

# Infectious Diseases

## Lesson 2

# SEPSIS SYNDROME

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# Objectives and learning goal

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# Objectives

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- To know the definitions of sepsis and related conditions
- To review all clinically relevant concepts on sepsis and related conditions

# Learning goal

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To promptly recognize and to know how to manage a patient with sepsis

# Contents

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- [Definitions](#)
- [Epidemiology](#)
- [Etiology](#)
- [Pathogenies](#)
- [Clinical manifestations](#)
- [Analysis abnormalities](#)
- [Diagnosis](#)
- [Treatment](#)
- [Prognosis](#)
- [Prevention](#)
- [Key messages](#)
- [Further reading](#)

# Definitions

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# Infection

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- Pathological process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms
- Invasion and multiplication of microorganisms such as bacteria, viruses, and parasites that are not normally present within the body

# Systemic inflammatory response syndrome (SIRS)

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## **At least two of the following conditions:**

- Fever (oral temperature  $> 38\text{ }^{\circ}\text{C}$ ) or hypothermia (oral temperature  $< 36\text{ }^{\circ}\text{C}$ )
- Heart rate  $> 90$  beats per minute
- Tachypnea ( $> 24$  respirations per minute), or hyperventilation (arterial  $\text{Pa CO}_2 < 32\text{ mm Hg}$ ) or invasive or noninvasive ventilation needed
- Leukocytosis ( $> 12,000/\text{mm}^3$ ), or leukopenia ( $< 4,000/\text{mm}^3$ ), or  $> 10\%$  bands in white blood cell count



# Sepsis

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- Systemic inflammatory response syndrome (SIRS), and
- Infection, confirmed or suspected

$$\boxed{\text{Infection}} + \boxed{\text{SIRS}} = \boxed{\text{Sepsis}}$$

# Causes of SIRS, partial list

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- Infections
- Pulmonary embolism
- Myocardial infarction
- Dissection of the aorta
- Cardiac tamponade
- Acute pancreatitis
- Acute adrenal failure
- Burns
- Traumatism
- Surgery
- Shock of any etiology
- Substance overdose

# Severe sepsis

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**Sepsis + dysfunction of at least one organ or system different to the site of infection. For example:**

- Cardiovascular: systolic blood pressure  $\leq 90$  mmHg, that responds to intravenous fluids
- Renal: urine output  $< 0.5$  ml/kg per hour despite adequate fluid
- Respiratory: arterial Pa O<sub>2</sub> / Fi O<sub>2</sub>  $\leq 250$
- Hematologic: platelet count  $< 80,000/\text{mm}^3$ , or 50 % decrease over the previous 3 days
- Metabolic acidosis: pH  $\leq 7.30$  and plasma lactate level  $>1.5$  times upper limit of normal

# Septic shock

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## **Sepsis + at least one of the two following conditions:**

- Hypotension (systolic blood pressure < 90 mmHg, or 40 mmHg lower than patient's normal) for at least 1 hour despite adequate fluid resuscitation
- Need for vasopressors to maintain systolic blood pressure  $\geq$  90 mm Hg or mean arterial pressure  $\geq$  70 mmHg

$$\boxed{\text{Sepsis}} + \boxed{\text{Maintained hypotension}} = \boxed{\text{Shock septic}}$$

Infection + SIRS = Sepsis

Sepsis + Maintained hypotension = Septic shock

# Refractory septic shock

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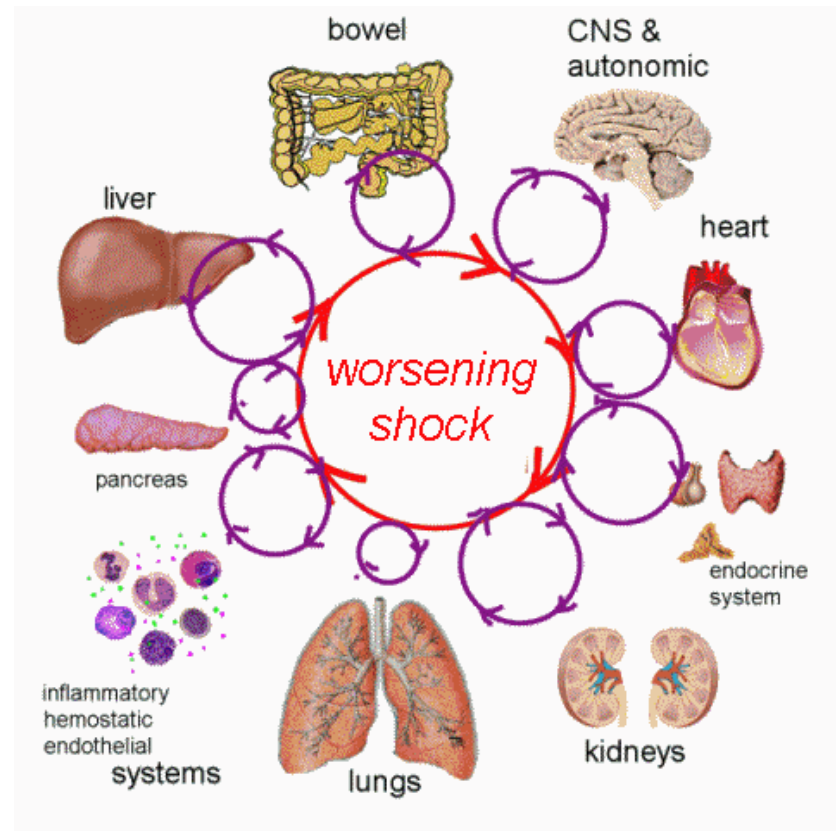
## Septic shock that ...

