

# SEPSIS



# The concept of infection - definition and types of infection

- Infection is a process characterized by the penetration and multiplication of infectious agents in the human body. The body's defense against infectious agents is based on mechanisms of nonspecific and specific protection.
- According to the place of origin:
  - local infections
  - systemic (generalized) infections

# Types of generalized infections

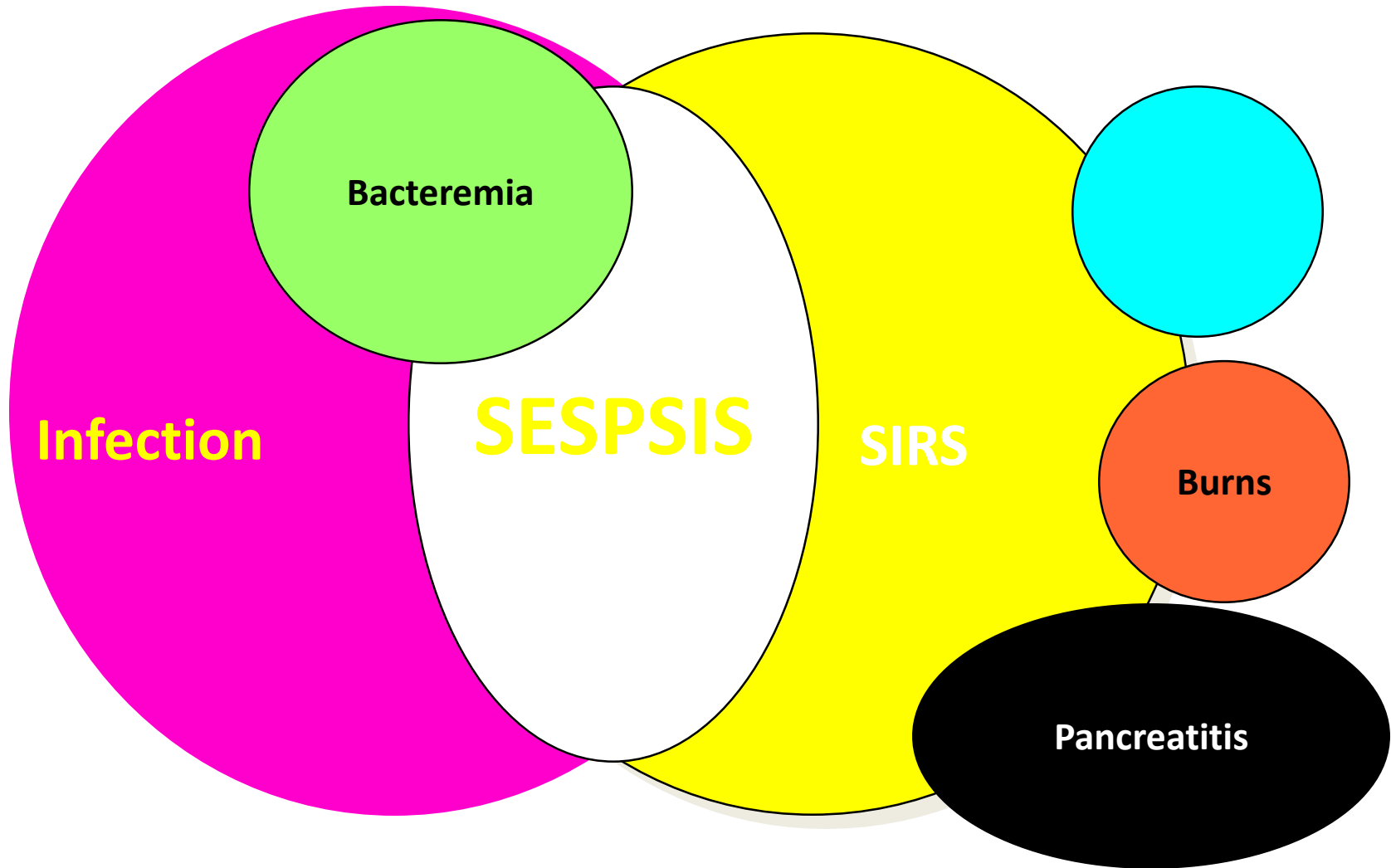
- Bacteremia is the presence and multiplication of bacteria in the blood, which can be transient or intermittent.
- Septicemia is a systemic disease caused by the spread of microorganisms and their toxins through the blood.
- Sepsis - a broader term than septicemia and refers to a systemic inflammatory response caused by microorganisms, regardless of whether they are spread through the blood or remain in a local focus.

