MAYO CLINIC

Don’t be Salty: Non-inotropic Strategies to Overcome Loop Diuretic Resistance

in Acute Decompensated Heart Failure

Lindsay Moreland-Head, PharmD

Pharmacy Grand Rounds
July 7, 2020

Abbreviations:

- ADHF: Acute Decompensated Heart Failure
- HF: Heart failure
- AA: African American
- PMH: Past medical history
- HTN: Hypertension
- T2DM: Type 2 Diabetes Mellitus
- HFrEF: Heart failure with reduced ejection fraction
- CAD s/p DES: Coronary artery disease status post drug eluting stents
- CO: Cardiac output
- RAAS: Renin-angiotensin-aldosterone system
- (S)BP: (systolic) blood pressure
- JVP: Jugular venous pressure
- BNP: Brain natriuretic peptide
- Na: Sodium
- Cl: Chloride
- CXR: Chest x-ray
- CT: Computerized tomography
- NKCC2: Sodium-potassium-chloride cotransporter
- GI: Gastrointestinal
- OAT: Organic anion transporter
- NSAID: Non-steroidal anti-inflammatory drug
- CKD: Chronic kidney disease
- (e)GFR: (estimated) glomerular filtration rate
- PK: Pharmacokinetics
- PD: Pharmacodynamics
- PCT: Proximal convoluted tubule
- DCT: Distal convoluted tubule
- PA: Pulmonary artery
- PCWP: Pulmonary capillary wedge pressure
- FE: Furosemide equivalents
- UF: Ultrafiltration
- RRT: Renal replacement therapy
- BMI: Body mass index
- ITT: Intent-to-treat
- BUN: Blood urea nitrogen
- HS: Hypertonic Saline
- CICU: Cardiac intensive care unit
- IQR: interquartile range
- LVAD: Left ventricular assist device
- K: Potassium

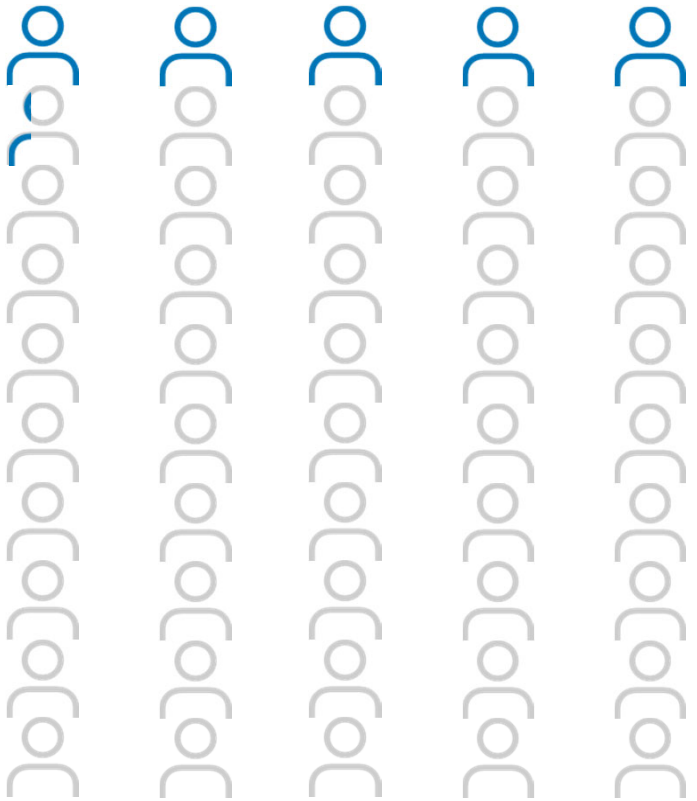
Learning Objectives

- Describe the pathophysiology of intravascular versus tissue congestion in ADHF.
- Explain the mechanisms of diuretic resistance in ADHF and why non-inotropic strategies may help augment diuresis.
- Discuss the literature on non-inotropic strategies to decongest patients and overcome loop diuretic resistance in ADHF.

Heart Failure By the Numbers

- ~6.5 million people in the U.S.
- ~24% of those in North America are admitted for ADHF with rales as a sign of congestion
- Development of congestion leading to ADHF increases mortality
- 30-50% of patients admitted for ADHF will leave with residual congestion, increasing mortality
- 1 in 8 deaths in 2017 due to heart failure

12.5% of deaths due to HF



Heart disease and stroke statistics—2019 update: a report from the American Heart Association
Centers for Disease Control and Prevention, National Center for Health Statistics. Underlying Cause of Death, 1999–2017.

Patient Case

MC is a 63-year-old AA male admitted to the hospital with a complaint of shortness of breath and pitting edema in his lower extremities. His PMH is significant for HTN, T2DM, HFrEF (30%) secondary to CAD s/p DES x3, and gout.

