A Shocking Presentation: Pressing Forward with Angiotensin II

A presentation for HealthTrust Members

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Sophia Pathan, PGY-1 Pharmacy Resident

Atlantic Health System

Disclosures

- The presenter has no financial relationships with any commercial interests pertinent to this presentation.

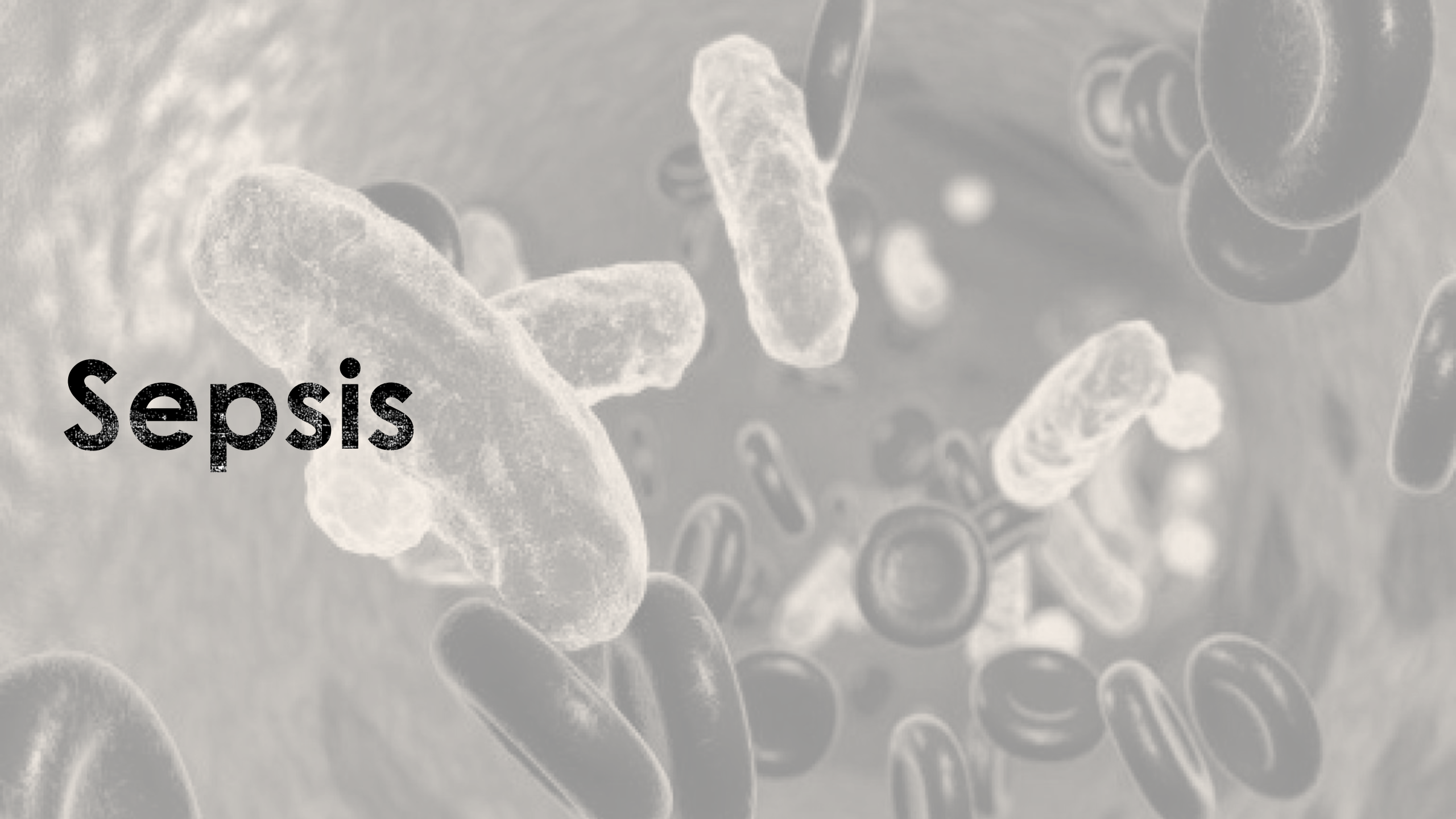
- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand, or drug.

Learning Objectives for Pharmacists

1. Describe the etiology and current treatment guidelines for septic shock
2. Differentiate the various vasoactive agents and their places in septic shock
3. Review the evidence and background of angiotensin II
4. Evaluate the role of angiotensin II in therapy

Learning Objectives for Pharmacy Technicians

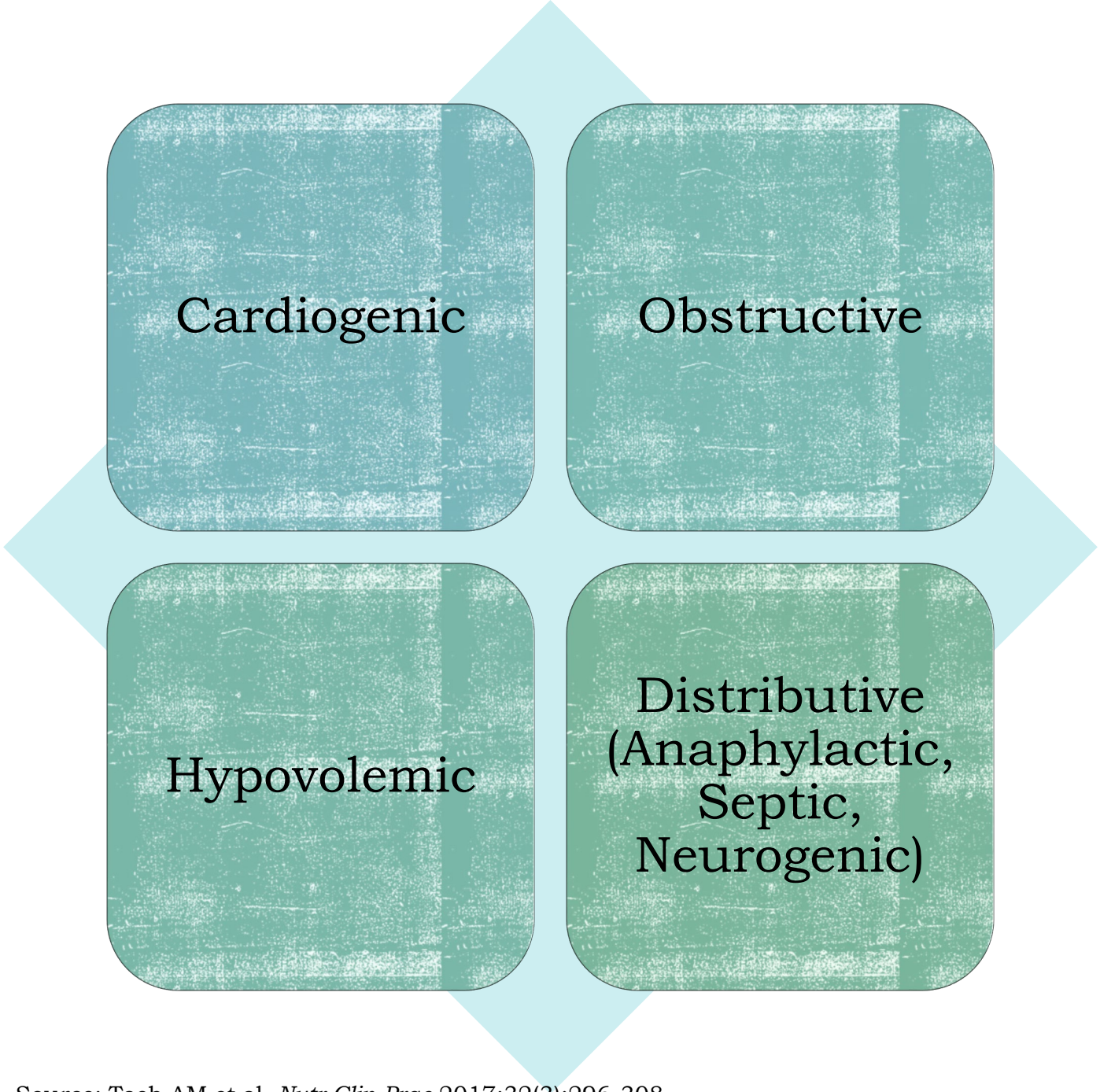
1. Describe the presentation of a patient in septic shock
2. List guideline recommendations for the treatment of septic shock
3. Review preparation and storage instructions for angiotensin II


Sepsis

Background

- Mortality rates in the United States are 15 to 25% for patients with sepsis, and about 40% for those who progress to septic shock
- Sepsis represents 30% of ICU admissions globally, and septic shock represents 62% of shock cases that require vasopressor therapy
- The first set of Surviving Sepsis Campaign Guidelines came out in 2004, then were revised in 2008, 2012, and finally 2016

Sources: Minasyan H. *J Crit Care* 2017;40:229-242.
Cleveland Clinic. "The Case for Angiotensin II in Vasodilatory Shock Patients Gathers More Steam." Accessed 29 Dec 2018.

