PRESSED FOR TIME: VASOPRESSORS FOR PATIENTS WITH SHOCK

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Adult Hospital Medicine Boot Camp
September 2021

Disclosures

- No relevant commercial relationships to disclose.
- Off-label use of midodrine will be discussed.

Objectives

- Explain the role of vasopressors in patients with shock
- Discuss differences in the pharmacology of vasopressors
- Discuss the literature behind vasopressors used in practice
- Select the appropriate vasopressor(s) when given a patient case
- Identify adjunct agents for blood pressure support in patients with hypotension

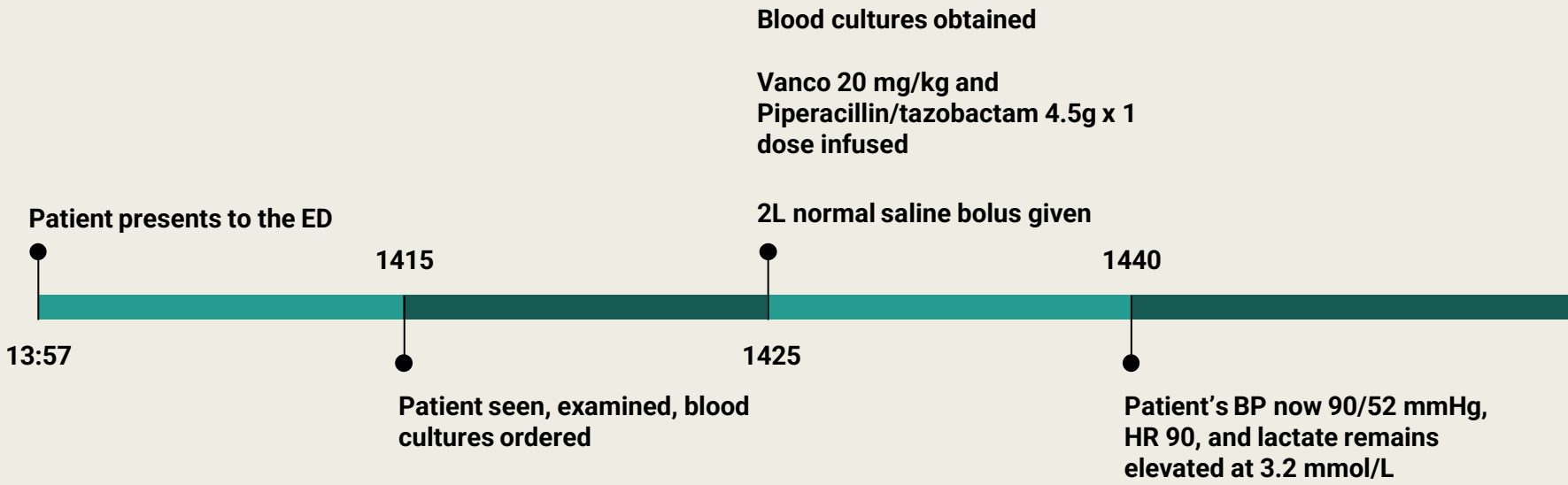
MEET JC

Meet JC

- 68 year old female
- PMH: type 2 diabetes, asthma, recurrent UTIs, peripheral neuropathy
- Weight: 66 kg
- Height: 167 cm
- Chief Complaint: increasing weakness over the past 1 week

- ED vital signs and labs:
  - *BP 80/47 mmHg*
  - *HR 96 bpm*
  - *Temp 38.5^{o} C*
  - *WBC 16.3 x 10^{9}/L*
  - *Lactate: 4.3 mmol/L*
  - *Procalcitonin: 62 ng/mL*
- 2 sets of blood cultures obtained, results pending

