Infectious Diseases

Lesson 2

SEPSIS SYNDROME

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Objectives and learning goal

Objectives

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

Learning goal

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

Contents

Definitions

Infection

- 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)

At least two of the following conditions:

- Fever (oral temperature > 38 °C) or hypothermia (oral temperature < 36 °C)
- Heart rate > 90 beats per minute
- Tachypnea (> 24 respirations per minute), or hyperventilation (arterial Pa CO_2 < 32 mm Hg) or invasive or noninvasive ventilation needed
- Leukocytosis (> 12,000/mm^3), or leukopenia (< 4,000/mm^3), or > 10 % bands in white blood cell count

Sepsis

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

Causes of SIRS, partial list

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

Severe sepsis

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

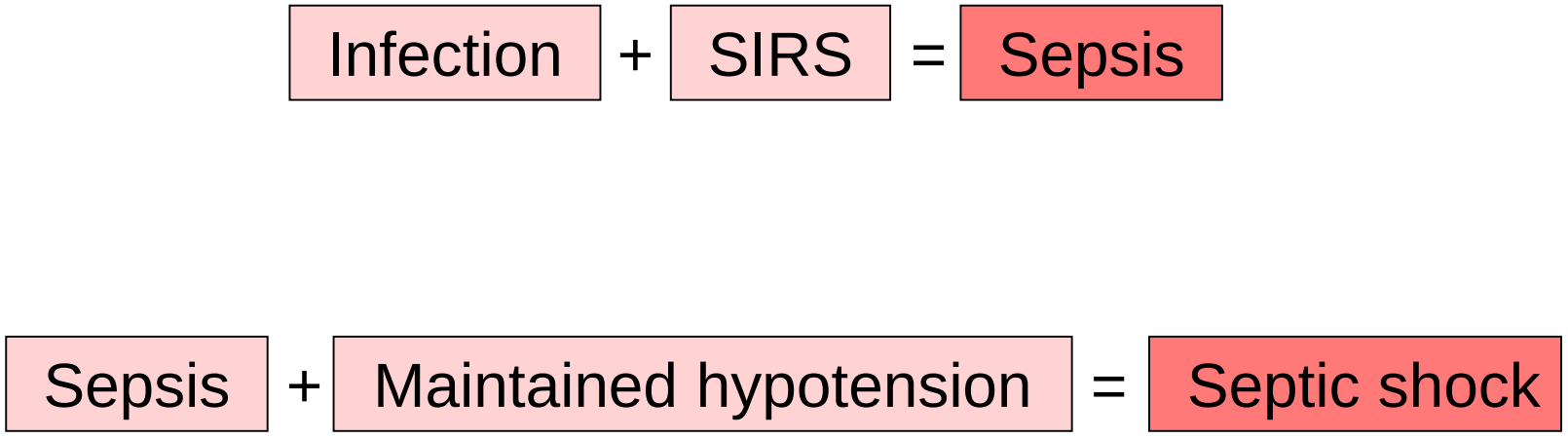
- Cardiovascular: systolic blood pressure ≤ 90 mmHg, that responds to intravenous fluids
- Renal: urine output < 0.5 ml/kg per hour despite adequate fluid
- Respiratory: arterial Pa O_2 / Fi O_2 ≤ 250
- Hematologic: platelet count < 80,000/mm^3, or 50 % decrease over the previous 3 days
- Metabolic acidosis: pH ≤ 7.30 and plasma lactate level >1.5 times upper limit of normal

Septic shock

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 ≥ 90 mm Hg or mean arterial pressure ≥ 70 mmHg