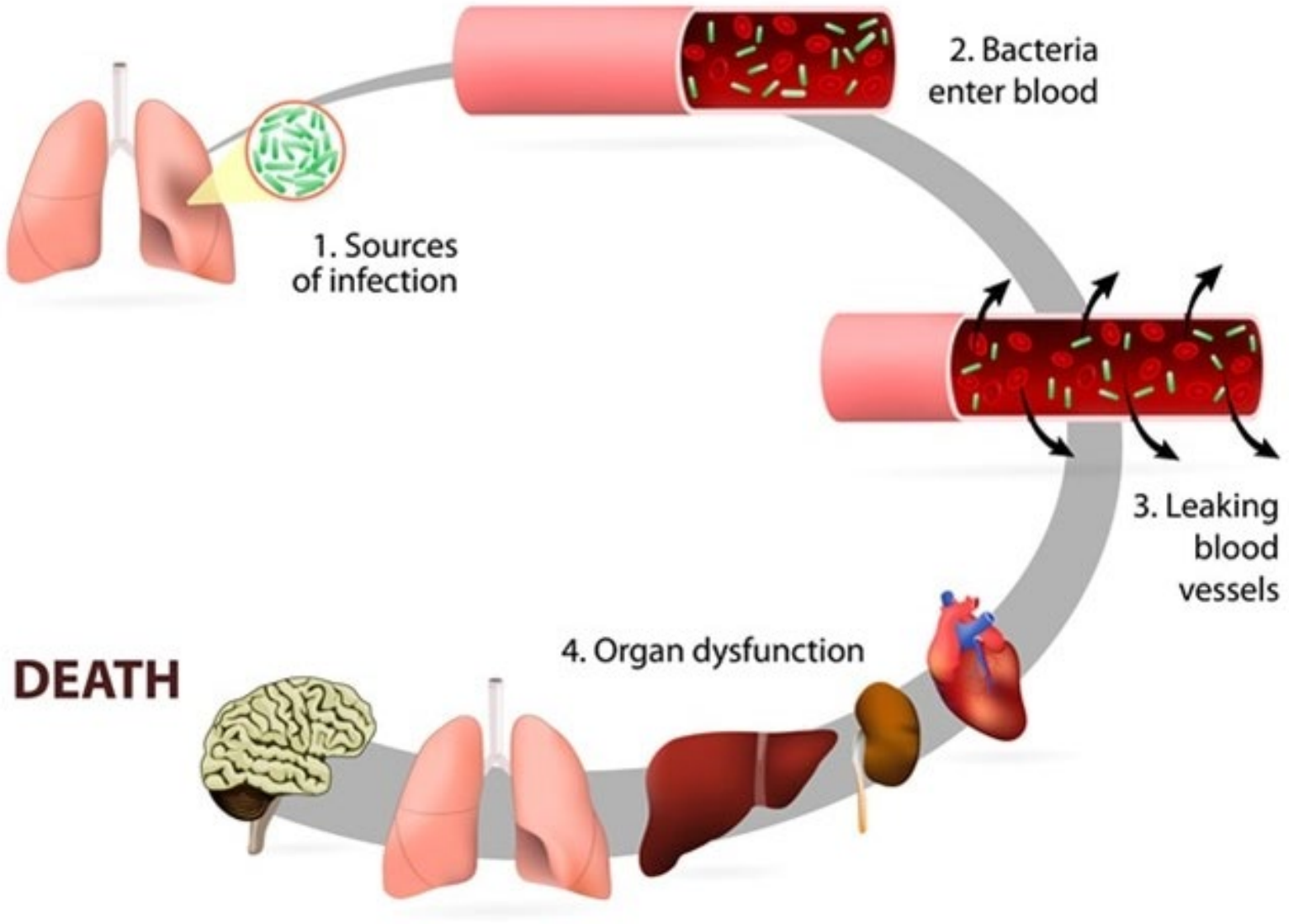


What is Shock?

Any state in which oxygen delivery to end organs is insufficient to sustain normal metabolic processes

Source: Taeb AM et al. *Nutr Clin Prac* 2017;32(3):296-308.

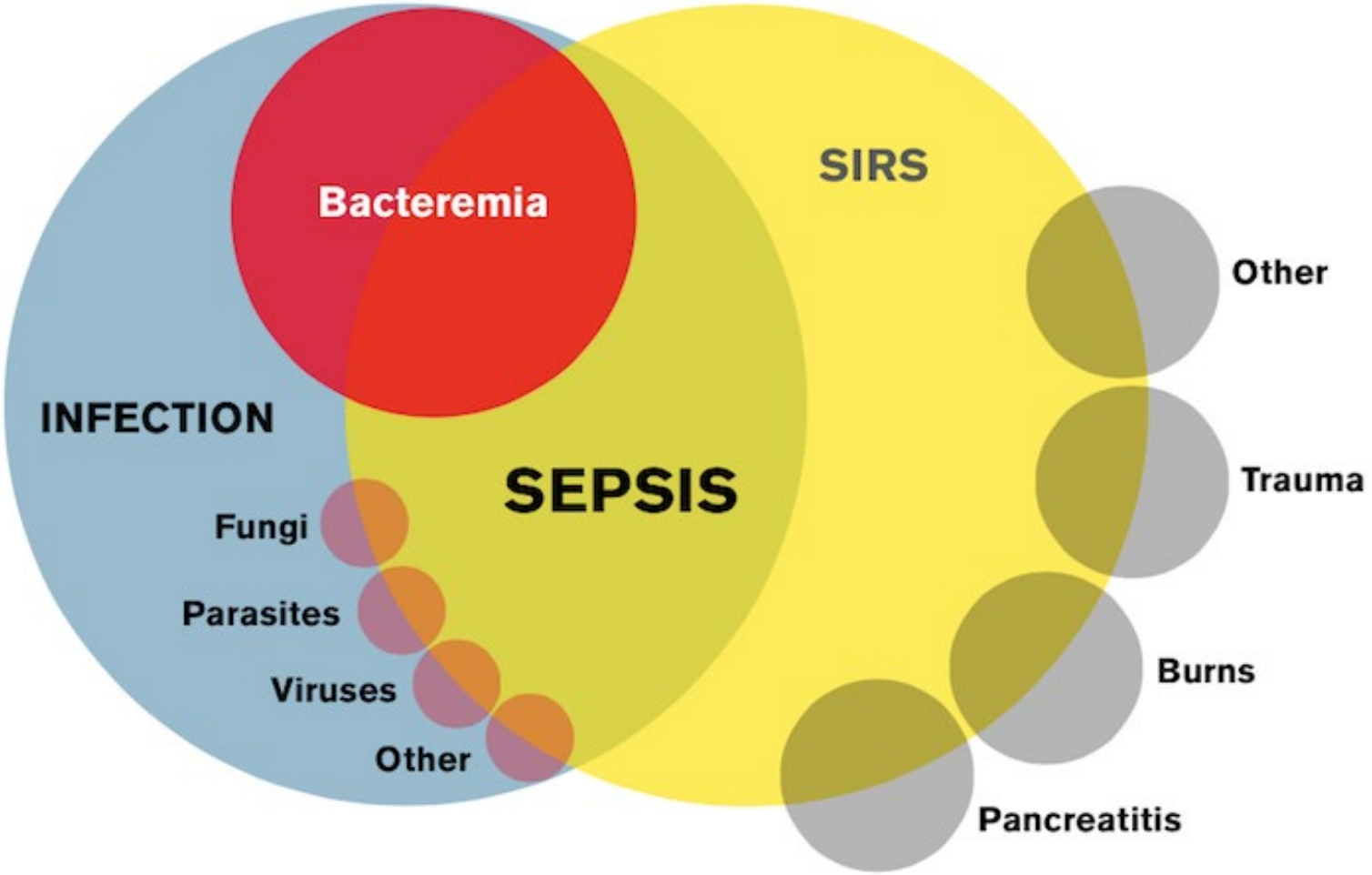
Pathophysiology



- Alterations to the endothelium occur
  - Increased leukocyte adhesion
  - Shift to a hypercoagulable state
  - Vasodilation
  - Loss of barrier function

Sources: Moranville MP, et al. *J Pharm Pract* 2011;24(1):44-60.
Remick DG. *Am J Pathol* 2007;170(5):1435–1444.

