

# ***Sepsis treatment***

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متخصص بیماریهای عفونی و تب  
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**TABLE 73.1 Sepsis Definitions**

TERM	DEFINITION
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**1991 Consensus Conference<sup>1</sup>**

SIRS

At least two of the following:

- Temperature  $>38^{\circ}\text{C}$  or  $<36^{\circ}\text{C}$
- Heart rate  $>90$  beats/min
- Respiratory rate  $>20$  breaths/min or arterial  $\text{CO}_2$   $<32$  mm Hg
- White blood cell count  $>12 \times 10^9/\text{L}$  or  $<4 \times 10^9/\text{L}$  or  $>10\%$  immature forms

Sepsis

Infection<sup>a</sup> + SIRS

Severe sepsis

Sepsis + acute organ dysfunction

Septic shock

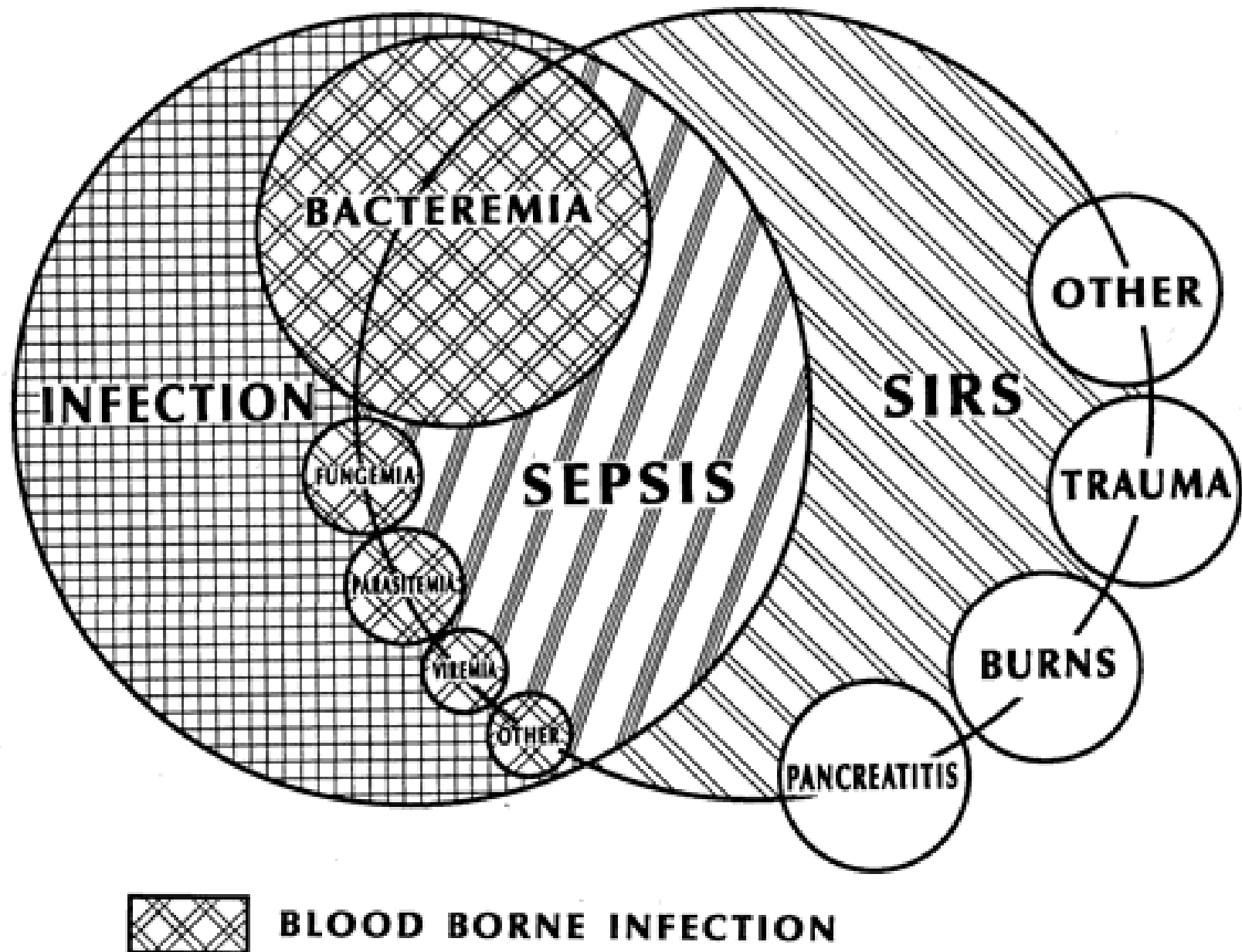
Sepsis + persistent hypotension after fluid resuscitation

**2001 International Sepsis Definitions Conference<sup>2</sup>**

No significant changes from 1991 definitions, with the addition that signs and symptoms of sepsis are more varied than captured by 1991 definitions; this resulted in the presentation of a list of these signs and symptoms for the diagnosis of sepsis

Mandell

# sepsis definitions



# Mandell sepsis definitions

## 2015 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)<sup>3</sup>

### Sepsis<sup>b</sup>

- Life-threatening organ dysfunction caused by dysregulated host response to infection
- Organ dysfunction can be identified as acute change in total SOFA score  $\geq 2$  points