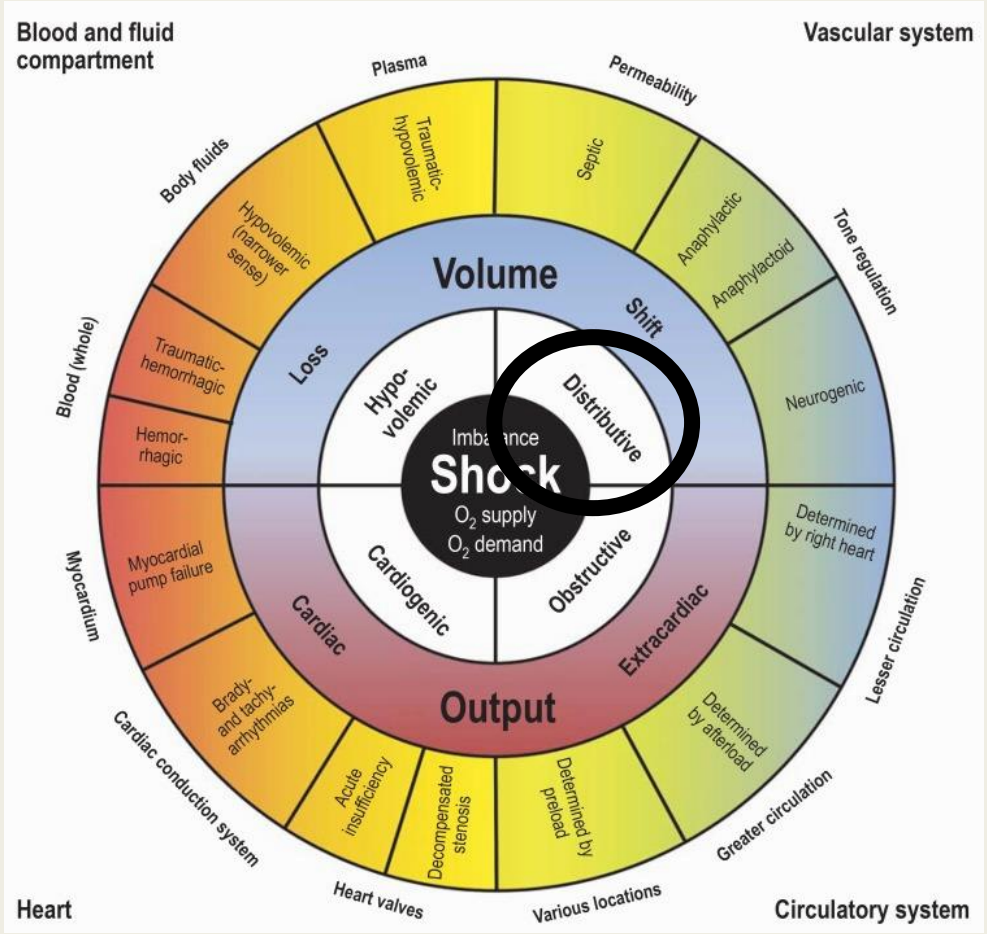
Meet JC


Blood cultures obtained
Vanco 20 mg/kg and Piperacillin/tazobactam 4.5g x 1 dose infused
2L normal saline bolus given
Patient presents to the ED
1415
1440
13:57
1425
Patient seen, examined, blood cultures ordered
Patient's BP now 90/52 mmHg, HR 90, and lactate remains elevated at 3.2 mmol/L

WHAT IS SHOCK?

"A severe mismatch between the supply and demand of oxygen"

Standl T, et al. *Dtsch Arztebl Int.* 2018; 115: 757-768.

