S01:E07 - Beyond the Basics

Critical Care Time Show Notes

Summary: On this episode of ***Critical Care Time***, Cyrus and Nick go beyond the basics of vasopressor management. During this episode - jam-packed with high-yield pearls - we discuss important topics such as how to titrate vasopressors, what can be done when vasopressors seem to be failing a patient and how to wean patients from vasopressors in order to successfully get them out of the ICU and ultimately home. Sit back, relax, and enjoy this hour long master-class on Vasopressors - Beyond the Basics!

Quick Take Home Points:

1. **Many patients will need more than one vasopressor** to get through their hospitalization
2. **For most folks, vasopressin is the best 2nd line vasopressor**
3. **Consider starting steroids - hydrocortisone AND fludrocortisone** - in patients with septic shock who require a second vasopressor
4. Always consider **reasons for persistent shock** - these can include conditions such as **adrenal insufficiency, undrained/untreated infection, stress cardiomyopathy** or the very-important-but-oft-misunderstood **dynamic LVOT obstruction**
5. When starting a third-line pressor, use this opportunity to **once again** consider untreated causes for persistent shock, but also **consider a trial of a vasodilator scavenger** as well as that third pressor
6. For most patients, **the third pressor should be epinephrine**, although there is a place for other agents such as phenylephrine, perhaps angiotensin II, and even-but-probably-not dopamine
7. **Exit strategies are important:** don't forget to de-resuscitate a patient who has gotten significant volume resuscitation if indicated (persistent oxygen requirement with evidence of pulmonary edema, for example) and have a strategy for managing patients who are a "tough wean" from vasopressors (stop norepinephrine before vasopressin, think about confounding conditions, consider midodrine)

Show Notes:

1. Initial approach to a person who is failing their first-line vasopressor therapy?
    a. Consider assessing, again, for volume responsiveness (250cc rapid fluid bolus vs passive-leg raise test, in conjunction with invasive cardiac output monitoring, non-invasive cardiac output monitoring and/or point of care ultrasound - aortic VTI assessment, carotid VTI assessment, etc.)
    b. Low threshold to add a second line vasopressor - almost universally **vasopressin**
2. What's so cool about vasopressin?
    a. Why? **There is no *maximum dose* of norepinephrine**, however, the law of diminishing returns likely plays a role - at some point you are saturating most

catecholamine receptors, and thus, it makes sense to approach a patient - especially in septic shock - through a different mechanism

b. There is evidence that, at increasing doses of norepinephrine, not only do returns diminish, but problems can arise such as:
    i. Increased tissue oxygen demand
    ii. Decreased renal blood flow
    iii. Decreased mesenteric blood flow
    iv. Increased pulmonary vascular resistance which → worsening RV function
    v. Increased tachyarrhythmias
c. There is some data to suggest patients in septic shock suffer from an acute deficiency of endogenous vasopressin
d. Collectively, this portends a synergistic effect between catecholamine and non-catecholamine vasopressors
    i. *LANDMARK TRIAL ALERT* - The VASTT Trial
        1. ICU patients with septic shock on at least 5mcg/min NE randomized to starting vasopressin vs increasing NE
        2. Early vasopressin group **trended** towards a mortality benefit (i.e. non-significant) but technically did not yield a mortality benefit
        3. However - In the subgroup with **less severe shock** (NE<14mcg/min), mortality was **~10% lower** at 30 and 90 days when vasopressin was added early → NNT of 10

3. What's the deal with steroids in septic shock?
    a. *Potential* for acute adrenal insufficiency in septic shock, resulting in a relative glucocorticoid deficiency, which can cause problems…
        i. This is **not** cut and dry!
            1. Much more support for adrenal insufficiency in those who are critically ill for 5-7 days or longer, than those who have a rapidly uptrending pressor requirement
        ii. Check out this great discussion regarding the history of glucocorticoid deficiency in septic shock
    b. Steroids do a few things..
        i. Increase ligand-receptor interactions between catecholamines and catecholamine receptors, and increase transcription of those receptors receptors, making a patient **more** receptive to catecholamine therapy
        ii. In animal models, induced glucocorticoid receptor deficiencies have catastrophic outcomes when it comes to laboratory induced septic shock vs non-knock out populations
    c. What's out there?
        i. Steroids in septic shock - selected studies
            1. Ananne Trial - 2002: Reduction in 28 day mortality with **hydrocortisone + fludrocortisone**, criticized due to wide-spread use of etomidate in these patients