- Lasts for >1 h, and
- Does not respond to
  - Fluid or
  - Vasopressor drug administration

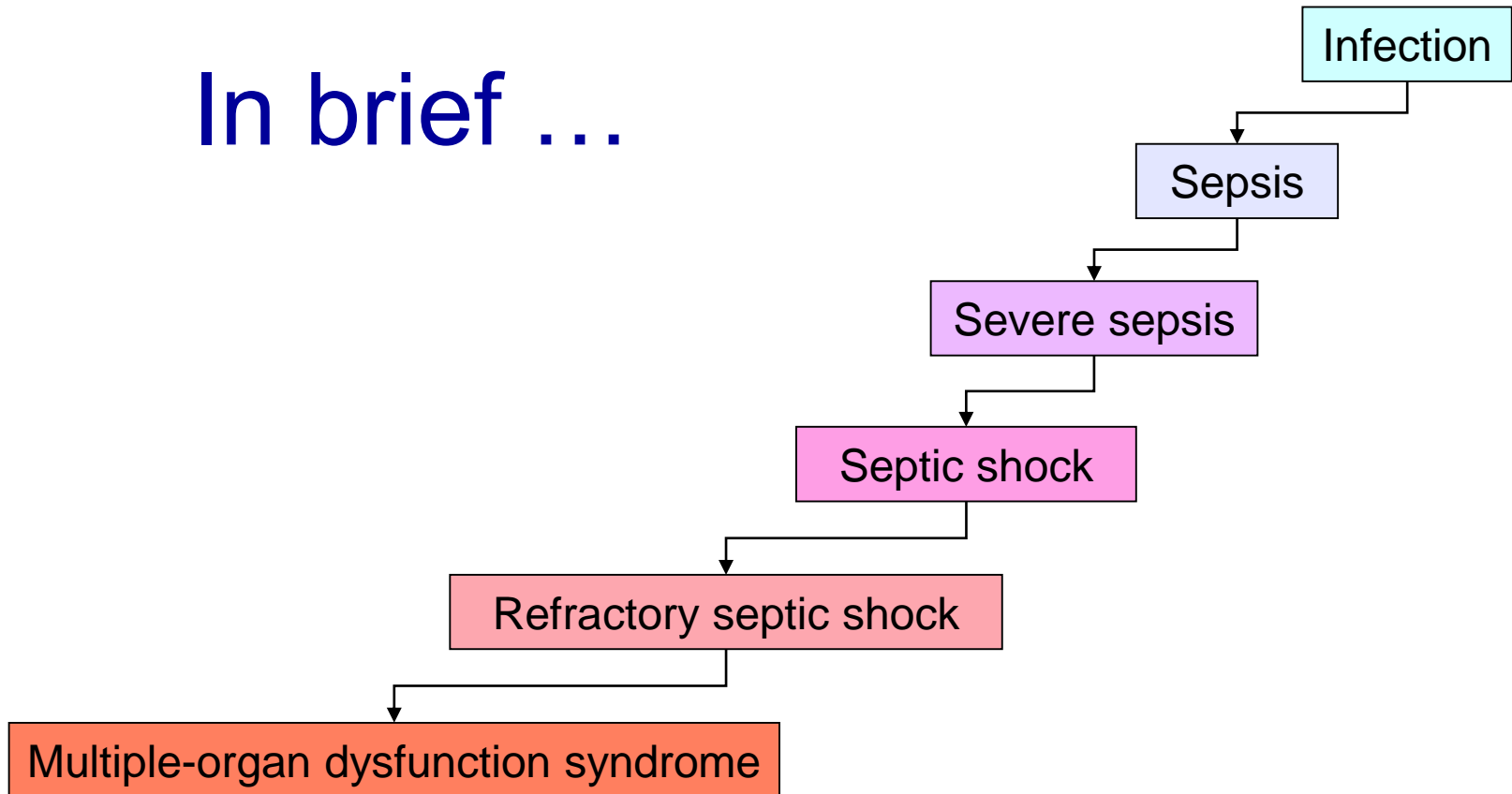
# Multiple-organ dysfunction syndrome

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**Dysfunction of more than one organ, requiring intervention to maintain homeostasis**



