

Sepsis and septic shock

Definitions and management

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Definition

- Sepsis is a life-threatening clinical syndrome that complicates severe infection and is characterized by systemic inflammation and widespread tissue injury.
- “Dysregulation” of the normal response, with a massive and uncontrolled release of pro-inflammatory mediators creating a chain of events that leads to widespread tissue injury.

Clinical syndromes

- Infection: invasion of normally sterile tissue by organisms
- Bacteremia: viable bacteria in the blood.
- SIRS
- sepsis
- severe sepsis



Systemic inflammatory response syndrome (SIRS)

It is clinically recognized by the presence of two or more of the following :

1. Temperature $>38.5^{\circ}\text{C}$ or $<35^{\circ}\text{C}$
2. Heart rate >90 beats/min
3. Respiratory rate >20 breaths/min or $\text{PaCO}_2 <32$ mmHg
4. WBC $>12,000$ cells/mm³, <4000 cells/mm³, or >10 percent immature (band) forms

Occurrence of Severe Sepsis

- In the late 1970s, it was estimated that **164,000** cases of sepsis occurred in the USA each year
- Records from hospitals in the US estimated an annual rate of more than **1,665,000** cases of sepsis between 1979 and 2000
- Another retrospective population-based analysis reported increased rates of sepsis and septic shock from 13 to 78 cases per 100,000 between 1998 and 2009

- The incidence of sepsis appears to be highest among **African-American males**
- The incidence is also greatest **during the winter**, probably due to the increased prevalence of respiratory infections .
- **Older patients ≥ 65 years of age account for the majority (60 to 85 %) of all episodes of sepsis; with an increasing aging population, it is likely that the incidence of sepsis will continue to increase in the future**

- 51.1% received ICU care and 17.3% received IMC care
- Incidence and mortality increased with age
- Case fatality rate: 28%
- Economic burden
 - \$22,100 per case
 - ~\$16.7 billion nationally

Early sepsis

- Infection and bacteremia may be early forms that can progress to sepsis.
- Guidelines place emphasis on the early identification of infected patients who may go on to develop sepsis as a way to decrease sepsis-associated mortality.
- The most commonly used scores are the quick Sequential (Sepsis-related) Organ Failure Assessment score (**qSOFA**) score , **NEWS**(the National Early Warning Score) and **SIRS** .

■ The qSOFA score is easy to calculate since it only has three components, each of which are readily identifiable at the bedside and are allocated one point:

- Respiratory rate ≥ 22 /minute
- Altered mentation
- Systolic blood pressure ≤ 100 mmHg

NEWS (National Early Warning Score)

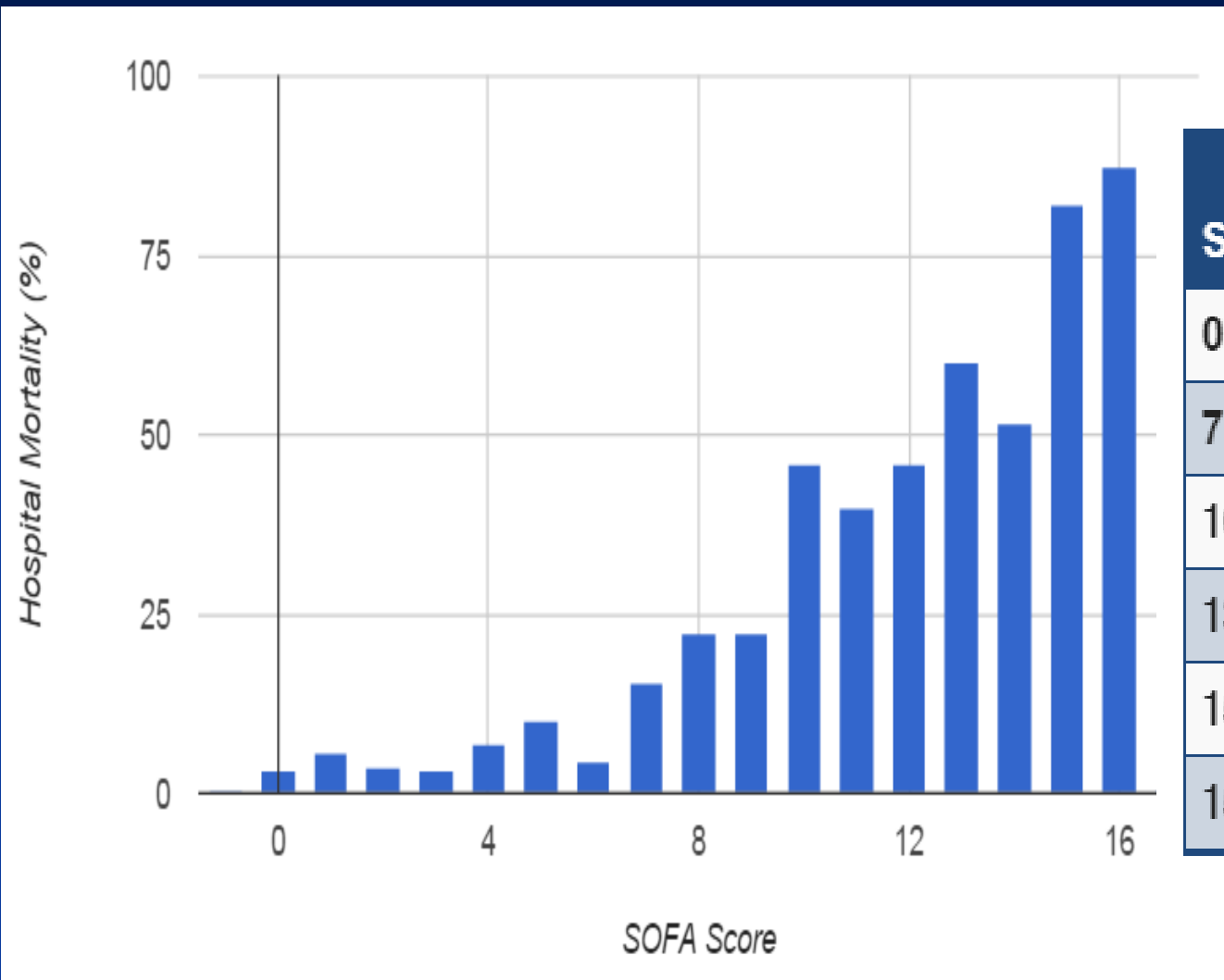
is an aggregate scoring system derived from six physiologic parameters ([calculator 2](#)):