# CIPPC (Systemic Inflammatory Response Syndrome)

- Systemic inflammatory response (SIRS) is an immune-metabolic reaction of the body to various agents defined by at least two of the following clinical signs:
- Temperature  $> 38$  degrees or  $< 36$
- Heart rate  $> 90/\text{min}$
- Respiratory rate  $> 20/\text{min}$  or  $\text{PaCO}_2 < 32\text{mmHg}$
- Leukocyte count  $> 12,000/\mu\text{L}$ ,  $< 4,000/\mu\text{L}$ , or  $> 10\%$  young, immature

- **Severe sepsis** - one or more signs of organ dysfunction due to hypoperfusion or hypotension, such as metabolic acidosis, impaired consciousness, oliguria, or respiratory distress syndrome.
- **Septic shock**- sepsis that results in hypotension despite adequate fluid replacement, leading to organ hypoperfusion and subsequent conditions, metabolic acidosis, oliguria, or impaired consciousness.
- **Multiple organ dysfunction syndrome (MODS)** is a disorder of the functioning of multiple organs that requires special therapeutic measures to maintain homeostasis.

# THE RELATIONSHIP BETWEEN SEPSIS AND SIRS



# Types of sepsis

- Sepsis arising outside the hospital environment – invasive widespread bacteria: *E. coli*, *Proteus*, *Staphylococcus*, *Enterococcus*
- Sepsis arising in the hospital environment where natural immune barriers are disrupted – multi-resistant hospital bacteria: *Pseudomonas*, *Serratia* spp, *Acinetobacter* spp, hospital-acquired *staphylococcus* and *enterococcus*
- Sepsis in immunocompromised individuals: splenectomy, HIV, agranulocytosis, immunosuppression (various bacteria, fungi, parasites)
- Sepsis in individuals with implants, valves, etc.

# Фактори који утичу на повећану инциденцу сепсе

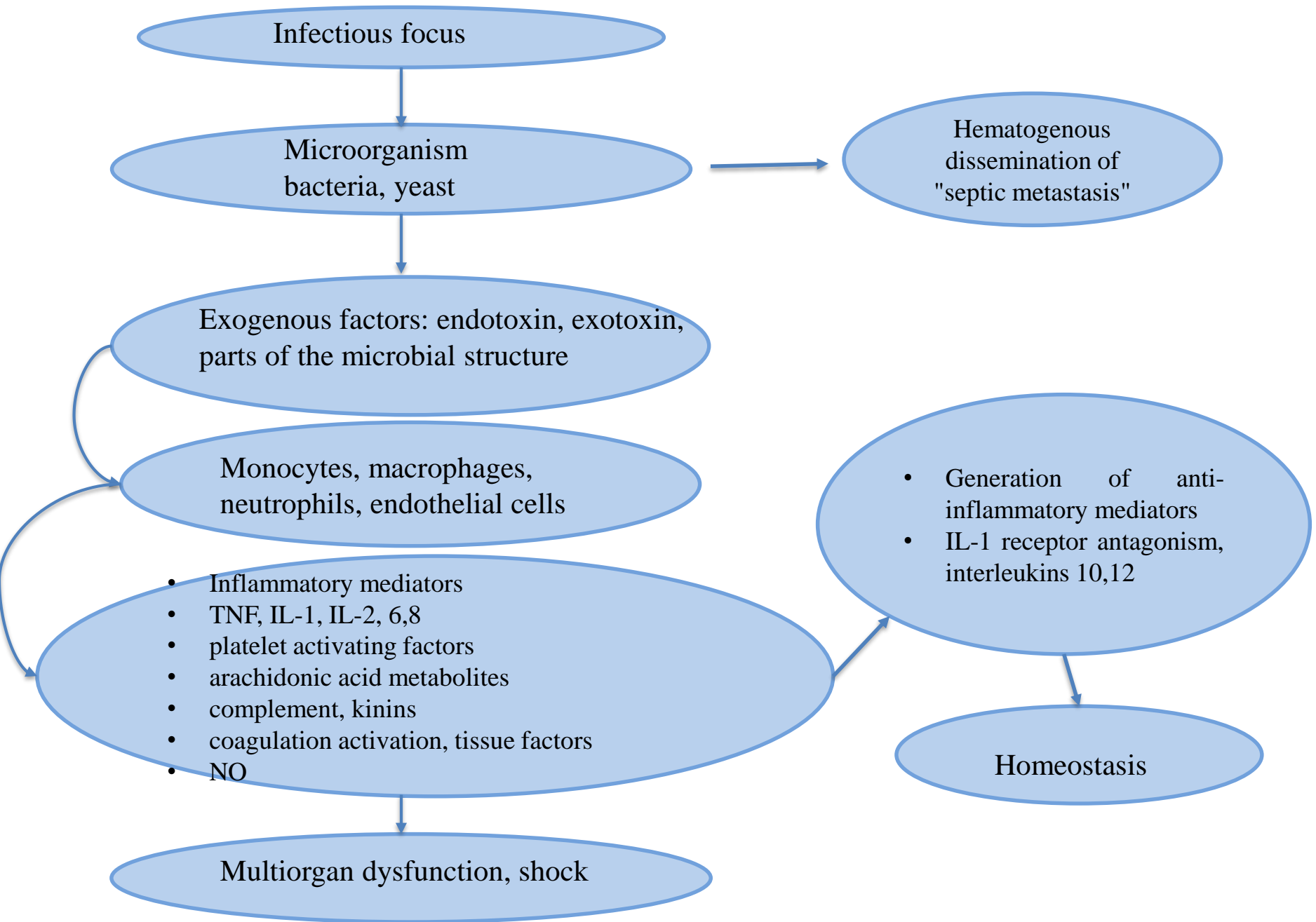
- Старосна доб
- Хроничне болести (цироза јетре, дијабетес...)
- Агресивна онколошка хемиотерапија и радиотерапија
- Имуносупресивна терапија код трансплантација органа и системских болести
- Повећана употреба хируршких протеза и катетера
- ХИВ инфекција
- Неадекватна употреба антибиотика и резистентни сојеви бактерија

