Sepsis/Septic Shock

Septicemia

- Septicemia is an infection that occurs when bacteria enter the bloodstream and spread.
- It is more common in people who are hospitalized or have other medical conditions.
- It requires immediate medical attention and antibiotic treatment.

Sepsis

Sepsis is a clinical syndrome of life-threatening organ dysfunction caused by a dysregulated response to infection.

- Bacterial infections are the most common cause of sepsis.

- Fever or hypothermia, leukocytosis or leukopenia, tachypnea and tachycardia are cardinal signs of the systemic response.

- In general, when an infectious etiology is proven or strongly suspected and the response results in hypofunction of uninfected organs, the term sepsis (or former severe sepsis) should be use .

Inflammation and blood clotting during sepsis causes reduced blood flow to limbs and vital organs, and can lead to organ failure and even death.

- **Septic shock**: there is critical reduction in tissue perfusion; acute failure of multiple organs, including the lungs, kidneys, and liver, can occur.

>>>Involves persistent hypotension (defined as the need for vasopressors to maintain mean arterial pressure ≥ 65 mm Hg, and a serum lactate level > 18 mg/dL [2 mmol/L] despite adequate volume resuscitation.

**Septic shock refers to sepsis accompanied by hypotension that cannot be corrected by the infusion of fluids.*

Mortality Risk

- recent scientific publication estimated that in 2017 there were 48.9 million cases and 11 million sepsis-related deaths worldwide, which accounted for almost 20% of all global deaths .

- Significant regional disparities in sepsis incidence and mortality exist; approximately 85.0% of sepsis cases and sepsis-related deaths worldwide occurred in low- and middle-income countries

Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet (London, England). 2020;395(10219):200-11.

- Sepsis is a major, world-wide health care problem that requires hospital admissions with high mortality risk.

>>>> represents a spectrum of disease with mortality risk ranging from moderate (eg, 10%) to substantial (eg, > 40%) depending on various pathogen and host factors along with the timeliness of recognition and provision of appropriate treatment.

- Septic shock is a subset of sepsis with significantly increased mortality due to severe abnormalities of circulation and/or cellular metabolism.

- Although mortality has decreased in the last decade, it remains over >20% percent → 1 in 5.

- Sepsis is associated with a mortality rate of 25–30% and mortality due to septic shock is 50–85%.

Signs of possibly harmful systemic response:

- Two or more o the following conditions:

(1) *fever* (oral temperature >38°C [>100.4°F]) or *hypothermia* (<36°C [<96.8°F])

(2) *tachypnea* (>24 breaths/min)

(3) *tachycardia* (heart rate >90 beats/min)

(4) *leukocytosis* (>12,000/µL), *leukopenia* (<4000/µL), or >10% bands

Sepsis (or severe sepsis):

- The harmful host response to infection; systemic response to proven or suspected infection *plus* some degree of organ hypofunction, i.e.:

1. Cardiovascular: Bp; Arterial **systolic blood pressure ≤90** mmHg or **mean arterial pressure ≤70 mmHg** that responds to administration of IV fluid.
2. Renal: Urine output <0.5 mL/kg per hour for 1 h despite adequate fluid resuscitation.
3. Respiratory: Pao2/Fio2 ≤250 , or if the lung is the only dysfunctional organ , & ratio ≤200.
4. Hematologic: Platelet count <80,000/µL or 50% decrease in platelet count from highest value recorded over previous 3 days.
5. Unexplained metabolic acidosis: A pH ≤7.30 or a base deficit ≥5.0 mEq/L and a plasma lactate level >1.5 times upper limit o normal or reporting lab

Septic shock

- Sepsis with hypotension (arterial blood pressure <u><90 mmHg systolic</u>, or 40 mmHg less than patient's normal blood pressure) for at least 1 h **despite adequate fluid resuscitation or Need for vasopressors** to maintain systolic blood pressure ≥90 mmHg or mean arterial pressure ≥70 mmHg.

- Refractory septic shock: Septic shock that lasts for >1 h and does not respond to fluid or vasopressor administration.

  - *Fluid resuscitation is considered adequate when the pulmonary artery wedge pressure is ≥12 mmHg or the central venous pressure is ≥8 mmHg.*

Who is at Risk to Develop Sepsis?

- Host Factors

Age, gender, genetics, comorbidities.

Elderly account for 60-85 percent of all cases of severe sepsis.

- Immunosuppression

Disease related, medications related.

- Exposure risk

Community acquired: pneumonia, urinary, wounds, trauma

Health care acquired: invasive devices, secondary infections and skin breakdown

Predisposing factors

- Diabetes mellitus
- Cirrhosis
- Leukopenia (especially that associated with cancer or treatment with cytotoxic drugs)
- Invasive devices (including endotracheal tubes, vascular or urinary catheters, drainage tubes, and other foreign materials)
- Prior treatment with antibiotics or corticosteroids
- Recent hospitalization (especially in an intensive care unit)

In surveys performed in intensive care units (ICUs) in the United States and Europe during the 1990s and 2000s, approximately 70% to 80% of the cases of severe sepsis in adults occurred in individuals who were already hospitalized for another reason.

**In 30% to 50% of the cases in these and other series, a definite microbial etiology was not found.*

Common sites of infection that can lead to sepsis include:

- The lungs: Infections such as pneumonia.
- The abdomen: An infection of the appendix (appendicitis), bowel problems, infection of the abdominal cavity (peritonitis), and gallbladder or liver infections.
- The urinary tract (kidneys or bladder): Urinary tract infections are especially likely if the patient has a urinary catheter to drain urine.

**Respiratory infections most often induce severe sepsis, followed by abdominal and urinary tract infections.*

- The central nervous system: Infections of the brain or the spinal cord.

- The skin: Bacteria can enter skin through wounds or skin inflammation, or through the openings made with intravenous (IV) catheters (tubes inserted into the body to give or drain fluids).

❖ *Conditions such as cellulitis (inflammation of the skin's connective tissue) can also cause sepsis.*

What causes sepsis?

- Common causes in immunocompetent patients include many different species of gram-positive and gram-negative bacteria.

- Immunocompromised patients may have uncommon bacterial or fungal species as a cause.

What causes sepsis?

- Sepsis can also be caused by fungal, parasitic, or viral infections.

- The source of the infection can be any of a number of places throughout the body.

Etiology

- Causative agents vary significantly depending on the region, hospital size, season, and type of unit (neonatal, transplantation, oncology, or hemodialysis units).
- Pathogenic organisms are identified in only around half of cases of sepsis.

❖ *Where organisms are identified, bacteria (gram-positive and gram-negative) are identified as the causative organism in approximately 90% of cases, with gram-positive bacteria and fungal infections increasing in frequency.*

Although for many years gram-negative bacteria were isolated from the majority of culture-positive patients with severe sepsis, the fraction of cases associated with gram-positive bacteria has steadily **increased**, and now *Staphylococcus aureus*, coagulase-negative staphylococci, and enterococci account for approximately 30% to 50% of the cases in most clinical series.

Another recent trend is the emergence of **fungi** (in particular, Candida spp.) as etiologic agents of severe sepsis; in some recent series, Candida spp. have caused **5% to 20%** of the microbiologically documented cases

- The resistance patterns of organisms continue to change and can differ greatly according to region.

- And many studies showed that >50% of isolates microrganisms in ICU were methicillin-resistant S aureus(MRSA).

- Over the last 2 decades, *vancomycin-resistant enterococci (VREs)* have emerged, with >10% of enterococci being VREs.

