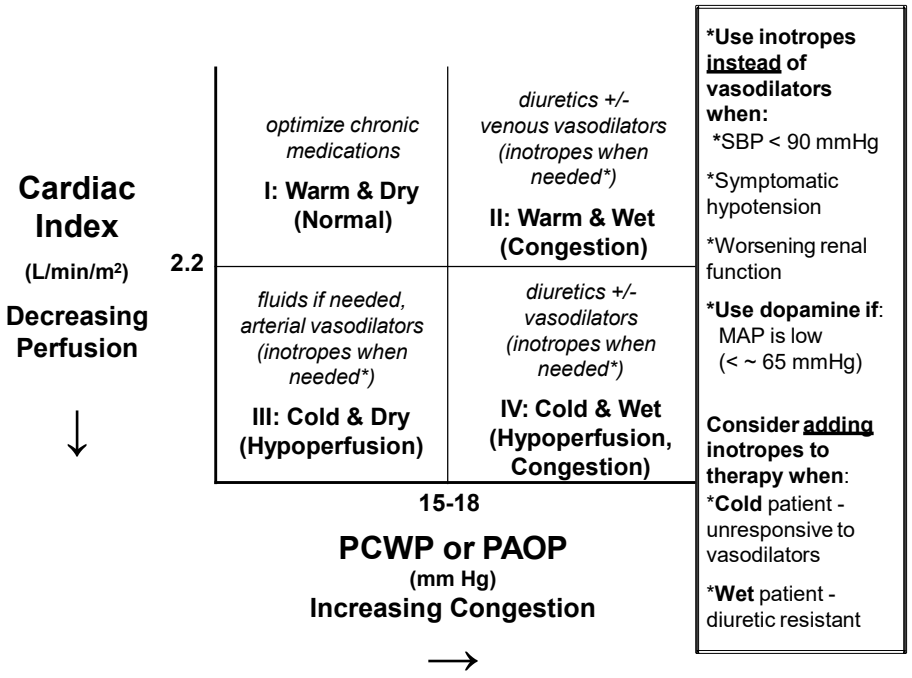

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Continuation of Chronic HF Therapies

- Recommended that chronic heart failure therapy is continued in most patients in the **absence of hemodynamic instability** or **contraindications**
  - Consider holding ACE, ARB, spironolactone (or dosage reduction) in patients with worsening renal function
  - Consider holding beta blocker (or dosage reduction) in patients hospitalized after recent beta blocker initiation/dosage increase
  - Beta blocker initiation is recommended in stable patients once euvolemic and discontinuation of IV medications (diuretics, vasodilators and inotropic agents)

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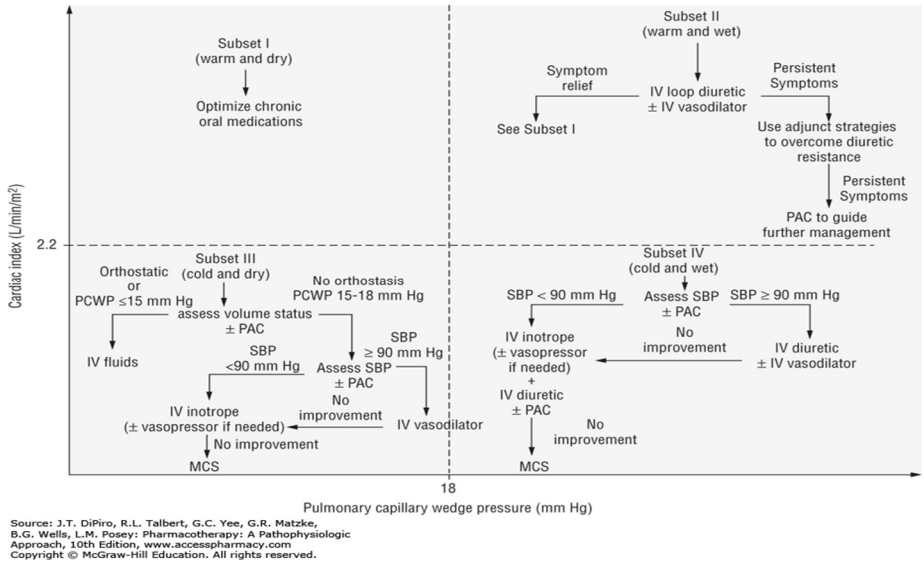

General management algorithm for acute decompensated heart failure based on clinical presentation.

Patients may be categorized into a hemodynamic subset based on signs and symptoms or invasive hemodynamic monitoring. Adjunct strategies for overcoming diuretic resistance include increasing the dose of loop diuretic; switching to a continuous infusion; adding a diuretic with an alternative mechanism of action, an IV vasodilator, or an IV inotrope; and in select patients, ultrafiltration or a vasopressin antagonist. (IV, intravenous; MCS, mechanical circulatory support; PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure.)

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