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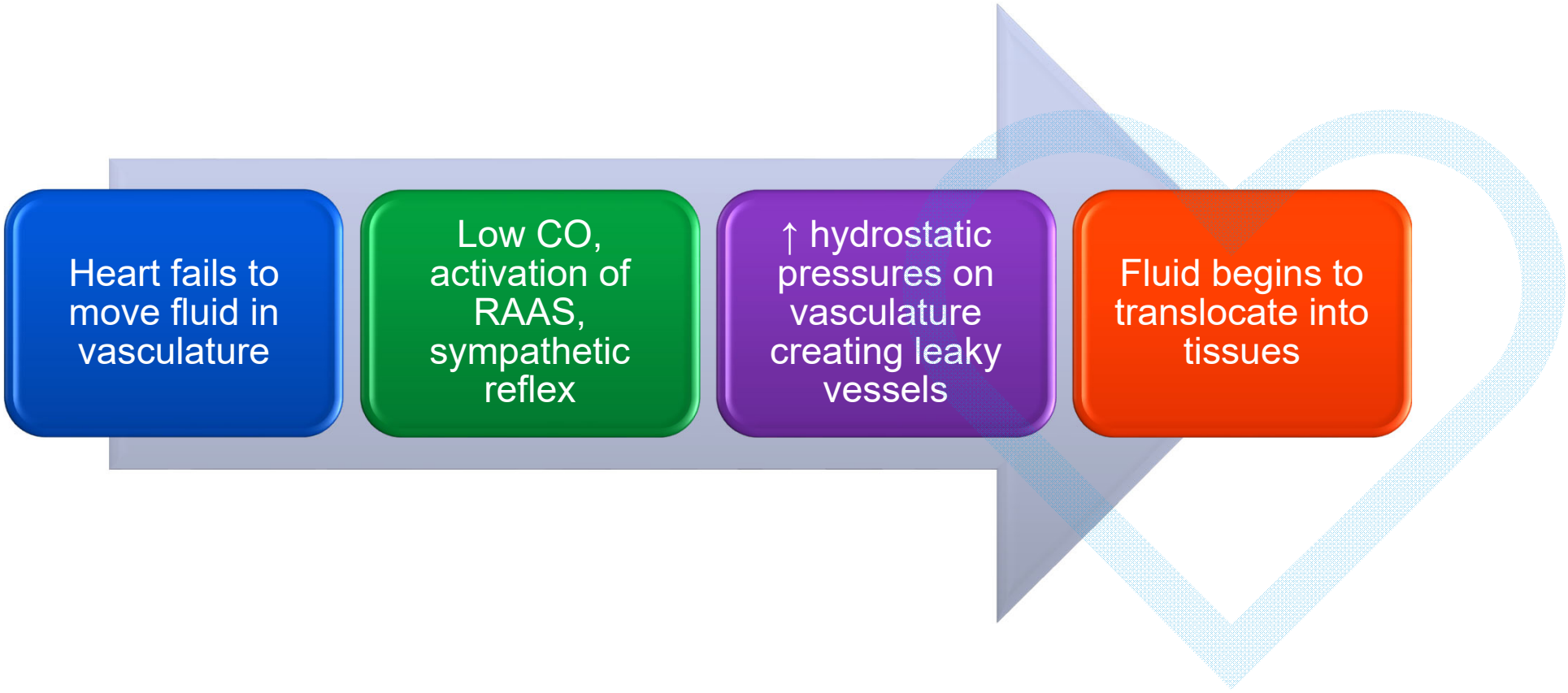
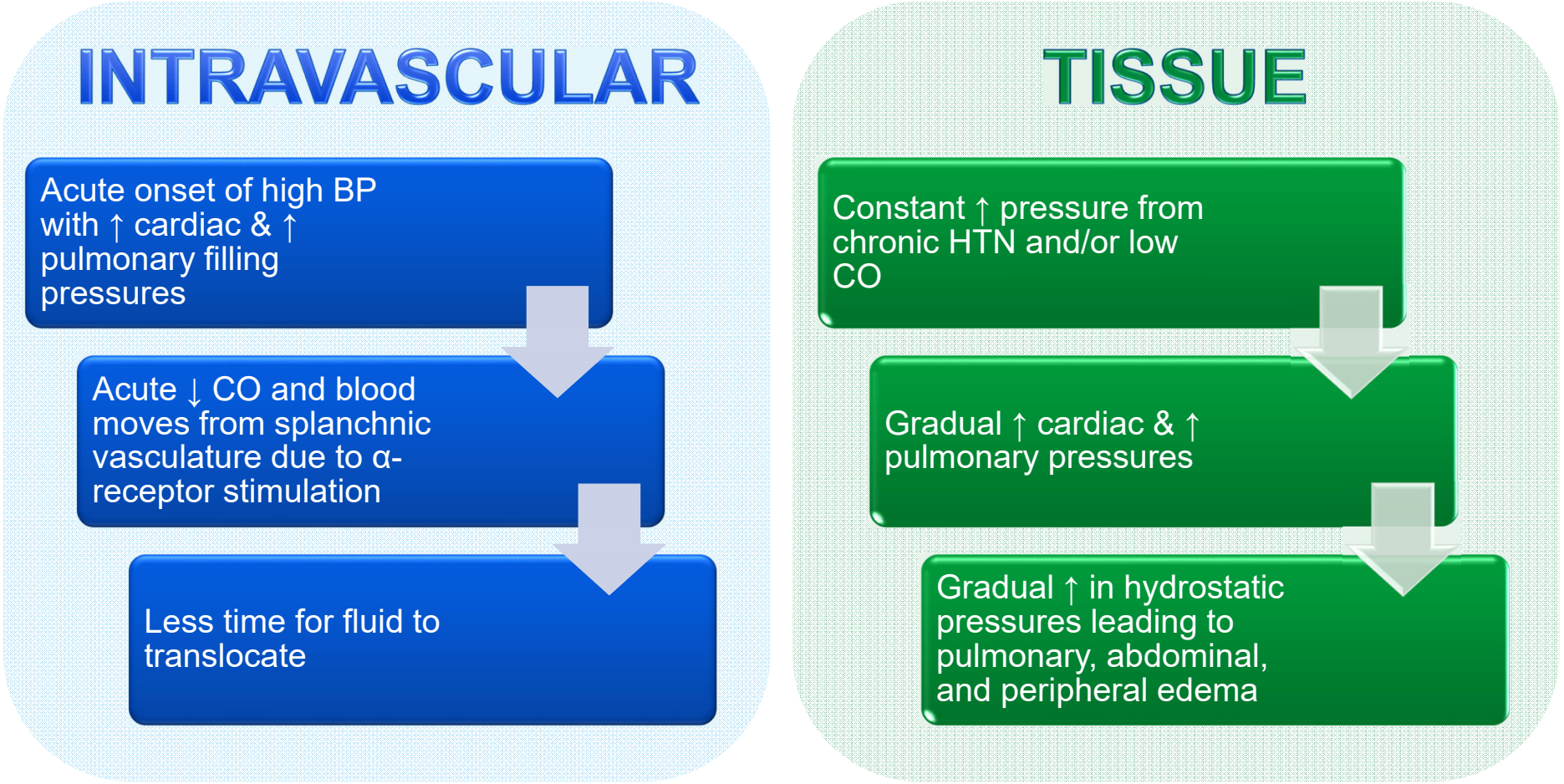
CONGESTION



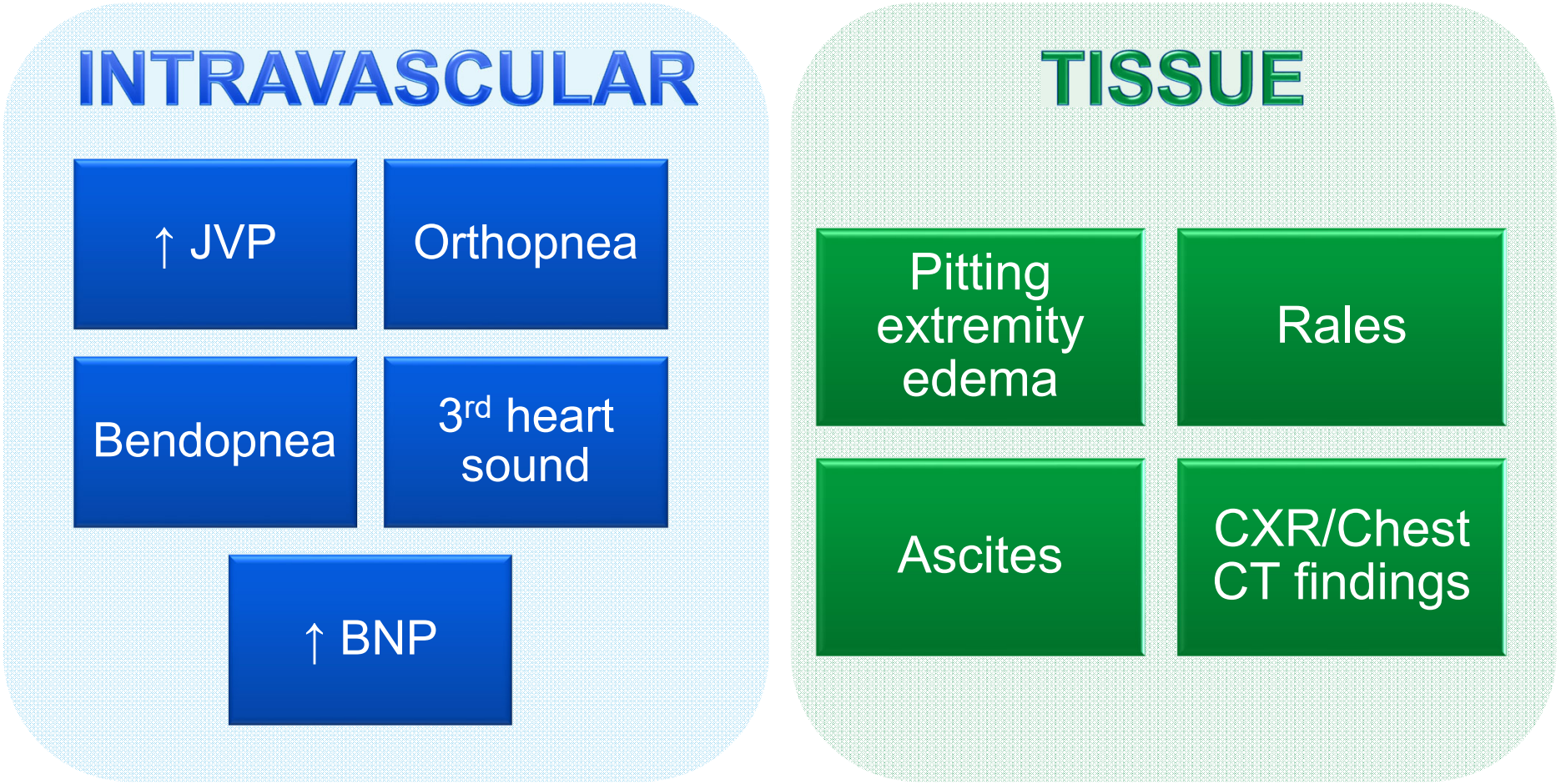
Boorsman EM et el. Nat Rev Cardiol. May 2020.