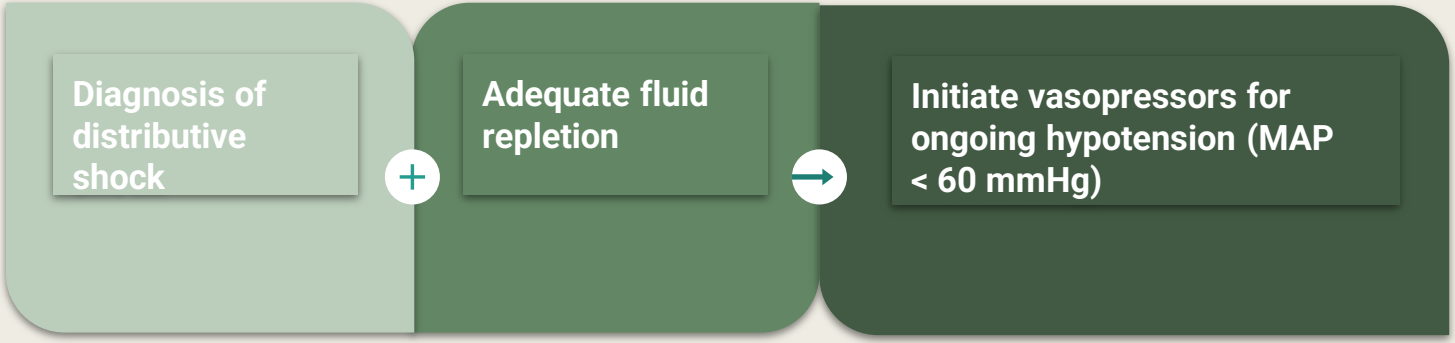


Standl T, et al. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6323133/figure/F1/?report=objectonly.

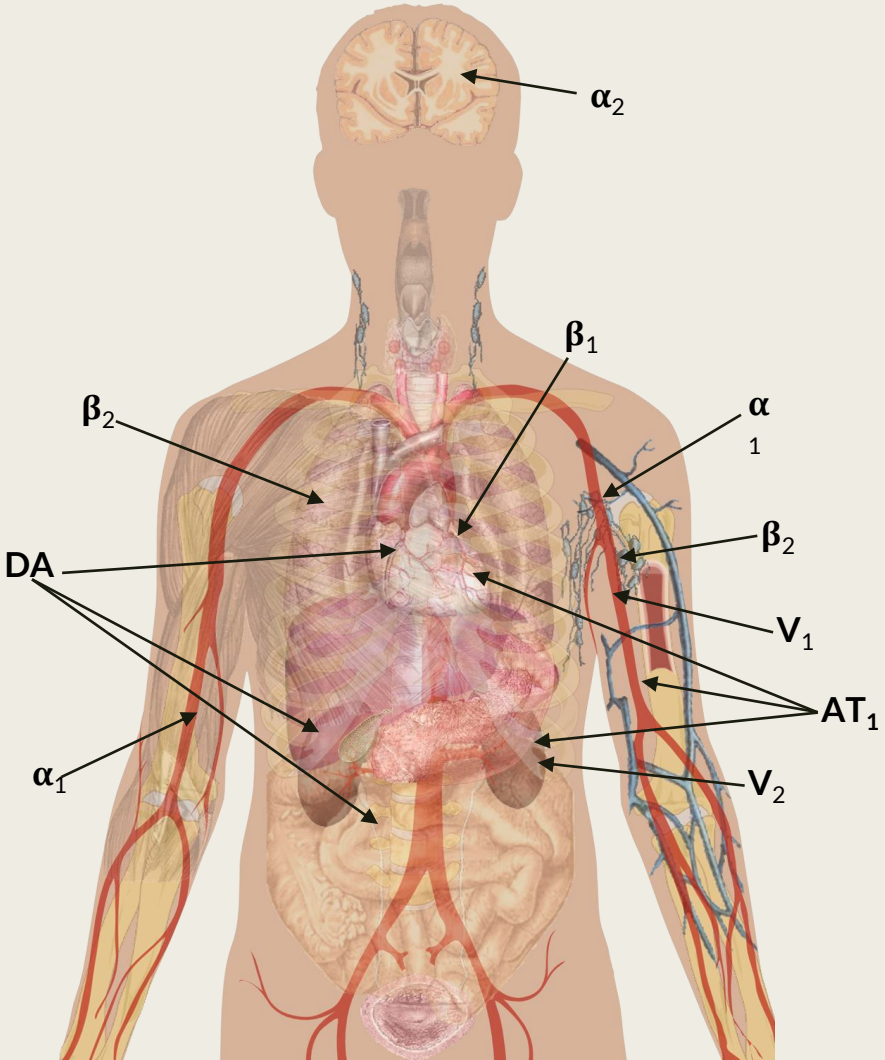
Resuscitation Goals

- Improve blood flow to vital organs
- Prevent irreversible tissue damage
- MAP > 65 mmHg

