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Sepsis Management in Adults: Pharmacotherapy Focus

The Surviving Sepsis Campaign, a joint effort of the Society of Critical Care Medicine and the European Society of Intensive Care Medicine, has been developing guidelines and other resources to reduce mortality in patients with sepsis and septic shock since 2002.[1] The most recent sepsis guidelines were developed in 2016. They are available at http://journals.lww.com/ccmjournal/Fulltext/2017/03000/Surviving_Sepsis_Campaign___International.15.aspx. These guidelines focus on early resuscitation and early antibiotics with frequent re-assessment. Hospitals often incorporate the guideline information into their protocols and pathways for sepsis management. Treatment of sepsis is complex. The Surviving Sepsis Campaign separates evidence-based interventions into "bundles" so that care can be streamlined and interventions can be implemented together in a way that optimizes their effect on clinical outcomes.[2] Participating hospitals can organize their protocols however they want, but the protocol should meet the standard set by the bundle.[2] Details about these bundles can be found at http://www.survivingsepsis.org/Bundles/Pages/default.aspx. Together the bundles provide an early resuscitation treatment strategy utilizing fluids and pressors to target certain goals within the first six hours of presentation.[8] The Joint Commission has severe sepsis/septic shock quality measures. Their Specifications Manual is available at https://www.jointcommission.org/specifications_manual_for_national_hospital_inpatient_quality_measures.aspx. Note that Appendix C provides a list of specific antibiotics and vasopressors that would satisfy the measures. Also note that patients receiving intravenous antibiotics for more than 24 hours prior to presentation of severe sepsis are excluded from measurement.[29] The chart below brings select sepsis pharmacotherapy information from these and other resources together. Although you may see "severe sepsis" mentioned below and in other resources, this term is being phased out. See our chart, *Sepsis and Septic Shock: New Definitions for Adults*, for explanations of the new definitions and their clinical implications.

Abbreviations: ACS = acute coronary syndrome; APACHE = Acute Physiology and Chronic Health Evaluation; CrCl = creatinine clearance; CVP = central venous pressure; GI = gastrointestinal; MAP = mean arterial pressure; EGDT = early goal-directed therapy; UFH = unfractionated heparin

Summary from the 2016 Surviving Sepsis Guideline for Adults and "Bundles"	Additional Information
EARLY RESUSCITATION	
• Within the first three hrs, all patients (even those with renal or heart failure) should receive at least 30 mL/kg of a crystalloid (e.g., normal saline) to correct hypoperfusion (e.g., hypotension or lactate ≥4 mmol/L [36 mg/dL]).[2,4,30] This fixed bolus, which is based on usual practice and volumes used in the ProCESS and ARISE studies, allows treatment to begin emergently, without having to await results of patient assessments.[4]	• EGDT is a treatment strategy utilizing fluids and pressors to target certain physiologic goals.[8] • The ARISE study in Australia and New Zealand randomized adults with sepsis on presentation to the emergency department to EGDT or usual care. All patients received antibiotics before randomization. Patients in the EGDT group were more likely to get vasopressors, blood, and dobutamine. They also received a larger volume of fluids. However, mortality at 90 days was not lower in the EGDT group. The patients in this study were relatively healthy

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Summary from the 2016 Surviving Sepsis Guideline for Adults and "Bundles"	Additional Information
EARLY RESUSCITATION, continued	

• Most patients will need more fluid.[4] Once fluid-resuscitated, give additional fluids based on frequent assessment of hemodynamics (e.g., heart rate, blood pressure, respiratory rate, temperature, urine output, arterial oxygen saturation, etc).[4]
• If lactate is elevated, recheck within the first six hrs.[2]
• If hypotension (MAP <65 mmHg) persists after initial fluid resuscitation, or initial lactate was ≥4 mmol/L, volume status and tissue perfusion should be assessed/documented within the first six hrs with either:[19]
  • Focused exam (vitals, cardiopulmonary and skin findings, pulse, capillary refill)[19]
  OR
  • Measurement of two of the following: CVP (see below), ScvO2 (goal ≥70%), bedside cardiovascular ultrasound, dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge.[8,19]
	and had early sepsis. The findings may reflect the improvement in sepsis mortality that has been occurring over the past 20 yrs. Also elements of EGDT may have "contaminated" the usual care group because more patients are now getting fluids and early antibiotics as part of usual care.[6]
	• In the multicenter ProCESS trial, adults presenting to the emergency department with suspected sepsis were randomized to EGDT; protocol-based therapy that did not require central venous catheter placement, inotropes, or blood transfusion; or usual care. In the ProCESS study, the fluid challenge was simplified to 1000 mL or more over 30 minutes for adults. There was no significant difference in 90-day or 1-year mortality, or need for cardiovascular, renal, or respiratory support.[10] These findings suggest that prompt identification and treatment of sepsis should be the focus of efforts to reduce mortality.[11]
	• The ProMISe trial in the UK randomized 1,260 patients with septic shock to EGDT or usual care. Patients were eligible if, within six hrs of emergency department presentation, they had presumed infection, two or more criteria for systemic inflammatory response syndrome, and either refractory hypotension or elevated lactate. Patients were randomized within two hrs of meeting inclusion criteria. Treatment intensity was greater in the EGDT group (i.e., more intravenous fluids, vasopressors, red cell transfusion, longer ICU stay). Ninety-day mortality was about 29% in both groups, but cost was higher in the EGDT group. Like ARISE and ProCESS, ProMISe suggests that EGDT does not provide a benefit over modern sepsis management that includes early diagnosis, antibiotics, and fluid resuscitation.[28]
	• Although these large trials did not show a mortality benefit for EGDT, its use can still be considered because study results could have been due to inclusion of less severely ill patients. EGDT is safe and provides clinicians with a method for quickly treating sepsis.[4] Data from patients entered into the Surviving Sepsis Campaign database show that in patients who are administered fluids and vasopressors in compliance with the guideline bundles, the odds of in-hospital mortality may be reduced to 0.63 (p<0.001) compared to patients in which this bundle component is not achieved.[3]