PATHOPHYSIOLOGY OF CONGESTION



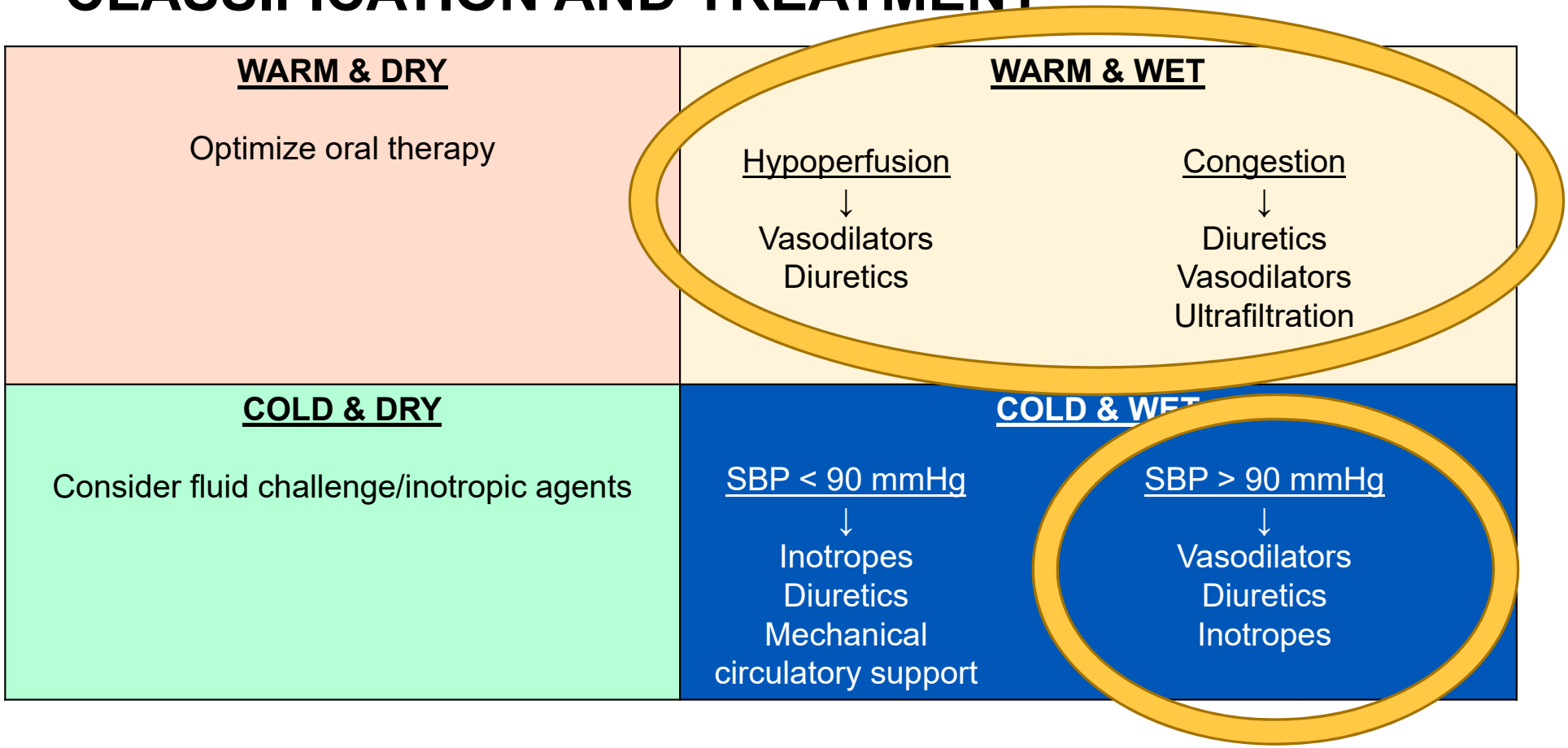
Boorsman EM et el. Nat Rev Cardiol. May 2020.

SIGNS & SYMPTOMS OF CONGESTION



Boorsman EM et el. Nat Rev Cardiol. May 2020.

CLASSIFICATION AND TREATMENT



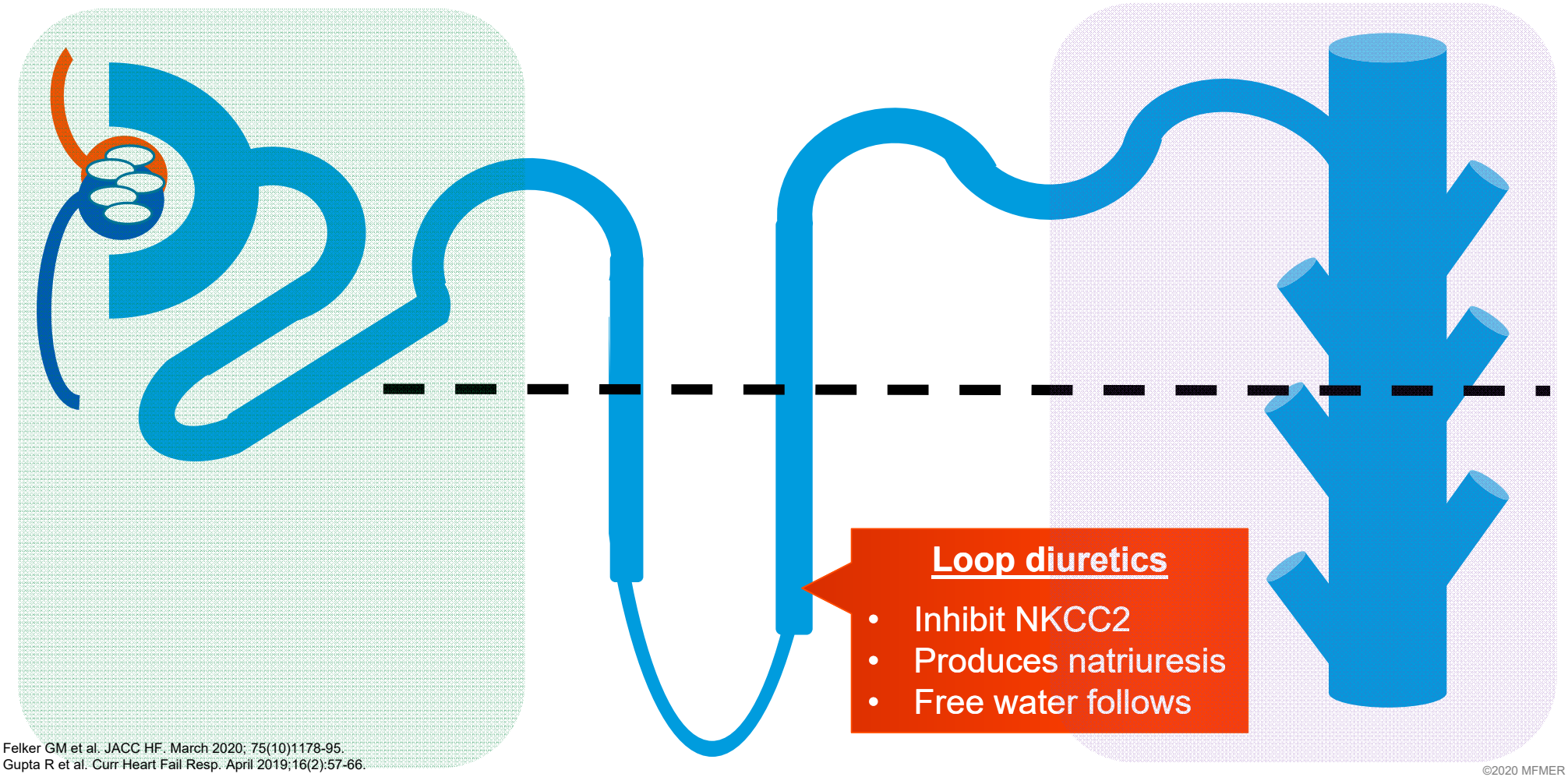
2013 ACCF/AHA Heart Failure Guidelines: Executive Summary. JACC.
Headley JM. Invasive Hemodynamic Monitoring: Physiological Principles and Clinical Applications. Edwards Life Sciences.
Jentzer JC et al. J Cardiovasc Pharmacol Ther. 2014;12:1-13.

CONGESTION TREATMENT

- Loop diuretic therapy mainstay of treatment
- ↓ Osmolality of circulating blood
- Slows shift from tissues to vasculature
- Neurohormonal activation and ↓ renal function
- Persistent tissue congestion

Boorsman EM et el. Nat Rev Cardiol. May 2020.
Felker GM et al. JACC HF. March 2020; 75(10)1178-95.
Gupta R et al. Curr Heart Fail Resp. April 2019;16(2):57-66.