- The significant number of *E coli* isolates that are now resistant to amoxicillin/clavulanic acid (around 40%).

More about Fungi >>

- The leading fungal pathogen causing sepsis has been identified as ***Candida*.**

in some centres , fungi were isolated from 17% of ICU patients with nosocomial infection.

- Fungi are more prevalent as isolates in patients with secondary or tertiary peritonitis, with Candida identified in up to 20% of patients with GI tract perforation.
- Risk factors include fecal soiling of the peritoneum, recurrent GI perforation, immunosuppressive therapy for neoplasm or in post-transplant patients, and the presence of inflammatory diseases.

➢ *These patients carry a high risk of mortality.*

PATHOPHYSIOLOGY

- Host mechanisms for sensing microbes.
- Local and systemic host responses to invading microbes:

➢Cytokines and other mediators

➢Coagulation factors

➢Control mechanisms ; local & systemic

➢Organ dysfunction and shock:

- Endothelial injury
- Septic shock

- The pathogenesis of septic shock is not completely understood. An inflammatory stimulus (eg, a bacterial toxin) triggers production of proinflammatory mediators, including tumor necrosis factor (TNF) and interleukin (IL)-1.

- These cytokines cause neutrophil–endothelial cell adhesion, activate the clotting mechanism, and generate microthrombi.

- They also release numerous other mediators, including leukotrienes, lipoxygenase, histamine, bradykinin, serotonin, and IL-2.

- They are opposed by anti-inflammatory mediators, such as IL-4 and IL-10, resulting in a negative feedback mechanism.

- Initially, arteries and arterioles dilate, decreasing peripheral arterial resistance; cardiac output typically increases.

- This stage has been referred to as warm shock. Later, cardiac output may decrease, blood pressure falls (with or without an increase in peripheral resistance), and typical features of shock appear.

- Even in the stage of increased cardiac output, vasoactive mediators cause blood flow to bypass capillary exchange vessels (a distributive defect).

- Poor capillary flow resulting from this shunting, along with capillary obstruction by microthrombi, decreases delivery of oxygen and impairs removal of carbon dioxide and waste products.

- Decreased perfusion causes dysfunction and sometimes failure of one or more organs, including the kidneys, lungs, liver, brain, and heart.

- Coagulopathy may develop because of intravascular coagulation with consumption of major clotting factors, excessive fibrinolysis in reaction thereto, and more often a combination of both.

Cytokines and other mediators

TNF-α (central mediator) stimulates leukocytes and vascular endothelial cells to release other cytokines (as well as additional TNF-α), to express cell-surface molecules that enhance neutrophil endothelial adhesion at sites of infection, and to increase prostaglandin and leukotriene production.

- TNF-α increase in most patients with severe sepsis or septic shock. And it can elicit fever, tachycardia, hypotension, an other responses. Larger doses o TNF-α induce shock and death.

Other proinflammatory molecules that contribute to innate host defense

- Chemokines, most prominently IL-8 and IL-17, attract circulating neutrophils to the infection site.

- IL-1β exhibits many of the same activities as TNF-α.

- TNF-α, IL-1β, interferon γ, IL-12, IL-17, and other proinfammatory cytokines probably interact synergistically with one another and with additional mediators.

Cytokines effect

➢Cytokine release leads to a large-scale inflammatory response

- Massive vasodilation.
- Increased capillary permeability.
- Decreased systemic vascular resistance…..Bp = SV x TPR.
- Blood clots form in the microvasculature.
- Hypotension reduces tissue perfusion causing tissue hypoxia.

❑Decreased tissue perfusion results in end organ dysfunction. *This is the pathophysiologic response that requires the fluid resuscitation.*

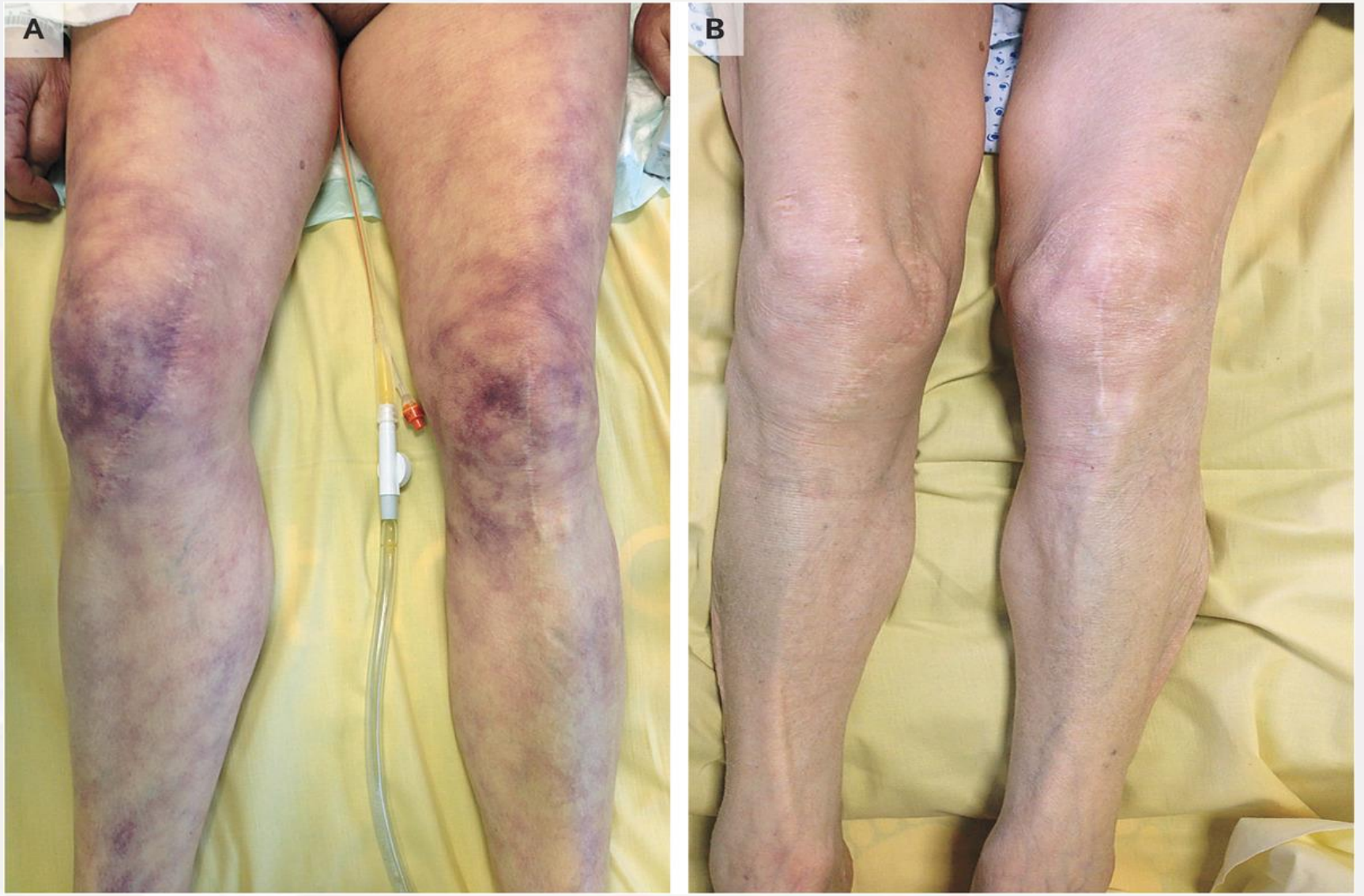
❑Even patients with heart failure or renal failure have this same response so they need fluids too.

