Adult Sepsis Empiric Antibiotic Guidelines

Preface: These guidelines outline empiric antibiotic recommendations from the Partners Sepsis Task Force and the Partners MDRO / Antibiotic Stewardship Collaborative for adult patients with suspected sepsis. Antibiotic choices should also take into account patient's histories, risk factors, and prior microbiology; severity of illness (e.g., broader antibiotics are generally warranted in critically ill patients, such as those with septic shock or respiratory failure); and each hospital's local antibiogram and pharmacy formularies.

Presumed	Community-Acquired /	Healthcare-Associated /
Source	Low Risk for Antibiotic Resistance ^a	High Risk for Antibiotic Resistance ^b
Unknown	 Vancomycin + Ceftriaxone Vancomycin + (Ceftazidime, Cefepime, or Piperacillin/Tazobactam) (if critically ill) Add Azithromycin or Levofloxacin if atypical pneumonia is possible Add Metronidazole if intraabdominal sepsis is possible and no other anaerobic coverage 	 Vancomycin + (Cefepime or Ceftazidime) ± Metronidazole Vancomycin + Piperacillin/Tazobactam Vancomycin + (Imipenem or Meropenem)* Add Azithromycin or Levofloxacin if atypical pneumonia is possible
Pulmonary	 Ceftriaxone + Azithromycin Levofloxacin is an alternative option, but should not be used as monotherapy if critically ill Add Vancomycin if critically ill, known MRSA colonization, or necrotizing pneumonia/empyema. 	 Cefepime Piperacillin/Tazobactam Imipenem or Meropenem* Add Vancomycin if critically ill, known MRSA colonization, or necrotizing pneumonia/empyema Add Aminoglycoside or Levofloxacin if critically ill and/or very high-risk for MDR gramnegatives (e.g. structural lung disease) Add Azithromycin or Levofloxacin if suspicion for Legionella
Gastrointestinal/	Ceftriaxone + Metronidazole	Piperacillin/Tazobactam
Intraabdominal	Piperacillin/Tazobactam (if critically ill)	Cefepime + Metronidazole
	Consider adding Vancomycin if critically ill	 Imipenem or Meropenem* Consider adding Vancomycin if critically ill
Skin/Soft Tissue	 Vancomycin + Ceftriaxone Add Metronidazole if infection involves the groin area. If necrotizing infection suspected (e.g. septic shock or crepitus), consult surgery and infectious diseases, and use Vancomycin + Piperacillin/Tazobactam + Clindamycin 	 Vancomycin + (Cefepime or Ceftazidime) Add Metronidazole if infection involves the groin area, or use Piperacillin/Tazobactam instead of Cefepime/Ceftazidime. If necrotizing infection suspected (e.g. septic shock or crepitus), consult surgery and infectious diseases, and use Vancomycin + (Piperacillin/Tazobactam or Imipenem or Meropenem) + Clindamycin
Urinary	 Ceftriaxone Cefepime or Ceftazidime (if critically ill) Fluoroquinolones alone should NOT be used as first-line treatment 	 Cefepime (or Ceftazidime) Imipenem or Meropenem* Add Vancomycin if severely ill, history of MRSA colonization in the urine, recent instrumentation, or indwelling foley

Bolded antibiotic choices below indicate preferred regimens in most scenarios

^a **Community-Acquired / Low Risk for Antibiotic Resistance -** consider low-risk if none of the following are present: recent antibiotic exposure, recent hospitalization, residence in a chronic care facility, hemodialysis, or immunocompromised.

^b Healthcare Associated / High Risk for Antibiotic Resistance - consider at risk if: recent antibiotic exposure, recent hospitalization, currently hospitalized > 5 days, residence in a chronic care facility, hemodialysis, or immunocompromised.

*Use Imipenem or Meropenem if suspected or known prior colonization/infection with pathogens resistant to Cefepime, Ceftazidime, or Piperacillin/Tazobactam

Beta-lactam Allergies: For most mild penicillin allergies (e.g. minor rash without hives), a 3rd, 4th, or 5th generation cephalosporin or carbapenem can be safely used; for mild cephalosporin allergies, a carbapenem can be used. If the patient has a severe beta-lactam allergy, alternative options for Gram-negative coverage in sepsis include: Aztreonam, Ciprofloxacin or Levofloxacin, and Aminoglycosides. ID should be consulted in cases of severe allergies and limited antibiotic choices. For additional information, refer to the Partners penicillin / cephalosporin hypersensitivity pathways (http://id.partners.org/allergy).

