TEACHING UNIT 6

IMMUNE RESPONSE TO TRANSPLANTED TISSUES

CONGENITAL IMMUNODEFICIENCY

SEPSIS AND SEPTIC SHOCK

IMMUNE RESPONSE TO TRANSPLANTED TISSUES

Dictionary

transplant	graft
The person who gives graft	donor
The person who accepts graft	recipient (host)
genetically identical animals (and grafts)	syngeneic animals (syngeneic grafts)
transplantation within the same species	allogeneic or allo-transplantation
transplantation between different species	xenogeneic or xeno-transplantation
antigens that are the target of rejection	Alloantigens and xenoantigens
antibodies and T lymphocytes that react against those antigens	Alloreactive and xenoreactive

Evidence that graft rejection is basically an immune response

Evidence	Conclusion
Prior exposure to donor MHC molecules leads to accelerated graft rejection	Graft rejection shows memory and specificity, two cardinal features of adaptive immunity
The ability to reject a graft rapidly can be transferred to a naive individual by lymphocytes from a sensitized individual	Graft rejection is mediated by lymphocytes
Depletion or inactivation of T lymphocytes by drugs or antibodies results in reduced graft rejection	Graft rejection requires T lymphocytes

...let us remember

Transplantation antigens

Proteins encoded by MHC genes:

- ✓ three genes for α chain of MHC molecule class I on each chromosome:

  3x2 = 6 different products of class I on each cell
- ✓ three genes for α chain and three or four genes for β chain (which can be combined) of class II on each chromosome

  ≈ 20 different products of MHC class II on each professional APC

- ✓ large number of HLA alleles in the population

...let us remember

... in each individual, CD4+ and CD8+ T lymphocytes that recognize their own MHC were selected in the thymus **(MHC restriction)**

... therefore, all mature CD4+ and CD8+ T lymphocytes in the periphery recognize peptides displayed only in the context of their own MHC

The conclusion would be: :

The individual does not have clones of T lymphocytes that recognize peptides in the context of other people's MHC products! ! !

Question:

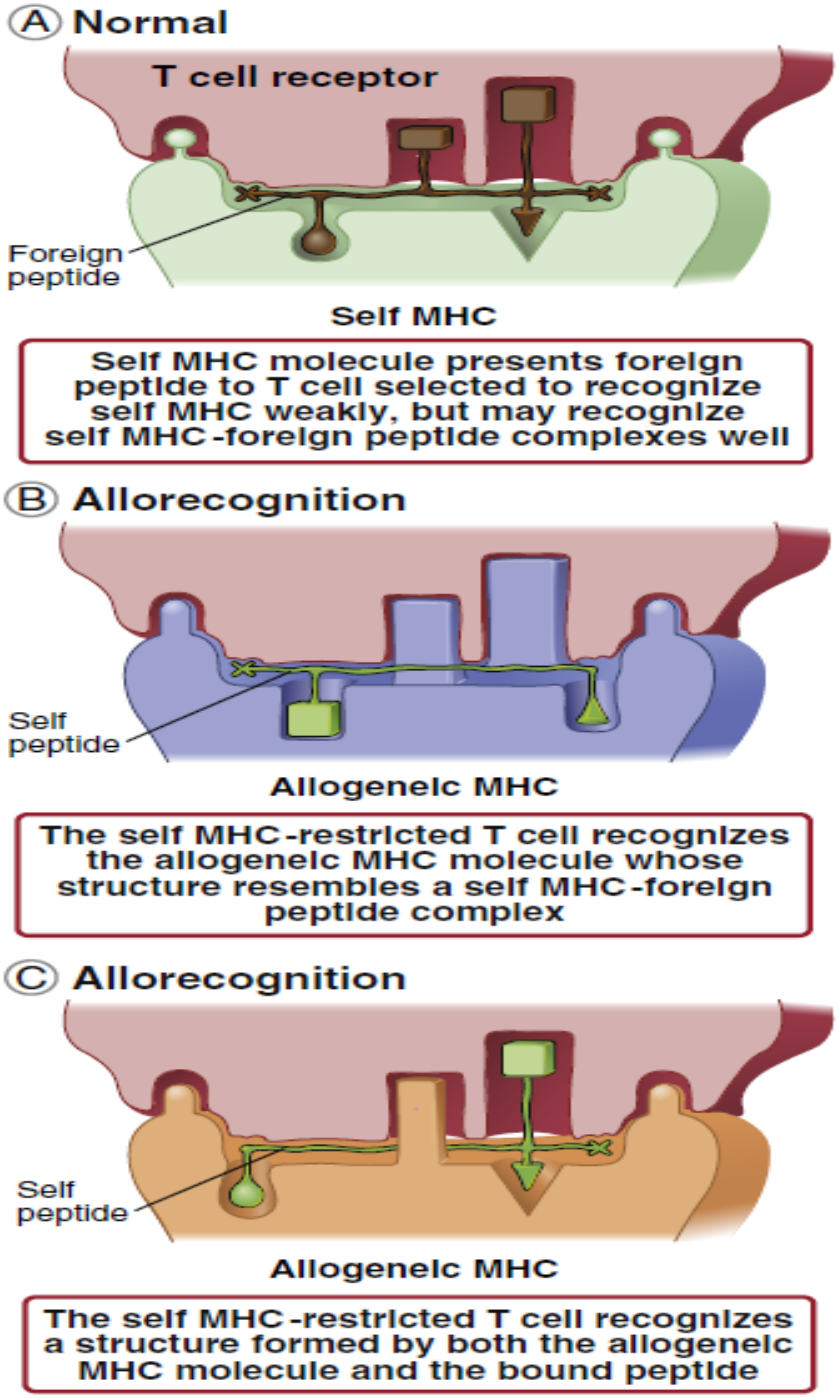
Why would one person's T lymphocytes recognize another person's MHC molecules?