Role of Vasopressors



A REVIEW OF ADRENERGIC RECEPTORS


α2
β1
β2
α1
β2
DA
V1
AT1
α1
V2

Adrenergic Receptors

Receptor	Location	Activity
α_1	vascular smooth muscle	vasoconstriction (↑ SVR)
α_2	postsynaptic CNS neurons	decreased sympathetic outflow
β_1	cardiac muscle	chronotropy, inotropy (↑ CO)
β_2	lung tissue vascular smooth muscle	bronchodilation vasodilation (↓ SVR)

SVR: systemic vascular resistance
CO: cardiac output

Overgaard, et al. *Circulation*. 2008;118:1047–1056.

Other Receptors

Receptor	Location	Activity
Vasopressin-1 (V_1)	vascular smooth muscle (mesentery, systemic, renal)	vasoconstriction (↑ SVR)
Vasopressin-2 (V_2)	distal tubule and renal collecting ducts	fluid retention
Dopamine	cardiac muscle mesentery renal vessels	coronary artery dilation mesenteric and renal vessel dilation
Angiotensin II type 1 receptor (AT_1)	vascular smooth muscle cardiac muscle adrenal cortex kidney	vasoconstriction (↑ SVR) and fibrosis cardiac hypertrophy and fibrosis aldosterone synthesis/secretion sodium reabsorption, ↓ renin secretion

Overgaard, et al. *Circulation*. 2008;118:1047–1056.
Sharman, et al. *Continuing Education in Anaesthesia Critical Care and Pain*. 2008; 8: 134–137.
Burnier. *Circulation*. 2001; 103: 904-912.

PHARMACOLOGY OF VASOPRESSORS

Norepinephrine

- Receptor activity:

α_1	β_1	β_2
+++	++	-

- Dosing: 1-30 mcg/minute IV infusion
- Titration: 1 mcg/min
- ADRs: tachycardia, arrhythmias, digital ischemia
- Contraindications: none

2016 Surviving Sepsis Campaign:

"We recommend norepinephrine as the first-choice vasopressor (strong recommendation, moderate quality of evidence)."

Overgaard, et al. *Circulation*. 2008;118:1047–1056.
Rhodes, et al. *Crit Care Med*. 2017; 45: 486-552.

Does Norepinephrine Use Change Outcomes in Shock?

Study Question	What factors influence outcomes in patients with septic shock?
Study Design	Prospective, observational cohort
Patient Population	Adult ICU patients (n=97) with septic shock
Exclusion Criteria	None
Study Drug	Norepinephrine (0.5 to 5 mcg/kg/min) + low-dose dopamine (5-15 mcg/kg/min) vs high-dose dopamine (16 to 25 mcg/kg/min)
Primary Outcome	Four factors associated with unfavorable outcome: elevated lactate, low UOP, pneumonia, and organ system failure index score ≥ 3. Use of norepinephrine was a protective factor. Use of dopamine did not influence outcome.
Conclusions	5 factors associated with outcome. Norepinephrine decreases in-hospital mortality
Limitations	Mortality rate 73%, non-randomized, management of sepsis different from modern practice

UOP = urine output

Martin, et al. *Crit Care Med*. 2000; 28: 2758-65.

Epinephrine

- Receptor activity:

α_1	β_1	β_2
+++	+++	++

- Dosing: 1-10 mcg/minute IV infusion
- Titration: 1 mcg/min
- ADRs: tachycardia, elevated lactate and glucose concentrations
- Contraindications: none

★ Initial vasopressor of choice in anaphylactic shock
★ Add-on to norepinephrine in septic shock

Overgaard, et al. *Circulation*. 2008;118:1047–1056.