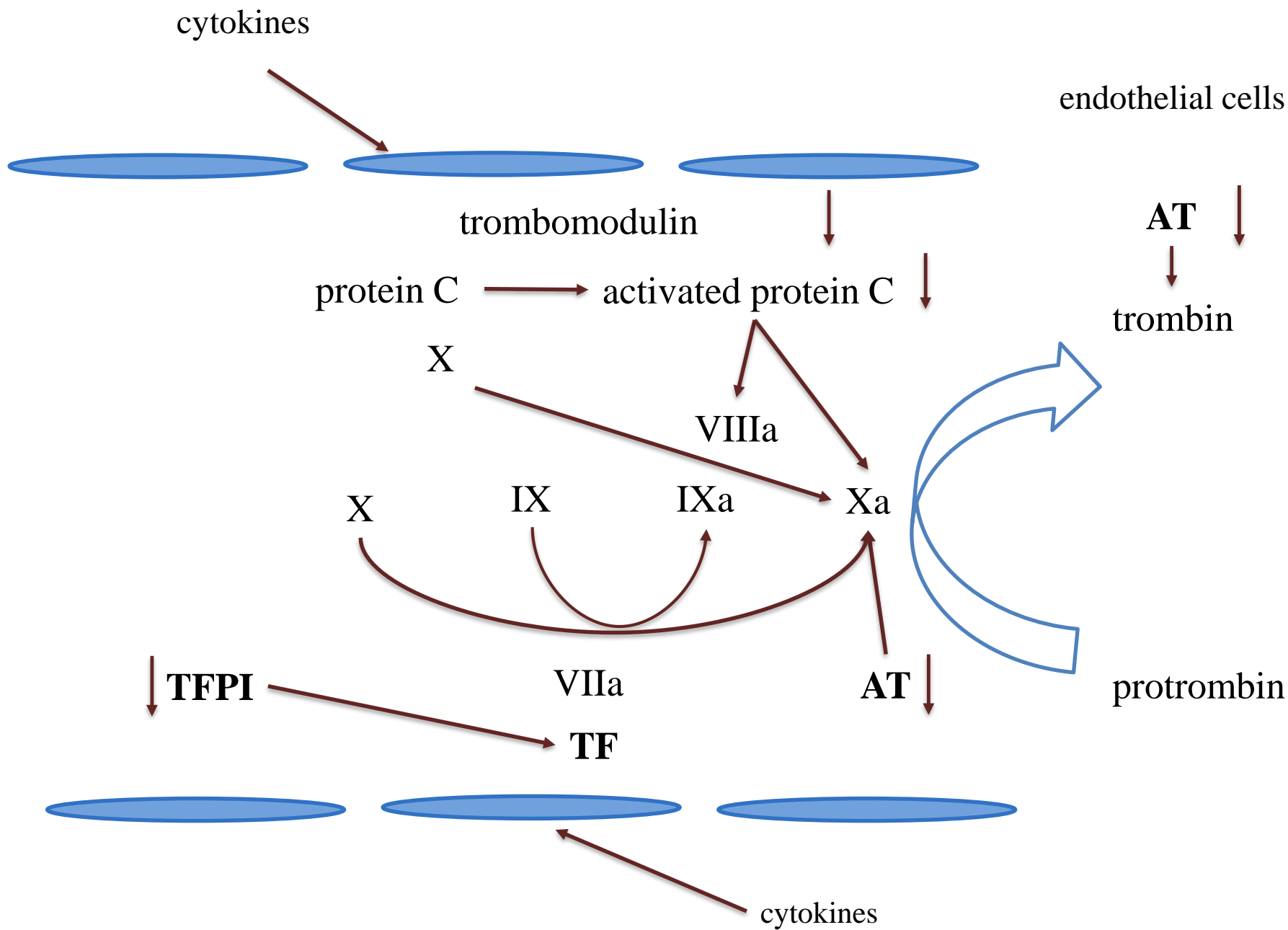


# Most common sites of primary infection

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- **LUNGS** (*S. pneumoniae*, *H. influenzae*, *Legionella*, *Chlamydia*....gram negative bacilli)
- **ABDOMINAL** (*E. coli*, *Bacteroides fragilis*....gram neg. bacilli, anaerobes and *Candida* sp.)
- **UROGENITAL TRACT** (*E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Proteus* sp....gram neg. bacilli and *Enterococcus* sp.)
- **SKIN** / soft tissue (*S. pyogenes*, *S. aureus*, *Clostridium* sp....gram neg. bacilli)
- **INFECTED INTRAVASCULAR CATHETERS** (*S. aureus*)





# SHOCK PHASES

- **COMPENSATED SHOCK PHASE** (early phase in which compensatory physiological mechanisms are activated, which tend to return functions to physiological parameters)
- **DECOMPENSATED (PROGRESSIVE) SHOCK PHASE** (compensatory reactions weaken and a drop in arterial pressure and tissue perfusion occurs, after which irreversible changes in the organism and death occur).

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## NEUROHUMOR COMPENSATORY MECHANISMS

**SYMPATHETIC STIMULATION** - baroreceptors in the aortocarotid region

Vasoconstriction in the skin, kidneys, splanchnic region → increased blood volume for vital regions of the body - brain and heart