Standard Antibiotic Dosing Regimens for Sepsis (consult pharmacy and/or local dosing guidelines for help with vancomycin dosing and antibiotic dosage adjustments in renal failure):

- Vancomycin load (20 mg/kg x 1, max 2 g) + maintenance (typically 15 mg/kg q8-12hours)
- Ceftriaxone 2 g IV every 24 hours, Ceftazidime 2 g IV every 8 hours, Cefepime 2 g IV every 8 hours
- Piperacillin/Tazobactam 4.5 g IV every 6 hours (3.375 g every 6 hours can be used for non-pneumonia or non-severe cases where Pseudomonas is not suspected)
- Imipenem 500 mg IV every 6 hours, Meropenem 1 g IV every 8 hours
- Levofloxacin 750 mg IV every 24 hours .
- Azithromycin 500 mg IV every 24 hours
- Metronidazole 500 mg IV every 8 hours
- Clindamycin 900 mg IV every 8 hours

Subsequent Antibiotic Management: Patients with suspected sepsis who are started on antibiotics will need to have them modified according to their clinical course and as diagnostic and microbiologic tests return. Generally, the 48-72 hour mark is an appropriate time for reassessment. Below are simple guidelines for modifying antibiotics.



SEPSIS ANTIBIOTIC REASSESSMENT PATHWAY

*Procalcitonin may also be considered to help guide antibiotic duration and early discontinuation in nonimmunocompromised ICU patients with suspected or proven sepsis (if available as rapid in-house testing at your hospital). Please refer to separate BWH Procalcitonin guidelines on the Partners Handbook for more information and guidance.

Quick SOFA - the Sepsis-3 recommendations also propose that amongst patients with suspected infection, two or more "quick SOFA" criteria identify patients likely to have sepsis and who are at high risk for adverse outcomes. Because these criteria are measurable at the bedside and available prior to return of diagnostics, the Sepsis-3 recommendations suggest calculating qSOFA in all patients with suspected infection.

- Systolic Blood Pressure ≤100 mmHg
- Respiratory Rate ≥22 bpm
- Altered Mental Status (GCS <15)

If patients have ≥ 2 qSOFA points, it is recommended that patients be urgently evaluated carefully for sepsis, including a full set of laboratory tests to evaluate for organ dysfunction, and prompt consideration of source control.

II. SEP-1 CMS Definition

The definitions used by the Centers for Medicare and Medicaid for the SEP-1 measure have adapted the prior definitions of "severe sepsis" and septic shock, which have been in place since the first consensus definitions of sepsis were released in 1992.¹⁴

Severe Sepsis – all 3 of the following, occurring within a 6 hour period:

- 1. Suspected or documented infection
- 2. ≥2 Systemic inflammatory response syndrome (SIRS) criteria:
 - Temperature >38.3 or <36.0
 - Heart rate >90
 - Respiratory rate >20
 - White blood cell count >12k, <4k, or >10% bands
- 3. Acute organ dysfunction attributable to infection (any one of the following):
 - SBP <90 mmHg or MAP <65 mmHg or SBP drop from baseline by >40 mmHg
 - Lactate >2.0 mmol/L
 - Respiratory failure = need for noninvasive or invasive ventilation
 - Creatinine >2.0 mg/dL or Urine output <0.5 cc/kg/hr x 2 hours
 - Bilirubin >2.0 mg/dL
 - Platelets <100k
 - INR >1.5 or PTT >60

Septic Shock - Severe sepsis and one of the following:

- 1. Persistent hypotension despite fluid resuscitation (30 cc/kg of crystalloid fluids), OR
- 2. Lactate ≥4.0 mmol/L

III. Partners Guidelines on Defining Sepsis and Identifying Patients At-Risk for Sepsis

The Partners Sepsis Collaborative recognizes the difficulty in precisely defining sepsis and septic shock. Currently, the medical community is in a state of transition as the new Sepsis-3 definitions gain acceptance and familiarity. However, CMS has stated that they have no plans to update their criteria in the near future. Furthermore, others have raised concerns about the lack of prospective validation of the new criteria (including quick SOFA), and the possibility of harm that could result from shifting focus from early sepsis/SIRS to qSOFA and organ dysfunction.^{15,16} While this is clearly a topic that will continue to evolve, our current approach is summarized below:

1. We agree with the Sepsis-3 approach to nomenclature, with "sepsis" referring to organ dysfunction from infection (rather than "severe sepsis"). However, the utility of the SOFA score for guiding clinical care is unclear. The SOFA score, which was designed as a research tool, is not easy to memorize, contains variables that are not routinely measured in many non-ICU patients (such as Pa02/Fi02 ratio and Glasgow Coma Scale), and relies on clinical signs that are rapidly becoming outdated (such as the vasopressor/inotrope scoring system). On the other hand, using well-defined single thresholds for organ dysfunction, such as some of the criteria used by CMS, is appealing. However, neither the CMS criteria nor SOFA help with the inherent subjectivity in deciding whether or not organ dysfunction is due to infection or another cause.

Thus, we recommend classifying patients as having "sepsis" if there is infection and either the CMS organ dysfunction thresholds are met OR there is a rise in SOFA score by ≥ 2 . However, using "severe sepsis" is still acceptable, given that this is the terminology used by CMS. Either way, clinicians should be as clear as possible when describing the clinical state of their patient (e.g., "sepsis with hypotension or acute kidney injury").

