PHARMACY TO DOSE
THE CRITICAL CARE PODCAST

Vasoactives in Septic Shock

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When teaching sepsis, do you focus on Sepsis-3 or do you also include the historical definition using the SIRS criteria?

- Valuable to go over the historical definition to discuss what SIRS is
- May see SIRS in the many other ICU patients that isn't sepsis or septic shock
- Good introduction to help cover historical aspects to teach what sepsis is not (SIRS v. Sepsis)

When should we be starting vasopressors in a hypotensive septic patient?

- Administer 30 mL/kg (or a few liters of crystalloid depending on patient's weight) and then start vasopressors
- The answer is probably more dynamic compared to a true fixed amount
- Dynamic markers of fluid responsiveness are the answer, probably, to the question of when to start vasopressors
- CLOVERS trial will help with answering this question comparing a restrictive approach to fluid administration to liberal administration

What is considered high-dose norepinephrine?

- Likely is around 0.2 mcg/kg/min of NE similar to the definition used for the ATHOS-3 trial
- By the time patients reach 0.4 mcg/kg/min of norepinephrine, generally think about adding a second-line vasopressor at this time, although this isn't universally accepted
- Once you reach >/= 1 mcg/kg/min and above rates of IV norepinephrine, you have probably reached "resuscitation doses"

How do you use corticosteroids and vasopressin for patients in septic shock?

- Historically, vasopressin was the second-line vasopressor with corticosteroids being added typically right after
- Cost considerations with vasopressin due to price increases make this complicated, and it brings into question the cost-effectiveness of vasopressin as a second-line agent

- With the recent corticosteroid trials (vasopressors discontinued sooner with not many additional adverse effects), corticosteroids have now shifted into the second-line agent when patients are receiving moderate or high doses of norepinephrine

When using corticosteroids for septic shock, do you use fludrocortisone in combination with hydrocortisone?

- Hydrocortisone 50mg IV q6hr is generally used as corticosteroid monotherapy when treating septic shock
- The bioavailability of fludrocortisone in septic shock was very low, likely due to the impaired absorption in shock states
- Hard to believe that the low absorption of fludrocortisone made a clinically significant difference in patient outcomes compared to hydrocortisone alone

Is there any utility to sending random cortisol levels or complete ACTH stimulation testing?

- If patients are hypotensive refractory to vasopressors and vasopressor doses are increasing, generally you should just add the corticosteroids
- If you are hesitant about adding corticosteroids, sending a random cortisol level may help influence your decision, especially if the random cortisol level < 10 mcg/dL or very high
- ACTH stimulation testing is not routinely used

What is the role of epinephrine in septic shock?

- Echocardiogram findings will greatly influence the decision to use epinephrine in patients with septic shock
- If the patient has a reduced EF or subjectively looks like they could use more inotropic support, then epinephrine would probably be added before vasopressin
- But epinephrine causes more tachyarrhythmias, and that creates a complex dilemma in these patients
- Generally, epinephrine is added as a third-line vasopressor after vasopressin

Do you prefer the use of dobutamine or epinephrine for inotropic support in septic shock?

- Depends on how much additional blood pressure support the patient needs
- If the blood pressure is maintained at goal with vasopressors and inotropic support is needed, dobutamine is generally the medication added
- For patients on moderate to high-dose vasopressors, still hypotensive, and in need of inotropic support, then epinephrine is generally the agent of choice

What is the role of HAT (Hydrocortisone, Ascorbic Acid, Thiamine) therapy in septic shock?

- This therapy isn't added routinely for all patients in septic shock
- When mainstream media (NPR, NY Times) started publishing articles discussing this therapy, patients' family members were requesting its use
- It is used on a case-by-case basis and is not a standard of care

What is the role of thiamine supplementation for patients in septic shock?

- There was a pilot study where all patients in septic shock received thiamine and in patients who were thiamine deficient, there was a reduction in mortality
- If you are thiamine deficient you shunt out of the Krebs cycle and increase lactate production
- The retrospective study completed at UK matched case-control patients in septic shock comparing those who received thiamine compared to those who did not. Found that patients who received thiamine cleared their lactate faster and had a reduction in mortality.
- All patients in septic shock at UK do not receive thiamine however, but it is added for patients with risk factors that may predispose patients to thiamine deficiency
- Some common risk factors are substance abuse and IV drug abuse, but less recognized risk factors also include patients who have been vomiting for 1-week straight or chronic TPN patients (were they receiving thiamine in their TPN?)

How should we use Angiotensin II in practice?