Sepsis + Maintained hypotension = Shock septic


Infection
+
SIRS
=
Sepsis
Sepsis
+
Maintained hypotension
=
Septic shock

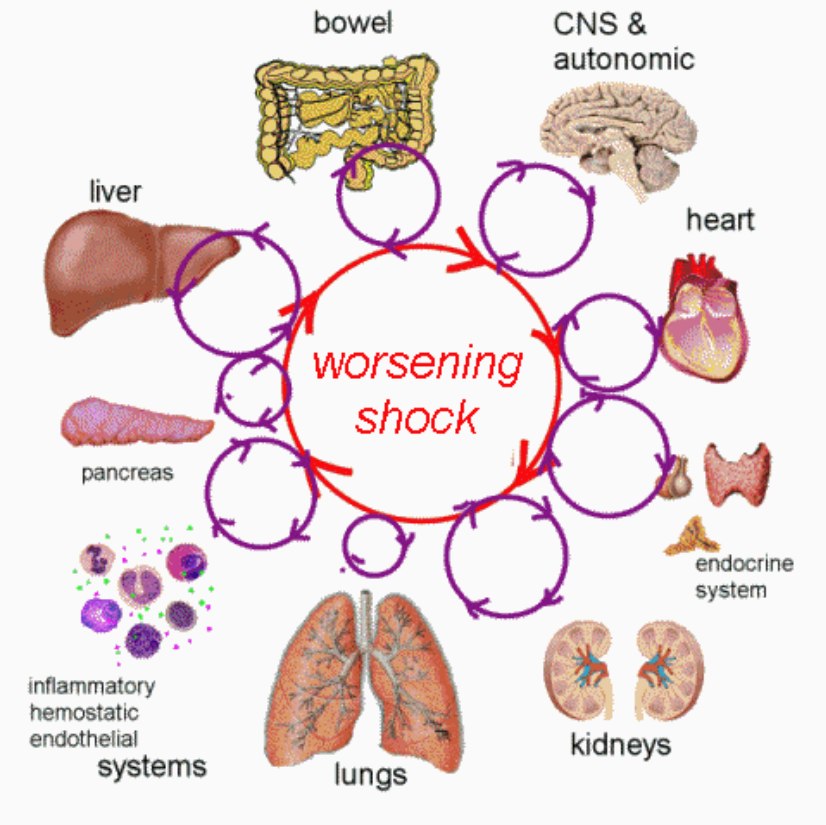
Refractory septic shock

Septic shock that …

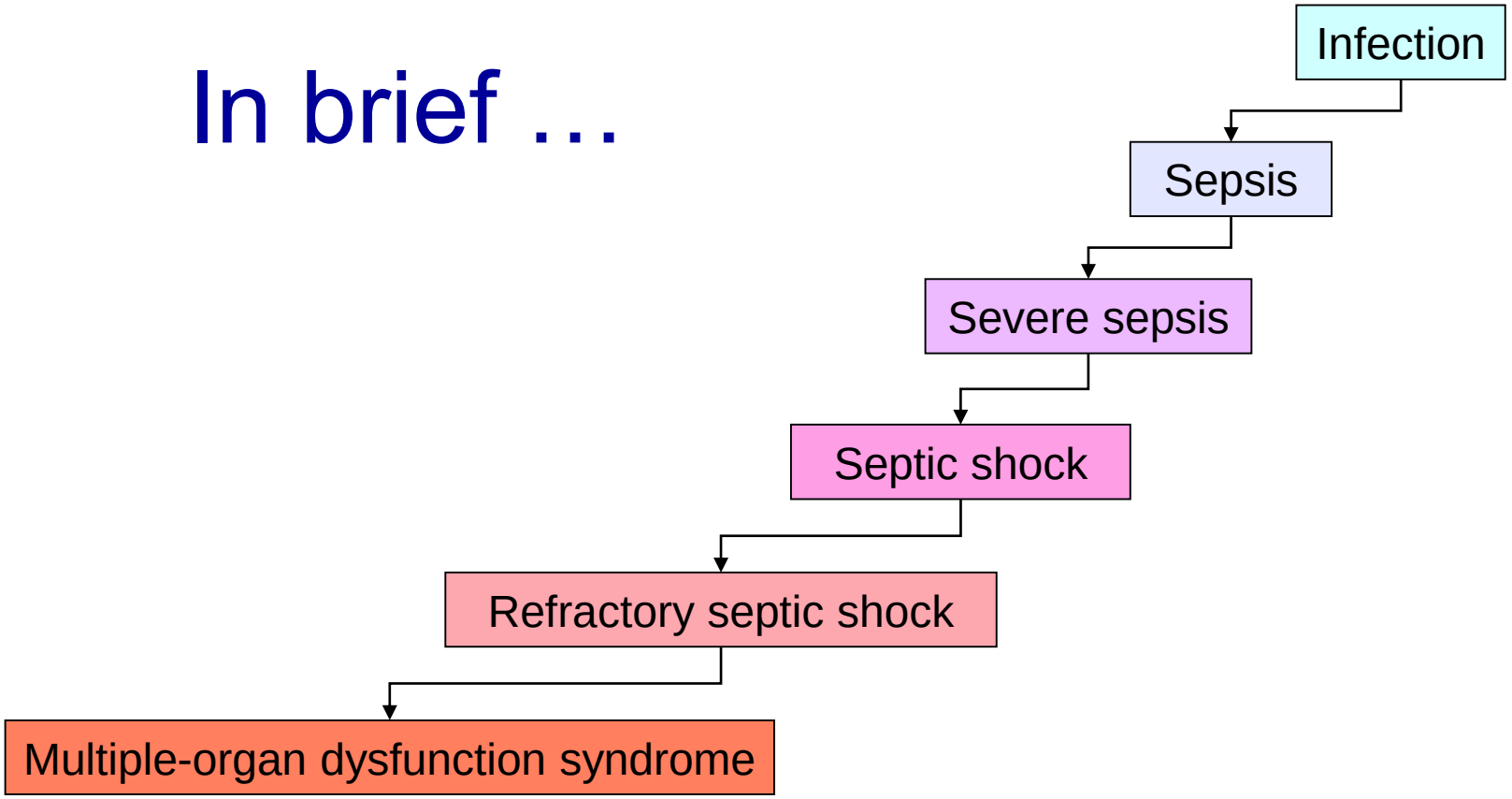
- Lasts for >1 h, and
- Does not respond to
  - Fluid or
  - Vasopressor drug administration