fact (paradox):

The reaction to foreign MHC is one of the strongest immune reactions

Explanation :

Allogeneic MHC molecules displaying peptides of an allogeneic cell can look like its own MHC with a foreign peptide – **cross reaction**

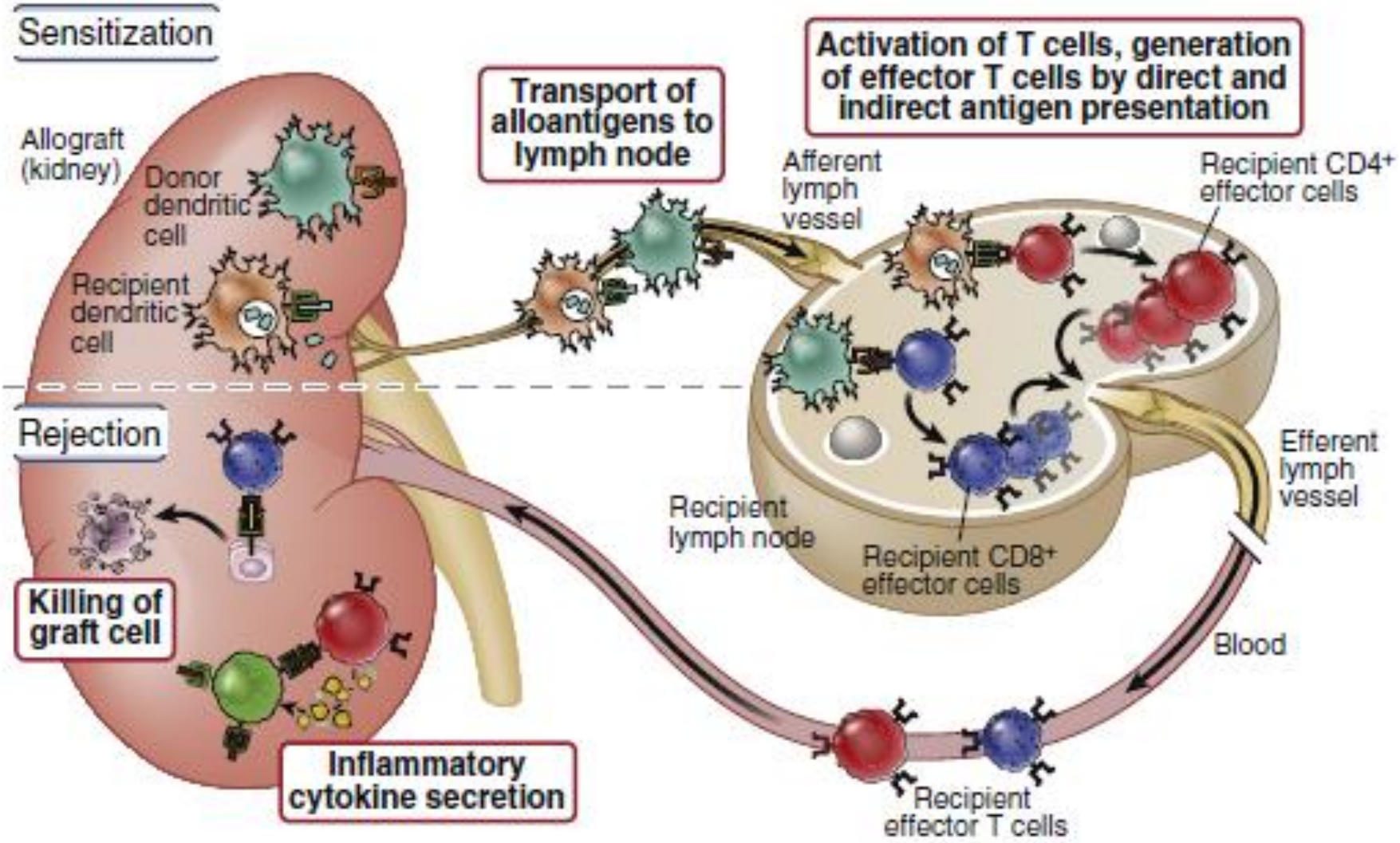


It can be seen that many clones can participate in the reactions

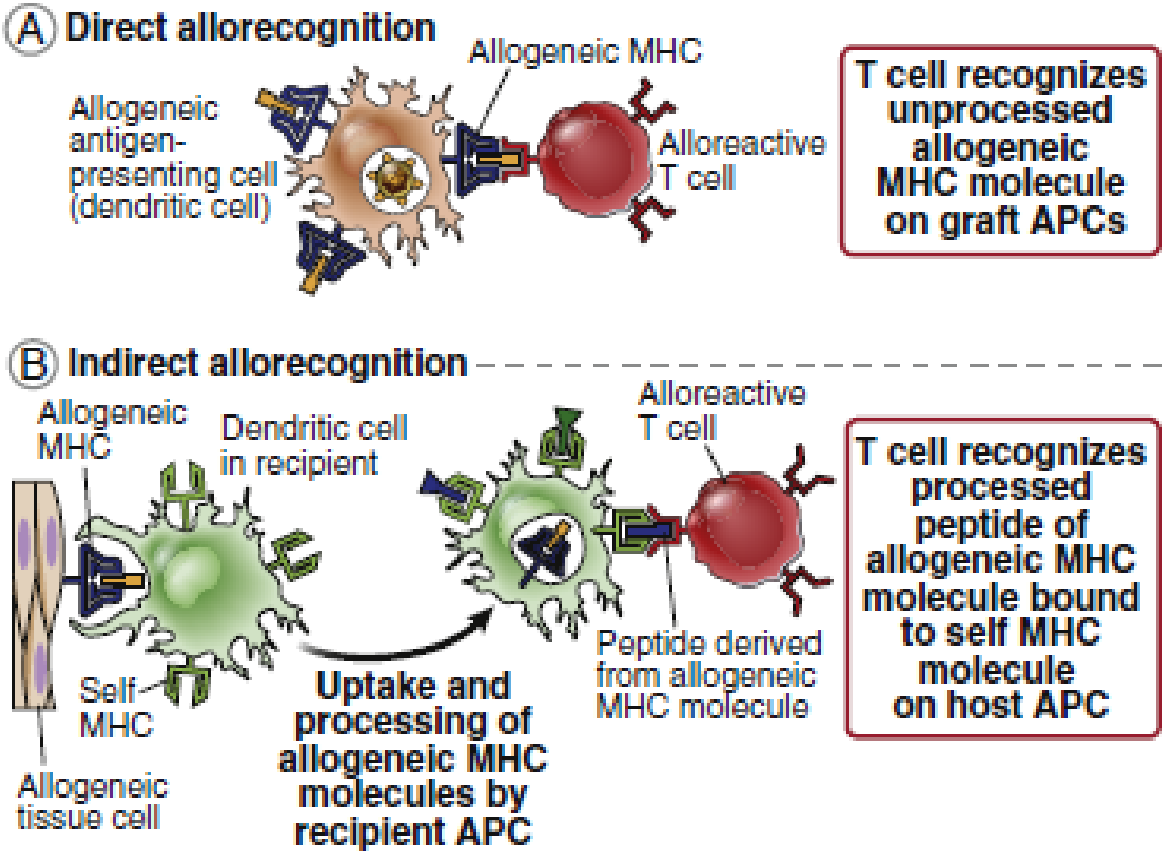
In addition, one cell of the allograft expresses thousands of MHC molecules, while in the case of infection only a small number of its own MHC molecules present the microorganism's peptide –

that is why the reaction of T lymphocytes to alloantigens is so strong

Induction of an immune response against the graft



Induction of an immune response against the graft



DIRECT RECOGNITION :

Only possible if the graft contains APCs (dendritic cells). This is how effector alloreactive T lymphocytes (CTL) are formed

