EM CASES SUMMARY

Episode 122 Sepsis & Septic Shock – What Matters Live from EM Cases Course

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The latest definitions of sepsis and septic shock

As per the Third International Consensus Definitions for Sepsis and Septic Shock [1]:

Sepsis is "life-threatening organ dysfunction caused by a dysregulated host response to infection" with a **SOFA** score ≥2.

Septic shock is "a subset of sepsis in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone", identified clinically by a vasopressor requirement to maintain a MAP ≥ 65 and serum lactate ≥ 2 mmol/L in the absence of hypovolemia.

Severe sepsis is no longer part of the definitions.

What is the best clinical tool to aid in the recognition of sepsis and septic shock?

While many cases of sepsis and septic shock are obvious clinically, occult septic shock may be missed early in the ED stay leading to poor outcomes. Early recognition of sepsis is essential. In cases that are not obvious, it is recommended to use a clinical tool to help prognosticate and guide management.

A recent retrospective study compared the clinical tools **SIRS**, **qSOFA**, and **NEWS** (National Early Warning Score) for the early identification of sepsis in the ED, and found that NEWS was more accurate that both SIRS and qSOFA for the early recognition of septic shock [2]. qSOFA had the lowest sensitivity and only moderate specificity while SIRS had poor specificity. NEWS had equivalent or superior value for most test characteristics relative to SIRS and qSOFA based on another recent retrospective study [3]. The beauty of the NEWS is that it can be calculated rapidly at triage without the need for blood test results and it allows for improved risk stratification.

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Lab tests in the early management of sepsis and septic shock

Lactate as a diagnostic marker for sepsis and septic shock

If you are still unsure if your patient is septic or not after calculating the NEWS, obtain a serum lactate early.

Tip: *Send a venous gas with your initial labs, and have the lab run the lactate on that so you get it back fast. You might be surprised to get back a very elevated lactate on a patient with an otherwise low pretest probability for sepsis, and this may help guide your management.*

We know that lactate is useful to help identify occult septic shock in those patients who don't present in florid septic shock, but it is very nonspecific and there are many false positives including any type of shock, liver failure, seizures, Type B Lactic Acidosis from many drugs including Ventolin/albuterol.

Procalcitonin as a diagnostic marker for sepsis and septic shock

So we know that lactate isn't perfect. Maybe there's another lab test that can help guide us when lactate fails us. Is there a role for obtaining a serum procalcitonin level on a patient who you're not sure has sepsis?

A meta-analysis from 2015 suggested that procalcitonin levels in early stages of sepsis are significantly lower among survivors as compared with nonsurvivors of sepsis [4]. However, a more recent retrospective study using the Sepsis-3 definition outlined above, found that procalcitonin using a cutoff of 0.41 ng/dL had a sensitivity of only 75% and specificity of 64% for sepsis and using a cutoff of 4.7 ng/dL had a sensitivity of only 66% and specificity of 79% for septic shock [5]. Procalcitonin lacks negative predictive value. Other studies suggest that procalcitonin may help risk stratify pneumonia and guide antibiotic de-escalation, but it's use in sepsis in the ED is probably not very helpful.

Resuscitation fluid of choice in sepsis and septic shock

SALT-ED trial looked at about 13,000 ED patients from a single center in an unblinded fashion, some of which were diagnosed with sepsis, who received more than 500cc of either saline or balanced crystalloid (1.5L on average) and then were admitted to hospital wards. They found that there was no significant difference in length of stay, but in a secondary outcome analysis, the saline group had a significantly higher 30 day composite of death, dialysis or creatinine >200% from baseline with an NNT of 111 [6].

SMART trial had a similar design, but with 15,800 patients admitted to the ICU. They had a pre-specified subgroup of about 2,000 septic patients and their primary outcome was a 30 day composite of death, dialysis or creatinine >200% from baseline. The saline group had significantly higher primary outcome (39% vs 34%) with a NNT of 20. In the secondary outcome analysis the septic patients who received saline had a higher mortality rate (29% vs 25%) compared to those who received balanced solutions (Ringer's or Plasmalyte) with an NNT = 24 [7].

While these studies have several flaws (non-blinded, composite end point, balanced solutions groups did not specify Ringer's Lactate vs Plasmalyte, adjusted analysis required to show significance, making claims based on secondary outcomes – to name a few), our expert nonetheless recommends Ringer's Lactate as the initial resuscitation fluid of choice in sepsis and septic shock because normal saline is thought to be associated with worsening hyperchloremic metabolic acidosis [8] as well as renal vasoconstriction from the chloride load resulting in poor renal function [9], and these recent studies, while flawed, do suggest worse renal function and possibly increased mortality with saline compared to balanced solutions.

Logistics of giving RL. You'll need one IV line for your antibiotics and a separate one for RL because Ceftriaxone, as well as some formulations of Piperacillin-Tazobactam are incompatible with Ringer's Lactate.

Endpoint of resuscitation: How much fluid should be given up front in sepsis and septic shock?