- It is difficult to provide an evidence-based way to use Angiotensin II
- The ATHOS-III trial was more of a Phase II trial demonstrating that Angiotensin II is a vasopressor

- More subgroup analyses from this study demonstrating it may be beneficial in patients who undergo CRRT or it could be good for patients with ARDS in septic shock
- Some unique sub-populations deserve to be studied further to understand its role for those patients. However due to its current cost, this may prohibit that and limit its utility to a third-line agent
- Other non-catecholamine vasopressors, such as vasopressin, don't carry a Black Box Warning that Angiotensin II does
- So there are cost and safety concerns with angiotensin II that limit its utility
- As of now, its place in therapy looks to be a third-line vasopressor agent in a potentially salvageable patient with the chance of a good outcome who has soaring vasoactive requirements

What is the general approach to using methylene blue as salvage therapy?

- Generally it isn't used very much, because when methylene blue is added it might be too little too late (patients already receiving ~1 mcg/kg/min of IV norepinephrine)
- Issues also arise with monitoring oxygenation via SpO_2 probes

Are there scenarios where you modify hemodynamic goals to assist with vasopressor weaning?

- Don't necessarily aim for a higher MAP target in septic shock
- The biggest patient populations who the MAP target is lowered would be cirrhotic patients, elderly patients, or baseline hypotensive patients (which can be challenging at times to identify)
- The MAP goal may be dropped to 55 or even 50, with monitoring of their mental status and urine output
- This is a good helpful intervention to assist with vasopressor weaning
- If there is a wide variation in their pulse pressure, a SBP goal may be used instead of a MAP goal

How do you manage adverse effects (e.g. tachyarrhythmias) related to vasopressors, do you treat the side effect or change the agent?

- The tachyarrhythmias from high-dose catecholamine vasopressors in a hypotensive septic shock patient are one of the most difficult situations to deal with

- Always look to optimize electrolytes and monitor their volume status before shifting to treatment or alternative agents
- When changing from norepinephrine to phenylephrine, it makes pharmacologic sense, but there is some data to suggest that septic shock patients did worse when receiving phenylephrine when there was a norepinephrine drug shortage
- Try to fix underlying causes rather than adding drugs
- May look to use amiodarone or esmolol if you are trying to treat the tachyarrhythmias
- Difficult to truly know if the tachyarrhythmias are due to catecholamines or from being critically ill in septic shock

What is the order of operations for weaning vasopressors in septic shock?

- Most of the data published, suggests you get more hypotension if you wean the vasopressin off first before weaning norepinephrine
- The caveat is that there seems to be no difference in patient-specific outcomes such as ICU length of stay or mortality
- The literature may guide you towards discontinuing vasopressin last, but a cost-effective analysis might lead you towards discontinuing the vasopressin first

Do you taper vasopressin off or simply discontinue it?

- No strong feelings one way or another, could do both strategies

Do you taper corticosteroids or discontinue them once they are out of the acute shock phase of sepsis?

- Once they are hemodynamically stable and off vasopressors, generally the corticosteroids are simply discontinued
- The longer patients are on corticosteroids (e.g. >/= 7 days), the argument gets better for tapering the corticosteroids

When do you consider using midodrine to assist with IV vasopressor weaning?

- For the patient maintaining on a very low dose of IV norepinephrine (e.g. 0.02-0.03 mcg/kg/min) and the RN is unable to wean, midodrine can be very useful
- Generally, not every septic shock patient with reduced vasopressor requirements receives midodrine to assist with weaning at UK
- Some data suggests it may reduce the duration of vasopressor infusions and reduce ICU length of stay
- But midodrine has side effects that may limit its utility such as bradycardia, drug-disease interactions (e.g. patient receiving midodrine and metoprolol/carvedilol), and transitions of care issues
- It can also be seen as a band-aid for septic shock patients, because it may mask if patients decompensate and hide how critically ill patients may become
- Midodrine is also not an extremely cheap medication
- When using midodrine to wean from IV vasopressors, the general starting dose is 10mg PO three times daily

What are some take-home points with vasoactives in septic shock?

- Whatever question you are asked as the Pharmacist rounding, usually it is difficult to answer directly. There is typically an underlying question or issue you need to address first to fully answer the direct question
- It is important to not take all studies at face value (one drug is better than the other), but think about what this means for you and what it means for the patient
    - What if the patient's MAP improves, but there is no difference in outcomes?
    - If you wean one vasopressor faster than another, and there is more hypotension but no change in clinical outcomes, is that way truly better?
- These things also get tricky when drug shortages and price increases occur
- Makes something already complex even more complex

What are future areas for research in septic shock?

- HAT "cocktail"
- Vasopressin analogues are actively being studied but the data hasn't been promising
- Angiotensin II
- CLOVERS trial – liberal vs. restrictive fluid administration in acute phase of septic shock