# In brief ...





# Epidemiology

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# Impact of sepsis syndrome

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- Incidence of severe sepsis or septic shock: 3 cases per 1,000 inhabitants and year
- 2/3 of sepsis cases in patients with significant underlying illnesses
- Occurs in 2 % of all hospitalizations, in 10 % of intensive care unit admissions
- Increase over last years due to:
  - Older population
  - Increased prevalence of chronic disease
  - Use of immunosuppressive drugs
  - Use of medical invasive procedures

# Etiology

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# Causative microorganisms

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- **Bacteriae:**
  - Gram-positive cocci
  - Gram-negative bacilli
  - Other
- Fungi
- Parasites
- Virus

# Source of infection leading to sepsis

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- **Lungs**
- **Abdomen**
- **Genitourinary tract**
- Wounds, including surgical
- Catheters
- Other

# Pathogenesis

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# Factors influencing the pathogenesis of sepsis - I

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- **Microorganisms**
  - **Endotoxins (bacterial wall)**
  - Exotoxins
- **Host cells**
  - **Macrophages**
  - **Neutrophils**
  - **Endothelial cells**
  - Dendritic cells
  - Lymphocytes

# Factors influencing the pathogenesis of sepsis - II

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- **Cytokines**
    - **Tumor necrosis factor alpha**
    - **Interleukin-1**
    - **Interleukin-10**
  - **Other substances**
    - Oxygen derivatives
    - Nitric oxide
    - Lipid mediators
- Proinflammatory
- Antiinflammatory
- 
- ```
graph LR; TNF[Tumor necrosis factor alpha] --- P[Proinflammatory]; IL1[Interleukin-1] --- P; IL10[Interleukin-10] --- A[Antiinflammatory];
```



# Factors influencing the pathogenesis of sepsis - III

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- **Body systems activation**
  - **Coagulation and fibrinolysis**
  - **Complement**
  - Neuroendocrine
- Organ dysfunction
  - Liver
  - Digestive tract

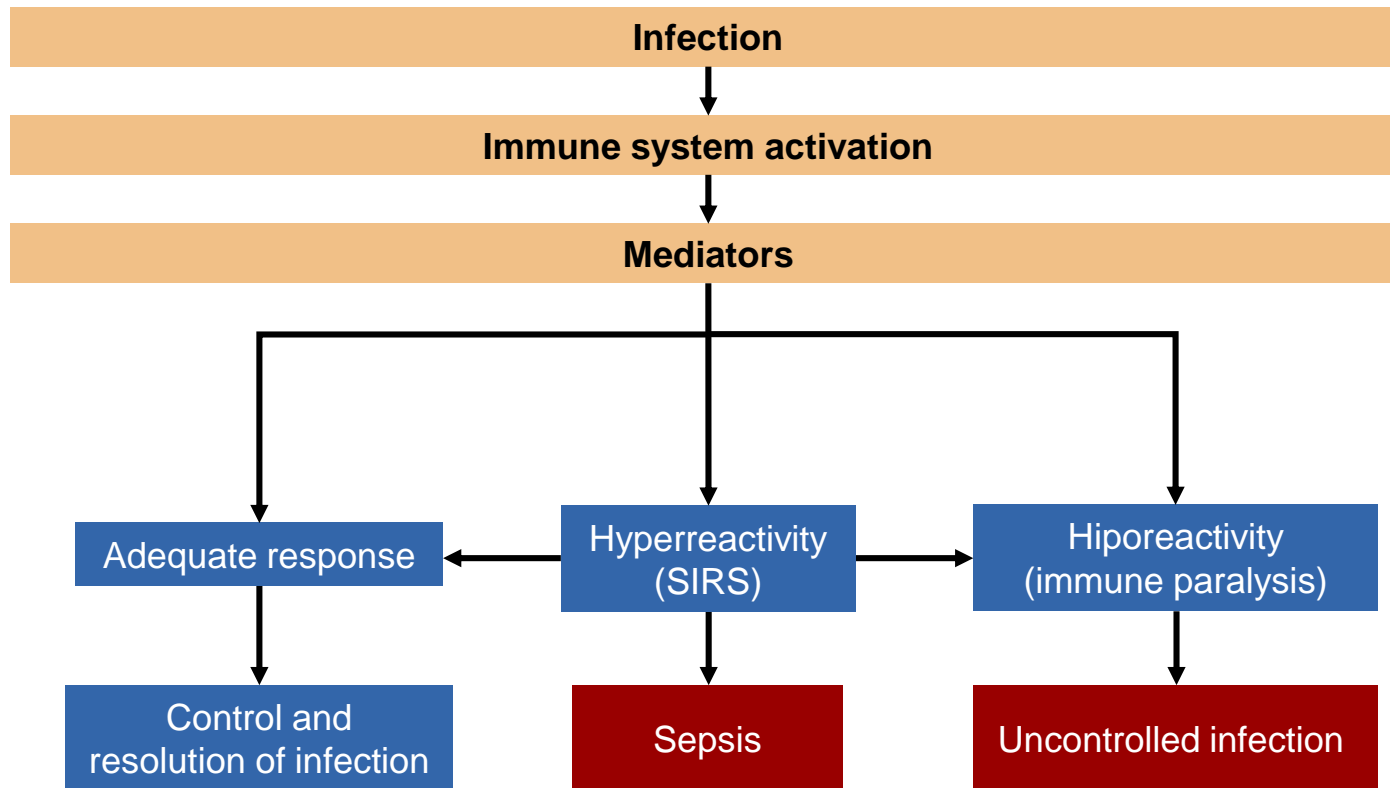
# Factors influencing the pathogenesis of sepsis - IV