There is no cookbook recipe here. The Surviving Sepsis Campaign 2018 Update [10] suggests starting a rapid administration of 30mL/kg crystalloid for patients with hypotension or a lactate ≥ 4, while the Canadian Guidelines from 2008 suggest "an initial bolus of 1–2 L of crystalloid or 500–1000 mL of colloid should be given over 30–60 minutes and repeated as required to correct tissue perfusion and/or blood pressure abnormalities."[11] The ProCESS [12], ARISE [13] and ProMISe [14] trials bring no clarity as to the optimal amount of fluid for sepsis and septic shock.

In practice, some patients will only need 1 litre, others will require 5. Titrate your fluids to the individual. In general, initial fluid resuscitation should be enough to keep the MAP ≥ 65 while end-organ perfusion is maintained (adequate urine output, level of awareness, capillary refill and decreasing lactate). It is reasonable to target a MAP of 60 or 55 in younger, otherwise healthy patients or 70-75 in patients with known untreated hypertension. **POCUS IVC width and collapsability** [15] are other measures that can aid in the determination of whether or not a patient with sepsis has been adequately volume resuscitated, but should not be used alone in this determination. Other measures such as end tidal CO2, pulse pressure variability and passive leg raise test to assess fluid responsiveness can also be integrated into decision making. Even for patients with a history of heart failure or who have signs of acute heart failure, crystalloid boluses should be given to maintain adequate end-organ perfusion. Fluid should be administered via at least two proximal large bore peripheral IVs, wide open, under pressure.

Endpoint of resuscitation: Lactate clearance vs Capillary refill time normalization

The 2019 ANDROMEDA-SHOCK RCT of 424 patients with septic shock compared normalization of Lactate vs normalization of capillary refill time in the resuscitation of patients with septic shock [16]. Using lactate clearance resulted in more fluid administered, more vasopressors and more epinephrine without any significant improvement in outcomes. There was a trend toward higher 28-day mortality in the lactate clearance group (35% in the capillary refill time group vs 43% in the lactate clearance group), a difference that did not reach statistical significance. These results question whether lactate clearance is the optimal endpoint of resuscitation in septic shock, and whether lactate-guided management may even cause harm.

Procalcitonin clearance has also been studied [17]. A prospective, observational cohort ICU study of patients with severe sepsis and septic shock found that 24- and 48-hour procalcitonin clearance scores were significantly higher in survivors. The area under the receiver operating characteristic curve was 0.76 for 24- and 48-hour procalcitonin clearance scores.

Starting norepinephrine in sepsis and septic shock: Is earlier better?

Probably. The Surviving Sepsis Campaign 2018 Update suggests starting norepinephrine if the patient is hypotensive *during or after* fluid resuscitation to maintain a MAP ≥ 65. There is no need to wait for 2-3L of crystalloid to go in. A more recent study, CENSER, is the first ever prospective randomized trial looking at vasopressors in sepsis. Patients in Thailand presumed to be septic with a MAP <65 were randomized to receive norepinephrine 0.05 micrograms/kg/min without titration for 24hrs or placebo [18]. The primary outcome was shock control by 6 hours. This was defined as sustained MAP>65 (>15 minutes) plus 2

consecutive hours of urine output >0.5ml/kg/hr or decrease in serum lactate >10% from the initial lactate level. 76.% in the early norepinephrine group vs 48% of the control group achieved shock resolution at 6 hours. Mortality was lower in the early norepinephrine group (16% vs 22%) but not statistically significant. This study is consistent with previous data that suggests that early initiation of norepinephrine is septic shock is preferable, although large RCTs are pending. Currently, the CLOVERS trial [19] is underway comparing early vasopressors to IV fluid resuscitation.

We know that we can give norepinephrine through a peripheral line safely and quickly if done carefully through a large proximal IV with hourly extremity checks. A central line is not a priority in the early resuscitation phase.

Dosing norepinephrine in septic shock

Start at 5 mcg/kg and titrate immediately after each q5minute BP check. This will likely require you to stay at the bedside. Note that a radial arterial line may underestimate MAP compared to a femoral arterial line by as much as 5mmHg in early septic shock and >5 in advanced shock, leading to higher doses of norepinephrine than are necessary. [20]

Vasopressin is the second line vasopressor in septic shock

Vasopressin reduces the need for norepinephrine but does not reduce mortality

The VANISH study suggested that while early vasopressin does maintain blood pressure and reduce the requirement for norepinephrine and renal replacement therapy, it does not reduce the number of renal replacement free days or mortality rate [21]. The VASST study did not show a mortality benefit from adding vasopressin if the MAP was adequately maintained with norepinephrine [22].

Vasopressin dosing 0.03-0.04 units/min

When should vasopressin be initiated in septic shock?

There is no clear evidence for the indications for staring vasopressin in patients with septic shock. Our expert recommends starting vasopressin when moderate doses of norepinephrine (as in 0.5 mcg/kg/min or 35 mcg/min) have been reached.