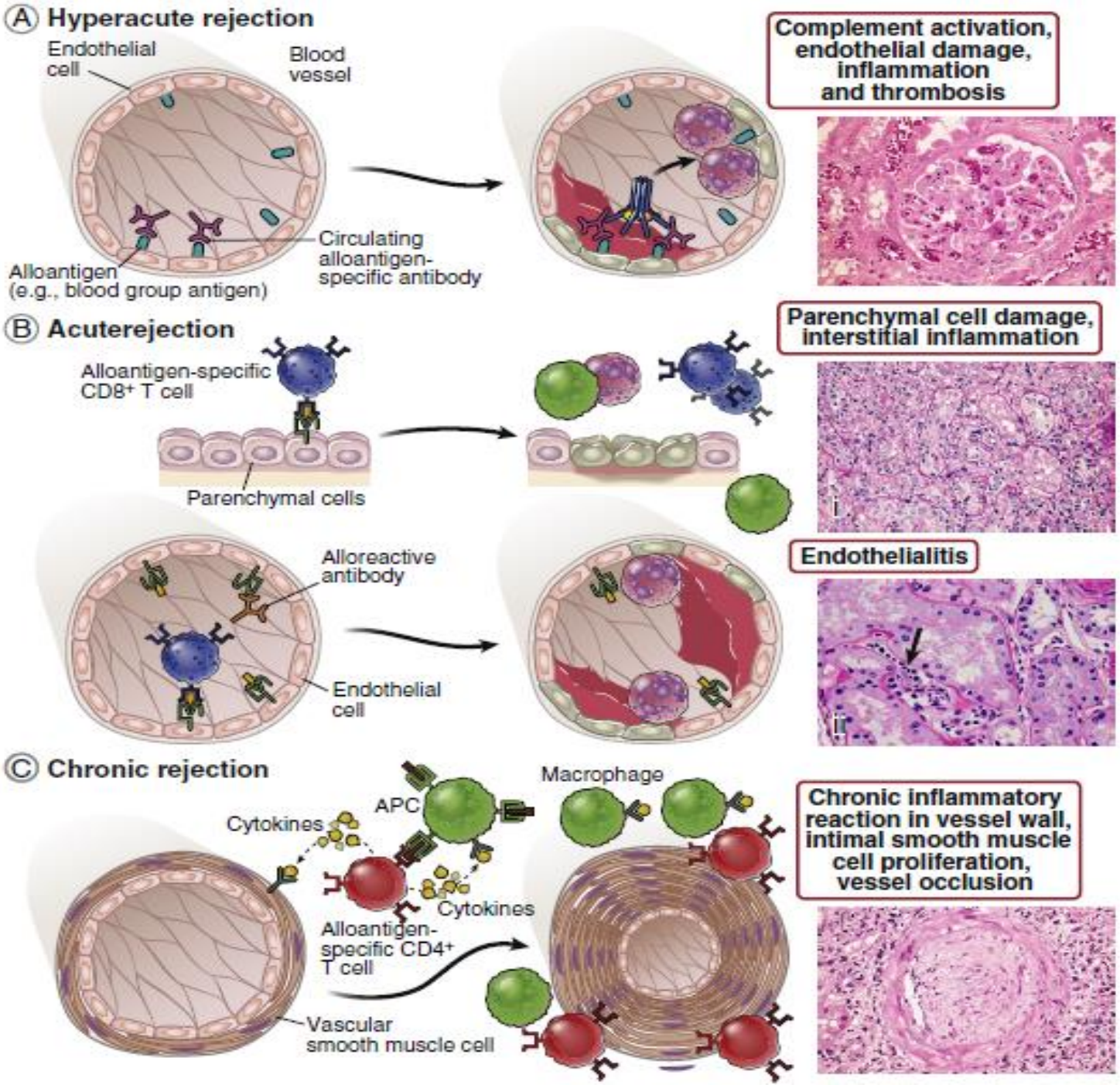
ACUTE REJECTION

INDIRECT RECOGNITION:

Host APCs phagocytose donor cells, process donor alloantigens (MHC and other proteins) and display them in the context of their own MHC **(Th)**

CHRONIC REJECTION

Immune mechanisms of graft rejection



Donor and recipient compatibility tests

- ABO compatibility test
- HLA allele matching test (HLA-A, HLA-B, HLA-DR)
- Checking the presence of preformed antibodies

Graft rejection therapy

Drug	Mechanism of action
Cyclosporine and tacrolimus	Blocks T cell cytokine production by inhibiting the phosphatase calcineurin and thus blocking activation of the NFAT transcription factor
Mycophenolate mofetil	Blocks lymphocyte proliferation by inhibiting guanine nucleotide synthesis in lymphocytes
Rapamycin (sirolimus)	Blocks lymphocyte proliferation by inhibiting mTOR and IL-2 signaling
Corticosteroids	Reduce inflammation by effects on multiple cell types
Antithymocyte globulin	Binds to and depletes T cells by promoting phagocytosis or complement-mediated lysis (used to treat acute rejection)
Anti-IL-2 receptor (CD25) antibody	Inhibits T cell proliferation by blocking IL-2 binding; may also opsonize and help eliminate activated IL-2R-expressing T cells
CTLA4-Ig (belatacept)	Inhibits T cell activation by blocking B7 costimulator binding to T cell CD28
Anti-CD52 (alemtuzumab)	Depletes lymphocytes by complement-mediated lysis

IMMUNOSUPPRESSION :

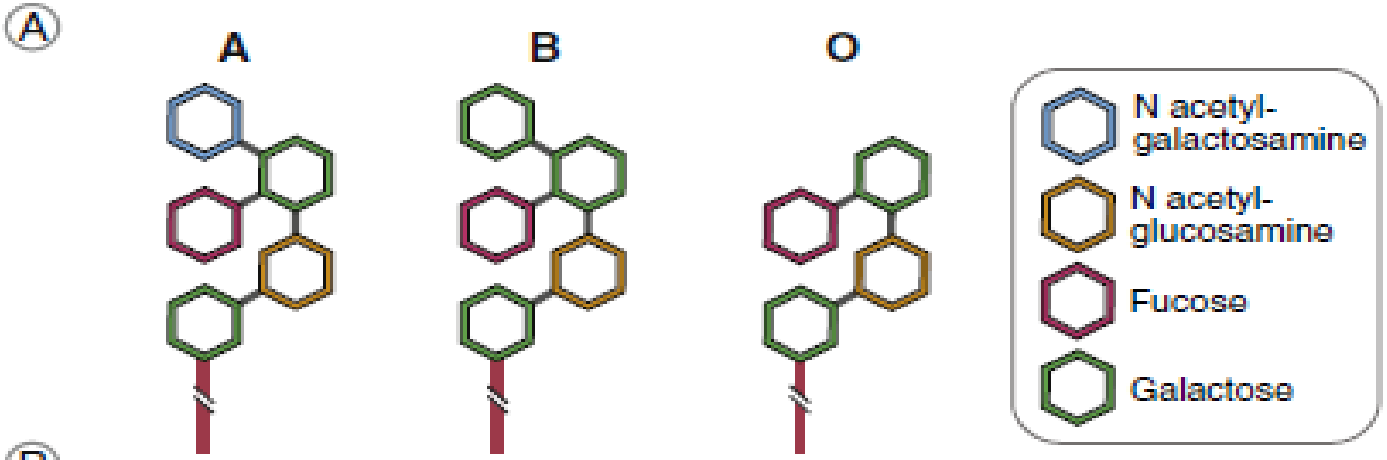
- susceptibility to intracellular infections
- malignant tumors caused by oncogenic viruses