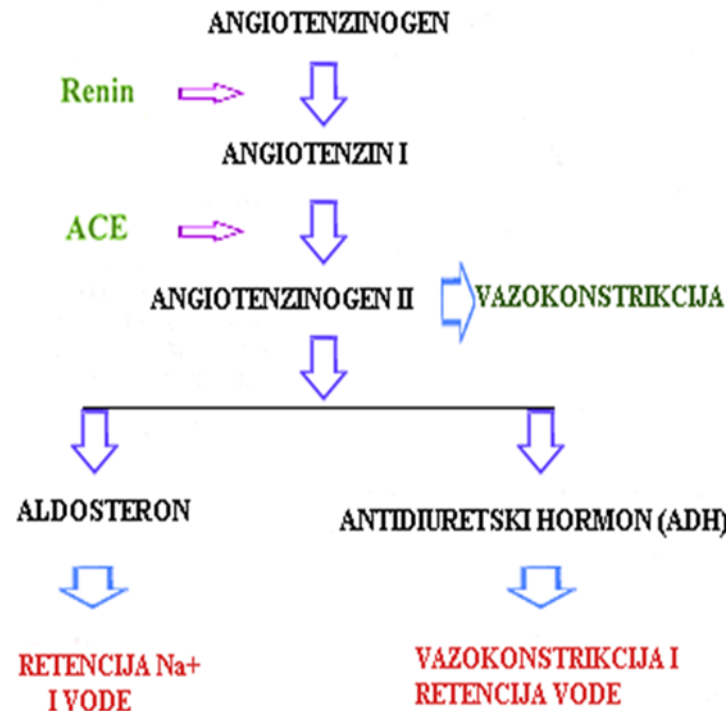
**VENOCONSTRICTION** → increased blood flow to the heart

**INCREASED HEART PUMP EFFICIENCY** → increased contractility, increased heart rate, increased myocardial excitability, increased myocardial tone

# COMPENSATED SHOCK

## NEUROHUMORAL COMPENSATORY MECHANISMS

### 2. ACTIVATION OF THE RENIN-ANGIOTENSIN SYSTEM (receptors in the juxtaglomerular apparatus of the kidney)



# COMPENSATED SHOCK

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## NEUROHUMOR COMPENSATORY MECHANISMS

### 3. INCREASED SECRETION OF “STRESS HORMONES” FROM THE ADRENAL GLANDS

CATECHOLAMINES - have the same positive effect on the heart, lead to vasoconstriction, lipolysis and glycogenolysis in the body

GLUCOCORTICOIDS AND MINERALOCORTICOIDS - stimulate glycogen and protein catabolism,  $\text{Na}^+$  and water retention in the kidneys

# COMPENSATED SHOCK

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All of the above mechanisms aim to increase the volume of circulating fluid and blood flow to the heart, while simultaneously increasing the contractile function of the heart, which leads to maintenance of cardiac output and an increase in arterial pressure (correction of the initial stimulus).