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Summary from the 2016 Surviving Sepsis Guideline for Adults and "Bundles"	Additional Information
EARLY RESUSCITATION, continued	

	• Joint Commission:[29] measure lactate within three hrs of presentation of severe sepsis. Documentation of crystalloid fluid resuscitation of 30 mL/kg is required for all patients in septic shock. Repeat lactate within six hrs of presentation if initially elevated.[29] If hypotension persists after initial fluid administration or initial lactate is ≥4 mmol/L, within six hrs of presentation of septic shock, assess volume status and tissue perfusion with:
	  • Focused exam: vitals, cardiopulmonary exam, capillary refill, peripheral pulse, AND skin exam
	OR
	  • Two of the following: CVP, ScvO2, cardiovascular ultrasound, passive leg raise/fluid challenge

MONITORING DURING EARLY RESUSCITATION	
• Dynamic measures (e.g., passive leg raises, fluid challenge against stroke volume measurement) are preferred over CVP and other static measures, if available.[4] • CVP measurement is among the options for assessment of volume status and tissue perfusion (see above).[2] • Do not use CVP alone (or other static measures of right or left heart pressure/volume) to guide fluid administration because CVP has limited utility to predict a response to a fluid challenge within the range of 8 to 12 mmHg ("normal").[4]	• In the ProCESS trial (see above), invasive monitoring was not associated with better outcomes (e.g., mortality) than clinical assessment of tissue perfusion.[10,11] • Consider serial serum lactate measurement if CVP monitoring is not done [Evidence level B; lower quality RCT].[12] • Joint Commission: CVP measurement is among the options for assessment of volume status and tissue perfusion (see above).[29]
ALBUMIN	
• Crystalloids are the initial fluid of choice, but albumin is suggested in addition to crystalloids if the patient requires significant amounts of crystalloid.[4]	• Although albumin helps increase MAP, it does not seem to improve survival in adults [Evidence level B; lower quality RCT].[5] • Avoid hetastarch.

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Summary from the 2016 Surviving Sepsis Guideline for Adults and "Bundles"	Additional Information
BLOOD	
• Transfuse when hemoglobin <7 g/dL (assuming no extenuating circumstances [e.g., ACS, hemorrhage, etc]).[4] • Recommendation based on Transfusion Requirements in Septic Shock (TRISS) and ProCESS trials.[4]	• A multicenter randomized study supports a transfusion threshold of 7 g/dL in adults, even those with GI bleeding.[15] Patients who developed ischemia or life-threatening bleeding, or who needed extracorporeal membrane oxygenation, could get a transfusion per the attending's discretion.[15] It is possible that sepsis patients with ACS may benefit from transfusion at 9 to 10 g/dL.[13]
VASOPRESSORS	