- **Respiration rate**
- **Oxygen saturation**
- **Systolic blood pressure**
- **Pulse rate**
- **Level of consciousness or new confusion**
- **Temperature**
 - 0 to 4 – low risk
 - 5 to 6 – medium risk
 - 7 or more – high risk

Clinical Criteria to Identify Patients With Sepsis

- SOFA score
 - Neurological system
 - Cardiovascular system
 - Respiratory system
 - Renal system
 - Hepatic system
 - Coagulation system

Variables	SOFA Score				
	0	1	2	3	4
Respiratory PaO ₂ /FIO ₂ (P/F) mmHg	>400	≤400	≤300	≤200 *	≤100 *
Coagulation Platelets x 10 ⁹ /μg	>150	≤150	≤100	≤50	≤20
Liver Bilirubin mg/dL	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12
Cardiovascular Hypotension	No hypotension	Mean arterial pressure < 70 mmHg	Dopamine ≤ 5 or dobutamine (any dose)	Dopamine > 5, epinephrine ≤ 0.1, or norepinephrine ≤ 0.1	Dopamine > 15, epinephrine > 0.1 or norepinephrine > 0.1
Central nervous system Glasgow Coma Score Scale	15	13–14	10–12	6–9	<6
Renal Creatinine mg/dL	<1.2	1–2–1.9	2.0–3.4	3.5–4.9 or UOP 200 to 500 mL/d	>5 or UOP <200 mL/d
* with ventilatory support.					



Maximum SOFA Score	Mortality
0 to 6	< 10%
7 to 9	15 - 20%
10 to 12	40 - 50%
13 to 14	50 - 60%
15	> 80%
15 to 24	> 90%

- The scores are calculated ...
- **Sepsis:** 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 $\geq 10\%$.
- **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%).

Adequate fluid resuscitation??

1. 20 to 30 mL/kg of colloid.
 2. Infusion of 30 mL/kg of saline solution.
- or A measured pulmonary capillary wedge pressure (PCWP) of 12 to 20 mmHg.

Mortality

The prognosis for a patient with severe sepsis can be approximated by **adding 15% to 20%** predicted mortality for each sepsis-induced dysfunctional organ.

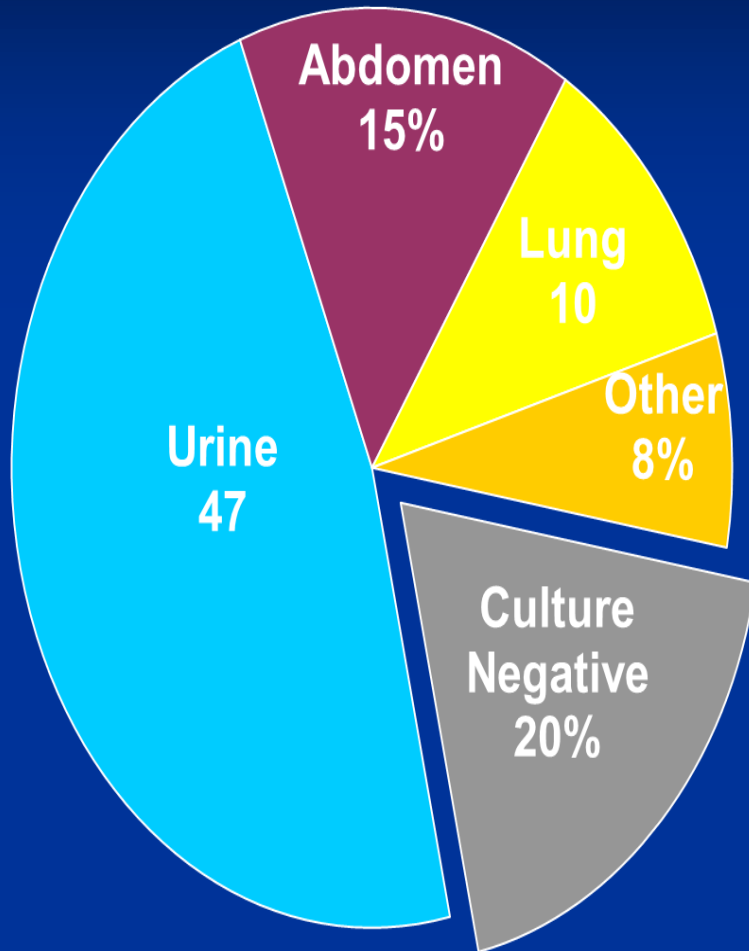
Risk Factors

- Intensive care unit admission
- Advanced age (≥ 65 years)
- Advanced age (≥ 65 years)
- Diabetes and obesity
- Cancer
- Previous hospitalization
- Genetic factors

Etiologic agents of sepsis

- ❑ **Bacteria** are the commonest underlying pathogens (mainly gram positive) .
- ❑ **Nonbacterial pathogens :**
 1. Fungi
 2. Rickettsiae
 3. Protozoa
 4. certain viruses.
- ❑ In approximately one-half of cases of sepsis, an organism is not identified (culture negative sepsis)

Where's the infection ?