TOLERANCE :

- costimulator blocking
- stimulating alloreactive cells to become regulatory

Transplantation of blood cells (transfusion)

ABO antigens are carbohydrates on membrane glycoproteins or glycosphingolipids, expressed on erythrocytes, endothelial cells and many other cells



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	Group A	Group B	Group AB	Group O
Red blood cell type	Type A	Type B	Type AB	Type O
Antigens present	A antigen	B antigen	A and B antigen	None
Antibodies present	Anti-B	Anti-A	None	Anti-A and Anti-B

Stem cell transplantation

Treatment of malignant blood cell tumors and restoration of damaged bone marrow cells

- Strong rejection reaction (HLA matching)
- Graft-versus-host disease
- Immunodeficiency of recipient

Immunodeficiencies

Diseases caused by insufficient immune response

Immunodeficiencies are disorders of one or more components of the immune system

Primary (congenital)	Secondary (acquired)
group of congenital diseases	they are caused by the action of environmental factors HIV chemotherapy radiation malnutrition

Physiological immunodeficiencies

- **physiological immunodeficiency in newborns**
- **Physiological selective IgA immunodeficiency in children**
- **physiological immunodeficiency in elder people**

Congenital (primary) immunodeficiencies

Congenital immunodeficiencies are the consequences of genetic disorders that are the cause of interruptions in the maturation or functioning of various components of the immune system.

One in every 500 people suffers from some immunodeficiency

Characteristics of immunodeficiencies and their manifestations

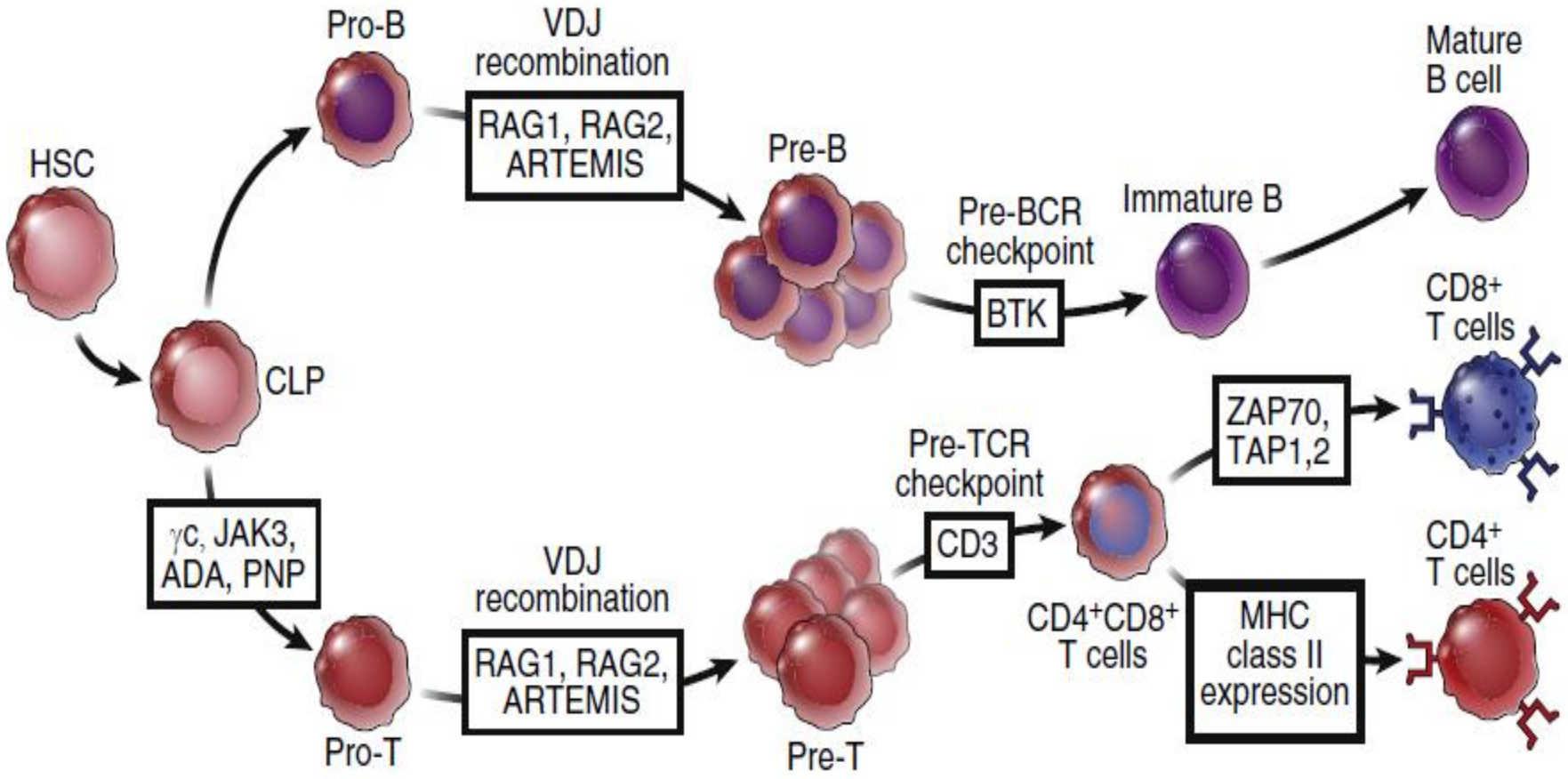
Type of immunodeficiency	Histopathology and laboratory abnormalities	Common infectious consequences
B cell deficiencies	Often absent or reduced follicles and germinal centers in lymphoid organs Reduced serum Ig levels	Pyogenic bacterial infections, enteric bacterial and viral infections
T cell deficiencies	May be reduced T cell zones in lymphoid organs Reduced DTH reactions to common antigens Defective T cell proliferative responses to mitogens in vitro	Viral and other intracellular microbial infections (e.g., *Pneumocystis jiroveci*, other fungi, nontuberculous mycobacteria) Some cancers (e.g., EBV-associated lymphomas, skin cancers)
Innate immune deficiencies	Variable, depending on which component of innate immunity is defective	Variable; pyogenic bacterial and viral infections