CAT Trial

Study Question	Is there a difference between epinephrine and norepinephrine in ability to achieve a MAP goal in the ICU?
Study Design	Prospective, double-blind, RCT in Australia
Patient Population	ICU patients 18 - 80 years old (n=280) who required vasopressors for any cause
Exclusion Criteria	Cardiac arrest, anaphylaxis, pheochromocytoma, hypoadrenalism, MAOI use, or expected death within 24 hours
Study Drug	Epinephrine infusion vs norepinephrine infusion
Primary Outcome	Time to achievement of MAP goal was 35.1 hrs for epinephrine group vs. 40 hrs for norepinephrine group (RR 0.88; 95% CI 0.69-1.12; P = 0.26)
Conclusions	No difference
Limitations	Large number of patients withdrawn from epinephrine group, sample size based on time to resolution of shock at 48hrs, other aspects of resuscitation performed according to the treating clinician

Myburgh, et al. *Intensive Care Med*. 2008; 34: 2226-34.

Epinephrine: Role in Anaphylactic Shock

WHEN TO USE:

ALWAYS!

HELPS WITH A, B, C'S

Simons, et al. *Curr Opin Allergy Clin Immunol*. 2010; 10: 354-361.

Epinephrine for Anaphylactic Shock

- Typically given by IM injection
  - Dose: 0.01 mg/kg (max of 0.5 mg)
  - Autoinjectors come ready-to-inject with 0.3 mg
  - Can repeat dose at 5-15 minute intervals
- For patients with continued hypotension after 2-3 IM doses, IV fluids should be administered
- If patient remains hypotensive, IV epinephrine infusion should be started

Simons, et al. *Curr Opin Allergy Clin Immunol*. 2010;10:354-361.

Dopamine

- Receptor activity:

Dose	α_1	β_1	β_2	Dopamine
0-5 mcg/kg/min	-	+	-	++
5-10 mcg/kg/min	+	++	-	++
10-20 mcg/kg/min	++	++	-	++

- ADRs: tachycardia, arrhythmias, digital ischemia, polyuria
- No such thing as “renal dose”
- Contraindications: pheochromocytoma, ventricular tachyarrhythmias

Overgaard, et al. *Circulation*. 2008;118:1047–1056.

SOAP II Trial

Study Question	Which agent is superior in the treatment of shock - dopamine or norepinephrine?
Study Design	Multicenter, RCT
Patient Population	Adult ICU patients (n=1679) with shock requiring vasopressor use
Exclusion Criteria	<18 years old, on vasopressor > 4 hrs, serious arrhythmia, declared brain dead
Study Drug	Dopamine (max 20 mcg/kg/min) or norepinephrine (max 0.19 mcg/kg/min)
Primary Outcome	No difference in rate of death at 28 days (OR 1.17; 95% CI 0.97 to 1.42; p=0.10). More arrhythmias in the dopamine group (24.1% vs. 12.4%, P<0.001). Subgroup analysis showed dopamine associated with increased rate of death at 28 days in cardiogenic shock (P=0.03)
Conclusions	Use of dopamine is associated with more adverse events
Limitations	Definition of shock, differences in target blood pressures, higher use of open-label norepinephrine in the dopamine group, treatment of underlying shock not discussed

De Backer, et al. *N Engl J Med*. 2010 Mar 4;362: 779-89.

Phenylephrine

- Receptor activity:

α_1	β_1	β_2
+++	-	-

- Dosing: 10-100 mcg/minute IV infusion
- Titration: 10 mcg/min
- ADRs: reflex bradycardia, myocardial ischemia, decreased cardiac output, severe peripheral ischemia
- Contraindications: none

★ May be pushed for intubation
★ Used for patients with tachyarrhythmias and aortic stenosis

Overgaard, et al. *Circulation*. 2008;118:1047–1056.