Sepsis

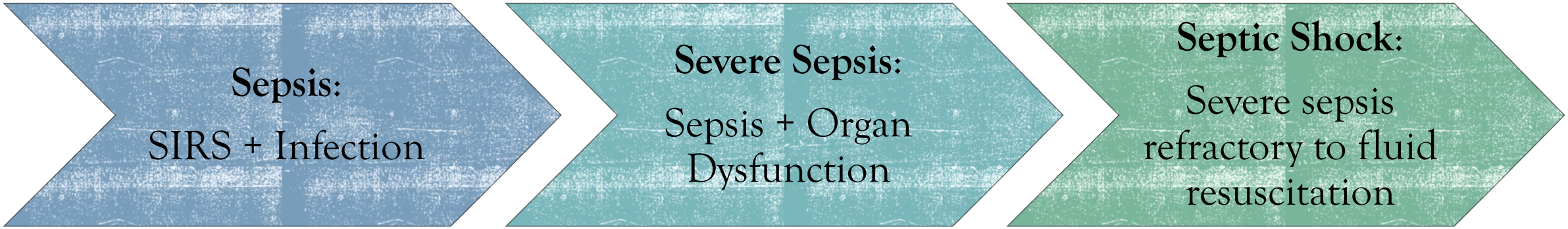


- Life-threatening organ dysfunction caused by dysregulated host response to infection
  - Systemic Inflammatory Response Syndrome (SIRS) + Infection

Source: Rhodes A, et al. *Crit Care Med* 2017;45:486-552.

Septic Shock

- **Septic Shock**: subset of sepsis with circulatory and cellular/metabolic dysfunction associated with higher risk of mortality
  - Sepsis-induced hypotension despite adequate fluid resuscitation



Sources: Taeb AM, et al. *Nutr Clin Pract* 2017;32(3):296-308.
Rhodes A, et al. *Crit Care Med* 2017;45:486-552.

Systemic Inflammatory Response Syndrome (SIRS) Criteria	Quick-Sequential Organ Failure Assessment (qSOFA)	Sequential Organ Failure Assessment (SOFA)
• Temperature [>38°C (100.4°F) or < 36°C (96.8°F)] • Tachycardia (HR > 90 bpm) • Tachypnea (respiratory rate > 20 or $PaCO_2$ < 32 mmHg) • WBCs (<4,000 or >12,000, or >10% bands)	• Altered Mental Status (Glasgow Coma Score < 15) • Tachypnea (respiratory rate > 22) • Systolic blood pressure ≤100 mmHg	• PaO_2/FiO_2 (mmHg) • Platelets (/mcL) • Glasgow Coma Score • Bilirubin (mg/dL) • MAP (mmHg) • Creatinine (mg/dL)

Assessment Tools

Souroces: Taeb AM, et al. *Nutr Clin Pract* 2017;32(3):296-308.
Rhodes A, et al. *Crit Care Med* 2017;45:486-552.
Gotts JE, et al. *BMJ* 2016;353:i1585-1605.

Lactate

- Measure lactate level
- Remeasure if initial lactate is > 2 mmol/L

Cultures

- Obtain blood cultures prior to administration of antibiotics

Antibiotics

- Administer broad spectrum antibiotics

Fluids

- Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

Pressors

- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥ 65 mmHg

Treatment: Sepsis Bundles

- Previous 3-hour and 6-hour bundles were combined into the hour-1 bundle

Source: Levy M, et al. *Crit Care Med* 2018;46(6):997-1000.

Vasopressors

Advantages

- Support during early resuscitation
- Assist therapeutically for those failing early resuscitation

Disadvantages

- Worsen already inadequate organ perfusion and perfusion in the periphery
- Increase left ventricular work to an unsustainable degree, worsening cardiac output and end-organ perfusion

Sources: Overgaard CB, et al. *Circulation* 2008;118:1047-1056.
Bissell BD, et al. *Ann Pharmacother* 2018;52(9):920-7.

Receptor Activity

Receptor	Actions	Pressor
Alpha-1 (α1)	Vasoconstriction due to stimulation of vascular walls	Norepinephrine, epinephrine, dopamine, phenylephrine
Beta-1 (β1)	Increased inotropy and chronotropy with minimal vasoconstriction	Norepinephrine, epinephrine, dopamine, dobutamine
Beta-2 (β2)	Stimulation in blood vessels causes vasodilation	Norepinephrine, epinephrine, dopamine, dobutamine
Dopamine (D1, D2)	Mesenteric, renal, and cerebral vascular dilation	Dopamine
Vasopressin (V1)	Vascular smooth muscle constriction; increased vasculature responsiveness to catecholamines	Vasopressin

Source: Overgaard CB, et al. *Circulation* 2008;118:1047-1056.

Norepinephrine

Epinephrine or vasopressin

Dobutamine, Phenylephrine, Dopamine

Goal: reverse hypotension and circulatory dysregulation to reach adequate perfusion pressure

Which Pressor?

Source: Overgaard CB, et al. *Circulation* 2008;118:1047-1056.

Dopamine vs Norepinephrine

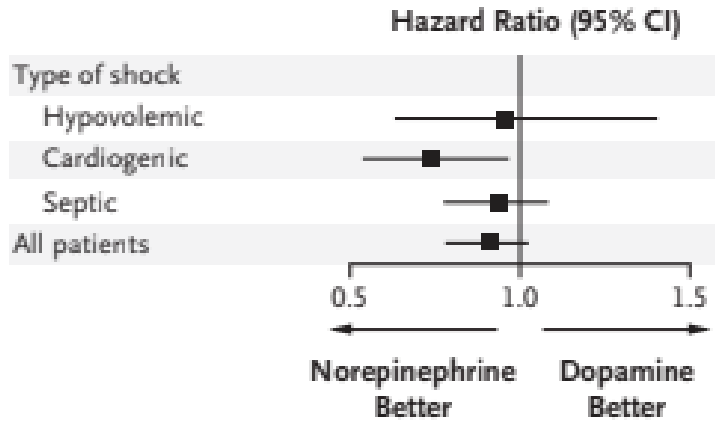


Figure 3. Forest Plot for Predefined Subgroup Analysis According to Type of Shock.

A total of 1044 patients were in septic shock (542 in the dopamine group and 502 in the norepinephrine group), 280 were in cardiogenic shock (135 in the dopamine group and 145 in the norepinephrine group), and 263 were in hypovolemic shock (138 in the dopamine group and 125 in the norepinephrine group). The P value for interaction was 0.87.

- Multicenter, randomized controlled trial
  - 859 dopamine patients
  - 821 norepinephrine patients
- No differences at baseline or rate of death (52.5% vs 48.5%, p = 0.10)
  - Subgroup analysis showed increased risk of death in dopamine patients with cardiogenic shock (p = 0.03)
- More arrhythmic events among the patients treated with dopamine (207 [24.1%]) than those treated with norepinephrine (102 [12.4%]), p < 0.001
- **No difference in rate of death**
- **Dopamine was associated with a greater number of adverse events**

Source: De Backer D, et al. *N Engl J Med* 2010;362(9):779-89.