Multiple-organ dysfunction syndrome

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



In brief …


Infection
Sepsis
Severe sepsis
Septic shock
Refractory septic shock
Multiple-organ dysfunction syndrome

Epidemiology

Impact of sepsis syndrome

- 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

Causative microorganisms

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

Source of infection leading to sepsis

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

Pathogenesis

Factors influencing the pathogenesis of sepsis - I

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

Factors influencing the pathogenesis of sepsis - II

- **Cytokines**
  - **Tumor necrosis factor alpha**
  - **Interleukin-1**
  - Interleukin-10

Proinflammatory

Antiinflammatory

- Other substances
  - Oxygen derivatives
  - Nitric oxide
  - Lipid mediators

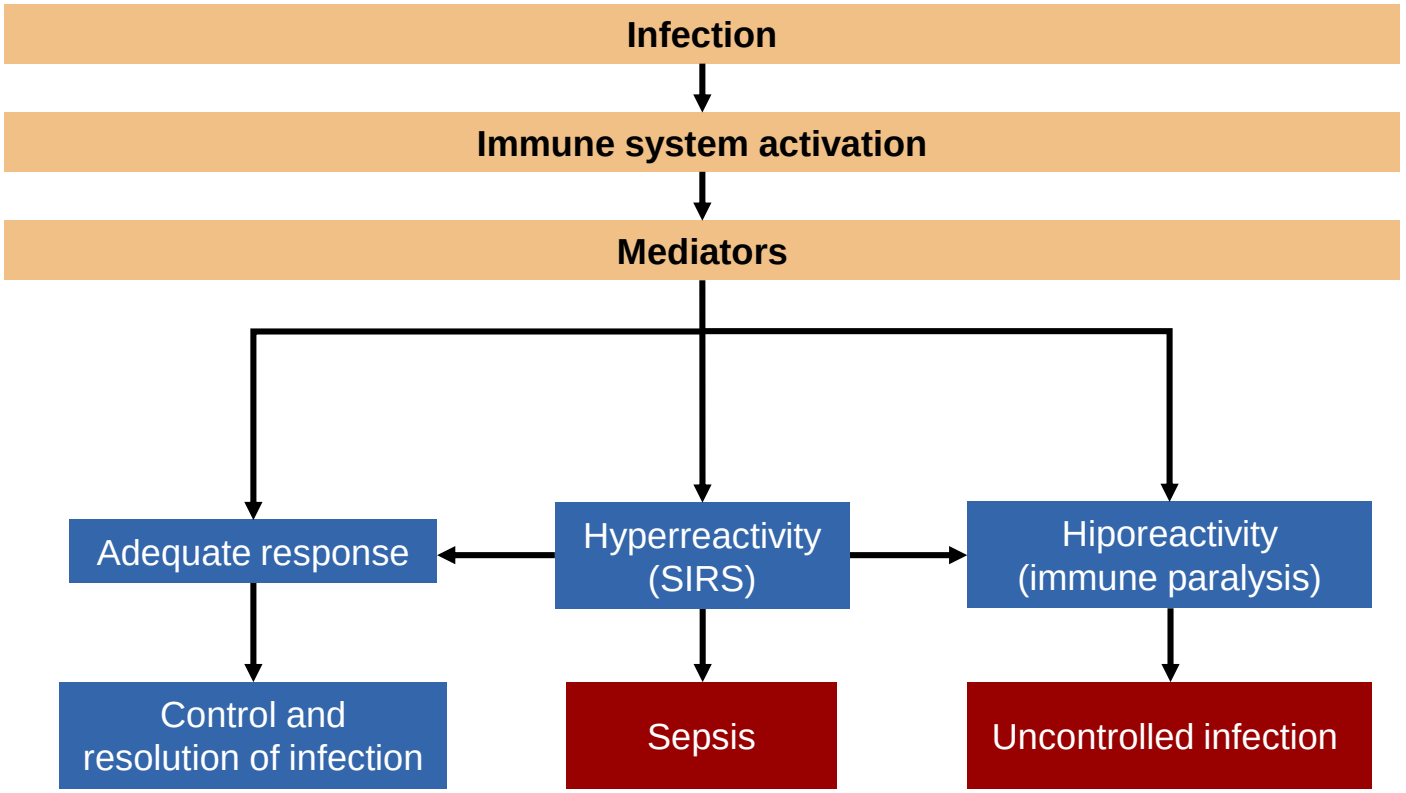
Factors influencing the pathogenesis of sepsis - III