Symptoms and Signs of Sepsis and Septic Shock

- Symptoms and signs of sepsis can be subtle and often easily mistaken for manifestations of other disorders (eg, delirium, primary cardiac dysfunction, pulmonary embolism), especially in postoperative patients.

- With sepsis, patients typically have fever, tachycardia, diaphoresis, and tachypnea; blood pressure remains normal.

- Other signs of the causative infection may be present.
- As sepsis worsens or septic shock develops, an early sign, particularly in older people or the very young, may be confusion or decreased alertness.
- Blood pressure decreases, yet the skin is paradoxically warm.
- Later, extremities become cool and pale, with peripheral cyanosis and mottling.
- Organ dysfunction causes additional symptoms and signs specific to the organ involved (eg**, oliguria, dyspnea**).



Mottling is blotchy, red-purplish marbling of the skin. Mottling most frequently occurs first on the feet, then travels up the legs

Multiple Organ Dysfunction Syndrome (MODS)

- MODS is altered organ function in an acutely ill patient requiring medical intervention to achieve homeostasis. Can be the end result of septic shock.

- Sepsis-related organ dysfunction →:

- Respiratory failure
- Liver failure
- Kidney failure
- Heart failure
- Gut permeability
- DIC (disseminated intravascular coagulation)
- Altered mental status
- Brain death

Diagnosis of Sepsis and Septic Shock

- Clinical manifestations….*(History & Physical Examination)*
- Blood pressure (BP), heart rate, and oxygen monitoring.
- Complete blood count (CBC) with differential, electrolyte panel , creatinine, lactate and ABGs.
- Invasive central venous pressure (CVP), PaO_2, and central venous oxygen saturation ($ScvO_2$) readings.

- Cultures of blood, urine, and other potential sites of infection, including wounds in surgical patients.

- Ultrasonography, CT, or MRI may be required, depending on the suspected source.

**Blood levels of C-reactive protein and procalcitonin are often elevated in severe sepsis and may facilitate diagnosis, but they are not specific. ->Ultimately, the diagnosis is clinical.*

- White blood cell (WBC) count may be decreased (< 4,000/mcL [< 4 × 109/L]) or increased (> 15,000/mcL [> 15 × 109/L]), and polymorphonuclear leukocytes may be as low as 20%.

- During the course of sepsis, the WBC count may increase or decrease, depending on the severity of sepsis or shock, the patient's immunologic status, and the etiology of the infection.

- Hyperventilation with respiratory alkalosis (low $PaCO_2$ and increased arterial pH) occurs early, in part as compensation for lactic acidemia. Serum bicarbonate is usually low, and serum and blood lactate levels increase.

- As shock progresses, metabolic acidosis worsens, and blood pH decreases.

- Early hypoxemic respiratory failure leads to a decreased PaO_2:FIO_2 ratio and sometimes overt hypoxemia with $PaO_2 < 70$ mm Hg.

- Diffuse infiltrates may appear on the chest x-ray due to acute respiratory distress syndrome (ARDS).

- BUN and creatinine usually increase progressively as a result of renal insufficiency.

- Bilirubin and transaminases may rise, although overt hepatic failure is uncommon in patients with normal baseline liver function.

- Many patients with severe sepsis develop relative adrenal insufficiency (ie, normal or slightly elevated baseline cortisol levels that do not increase significantly in response to further stress or exogenous adrenocorticotropic hormone [ACTH]).

- Adrenal function may be tested by measuring serum cortisol at 8 AM; a level < 5 mcg/dL (< 138 nmol/L) is inadequate.

- Alternatively, cortisol can be measured before and after injection of 250 mcg of synthetic ACTH; a rise of < 9 mcg/dL (< 248 nmol/L) is considered insufficient.

- However, in refractory septic shock, no cortisol testing is required before starting corticosteroid therapy.

- Hemodynamic measurements with a central venous or pulmonary artery catheter can be used when the specific type of shock is unclear or when large fluid volumes (eg, > 4 to 5 L balanced crystalloid within 6 to 8 hours) are needed.

- Bedside echocardiography in the ICU is a practical and noninvasive alternative method of hemodynamic monitoring. In septic shock, cardiac output is increased and peripheral vascular resistance is decreased, whereas in other forms of shock, cardiac output is typically decreased and peripheral resistance is increased.

- Neither CVP nor pulmonary artery occlusive pressure (PAOP) is likely to be abnormal in septic shock, unlike in hypovolemic, obstructive, or cardiogenic shock.

- Other causes of shock (eg, hypovolemia, myocardial infarction [MI]) should be ruled out via history, physical examination, ECG, and serum cardiac markers.

- Even in the absence of MI, hypoperfusion caused by sepsis may result in ECG findings of cardiac ischemia including nonspecific ST-T wave abnormalities, T-wave inversions, and supraventricular and ventricular arrhythmias.

- It is important to detect organ dysfunction as early as possible.

How???

A number of scoring systems have been devised, but the sequential organ failure assessment score (SOFA score) and the quick SOFA score (qSOFA) have been validated with respect to mortality risk and are relatively simple to use.

Sequential (sepsis-related) Organ Failure Assessment (SOFA)

- It was initially designed to sequentially assess the severity of organ dysfunction in patients who were critically ill from sepsis.

- Since multiple organ dysfunction is common in critically ill patients, it has since been used to predict mortality in those with organ failure from other causes including those with acute liver failure from acetaminophen overdose, chronic liver failure , and cancer, as well as in patients who have undergone cardiac surgery or hematopoietic stem cell transplant .

- SOFA uses simple measurements of major organ function to calculate a severity score. The scores are calculated 24 hours after admission to the ICU and every 48 hours thereafter (thus, the term "Sequential" Organ Failure Assessment).

- The mean and the highest scores are most predictive of mortality.

➢The SOFA severity score is based upon the following measurements of organ function :

- Respiratory system – the ratio of arterial oxygen tension to fraction of inspired oxygen (PaO2/FiO2)
- Cardiovascular system – the amount of vasoactive medication necessary to prevent hypotension.
- Hepatic system – Bilirubin level
- Coagulation system – Platelet concentration

Neurologic system – Glasgow coma score

Renal system – Serum creatinine or urine output

Sequential Organ Failure Assessment (SOFA) Score

Parameter	Score: 0	Score: 1	Score: 2	Score: 3
PaO2/FIO2	< 400 mm Hg (53.3 kPa)	< 400 mm Hg (53.3 kPa)	< 300 mm Hg (40 kPa)	< 200 mm Hg (26.7 kPa) with respiratory support
Platelets	≥ 150 × 10^3/mcL (≥ 150 × 10^9/L)	< 150 × 10^3/mcL (< 150 × 10^9/L)	< 100 × 10^3/mcL (< 100 × 10^9/L)	< 50 × 10^3/mcL (< 50 × 10^9/L)
Bilirubin	< 1.2 mg/dL (20 micromole/L)	1.2–1.9 mg/dL (20–32 micromole/L)	2.0–5.9 mg/dL (33–101 micromole/L)	6.0–11.9 mg/dL (102–204 micromole/L)

Sequential Organ Failure Assessment (SOFA) Score

Parameter	Score: 0	Score: 1	Score: 2	Score: 3
Cardiovascular	MAP ≥ 70 mm Hg	MAP < 70 mm Hg	Dopamine < 5 mcg/kg/minute for ≥ 1 hour *or* Any dose of dobutamine	Dopamine 5.1–15 mcg/kg/minute for ≥ 1 hour *or* Epinephrine ≤ 0.1 mcg/kg/minute for ≥ 1 hour *or* Norepinephrine ≤ 0.1 mcg/kg/minute for ≥ 1 hour

* A higher score indicates better neurologic function.

