

Beyond the Sepsis Order Set

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Sepsis is the 7th leading cause of death in the US,¹ and a focus of early intervention and protocolized care by CMS and Emergency Departments

across the country. Our EMRs have pop-up “Sepsis Warnings,” and we must often explain to our EMR why we have not yet clicked on that wonderful sepsis order set. Are we so pressured to rapidly identify and treat sepsis that we might misdiagnose significant sepsis imitators? Couldn't we just click the boxes and call the hospitalist for admission?

Not All SIRS Is Sepsis

Systemic Inflammatory Response Syndrome (SIRS) often arises from noninfectious causes. Consider other immune targets such as autoimmune disorders, especially lupus, Graft Versus Host Disease, and vasculitides. Microangiopathic hemolytic anemia (TTP, HUS) often imitates sepsis, microvascular ischemia, organ dysfunction, and lactic acidemia. Let's not forget everyone's favorite clot in a blood vessel: pulmonary embolus. PE can cause fever, tachycardia, tachypnea, sepsis alert and even pulmonary infarct, with infiltrate on chest X-ray imitating pneumonia. PE may even arise from a DVT with associated cellulitis, giving us the old fake-out/not entirely relevant infectious source.

Adrenal crisis from Addison's Disease or from withdrawal of exogenous corticosteroids can certainly set the inflammatory cascade in motion, manifesting as SIRS and even shock. Tumor Lysis Syndrome (TLS) - especially in leukemia before or just after initial treatment - can produce an intense inflammatory response. Associated hyperkalemia, hyperphosphatemia, hypocalcemia and renal failure can be immediately life-threatening. Pancreatitis with SIRS can be septic (obstructive) or aseptic (alcohol, triglycerides, Bactrim, HCTZ, etc.). Even heavy metal fume disease (welders) and vaping can instigate severe febrile lung disease.

All of these disorders may produce EMR “Sepsis Warning,” and severe morbidity/mortality if we rush to the final diagnosis of sepsis while failing to treat the presenting disease process specifically.

Not All Fevers Are Even Inflammatory

Patients may have fever, tachycardia, etc., without primarily inflammatory causes. Heat exhaustion and heat stroke should not be overlooked in the right setting. Toxicologic etiology, e.g., salicylate poisoning, sympathomimetic ingestion (cocaine, methamphetamine), Neuroleptic Malignant Syndrome, Malignant Hyperthermia (seen in EDs from succinylcholine), and Serotonin Syndrome all require timely and specific therapy. Thyroid storm is another unique life-threatening process which may pop up that “Sepsis

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Warning” in our minds and our EMRs.

Even Sepsis is Not Always Straightforward

If you were chosen for the reality TV show “American Ninja Doctor” and had one antibiotic to bring, what would it be? I would choose Zosyn. It's amazing. It covers Gram everything above and below the diaphragm, anaerobes and aerobes including Pseudomonas. It qualifies as sepsis “monootherapy.” I'm pretty sure it restores hair loss and increases self-esteem. Some people may be allergic, but hey, its reality TV and we have to think ratings...

Turning off the TV and returning to the ED, we quickly realize no one drug or cocktail will optimally address every septic patient. Recent cultures results may reveal MRSA, ESBL, or multi-drug resistant bacteria. Travel history may predispose to fungal agents (desert Southwest, Ohio River Valley), rickettsia (camping, hiking), Q fever or Anthrax (farm settings), or even malaria. These sorts of historical pearls should trigger ID consults from the ED. We wouldn't wait until the patient gets upstairs to start antibiotics; why wait to start the *right* antibiotics?

We treat more immunosuppressed patients than ever on chemotherapy, living with HIV, and managing autoimmune diseases with immunomodulating drugs. Serious opportunistic infections include PCP, fungi, tuberculosis, and parasites, in addition to all the more typical bacteria.

Finally, we have recently witnessed the SARS coronavirus and the annual flu epidemic producing extreme illness, often in otherwise healthy people.

Find the Pus and Drain It Early

Antibiotics and the immune system require a blood supply to reach a source of infection. Infections with poor blood supply (necrotic tissue, abscesses, empyema) need to be identified and drained/excised. Obtain CT scans to search for abscesses, perforation, or gas in the urinary bladder, gall bladder or in the skin (necrotizing fasciitis), impacted pyelonephritis behind a ureteral stone, ascending cholangitis behind a biliary stone, or toxic megacolon. Consider decubitus X-rays to distinguish empyema from effusions. Consult your interventional radiologists and surgeons to drain pus early and remove necrotic tissue. Transfer such patients if necessary. Don't wait and see how antibiotics work. Decompress urinary and bowel obstructions with Foleys and nasogastric tubes in the ED.