LOOP DIURETIC SITE ACTION IN NEPHRON



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Dr. Ace comes to examine MC and finds an elevated JVP, rales, and mild ascites. He diagnoses him with decompensated HF.

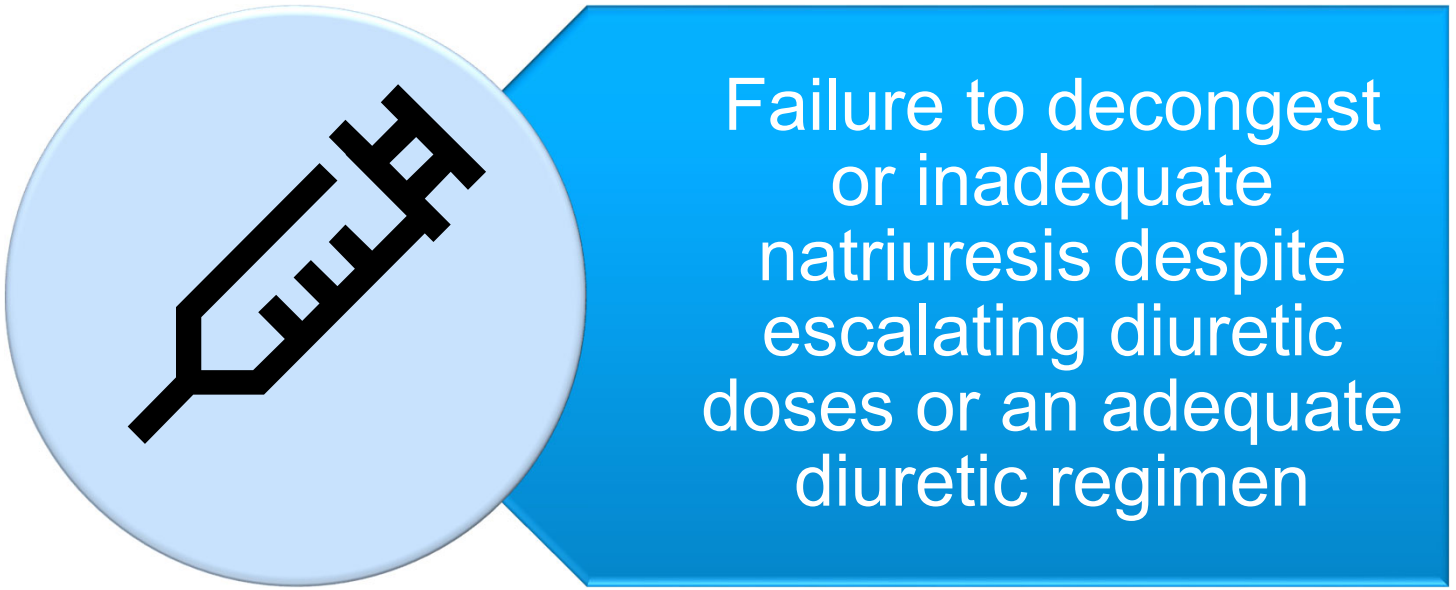
Assessment Question

Based on MC's presentation and exam findings, what type of congestion is present?

- Tissue congestion
- Intravascular congestion
- Mixed tissue and intravascular congestion

- Describe the pathophysiology of intravascular versus tissue congestion in ADHF.
- Explain the mechanisms of diuretic resistance in ADHF and why non-inotropic strategies may help augment diuresis.
- Discuss the literature on non-inotropic strategies to decongest patients and overcome loop diuretic resistance in ADHF.

DIURETIC RESISTANCE



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FURTHER DEFINED AS...

- Lack of adequate decrease in total body water
  - Weight
  - Urine based metrics
- Misses potential upstream cause of volume—Na (and Cl)
- Urine Na is a marker of natriuresis
- Urine Na has been found to correlate with predicted outcomes after loop diuretic administration alone
- Studies have shown that urine Na <35-65 mmol/L result in worse clinical outcomes such as worsening HF, ↑ 30 readmissions, poor diuretic response, decrease weight loss, etc.

Mullens W et al. Eur J Heart Fail 2019;21:137–55.
Felker GM et al. JACC HF. March 2020; 75(10)1178-95.
Gupta R et al. Curr Heart Fail Resp. April 2019;16(2):57-66.

PK/PD EFFECTS ON LOOP DIURETICS

GI Absorption	Delivery to Kidney, Secretion to tubule, Binding to NKCC2	Nephron Adaptations & Remodeling
• Oral administration • Which loop diretic is used • Furosemide slower absorption and lower bioavailabilty • Gut edema may slow absorption & natriuresis	• >90% bound to albumin • Must use OAT to enter proximal tubule which may develop resistance • Chronic NSAID use may ↑ NKCC2 • CKD: suppresses Na reabsorption in nephron	• At least partially excreted via kidneys—especially prolongs furosemide half-life • Chronic use creates compensatory Na retention distally and potentially proximally

Boorsman EM et el. Nat Rev Cardiol. May 2020.
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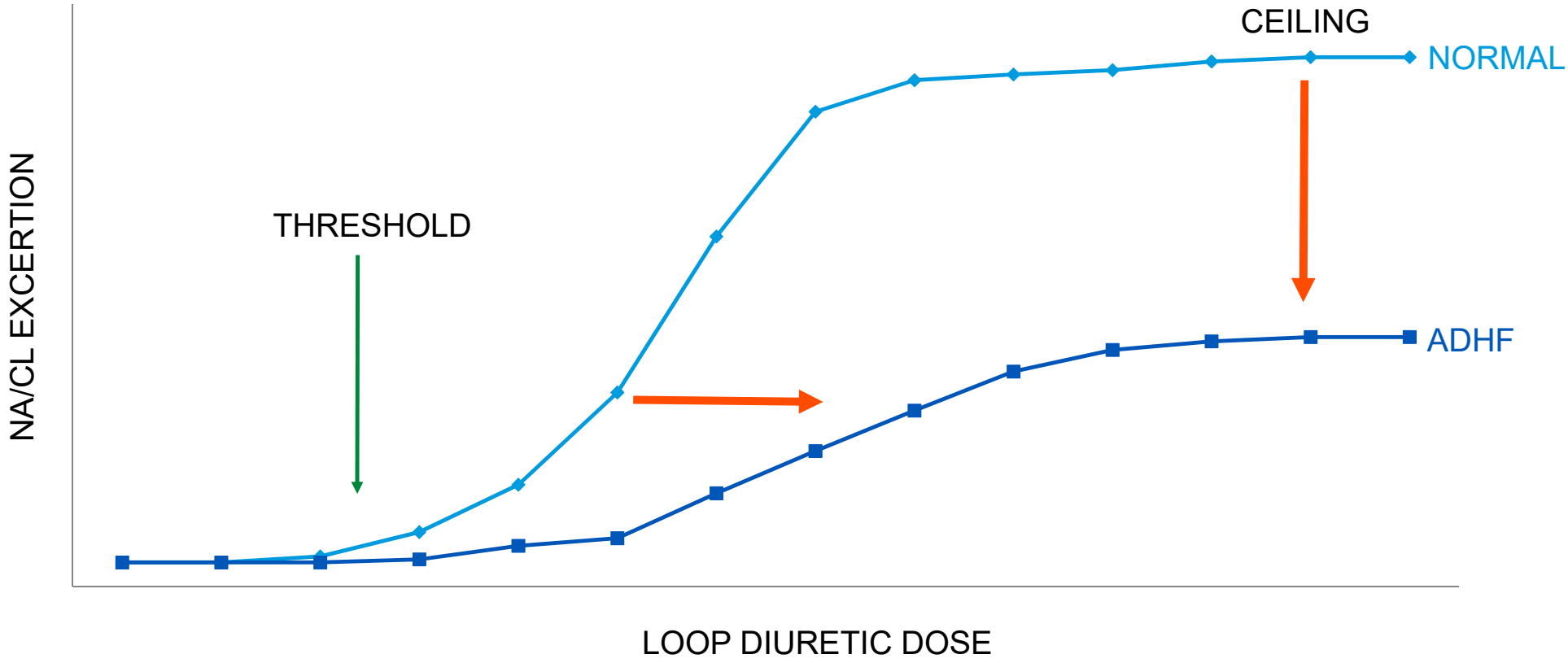
LOOP DIURETIC DOSE RESPONSE