FIO2 = fractional inspired oxygen; kPa = kilopascals; MAP = mean arterial pressure; PaO2 = arte partial pressure.

Adapted from Singer M, Deutschman CS, Seymour CW, et al: The third international consensus sepsis and septic shock (sepsis-3). *JAMA* 315:801–810, 2016. doi:10.1001/jama.2016.0287

Identification of early sepsis (qSOFA)

- The 2016 SCCM/ESICM* task force have described this assessment score for patients outside the intensive care unit as a way to facilitate the identification of patients potentially at risk of dying from sepsis.
- This score is a modified version of the Sequential (Sepsis-related) Organ Failure Assessment score (SOFA) called the quickSOFA (qSOFA) score.
- A score **≥2** is associated with poor outcomes due to sepsis.

* European Society of Intensive Care Medicine (**ESICM**) alongside the Society of Critical Care Medicine (**SCCM**)

qSOFA score

- The qSOFA score is based on the blood pressure, respiratory rate, and the Glasgow coma scale .

➔ *does not require waiting for lab results.*

The quick SOFA (qSOFA) score is a tool to help identify patients with early sepsis outside of the ICU.

qSOFA


Hypotension
Systolic BP
<100 mmHg
Altered
Mental
Status
Tachypnea
RR >22/Min
Score of ≥2 Criteria Suggests a Greater Risk of a Poor Outcome

- For patients with a suspected infection who are not in the intensive care unit (ICU), the ***qSOFA*** score is a better **predictor** of inpatient mortality than the systemic inflammatory response syndrome (SIRS) .
  ….(early transfer to ICU.)

- For patients with a suspected infection who are in the intensive care unit (ICU), the **SOFA** score is a better **predictor** of inpatient mortality than the systemic inflammatory response syndrome (SIRS) and qSOFA score

- As an organ dysfunction score, SOFA can be used to identify those whose organ dysfunction is "life- threatening" such that an increase in the SOFA score ≥2 is associated with a mortality of ≥10 percent.

- Septic shock – Patients with a SOFA score ≥2 who also have a vasopressor requirement and an elevated lactate >2 mmol/L (>18 mg/dL)despite adequate fluid resuscitation have a predicted mortality of 40 percent.

Treatment of Sepsis and Septic Shock

- Perfusion restored with IV fluids and sometimes vasopressors
- Oxygen support
- Broad-spectrum antibiotics
- Source control
- Sometimes other supportive measures (eg, corticosteroids, insulin)

The following should be monitored frequently (as often as hourly):

➢ ***Patients with septic shock should be treated in an intensive care unit (ICU).***

- Central venous pressure (CVP), pulmonary artery occlusion pressure (PAOP), or central venous oxygenation saturation (ScvO2)
- Arterial blood gases (ABGs)
- Blood glucose, lactate, and electrolyte levels
- Renal function ; Urine output, a good indicator of renal perfusion, should be measured (in general, indwelling urinary catheters should be avoided unless they are essential).

**The onset of oliguria (eg, < about 0.5 mL/kg/hour) or anuria, or rising creatinine may signal impending renal failure.*

Perfusion restoration

- IV fluids are the first method used to restore perfusion.
- Balanced isotonic crystalloid is preferred.

- Some clinicians add albumin to the initial fluid bolus in patients with severe sepsis or septic shock; albumin is more expensive than crystalloid but is generally a safe complement to crystalloid.

**Starch-based fluids (eg, hydroxyethyl starch) are associated with increased mortality and should not be used.*

Crystalloid Fluids

- The Society of Critical Care Medicine suggests isotonic saline (normal saline) or balanced salt solutions (lactated Ringers) for initial fluid resuscitation.

- Initially, 1 L of crystalloid is given rapidly. Most patients require a minimum of 30 mL/kg in the first 4 to 6 hours.

** However, the goal of therapy is not to administer a specific volume of fluid but to achieve tissue reperfusion without causing pulmonary edema due to fluid overload.*

- Sepsis without hypotension:
- For most patients, the provider will likely order a fluid bolus based on their assessment, but there is no specific requirement.

- Severe sepsis with hypotension or lactate ≥ 4 mmol/L:
- 30 mL/kg of actual body weight for patients with a BMI < 30
- 30 mL/kg of ideal body weight for patients with a BMI > 30

- Estimates of successful reperfusion include ScvO2 and lactate clearance (ie, percent change in serum lactate levels).

- Target ScvO2 is ≥ 70%.

- Lactate clearance target is 10 to 20%.

- Risk of pulmonary edema can be controlled by optimizing preload; fluids should be given until CVP reaches 8 mm Hg (10 cm water) or PAOP reaches 12 to 15 mm Hg; however, patients on mechanical ventilation may require higher CVP levels.

- The quantity of fluid required often far exceeds the normal blood volume and may reach 10 L over 4 to 12 hours. PAOP or echocardiography can identify limitations in left ventricular function and incipient pulmonary edema due to fluid overload.

- If a patient with septic shock remains hypotensive after CVP or PAOP has been raised to target levels, Norepinephrine may be given to increase mean blood pressure (BP) to at least 65 mm Hg.

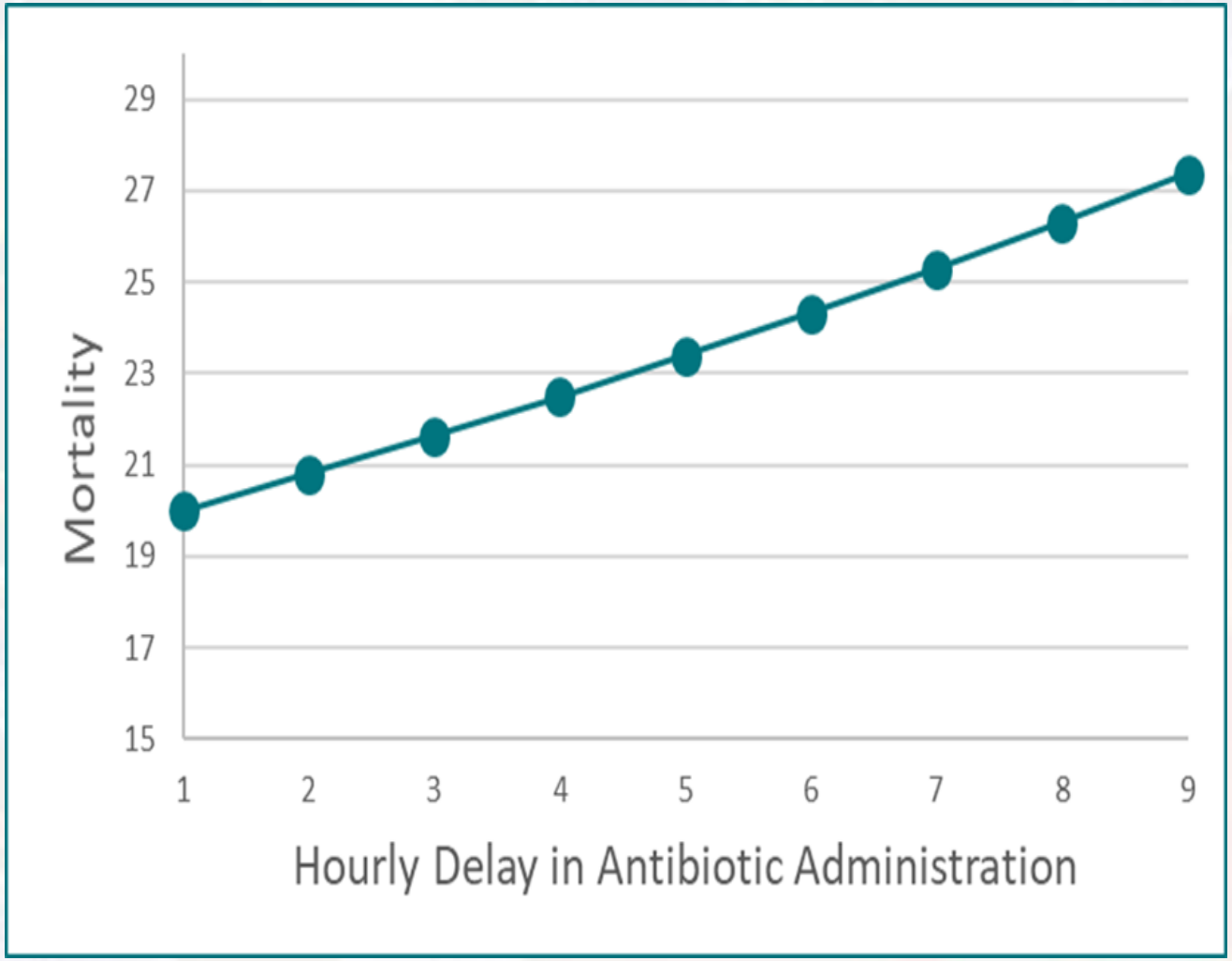
**vasoconstriction caused by higher doses of these drugs may cause organ hypoperfusion and acidosis.*