VASST Trial

- Multicenter, randomized double-bind trial of 778 septic shock patients (396 vasopressin and 382 norepinephrine patients)
- **No significant difference between the vasopressin and norepinephrine groups in the 28-day mortality rate**
  - 35.4% vs 39.3%, p = 0.26
- 90-day mortality (43.9% vs 49.6%, p = 0.11)
- No differences in the overall rates of serious adverse events (10.3% and 10.5%, p = 1.00)

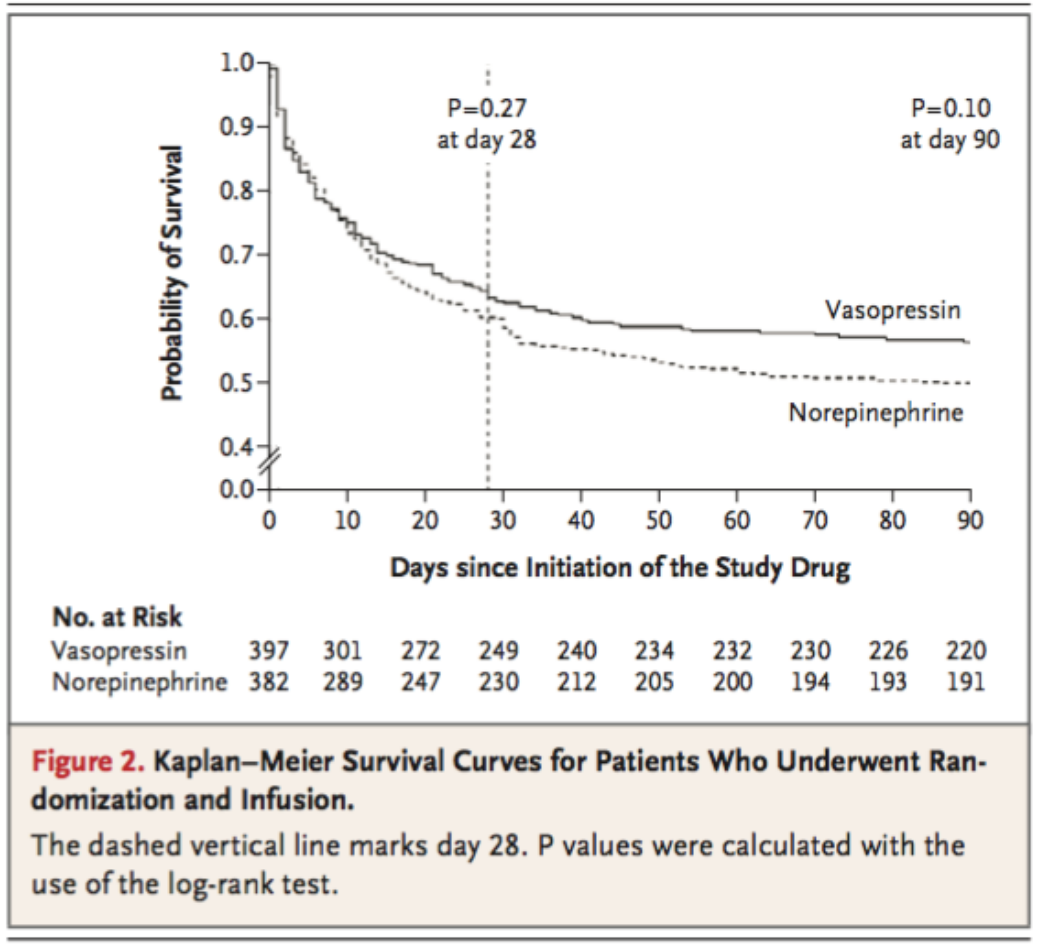
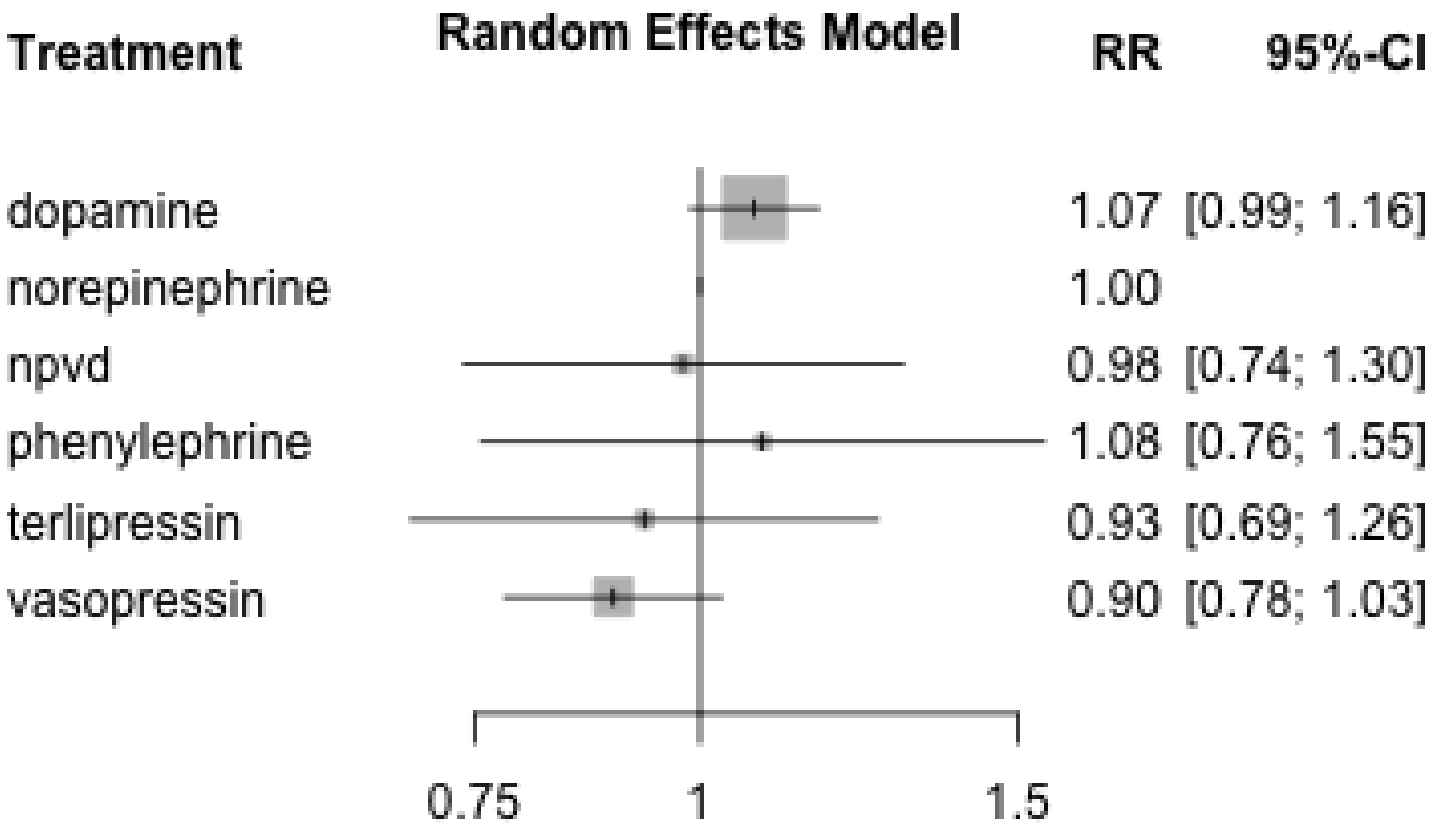


Figure 2. Kaplan–Meier Survival Curves for Patients Who Underwent Randomization and Infusion.

The dashed vertical line marks day 28. P values were calculated with the use of the log-rank test.

Source: Russel JA, et al. *N Engl J Med* 2008;358(9):877-887.

Pressor Mortality Benefit?