New heart block in IVDA and other endocarditis patients suggests purulent involvement of the conduction system, anatomically adjacent to



the aortic valve. Notify your CT surgeon and cardiologist about this possibility. MRSA or Strep pneumonia can cause devastating purulent pneumonia even in a previously healthy young person. Such suspicion should prompt consultation for early bronchoscopy, and the addition of Vancomycin to your treatment regimen.

We Support You 100%: Aggressive IV Fluid Bolus

The 30 cc/kg crystalloid bolus for septic shock patients in the first three hours might be the most controversial part of this whole sepsis ordeal. We've gone from not wanting to drown old people to...drowning old people. Septic shock patients young and old who may be morbidly obese, have premorbid CHF, or ESRD on dialysis may not tolerate being connected to a fire hose. Then again, they may need it to survive.^{2,3} Opinion, recommendation and mandates are common, while we lack definitive data.² So, what do we do?

We can use noninvasive bedside testing for interim evaluations of fluid resuscitation,³ i.e., does passive leg raising still decrease tachycardia after the 10 cc/kg? After 20 cc/kg? Is the patient developing pulmonary edema? How is urine output? Capillary refill? For obese patients, we can dose our 30 cc/kg bolus on ideal body weight. Noninvasive ultrasound assessment of the internal jugular vein or IVC is another option. Consider ongoing invasive monitoring through a central line in these more complicated patients at special risk for over- and under-resuscitation. CVP 8 – 12 cm H₂O seems reasonable.⁴

Finally, what kind of crystalloid fluid should we use? Consider NSS is hypertonic and pH adjusted with HCl to as low as 4.5. Additionally, the Cl⁻ (154 mEq/L) contributes to hyperchloremic acidosis especially after infusion > 2 L. This acidosis promotes organ dysfunction and K⁺ entry into the extracellular space, contributing to hyperkalemia, especially in renal failure patients.

Alternatively, Lactated Ringers (LR) is isotonic (137 mEq Sodium/L), displays pH ~ 6.5, and avoids hyperchloremic acidosis is avoided by decreasing chloride administration (~109 mEq/L vs. 154 mEq/L). Depending on the metabolic

and redox state, the lactate (28 mEq/L) can enter the Krebs Cycle as pyruvate to produce ATP, or can be converted to our natural blood buffer, namely bicarbonate.

Contrary to urban legend, LR should not worsen sepsis nor cause elevated follow-up lactate. Remember that lactate is not the problem, but rather a marker of failed O₂ utilization by tissue due to local hypoxia and/or metabolic dysfunction. Lactate exhibits dynamic equilibrium with bicarbonate and the Krebs cycle, not simply accumulating in a bowl into which we pour our fluid.

Regarding concerns over potassium, LRs 4 mEq K⁺/L is physiologic. The 1/3 of administered crystalloid remaining intravascular would contribute 1.3 mEq to the average 5L blood volume = increase of 0.26 mEq/L. NSS-induced acidosis may promote increased K⁺, though it contains none itself, through acidosis-induced extracellular K⁺ migration from whole body stores. LR diminishes this phenomenon.

Other "physiologic" crystalloid solutions such as Plasmalyte, and its generic equivalent Normosol, use acetate and gluconate as anions, rather than lactate. The acetate seems to be helpful, in a way similar to lactate; we aren't sure what happens to gluconate,

especially in renal failure.

How about cost? NSS and LR cost about the same per liter, around \$1; Normosol ~\$6/L and Plasmalyte ~\$10/L. However, improved outcomes with more physiologic fluids should decrease overall cost of care, making NSS relatively expensive. LR is widely available, inexpensive and more physiologic than NSS.

A plethora of good literature now supports that aggressive resuscitation with LR in septic patients actually lowers lactate levels and improves clinical outcomes vs. NSS.^{3,5,6}

Pressing the Issue

Hypotension is so detrimental; consider administering inotropes/pressors simultaneously with the initial fluid bolus,^{7,8} i.e., hitting hemodynamic goals ASAP. You can always back down the inotrope/pressor if fluid response is robust. Choice of optimal pressor remains murky, although Surviving Sepsis Campaign Guidelines recommend Norepinephrine as first line.⁹ Recently criticized for inducing atrial fibrillation,¹⁰ Dopamine may well serve the patient with CAD and/or CHF who needs inotropy and may



not tolerate coronary vasoconstriction. If hypotension persists,

consider premorbid confounding factors, e.g., beta-blocker use, alpha-2 agonists, sympathetic neuropathy (age, diabetes), and adrenal insufficiency as factors preventing adequate resuscitation. Consider administering hydrocortisone, to increase sympathetic receptor expression and improve efficacy of the most common pressors and inotropes. Send off a baseline cortisol to guide later therapy upstairs about relative hypoadrenalism. If still ineffective, consider adding milrinone (inotrope) and/or vasopressin (pressor), independent of the sympathetic system.¹¹

You're So Sweet

Glycemic control has demonstrated improvement in septic patients, but is often overlooked. We shouldn't expect improved survivability if our septic patient with a glucose of 385 develops DKA before admission. Aim for glucose \leq 180 mg/dL, while avoiding hypoglycemia.⁹ Insulin puts all that glucose inside the cells where it can produce ATP so our pressors, inotropes and cellular machinery can work.