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

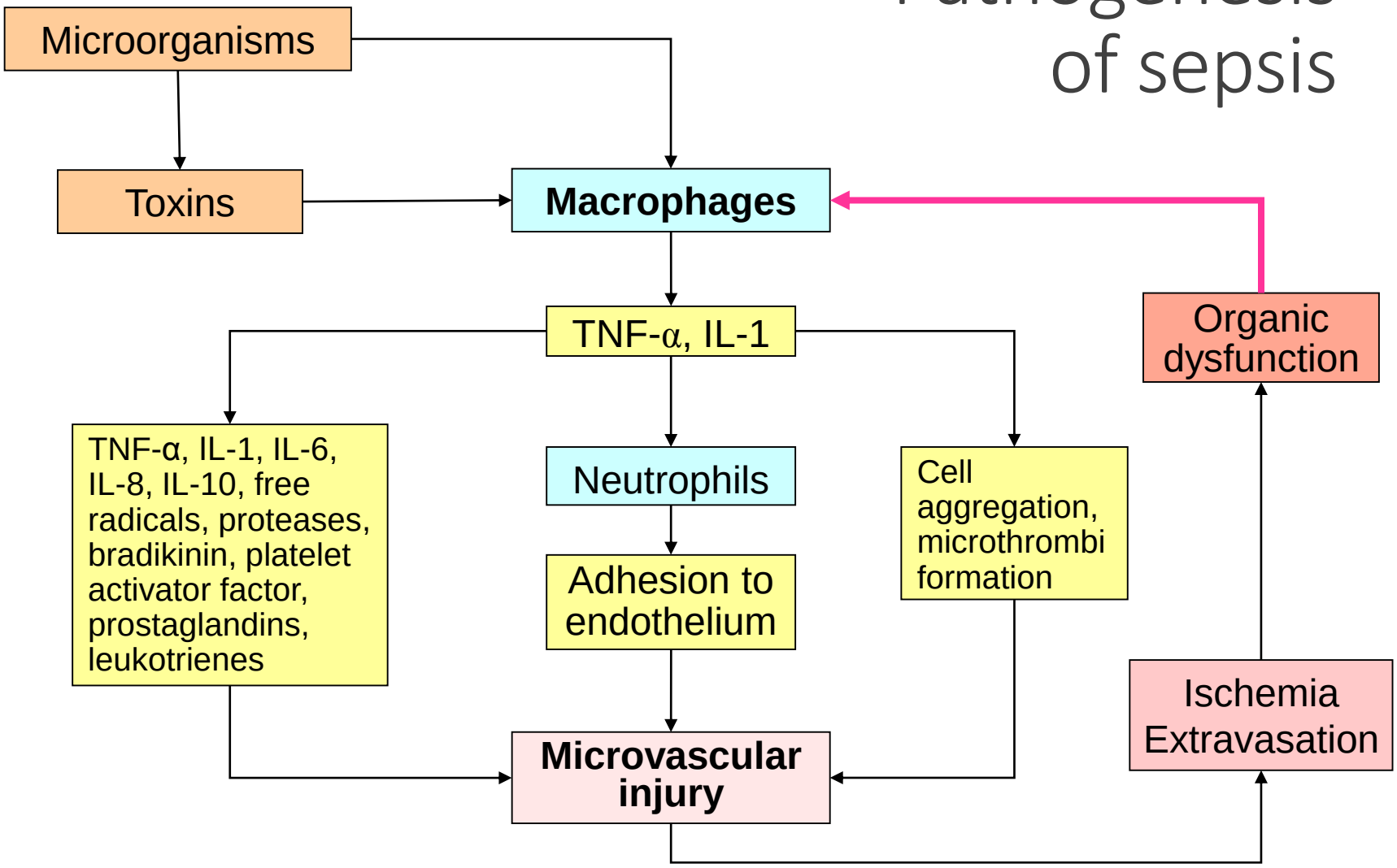
Factors influencing the pathogenesis of sepsis - IV