Antibiotic timing, administration and choice in sepsis and septic shock

Timing of antibiotic administration in sepsis and septic shock

We know that with each passing hour that antibiotics are *not* initiated in septic shock, survival drops – it's a time bomb. Which may *not* be the case for sepsis *without* septic shock [23]. Nonetheless, this prompted the newest Surviving Sepsis Campaign Guidelines to mandate antibiotics within the 1st hour of the patient hitting triage for anyone suspected of sepsis as part of their Sepsis Management Bundle [10]. There has been a huge backlash against this mandate, because we would end up giving expensive antibiotics to many patients who do not need them, possibly get distracted from other possible life threatening diagnoses, and contribute to antibiotic resistance. This mandate may be neither safe, nor feasible. A recent review article in Annals of EM looked at the evidence for improved survival for the 1-hour management bundle concluded that there was no high or moderate level evidence for benefit [23]. Rather than aiming for antibiotic administration within 1 hour of arrival at the ED, our expert recommends to aim for antibiotic administration *within 1 hour of the diagnosis being made.*

How fast should antibiotics be given in sepsis and septic shock? We use push dose pressors – why not push dose antibiotics?

Once the decision to give IV antibiotics has been made they should be given over 5 minutes (rather than the usual 30 minutes) in order to reach peak effect as early as possible. The exception is vancomycin which must be given slowly. Give the most important antibiotic first, and consider administering the second antibiotic orally at the same time as the IV antibiotic if the second antibiotic has excellent bioavailability (e.g. cephalexin, ciprofloxacin, doxycycline etc).

Which antibiotics are best for sepsis without an apparent source? We also know from a study out of Chest in 2009 that inappropriate antibiotic choice decreases survival in sepsis [24]. So it is important to choose your antibiotics wisely based on local antibiograms. Work with your ID team to develop local guidelines and ideally build them into your EMR. Resist the urge to give piperacillin-tazobactam and vancomycin to all septic patients. This may result in higher resistance rates and missing important bacteria such as toxin producing organisms requiring Clindamycin or Legionella requiring Ampicillin. This highlights the importance of searching for the source of infection early. Chest, urine, abdomen are #1, #2 and #3 of sources of infection that are not immediately obvious on clinical exam. After that, don't forget line sepsis and meningitis because those require removal of the line and early LP.

What are the indications for steroids in septic shock?

There has been much conflicting evidence for the benefit of steroids in septic shock. The latest ADRENAL [25] and APROCH-SS [26] studies last year unfortunately did not clarify the issue.

ADRENAL was an international, double-blind RCT of 3800 vented ICU patients with septic shock randomized to hydrocortisone infusion 200mg/day or placebo for 7 days. Primary outcome was 90 day mortality which was about 28% in both groups. However secondary outcomes of shock reversal, ventilator free days, LOS in the ICU, and fewer blood transfusions required would improved in the hydrocortisone group.

APROCCHSS (Activated Protein C and Corticosteroids for Human Septic Shock) trial was a multicenter, double blind RCT comparing hydrocortisone + fludrocortisone therapy vs activated protein C vs combination of three drugs vs respective placebo. Primary outcome was 90 day mortality which was 43% in the hydrocortisone group vs 49% in the placebo group. These patients were sicker than the patients in the ADRENAL trial. In other words, beneficial effects may only be seen in those patients with the highest illness severity scores.
Bottom line: Although the evidence is mixed as to whether or not steroids are beneficial in septic shock, our expert recommends administering steroids for:

1. Vasopressor refractory shock (i.e. patient remains in shock despite norepinephrine 0.5mcg/kg/min)
2. Patients who are taking steroid medications at baseline
3. Patients with concomitant adrenal suppression

Another fairly recent retrospective small single center observational study looked at mortality rates among patient with septic shock who received thiamine, steroids and vitamin C (47 pts in each arm, 1.5 g vitamin C IV every 6 hours, hydrocortisone 50 mg IV every 6 hours, and thiamine 200 mg IV every 12 hours)[27]. Mortality was 8.5% in those treated with the cocktail of all 3 medications vs 40% in those not. Although this is a large outcome difference, larger RCTs are pending to guide practice.

Take home points on sepsis and septic shock

Calculate NEWS to detect subtle cases of occult septic shock.

Less saline, more Ringer's, even if acute heart failure, especially in renal failure and severe acidosis.

Norepinephrine whenever MAP <65 – earlier rather than later.

Early antibiotics (within 1hr of the *diagnosis* rather than 1 hour of arrival at ED), given over 5 minutes (except vancomycin over 30 minutes), chosen wisely according to local antibiograms.

Use a combination of MAP, GCS, urine output, initial lactate, capillary refill time, POCUS IVC to guide initial fluid resuscitation, individualized to each patient.

If the lactate is rising despite resuscitative efforts call your intensivist. Early to ICU is preferable, but remember that capillary refill time may be as good, or even better than lactate at guiding resuscitation.

Consider vasopressin and hydrocortisone if a MAP of 65 cannot be maintained with 35mcg/min norepinephrine and ongoing fluid resuscitation.

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