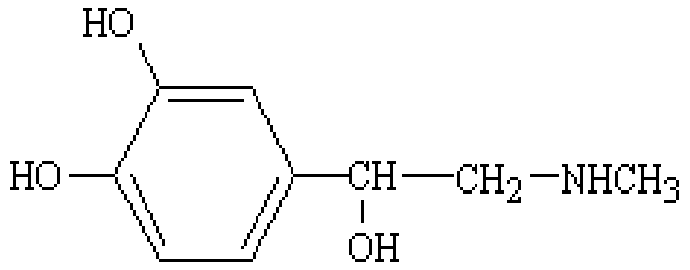


'NPVD' denotes non-protocol vasoactive drugs with or without placebo

- No differences in mortality outcomes in any of 28 studies comparing different vasopressors or combinations
- Network forest plot comparing vasopressor regimens vs norepinephrine from 22 studies
  - p = 0.97
  - RR > 1 indicates increased mortality risk
  - RR < 1 indicates reduced mortality risk

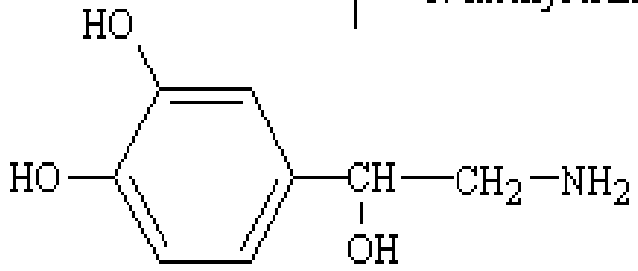
Source: Gamper G, et al. *Cochrane Database of Syst Rev* 2016;2:1-88.

WHY DO WE NEED ANOTHER VASOPRESSOR?



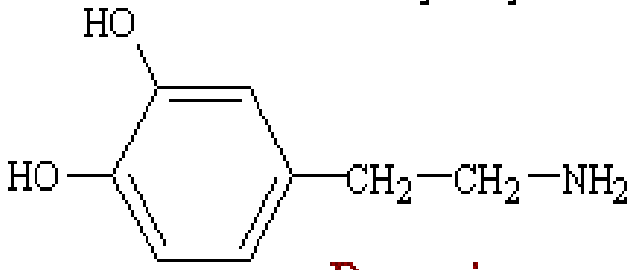
Epinephrine

Norepinephrine
N-methyl transferase



Norepinephrine

Dopamine-
B-hydroxylase



Dopamine

- Human body has three endogenous vasopressors
  - Catecholamines
  - Non-Catecholamines
    - Vasopressin
    - Angiotensin II
- Importance of combination therapy, different mechanisms
  - Epinephrine to norepinephrine → same receptors

Source: Asfar P, et al. *Crit Care Med* 2014;42(8):1961-63.

Angiotensin II

The Importance of Multimodal Therapy

Background

Angiotensin II has been given to human patients since 1941 and has been given to healthy subjects for up to 11 days

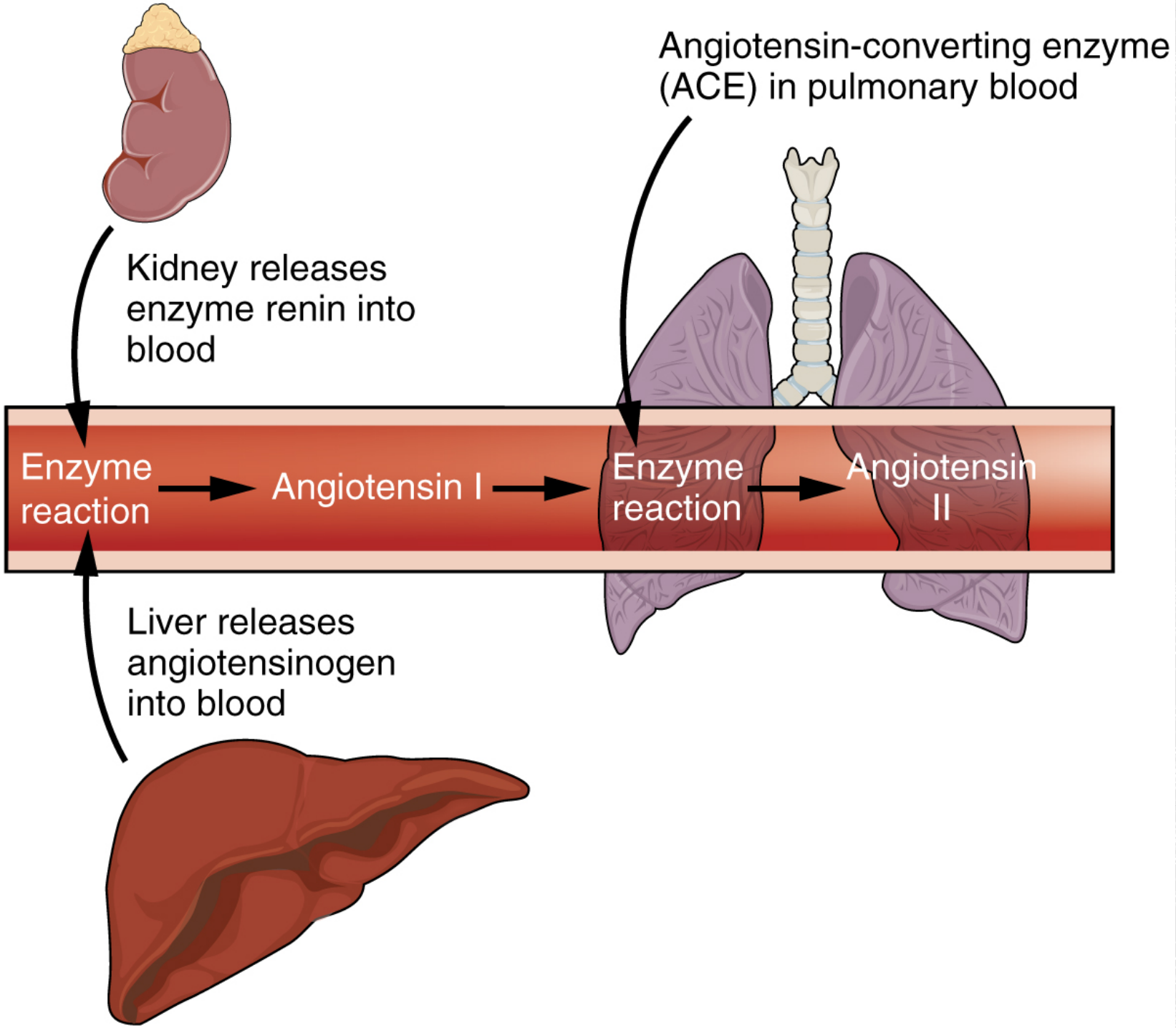
Administered to pregnant women in the mid-1960s to identify those at risk for preeclampsia

Given to children with cancer, septic shock, and congenital cardiac shunts

Previously available for research purposes only

- Bovine angiotensin amide was previously marketed by Ciba-Geigy (now merged with Novartis) under the trade name Hypertensin for "states of shock and circulatory collapse"
  - Their NDA was withdrawn from the market in 2009 by applicant request

Source: Asfar P, et al. *Crit Care Med* 2014;42(8):1961-63.
Busse LW, et al. *Crit Care Med* 2017:1-10.



Effects of Angiotensin II

Dosing

Administration via central line is recommended

Initial: 20 ng/kg/minute IV by continuous infusion

Maintenance/Titration: Monitor blood pressure response and titrate every 5 min up to 15 ng/kg/min to maintain target MAP

Doses as low as 1.25 ng/kg/min may be used

Do not exceed 40 ng/kg/min maintenance doses

Do not exceed 80 ng/kg/min in the first 3 hours of treatment

Source: Giapreza (angiotensin II) injection [package insert]. San Diego, CA: La Jolla Pharmaceutical Company; 2018.

Pharmacokinetics

Absorption: serum levels of angiotensin II are similar at baseline and hour 3 after intravenous infusion

After 3 hours of treatment the serum level of angiotensin I is reduced by approximately 40%

Half-Life: < 1 minute

Median time to reach target MAP was about 5 minutes

Distribution: no studies done

Metabolism: metabolized by aminopeptidase A and ACE2 in plasma, erythrocytes, and major organs (intestine, kidney, liver, and lung)

Excretion: no studies done

Source: Giapreza (angiotensin II) injection [package insert]. San Diego, CA: La Jolla Pharmaceutical Company; 2018.

Storage and Administration

Unopened vials should be stored in the refrigerator (36-46°F, 2-8°C)

Dosage Forms: 2.5 mg/mL and 5 mg/2 mL

Dilute 1 mL in 0.9% sodium chloride to achieve a final concentration of 5000 ng/mL or 10000 ng/mL

Diluted solution may be stored at room temperature or under refrigeration

Discard diluted solution after 24 hours at room temperature or refrigeration

Source: Giapreza (angiotensin II) injection [package insert]. San Diego, CA: La Jolla Pharmaceutical Company; 2018.