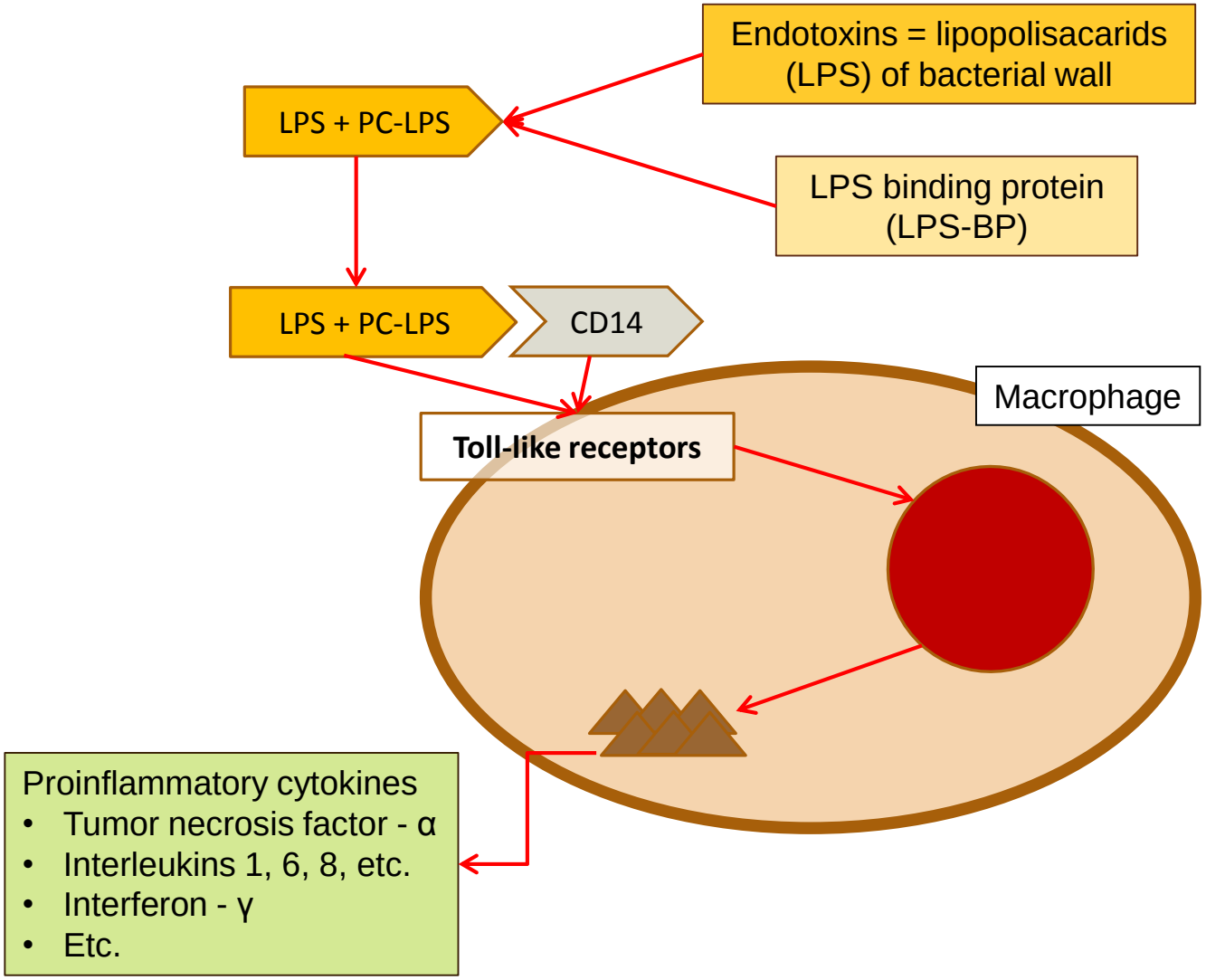
- Diverse cell receptor dysregulation
- Acceleration of apoptosis
- **Genetic factors**
- Iatrogenic effects