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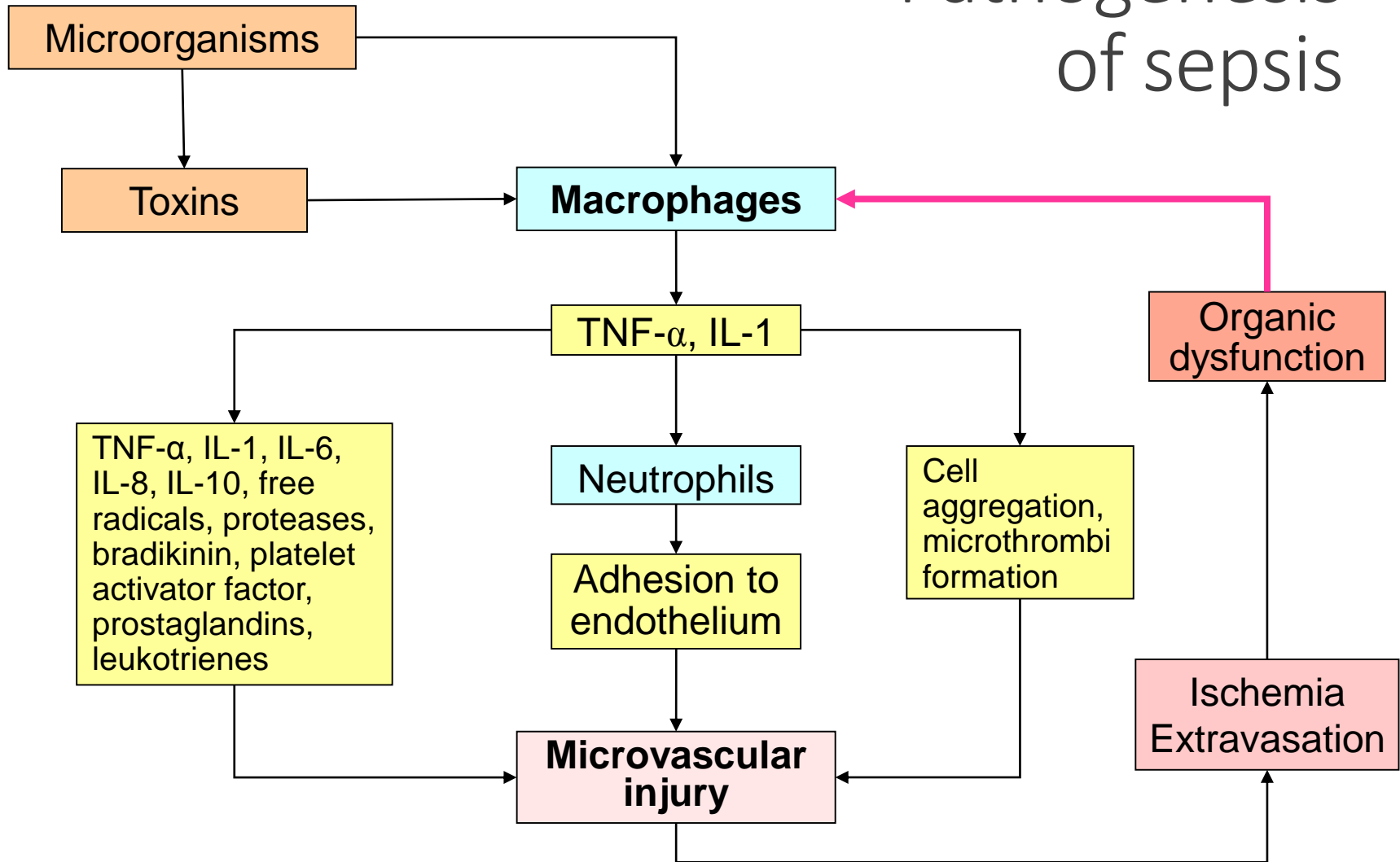
- Diverse cell receptor dysregulation
- Acceleration of apoptosis
- **Genetic factors**
- Iatrogenic effects