Common sites of origin:

Genitourinary tract: indwelling catheters

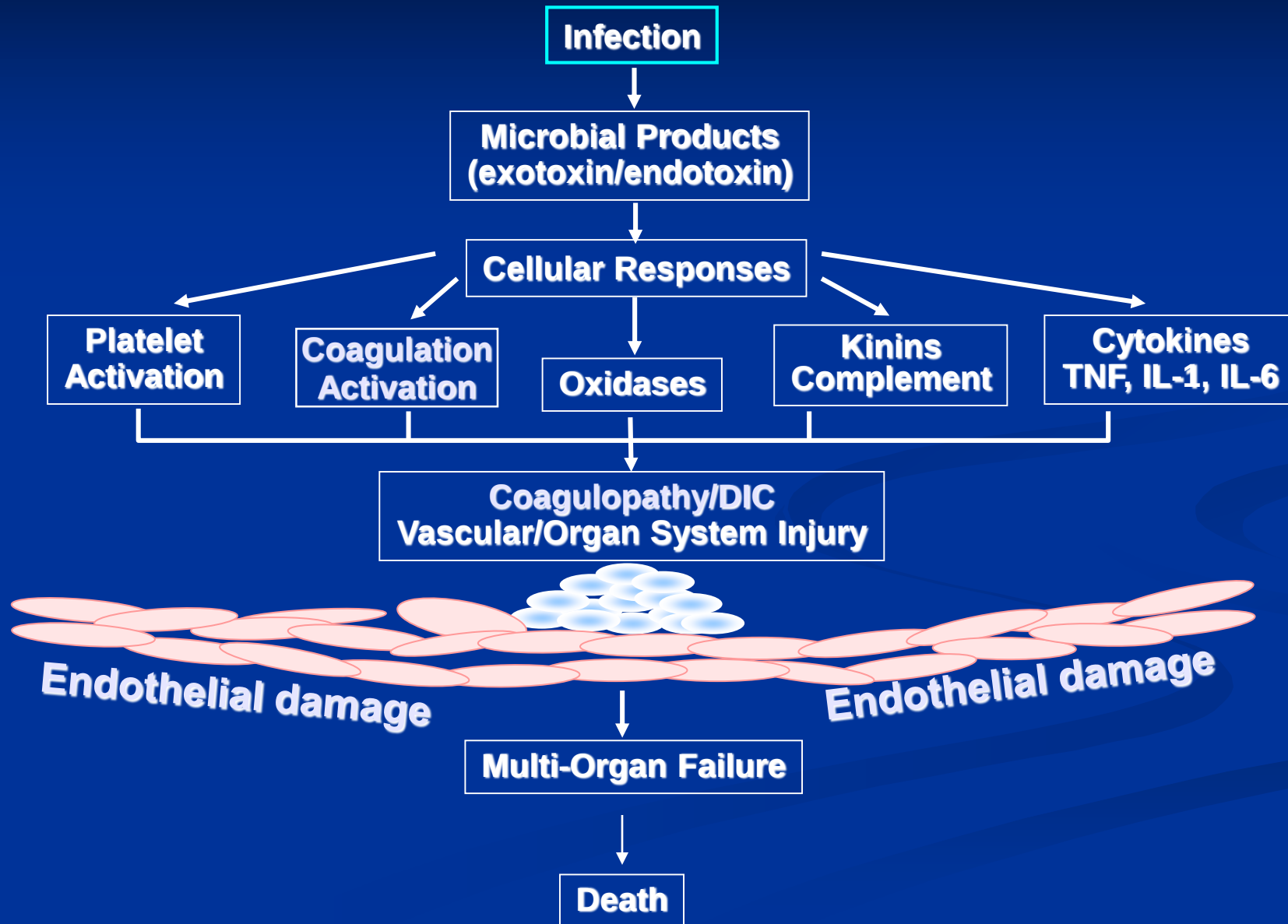
Abdomen: cholecystitis ,
peritonitis , intraabdominal
abscess, appendicitis,
pancreatitis