2. CORTICUS - 2008: Hydrocortisone expedited shock-reversal without a mortality benefit
    a. Fludrocortisone was not used
3. HYPRESS - 2016: Hydrocortisone did not have any significant impact on mortality or shock reversal, resulted in increased hyperglycemia, may have improved rates of delirium (somewhat of an unusual finding given conventional wisdom as pertaining to steroids in the inpatient setting and the signal for delirium)
    a. Fludrocortisone was not used
    b. Very heterogeneous patient population as far as primary diagnosis, making subgroup analysis difficult
4. APROCCHSS - 2018: In those with septic shock who received hydrocortisone and fludrocortisone, all-cause mortality at 90 days was significantly improved vs those who did not
5. ADRENAL - 2018: In those with septic shock who received a **continuous infusion of hydrocortisone for their shock** (no fludrocortisone) there was no mortality benefit seen, but there may be improvements in some secondary outcomes such as time to extubation, or ICU LOS
    a. Continuous infusions are **not** physiologic
6. JAMA Meta-Analysis - 2023 - Hydro + Fludro vs Hydro Alone in Septic Shock:
    a. Nearly 90,000 patients included
    b. Composite Outcome: in-hospital death OR discharge to hospice
    c. >8% absolute risk reduction ($p<0.001$) in those treated **with hydrocortisone & fludrocortisone** vs hydrocortisone alone

ii. Steroids in respiratory diseases
1. CAPE-COD Trial: Patients with severe CAP in the ICU who received hydrocortisone had improved mortality vs those that received placebo
2. RECOVERY: Patients with COVID pneumonia who were hospitalized, with an oxygen requirement, had improvement in 28 days mortality

4. So you've added vasopressin **and** steroids… but the patient still isn't getting better.
    a. Considerations
        i. Go to the beside and re-evaluate the patient
            1. Use point-of-care ultrasound to interrogate the heart, the lungs, and any other areas that could be hiding an untreated source of infection, or site of hemorrhage

a. Some basic things to look for: pericardial effusion / tamponade (not that subtle), pneumothorax with tension physiology (*really* not that subtle), perinephric abscess, empyema/loculated pleural effusion.
b. More advanced concepts: assess for evidence of cardiogenic shock
    i. LV function via global assessment, LVOT VTI
    ii. RV function via TAPSE, RVOT VTI
    iii. Assess for **dynamic LVOT obstruction**

ii. Undrained source of infection?
1. Abscesses aren't well treated with antibiotics - especially those that are larger than 5cm
    a. First: Look with U/S and see if you find anything, then consider a CT scan to further interrogate an U/S finding **or** to identify something that your U/S missed
    b. Second: Think about broadening coverage if the clinical context suggests that would be helpful

iii. Stress Cardiomyopathy?
1. Sepsis-induced myocardial dysfunction (SIMD)
    a. Reversible myocardial depression, usually seen in the LV but may manifest as systolic and diastolic, right and left sided, cardiac dysfunction that contributes to a patient's shock state
    b. May be seen in up to 40% of patients with septic shock, portends a worse outcome.
2. Sepsis-induced takotsubo cardiomyopathy
    a. "Aka apical ballooning syndrome"
    b. "...generally characterized by reversible systolic dysfunction of the apical and/or mid segments of the LV, with a presentation mimicking myocardial infarction"
    c. Severe LV dysfunction, ***usually* without biomarker elevation**
    d. ST-elevations **can be seen** and make this difficult to differentiate from STEMI - especially given presence of chest pain, even more so if biomarker elevation is present
    e. Reversal often seen on echo within weeks of sepsis resolution
3. Tips
    a. Increased SVR can **unmask** these processes
    b. Consider using **inotropes** such as dobutamine to support these patients until their cardiac function improves