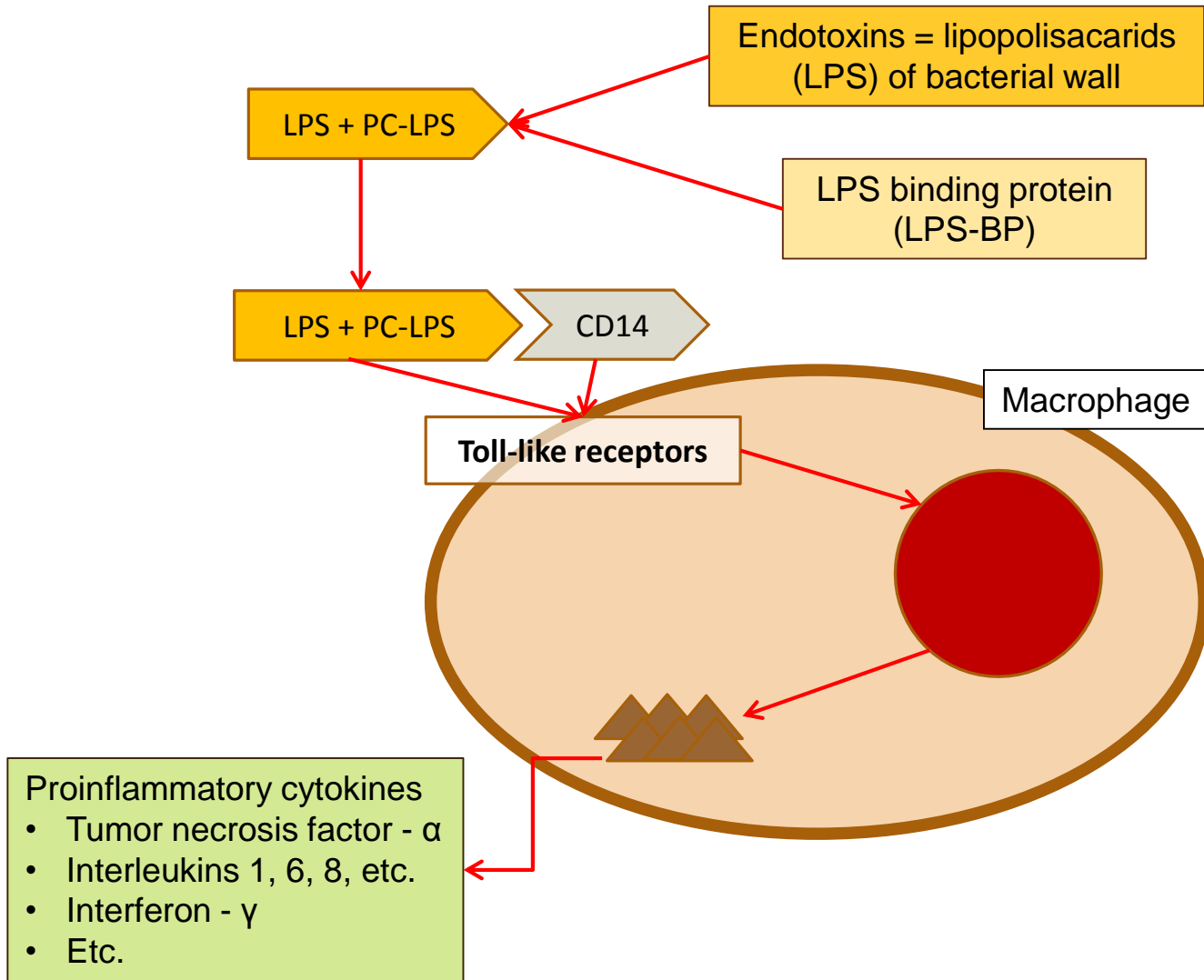
# Infection, sepsis and inflammatory response

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# Pathogenesis of sepsis





# Pathogenesis of septic shock

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- **Decreased systemic vascular resistance**, caused by:
  - Nitric oxide
  - Bradykinin
  - Prostacyclin
- Circulatory volume depletions caused by increased vascular permeability, etc.
- Abnormal distribution of blood among different organs

# Clinical manifestations

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# Clinical manifestations come from ...