Lungs: pneumonia , empyema

Central nervous system:
meningitis

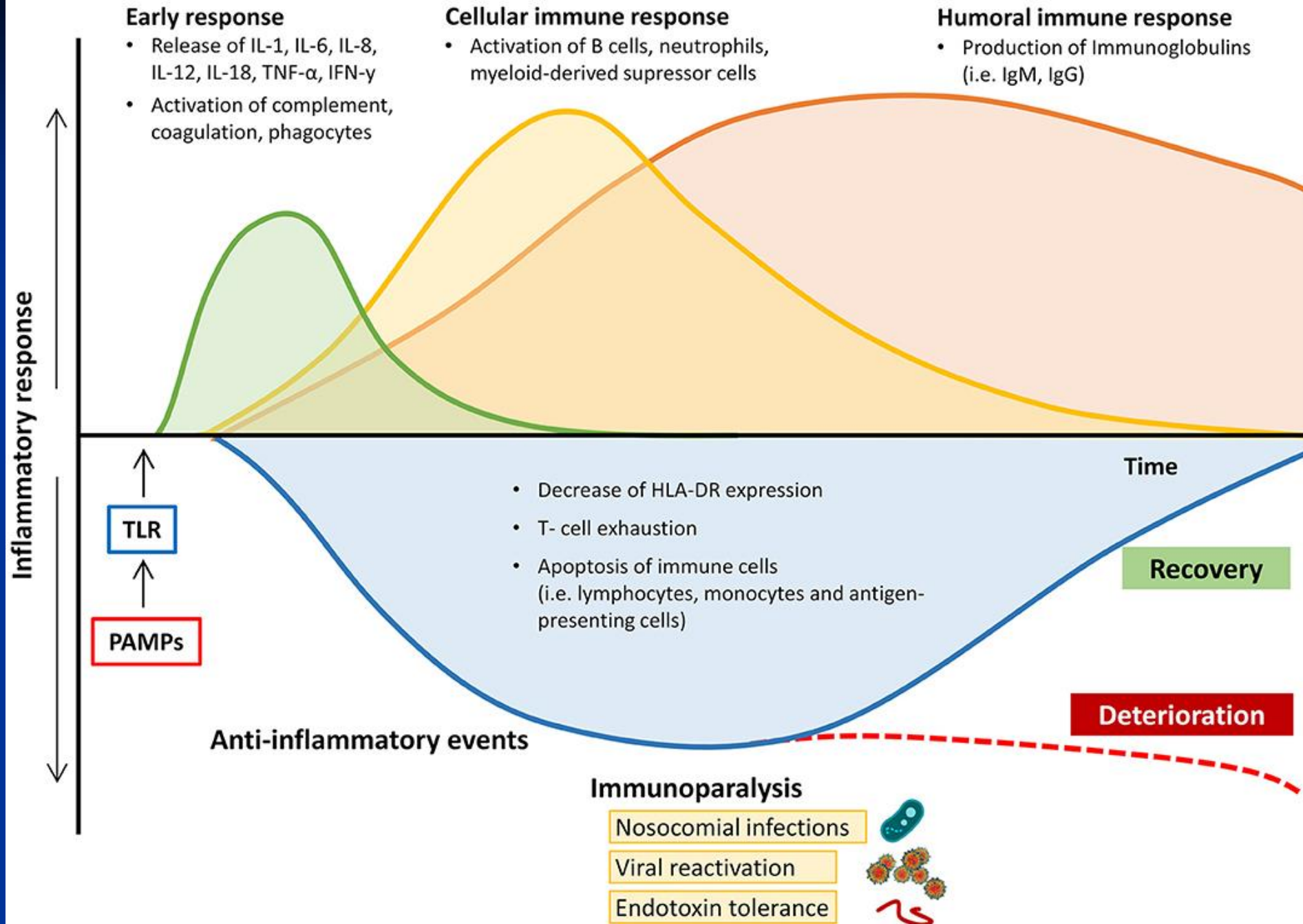
Skin and soft tissue: cellulitis ,
trauma, catheters

Pathogenesis of Severe Sepsis



Innate immune system

Adaptive immune system



Clinical Presentation

- Symptoms and signs specific to an infectious source (eg, cough and dyspnea may suggest pneumonia, pain and purulent exudate in a surgical wound may suggest an underlying abscess).

Symptoms

Nonspecific Symptoms include :

- Sweat chills or rigors,
- Breathlessness
- Nausea and vomiting
- Diarrhea
- Headache
- Confusion

Attention

The index of suspicion for sepsis must be high (especially in older patients) when any of the following nonspecific clinical signs or symptoms of infection are present: delirium, weakness, anorexia, malaise, urinary incontinence, or falls.

Clinical signs

- Fever temperature $>(38.3^{\circ}\text{ C})$ or Hypothermia temperature $< (36^{\circ}\text{ C})$
- Heart rate >90 beats/min
- Hypotension SBP <90 mmHg, or MAP <70 mmHg, SBP fall of >40 mmHg from baseline
- Prolonged capillary refill time or tissue mottling – indicates poor tissue perfusion
- Altered mental state from baseline
- Decreased urine output (< 0.5 mL/kg/hour)
- Cold clammy skin

Mottled skin



■ Tachypnea

- Without hypoxia - consider compensatory respiratory alkalosis for metabolic acidosis (lactic acidosis)
- With hypoxia - consider pneumonia with acute lung injury/acute respiratory distress syndrome (ALI/ARDS) or pulmonary edema or pulmonary embolism



Fig. 44.10 Cutaneous changes in toxic shock. (a) Localized infection at the edge of a patch of eczema in a patient presenting with staphylococcal toxic shock syndrome. (b) Desquamation of the palm following an episode of staphylococcal toxic shock. Courtesy of Dr M Jacobs.