# DECOMPENSATED SHOCK

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- Capillary vasoconstriction worsens tissue ischemia. Ischemia and hypoxia affect energy metabolism and the state of endothelial cells in the capillaries themselves. Arteriolar and precapillary sphincters relax and vasodilate. Blood begins to stagnate in the microcirculation, which leads to a disproportion between the volume of circulating blood and the increased volume of the circulatory system. The result is relative hypovolemia.
- Due to vasodilation and an increase in the amount of blood in the capillaries, the hydrostatic pressure in them increases and fluid is filtered from the capillaries into the interstitium, which further worsens hypovolemia and hypotension.

# DECOMPENSATED SHOCK

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- Prolonged ischemia leads to damage to the endothelial cells of the capillaries and paralysis of the precapillary and postcapillary sphincters, when they cease to respond to neurohumoral stimuli of the vasomotor center.
- A large amount of blood is retained in the widely dilated capillary pool, jeopardizing the energy and metabolic processes in all cells in the body.
- Generalized hypoperfusion is also reflected in the heart cells. Reduced energy production in them also weakens their contractile function, so the heart pumps an already reduced amount of blood into the systemic circulation, which further worsens tissue perfusion and leads to hypoxic cell damage (circulus vitiosus).

# MULTIPLE ORGAN DYSFUNCTION SYNDROME (MODS)



# DAMAGE TO INDIVIDUAL ORGANS IN SHOCK

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- KIDNEYS – acute tubular necrosis and acute renal failure with oliguria, anuria and electrolyte disturbances.
- LUNGS – except in septic shock, they are late susceptible to hypoxic damage, due to the high oxygen content in them. Pulmonary changes in shock (“shock lung”) are a consequence of diffuse damage to the alveoli and their collapse, with the formation of hyaline membranes and impaired gas exchange at the alveolar-capillary membrane – ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)
- CNS – ischemic encephalopathy, from transient confusion with complete recovery in mild cases, to coma and general brain death in severe cases

# DAMAGE TO INDIVIDUAL ORGANS IN SHOCK

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- HEART – myocardial dysfunction leads to acute insufficiency, due to myocardial hypoxia and increased energy requirements on the other hand. Myocardial infarction is also possible.
- GIT – “stress ulcer” in the stomach, ischemic necrosis of the mucosa and bleeding in the intestine, as a result of prolonged intense vasoconstriction in the splanchnic region. Reversible fatty degeneration and centrilobular necrosis of hepatocytes may occur in the liver if ischemia lasts longer
- ADRENAL GLANDS – possible acute insufficiency (especially if the cause of shock is infection or trauma and there is developed DIC) → dehydration, hypotension, hypoglycemia, impaired consciousness

# CLINICAL PICTURE OF SEPSIS AND SEPTIC SHOCK

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- signs of disease of the initial focus of sepsis (focus):
- abdominal pain (abscess, adnexitis, appendicitis)
- lumbar pain (in kidney disease)
- purulent changes on the skin
- increased body temperature, chills, fever (however, about 30% have a low temperature or are afebrile)
- tachypnea (hyperventilation) - sometimes a pathological finding on the lungs in terms of pneumonia or pulmonary edema
- tachycardia, arrhythmia, murmurs
- hepatosplenomegaly (soft septic spleen)
- pallor of the complexion, less often jaundice or skin changes in the form of pustules, bullae, ulcerations, necrosis...
- hemorrhagic changes on the skin (petechiae, hematomas...)
- redness, swelling, pain, limited joint mobility
- mental alteration (from confusion to loss of consciousness), neurological deficits and/or meningeal signs











# Investigations that need to be performed in a septic patient

- Erythrocyte sedimentation rate
- Complete blood count
- C-reactive protein
- Glucose
- Electrolytes (sodium, potassium, chlorine)
- Blood lactate
- Acid-base status
- Bilirubins, aminotransferases, alkaline phosphatase
- Coagulation
- Urea, creatinine
- Urine sediment
- Lumbar puncture (in case of impaired consciousness)
- Chest X-ray
- Abdominal ultrasound
- Heart ultrasound (in case of suspected endocarditis)
- Electrocardiogram...
- Bacteriological tests
- Blood cultures
- Urine culture
- Cerebrospinal fluid culture
- Culture of material obtained from possible abscesses
- Sputum culture (in case of pneumonia)...