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- ... concomitant illnesses
- ... the infection causing sepsis
- ... sepsis itself
- General symptoms
- Symptoms from different affected organs



**Complex and varied clinical presentation**



# General manifestations

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- Fever
- Hypothermia, alcohol abusers or old patients
- Hyperventilation
- Hypotension
- Signs of de DIC
  - Ischemia
  - Bleeding



Sepsis and DIC due to *Neisseria meningitidis*



Purpura and edema due to *N. Meningitidis* sepsis and DIC

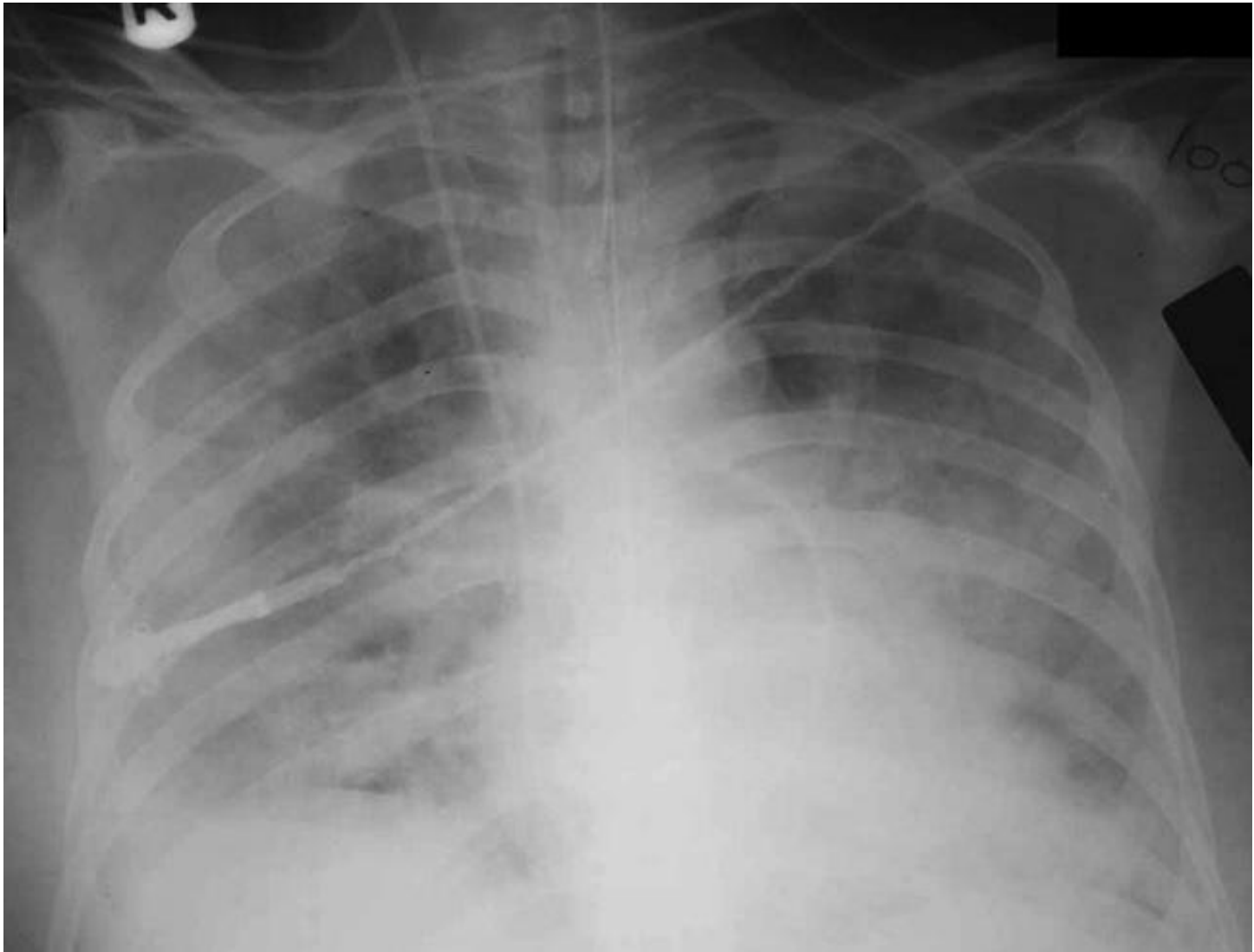
# Heart and lung manifestations

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- Myocardial pathology
- Lung ventilation – perfusion mismatch → hypoxia
- **Increased alveolar capillary permeability → adult respiratory distress syndrome → hypoxia**