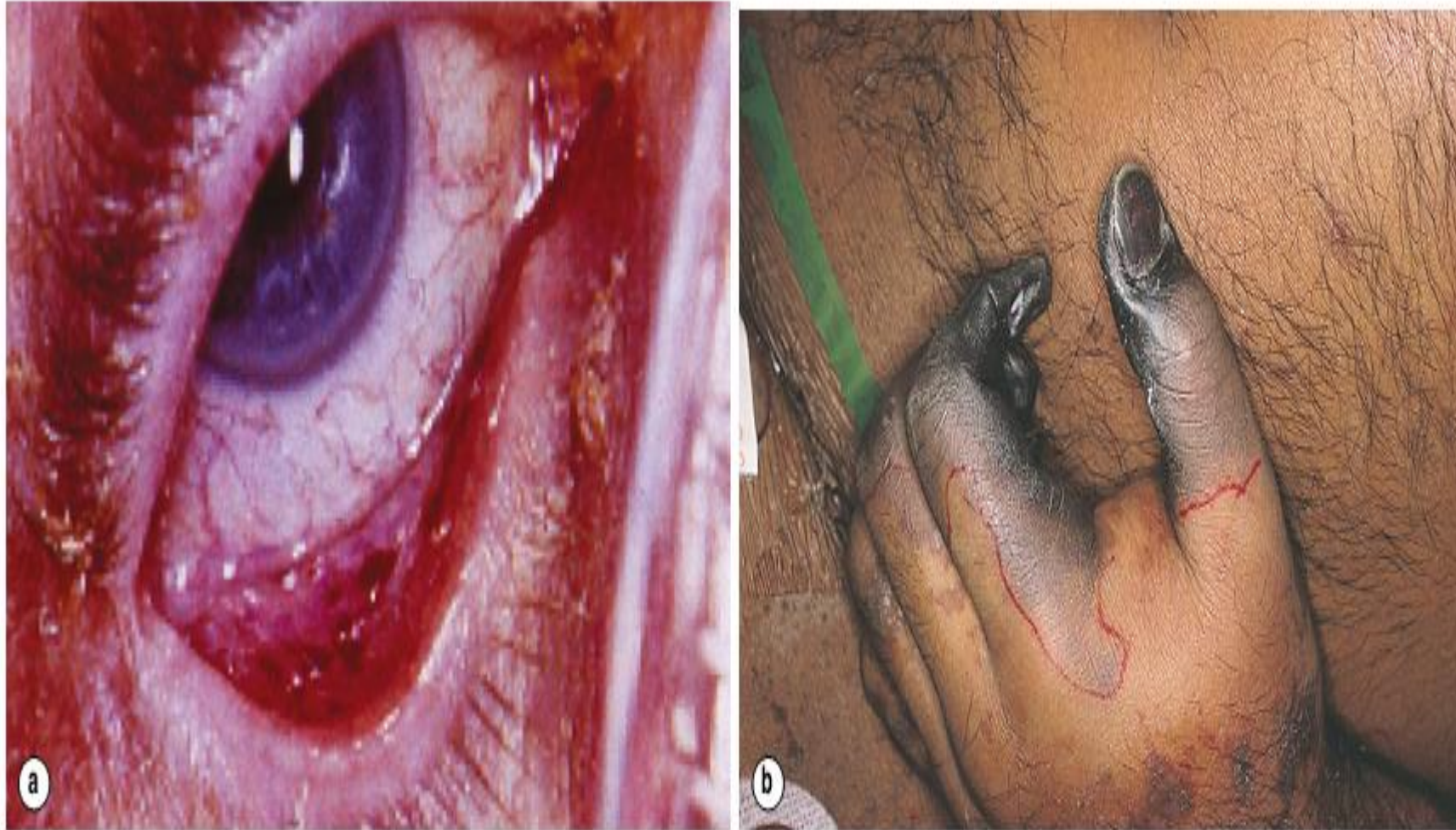


Fig. 44.9 Cutaneous changes in meningococcal infection. (a) Petechial hemorrhages are the hallmark of meningococcal infection and may be found on the periphery or, as in this case, the conjunctivae. (b) In severe disease the purpura may become confluent (purpura fulminans) and lead to severe digital gangrene. Courtesy of J Cohen, Brighton.

ذات مومنت لما تحلف قسم الاطباء



ايه اول حاجة فكرت فيها بعد ما حلفت القسم ???



اصوم ٣ ايام

ديناصور الطب المتقرض

Laboratory

1. Lactate (this test is collected on ice)
2. Chem (Bl.sugar ,KFT, LFT, electrolytes)
3. Bilirubin
4. CBC
5. PT/INR, PTT
6. Blood Cultures x 2
7. ABG
8. ECG
9. Portable CXR
10. UA/Urine Culture
11. CK, CKMB, Troponin – I

NOVEL TESTS

Various biologic markers of sepsis have been studied, for example, procalcitonin and Mid-regional pro-Adrenomedullin (MR-proADM), but none of them has been validated for routine clinical use.

Suspected site	Symptoms/signs	Initial microbiologic evaluation
Upper respiratory tract	Pharyngeal inflammation plus exudate ± swelling and lymphadenopathy	Throat swab for aerobic culture
Lower respiratory tract	Productive cough, pleuritic chest pain, consolidative auscultatory findings	Sputum of good quality, rapid influenza testing, urinary antigen testing (eg, pneumococcus, legionella; not recommended in children), quantitative culture of protected brush or bronchoalveolar lavage
Urinary tract	Urgency, dysuria, loin, or back pain	Urine culture and microscopy showing pyuria
Vascular catheters: arterial, central venous	Redness or drainage at insertion site	Culture of blood (from the catheter and a peripheral site), culture catheter tip (if removed)
Indwelling pleural catheter	Redness or drainage at insertion site	Culture of pleural fluid (through catheter)
Wound or burn	Inflammation, edema, erythema, discharge of pus	Gram stain and culture of draining pus, wound culture not reliable
Skin/soft tissue	Erythema, edema, lymphangitis	Culture blister fluid or draining pus; role of tissue aspirates not proven

Central nervous system	Signs of meningeal irritation	CSF cell count, protein, glucose, Gram stain, and culture ^Δ
GI	Abdominal pain, distension, diarrhea, and vomiting	Stool culture for Salmonella, Shigella, or Campylobacter; detection of Clostridium difficile toxin
Intra-abdominal	Specific abdominal symptoms/signs	Aerobic and anaerobic culture of percutaneously or surgically drained abdominal fluid collections
Peritoneal catheter	Cloudy PD fluid, abdominal pain	Cell count and culture of PD fluid
Genital tract	Women: Low abdominal pain, vaginal discharge Men: Dysuria, frequency, urgency, urge incontinence, cloudy urine, prostatic tenderness	Women: Endocervical and high vaginal swabs onto selective media Men: Urine Gram stain and culture
Bone	Pain, warmth, swelling, decreased use	Blood cultures, MRI, bone cultures at surgery or by interventional radiology
Joint	Pain, warmth, swelling, decreased range of motion	Arthrocentesis with cell counts, Gram stain, and culture