iv. Dynamic LVOT Obstruction

1. Seen in a few scenarios…
    a. A hypertrophic LV (perhaps due to long-standing hypertension) is generally associated with a narrowed LVOT and may set the stage
    b. Classically seen in those with **hypertrophic (obstructive) cardiomyopathy**
    c. Can also be seen in scenarios where **the changes in loading conditions** can lead to the development of a gradient between LV & LVOT
        i. Examples: hypovolemia, hypotension, increased HR / inotropy
2. The narrowed LVOT results in an increased pressure gradient with respect to the LV relative to the aorta
3. Blood travels through the narrow LVOT at a pathologically high velocity, which can pull the papillary muscles into the LVOT with every ejection of blood, resulting in **systolic anterior motion** of the mitral valve (aka **SAM**) which leads to further narrowing of the LVOT and mitral regurgitation
4. These patients are often asymptomatic at baseline, may have subtle/mild symptoms with exertion, but can often have their disease unmasked during critical illness - especially when inotropes increase LV contractility, thereby increasing the gradient and ultimately causing a **dynamic LV outflow obstruction** to manifest
5. When to suspect: Patient who **gets worse** with increasing doses of pressors (or "*vasopressor refractory shock*"), + ?new systolic murmur, + ?new pulmonary edema due to mitral regurgitation
    a. May also see a very narrow pulse-pressure due to reductions in stroke volume (SV proportional to PP)
6. Diagnosis: POCUS!
    a. High-velocity, late-peaking continuous-wave doppler signal across the LVOT (dagger shaped tracing)
        i. V usually > 300cm/sec
7. Treatment
    a. **Correct hypovolemia** if relevant
    b. **Increase afterload** without increasing inotropy (consider phenylephrine, vasopressin, angiotensin II)
    c. **Stop inotropes** if patient is on them
    d. **Consider** beta blockade

v. Anaphylaxis?
1. Review medications - did this patient get started on something new?

2. Anaphylaxis can be cryptic in patients with a secure airway who are sedated
3. Consider a trial of therapy (anti-histamines, steroids if not on them, epinephrine) and assess for response if you cannot definitively rule out anaphylaxis

vi. Acidosis?
1. Acidosis contributes to **decreased smooth muscle tone** which contributes to stubborn vasodilation
2. Acidosis contributes to **a negative inotropic effect** on the heart resulting in varying degrees of pump failure
3. Acidosis **impairs the ability of vasopressors** to interact with their respective receptors
4. Treatments?
    a. Increase minute ventilation on the ventilator
    b. Consider bicarbonate boluses & infusion
    c. Consider continuous renal-replacement therapy

vii. Vasoplegia?
1. "... a condition characterized by persistent low systemic vascular resistance despite a normal or high cardiac index, resulting in profound and uncontrolled vasodilation."
    a. A bit of a wastebasket term in some respects, that describes persistent shock despite augmented cardiac function
2. This may be better understood when viewed from the paradigm of an imbalance between vasoconstrictive and vasodilatory factors, such as nitric oxide, adenosine, prostanoids and endothelins
3. Treatment includes all the aforementioned interventions, plus the use of nitric oxide scavengers

b. Once you've appropriately assessed the patient and considered the above causes for refractory shock, it's appropriate to focus on "defending the MAP" once again, and to do this, we recommend two interventions in general

i. Adding a third pressor - usually epinephrine
1. Epinephrine provides inotropy - more so than norepinephrine - as well as afterload augmentation
    a. At increasing doses, it can be problematic by increasing the frequency of tachyarrhythmias
2. Dopamine has generally fallen out of favor due to numerous studies (SOAP-II) - due to trends towards increased mortality and a strong tendency to cause tachyarrhythmias
    a. May have a role in bradycardic patients?
3. Phenylephrine may be helpful - especially in dynamic LVOT obstruction or in patients who are tachycardic (ex A-Fib with RVR)