### Septic shock

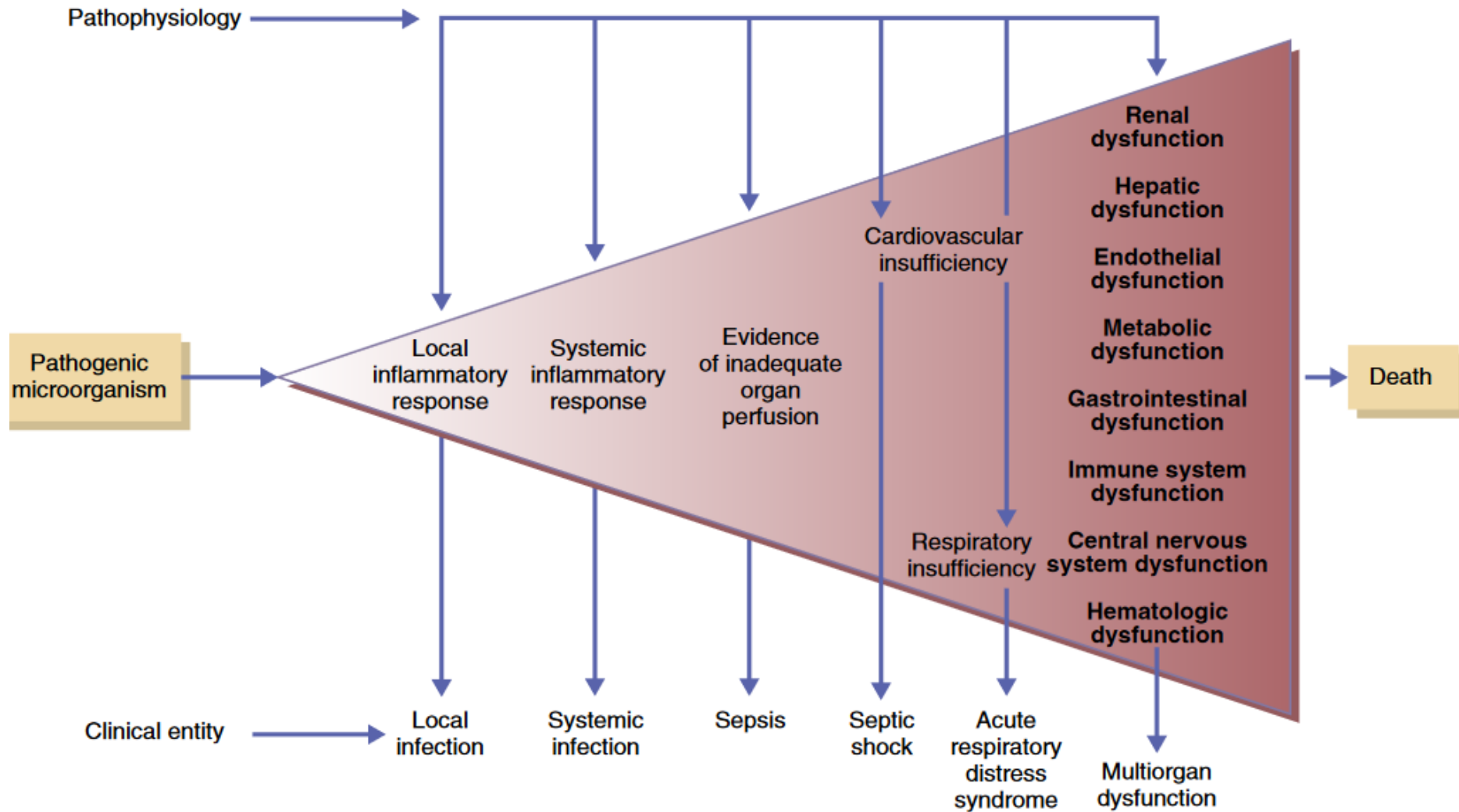
- Sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
- Clinically defined as sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure  $\geq 65$  mm Hg and with serum lactate  $> 2$  mmol/L

<sup>a</sup>Suspected or proven.

<sup>b</sup>In the new sepsis definition, the presence of organ dysfunction is central and a requirement; previously, organ dysfunction identified “severe” sepsis, a term that was abandoned in the Sepsis-3 definition.

CO<sub>2</sub>, Carbon dioxide; SIRS, systemic inflammatory response syndrome; SOFA, Sequential [Sepsis-related] Organ Failure Assessment.

# sepsis definitions Pathophysiology



**Fig. 91.1** The spectrum of illness and nomenclature for sepsis pathophysiology.

# Mandell sepsis definitions

**TABLE 73.2 SOFA Score**

ORGAN SYSTEM	SCORE
Respiration	
Pao <sub>2</sub> /Fio <sub>2</sub> , mm Hg (kPa)	
<400 (53.3)	1
<300 (40)	2
<200 (26.7) with respiratory support	3
<100 (13.3) with respiratory support	4
Central nervous system	
GCS score	
13–14	1
10–12	2
6–9	3
<6	4
Cardiovascular	
MAP or use vasopressors (μg/kg/min)	
MAP <70 mm Hg	1
Dopamine <5 or dobutamine (any dose) <sup>a</sup>	2
Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1	3
Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1	4

# Mandell sepsis definitions

## Liver

Bilirubin, mg/dL ( $\mu\text{mol/L}$ )

1.2–1.9 (20–32) 1

2.0–5.9 (33–101) 2

6.0–11.9 (102–204) 3

>12.0 (204) 4

## Coagulation

Platelets,  $\times 10^3/\mu\text{L}$

<150 1

<100 2

<50 3

<20 4

## Renal

Creatinine, mg/dL ( $\mu\text{mol/L}$ ) or urine output, mL/day

1.2–1.9 (110–170) 1

2.0–3.4 (171–299) 2

3.5–4.9 (300–440) or <500 3

>5.0 (440) or <200 4

$F_{\text{IO}_2}$ , Fraction of inspired oxygen; GCS, Glasgow Coma Scale (scores range from 3 to 15; higher score indicates better neurologic function);  $\text{MAP}$ , mean arterial pressure;  $\text{PaO}_2$ , partial pressure of oxygen; SOFA, Sequential [Sepsis-related] Organ Failure Assessment.

The SOFA score can be used to measure the severity of organ dysfunction. The aggregate score is calculated by summing the worst scores for each of the organ systems.

<sup>a</sup>Catecholamine doses are given as  $\mu\text{g/kg/min}$  for at least 1 hour.

From Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996;22:707–710.

# sepsis definitions

**TABLE 91.1 Diagnostic Criteria for Sepsis<sup>a</sup>**

## General Criteria

Life-threatening organ dysfunction caused by a dysregulated response to infection

## Organ Dysfunction Criteria

Change in Sequential (Sepsis-related) Organ Failure Assessment (SOFA)<sup>b</sup> score of  $\geq 2$  points. It can be used to measure the severity of organ dysfunction.

## SOFA Scoring (Range 0–4 Per Category, 0–24 Total Score Range)

Criterion	0	1	2	3	4
Respiration; $P_{aO_2}/F_{iO_2}$ (torr)	$>400$	$\leq 400$	$\leq 300$	$\leq 200$ with respiratory support	$\leq 100$ with respiratory support
Platelets ( $\times 10^3/\text{mm}^3$ )	$>150$	$\leq 150$	$\leq 100$	$\leq 50$	$\leq 20$
Bilirubin (mg/dL)	$<1.2$	1.2–1.9	2.0–5.9	6.0–11.9	$>12.0$
Glasgow Coma Scale	15	13–14	10–12	6–9	$<6$
Hypotension <sup>c</sup>	None	MAP $<70$ mm Hg	Dopamine $\leq 5$ or dobutamine (or any dose of vasopressin)	Dopamine $>5$ or epi $\leq 0.1$ or norepi $\leq 0.1$ (or phenylephrine 100–300 mcg bolus)	Dopamine $>15$ or epi $>0.1$ or norepi $>0.1$ (or phenylephrine $>300$ mcg bolus)
Creatinine (mg/dL) or urine output (mL/day)	$<1.2$	1.2–1.9	2.0–3.4	3.5–4.9 $<500$ mL/day	$>5.0$ $<200$ mL/day

## Septic Shock Criteria

Vasopressor requirement to maintain a mean arterial pressure of 65 mm Hg or greater, AND

Hyperlactatemia (serum lactate  $>2$  mmol/L [ $>18$  mg/dL])

From Singer M, Deutschman CS, Seymour CW, et al: The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), JAMA 315(8):801-10, 2016.

$F_{iO_2}$ , Fraction of inspired oxygen;  $INR$ , international normalized ratio;  $MAP$ , mean arterial pressure;  $P_{aO_2}$ , partial pressure of oxygen.

<sup>a</sup>The criteria include documented or suspected infection and some of the variables listed.

<sup>b</sup>Assuming baseline SOFA of 0 in most cases.

<sup>c</sup>Adrenergic agents must be administered for at least 1 hour to count; doses are in mcg/kg/min.