# LABORATORY FINDINGS IN SEPSIS

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- Leukocytosis, leukopenia, thrombocytopenia, anemia
- Complete hemostasis: prolonged PTT, APTT
- Acute phase reactants: accelerated sedimentation rate, elevated fibrinogen, C-reactive protein, procalcitonin (PCT)
- Renal disorders: ↑ creatinine, urea, potassium, sodium, chlorides
- Acid-base status: respiratory alkalosis (initially, due to hyperventilation), later metabolic acidosis
- Increased AST, ALT, bilirubin
- Hyperglycemia; hypoglycemia rare
- Hypoalbuminemia

# DIAGNOSING SEPSIS

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- Clinical picture
- Hematological and biochemical analyses
- Isolation of microorganisms: blood culture, urine culture, swabs...
- Additional examinations (radiographs, scanner, magnetic resonance imaging, echocardiogram, lumbar puncture...)



# DIFFERENTIAL DIAGNOSIS OF SEPSIS

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- Infectious diseases: leptospirosis, typhus and typhus fever, brucellosis, malaria, kala-azar
- Malignant, hematological diseases (lymphomas)
- Systemic connective tissue diseases
- Pancreatitis
- Anaphylaxis
- Adrenal insufficiency
- Pulmonary embolism
- Hypovolemia of various causes
- Massive aspiration/atelectasis

# TREATMENT PLAN FOR SEPSIS AND SEPTIC SHOCK

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Sanitizing the septic source (surgical wound treatment, drainage of pus, removal of the central catheter, etc.)

Application of adequate antibiotic therapy

Correction of homeostatic disorders

Maintenance of vital functions

Application of drugs that affect immune processes

Implementation of specific therapeutic procedures for severe sepsis

The choice of antibiotics in sepsis is made according to:

the presumed source of sepsis and the expected causative agent

the condition and age of the patient, other diseases and conditions (allergies, pregnancy)

the site of infection (outpatient and inpatient)

previous diagnostic and therapeutic procedures

# SIX EMERGENCY PROCEDURES IN THE TREATMENT OF PATIENTS WITH SUSPECTED SEPSIS:

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- give oxygen – high flow
- take blood for blood culture
- administer antibiotics
- initiate intravascular volume replacement
- check hemoglobin and lactate levels
- monitor “hourly” diuresis

# Recommendations for empiric antimicrobial therapy



Recommendations for empiric antimicrobial therapy	
Urinary tract	3rd generation cephalosporins; Quinolones; Piperacillin, mezlocillin, or ticarcillin ± aminoglycosides
External urinary tract	3rd generation cephalosporins ± metronidazole; Ticarcillin/clavulanate Ampicillin/sulbactam Piperacillin/tazobactam, all ± aminoglycosides



# Recommendations for empirical antimicrobial therapy

Intrahospital infections without the presence of neutropenia  
(neutrophils 1000/mm<sup>3</sup>)

Cefepime (monotherapy)

Imipenem

3rd generation cephalosporin ±  
metronidazole;

Piperacillin/tazobactam;

} +Aminoglycosides

Intrahospital infections with neutropenia  
(neutrophils <1000/mm<sup>3</sup>)

Ticarcillin/clavulanate

Piperacillin/tazobactam

Carbapenem ± aminoglycoside;

Ceftazidime + aminoglycoside

} + Aminoglycosides

Vancomycin

**Table 3: Antibiotic selection options for patients with simple sepsis, community acquired, immunocompetent patients requiring hospitalization.**

Simple Sepsis (Community Acquired)	Antibiotic A (Select one of the following)	Antibiotic B (Select one of the following)	+/- Antibiotic C (Select one of the following)
Undifferentiated	<ul style="list-style-type: none"> <li>Ceftriaxone 2g IV q24h</li> <li>Levofloxacin 750mg IV Q24H</li> </ul>		
Pneumonia	<ul style="list-style-type: none"> <li>Ceftriaxone 1g IV Q24H <u>plus</u> Azithromycin 500mg IV q24h</li> <li>Ceftriaxone 1g IV q24H <u>plus</u> Doxycycline 100mg IV Q12H</li> <li>Levofloxacin 750mg IV Q24H</li> </ul>		
Urinary Tract Infection	<ul style="list-style-type: none"> <li>Ceftriaxone 1g IV Q24H</li> <li>Ciprofloxacin 400mg IV Q12H</li> </ul>		
Intra-abdominal Infection	<ul style="list-style-type: none"> <li>Ceftriaxone 1g IV Q24H</li> <li>Ciprofloxacin 400mg IV Q12H</li> </ul>	Metronidazole 500mg IV Q8H	
Skin/Skin Structure Infection – Pure cellulitis	Cefazolin 2g IV Q8H	Vancomycin Loading Dose + vancomycin 15mg/kg	
Skin/Skin Structure Infection with Special Risks (Special Risks: malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, animal bites, diabetic foot ulcer)	<ul style="list-style-type: none"> <li>Piperacillin-tazobactam 3.375g IV Q8H extended infusion</li> <li>Meropenem 1g IV Q8H extended infusion</li> <li>Cefepime 1g IV Q6H <u>plus</u> Metronidazole 500mg IV Q8H</li> </ul>	Vancomycin Loading Dose + vancomycin 15mg/kg	
Bacterial Meningitis – “Spontaneous”	Ceftriaxone 2g IV q12h	Vancomycin Loading Dose + vancomycin 15mg/kg	Ampicillin 2g IV Q4H (>50 years of age)