- 2. We agree with that the systemic inflammatory response syndrome criteria should not be used to define sepsis; however, **they can be still useful in identifying patients who are potentially infected**.
- 3. We agree that qSOFA is an important marker of illness that can be used to identify patients who need closer monitoring and potentially more aggressive care. However, we believe that qSOFA alone is insufficient as a screening tool, as it has low sensitivity and identifies patients who likely already have organ dysfunction. An ideal screening tool would have high sensitivity and identify patients early in the sepsis pathway.

Other physiologic variables, such as elevated shock index (heart rate / systolic blood pressure ratio >1), have been shown to predict imminent septic shock and poor outcomes in patients presenting with infection.¹⁷ Furthermore, patient risk factors, such as age, immunocompromised status, and other comorbid conditions also influence the risk of sepsis and adverse outcomes. The screening criteria used in our electronic best-practice alerts takes into account these factors, in addition to qSOFA.

- 4. We believe that defining septic shock as the need for vasopressors and a persistently elevated lactate as per Sepsis-3 is less useful than the CMS criteria for septic shock (persistent hypotension despite fluids, or lactate ≥4.0 mmol/L), since the latter has more clear implications for early management i.e., rapid fluid administration (for lactate ≥4.0) or other signs of hypoperfusion, monitoring serial lactates, and initiating vasopressors in a timely fashion for fluid-refractory hypotension.
- 5. For coding / billing purposes, we agree with the Sepsis-3 recommendations that patients now called "sepsis" (infection with organ dysfunction) should be coded as "severe sepsis."

APPENDIX B: The CMS Sepsis Measure (SEP-1)

In October 2015, the Centers for Medicaid and Medicare released a new performance measure, called the SEP-1 measure. This measure is based on recommendations from the Surviving Sepsis Campaign.¹ Currently, hospitals are only required to report this data, but a transition to pay-for-performance is under consideration. The SEP-1 measure requires a series of actions for patients with severe sepsis or septic shock. It is an all-or-nothing measure, meaning that failure of any one part of the bundle leads to noncompliance.

3 HOUR BUNDLE

For all severe sepsis patients:

- 1. Measure lactate level
- 2. Blood cultures prior to antibiotics
- 3. Broad spectrum antibiotics

For severe sepsis with hypotension

4. Administer 30 cc/kg (actual body weight) of crystalloid fluids (normal saline or lactated ringers) 6 HOUR BUNDLE

For severe sepsis with initial lactate >2.0 mmol/L:

5. Remeasure lactate

For septic shock with persistent hypotension after 30 cc/kg fluid challenge:

6. Vasopressors to target MAP ≥ 65 mmHg

For septic shock with persistent hypotension after fluids, or initial lactate \geq 4.0 mmol/L:

- 7. Repeat volume status and tissue perfusion assessment:
 - a. Repeat focused exam: vital signs, cardiopulmonary, capillary refill, pulse and skin findings, OR
 - b. 2 of the following: Measure CVP, Measure ScvO2, Bedside CV ultrasound, Assess fluid responsiveness by passive leg raise or fluid challenge

Hypotension is defined as SBP <90, MAP <65, or decline in baseline SBP by >40 mmHg. Persistent hypotension is defined as the above criteria occurring within 1 hour of completing a 30 cc/kg fluid bolus.

Exclusion criteria for the SEP-1 measure include transfer from an outside hospital, and documentation of limitations in care (e.g., refusal of fluids, antibiotics, vasopressors, blood draws, or transition to comfort care measures) within 3 hours of severe sepsis presentation or 6 hours of septic shock presentation.

Preliminary data from Partners hospitals indicate compliance rates around 30-40%. The most common reasons for failing the measure are failure to recheck lactates within 6 hours when initial lactate levels are elevated, failure to administer the 30 cc/kg fluid bolus in response to hypotension, and failure to document a repeat volume status assessment within 6 hours of septic shock.

There is considerable controversy over the new CMS measure.^{18,19} The measure has adopted Surviving Sepsis Campaign guidelines, which represent a combination of best available evidence and expert opinion, to mandate specific actions for all patients. For example, prescriptive fluid requirements regardless of assessed volume status may not be beneficial for some patients, and the requirement for a 5-point volume reassessment is not based in evidence. However, we believe that the core aspects of the SEP-1 measure (in particular, rapid administration of antibiotics and fluids for hypotension, serial lactate measurements, and timely initiation of vasopressors for fluid-refractory hypotension) represent sound clinical practice for most patients.

We encourage clinicians to use the PHS algorithm and recommendations (which incorporate aspects of the CMS SEP-1 measure) as adjuncts to good clinical judgement. We believe that the actions in the PHS algorithm represent best care for the vast majority of patients with sepsis and septic shock, and that deviation from them can be justified but should be accompanied by documentation reflecting the clinical decision made.

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