Adult respiratory distress syndrome



Adult respiratory distress syndrome

# Neurologic manifestations

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- Encephalopathy: obtundation and disorientation
- Worsening of previously present symptoms
- Polyneuropathy:
  - Axonal
  - Motor → weakness and muscular atrophy
  - Distal
  - Frequently impedes ventilator weaning

# Skin manifestations

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- Microorganisms and toxins → macules, papules, pustules, bullae, cellulitis, bruising, etc.
- DIC → petechiae and purpura
- Peripheral hypoperfusion → slow capillary filling, distal cyanosis and necrosis



Macules and bullae



## Morbilliform rash





Hand gangrene due to sepsis and DIC

# Gastrointestinal manifestations

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- Nonspecific gastrointestinal symptoms such as nausea, diarrhea, etc.
- Mild cholestasis
- Paralytic ileus
- Other conditions:
  - Stress ulcers in the stomach
  - Acute hepatocellular necrosis
  - Acute intestinal ischemia



Normal



Paralytic ileus

# Kidney manifestations

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- Decreased urine output
- Renal failure
- Renal hypoperfusion → acute tubular necrosis

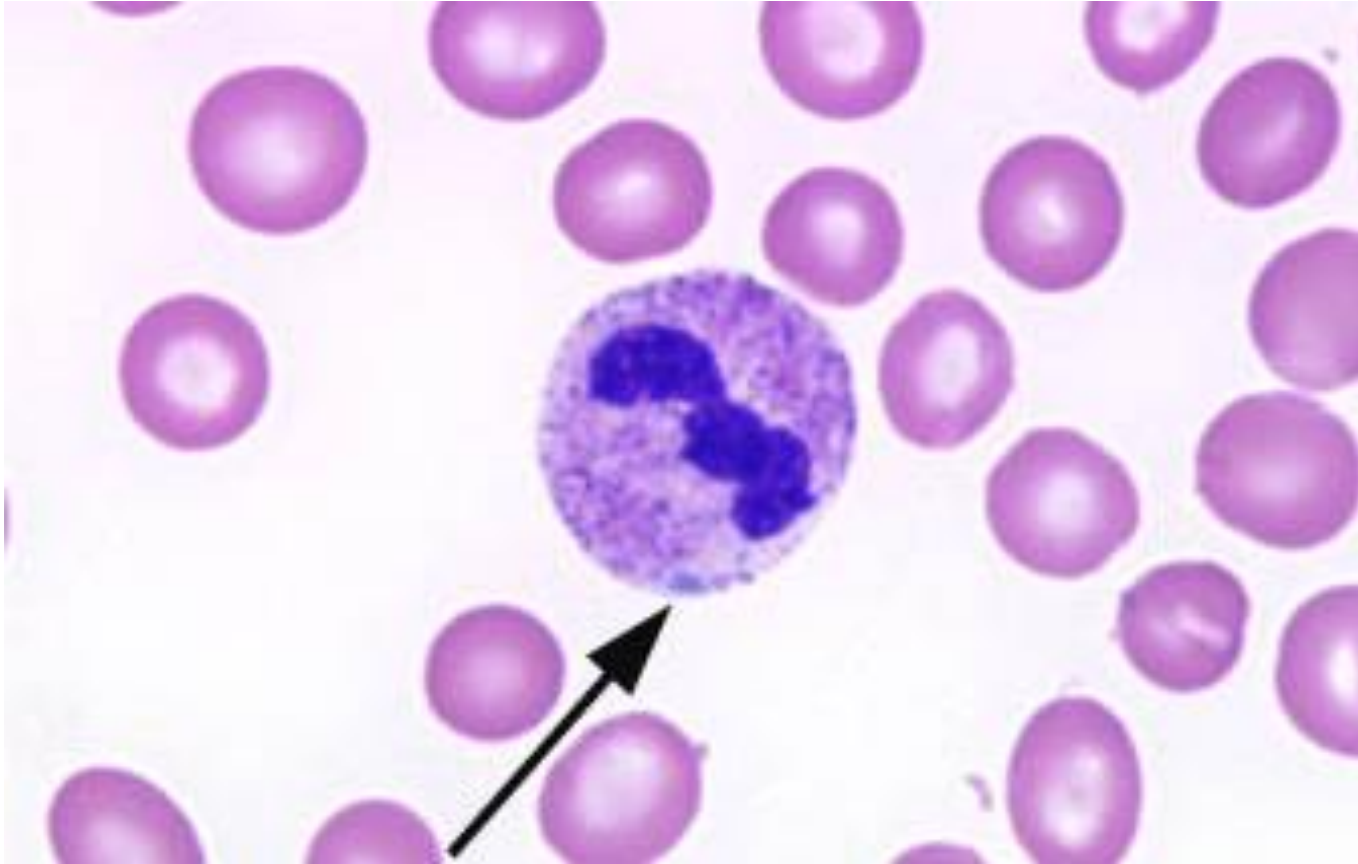
# Analysis abnormalities

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# Frequent alterations - I

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- Leukocytosis with left shift
- Thrombocytopenia
- Increased bilirubin and liver enzymes
- Respiratory alkalosis → metabolic acidosis
- Increased lactic acid
- Hyperglycemia
- Hypoalbuminemia
- Hypoxia



Toxic granulation and Döhle body (arrow)



# Frequent alterations - II

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- Increased creatinine and blood urea nitrogen
- Proteinuria
- DIC:
  - Prolonged prothrombin time, or increased international normalized ratio
  - Prolonged activated partial thromboplastin time
  - Decreases fibrinogen
  - Presence of D dimer or other fibrin degradation products

# Diagnosis

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# Relevance and difficulties

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- **Sepsis, essentially a clinical diagnosis**
- Must be diagnosis “asap”
- Differential diagnosis is extensive:
  - That of SIRS
  - That of shock

# Helpful diagnostic procedures

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- Microbiology studies:
  - Gram stain and culture of body specimens
  - Molecular techniques
  - Serologies and other tests
- Procalcitonin serum level:
  - ↑ in bacterial infections
  - Useful for diagnosis, prognosis and control of response to treatment
- Image studies



Pneumonia



Acute cholecystitis

# Treatment

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# Principles of treatment

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- Start treatment **“asap”**
- In an Intensive Care Unit (ICU) (or in an Emergency Room [ER])
- **At the same time:**
  - Control of infection
  - Supportive measures