**Table 1: Antibiotic selection options for healthcare associated and/or immunocompromised patients with severe sepsis/septic shock**

Severe Sepsis or Septic Shock (Healthcare associated OR Immunocompromised)	Antibacterial A (Select one of the following)	Antibacterial B (Select one of the following)	+/- Antibacterial C (Select one of the following)	+/- Antifungal
Undifferentiated or Vascular Access Device Infection	<ul style="list-style-type: none"> <li>Piperacillin-tazobactam 4.5g IV Q8H extended infusion</li> <li>Cefepime 2g IV Q8H extended infusion</li> <li>Meropenem 1g IV Q8H extended infusion – if at risk for ESBL infection</li> <li>Aztreonam 2g IV q8h</li> </ul>	<ul style="list-style-type: none"> <li>Vancomycin Loading Dose + vancomycin 15mg/kg</li> <li>Linezolid 600mg IV q12h - if at risk of VRE infection</li> </ul>	Tobramycin 7mg/kg IV Q24H - if at risk of P. aeruginosa infection	Caspofungin 70mg IV ONCE + caspofungin 50 mg IV Q24H - if at risk of invasive candidiasis
Pneumonia	<ul style="list-style-type: none"> <li>Piperacillin-tazobactam 4.5g IV Q8H extended infusion</li> <li>Meropenem 1g IV Q8H extended infusion – if at risk for ESBL infection</li> <li>Cefepime 2g IV Q8H extended infusion</li> <li>Aztreonam 2g IV q8h</li> </ul>	<ul style="list-style-type: none"> <li>Vancomycin Loading Dose + vancomycin 15mg/kg</li> <li>Linezolid 600mg IV Q12H</li> </ul> <p><u>PLUS</u></p> <ul style="list-style-type: none"> <li>Levofloxacin 750mg IV Q24H</li> <li><u>If fluoroquinolone allergy:</u> Azithromycin 500mg IV Q24H <u>plus</u> Tobramycin 7mg/kg IV Q24H - if at risk of P. aeruginosa infection</li> </ul>		
Urinary Tract Infection	<ul style="list-style-type: none"> <li>Piperacillin-tazobactam 4.5g IV Q8H extended infusion</li> <li>Meropenem 1g IV Q8H extended infusion – if at risk for ESBL infection</li> <li>Aztreonam 2g IV q8h</li> </ul>	<ul style="list-style-type: none"> <li>Vancomycin Loading Dose + vancomycin 15mg/kg</li> <li>Linezolid 600mg IV Q12H - if at risk of VRE infection</li> </ul>	+/- Tobramycin 5mg/kg IV Q24H - if at risk of P. aeruginosa infection	
Intra-Abdominal Infection	<ul style="list-style-type: none"> <li>Piperacillin-tazobactam 4.5g IV Q8H extended infusion</li> <li>Meropenem 1g IV Q8H extended infusion – if at risk for ESBL infection</li> <li>Cefepime 2g IV Q8H extended infusion <u>plus</u> Metronidazole 500mg IV Q8H</li> <li>Aztreonam 2g iv q8h <u>plus</u> Metronidazole 500mg iv q8h</li> </ul>	<ul style="list-style-type: none"> <li>Vancomycin Loading Dose + vancomycin 15mg/kg</li> <li>Linezolid 600mg IV q12h - if at risk of VRE infection</li> </ul>		Caspofungin 70mg IV ONCE + caspofungin 50 mg IV Q24H - if at risk of invasive candidiasis