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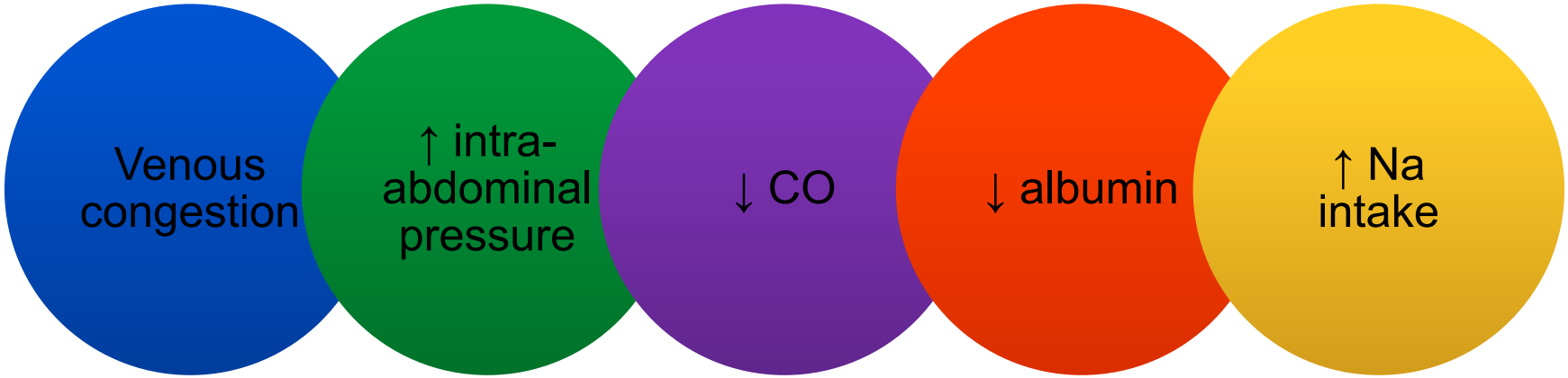
PRE-RENAL MECHANISMS OF DIURETIC RESISTANCE



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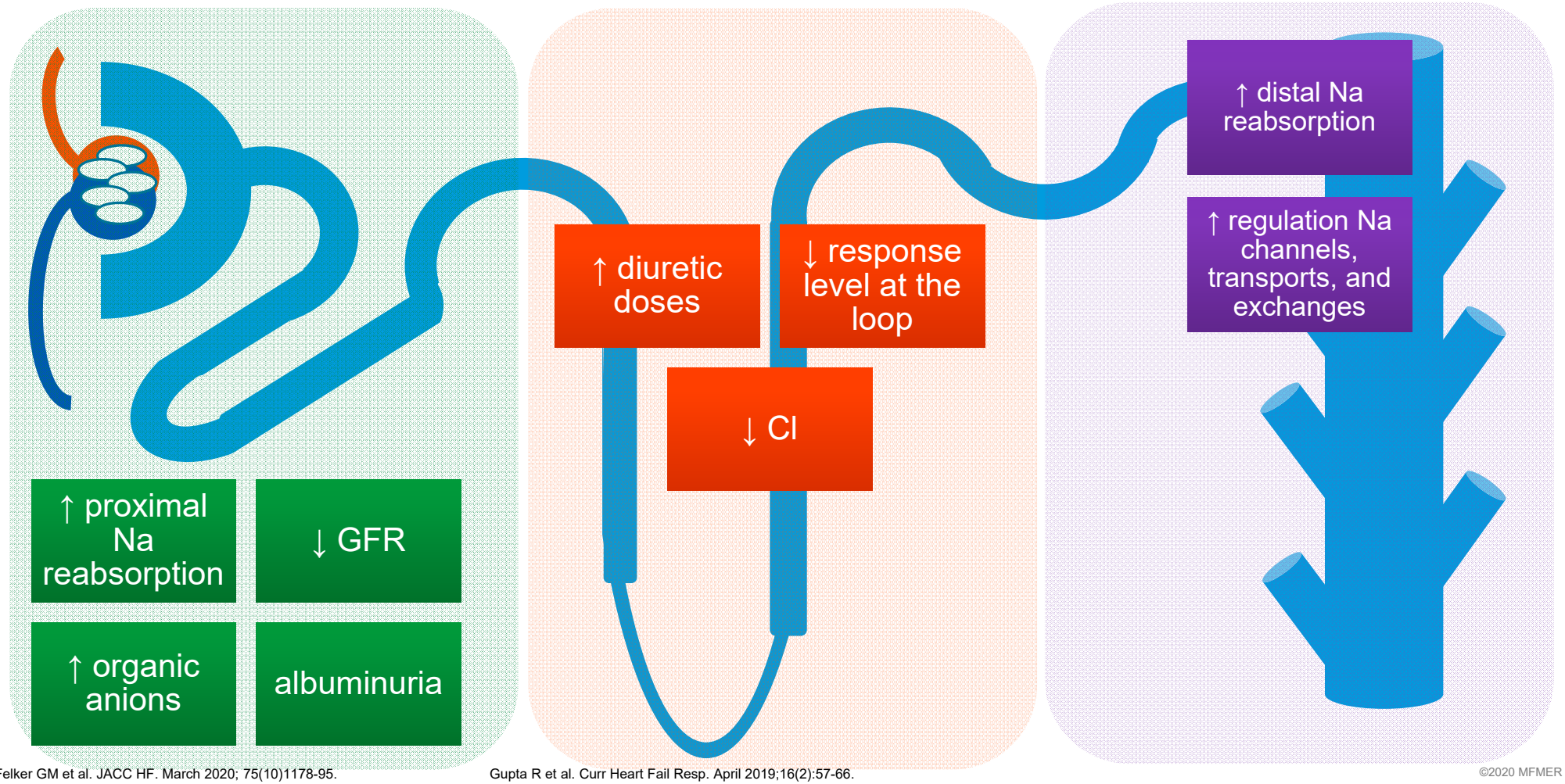
INTRA-RENAL MECHANISMS OF DIURETIC RESISTANCE



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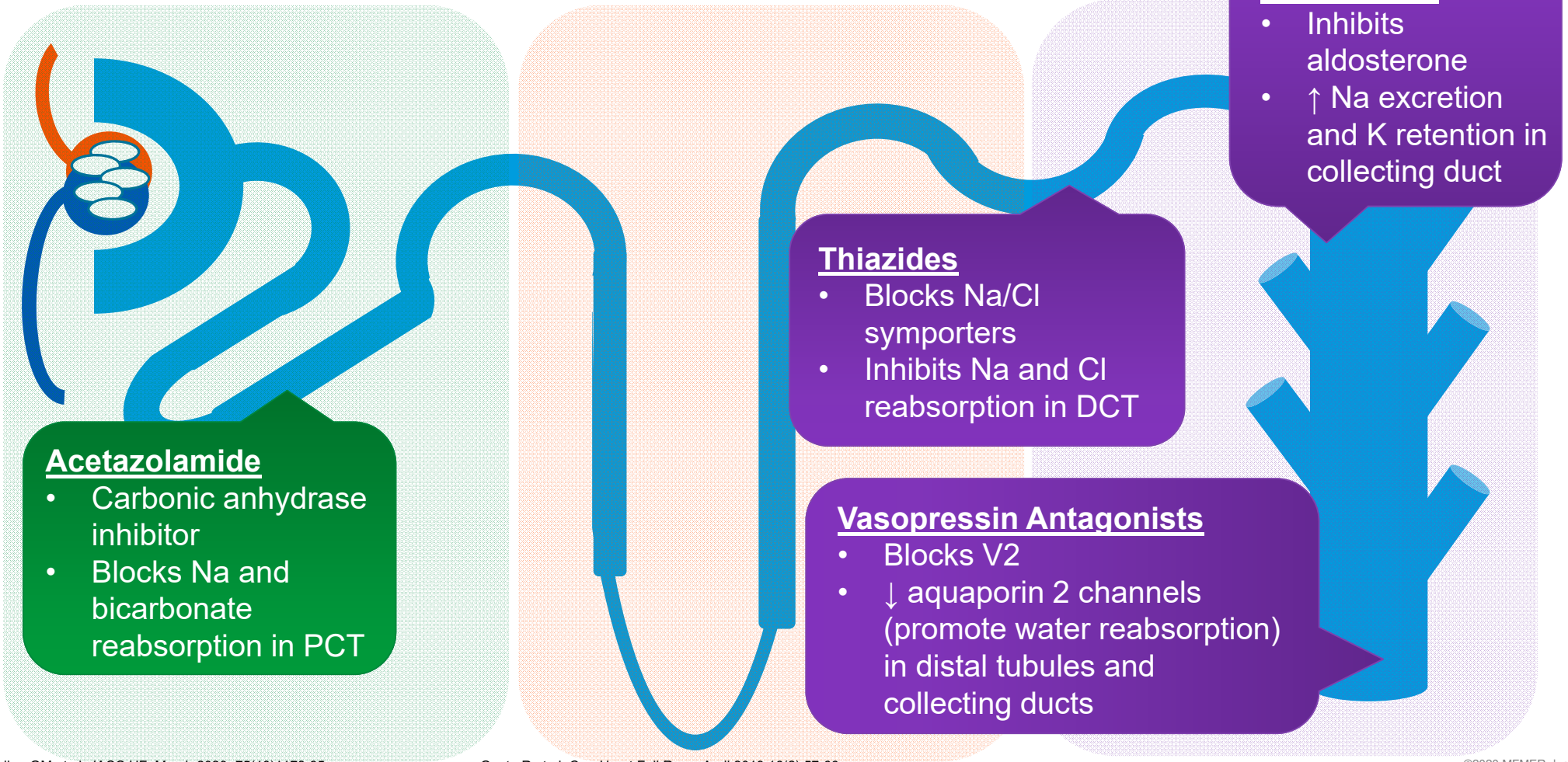
SEQUENTIAL BLOCKADE