Severe forms of immunodeficiency open the door to infections with microorganisms that are not usually considered virulent, including many members of the body's normal microflora or environmental microorganisms.

Defects in innate immunity

Disease	Functional deficiencies	Mechanisms of defect
Chronic granulomatous disease	Defective production of reactive oxygen species by phagocytes; recurrent intracellular bacterial and fungal infections	Mutations in genes of phagocyte oxidase complex; phox-91 (cytochrome b_{558} α subunit) is mutated in X-linked form
Leukocyte adhesion deficiency type 1	Defective leukocyte adhesion to endothelial cells and migration into tissues linked to decreased or absent expression of β_2 integrins; recurrent bacterial and fungal infections	Mutations in gene encoding the β chain (CD18) of β2 integrins
Leukocyte adhesion deficiency type 2	Defective leukocyte rolling on endothelium and migration into tissues because of decreased or absent expression of leukocyte ligands for endothelial E- and P-selectins; recurrent bacterial and fungal infections	Mutations in gene encoding GDP-fucose transporter-1, required for transport of fucose into the Golgi and its incorporation into sialyl-Lewis X
Chediak-Higashi syndrome	Defective vesicle fusion and lysosomal function in neutrophils, macrophages, dendritic cells, NK cells, cytotoxic T cells, and many other cell types; recurrent infections by pyogenic bacteria	Mutations in gene encoding LYST, a protein involved in fusion of vesicles (including lysosomes)
Toll-like receptor signaling defects	Recurrent infections caused by defects in TLR signaling	Mutations in TLR3 and MyD88 compromise NF-κB activation and type I interferon production in response to microbes