Severe Sepsis or Septic Shock (Healthcare associated OR Immunocompromised)	Antibacterial A (Select one of the following)	Antibacterial B (Select one of the following)	+/- Antibacterial C (Select one of the following)	+/- Antifungal
Skin/Skin Structure Infection – Pure cellulitis	Vancomycin Loading Dose + vancomycin 15mg/kg	<ul style="list-style-type: none"> <li>Cefazolin 2g IV Q8H</li> </ul>		
Skin/Skin Structure Infection with Special Risks (Special Risks: malignancy on chemotherapy, neutropenia, severe cell- mediated immunodeficiency, immersion injuries, animal bites, diabetic foot ulcer)	<ul style="list-style-type: none"> <li>Piperacillin-tazobactam 4.5g IV Q8H extended infusion</li> <li>Meropenem 1g IV Q8H extended infusion – if at risk for ESBL infection</li> <li>Cefepime 2g IV Q8H extended infusion <u>plus</u> Metronidazole 500mg IV Q8H</li> <li>Aztreonam 2g iv q8h <u>plus</u> Metronidazole 500mg iv q8h</li> </ul>	Vancomycin Loading Dose + vancomycin 15mg/kg		
Necrotizing Fasciitis (including Fournier's Gangrene), Clostridial Gas Gangrene or Myonecrosis	<ul style="list-style-type: none"> <li>Piperacillin-tazobactam 4.5g IV Q8H extended infusion</li> <li>Meropenem 1g IV Q8H extended infusion – if at risk for ESBL infection</li> <li>Cefepime 2g IV Q8H extended infusion <u>plus</u> Metronidazole 500mg IV Q8H</li> <li>Aztreonam 2g iv Q8H <u>plus</u> Metronidazole 500mg iv q8h</li> </ul>	<ul style="list-style-type: none"> <li>Vancomycin Loading Dose + vancomycin 15mg/kg</li> <li>Linezolid 600mg IV Q12H</li> </ul>	± Clindamycin 600mg IV Q8H (use in combination with vancomycin for toxin suppression)	
Bacterial Meningitis – “Spontaneous”	Ceftriaxone 2g IV Q12H	Vancomycin Loading Dose + vancomycin 15mg/kg	<ul style="list-style-type: none"> <li>Ampicillin 2g IV Q4H (&gt;50 year of age OR immunocompromised)</li> <li><u>If penicillin allergy:</u> Meropenem 2g IV Q8H extended infusion</li> </ul>	
Bacterial Meningitis – Post- Trauma or Neurosurgery	<ul style="list-style-type: none"> <li>Cefepime 2g iv q8h extended infusion</li> <li>Meropenem 2g IV Q8H extended infusion</li> <li>Aztreonam 2g iv Q8H <u>plus</u> Ciprofloxacin 500mg iv q8h</li> </ul>	Vancomycin Loading Dose + vancomycin 15mg/kg		



# Adequate fluid replacement:

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- first hours quickly
- mandatory control of blood pressure, central venous pressure and hourly diuresis (left ventricular filling pressure)
- crystalloid solutions (0.9% NaCl, 5% Glucose, Ringer), 4-6 liters, electrolyte control
- colloid solutions (blood plasma, albumin)
- transfusion of deplasmated erythrocytes (hemoglobin <80)
- sympathomimetics: dopamine, noradrenaline, dobutamine

- Maintenance of other functions:
  - oxygen therapy, artificial ventilation
  - correction of acidosis
  - correction of hypocalcemia
  - correction of adrenal insufficiency
  - correction of hyper and hypoglycemia
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- Immunotherapy of septic shock:
  - corticosteroids?
  - Antiendotoxin monoclonal antibodies
  - Anti-TNF antibodies
  - IL-1 receptor antagonists
  - Protein C (inactivates factors Va and VIIIa, stimulates fibrinolysis, inhibits PMN-a, reduces IL production and cell adhesion to the vascular endothelium)

# Prognostic factors of sepsis

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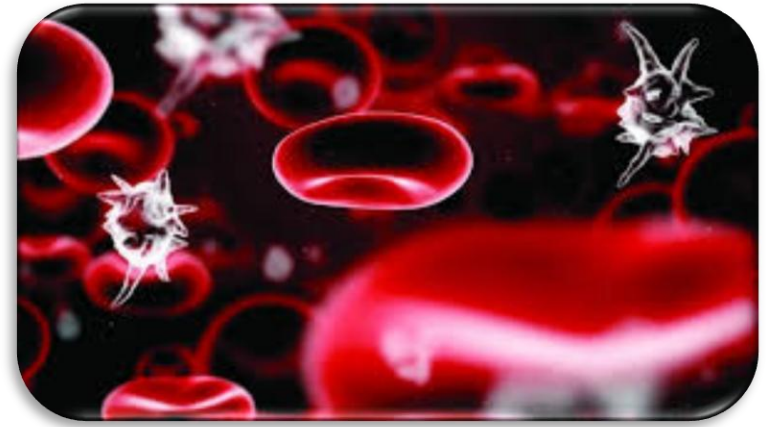
- Immune system status
- Age
- Previous illnesses
- Type and resistance of the isolated microorganism
- Speed of diagnosis and timely initiation of antimicrobial therapy....
- APACHE scor, Sofa scor

# Sepsis mortality rate

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- Overall mortality rate 30% - 50%
- Mortality according to defined criteria
- SIRS = 7%
- Sepsis = 16%
- Severe sepsis = 20%
- Septic shock = 46%





**THANK YOU!**