Oxygen support

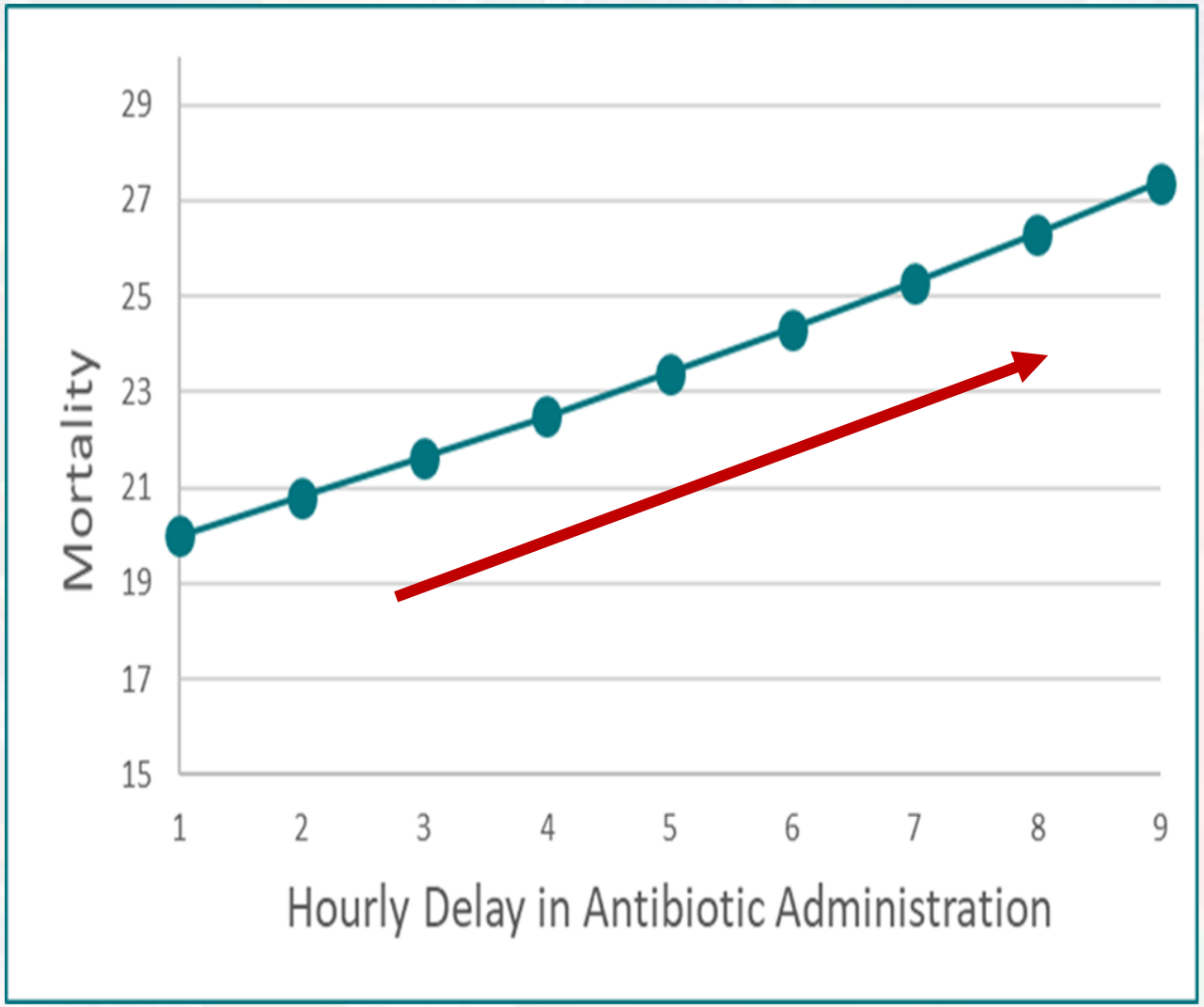
- Oxygen is given by mask or nasal prongs. Tracheal intubation and mechanical ventilation may be needed subsequently for respiratory failure (see Mechanical ventilation in ARDS).

Antibiotics

- Antibiotics are the life-saving treatment for an infection
- Every hour antibiotic initiation is delayed increases the risk for mortality by four to eight percent (6%).
- Preferably after the second set of cultures; however, if the second set is going to be delayed more than 30 minutes, antibiotics should be started after the first set.



- For every hour delay in antibiotic administration, mortality increases 4-8%



- For every hour delay in antibiotic administration, mortality increases 4-8%

Antibiotics

- Parenteral antibiotics should be given as soon as possible after specimens of blood, body fluids, and wound sites have been taken for Gram stain and culture.
- Prompt*(as soon as possible)* empiric therapy, started immediately after suspecting sepsis, is essential and may be lifesaving.
- Antibiotic selection requires an educated guess based on the suspected source (eg, pneumonia, urinary tract infection), clinical setting, knowledge or suspicion of causative organisms and of sensitivity patterns common to that specific inpatient unit or institution, and previous culture results.

- Typically, broad-spectrum gram-positive and gram-negative bacterial coverage is used initially; immunocompromised patients should also receive an empiric antifungal drug.
- There are many possible starting regimens; when available, institutional trends for infecting organisms and their antibiotic susceptibility patterns (antibiograms) should be used to select empiric treatment.

- In general, common antibiotics for empiric gram-positive coverage include vancomycin and linezolid.
- Empiric gram-negative coverage has more options and includes broad-spectrum penicillins (eg, piperacillin/tazobactam), 3rd- or 4th-generation cephalosporins, imipenems, and aminoglycosides.
- Initial broad-spectrum coverage is narrowed based on culture and sensitivity data.