Vasopressin

- Receptor activity:

V_1	V_2
+++	++

- Dosing: 0.01-0.04 units/minute IV infusion
- Titration: +/-, consider 0.01 units/min
- ADRs: digital and mesenteric ischemia, fluid retention

★ Deficiency in critical illness
★ Catecholamine- sparing
★ Doses > 0.04 units/min reserved for salvage therapy

Overgaard, et al. *Circulation*. 2008;118:1047–1056.

VASST Trial

Study Question	Does low-dose vasopressin decrease mortality vs. norepinephrine in patients treated with conventional vasopressors?
Study Design	Multicenter, double-blind, RCT
Patient Population	Patients > 16 years old (n=779) with septic shock on ≥ 5 mcg/min norepinephrine
Exclusion Criteria	ACS, prior vasopressin use, mesenteric ischemia, HFrEF, condition with high mortality rate, death expected within 12 hrs, severe hyponatremia
Study Drug	Vasopressin infusion (max 0.03 units/min) or norepinephrine infusion (max 15 mcg/min)
Primary Outcome	No difference in 28-day or in 90-day mortality. No significant difference in serious adverse events
Conclusions	Low-dose vasopressin did not reduce mortality compared to norepinephrine in patients with septic shock
Limitations	Did not meet power, patients at goal MAP at baseline (>70 mmHg) and not enrolled early (mean time to enrollment 12 hrs)

Russell, et al. *N Eng J Med*. 2008; 358:877-887.

Angiotensin II

- Mechanism: Binds angiotensin II type 1 receptor on vascular smooth muscle and causes muscle contraction (vasoconstriction)
- Dosing: 1.25-80 ng/kg/min IV infusion
  - *80 ng/kg/min only recommended during the 1st three hours of infusion*
  - Titrate by 5-10 ng/kg/min
- ADRs: peripheral ischemia, tachycardia, acidosis, hyperglycemia, thromboembolism, delirium, fungal infections

Added for refractory shock after inadequate response to other vasopressor agents

Angiotensin II. Micromedex® Solutions. http://micromedex.com.

ATHOS-3 Trial

Study Question	Does adding angiotensin II to background vasopressors improve blood pressure in patients with catecholamine-resistant vasodilatory shock?
Study Design	International, double-blind, placebo-controlled RCT
Patient Population	Adult patients (n=321) on ≥ 0.2 mcg/kg/min norepinephrine or equivalent after volume resuscitation
Exclusion Criteria	Burns > 20% BSA, ACS, bronchospasm, liver failure, mesenteric ischemia, active bleeding, neutropenia, VA-ECMO, high-dose glucocorticoid use, CI < 2.3 L/min/m^2
Study Drug	Angiotensin II infusion vs placebo infusion
Primary Outcome	Significantly more patients in angiotensin II group met primary endpoint of MAP ≥ 75mmHg or an increase of at least 10mmHg at hour 3 (P<0.001)
Conclusions	Angiotensin II increased blood pressure and allowed reduction of catecholamine doses in patients with vasodilatory shock on high-dose vasopressors
Limitations	Not truly blinded, small sample size, not powered to detect mortality, lack of long-term follow-up

Khanna, et al. *N Eng J Med*. 2017; 377:419-430.

Summary of Vasopressor Receptor Activity

Drug	α_1	β_1	β_2	Dopamine	V_1	V_2	Angiotensin	Physiologic Effect
Norepinephrine	+++	++	-	-	-	-	-	SVR ↑↑, CO ↑/-
Epinephrine	+++	+++	++	-	-	-	-	CO ↑↑, SVR ↑ or ↓
Dopamine *0-5 mcg/kg/min*	-	+	-	++	-	-	-	CO ↑
Dopamine *5-10 mcg/kg/min*	+	++	-	++	-	-	-	CO ↑, SVR ↑
Dopamine *10-20 mcg/kg/min*	++	++	-	++	-	-	-	SVR ↑↑
Vasopressin	-	-	-	-	+++	++	-	SVR ↑↑, CO ↓/-
Angiotensin II	-	-	-	-	-	-	+++	SVR ↑↑, CO ↓/-

“HELP!
I Have No Central Line!”