a. Will not provide any cardiac support in the setting of stress cardiomyopathy

4. Angiotensin II
    a. Only major study involved AT2 vs Placebo
    b. Beneficial with those who have high renin levels but are not producing endogenous angiotensin
        i. Unfortunately using a renin-assay to guide therapy is impractical for most
    c. Often not available on hospital formularies
    d. When available… the drug is somewhat expensive - although this has been mitigated by the company as of late through provision of test-doses that can be trialed rather than larger quantities
    e. Sometimes this is a fine option, the issue is "...it's hard to know *a priori* who will respond and who won't."

ii. Vasodilator scavengers - can be helpful to treat underlying "vasoplegia" - specifically the element of increased vasodilators relative to vasoconstrictors

1. Methylene Blue
    a. Nitric oxide scavenger
    b. Increases MAP, increases SVR, decreases vasopressor requirement
    c. At least one 2022 meta-analysis suggests decreased mortality when added to vasopressors in those with distributive shock
    d. May even be a role for early use (first 24 hours) in septic shock
    e. Results in green/blue urine
2. Hydroxycobalamin
    a. Nitric oxide scavenger & hydrogen sulfide scavenger
    b. Less evidence versus methylene blue
    c. Results in dark-red urine, which can trick dialysis machines into thinking blood is leaking into the dialysate and therefore may severely hamper efficiency

5. De-resuscitation and weaning from vasopressors
    a. De-resuscitation
        i. Patients often receive fluids - perhaps overzealous amounts of fluids - as part of their resuscitation
        ii. Patients in shock generally have a low MAP, and if they have been overly "tanked-up" they may have a normal-to-high CVP resulting in a low renal perfusion pressure, which may in turn limit their ability to maintain fluid balance through consistent UOP

iii. Once the shock state has resolved, a patient may need some degree of diuresis (usually a loop diuretic) to mobilize extravascular fluid (especially resuscitation associated pulmonary edema)

b. Weaning
   i. Move the goalposts
      1. Remember "The 65 Trial" and how, in some populations, it may be reasonable to target a lower MAP goal
      2. If a patient is asymptomatic - and able to participate in PT for example - at a lower MAP, then that may be an acceptable number for that patient
      3. What is worse is chaining a patient to the bed due to what **is now** asymptomatic hypotension without signs of shock, because of the number… thereby adding to their likelihood of sarcopenia & ICU-associated debility
   ii. Wean in the right order
      1. Evidence suggests that weaning norepinephrine before vasopressin will get folks off pressors faster than the reverse
   iii. Consider persistent causes for hypotension and treat them
      1. Chronic adrenal insufficiency or hypothyroidism can be masked by critical illness
      2. Consider these diagnoses in those who have a lingering pressor requirement, and initiate treatment for them if present
   iv. Consider midodrine - if not already done!
      1. Oral midodrine may liberate patients more quickly from the ICU
      2. A single center, retrospective study in one ICU demonstrated a significant reduction in vasopressor requirement and ICU length of stay
      3. MIDAS Trial: midodrine was NOT helpful in regards to liberating patients from the ICU and vasopressor requirements
      4. There is an ongoing RCT (LIBERATE) looking at this question, again, hoping to expand on the work done in MIDAS
      5. Based on available data and an overall favorable risk-to-reward ratio, we recommend using midodrine…
         a. …either early in patients who are thought to be at risk for needing a prolonged vasopressor course (more elderly patients with more comorbid conditions)
         b. … or as a means to wean from vasopressors in a more "reactionary" manner, to facilitate PT and ICU discharge
      6. **Important: Make sure the midodrine is STOPPED prior to discharge** or a plan is in place for midodrine management once discharge occurs

a. Do not make the mistake of sending home a patient on their antihypertensives and midodrine!!!

SoMe.:

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