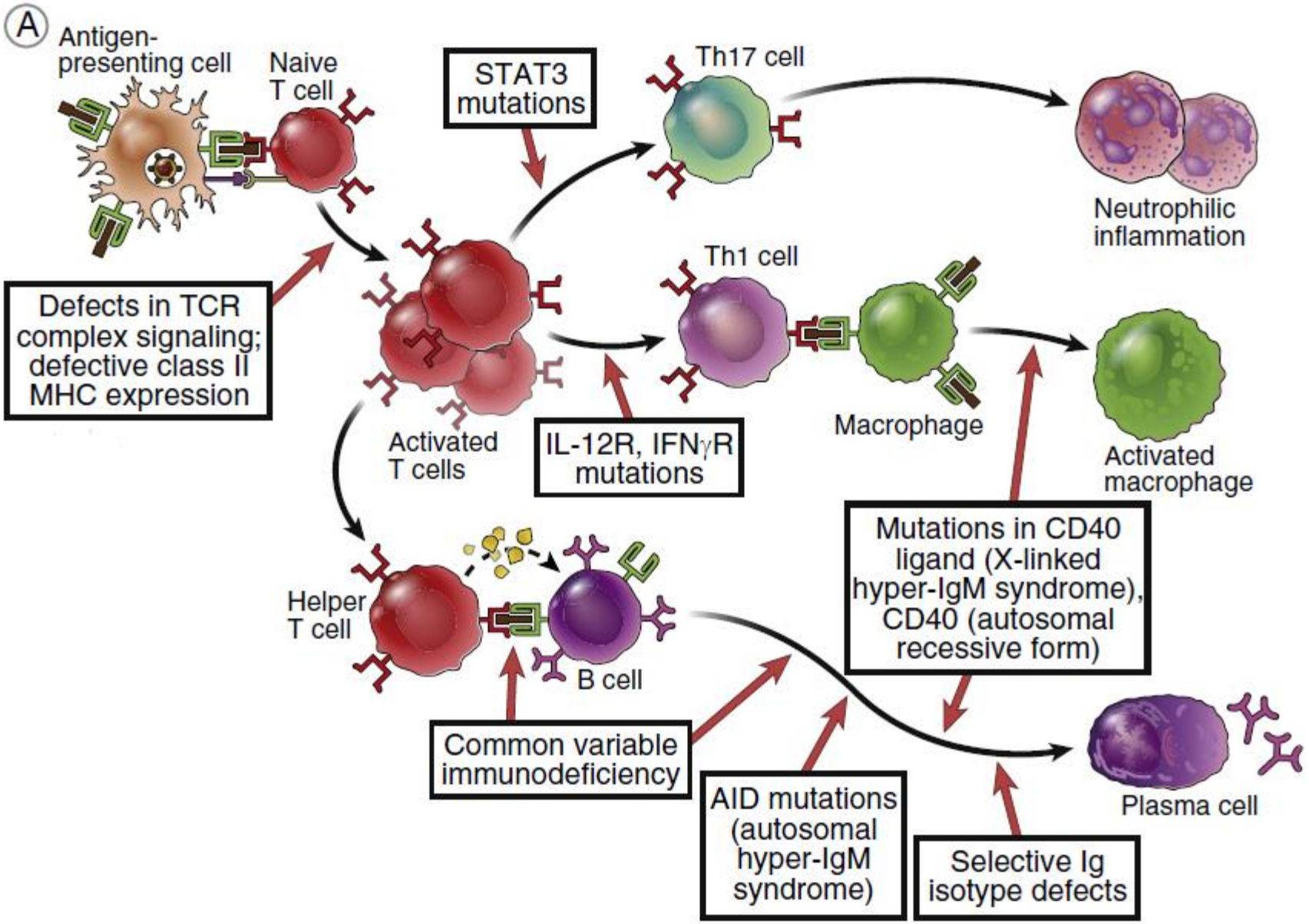
Disorders in the maturation of lymphocytes



Severe combined immunodeficiency (SCID)		
Disease	Functional deficiencies	Mechanism of defect
X-linked SCID	Markedly decreased T cells; normal or increased B cells; reduced serum Ig	Cytokine receptor common γ chain gene mutations, defective T cell maturation due to lack of IL-7 signals
Autosomal recessive SCID due to ADA, PNP deficiency	Progressive decrease in T and B cells (mostly T); reduced serum Ig in ADA deficiency, normal B cells and serum Ig in PNP deficiency	ADA or PNP deficiency leads to accumulation of toxic metabolites in lymphocytes
Autosomal recessive SCID due to other causes	Decreased T and B cells; reduced serum Ig	Defective maturation of T and B cells; may be mutations in *RAG* genes and other genes involved in VDJ recombination or IL-7R signaling
DiGeorge syndrome	Decreased T cells; normal B cells; normal or decreased serum Ig	Anomalous development of 3rd and 4th branchial pouches, leading to thymic hypoplasia

B cell immunodeficiencies		
Disease	Functional deficiencies	Mechanism of defect
X-linked agammaglobulinemia	Decrease in all serum Ig isotypes; reduced B cell numbers	Block in maturation beyond pre-B cells, because of mutation in Bruton tyrosine kinase (BTK)
Ig heavy chain deficiencies	IgG1, IgG2, or IgG4 absent; sometimes associated with absent IgA or IgE	Chromosomal deletion involving Ig heavy-chain locus at 14q32

Disorders of lymphocyte activation and function



Disorders of lymphocyte activation and function

B

Disease	Functional deficiencies	Mechanisms of defect
X-linked hyper-IgM syndrome	Defects in helper T cell–dependent B cell and macrophage activation	Mutations in CD40 ligand
Selective Ig deficiency	Reduced or no production of selective Ig isotypes; susceptibility to infections or no clinical problem	Mutations in Ig genes or unknown mutations
Common variable immunodeficiency	Reduced immunoglobulins; susceptibility to bacterial infections	Mutations in receptors for B cell growth factors, costimulators
Defective class II MHC expression: The bare lymphocyte syndrome	Lack of class II MHC expression and impaired $CD4^+$ T cell activation; defective cell–mediated immunity and T cell–dependent humoral immunity	Mutations in genes encoding transcription factors required for class II MHC gene expression
Defects in T cell receptor complex expression or signaling	Decreased T cells or abnormal ratios of $CD4^+$ and $CD8^+$ subsets; decreased cell–mediated immunity	Mutations or deletions in genes encoding CD3 proteins, ZAP-70
Defects in Th1 differentiation	Decreased T cell–mediated macrophage activation; susceptibility to infection by atypical mycobacteria and other intracellular pathogens	Mutations in genes encoding IL-12, the receptors for IL-12 or interferon-γ, STAT1
Defects in Th17 differentiation	Decreased T cell–mediated inflammatory responses; mucocutaneous candidiasis, bacterial skin abscesses	Mutations in genes encoding STAT3, IL-17, IL-17R
X-linked lymphoproliferative syndrome	Uncontrolled EBV-induced B cell proliferation and CTL activation; defective NK cell and CTL function and antibody responses	Mutations in gene encoding SAP (an adaptor protein involved in signaling in lymphocytes)