- Vasopressors that can be given via peripheral line (temporarily):
  - Phenylephrine
  - Norepinephrine
  - Epinephrine

- Tran et al: “Out of 1835 patients, 7% had complications of peripheral vasopressor administration, of which 96% were minor”

Tran et al. *Am J Emerg Med*. 2020; 38: 2434-2443.

Weaning of Vasopressors

- Clinical vs Laboratory Criteria
  - MAP, lactate, invasive monitoring
  - Urine output, mentation, echocardiographic evaluation, capillary refill
- Found to be similar for resuscitation monitoring with respect to mortality

Hernandez et al. *JAMA*. 2019; 321:654-664.

Which Vasopressor Do I Wean First?

- No standard practice

- Wu et al: “In adults with septic shock treated with concomitant [vasopressin] and [norepinephrine] therapy, discontinuing [vasopressin] first may lead to a higher incidence of hypotension but is not associated with mortality or ICU LOS.”

Wu et al. *Shock*. 2020; 53:50-57.

NURSE: “MY PATIENT IS STILL ON A LOW RATE OF NOREPINEPHRINE SINCE YESTERDAY!”

SOMEONE SOMEWHERE: “ADD MIDODRINE.”

Midodrine for Vasopressor Weaning

Study Question	What is the effect of adding midodrine to vasopressors in adults recovering from shock?
Study Design	Systematic review and meta-analysis
Patient Population	Adult patients (n=2533) with shock after midodrine vs no midodrine
Result	Similar ICU and hospital length of stay; similar vasopressor duration; similar mortality
Conclusions	Midodrine has no effect (susceptible to heterogeneity)
Limitations	Lack of standardized initiation and dosage

Hammond, et al. *J Intensive Care Med*. 2020; 35: 1209-1215.

MIDAS

Study Hypothesis	Midodrine shortens the duration of vasopressor requirements
Study Design	International, multicenter, randomized, placebo-controlled, prospective RCT
Patient Population	Adult patients (n=132) receiving a single vasopressor for ≥ 24 hours
Exclusion Criteria	Inadequate tissue oxygenation, hypovolemic shock or hypotension due to adrenal insufficiency, liver failure, chronic renal, heart disease (left ventricular ejection fraction<30%), acute urinary retention, pheochromocytoma, thyrotoxicosis, or bradycardia (heart rate<50 beats/min)
Study Drug	Midodrine 20mg oral or placebo every 8 hours
Primary Outcome	No significant difference in time to vasopressor discontinuation (P<0.62)
Conclusions	Midodrine did not decrease duration of vasopressors and was not effective for the treatment of hypotension in critically ill
Limitations	Broad eligibility criteria, low sample size