# Mandell sepsis definitions

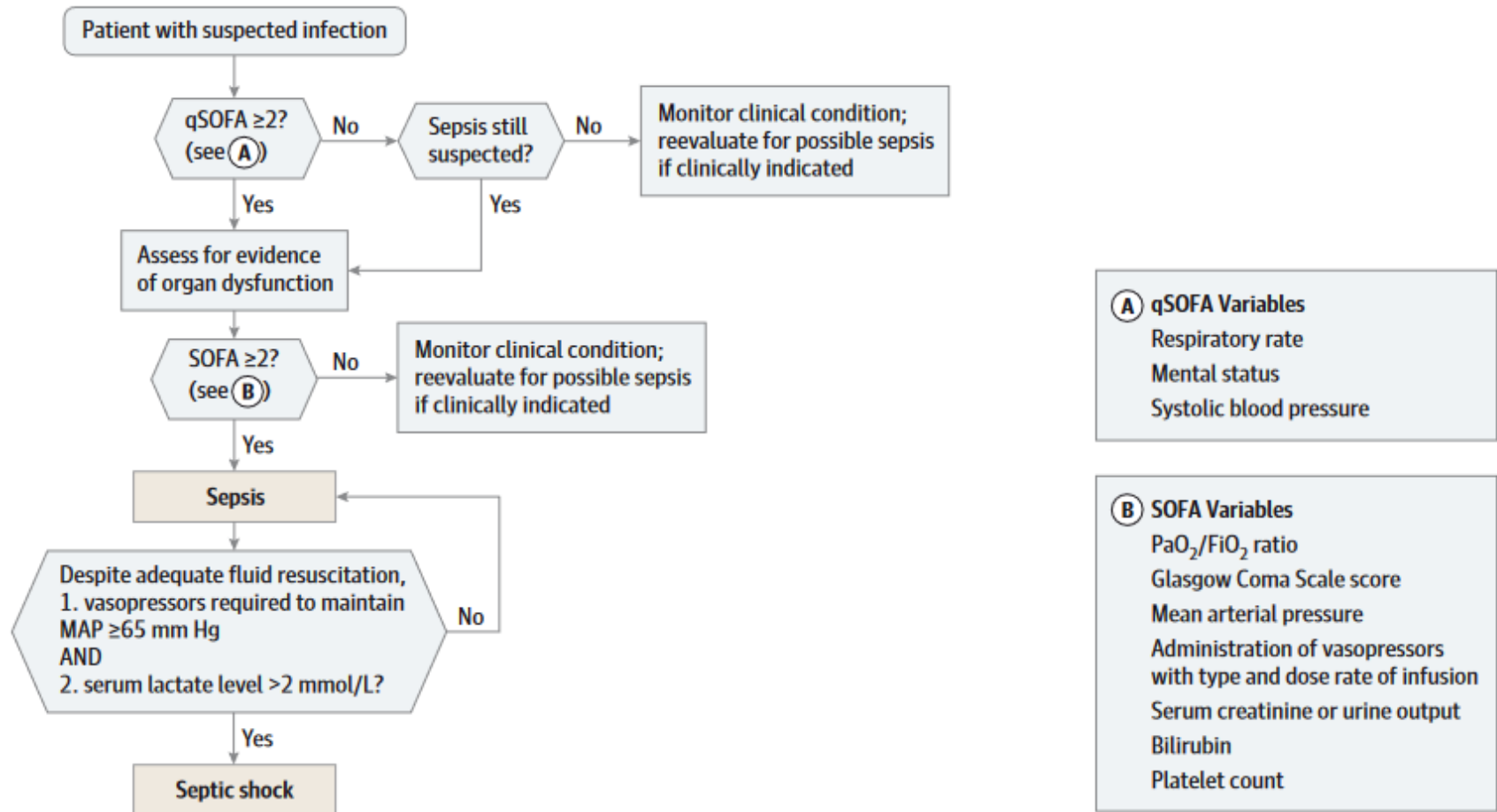
## Box 1 The 'quickSOFA' (qSOFA) score

Patients outside the ICU are at risk of sepsis development if two or more of the following are abnormal:

- ▶ Elevated respiratory rate  $\geq 22$  breaths per minute
- ▶ Altered mental status (Glasgow Coma Scale score  $< 15$ )
- ▶ Systolic blood pressure of 100 mm Hg or less

# Mandell sepsis definitions

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

**TABLE 73.3 Risk Factors for Sepsis**

## Demographic Factors

- Older age (>65 years old) ● افزایش سن جمعیت
- Male sex ●
- Black race ● افزایش طول عمر بیماران با بیماریهای مزمن
- Nutrition ●
- Vaccination status ● افزایش بروز در بیماران ایدزی
- Genetic polymorphisms ● استفاده از داروهای آنتی میکروبیال

## Environmental Factors

- Poor socioeconomic status ● داروهای ایمونوساپرسیو
- Seasonal variation and contacts ● کاتتر ها و وسایل مکانیکی
- Disease outbreaks ●
- Travel ●

## Comorbidities

- Diabetes
- Chronic obstructive pulmonary disease
- Cancer
- Chronic renal disease
- Chronic liver disease
- Human immunodeficiency virus
- Use of immunosuppressive agents

## Hospital Factors

- Duration of hospitalization
- Antibiotic resistance
- Catheters (e.g., urine catheters, intravenous lines)
- Complications of surgery (wound infection, emergency vs. elective surgery)

# Severe Sepsis: Pathophysiology

***Endothelial Dysfunction and  
Microvascular Thrombosis***



***Hypoperfusion/Ischemia***



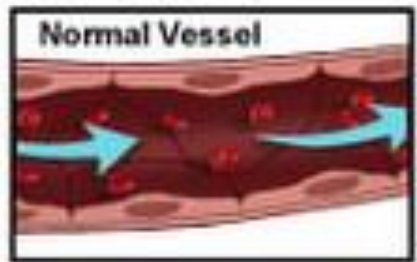
***Acute Organ Dysfunction  
(Severe Sepsis)***



***Death***

# Pathophysiology

## Effects of Sepsis



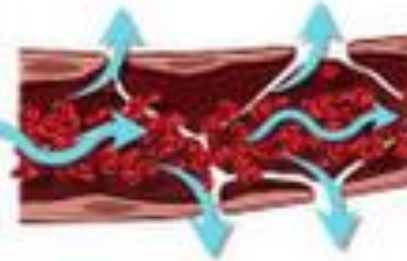
①

Bacteria enter blood and trigger complex immunologic reactions

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②

Vasodilation occurs, and fluid leaks from blood vessels into surrounding tissues



③

Leaking vessels impair the body's ability to pump blood, (containing vital nutrients) to surrounding tissues and organs.