TABLE 75-4 Empirical Antibiotic Options for Patients with Severe Sepsis or Septic Shock

	SUSPECTED SOURCE				
	Lung	**Abdomen**	**Skin/Soft Tissue**	**Urinary Tract**	**Source Uncertain**
Major Community-Acquired Pathogens	*Streptococcus pneumoniae* *Haemophilus influenzae* *Legionella* *Chlamydia pneumoniae*	*Escherichia coli* *Bacteroides fragilis*	*Streptococcus pyogenes* *Staphylococcus aureus* Polymicrobial	*E. coli* *Klebsiella* species *Enterobacter* species *Proteus* spp. Enterococci	
Empirical Antibiotic Therapy	Moxifloxacin *or* levofloxacin *or* azithromycin *plus* cefotaxime *or* ceftazidime *or* cefepime *or* piperacillin-tazobactam	Imipenem *or* meropenem *or* doripenem *or* piperacillin-tazobactam ± aminoglycoside If biliary source: piperacillin-tazobactam, ampicillin-sulbactam, *or* ceftriaxone with metronidazole	Vancomycin *or* daptomycin *plus either* imipenem *or* meropenem *or* piperacillin-tazobactam; ± clindamycin (see text)	Ciprofloxacin *or* levofloxacin (if gram-positive cocci, use ampicillin *or* vancomycin ± gentamicin)	Vancomycin *plus either* doripenem *or* ertapenem *or* imipenem *or* meropenem
Major Commensal or Nosocomial Microorganisms	Aerobic gram-negative bacilli	Aerobic gram-negative rods Anaerobes *Candida* spp.	*Staphylococcus aureus* (? MRSA) Aerobic gram-negative rods	Aerobic gram-negative rods Enterococci	Consider MDRO if in area of high prevalence Consider echinocandin if neutropenic or indwelling intravascular catheter
Empirical Antibiotic Therapy	Imipenem *or* meropenem *or* doripenem *or* cefepime (if *Acinetobacter baumanii* or carbapenem-resistant *Klebsiella* in ICU, add colistin)	Imipenem *or* meropenem ± aminoglycoside (consider echinocandin)	Vancomycin *or* daptomycin *plus* imipenem-cilastatin *or* meropenem *or* cefepime, ± clindamycin	Vancomycin *plus* imipenem *or* meropenem *or* cefepime	Cefepime *plus* vancomycin ± caspofungin

Dosages for intravenous administration (normal renal function):

*Imipenem-cilastatin, 0.5-1.0 g q6-8h
*Meropenem, 1-2 g q8h
*Doripenem, 0.5 g q8h
Piperacillin-tazobactam, 3.375 g q4h or 4.5 g q6h
Vancomycin, load 25-30 mg/kg, then 15-20 q8-12h
Cefepime, 1-2 g q8h
Levofloxacin, 750 mg q24h
Ciprofloxacin, 400 mg q8-12h
Moxifloxacin, 400 mg qd
Ceftriaxone, 2.0 g q24h
Caspofungin, 70 mg, followed by 50 mg q24h
Colistin: loading dose = 5 mg/kg body weight. For maintenance dosing, see University of California, Los Angeles Dosing Protocol: www.infectiousdiseases-ucla-affiliated.org/Intranet/FILES/ColistinDosing.pdf

*Carbapenems are less susceptible to extended-spectrum β-lactamases; base choice on local resistance pattern.
ICU, intensive care unit; MDRO, multidrug-resistant organisms; MRSA, methicillin-resistant *Staphylococcus aureus*.
For MDRO, resistance usually includes carbapenems.

Source control

- The source of infection should be controlled as early as possible. IV and urinary catheters and endotracheal tubes should be removed if possible or changed.

- Abscesses must be drained, and necrotic and devitalized tissues (eg, gangrenous gallbladder, necrotizing soft-tissue infection) must be surgically excised.
- If excision is not possible (eg, because of comorbidities or hemodynamic instability), surgical drainage may help …(by interventional radiology for example)

**Source control: identify and stop the infection*

**If the source is not controlled, the patient's condition will continue to deteriorate despite antibiotic therapy. (@surgery teams)*

Blood Cultures

- Appropriate antibiotics are essential, but until the organism is identified, broad spectrum treatment is necessary to cover most likely sources.
- Surgical removal of infection may be the most appropriate solution.

➢ *Why two sets of blood cultures?*

- Corroboration of matching sets confirms treatment of a true pathogen versus a contaminate

- The goal is to prevent culture negative severe sepsis (CNSS) and septic shock.

*Of 6.8 million severe sepsis admissions, 47 percent were culture negative

*CNSS was seen as a statistically significant independent predictor of death

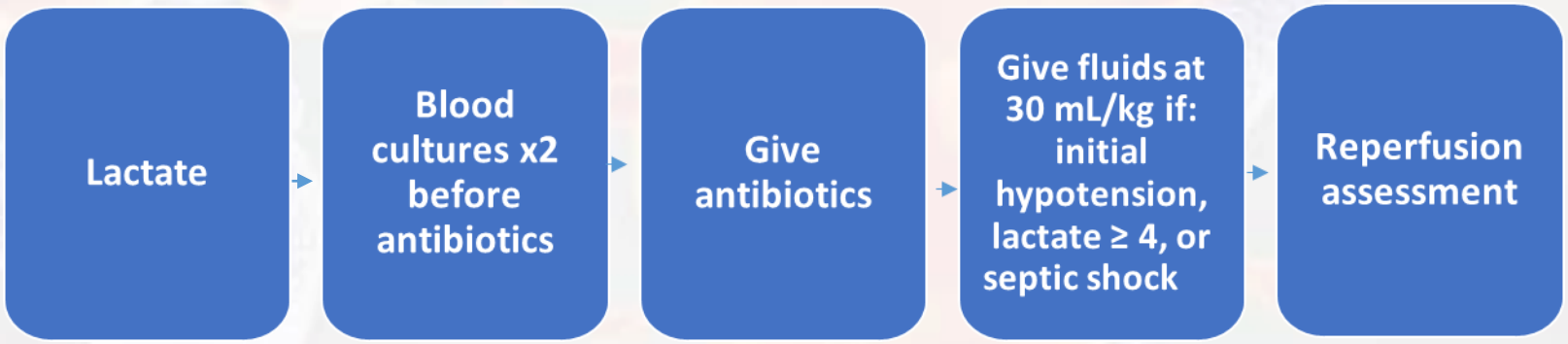
Other supportive measures

- Normalization of blood glucose improves outcome in critically ill patients, even those not known to be diabetic, because hyperglycemia impairs the immune response to infection. A continuous IV insulin infusion (starting dose 1 to 4 units/hour) is titrated to maintain glucose between 110 and 180 mg/dL (7.7 to 9.9 mmol/L). This approach necessitates frequent (eg, every 1 to 4 hours) glucose measurement.

- Corticosteroid therapy may be beneficial in patients who remain hypotensive despite treatment with IV fluids, source control, antibiotics, and vasopressors.
- There is no need to measure cortisol levels before starting therapy. Treatment is with replacement rather than pharmacologic doses. One regimen consists of hydrocortisone 50 mg IV every 6 hours (or 100 mg every 8 hours).

* *Continued treatment is based on patient response.*

Treatment bundle



Surviving Sepsis Campaign (SSC)

- The international Surviving Sepsis Campaign (SSC) is a joint initiative of the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM), who are committed to reducing mortality and morbidity from sepsis and septic shock worldwide.

- The SSC is led by multidisciplinary international experts committed to improving time to recognition and treatment of sepsis and septic shock, which are leading causes of death worldwide.

- SCCM is also committed to improving outcomes for sepsis survivors, especially those with post-sepsis syndrome.