• Vasopressors are administered if hypotension does not respond to initial fluid resuscitation (see above).[2] In the case of severe hypotension, do not wait for completion of fluid bolus to start vasopressor.[8]
• The initial MAP target is 65 mmHg.[4]
• Vasopressors are part of the 6-hour bundle.[2]
• Norepinephrine is the initial vasopressor of choice. It increases tissue perfusion by increasing MAP.
  • Compared to dopamine, norepinephrine has a better effect on mortality, has little effect on heart rate or stroke volume, is less arrhythmogenic, and may be more effective for treating hypotension.[4]
  • Norepinephrine may have fewer adverse effects than epinephrine.[4]
• Epinephrine can be added if norepinephrine is inadequate at achieving MAP target.[4]
  • No evidence that it worsens outcomes.[4]
  • May increase lactate production.[4]
• Vasopressin can be added to norepinephrine to increase MAP, or for a norepinephrine-sparing effect.[4]
  • Sepsis patients have a relative vasopressin deficiency.[4]
  • Reserve high doses (e.g., >0.03 units/min) for refractory cases due to risk of ischemia.[4]
	• Data from patients entered into the Surviving Sepsis Campaign database show that in patients who are administered vasopressors and fluids in compliance with the guideline bundles, the odds of in-hospital mortality may be reduced to 0.63 ($p<0.001$) compared to patients in which this bundle component is not achieved.[3]
	• A MAP target of 80 to 85 mmHg is not more beneficial than a MAP target of 65 to 70 mmHg in most adults.[14,16] In patients with pre-existing hypertension, the higher target is associated with less need for renal-replacement therapy.[16] A systolic goal of 90 mmHg has also been used in some older clinical trials.[17]
	• Joint Commission: Give vasopressors only if hypotension persists after fluid administration, within six hrs of presentation of septic shock.[29]
	• *Giapreza* (angiotensin II) causes vasoconstriction and aldosterone release, and is indicated to increase blood pressure in adults with septic or other distributive shock.[31] Based on the study population, consider it for patients who remain hypotensive despite fluid and vasopressors (e.g., norepinephrine, vasopressin, epinephrine) at a median "norepinephrine equivalent" dose of 0.33 mcg/kg/min.[32] Angiotensin II will effectively increase MAP in about 70% of patients (i.e., increase from baseline of 10 mmHg, or an increase to 75 mmHg).[32] It may also reduce 28-day mortality in sicker patients (i.e., baseline APACHE II scores >30).[33] Patients with acute respiratory distress syndrome per chest x-ray may especially benefit.[32] It also might have an advantage in patients taking angiotensin-converting enzyme inhibitors, but seems not to work as well in patients taking angiotensin receptor blockers.[31,32] Angiotensin II poses a risk of venous thromboembolism (VTE), so VTE prophylaxis is recommeded.[31] **Note**: units for *Giapreza* dosing are NANOgrams/kg/min.[31]

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Summary from the 2016 Surviving Sepsis Guideline for Adults and "Bundles"	Additional Information
VASOPRESSORS, continued	

• Dopamine or dobutamine can be used selectively.[4]
  • Dobutamine is suggested for persistent hypoperfusion despite appropriate fluids and vasopressors.[4]
  • Dopamine could be used as a norepinephrine alternative in select patients (e.g., poor systolic function with bradycardia and low arrhythmia risk).[4]
  • Do not use dopamine for "renal protection."[4]
  • Dopamine may have immunosuppressive effects.[4]
• Titrate vasopressors to improve perfusion. Reduce dose or discontinue if hypotension worsens or arrhythmias develop.	

ANTIBIOTICS	

• Blood cultures (two sets) should be drawn, then broad-spectrum antibiotics administered, within one hr of suspecting sepsis or septic shock.[4] This is part of the initial 3-hr bundle.[2]
• Choose antibiotics that cover the likely pathogens (bacteria, fungi, and/or viruses) and that distribute adequately into the probable source(s) of infection. Consider resistance patterns.[4]
• When IV access is limited, beta-lactams that can be administered via rapid IV push are advantageous.[4] See https://www.aliem.com/015/trick-iv-push-antibiotics/.
• Avoid intramuscular antibiotics unless vascular access cannot be established in a timely fashion.[4]
• Optimize dosing based on pharmacokinetics and pharmacodynamics specific to this population.[4]
  • Use the maximum dose, even in renal patients (e.g., vancomycin loading dose 25 to 30 mg/kg actual weight, levofloxacin 750 mg, piperacillin/tazobactam 4.5 g).[4]
  • Target a vancomycin trough of 15 to 20 mg/L.[4]
	• In the ProCESS trial (see above), 97% of patients received antibiotics by 6 hrs after randomization, and 76% had received antibiotics by the time they were randomized, which occurred a mean of 3 hrs after presentation.[11]
	• There may be over a 10% absolute reduction in mortality when antibiotics are given within one hr of triage.[7] Although a recent meta-analysis suggests that exact timing may not affect mortality, antibiotic choice was not assessed.[25]
	• With standard doses, up to 84% of patients with severe sepsis/shock may not achieve adequate antibiotic levels.[22] Although there is no proof that higher initial doses improve outcomes, consider these dosing principles:
	  • These patients may have positive fluid balance and increased volume of distribution due to fluids, renal failure, and/or capillary leak.[20,24] Use the maximum dose, loading dose, or consider a 25% to 50% higher loading dose.[20,24] Loading doses may be especially important for hydrophilic antibiotics (e.g., aminoglycosides, vancomycin, beta-lactams, daptomycin, linezolid, colistin).[4,21,23,24]
	  • First dose should not be reduced, regardless of the type or severity of renal dysfunction (e.g., chronic, acute, dialysis).[24]
	  • In acute kidney injury, consider starting with a normal maintenance dose due to compensatory nonrenal clearance and rapidly changing kidney function.[20]