Decreased blood flow to organs results in poor nutrient exchange and tissue swelling

④

**SHOCK**

**MULTI-SYSTEM ORGAN FAILURE**

**Respiratory failure**



Alveoli collapse and fill with fluid

**Osteomyelitis**



Infection in bone causes deterioration

**Brain damage**

Brain swells and is deprived of oxygen



Kidneys shut down

**Kidney failure**



# microbiology

Microorganism	Episodes with Bloodstream Infection, % (n = 436)	Episodes Documented but not Bloodstream Infection, % (n = 430)	Total Episodes, % (n = 866)
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Gram-negative bacteria <sup>a</sup>	35	44	40
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Gram-positive bacteria <sup>b</sup>	40	24	31
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Fungi	7	5	6
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Polymicrobial	11	21	16
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Classic pathogens <sup>c</sup>	5	5	5
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## Sources of sepsis

- Respirator 38%
- Urinary tract 21%
- Intra-abdominal 16.5%
- CRBS 2.3%
- Device 1.3%
- CNS 0.8%
- Others 11.3%



# Mandell sepsis microbiology

**TABLE 73.4 Distribution in Percentages of Identified Organisms in Culture-Positive Infected Patients Included in the EPIC II Study According to Geographic Region**

ORGANISM	WESTERN EUROPE	EASTERN EUROPE	CENTRAL/SOUTH AMERICA	NORTH AMERICA	OCEANIA	AFRICA	ASIA
<b>Gram-Positive</b>							
<i>Staphylococcus aureus</i>	20%	22%	19%	27%	28%	30%	16%
<i>Staphylococcus epidermidis</i>	11%	12%	9%	12%	8%	15%	9%
<i>Streptococcus pneumoniae</i>	5%	5%	3%	4%	3%	6%	2%
<i>Enterococcus</i> spp.	13%	15%	4%	10%	9%	0%	6%
Other	7%	4%	4%	11%	9%	7%	4%
<b>Gram-Negative</b>							
<i>Escherichia coli</i>	17%	15%	14%	14%	13%	11%	17%
<i>Enterobacter</i>	7%	8%	9%	8%	3%	7%	5%
<i>Klebsiella</i> spp.	10%	21%	16%	9%	12%	19%	21%
<i>Pseudomonas</i> spp.	17%	29%	26%	13%	15%	15%	30%
<i>Acinetobacter</i> spp.	6%	17%	14%	4%	4%	15%	19%
Other	18%	15%	17%	11%	21%	20%	15%
Anaerobes	5%	3%	1%	8%	3%	2%	3%
<b>Fungi</b>							
<i>Candida</i>	19%	19%	13%	19%	13%	11%	16%
<i>Aspergillus</i>	2%	1%	1%	3%	2%	0%	1%

Parasites accounted for 1% or fewer of all isolates in all regions. Percentages do not necessarily equal 100 because patients may have had more than one type of infection or microorganism.

Data from Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA. 2009;302:2323–2329.

# sepsis microbiology

**TABLE 91.2 Microorganisms Commonly Identified in Septic Patients Based on Host Factors**

Host Factor	Organisms to Consider
Asplenia	Encapsulated organisms, particularly <i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria meningitidis</i> , <i>Capnocytophaga canimorsus</i>
Cirrhosis	<i>Vibrio</i> , <i>Salmonella</i> , and <i>Yersinia</i> species; encapsulated organisms, other gram-negative rods
Alcohol abuse	<i>Klebsiella</i> species, <i>S. pneumoniae</i>
Diabetes	<i>Mucormycosis</i> , <i>Pseudomonas</i> species, <i>Escherichia coli</i> , group B streptococci
Neutropenia	Enteric gram-negative rods, <i>Pseudomonas</i> , <i>Aspergillus</i> , <i>Candida</i> , <i>Mucor</i> species, <i>Staphylococcus aureus</i> , streptococcal species
T-cell dysfunction	<i>Listeria</i> , <i>Salmonella</i> , and <i>Mycobacterium</i> species, herpesviruses (including herpes simplex, cytomegalovirus, varicella-zoster virus)
Acquired immunodeficiency syndrome	<i>Salmonella</i> species, <i>S. aureus</i> , <i>Mycobacterium avium</i> complex, <i>S. pneumoniae</i> , group B streptococci



# Diagnosis

- Basic

- ✦ WBC
- ✦ Platelets
- ✦ Coags
- ✦ Renal function
- ✦ Glucose
- ✦ Albumin
- ✦ LFT
- ✦ ABG

- لکوسیتوز با شیفٹ
- به چپ
- ترومبوسیتوپنی
- افزایش بیلی روبین
- پروتئین در ادرار
- لکوپنی
- آزوتمی

- Specific ?Source

- ✦ Urine
- ✦ CxR
- ✦ Blood Cultures
- ✦ Biopsy

## ACUTE FEVER WITH LOCALIZING SIGNS ON EXAMINATION AND WITH NEUTROPHIL LEUKOCYTOSIS

Signs and symptoms	Disease	Investigations
Dyspnoea, cough, pleuritic pain, discoloured sputum	Bacterial pneumonia	Chest X-ray, sputum culture
Severe sore throat	Streptococcal tonsillitis, diphtheria	Throat culture
Frequency, dysuria, loin pain	Pyelonephritis, UTI	US, urine culture
Headache, neck stiffness	Bacterial meningitis	LP, culture, latex agglut.
Ear secretion, headache	Otitis	Ear culture
Bloody diarrhea	Bacillary dysentery	Stool culture
Pain & swelling at a joint	Septic arthritis	Joint aspiration, NMR
Bone pain (worse at night)	osteomyelitis	X-ray, CT, NMR
Local lymphadenopathy general. lymphadenopathy	Plague, abscess, tularemia	Culture, serology
Cutaneous inflammation	erysipelas, cellulitis	Culture, ASLO

# Treatment of Sepsis

**Table 3.** Summary of Emergency Physician's perspectives reported in this manuscript.

Pillars of Treatment	Emergency Physician's Perspectives
<b>Antimicrobials</b>	<ul style="list-style-type: none"> <li>- Culture samples are required before administration of antimicrobials;</li> <li>- Treatments should be based on clinical/epidemiological criteria and promptly started;</li> <li>- Frequent re-assessments of patients' condition and PCT levels are advisable for an adequate reduction strategy;</li> <li>- Short courses of antimicrobial treatments may be indicated.</li> </ul>
<b>Fluids</b>	<ul style="list-style-type: none"> <li>- Balanced crystalloids are the fluid of choice;</li> <li>- Individualized resuscitation strategies based on FT and FR are preferable;</li> <li>- Approaches based on small and repeated boluses (250–500 mL) of crystalloids with continuous hemodynamic monitoring are advised.</li> </ul>
<b>Vasoactive Agents</b>	<ul style="list-style-type: none"> <li>- Vasopressors are required if a patient's MAP is &lt;65 mmHg despite fluid replacement;</li> <li>- NE at a dose of 0.1–1.2 µg/kg/min is the drug of choice for septic patients;</li> <li>- Early administration of NE could prevent fluid overload, thereby reducing mortality;</li> <li>- VP at a dose of 0.25–0.5 µg/kg/min may be combined with NE if target MAP is not achieved.</li> </ul>
<b>Oxygenation and Ventilation Support</b>	<ul style="list-style-type: none"> <li>- Oxygenation should be started at 15 L/min via a reservoir mask;</li> <li>- The target values for titration should be SpO<sub>2</sub> 94–98% or SpO<sub>2</sub> 88–92% if the patient is at risk of hypercapnic respiratory failure;</li> <li>- If NIV/MV is needed, a low tidal volume (6 mL/kg) is advisable;</li> <li>- HFNC may be used in septic patients with hypoxic respiratory failure.</li> </ul>
<b>Other Treatments</b>	<ol style="list-style-type: none"> <li>(1) Heparin               <ul style="list-style-type: none"> <li>- LMWH rather than UFH should be used to prevent VTE;</li> <li>- Mechanical prophylaxis is advised for patients unsuitable for heparin treatment.</li> </ul> </li> <li>(2) Insulin               <ul style="list-style-type: none"> <li>- The use of insulin is advisable to achieve a glucose target between 144–180 mg/dL.</li> </ul> </li> <li>(3) Proton Pump Inhibitors               <ul style="list-style-type: none"> <li>- PPI treatment may be necessary to prevent stress ulcers.</li> </ul> </li> <li>(4) Renal Replacement Therapy               <ul style="list-style-type: none"> <li>- Although AKI is a common complication of sepsis, RRT may only be indicated in some subsets of patients.</li> </ul> </li> <li>(5) Steroids               <ul style="list-style-type: none"> <li>- Hydrocortisone may be considered in patients with vasopressor-resistant, inadequate MAP.</li> </ul> </li> <li>(6) Sodium Bicarbonate               <ul style="list-style-type: none"> <li>- Sodium bicarbonate may be given to patients with severe bicarbonate levels &lt; 5 mEq/L and/or pH &lt; 7.1 or AKI stage 2 or 3.</li> </ul> </li> <li>(7) Acetaminophen               <ul style="list-style-type: none"> <li>- Acetaminophen should be administered as a symptomatic drug.</li> </ul> </li> </ol>