Adverse Effects and Drug Interactions

Higher incidence of arterial and venous thrombotic and thromboembolic events

Use requires venous thromboembolism (VTE) prophylaxis unless contraindicated

Adverse Reactions: thromboembolic events, thrombocytopenia, tachycardia, fungal infection, delirium, acidosis, hyperglycemia, peripheral ischemia

Concomitant ACE inhibitor use may increase response

Concomitant Angiotensin Receptor Blocker use may decrease response

Source: Giapreza (angiotensin II) injection [package insert]. San Diego, CA: La Jolla Pharmaceutical Company; 2018.

The Studies

Angiotensin II for the Treatment of High-Output Shock

ATHOS-3

- **Methods**:
  - Prospective
  - Multi-center
  - Double-blind
- 321 adults with refractory septic or other distributive shock randomized 1:1 to angiotensin II or placebo
- **Primary Endpoint**: percent who achieved either a MAP ≥ 75 mmHg or a ≥ 10 mmHg increase in MAP without an increase in baseline vasopressor therapy at 3 hours

Source: Khanna A, et al. *N Engl J Med* 2017;377:419-30.

ATHOS-3: Trial Design

Inclusion Criteria

- Age ≥ 18
- Vasodilatory shock despite treatment with IV fluid resuscitation and high dose vasopressors
  - ≥ 25 mL/kg over 24 hours
  - > 0.2 mcg/kg/min norepinephrine equivalent dose for 6-48 hours

Exclusion Criteria

- Acute coronary syndrome
- Active bleeding
- Burn injuries > 20% of total body-surface area
- Liver failure
- Severe asthma or bronchospasm
- High dose glucocorticoids

Source: Khanna A, et al. *N Engl J Med* 2017;377:419-30.

Characteristic	Angiotensin II (n = 163)	Placebo (n = 158)
Median Age, year	63 (72-75)	65 (53-75)
Male sex, n (%)	92 (56.4)	103 (65.2)
Median MAP, mmHg (IQR)	66.3 (63.7-69)	66.3 (63-68.3)
MAP < 65 mmHg, n (%)	52 (31.9)	50 (31.6)
Median APACHE II score (IQR)	27 (22-33)	29 (22-34)
Cardiac Index L/min/m^2, median (IQR)	3.0 (2.6-3.8)	3.2 (2.7-3.9)
Central Venous Pressure mmHg, median (IQR)	13 (10-15)	12 (10-16)
Exposure to ACE inhibitors, n (%)	15 (9.2)	15 (9.5)
Exposure to ARBs, n (%)	11 (6.7)	11 (7)
Receipt of vasopressin 6 hours before randomization, n (%)	113 (69.3)	111 (70.3)
Median vasopressor dose in norepinephrine equivalents, mcg/kg/min (IQR)	0.33 (0.23-0.56)	0.34 (0.23-0.56)

ATHOS-3: Baseline Characteristics

Source: Khanna A, et al. *N Engl J Med* 2017;377:419-30.

ATHOS-3: Causes of Shock

	Angiotensin II (n = 163)	Placebo (n = 158)
Sepsis	127 (77.9)	132 (83.5)
Other, potentially sepsis	20 (12.3)	11 (7)
Pancreatitis	0	2 (1.3)
Postoperative vasoplegia	10 (6.1)	9 (5.7)
Multifactorial	6 (3.7)	4 (2.5)

Values are reported as n (%) unless otherwise specified

Source: Khanna A, et al. *N Engl J Med* 2017;377:419-30.

	Angiotensin II (n=163)	Placebo (n=158)	p-value
MAP response at 3 hours, n (%)	114 (69.9)	37 (23.4)	< 0.001
Mean change in cardiovascular SOFA at 48h ± SD	-1.75 ± 1.77	-1.28 ± 1.65	0.01
Mean change in total SOFA at 48h ± SD	1.05 ± 5.50	1.04 ± 5.34	0.49
Mean change in norepinephrine-equivalent dose by hour 3 ± SD	-0.03 ± 0.10	0.03 ± 0.23	< 0.001
7-day mortality, n (%)	47 (29)	55 (35)	0.22
28-day mortality, n (%)	75 (46)	85 (54)	0.12

ATHOS-3: Results

Source: Khanna A, et al. *N Engl J Med* 2017;377:419-30.

ATHOS-3 Adverse Events

	Angiotensin II n (%)	Placebo n (%)
Overall in ATHOS-3	142 (87.1%)	145 (91.8%)
Cardiovascular Events		
Thromboembolic Events	21 (12.9%)	8 (5.1%)
DVT	7 (4.3%)	0
Tachycardia	14 (8.6%)	9 (5.7%)
Other Adverse Events		
Delirium	9 (5.5%)	1 (0.6%)
Hyperglycemia	7 (4.3%)	4 (2.5%)
Acidosis	9 (5.5%)	1 (0.6%)
Peripheral Ischemia	7 (4.3%)	4 (2.5%)
Fungal Infection	10 (6.1%)	2 (1.3%)

Source: Khanna A, et al. *N Engl J Med* 2017;377:419-30.

ATHOS-3: Critiques

Baseline Characteristics

- Small sample size (n = 321) that might not have been in refractory shock
  - Baseline MAP $\geq$ 65 in majority of patients
  - Refractory shock was defined as norepinephrine equivalent dose > 0.2 mcg/kg/min, but other studies use 0.5-2 mcg/kg/min
- Baseline cardiac index $\geq$ 3 L/min/m^2
- Majority of patients were septic, so data might not be generalizable to other types of shock

Sepsis Data

- No information on amount or type of fluid volume administered
- No data on antibiotic use, which has a strong correlation with mortality

Source: Khanna A, et al. *N Engl J Med* 2017;377:419-30.

Primary Outcome

- Composite of an increase in MAP or a MAP > 75
- No statistically significant patient-centered outcomes: ICU length of stay, hospital length of stay, need for renal replacement therapy, and mortality differences

Other Outcomes

- Short study duration and follow-up time
- Improvement in cardiovascular SOFA Score
  - No decrease in total SOFA Score
  - Baseline SOFA not reported
  - Related to decreased pressor requirements due to addition of angiotensin II

ATHOS-3: Critiques

Source: Khanna A, et al. *N Engl J Med* 2017;377:419-30.

THE SEQUENTIAL ORGAN FAILURE ASSESSMENT (SOFA) SCORE

SYSTEM	0	1	2	3	4
Respiration PaO2/FIO2 mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets $\times 10^3$/uL	≥150	<150	<100	<50	<20
Liver Bilirubin mg/dL (umol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70mmHg	MAP <70mmHg	Dopamine <5 or Dobutamine (any dose)	Dopamine 5.1 - 15 or Epinephrine ≤ 0.1 or Norepinephrine ≤ 0.1	Dopamine >15 or Epinephrine >0.1 or Norepinephrine >0.1
CNS GCS Score	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dl (umol/L) **Urine Output, ml/d**	<1.2 (110)	1.2 -1.9 (110-170)	2.0 - 3.4 (171-299)	3.5 - 4.9 (300 -440) <500	> 5.0 (440) <200

ATHOS-3: Critiques

ADRs

- Serious adverse events (60.7% vs 67.1% placebo)
  - Adverse event-related drug discontinuation (14.1% vs 21.5% placebo)
  - All adverse events (87.1% vs 91.8% placebo)
- Underpowered for rare ADRs (163 patients)

Dosing

- Higher doses over the first three hours were used to prove efficacy, while safety was achieved by dropping to lower doses after three hours
- Difficult to determine the safety and efficacy of a dose for > 3 hours
  - Could have led to unblinding in study

Source: Khanna A, et al. *N Engl J Med* 2017;377:419-30.