Infection, sepsis and inflammatory response



Pathogenesis of sepsis




Endotoxins = lipopolisacarids (LPS) of bacterial wall
LPS + PC-LPS
LPS binding protein (LPS-BP)
LPS + PC-LPS
CD14
Macrophage
Toll-like receptors
Proinflammatory cytokines
• Tumor necrosis factor - α
• Interleukins 1, 6, 8, etc.
• Interferon - γ
• Etc.

Pathogenesis of septic shock

- **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

Clinical manifestations come from …

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

Complex and varied clinical presentation

General manifestations

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

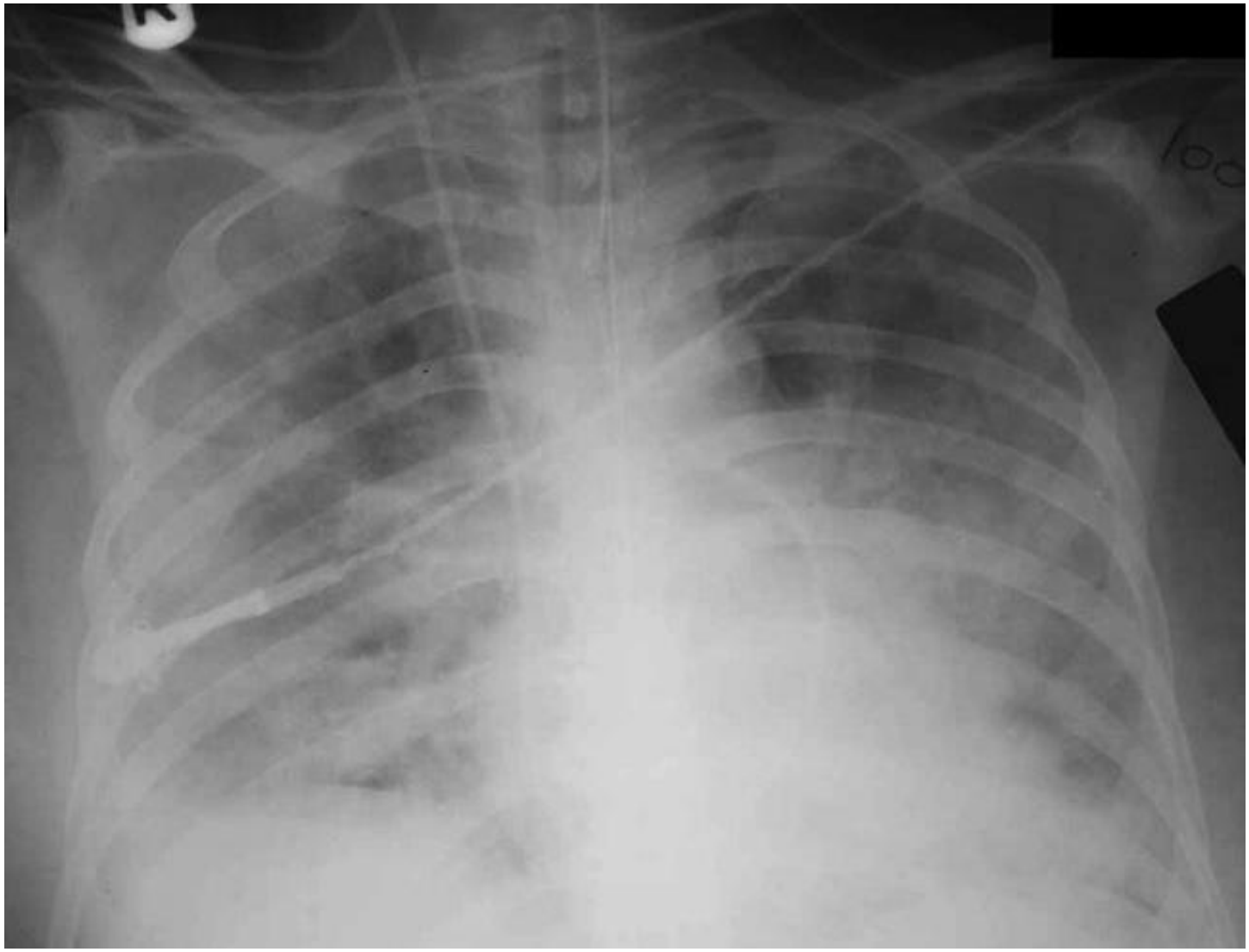
Sepsis and DIC due to *Neisseria meningitidis*