Note: AKI: acute kidney injury; FR: fluid responsiveness; FT: fluid tolerance; HFNC: high-flow nasal cannula; LMWH: low-molecular-weight heparin; MAP: mean arterial pressure; NE: norepinephrine; PCT: procalcitonin; PPI: proton pump inhibitor; RRT: renal replacement therapy; SSC: surviving sepsis campaign; UFH: unfractionated heparin; VP: vasopressin; VTE: venous thromboembolism.

# Antimicrobial therapy

- Antimicrobial therapy is the first pillar of sepsis/septic shock treatment.
- Empiric antimicrobial therapy at the time of sepsis's identification and after the collection of cultures .
- Microbiological samples include blood and fluid or tissue from other sites deemed proper based on a clinical evaluation (urine or cerebrospinal fluid).
- The choice of empiric antimicrobial therapy based on clinical (site of infection, pre-vious antibiotic use, immunosuppression, and risk factors for resistant organisms) and epidemiological criteria.

# Antimicrobial therapy

- In septic shock, multidrug antimicrobial regimens with a wide spectrum of activity should be used (carbapenems and anti-Gram-negative antimicrobials with dual coverage).
- Dual coverage for Gram-negative organisms might be appropriate in cases of high suspicion for multidrug-resistant organisms (*Pseudomonas aeruginosa* or *Acinetobacter baumannii*).
- Dual coverage for Gram-positive organisms and methicillin-resistant *Staphylococcus aureus* (MRSA) should be considered for patients with a high risk of infection due to these pathogen.

# Antimicrobial Therapy and Source Control

## Mandell

### Antimicrobial Therapy

- 1 Intravenous antimicrobials should be initiated as soon as possible after recognition and within 1 hour for both sepsis and septic shock.
- 2 Empirical broad-spectrum therapy is recommended with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and potentially fungal or viral coverage).
- 3 Antimicrobial therapy should be narrowed once pathogen identification and sensitivities are established or adequate clinical improvement is noted.
- 4 Sustained systemic antimicrobial prophylaxis is not recommended in patients with severe inflammatory states of noninfectious origin (e.g., severe pancreatitis, burn injury).
- 5 Dosing strategies of antimicrobials should be optimized based on accepted pharmacokinetic/pharmacodynamic principles and specific drug properties in patients with sepsis or septic shock.
- 6 It is suggested to use empirical combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogens for initial management of septic shock.
- 7 It is suggested that combination therapy is not routinely used for ongoing treatment of most other serious infections including bacteremia and sepsis without shock.<sup>a</sup>
- 8 The use of combination therapy for routine treatment of neutropenic sepsis/bacteremia is not recommended.<sup>a</sup>



# Antimicrobial Therapy and Source Control

## Mandell

- 9 If combination therapy is used for septic shock, it is recommended to deescalate with discontinuation of combination therapy within the first few days in response to clinical improvement or evidence of infection resolution. This applies to both targeted (for culture-positive infections) and empirical (for culture-negative infections) combination therapy.<sup>a</sup>
- 10 Antimicrobial treatment duration of 7–10 days is adequate for most serious infections associated with sepsis and septic shock.
- 11 Longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *Staphylococcus aureus*, some fungal and viral infections, or immunologic deficiencies including neutropenia.
- 12 Shorter courses are appropriate in some patients, particularly patients with rapid clinical resolution following effective source control of intraabdominal or urinary sepsis and patients with anatomically uncomplicated pyelonephritis.
- 13 Daily assessment for deescalation of antimicrobial therapy in patients with sepsis and septic shock is recommended.
- 14 Measurement of procalcitonin levels can be used to support shortening the duration of antimicrobial therapy in sepsis patients.
- 15 Procalcitonin levels can be used to support discontinuation of empirical antibiotics in patients who initially appeared to have sepsis but subsequently have limited clinical evidence of infection.

### Source Control

- 1 A specific anatomic diagnosis of infection requiring emergent source control should be identified or excluded as rapidly as possible in any patient with sepsis. Required source control interventions should be implemented as soon as medically and logistically possible.
- 2 Prompt removal of intravascular access devices that are a possible source of sepsis or septic shock is recommended after other vascular access has been established.

# Empiric antimicrobial therapy

**TABLE 70-4 -- Empirical Antibiotic Options for Patients with Severe Sepsis or Septic Shock**

	Suspected Source				
	Lung	Abdomen	Skin/Soft Tissue	Urinary Tract	Meninges
Major community-acquired pathogens	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Legionella</i> <i>Chlamydophila pneumoniae</i>	<i>Escherichia coli</i> <i>Bacteroides fragilis</i>	<i>Streptococcus pyogenes</i> <i>Staphylococcus aureus</i> Polymicrobial	<i>E. coli</i> <i>Klebsiella</i> species <i>Enterobacter</i> species <i>Proteus</i> species Enterococci	<i>S. pneumoniae</i> <i>Neisseria meningitidis</i> <i>Listeria monocytogenes</i> <i>H. influenzae</i>
Empirical antibiotic therapy	Moxifloxacin <i>plus</i> either cefotaxime <i>or</i> ceftriaxone	Imipenem-cilastatin* <i>or</i> meropenem <i>or</i> piperacillin-tazobactam $\pm$ aminoglycoside	Vancomycin <i>plus</i> either imipenem <i>or</i> meropenem <i>or</i> piperacillin-tazobactam	Ciprofloxacin <i>or</i> levofloxacin (If gram-positive cocci, use ampicillin <i>plus</i> gentamicin)	Vancomycin <i>plus</i> ampicillin <i>plus</i> either ceftriaxone <i>or</i> cefepime
Major commensal or nosocomial microorganisms	Aerobic gram-negative bacilli	Aerobic gram-negative rods Anaerobes <i>Candida</i> species	<i>Staphylococcus aureus</i> (? MRSA) Aerobic gram-negative rods	Aerobic gram-negative rods Enterococci	Aerobic gram-negative rods Staphylococci
Empirical antibiotic therapy*	Imipenem-cilastatin* <i>or</i> meropenem <i>or</i> cefepime	Imipenem-cilastatin* <i>or</i> meropenem $\pm$ aminoglycoside (Consider amphotericin B)	Vancomycin <i>plus</i> imipenem-cilastatin* <i>or</i> meropenem <i>or</i> cefepime	Vancomycin <i>plus</i> imipenem-cilastatin* <i>or</i> meropenem <i>or</i> cefepime	Cefepime <i>plus</i> vancomycin



Table 2. Main empiric antimicrobial therapies according to the site of infection.