Post-hoc Analyses

Multivariate Analysis of Obtaining Target MAP at Hour 3 (mITT)

Parameter	Odds Ratio (95% CI)	p-value
Treatment with angiotensin II vs placebo	12.4 (6.72-22.8)	**< 0.001**
Age ≥ 65 vs < 65 years	0.99 (0.56-1.74)	0.98
MAP at baseline < 65 vs ≥ 65 mmHg	0.67 (0.36-1.23)	0.20
APACHE II score at baseline > 30 vs ≤ 30	1.04 (0.58-1.85)	0.90
Albumin at baseline < 2.5 vs ≥ 2.5 g/dL	0.40 (0.22-0.72)	**0.002**
Prior exposure to ARBs vs no exposure	0.24 (0.07-0.79)	**0.02**
Chest X-ray finding of ARDS vs no finding	2.03 (1.07-3.86)	**0.03**
Baseline NE equivalent dose ≥ 0.5 vs < 0.5 mcg/kg/min	0.40 (0.21-0.77)	**0.006**

Source: Khanna A, et al. *N Engl J Med* 2017;377:419-30.

Effect of Disease Severity on Survival

- Abstract only
- Subgroup analysis of ATHOS-3 looking at patients with high severity of illness
  - Defined as APACHE II > 30 (n = 123) or MAP < 65 mmHg (n = 102)
- No difference in 28-day all-cause mortality – but underpowered to address mortality differences
  - APACHE II > 30: 51.8% vs 70.8% (HR 0.62, 95% CI 0.39-0.98, p = 0.037)
  - MAP < 65: 54.2% vs 70.4% (HR = 0.66, 95% CI 0.40-1.09, p = 0.10)
  - All patients: 46.1% vs 53.9% (HR = 0.78, 95% CI – 0.57 – 1.07, p = 0.12)

Source: Szerlip H, et al. *Crit Care Med* 2018;46:3.

Norepinephrine-Equivalent Doses

- Abstract only
- Subgroup analysis of ATHOS-3 looking at effect of angiotensin II on norepinephrine equivalent dose (NED) reduction and adverse effects
- 65% of patients (n = 106) had a reduction in NED of ≥50%, compared with only 44% of patients (n = 69) treated with placebo

NED reduction of ≥50% resulted in fewer serious adverse events compared with NED reduction <50%

- 86% vs 47% ($p < 0.0001$) when treated with angiotensin II
- 80% vs 51% ($p = 0.0002$) when treated with placebo

NED reduction of ≥50% resulted in fewer adverse events resulting in death compared with NED reduction <50%

- 72% vs 33% ($p < 0.0001$) when treated with angiotensin II
- 67% vs 36% ($p = 0.0002$) when treated with placebo

Source: Ferrada P, et al. *Crit Care Med* 2019;47(1):786.

Acute Respiratory Distress Syndrome

- Abstract only
- Subgroup analysis of ATHOS-3 looking at patients with Acute Respiratory Distress Syndrome (ARDS)
- Primary MAP endpoint more likely with angiotensin II versus placebo → odds ratios all statistically significant

Mild	Moderate	Severe

• OR: 6.7
  • p < 0.01
• Mortality:
42% vs 53%
	• OR: 6.6
	  • p < 0.01
	• Mortality:
	55% vs 55%
		• OR: 8.4
		  • p < 0.01
		• Mortality:
		50% vs 74%

Source: Busse L, et al. *Crit Care Med* 2018;22:69.

Renal Replacement Therapy

- 105 patients with acute kidney injury (AKI) from ATHOS-3 were included
  - 60 patients received placebo
  - 45 patients received angiotensin II
- Baseline characteristics were similar in both groups, except
  - Baseline Model for End-stage Liver Disease score, median (25.5 placebo vs 23 angiotensin II, p = 0.0095)
  - Baseline norepinephrine equivalent dose in mcg/kg/min (0.46 placebo vs 0.36 angiotensin II, p = 0.0194)

Source: Tumlin JA, et al. *Crit Care Med* 2018;46(6):950-7.

Renal Replacement Therapy

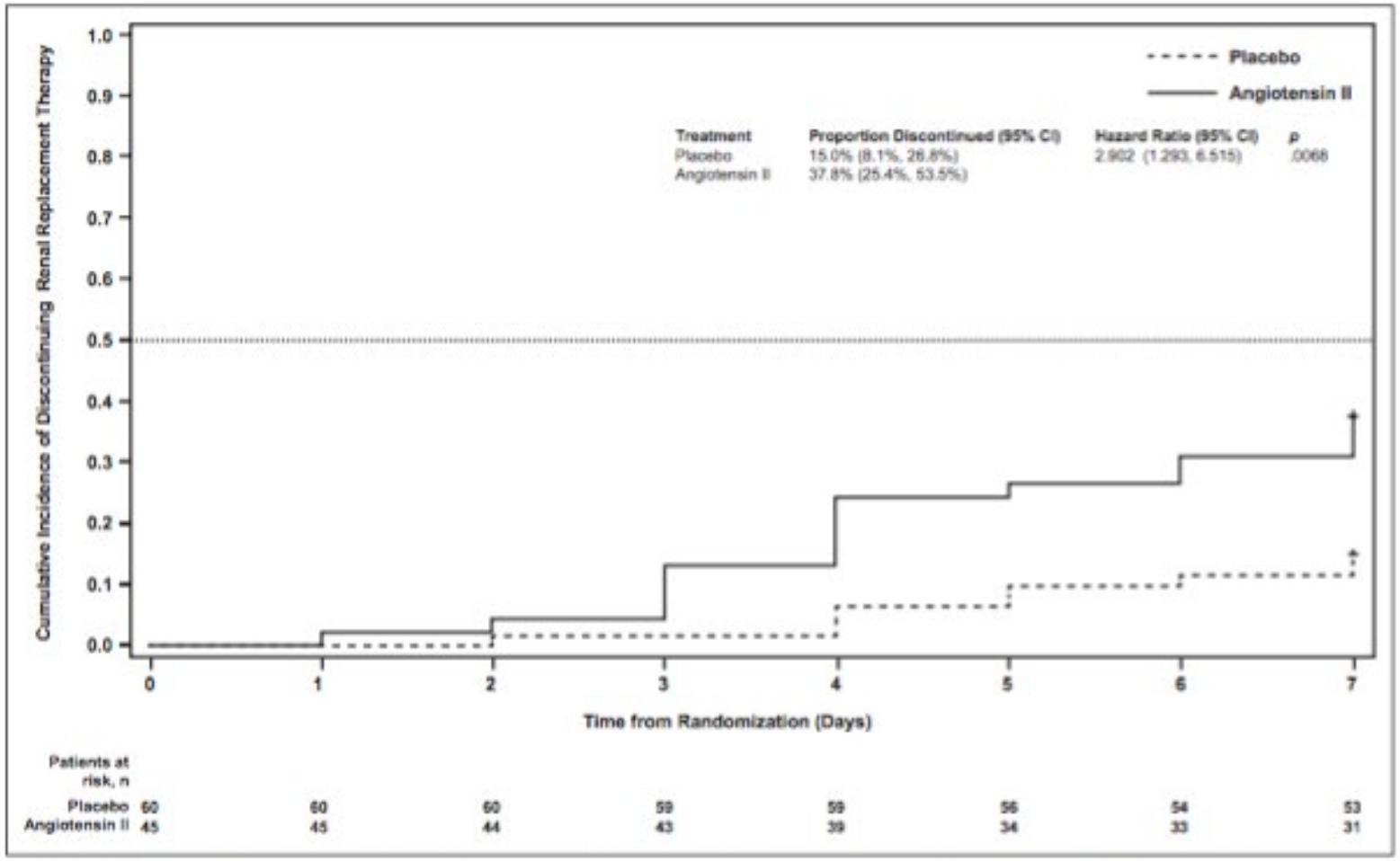


Figure 2. Cumulative incidence of time to discontinuation of renal replacement therapy through day 7. Subjects with death prior to day 7 are censored at day 7. Patients in the angiotensin II group were more likely to discontinue renal replacement therapy within 7 days than those in the placebo group ($p = 0.0068$).

- Survival rates through day 28 were 53% (95% CI, 38-67%) and 30% (95% CI, 19-41%) in patients treated with angiotensin II and placebo (p = 0.012)
- By day 7, 38% (95% CI, 25-54%) of angiotensin II patients discontinued RRT versus 15% (95% CI, 8-27%) placebo (p = 0.007)

Source: Tumlin JA, et al. *Crit Care Med* 2018;46(6):950-7.