SEP-1

- “SEP-1” is shorthand for “The Severe Sepsis and Septic Shock Management Bundle.”

- It lays out guidelines for frontline hospital clinicians fighting sepsis.
- SEP-1 focuses on timely sepsis recognition and early intervention with lifesaving therapies.
- This emphasis on timing is critically important, as saving lives and limbs from sepsis is all about time: each hour of delay before a septic patient is treated is associated with a 4-9% increased risk of mortality.

- ❑The SEP-1 measure treatment bundle is based on recommendations from the 2021 Surviving Sepsis Guidelines.
- Once a sepsis patient is identified, the goal is to get antibiotics started as quickly as possible. The lactate and blood cultures need to be done prior to starting the antibiotic (in particular, the blood cultures).
- If the patient has initial hypotension, defined as a SBP < 90 or a MAP < 65, a lactate ≥ 4 or septic shock, a **30mL/kg fluid bolus is required**.
- If there is persistent hypotension (hypotension after the initial fluid bolus as evidenced by two BP readings within the hour after the bolus is completed), a **vasopressor should be started; norepinephrine (Levophed) is the preferred vasopressor**.
- For any patient with persistent hypotension, an initial lactate ≥ 4 or septic shock, a tissue reperfusion assessment must be performed by the provider.
- Any time the initial lactate is > 2, a repeat lactate must be done to reassess tissue perfusion (*regardless of fluid resuscitation*).

MEDICAL EMERGENCY

Initiate bundle upon recognition of sepsis/septic shock.

May not complete all bundle elements within one hour of recognition.

1 Measure lactate level.

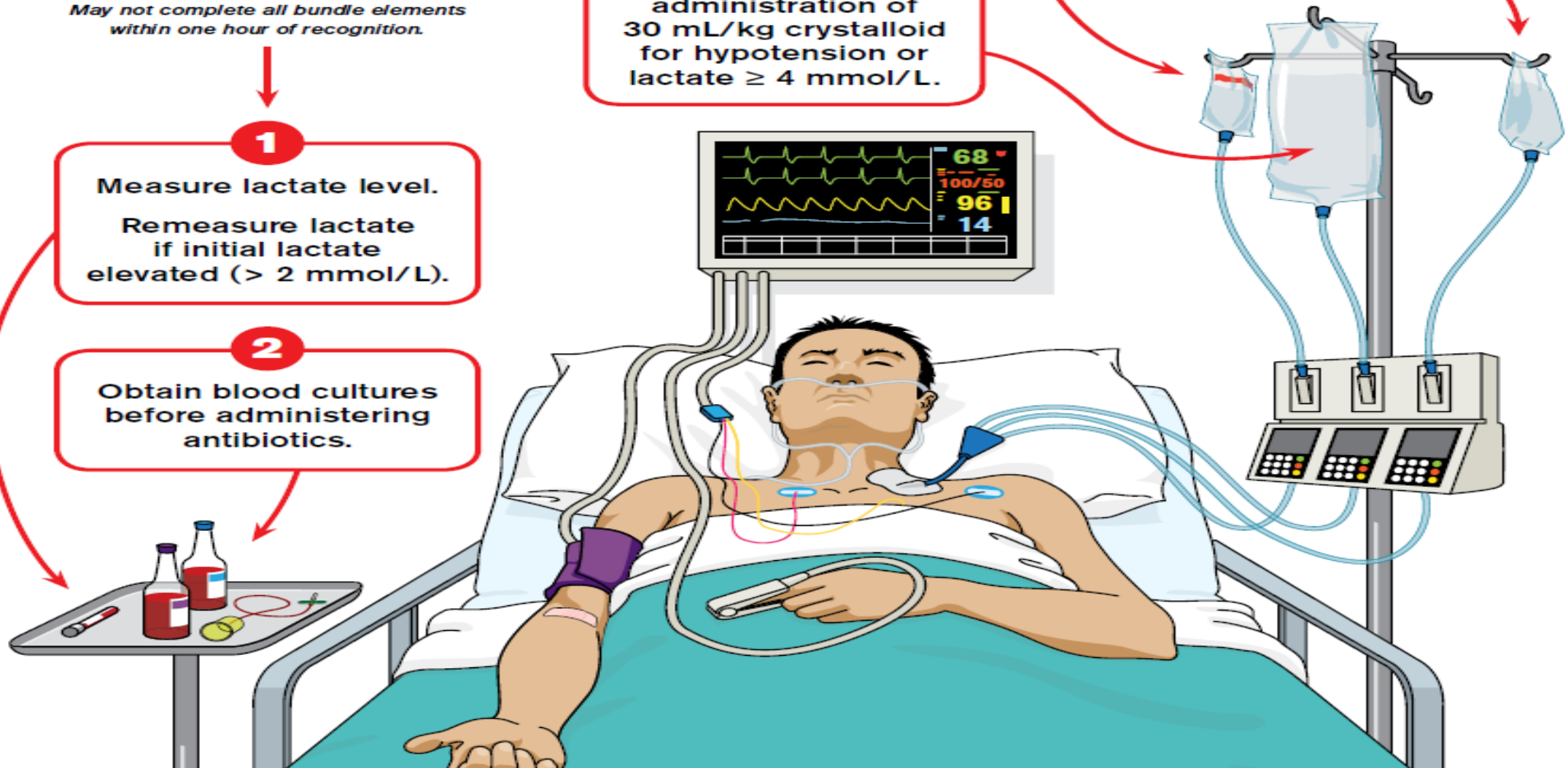
Remeasure lactate if initial lactate elevated (> 2 mmol/L).

2 Obtain blood cultures before administering antibiotics.

3 Administer broad-spectrum antibiotics.

4 Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L.

5 Apply vasopressors if hypotensive during or after fluid resuscitation to maintain a mean arterial pressure ≥ 65 mm Hg.



Hour-1 Bundle..

- Initial Resuscitation for Sepsis and Septic Shock

1) Measure lactate level.
2) Obtain blood cultures before administering antibiotics.
3) Administer broad-spectrum antibiotics.
4) Begin rapid administration of 30mL/kg crystalloid for hypotension or lactate ≥4 mmol/L.
5) Apply vasopressors if hypotensive during or after fluid resuscitation to maintain a mean arterial pressure ≥ 65 mm Hg.
*Remeasure lactate if initial lactate elevated (> 2 mmol/L).

Sepsis Bundles

- **Time Zero:** time zero is recognition time: for the ED that is triage completion time.