Infection Site	I Choice	II Choice	Allergy to Penicillin	Risk Factors for ESBL+	Risk Factors for MRSA
Pulmonary [57,58]	<b>CAP</b>	Amoxicillin/ Clavulanate 2.2 g/tid + Azithromycin 500 mg/die or Clarithromycin 500 mg/bid	Levofloxacin 750 mg/die	Levofloxacin 750 mg/die or Meropenem 2 g LD followed by 2 g/tid	Piperacillin/ Tazobactam 9 g LD followed by 18 g/die + Levofloxacin 750 mg/die or Meropenem 2 g LD followed by 2 g/tid
	<b>HAP</b>	Piperacillin/ Tazobactam 9 g LD followed by 18 g/die or Cefepime 1 g LD followed by 2 g/tid + Linezolid 600 mg/bid	Levofloxacin 750 mg/die + Linezolid 600 mg/bid	Levofloxacin 750 mg/die + Linezolid 600 mg/bid	Piperacillin/ Tazobactam 9 g LD followed by 18 g/die or Cefepime 1 g LD followed by 2 g/tid + Gentamicin 5–7 mg/kg/die + Linezolid 600 mg/bid or Vancomycin 25–30 mg/kg LD than 20 mg/kg/bid
	<b>VAP</b>	Piperacillin/ Tazobactam 9 g LD followed by 18 g/die or Cefepime 1 g LD followed by 2 g/tid + Linezolid 600 mg/bid	Levofloxacin 750 mg/die + Linezolid 600 mg/bid	Levofloxacin 750 mg/die + Linezolid 600 mg/bid	Piperacillin/ Tazobactam 9 g LD followed by 18 g/die or Cefepime 1 g LD followed by 2 g/tid + Linezolid 600 mg/bid or Vancomycin 25–30 mg/kg LD

# Antimicrobial therapy

Infection Site		I Choice	II Choice	Allergy to Penicillin	Risk Factors for ESBL+	Risk Factors for MRSA
Abdominal [60,61]	Community	Amoxicillin/Clavulanate 2.2 g/tid or Ceftriaxone 2 g/die + Metronidazole 500 mg/qid	Piperacillin/Tazobactam 9 g LD followed by 18 g/die	Ciprofloxacin 500 mg/bid + Metronidazole 500 mg/qid	Meropenem 2 g LD followed by 2 g/tid	Meropenem 2 g LD followed by 2 g/tid + Vancomycin 25–30 mg/kg LD than 20 mg/kg/bid
	Nosocomial	Piperacillin/Tazobactam 9 g LD followed by 18 g/die	Meropenem 2 g LD followed by 2 g/tid	Ciprofloxacin 500 mg/bid + Metronidazole 500 mg/qid	Meropenem 2 g LD followed by 1 g/tid	Meropenem 2 g LD followed by 2 g/tid + Tigecycline 100 mg LD followed by 100 mg/bid ± Caspofungin 70 mg LD followed by 50 mg/die
Urinary [59]	Community	Piperacillin/Tazobactam 9 g LD followed by 18 g/die	Ciprofloxacin 500 mg/bid	Ciprofloxacin 500 mg/bid	Piperacillin/Tazobactam 9 g LD followed by 18 g/die	Piperacillin/Tazobactam 9 g LD followed by 18 g/die or Meropenem 2 g LD followed by 2 g/tid
	Nosocomial	Piperacillin/Tazobactam 9 g LD followed by 18 g/die	Meropenem 2 g LD followed by 2 g/tid	Meropenem 2 g LD followed by 2 g/tid	Meropenem 2 g LD followed by 2 g/tid	Meropenem 2 g LD followed by 2 g/tid

# Antimicrobial therapy

CNS [62]	<50 years	Dexamethasone 0.1 mg/kg/qid + Ceftriaxone 2 g/die ± Acyclovir 10 mg/kg/tid	Dexamethasone 0.1 mg/kg/qid + Meropenem 2 g LD followed by 2 g/tid ± Acyclovir 10 mg/kg/tid	Dexamethasone 0.1 mg/kg/qid + Meropenem 2 g LD followed by 2 g/tid ± Acyclovir 10 mg/kg/tid	/	/
	>50 years	Dexamethasone 0.1 mg/kg/qid + Ceftriaxone 2 g/die + Ampicillin 12 g/die ± Acyclovir 10 mg/kg/tid	Dexamethasone 0.1 mg/kg/qid + Meropenem 2 g LD followed by 2 g/tid ± Acyclovir 10 mg/kg/tid	Dexamethasone 0.1 mg/kg/qid + Meropenem 2 g LD followed by 2 g/tid ± Acyclovir 10 mg/kg/tid	/	/
Skin [63,64]	Cellulitis	Amoxicillin/ Clavulanate 2.2 g/tid ± Clindamycin 600 mg/qid	Ceftriaxone 2 g/die	Levofloxacin 750 mg/die	Piperacillin/ Tazobactam 9 g LD followed by 18 g/die + Meropenem 2 g LD followed by 2 g/tid	Daptomycin 8–10 mg/kg/die or Vancomycin 25–30 mg/kg LD than 20 mg/kg/bid
	NF	Daptomycin 8–10 mg/kg/die + Clindamycin 600 mg/qid + Piperacillin/ Tazobactam 9 g LD followed by 18 g/die	/	Daptomycin 8–10 mg/kg/die + Clindamycin 600 mg/qid + Meropenem 2 g LD followed by 2 g/tid	Daptomycin 8–10 mg/kg/die + Clindamycin 600 mg/qid + Meropenem 2 g LD followed by 2 g/tid	Daptomycin 8–10 mg/kg/die + Clindamycin 600 mg/qid + Meropenem 2 g LD followed by 2 g/tid

# Antimicrobial therapy

Infection Site	I Choice	II Choice	Allergy to Penicillin	Risk Factors for ESBL+	Risk Factors for MRSA
<b>Gyn</b> [65]	Clindamycin 600 mg/qid + Gentamicin 5–7 mg/kg/die	/	Clindamycin 600 mg/qid + Gentamicin 5–7 mg/kg/die	Meropenem 2 g LD followed by 2 g/tid	Meropenem 2 g LD followed by 2 g/tid
<b>Undefined</b> [66]	Piperacillin/ Tazobactam 9 g LD followed by 18 g/die + Daptomycin 8–10 mg/kg/die or Vancomycin 25–30 mg/kg LD than 20 mg/kg/bid ± Caspofungin 70 mg LD followed by 50 mg/die	Daptomycin 8–10 mg/kg/die or Vancomycin 25–30 mg/kg LD than 20 mg/kg/bid + Meropenem 2 g LD followed by 2 g/tid ± Caspofungin 70 mg LD followed by 50 mg/die	Daptomycin 8–10 mg/kg/die or Vancomycin 25–30 mg/kg LD than 20 mg/kg/bid + Meropenem 2 g LD followed by 2 g/tid ± Caspofungin 70 mg LD followed by 50 mg/die	Daptomycin 8–10 mg/kg/die or Vancomycin 25–30 mg/kg LD than 20 mg/kg/bid + Meropenem 2 g LD followed by 2 g/tid ± Caspofungin 70 mg LD followed by 50 mg/die	Daptomycin 8–10 mg/kg/die or Vancomycin 25–30 mg/kg LD than 20 mg/kg/bid + Meropenem 2 g LD followed by 2 g/tid ± Caspofungin 70 mg LD followed by 50 mg/die