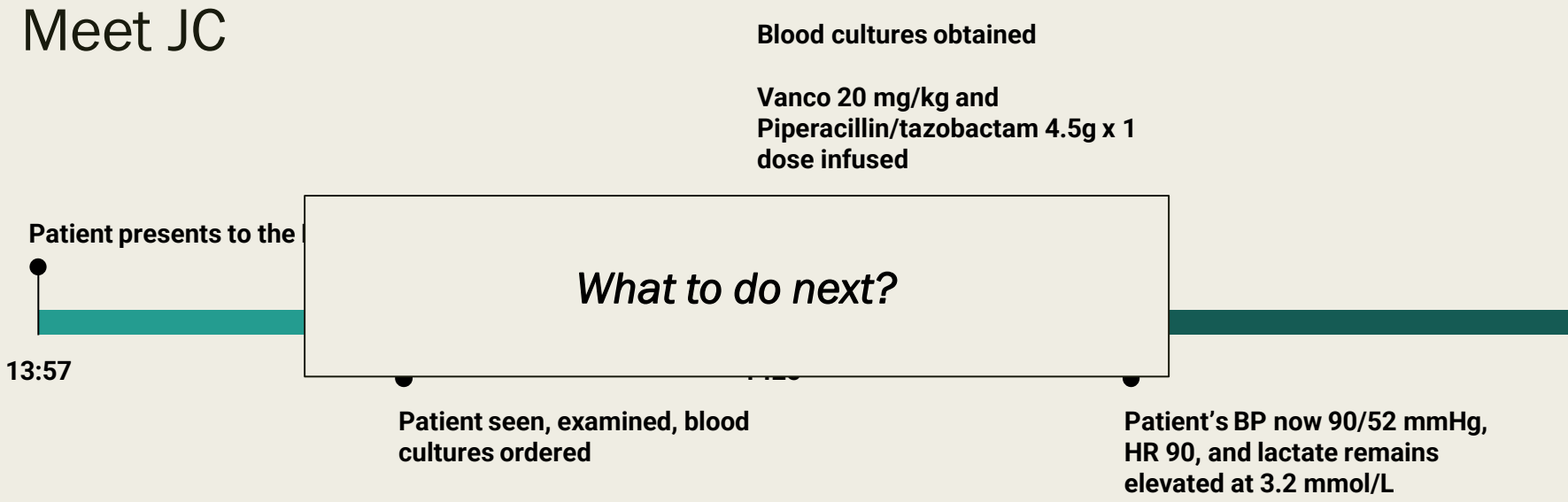
Santer, et al. *Intensive Care Med*. 2020; 46: 1884-1893.

Topics for Another Time…

- When to add steroids for shock
- Use of other off-label agents such as hydroxocobalamin and methylene blue

LET'S RETURN TO PATIENT JC...

Meet JC


Blood cultures obtained
Vanco 20 mg/kg and Piperacillin/tazobactam 4.5g x 1 dose infused
Patient presents to the
What to do next?
13:57
Patient seen, examined, blood cultures ordered
Patient's BP now 90/52 mmHg, HR 90, and lactate remains elevated at 3.2 mmol/L

Case Question #1

- JC has been given the diagnosis of septic shock by ED providers. She has been cultured and given IV fluids and antimicrobials. Given her most recent vitals/labs, what is the next best course of action?

    a. *Start dopamine IV infusion at 5 mcg/kg/min, with titration based on MAP*

    b. *Start phenylephrine IV infusion at 20 mcg/min, with titration based on MAP*

    c. *Start norepinephrine IV infusion at 5 mcg/min, with titration based on MAP*

    d. *Give 1L bolus of normal saline, then reassess*

Case Question #2

- JC's MAP responded to norepinephrine initially, but now she is requiring escalating doses of norepinephrine in order to maintain a MAP > 65 mmHg. Her norepinephrine is currently infusing at 30 mcg/min, her MAP is 63 mmHg and her HR is 107 bpm. What should you do next?

  a. *Add dopamine IV infusion at 5 mcg/kg/min, with titration based on MAP*

  b. *Add vasopressin at 0.04 units/min*

  c. *Increase norepinephrine IV infusion as needed, up to 100 mcg/min, with titration based on MAP*

  d. *Add angiotensin II IV infusion at 80 ng/kg/min, with titration based on MAP*

Case Question #3

- A patient comes to the ED with altered mental status and is found to have a large necrotic wound that seems infected. Upon exam you note a BP of 73/55 and the patient appears to be in atrial fibrillation with a HR of 110-120. Which vasopressor agent is the best to initiate if there is no response to IV fluids?

    a. *Start dopamine IV infusion at 5 mcg/kg/min, with titration based on MAP*

    b. *Start phenylephrine IV infusion at 20 mcg/min, with titration based on MAP*

    c. *Start norepinephrine IV infusion at 5 mcg/min, with titration based on MAP*

    d. *Start epinephrine IV infusion at 5 mcg/min, with titration based on MAP*

Take Home Points

Vasopressors help maintain hemodynamics after patients fail fluid resuscitation

Physiologic effects and adverse effects of each vasopressor vary according to receptor activity

Patient comorbidities should be taken into consideration when selecting a vasopressor agent

When in doubt, start norepinephrine

Thank You!

Questions?

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