Acetazolamide
- Carbonic anhydrase inhibitor
- Blocks Na and bicarbonate reabsorption in PCT

Thiazides
- Blocks Na/Cl symporters
- Inhibits Na and Cl reabsorption in DCT

Vasopressin Antagonists
- Blocks V2
- ↓ aquaporin 2 channels (promote water reabsorption) in distal tubules and collecting ducts

Aldosterone Antagonists
- Inhibits aldosterone
- ↑ Na excretion and K retention in collecting duct

Felker GM et al. JACC HF. March 2020; 75(10)1178-95.
Gupta R et al. Curr Heart Fail Resp. April 2019;16(2):57-66.

Patient Case

MC is on a furosemide drip at 25 mg/hour after being titrated to help manage his congestion from ADHF. His weight is remaining unchanged, urine output is decreasing, and he is developing hyponatremia. Dr. Ace decides to give tolvapatan.

Assessment Question

How may tolvapatan help augment diuresis and overcome resistance?

- Increases bicarbonate excretion to help with alkalosis
- Creates further natriuresis in DCT
- Increases K by acting in collecting duct
- Increases water output and prevent further hyponatremia

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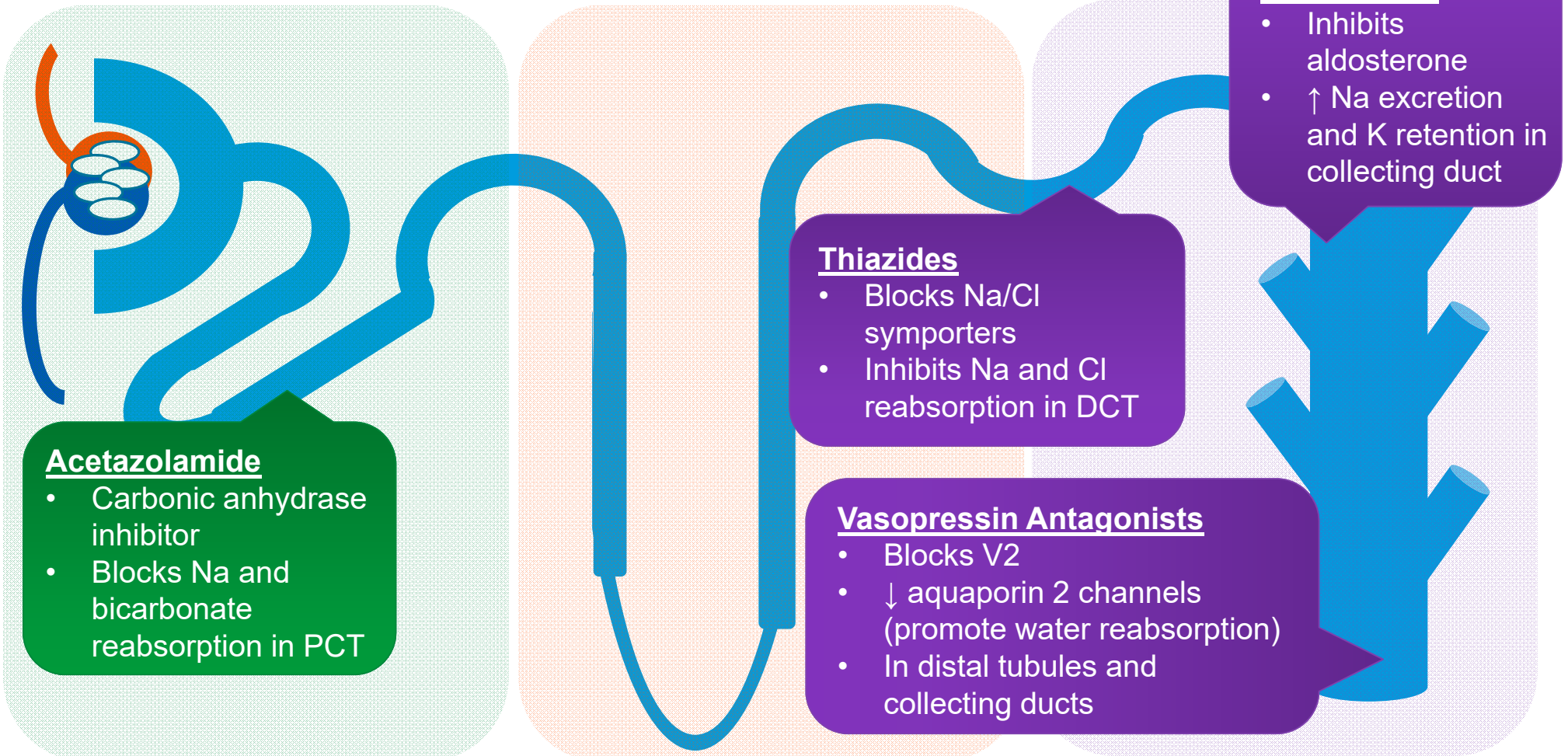

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ACETAZOLAMIDE

1952: First diuretic

- Popular until 1966 when furosemide entered the market

Several smaller studies and a meta-analysis

- Showing a potential increase in natriuresis when given in addition to loop diuretics
- Also may improve respiratory symptoms

Acetazolamide in Decompensated Heart Failure With Volume OveRload (ADVOR)

- Prospective trial currently enrolling to answer: "Is adding acetazolamide to a high dose loop diuretic regimen effective at decongesting a patient in ADHF?"
- Primary outcome: treatment success (decongestion achieved) on the morning of day 4 without the need for escalating diuretic strategy on the morning

Verbrugge, F et al. Eur. J Heart Fail. 2019;21:1415–1422.
Imiela T et al. Clin Drug Investig. 2017 Dec;37(12):1175-1.
Mullens, W. et al. Eur J Heart Fail. 2018;20:1591–1600.
Wongboonsin, J et al. J Clin Med. 2019;8,:E349.
Nunez J et al. Cardiovasc Ther. 2018 Dec;36(6):e12465

RECENT THIAZIDE LITERATURE

Jentzer et al.

- Reviewed and examined several thiazide-type diuretics
- Showed doubling in daily urine sodium excretion to induce weight loss and edema resolution
- Associated with risk of severe hypokalemia, hyponatremia, hypotension, and worsening renal function

Ng et al.