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

Heart and lung manifestations

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

Adult respiratory distress syndrome



Adult respiratory distress syndrome

Neurologic manifestations

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

Skin manifestations

- 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

- Nonspeciphic 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

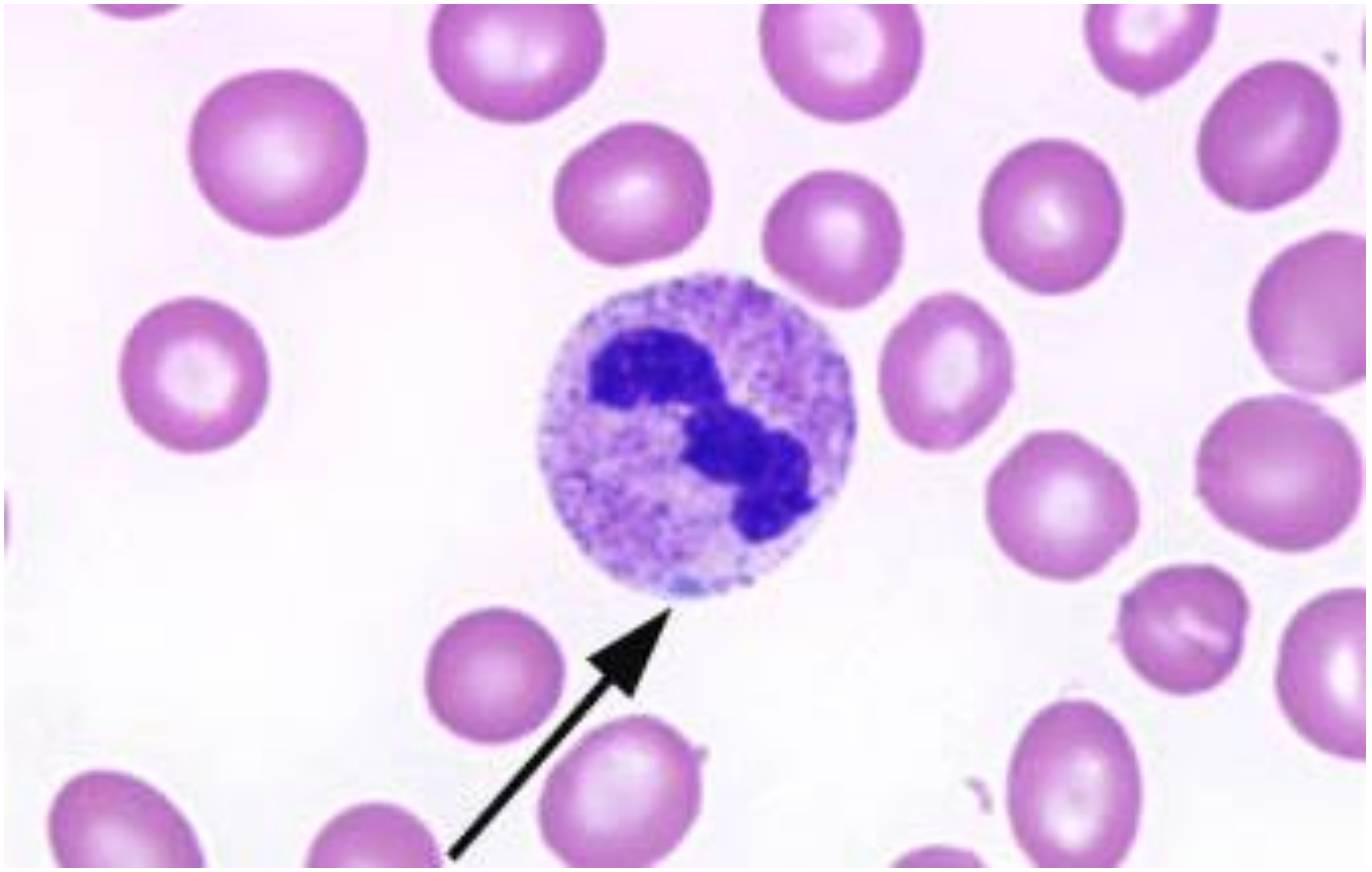
Kidney manifestations

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

Analysis abnormalities

Frequent alterations - I

- 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

- 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

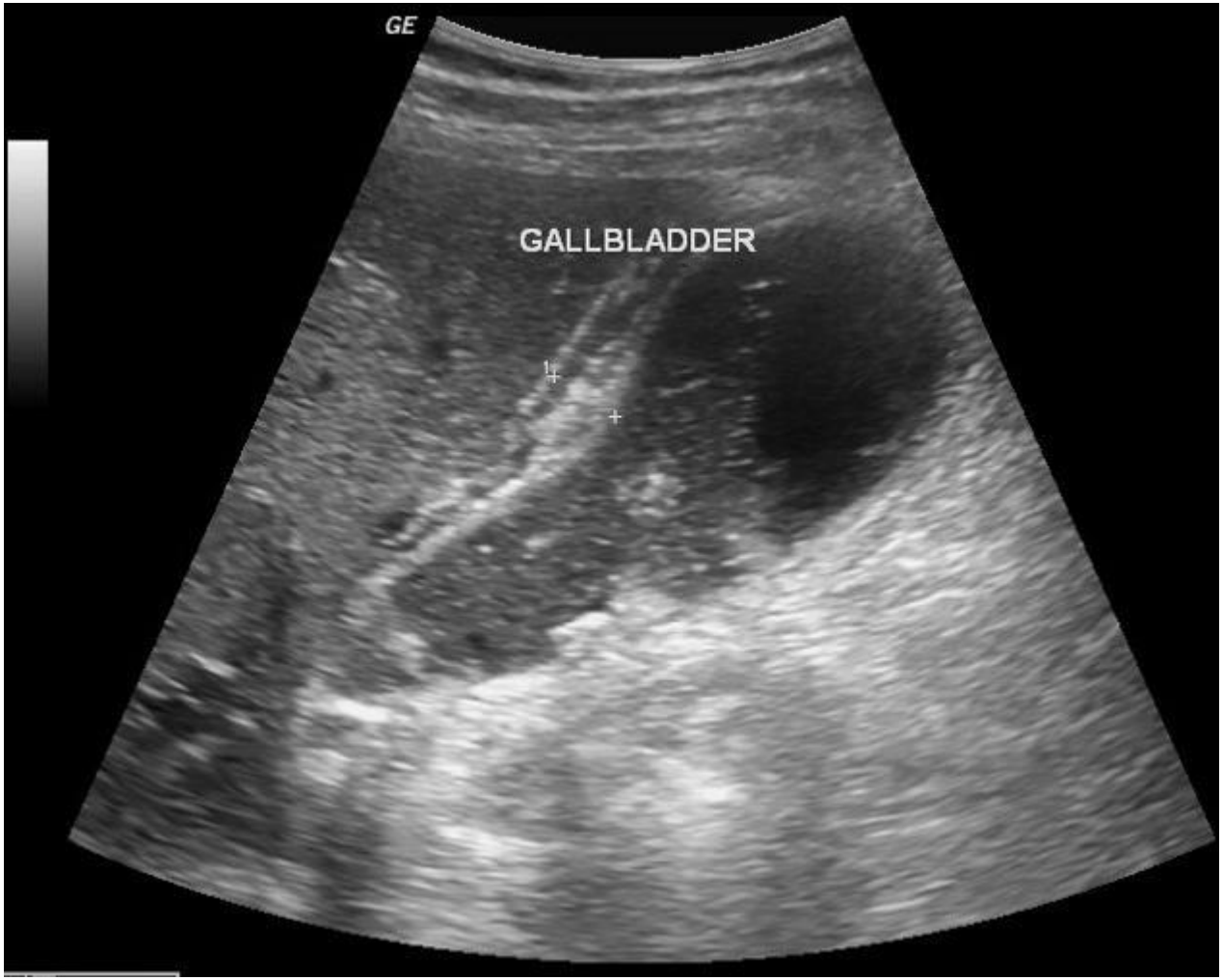
Relevance and difficulties

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

Helpful diagnostic procedures

- 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

Principles of treatment

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

Control of infection

- 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

- 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

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

Prognosis

Sepsis, a condition with a grim prognosis

- 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

General measures

- 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

To remember…

- 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

Used references

- 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

- 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