Note: Bid: bis in die; CAP: community-acquired pneumonia; CNS: central nervous system; HAP: hospital-acquired pneumonia; LD: loading dose; NF: necrotizing fasciitis; qid: quarter in die; tid: tris in die; VAP: ventilator-associated pneumonia.



# Empiric antimicrobial therapy

**TABLE 91.4 Initial Antibiotic Recommendations for Adult Patients With Sepsis**

Indication	Recommended Dosages <sup>a</sup>
Empirical coverage (source unknown)	Vancomycin 15 mg/kg q12h plus piperacillin-tazobactam <sup>b</sup> 3.375 g IV q6h or imipenem 0.5 g IV q6h or meropenem 1.0 g IV q8h with or without an aminoglycoside (e.g., tobramycin 5 mg/kg IV q24) <sup>c</sup>
Community-acquired pneumonia (CAP)	Ceftriaxone 1 g IV q24h plus azithromycin 500 mg IV q24h or a fluoroquinolone (e.g., moxifloxacin 400 mg IV q24h or levofloxacin 750 mg IV q24h) <sup>d</sup>
Community-acquired urosepsis	Piperacillin-tazobactam 3.375 g IV q6h or ciprofloxacin 400 mg IV q12h
Meningitis	Vancomycin 15 mg/kg IV q6h plus ceftriaxone 2 g IV q12h plus dexamethasone 0.15 mg/kg IV q6h × 2–4 days, preferably before antibiotics; add ampicillin 2 g IV q4h if listeria is suspected.
Nosocomial pneumonia	Vancomycin 15 mg/kg q12h plus piperacillin-tazobactam 4.5 g IV q6h or imipenem 0.5 g IV q6h or meropenem 1 g IV q8h or cefepime 2 g IV q8h plus an aminoglycoside (e.g., amikacin 15 mg/kg IV q24h or tobramycin 5–7 mg/kg IV q24h) or levofloxacin 750 mg IV q24h. Some authorities substitute linezolid 600 mg IV q12h for vancomycin if MRSA is a significant concern or known to be the cause.
Neutropenia	Cefepime 2 g IV q8h; add vancomycin 15 mg/kg IV q12h if a central line is present and infection is a concern. Add antifungal coverage with caspofungin 70 mg IV × 1, then 50 mg IV q24h if fever persists ≥5 days. For suspected or proven invasive aspergillosis, voriconazole 6 mg/kg IV q12h × 2, then 4 mg/kg IV q12h should be used.
Cellulitis and skin infections	Vancomycin 15 mg/kg IV q12h. Add piperacillin-tazobactam 3.375 g IV q6h in diabetics and immunocompromised patients. If necrotizing fasciitis is suspected, add clindamycin 900 mg. IV; surgical debridement is crucial.

IV, Intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

<sup>a</sup>Assumes normal renal function; dose adjustments are required with impaired creatinine clearance.

<sup>b</sup>Substitute aztreonam 2 g IV q8h if patient is allergic to penicillin.

<sup>c</sup>Monitor drug levels of aminoglycosides (i.e., peak and trough).

<sup>d</sup>Substitute cefepime or a carbapenem and azithromycin ± an aminoglycoside if the patient has severe CAP or health care–associated pneumonia.

# **Empirical Antibiotic**

## **Antimicrobial therapy**

### **Clinical Condition**

### **Antimicrobial Regimens (Intravenous Therapy)**

**Immunocompetent adult** The many acceptable regimens include (1) piperacillin-tazobactam (3.375 g q4–6h); (2) imipenem-cilastatin (0.5 g q6h) or meropenem (1 g q8h); or (3) cefepime (2 g q12h). If the patient is allergic to -lactam agents, use ciprofloxacin (400 mg q12h) or levofloxacin (500–750 mg q12h) plus clindamycin (600 mg q8h). Vancomycin (15 mg/kg q12h) should be added to each of the above regimens.

**Neutropenia (<500 neutrophils/L)**

Regimens include (1) imipenem-cilastatin (0.5 g q6h) or meropenem (1 g q8h) or cefepime (2 g q8h); (2) piperacillintazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h). Vancomycin (15 mg/kg q12h) should be added if the patient has an indwelling vascular catheter, has received quinolone prophylaxis, or has received intensive chemotherapy that produces mucosal damage; if staphylococci are suspected; if the institution has a high incidence of MRSA infections; or if there is a high prevalence of MRSA isolates in the community. Empirical antifungal therapy with an echinocandin (for caspofungin: a 70-mg loading dose, then 50 mg daily) or a lipid formulation of amphotericin B should be added if the patient is hypotensive or has been receiving broad-spectrum antibacterial drugs.

**Splenectomy**

Cefotaxime (2 g q6–8h) or ceftriaxone (2 g q12h) should be used. If the local prevalence of cephalosporin-resistant pneumococci is high, add vancomycin. If the patient is allergic to -lactam drugs, vancomycin (15 mg/kg q12h) plus either moxifloxacin (400 mg q24h) or levofloxacin (750 mg q24h) or aztreonam (2 g q8h) should be used.

**IV drug user**

Vancomycin (15 mg/kg q12h)

**AIDS**

Cefepime (2 g q8h) or piperacillin-tazobactam (3.375 g q4h) plus tobramycin (5–7 mg/kg q24h) should be used. If the patient is allergic to -lactam drugs, ciprofloxacin (400 mg q12h) or levofloxacin (750 mg q12h) plus vancomycin (15 mg/kg q12h) plus tobramycin should be used.

# multidrug-resistant organisms

**Table 1.** Main risk factors for multi-drug resistant pathogens.

<i>MRSA</i>	1.	Previous infection/colonization by MRSA in the last 12 months
	2.	Hemodialysis or peritoneal dialysis
	3.	Presence of central venous catheters or intravascular devices
	4.	Administration of multiple antibiotics in the last 30 days (in particular with cephalosporins or fluoroquinolones)
	5.	Immunodepression
	6.	Immunosuppressor treatments
	7.	Rheumatoid arthritis
	8.	Drug addiction
	9.	Patients coming from long-term care facilities or who have undergone hospital stay in the last 12 months
	10.	Close contact with patients colonized by MRSA
<i>ESBL</i>	1.	Previous infection/colonization with ESBL in the last 12 months
	2.	Prolonged hospitalization (>10 days, in particular in ICU/hospice/long-term care facilities)
	3.	Presence of permanent urinary catheter
	4.	Administration of multiple antibiotics in the last 30 days (particularly with cephalosporins or fluoroquinolones)
	5.	Patients with percutaneous endoscopic gastrostomy

# multidrug-resistant organisms

Table 1. Cont.