- Retrospective cohort of ADHF of 242 patients
- Metolazone in addition to furosemide vs. furosemide alone
- No difference in primary outcomes: ↑ mean hourly urine output and incidence of worsening renal function

Brisco-Bacik et al.

- Retrospective observational study of 14,000 patients across 3 hospitals with propensity matching (39 variables)
- Loop diuretic dose increases vs. adding metolazone
- "Metolazone was independently associated with hypokalemia, hyponatremia, worsening renal function and increased mortality"

Jentzer JC et al. J Am Coll Cardiol 2010; 56:1527–34.
Ng et al. J Cardiovasc Pharmacol. Ther. 2013;18:345–53.
Brisco-Bacik MA et al. J Am Heart Assoc 2018;7:e009149.

UPCOMING THIAZIDE LITERATURE

CLORTIC

- Prospective, randomized, placebo-controlled trial
- Hydrochlorothiazide vs. loop diuretics alone
- Primary outcome: change in body weight and patient-reported dyspnea from baseline until discharge

Metolazone vs. Chlorothiazide for ADHF with diuretic resistance

- Prospective, randomized, open label study
- PO metolazone 5 mg vs. IV chlorothiazide 500 mg
- Primary outcome: net urine output at 24 hours

ClinicalTrials.gov NCT01647932
ClinicalTrials.gov NCT03574857

ALDOSTERONE ANTAGONISTS

Ferreira et al.

- Single-blinded
- 100 ADHF patients
- Spironolactone 50-100 mg vs. standard of care
- Showed benefits in primary endpoint: proportion of patients free of congestion on day 3

ATHENA-HF

- Randomized, double-blinded, controlled
- 360 ADHF patients
- Spironolactone 100 mg vs. 25 mg vs. placebo
- No significance in primary endpoint: ↓ NT-pro-BNP level from baseline to 96 hours

Pilot Study—Outpatient

- Recruitment completed (10 patients per arm)
- Spironolactone 100 mg x 7 days vs. 25 mg daily
- Primary outcome: change in body weight at 7 days

Ferreira, Jet al. Eur J ntern. Med. 2014;25:67–72.
ATHENA- HF. JAMA Cardiol. 2017;2:950–8.
ClinicalTrials.gov NCT02585843.

TOLVAPTAN

EVERST

- 4133 hospitalized for ADHF randomized within 48 hours
- Tolvaptan 30 mg daily vs. placebo for minimum of 60 days
- Primary endpoints: all cause mortality and CV death or hospitalization
- No differences in primary outcomes for non-inferiority or superiority
- ↑ serum Na and thirst requiring discontinuation in 4 patients

TACTICS-HF

- 257 patients randomized with 24 hours
- Tolvaptan 30 mg daily vs. placebo with fixed dose furosemide therapy in background
- Primary endpoint: proportion of patients responded in 24 hours
- No difference in response
- ↑ weight loss, net fluid loss, and worsening renal function

EVEREST . Expert Rev Cardiovasc Ther. 2008;6:1331–38.
The EVEREST Outcome Trial. JAMA. March 2007;297(12):1319-31.
TACTICS-HF. JACC. March 2017;69(11):1399-1406.

BUT WHICH AGENT SHOULD I USE?

3T Trial

Design	• Single center, prospective, randomized, double-dummy • Randomized 1:1:1 without stratification - Metolazone 5 mg PO BID - Chlorothiazide 500 mg IV BID - Tolvaptan 30 mg PO daily
Key Inclusion Criteria	Hypervolemia • PA catheter with PCWP >19 and ≥ 1 sign of hypervolemia on physical exam OR • ≥ 2 signs of hypervolemia on physical exam (peripheral edema, ascites, rales) Loop resistance • Total urine output <2L in prior 12 hours while receiving IV therapy of FE ≥240 mg/day in at least previous 12 hours
Key Exclusion Criteria	• Renal replacement therapy • SBP <85 mmHg • eGFR <15 ml/min/1.73 $m^{2,}$ K <3 mEq/L, NA <130 or >145 mEq/L • Severe liver disease or malnutrition • Inability for standing weights • Use of thiazides within 24 hours or other non-study diuretic use

The 3T Trial. JACC HF. 2020:8(3):157-68.

3T Trial

Primary Endpoint	• Change in weight from baseline to 48 hours via standing scale
Secondary Endpoints	• 48-hour urine output • Patient reported congestion • Electrolyte changes • Escalation and de-escalation of decongestion therapies • Treatment failures (non-study diuretics, UF, RRT)
Urine Sub-study	• Last 16 patients enrolled • Collected: urine samples and blood draws at timed intervals • To evaluate PK of the diuretics and urine electrolyte profiles

The 3T Trial. JACC HF. 2020:8(3):157-68.

3T Trial

Baseline Population	• Metolazone: highest loop dose • Chlorothiazide: older, highest T2DM*, higher patient reported congestion* • Tolvaptan: white, higher BMI, more HFrEF*, less HTN and CKD, lower loop dose
Key Results	Cumulative weight loss ITT (kg) • M 4.6 vs. C 5.8, p=0.292; M 4.6 vs. T 4.1, p=0.456 Cumulative weight loss per-protocol (kg) • M 4.7 vs. C 6.1, p=0.188; M 4.7 vs. T 4.1, p=0.579 Change in Na and Cl from baseline • Na: M -1 vs. T +4, p=0.001 • Cl: M -7 vs. T +2, p<0.001
Urine Sub-study Results	• C > M in natriuresis at 24 hours but not 48 hours • T < thiazides in natriuresis, but more pronounced with C • C & T resulted in less urinary K loss

*Statistically significant; M-metolazone, C-chlorothiazide, T-tolvaptan

The 3T Trial. JACC HF. 2020:8(3):157-68.

3T Trial

Considerations	• No difference was shown in primary outcomes • All showed improved diuretic efficacy • Weight loss of ~4 kg, and urine output of ~8.8 L over 48 hours • Lower power than anticipated • Not designed for non-inferiority • Safe with transient changes in kidney function and electrolytes • Single-center with younger patients

The 3T Trial. JACC HF. 2020:8(3):157-68.

SEQUENTIAL BLOCKADE SUMMARY

Electrolyte & Lab Abnormalities

- Na
- K
- Cl
- SCr/BUN and renal function

GI tract/Absorption issues

- Edema
- Onset of action
- GI tract intact?

Cost

- Acetazolamide 500mg IV: ~$46.07, 250 mg PO: $4.71
- Metolazone 5 mg: ~$2.89
- Chlorothiazide 500 mg IV: $197.63
- Tolvaptan 30 mg: ~$321.96

US Pricing. Wolters Kluwer UpToDate, Inc.;

HYPERTONIC SALINE

Boorsman EM et el. Nat Rev Cardiol. May 2020.

HS IN THE RECENT LITERATURE

1.7% saline as slow continuous infusion

- Administered at 0.35 mL/min with loop diuretic administration
- Tested if osmotic improvements occurred at slow infusion rate
- Results similar to prior studies that received bolus HS therapy, ↑ diuretic efficiency

HS in conjunction with ↑ dose furosemide

- 42 patients randomized 1:1:1 to doses 125 mg, 250 mg, 500 mg
- 0-24 hours→ doses diluted in 0.9% NaCl; 24-48 hours→ doses diluted in 1.4% NaCl
- ↑ total urine output, sodium excretion, urinary osmolality, and furosemide urine delivery in all patients and at all time points

HS Effect on Body Weight and SCr in ADHF

- 250 mg IV furosemide with 150 mL 3% saline BID for ~2.3 days
- 47 patients with -1.4 kg vs. -0.4 kg, p=0.017
- No change in renal function

Impact of HS on ADHF

- 100 mg IV furosemide (over 1 hour) with 100 mL HS with 500 mL water restriction
- 132 patients in each group
- ↑ urination and ↓ hospitalized days with 4 days vs. 7 days, p<0.01

Okuhara Y et al. J Card Fail 2014;20:295–301.
Lafreniere G et al. World J Cardiol 2017;9:685-92.
Paterna S et al. Adv Ther 2015;32:971-82.
Wan Y et al. Int Heart J 2017;58:601-7.