Disease State	Outcome	Considerations	Benefit?
High severity of illness	Lower 28-day mortality in high APACHE II patients but not overall	Questionable definition of high severity of illness	?
Norepinephrine-equivalent doses	Lower adverse events and adverse events leading to death	Use of angiotensin II leads to lower doses of pressors and less side effects of each pressor	Yes
Acute Respiratory Distress Syndrome	More likely to respond hemodynamically	Angiotensin conversion is in the lungs	Yes
Renal Replacement Therapy	Potential benefit in RRT patients	Kidneys may be susceptible to effects of perfusion pressure to maintain blood flow	Yes

Post-hoc Analyses Summary

CONSIDERATIONS

What does this mean for angiotensin II?

Looking Ahead

Investigators foresee a future involving phenotyping to identify the best candidates for angiotensin II

Later-line vasopressor therapy

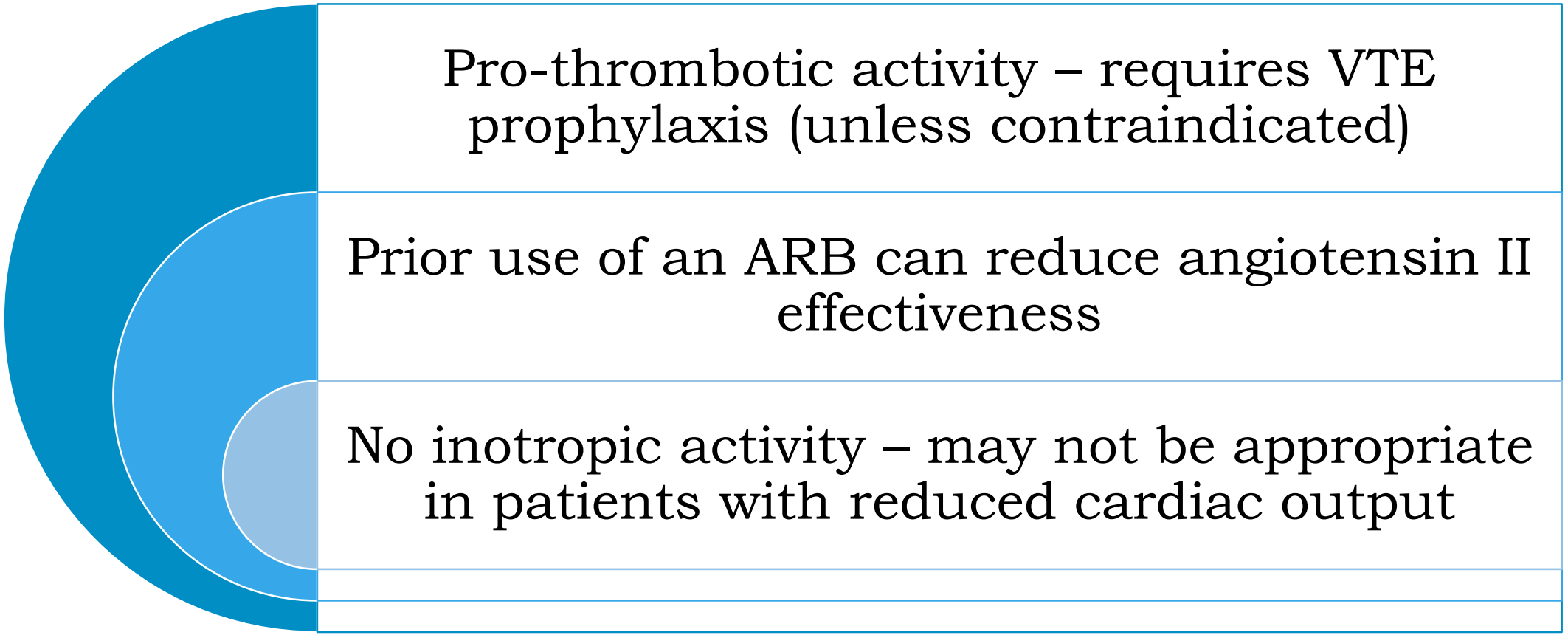
Wholesale Acquisition Cost (WAC) is $1500 per vial

- Available through CMS New Technology Add-on Payment (NTAP) program at select hospitals
- Effective October 1, 2018 (Fiscal Year 2019), Medicare will provide an add-on payment of up to $1500 per qualifying case to Inpatient Prospective Payment System (IPPS)-participating acute care hospitals

Norepinephrine $67 daily → Epinephrine $134 daily → Vasopressin $386 daily → Angiotensin II $2250 daily

Source: Bissell BD, et al. *Ann Pharmacother* 2018;52(9):920-7.

Cautions with Angiotensin II



Source: Bissell BD, et al. *Ann Pharmacother* 2018;52(9):920-7.

Recommendations

- Norepinephrine is the first line pressor in most shock states
- Specific patient populations may experience benefit from using angiotensin II as a vasopressor therapy
- Cost considerations and lack of meaningful outcomes data for angiotensin II limit its use to after failure of other pressors to control patient hemodynamics

Summary

Septic shock is treated with 30 mL/kg crystalloids, broad spectrum antibiotics, and vasopressors if shock is refractory to fluids

Norepinephrine is the current first-line pressor for shock, followed by epinephrine or vasopressin

Angiotensin II offers a third class of vasopressor to potentially use after first-line and second-line agents

Lack of clinical outcomes data and increased cost can limit the use of angiotensin II

Assessment

Assessment Question 1 - Pharmacists

- Which of the following is NOT a component of the qSOFA score to determine if a patient has sepsis?
  a. Low blood pressure
  b. High respiratory rate
  c. Increased temperature
  d. Altered mental status

Assessment Response 1 - Pharmacists

- Which of the following is NOT a component of the qSOFA score to determine if a patient has sepsis?
  a. Low blood pressure
  b. High respiratory rate
  c. Increased temperature
  d. Altered mental status

Assessment Question 2 - Pharmacists

- Angiotensin II reduces mortality in septic shock patients.
  a. True
  b. False

Assessment Response 2 - Pharmacists

- Angiotensin II reduces mortality in septic shock patients.
  a. True
  b. **False**

Assessment Question 3 - Pharmacists

- Patients with which disease states are likely to have increased benefit from using angiotensin II?
  a. Acute respiratory distress syndrome
  b. Acute kidney injury
  c. Liver failure with MELD scores > 23
  d. A and B
  e. All of the above

Assessment Response 3 - Pharmacists

- Patients with which disease states are likely to have increased benefit from using angiotensin II?
  a. Acute respiratory distress syndrome
  b. Acute kidney injury
  c. Liver failure with MELD scores > 23
  d. A and B
  e. All of the above

Assessment Question 1 – Pharmacy Technicians

- What medication classes can be used in the treatment of septic shock?
  a. Antibiotics
  b. Vasopressors
  c. Fluids
  d. A and B
  e. All of the above

Assessment Response 1 – Pharmacy Technicians

- What medication classes can be used in the treatment of septic shock?
  a. Antibiotics
  b. Vasopressors
  c. Fluids
  d. A and B
  e. **All of the above**

Assessment Question 2 – Pharmacy Technicians

- Where should unopened vials of angiotensin II be stored?
  a. Room temperature
  b. Refrigerator
  c. Freezer
  d. All of the above are appropriate

Assessment Response 2 – Pharmacy Technicians

- Where should unopened vials of angiotensin II be stored?
  a. In the pharmacy at room temperature
  b. Refrigerator
  c. Freezer
  d. All of the above are appropriate

When to Use Vasopressors

Norepinephrine

- Vasodilatory Shock
- Septic Shock
- Cardiogenic Shock

Epinephrine

- Anaphylactic Shock
- Cardiogenic Shock
- Septic Shock

Dopamine

- Shock with bradycardia

Phenyephrine

- Vasodilatory Shock
- Later-line agent for Septic Shock

Dobutamine

- Cardiogenic Shock
- Later-line agent for Septic Shock

Vasopressin

- Vasodilatory Shock
- Septic Shock

Angiotensin II

- Vasodilatory Shock
- Septic Shock

Thank you!

Sophia Pathan, PGY-1 Pharmacy Resident

Atlantic Health System

Sophia.Pathan@atlantichealth.org