Prognosis

- Sepsis has a high mortality rate which is estimated from **10 to 52 percent**
- In another study, the mortality associated with **sepsis was $\geq 10\%$** while that associated with **septic shock was $\geq 40\%$**
- During hospital admission, sepsis may increase the risk of acquiring a subsequent hospital-related infection.(**13.5 % admissions of patients with sepsis reported icu irelated infection**)

Long-term prognosis

- Increased risk of death (up to 20 %) within 6 m after discharge
- Increased risk of further sepsis and recurrent hospital admissions (up to 10 % are readmitted).
- Patients who survive sepsis are more likely to be admitted to acute care and/or long term care facilities in the first year
- Have a persistent decrement in their quality of life

Clinical Phenotypes

- An **alpha** phenotype (pt. on lowest dose of a vasopressor) had the lowest mortality at 5 %
- The **beta** phenotype (older pt. with chronic illnesses and renal dysfunction) had a mortality of 13 %
- The **gamma** phenotype (pt. with pulmonary dysfunction) had a mortality of 24 %
- The **Delta** phenotype (pt. with liver dysfunction and septic shock) had the highest mortality at 40 %.

Bad Prognostic Factors

- Specific Phenotype
- Hypothermia, Leukopenia, Thrombocytopenia
- Persistent Elevation Of Procalcitonin
- Site of infection
- Antimicrobial therapy
- Hyperchloremia
- Comorbidities: new-onset AF, AIDS, cancer, Liver Dis.
- Type of infection : **MDROs OR NOT**
- Age : age above 40 years
- Hyperglycemia
- Hypocoagulability: a 6 fold  in the risk of death

Noninfectious mimics of sepsis

1. Acute myocardial infarction
2. Acute pulmonary embolus
3. Acute pancreatitis
4. Fat emboli syndrome
5. Acute adrenal insufficiency
6. Acute gastrointestinal hemorrhage
7. Overzealous diuresis
8. Transfusion reactions
9. Adverse drug reactions
10. Procedure-related transient bacteremia
11. Amniotic fluid embolism

Management of Sepsis

- Recognition
 - Resuscitation (A B C)
 - Source control And Antibiotics
 - Corticosteroids
 - Glucose Control
 - Transfusion Strategies
 - Mechanical Ventilation in Sepsis
 - Miscellaneous Issues
-

Mortality Reduction?

- Early recognition of sepsis
- Timely hemodynamic monitoring
- Aggressive Volume Repletion
- Prompt cultures and antibiotics
- Preventing Hospital Complications



25% reduction in mortality

Heamodynamic Goals

- Central venous pressure: 8 – 12 mmHg
 - Mean arterial pressure: ≥ 65 mmHg
 - Urine output: 0.5 mL/kg/h
 - Central venous (SVC) or mixed venous oxygen saturation: $\geq 70\%$
-

Early Goal Directed Therapy

- ❑ Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock.
- ❑ New England Journal of Medicine. 2001;345:1368–1377.

Early Goal Directed Therapy (cont.)

■ EGD^T

- Lactate >4 or SBP <90
- CVP monitor
- 500ml NS Q30min until CVP >8
- If MAP <65 - pressors
- If SCvO₂ <70
 - Tranfused to Hct 30
 - Dobutamine to get SCvO₂ to 70

■ 263 Patients in ED

- 133 Standard Care, 130 EGD^T
- Mortality 46.5% vs 30.5% (p=0.009)

Stabilize Respiration

- Supplemental O₂ should be supplied to all patients with sepsis, who have indications for oxygenation, and oxygenation should be monitored continuously with pulse oximetry. Ideal target values for O₂ sat. are unknown but we typically target values between 90 and 96 %.
- Intubation and MV may be required to support the **increased work of breathing** that typically accompanies sepsis, or for **airway protection** since encephalopathy and a depressed level of consciousness frequently complicate sepsis.

Assess perfusion

- Hypotension is the most common indicator that perfusion is inadequate.
- An arterial catheter may be inserted
- Critical hypoperfusion can also occur in the absence of hypotension

Assess perfusion

Most patients need at least 4 to 6 L of IV replacement within the first 6 hours,

Whether to use crystalloid or colloid is controversial, with normal saline being the fluid of choice in most patients. (SAFE) trial, 6997

critically ill patients

Fluid therapy should be administered in well-defined (eg, 500 mL), rapidly infused boluses

□ Volume status, tissue perfusion, blood pressure, and the presence or absence of pulmonary edema must be assessed before and after each bolus.

Sepsis campaign 2012

1-Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).

2-. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).

3. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids. (grade 1C).

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Vasopressors

- Norepinephrine is standard first-line pressor for central administration (SCCM Strong recommend.),
- Consider addition of vasopressin (up to 0.03 units/minute) if norepinephrine requirement is rising (SCCM Weak recommendation)
- Epinephrine may also be added to vasopressin to raise MAP (SCCM Weak recommendation)
- Consider dobutamine for ongoing hypoperfusion despite adequate intravascular volume repletion and vasopressor use but reduce or discontinue in case of worsening hypotension or arrhythmia

Sepsis campaign 2012

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).