<i>Pseudomonas aeruginosa</i>	1.	Previous infection/colonization with <i>P. aeruginosa</i> in the last 12 months
	2.	Administration of multiple antibiotics in the last 30 days (particularly with cephalosporins or fluoroquinolones)
	3.	Pulmonary anatomic abnormalities with recurrent infections (e.g., bronchiectasis)
	4.	Elderly patients (>80 years)
	5.	Scarce glycemic control in diabetic subjects
	6.	Presence of permanent urinary catheter
	7.	Prolonged steroid use (>6 weeks)
	8.	Neutropenic fever
	9.	Cystic fibrosis
<i>Candida spp.</i>	1.	Immunodepression
	2.	Presence of central venous catheters or intravascular devices
	3.	Patients in total parenteral nutrition
	4.	Prolonged hospitalization (>10 days, particularly in an ICU)
	5.	Recent surgery (particularly abdominal surgery)
	6.	Prolonged wide-range antibiotic administration
	7.	Previous necrotizing pancreatitis
	8.	Recent fungal infection/colonization

Note: ESBL: Extended Spectrum Beta-lactamase; ICU: Intensive Care Unit; MRSA: Methicillin-Resistant *Staphylococcus aureus*.



# Definitive antimicrobial therapy

MDR Pathogens	Antibiotic Therapy (Doses Based on Normal Renal Function)
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Vancomycin 15 mg/kg q12h. (Target vancomycin blood trough level = 15-20 µg/mL) <i>or</i> Linezolid 600 mg q12h IV/PO

# Definitive antimicrobial therapy

*Pseudomonas  
aeruginosa*

Cephalosporins 3rd/4th generation: (e.g., cefepime 2 g q8-12h IV  
*or*  
ceftazidime 2 g q8h IV)  
*or*  
carbapenem (e.g., imipenem 1 g q8h, *or* meropenem 1 g q8h)  
*or*  
e.g., piperacillin-tazobactam 4.5 g q6h IV or 3.375 g 6 hr over 4-hr infusion  
*plus*  
Aminoglycoside (e.g., amikacin 15 mg/kg/day IV, gentamicin 5-7 mg/kg/day IV, *or* tobramycin 5-7 mg/kg/day IV)  
*or*  
Antipseudomonal fluoroquinolone (e.g., ciprofloxacin 400 mg q8h IV)  
*or*  
levofloxacin 750 mg qd IV)

# Definitive antimicrobial therapy

*Acinetobacter*  
*species*

Carbapenem (imipenem,  
meropenem) See doses  
above

*plus*

Aminoglycoside (amikacin,  
gentamicin, or tobramycin),  
see doses above

*or*

Polymyxin B or Colistin (see  
Ch. 32 for dose)

ESBL+  
*Klebsiella*  
*pneumoniae*  
*or*

Carbapenem (imipenem,  
meropenem), see doses  
above

±Aminoglycoside (amikacin,  
gentamicin, or tobramycin),  
see doses above

*Escherichia coli*  
*or*  
*Enterobacter species*

# Definitive antimicrobial therapy

## Staphylococcus aureus

- The choice of treatment of methicillin-sensitive Staphylococcus aureus (MSSA) are **beta-lactams, such as oxacillin or C1st.**
- in MRSA, or in hemodynamically unstable, severe bacteremia patients, treatment options are **vancomycin, ceftaroline, or daptomycin .**
- in infection localized or nonbacteremic in hemodynamically stable patients, the treatment options are **clindamycin, linezolid, tetracycline, or trimethoprim-sulfamethoxazole**

# Definitive antimicrobial therapy

## enterococci

- In enterococci causing urinary tract infections, the antibiotic of choice is a **beta-lactam-type ampicillin**.
- In bacteremic infection, susceptible a **lactam plus and aminoglycoside** is recommended
- In resistance to beta-lactams, **vancomycin, linezolid, daptomycin, and tigecycline**.

# Antimicrobial therapy

**Table 8.1** Antibiotics committed according to the type of beta-lactamase

Penicillins	C1 <sup>st</sup>	C2 <sup>nd</sup>	Monobactam (Aztreonam)	C3 <sup>rd</sup> and C4 <sup>th</sup>	Carbapenems
<b>Penicillinase</b>					
<b>BSBLs</b>					
<b>ESBLs/ AmpC<sup>a</sup></b>					
<b>Class A Carbapenemases ESBLs (KPC – GES)</b>					
<b>Class A Carbapenemases (Sme, IMI, NMC)</b>			<b>b</b>		
<b>Class B Carbapenemases (MBL)</b>				<b>VIM, IMI, NDM</b>	
<b>Class D Carbapenemases (Oxa-48 and derivatives)</b>			<b>Oxa–163 (Enterobacteriaceae), oxa 146 (<i>Acinetobacter</i>)</b>		

Created by the authors

*KPC Klebsiella pneumoniae* producer of carbapenems, *GES* Guiana extended spectrum, *MBL* metallo-beta-lactamase, *BSBLs* broad-spectrum beta-lactamases, *ESBLs* extended-spectrum beta-lactamases, *C1st* first-generation cephalosporin, *C2nd* second-generation cephalosporin, *C3rd* third-generation cephalosporin, *C4th* fourth-generation cephalosporin

<sup>a</sup>See box key markers to differentiate ESBLs of AmpC

<sup>b</sup>Can be susceptible or resistant

## gram-negative bacteria, Definitive antimicrobial therapy

- In chromosomal or plasmid AmpC producing germs, third-generation cephalosporins are resistant .
- In hyperproducers of AmpC, it is suggested not to use penicillin or antibiotic inhibitors of beta-lactamase, such as amoxicillin-clavulanate, ampicillin-sulbactam, or piperacillin-tazobactam and not to use of first, second or third-generation cephalosporins. And may be resistant to C4.
- Carbapenems can be used in those germs .
  - cefepime, cefotaxime, ceftriaxone, and piperacillin-tazo-bactam are less reliable for infections caused by ESBLs producing strains.
  - carbapenems are the antibiotics of choice for severe infections by ESBLs-producing germs .
  - Aminoglycosides may be treatment options against ESBLs-producing strains in urinary tract infections in hemodynamically stable patients .
- In carbapenemase-producing bacteria are associated with high morbidity and mortality, especially in patients with a long hospital stay, patients in intensive care units, and patients using medical devices. Antibiotics choice is fosfomicin, polymyxin (among these colistin and polymyxin B), chloramphenicol, and rifampin

## Duration of Therapy

- If you know what you are treating and patient has steady improvement

Disease Process	Duration
Community-acquired pneumonia	5-7 days
Hospital/healthcare-acquired pneumonia	7 days
Ventilator-associated pneumonia	7 days
Urosepsis	7 days
Pyelonephritis	7 days
Skin and soft-tissue infection	5-7 days
Intra-abdominal infection with source control	4 days

- If you don't know what you are treating and the patient has steady improvement, 7 days is likely an adequate course
- If the patient is not improving, then additional evaluation is



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