Real World Use of HS in Refractory ADHF

Purpose	• Investigate safety and effectiveness of HS in refractory ADHF
Design	• Single center, retrospective chart review • Follow for 3 days on either side of intervention
Key Inclusion Criteria	• March 2013-December 2017 in the CICU or cardiac step-down unit • Orders of 3% NaCl • If multiple doses: separate observation when time between doses >7 days
Key Exclusion Criteria	• No active management for ADHF • 3% NaCl order for another indication
Administration of HS	• Site developed protocol of when able to use HS • 150 mL 3% NaCl over 30 minutes via pump—preferable through central line, but okay through peripheral with at least 20 gauge • IV loop diuretics must be administered simultaneously • Intensive monitoring required

Griffen M et al. JACC:HF. March 2020;8(3):199-208.

Real World Use of HS in Refractory ADHF

Results	• 40 patients with 50 distinct admissions with 5 patients having more than 1 episode of HS administration • 58 distinct episodes of HS administration • Median of 3 doses per treatment episode (IQR: 2-7 doses)
Key Baseline Characteristics	• Median age: 60 years • 45/58 were female • 25 had a LVAD • 35% were HFrEF • Median electrolyte values; Na-131, Cl-88, SCr-1.8 • Inotrope/pressor: 64% • Median loop diuretic dose in FE 24 hours prior: 400 mg • Majority of patients used thiazide, acetazolamide, and/or tolvaptan prior to HS administration • High acuity of illness: 47% experienced death, re-hospitalization, or discharge to hospice

Griffen M et al. JACC:HF. March 2020;8(3):199-208.

Real World Use of HS in Refractory ADHF

Safety (change per day)	Respiratory: • % change of patients on oxygen: Pre: +0.2, Post: -0.2, p=0.19 Electrolytes/chemistry • Na (mEq/L)—Pre: -1.0, Post: +0.9, p <0.001 • Cl (mEq/L)—Pre:-1.1, Post +0.5, p <0.001 • SCr (mg/L)—Pre: +0.1, Post –0.1, p <0.001
Efficacy (change per day)	Net weight change, p <0.0001 • Pre: –0.02 kg, Post: -1.1 kg Net fluid loss • Pre: 30 ml, Post: 337 ml, p=0.03 Change in urine output • Pre: -23 ml, Post: 379, p=0.01
Other Key Results	• 2 patients with Na +5 mmol/L qt 6 hours and +7 mmol/L at 24 hours—neither had adverse neurologic events • Net urine output: Day 1—489 ml, Day 2—1019 ml, Day 3—921 ml • Weight ↓ compared to prior (kg): Day 1— 0.6, Day 2—2.0, Day 3—3.1

Griffen M et al. JACC:HF. March 2020;8(3):199-208.

Real World Use of HS in Refractory ADHF

Considerations	• Single center and primarily ordered by 1 physician • All interventions including duration of HS therapy were at the discretion of treating cardiologists • Treat cardiologists also determined diuretic resistance • Appears to be safe • Delayed effects • Barrier with giving Na in ADHF • Hypothesis generating

Griffen M et al. JACC:HF. March 2020;8(3):199-208.

IN SUMMARY

- It is essential to clinically assess each patient and define the main type of congestion
- Consider what compensatory mechanisms for loop diuretic resistance may be playing a role
- Consider obtaining a spot urine Na to assess loop diuretic dose optimization
- Most studies use doses of FE 240 mg to include patients
- It appears there is no one better strategy to augment diuresis when it comes to sequential blockade of loop diuretics
- Continually assess electrolytes and labs to adjust strategy
- HS may be an alternative strategy that could be considered in those with refractory fluid on board despite diuretic requirements

Patient Case

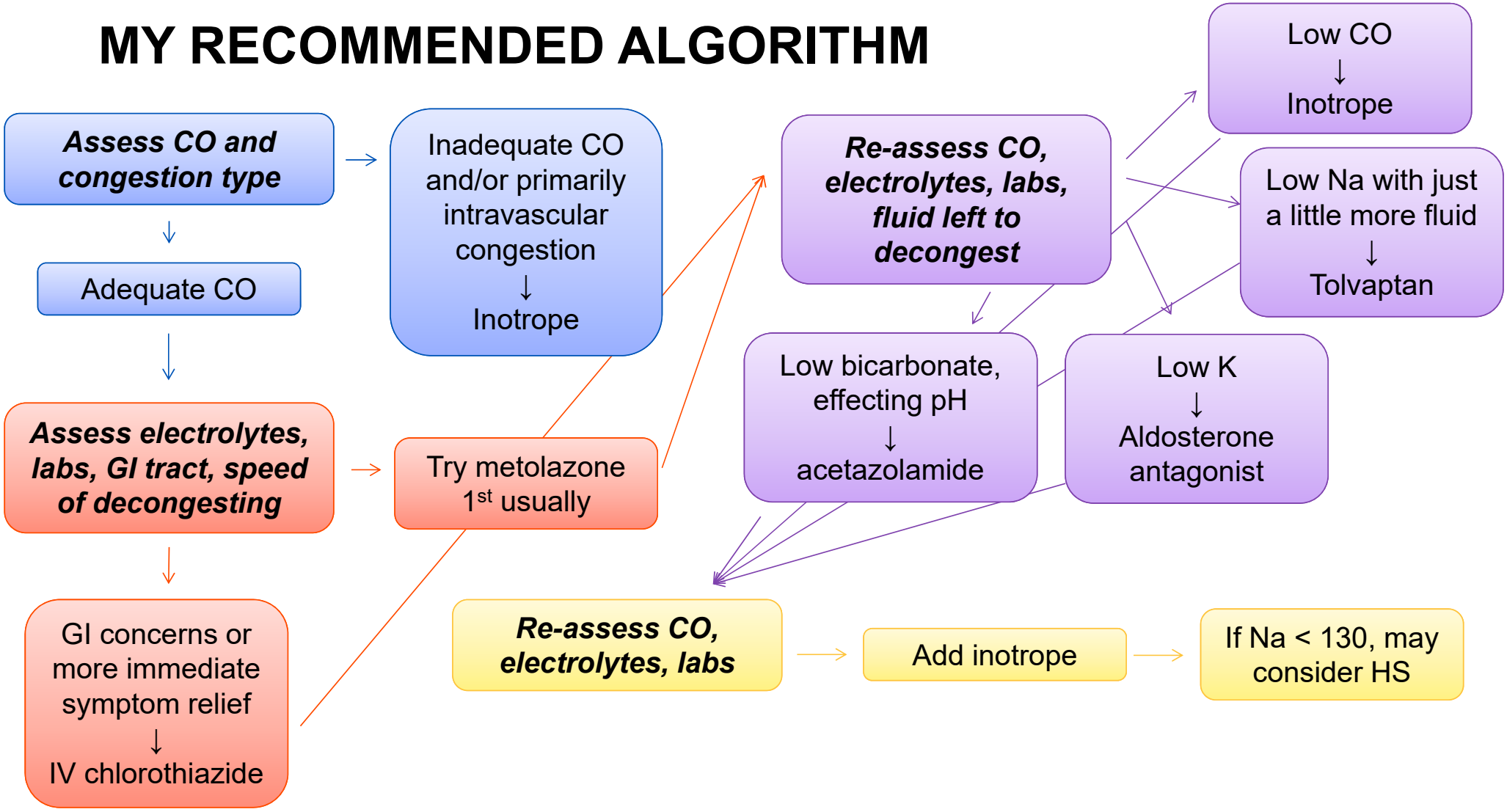
Despite MC continuing on a furosemide drip and being started on tolvaptan, congestion remains. His Na is slightly low at 133, and he is cold to the touch. Dr. Ace read something about using hypertonic saline.

Assessment Question

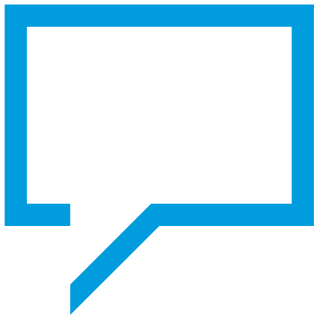
Based on the literature reviewed today, what therapy would you recommend for MC?

- Increase the furosemide drip to 30 mg/hour
- Add metolazone 5 mg PO daily
- Trial 150 mL 3% HS bolus
- Double tolvaptan dosing

MY RECOMMENDED ALGORITHM



QUESTIONS



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