Corticosteroids

- Corticosteroids suggested if septic shock unresponsive to fluid resuscitation and moderate-to-high dose vasopressors (SCCM/ESICM Conditional recommendation, Low quality of evidence)
- Low dose (such as hydrocortisone 400 mg/day IV) and long course(> 3 days) suggested over high dose and short course(< 3 days)

Additional therapies

■ Red blood cell transfusions

Transfusion is indicated if hemoglobin (Hgb) < 7 g/dL (assuming absence of myocardial ischemia, severe hypoxemia, acute hemorrhage, or ischemic heart disease) (SCCM Strong recommendation, High-quality evidence)

- Glucose control with insulin drip to keep serum glucose ≤ 180 mg/dL (10 mmol/L) and ≥ 110 mg/dL (6.1 mmol/L) (SCCM Strong recommendation, High-quality evidence)
- For intubated patients, minimize sedation (SCCM Best practice statement) and use weaning protocol (SCCM Strong recommendation, Moderate-quality evidence)

- Renal replacement therapy with intermittent hemodialysis or continuous venovenous hemofiltration (latter may be easier to manage in hemodynamically unstable patients) may be needed in patients with acute kidney injury (SCCM Weak recommendation, Moderate-quality evidence)
- Deep vein thrombosis (DVT) prophylaxis is recommended (SCCM Strong recommendation, Moderate-quality evidence)

- Stress ulcer prophylaxis with histamine-2 receptor antagonist or proton pump inhibitor recommended for patients with risk factors for gastrointestinal bleeding (SCCM Strong recommendation, Low-quality evidence)
- Nutrition - initiate enteral nutrition early in patients who can be fed enterally (SCCM Strong recommendation, Moderate-quality evidence)

Ongoing management

Two possible outcomes:

- Despite aggressive therapy, the patient may have persistent hypoperfusion and progressive organ failure. → **Reassess therapy, control of the septic focus, the accuracy of the diagnosis and the possibility that unexpected complications**
- The patient may have responded to the above interventions with restored perfusion and a ScvO₂ greater than 70 percent → **continue to have their clinical and laboratory parameters followed closely**

Monitoring

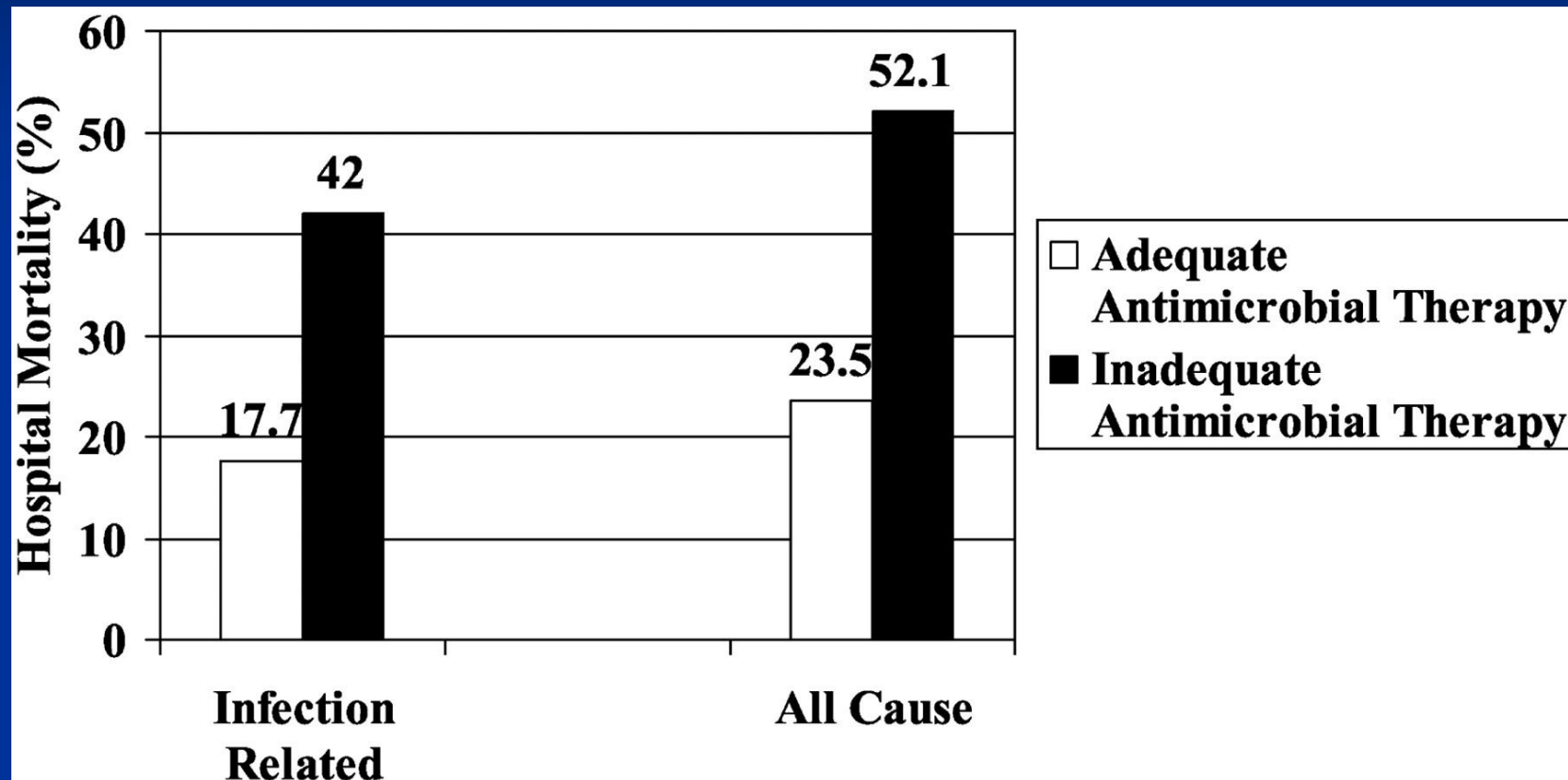
- All patients should be followed clinically for:
 1. Mean arterial pressure (MAP)(≥ 65 mmhg)
 2. Urine output (more than 0.5 ml/kg/h)
 3. Heart rate
 4. Respiratory rate
 5. Skin color
 6. Temperature
 7. Pulse oximetry O₂ sat more than 90%
 8. Mental status.