- **3 Hour Bundle:** everything in this bundle must be completed ***prior to 3 hours after time zero***
  - Lactate drawn *repeat in 4 hours if > 2.0
  - Blood Cultures drawn *2 sets - can be drawn concurrently with 2 separate venipuncture
  - Antibiotic delivery *goal all antibiotics initiated within 1 hour of order time
  - Fluid Resuscitation Bolus *For SBP < 90; MAP < 70; Lactate > 4.0

- **6 Hour Bundle:** everything in this bundle must be completed prior to 6 hours after time zero
  - Addition of vasopressors ➔Norepinephrine preferred
  - Repeat lactate *If initial >2
  - Central line insertion
  - Monitor CVP
  - Monitor ScV02

Lactate

- The pathophysiology behind this is that as the body goes further down the sepsis continuum and the hypoperfusion of end organs increases (due to hypovolemia and coagulopathic responses), there is more anaerobic metabolism and the byproduct is the production of lactate.
- The higher the lactate, the higher the risk for mortality

- With sepsis, lactate is viewed as a marker of global tissue perfusion.
- Lactate has some predictive use:
- Sustained > 6 hours, an elevated lactate foreshadows increased mortality
- Mortality increases as lactate levels increase

Lactate Level	Mortality
0-2.5 mmol/L	4.9 percent mortality
2.5-4.0 mmol/L	9.0 percent mortality
> 4.0 mmol/L	28.4 percent mortality

- Documentation of Tissue Perfusion Reassessment

Provider documentation of 5 of 8 of the following:

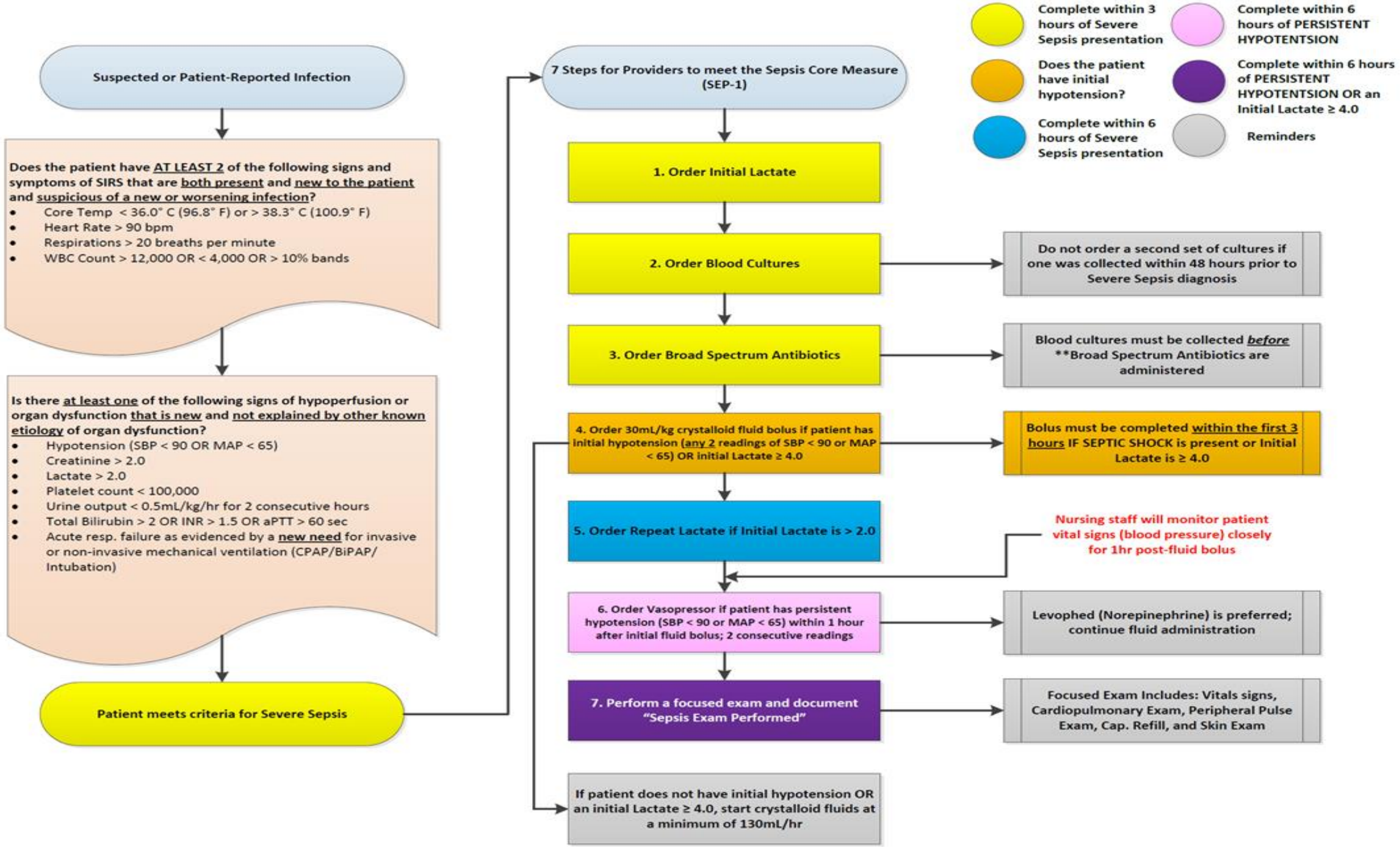
- Arterial oxygenation
- Vital signs
- Cardiopulmonary exam
- Capillary refill exam
- Peripheral pulse evaluation
- Skin exam
- Shock index
- Urine output

Provider documentation of one of the following:

- Central venous pressure measurement
- Central venous oxygen measurement
- Bedside cardiovascular ultrasound
- Result of passive leg raise or fluid challenge

Provider documentation of completion of perfusion reassessment:

- I have completed a full physical assessment
- Sepsis reassessment completed
- Sepsis tissue perfusion reassessment completed


Complete within 3 hours of Severe Sepsis presentation
Complete within 6 hours of PERSISTENT HYPOTENTSION
Does the patient have initial hypotension?
Complete within 6 hours of PERSISTENT HYPOTENTSION OR an Initial Lactate ≥ 4.0
Complete within 6 hours of Severe Sepsis presentation
Reminders
Suspected or Patient-Reported Infection
Does the patient have AT LEAST 2 of the following signs and symptoms of SIRS that are both present and new to the patient and suspicious of a new or worsening infection?
Core Temp < 36.0° C (96.8° F) or > 38.3° C (100.9° F)
Heart Rate > 90 bpm
Respirations > 20 breaths per minute
WBC Count > 12,000 OR < 4,000 OR > 10% bands
Is there at least one of the following signs of hypoperfusion or organ dysfunction that is new and not explained by other known etiology of organ dysfunction?
Hypotension (SBP < 90 OR MAP < 65)
Creatinine > 2.0
Lactate > 2.0
Platelet count < 100,000
Urine output < 0.5mL/kg/hr for 2 consecutive hours
Total Bilirubin > 2 OR INR > 1.5 OR aPTT > 60 sec
Acute resp. failure as evidenced by a new need for invasive or non-invasive mechanical ventilation (CPAP/BiPAP/ Intubation)
Patient meets criteria for Severe Sepsis
7 Steps for Providers to meet the Sepsis Core Measure (SEP-1)
1. Order Initial Lactate
2. Order Blood Cultures
Do not order a second set of cultures if one was collected within 48 hours prior to Severe Sepsis diagnosis
3. Order Broad Spectrum Antibiotics
Blood cultures must be collected before **Broad Spectrum Antibiotics are administered
4. Order 30mL/kg crystalloid fluid bolus if patient has initial hypotension (any 2 readings of SBP < 90 or MAP < 65) OR initial Lactate ≥ 4.0
Bolus must be completed within the first 3 hours IF SEPTIC SHOCK is present or Initial Lactate is ≥ 4.0
5. Order Repeat Lactate if Initial Lactate is > 2.0
Nursing staff will monitor patient vital signs (blood pressure) closely for 1hr post-fluid bolus
6. Order Vasopressor if patient has persistent hypotension (SBP < 90 or MAP < 65) within 1 hour after initial fluid bolus; 2 consecutive readings
Levophed (Norepinephrine) is preferred; continue fluid administration
7. Perform a focused exam and document "Sepsis Exam Performed"
Focused Exam Includes: Vitals signs, Cardiopulmonary Exam, Peripheral Pulse Exam, Cap. Refill, and Skin Exam
If patient does not have initial hypotension OR an initial Lactate ≥ 4.0, start crystalloid fluids at a minimum of 130mL/hr

Thank You