# Control of infection

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- Drainage if needed:
  - Percutaneous needle aspiration
  - Surgery
- Antimicrobials:
  - After obtaining specimens for gram and culture
  - Individualize the election
  - Broad-spectrum → narrow-spectrum when possible

# Supportive measures

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- Main objective: to maintain the provision of **oxygen** and other **vital substrates** to the distinct organs
- If hypotension: intravenous perfusions → inotropic agents → corticosteroids → (vasopressin)
- If hypoxia: noninvasive or invasive ventilation with low volumes
- Other commonly needed treatments:
  - Dialysis
  - Transfusions
  - Bicarbonate, if lactic acidosis
  - Rehabilitation if clinical improvement

# Antagonists of mediators of SIRS

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- Drotrecogin- $\alpha$  (recombinant activated C-reactive protein)
  - Antiinflammatory
  - Antithrombotic
  - Anticoagulant
- Endotoxin antagonists
- Etc.

# Prognosis

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# Sepsis, a condition with a grim prognosis

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- Death at 30 days:
  - > 25 % of those with severe sepsis
  - > 50 % of those with septic shock
- Factors that increase the risk of death:
  - Advanced age
  - Preexistent comorbidity
  - Sepsis caused by hospital acquired pneumonia
  - Sepsis due to ...
    - *Pseudomonas aeruginosa*
    - *Candida albicans*
    - Multiresistant *Enterococcus faecium*
- Sepsis is an independent predictor of death

# Prevention

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# General measures

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- Treatment of infections “asap”
- Any measures that prevent infections:
  - Adequate use of vaccines
  - Use of antibiotic prophylaxis when needed, as for example in advanced HIV-infection
  - Treatment of immunodeficiencies when feasible
  - Judicious use of immunosuppressants and invasive diagnostic procedures
  - Avoid the unjustified use of antibiotics
  - Etc.

# Key messages

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# To remember...

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- Sepsis is a very common condition that may adopt many clinical presentations
- Prompt diagnosis and treatment of sepsis is key to reduce mortality of the disease

# Further reading

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# Used references

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- Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill, 2012. Chapter 271.
- Dellinger RP, Levy MM, Rhodes A et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. Crit Care Med 2013; 41: 580-637.
- Angus DC, van der Poll T. Severe sepsis and septic shock. N Engl J Med 2013; 369: 840-51.

# Preparing the exam

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- Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, editors. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill, 2012. Chapter 271.
- These slides