Identification of the septic focus

Choosing antibiotics in sepsis

- There is no, single, “best” regimen
 - Consider the site of the infection
 - Consider which organisms most often cause infection at that site
 - Choose antibiotic(s) with the appropriate spectrum
 - After obtaining cultures, give antibiotics **quickly** and empirically at appropriate dose
-

Adequate *initial* antibiotic therapy reduces mortality



Kollef et al, Chest 1999 115:462

TIME

A retrospective analysis of 2731 patients with septic shock demonstrated that the time to initiation of appropriate antimicrobial therapy **was the strongest predictor of mortality**

Empirical therapy

Combining **vancomycin** with one of the following:

Cephalosporin, 3rd or 4th generation (eg, ceftriaxone or cefotaxime), or

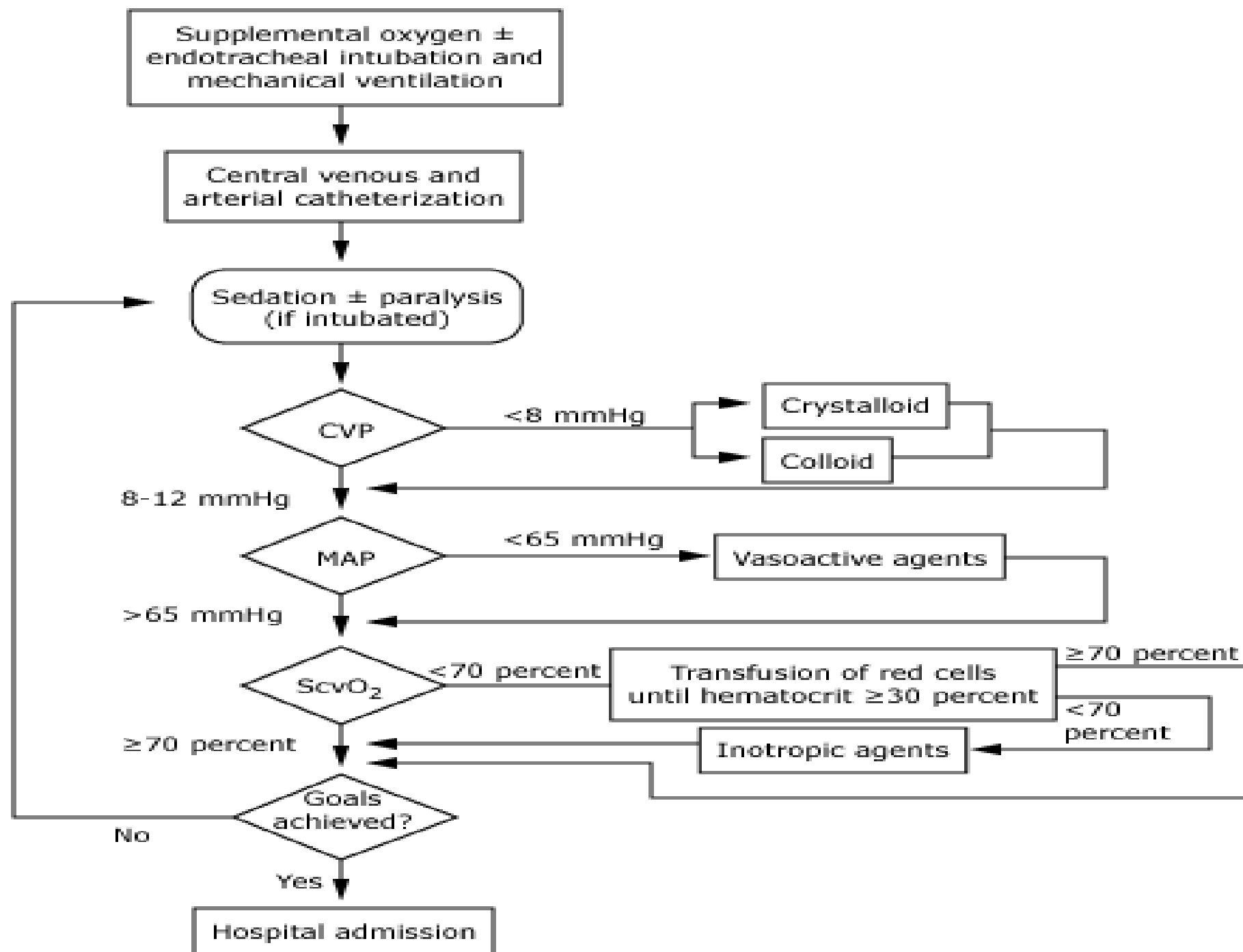
Beta-lactam/beta-lactamase inhibitor (eg, piperacillin-tazobactam, ticarcillin-clavulanate), or

Carbapenem (eg, imipenem or meropenem).

If Pseudomonas suspected

combine **vancomycin** with two of the following :

- 1-**Antipseudomonal cephalosporin** (eg, ceftazidime,) or
- 2-**Antipseudomonal carbapenem** (eg, imipenem, meropenem), or
- 3-**Antipseudomonal beta-lactam/beta-lactamase inhibitor** (eg, piperacillin-tazobactam, ticarcillin-clavulanate), or
- 4-**Fluoroquinolone** with good anti-pseudomonal activity (eg, ciprofloxacin), or
- 5-**Aminoglycoside** (eg, gentamicin, amikacin), or
- 6-**Monobactam** (eg, aztreonam)



SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:

- 1) Measure lactate level
- 2) Obtain blood cultures prior to administration of antibiotics
- 3) Administer broad spectrum antibiotics
- 4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥ 4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:

- 5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
- 6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥ 4 mmol/L (36 mg/dL):
 - Measure central venous pressure (CVP)*
 - Measure central venous oxygen saturation (ScvO₂)*
- 7) Remeasure lactate if initial lactate was elevated*

Thank you