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Summary from the 2016 Surviving Sepsis Guideline for Adults and "Bundles"	Additional Information
ANTIBIOTICS, continued	
• Give beta-lactams as rapid infusions at frequent intervals, or as an extended/continuous infusion after giving the first dose over 30 minutes.[4] • Multidrug therapy is used to provide broad empiric coverage in septic patients and may include combination therapy (i.e., double coverage) to hasten bacterial clearance in septic shock.[4] Evidence supporting initial double coverage is stronger for septic shock vs sepsis without shock, but benefit cannot be ruled out for certain infections (e.g., multidrug resistant gram-negatives, severe pneumococcal or neutropenic infection).[4] • Combination therapy should be de-escalated once improvement is noted, whether used for culture-positive infection or empiric coverage. • Empiric coverage should be narrowed once culture and sensitivity results are obtained, and/or improvement is seen.[4] • Treatment for seven to ten days is suggested, although a longer duration may be appropriate in certain situations (e.g., abscess that cannot be drained, fungal infection, slow response). A shorter course may be appropriate for rapidly controlled urinary or intra-abdominal infections.[4] • Consider using plasma procalcitonin levels to inform decisions about empiric antimicrobial discontinuation if evidence suggests the patient does not have an infection.[4]	• Patients with multisystem dysfunction/failure may have renal hyperfiltration (CrCl >120 mL/min/1.73 m^2) and/or volume overload, so conservative dosing may result in inadequate levels.[20,24] • Give a loading dose when starting continuous-infusion antibiotics to quickly achieve a level above the MIC.[21,24] • Ensure dosing is appropriate for the type of renal replacement (e.g., dialysis), if applicable. In the absence of specific dosing information for the given machine and filter, for continuous renal replacement:[20] • consider dosing as for CrCl 25 to 50 mL/min. OR • if the drug fraction expected to be removed is known (Fr_{ec}), dose = anuric dose/(1-Fr_{ec}); interval = anuric dosing interval x (1-Fr_{ec}) OR dose = normal dose x (nonrenal clearance + [effluent rate x sieving coefficient])/normal clearance • Consider continuous infusion or extended-interval dosing for beta-lactams (e.g., piperacillin/tazobactam over 240 minutes every eight hrs), especially for sicker patients (e.g., APACHE score ≥17).[26,27] • Assess the regimen at least daily due to rapidly changing conditions.[24] Modify dosing based on renal function, drug levels, evidence of toxicity (e.g., beta-lactam neurotoxicity), and volume status.[20,24] • Joint Commission: blood cultures should be drawn, then antibiotics given, within three hrs of presentation of severe sepsis.[29]

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Summary from the 2016 Surviving Sepsis Guideline for Adults and "Bundles"	Additional Information
HYDROCORTISONE	
• Use as an adjunct to vasopressors and fluids when they are inadequate in septic shock.[4] • Recommended daily adult dose is 200 mg.[4] • Continuous infusion preferred over boluses to minimize hyperglycemia.[4] • Lab tests such as cortisol and ACTH are not useful to help determine which septic patients will respond to steroids.[4]	• A meta-analysis of 33 studies concluded that ≥3 days of a low-dose corticosteroid (i.e., hydrocortisone 400 mg or less per day) reduces 28-day mortality and length of ICU stay.[9] • Mortality benefit might exist only for patients with APACHE II score ≥30.[18]
VENOUS THROMBOEMBOLISM PROPHYLAXIS	
• LMWH is preferred over UFH.[4] • Dalteparin (*Fragmin*) or UFH is preferred if CrCl <30 mL/min.[4] • Combine with mechanical prophylaxis if possible.[4] • Use mechanical prophylaxis if pharmacologic prophylaxis is contraindicated.[4]	
STRESS ULCER PROPHYLAXIS	
• Proton pump inhibitors or H2-blockers when stress ulcer prophylaxis is indicated (i.e., patients with risk factors for GI bleed).[4]	

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Levels of Evidence

In accordance with the trend towards Evidence-Based Medicine, we are citing the **LEVEL OF EVIDENCE** for the statements we publish.

Level	Definition
A	High-quality randomized controlled trial (RCT) High-quality meta-analysis (quantitative systematic review)
B	Nonrandomized clinical trial Nonquantitative systematic review Lower quality RCT Clinical cohort study Case-control study Historical control Epidemiologic study
C	Consensus Expert opinion
D	Anecdotal evidence In vitro or animal study

Adapted from Siwek J, et al. How to write an evidence-based clinical review article. *Am Fam Physician* 2002;65:251-8.

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