Feed Me, Seymour

In addition to fluid resuscitation, consider *metabolic* resuscitation. Cachectic, malnourished, alcoholic, and gastric bypass patients may require nutrients essential to energy production like Thiamine and other B vitamins. Numerous patients may have unexpected critical nutritional deficiencies: Hydralazine and Isoniazid promote Pyridoxine (B6) deficiency; Phenytoin causes Folate (B9) deficiency.

Single-dose Thiamine and MVI in the ED might be helpful in such patients. Avoid the vasodilatory Magnesium of the "Banana Bag"; instead order Thiamine and multivitamin IV/IM. Fun fact: Vitamin C, found in MVI, is actually required for humans' response to sepsis, including production of catecholamines, vasopressin, cortisol and interferon.^{12,13}

Now Breathe

That fluid overload and pulmonary edema you see in your declining patient on repeat CXR may actually represent ARDS. After all, septic shock means organ dysfunction, and ARDS

is what happens to failing lungs in this setting. For any septic shock patient requiring intubation, strongly consider ARDSNet settings for the ventilator.^{9,14} For alert septic shock patients with noticeable work of breathing but without respiratory failure, consider decreasing their metabolic expenditure by starting BIPAP.¹⁴

Sepsis Can Get Complicated

Be vigilant for *sudden* changes in status. This may indicate any number of complications, including respiratory failure in the nonintubated, or hypophosphatemia causing respiratory muscle weakness in DKA patients (after insulin administration and delayed admission to ICU). Other respiratory issues include right mainstem migration of the endotracheal tube with left lung atelectasis, mucus plug in lung or ET tube, air trapping, tension pneumothorax, and asynchrony with the ventilator. Cardiac issues include supervening arrhythmia, myocardial infarction, and AV node involvement in endocarditis. Finally, hollow viscus perforation or phlegmon erosion into a vascular structure can cause sudden collapse. With sudden changes, don't just order another liter of fluid or increase the pressor; go to the bedside and reassess the whole patient.

So Now What Do I Do on My Next Shift?

Aggressive LR resuscitation, well-considered broad-spectrum antibiotics and "sepsis workup" seem prudent and necessary in patients with suspected sepsis. Further therapy should be guided by the presence of hypotension and/or lactate; consider early pressors/inotropes. Savvy clinicians will utilize frequent reassessment, EMR evaluation, and historical risk factors to confirm sepsis, atypical sepsis, or sepsis masquerader.

We should re-open our decision-making if a septic source cannot be found or if the patient is not responding as expected. Is there a source of pus to drain? Is there possibly an unusual infectious agent? Do we need to obtain cerebrospinal fluid? Could we address

significant comorbidities - malnutrition, medication effect, hyperglycemia or organ failure? Has a critical complication developed that requires immediate action? Have we considered other processes like heat exposure, toxic ingestion or PE? Could vascular, endocrine or autoimmune disease be masquerading as sepsis, requiring a different tailored clinical response? These are the clinical challenges we must face beyond the Sepsis Order Set. ●

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We've gone from NOT WANTING TO DROWN
OLD people to, well, drowning old people.

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Follow the QR code for a Critical Care Hacks solution to make rewarming a little easier

Passively rewarm

- Remove cold/wet clothing
- Give warm blankets
- Rewarm at 1.5 degrees Celsius/hour

Mild
(32-35C)
Shivering

Moderate
(28-32C)
AMS
No shivering

Actively rewarm externally, minimally invasive methods

- Warm IVF
- Bare hugger
- Be cautious with movement, myocardium prone to arrhythmias, *if central access needed, only femoral lines

Accidental Hypothermia



Invasive measures + Modified ACLS

- Airway: standard ACLS (warm air if possible), try to avoid depolarizing paralytics
- Breathing: no changes
- Circulation: consider ultrasound assistance
 - Vtach/Vfib shock x 1, at most x 3 then no shocks until > 30 degrees Celsius
 - European guidelines: Epi only if T > 30 with double the interval i.e. 6-10 min between doses (US no clear guideline)
- Active rewarming (IV fluids, bladder irrigation), bilateral chest tubes (high anterior/low posterior), peritoneal lavage, ECMO
- Time of death when warm and dead, i.e. >30 degrees (vague guideline)

Pulseless

Severe
<28C
Unconscious

Invasive measures

- IVF
- Bladder lavage
- Chest tubes, right sided only to avoid myocardium stimulation
- Peritoneal lavage
- ECMO

*Likely futile efforts if K >12, T <14C

*Consider broad etiology, hypoglycemia, sepsis, drugs/EtOH, other toxic/metabolic