Immunodeficiency can be one of the components of some systemic diseases that affect a number of organ systems

Wiskott-Aldrich syndrome:

- eczema
- reduced number of thrombocytes
- immunodeficiency

Ataxia-telangiectasia :

- gait disorders (ataxia)
- malformations of blood vessels (telangiectasia)
- immunodeficiency

Therapy of congenital immunodeficiencies

- Transplantation of hematopoietic stem cells (SCID)
- IV injection of pooled immunoglubulin -IVIG (selective disorders of B lymphocytes)
- Gene therapy

SEPSIS AND SEPTIC SHOCK

Sepsis

Sepsis is a general clinical term that describes the signs and symptoms of a generalized and often uncontrolled inflammatory response

Disseminated infection

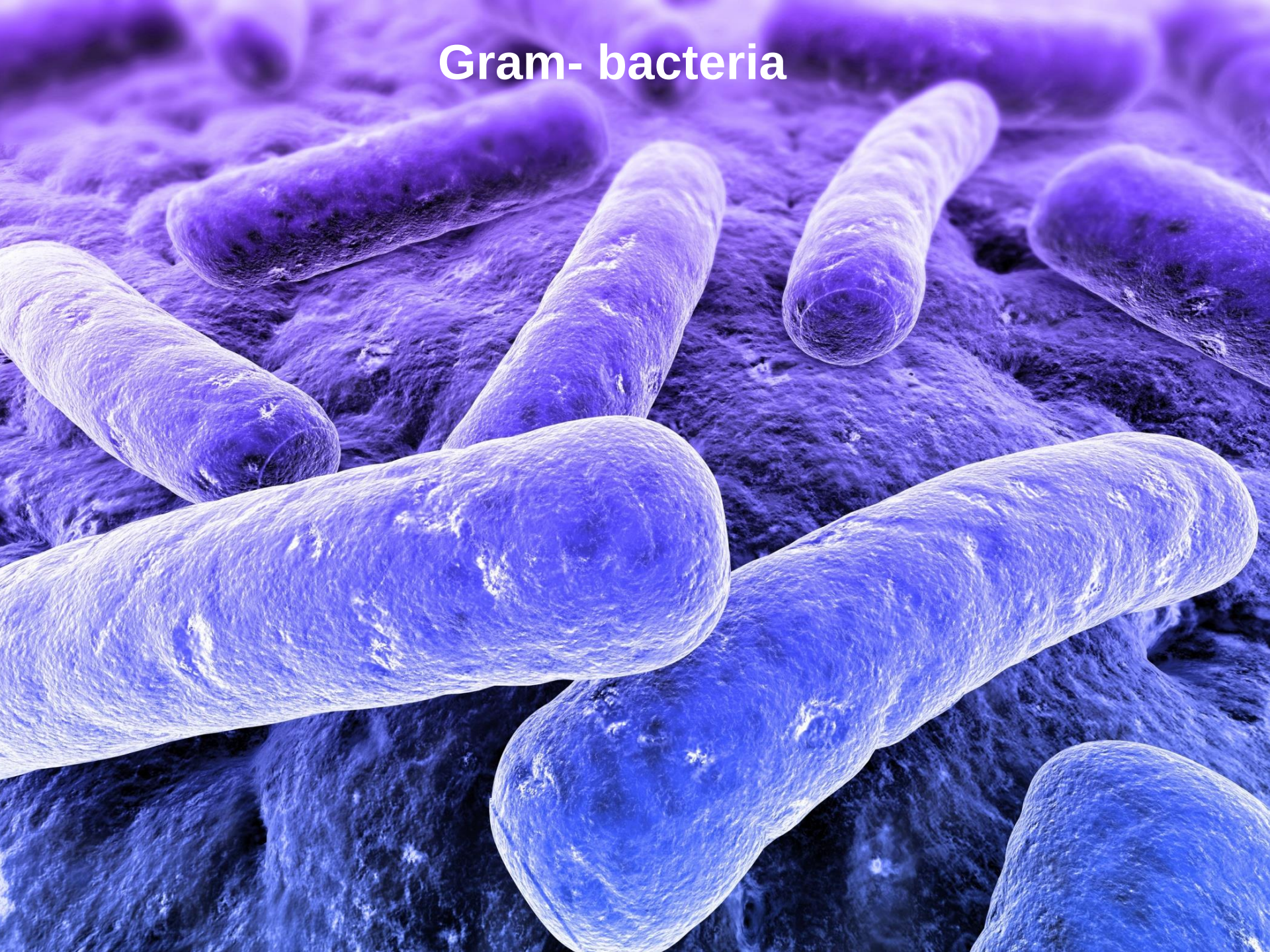
Despite great advances in antibiotic therapy, sepsis is still one of the ten leading causes of death in critically ill patients

Etiology

- Gram-bacteria (60%)
- Gram+ coca (20%)
- Fungi (2-5%)
- Mycobacteria
- Viruses
- Protozoa

- The penetration of microorganisms into the bloodstream is not decisive for the onset of sepsis. Systemic spread of micro-organism products also causes sepsis.

Gram- bacteria



Etiology

Risk factors for Gram-bacteremia:

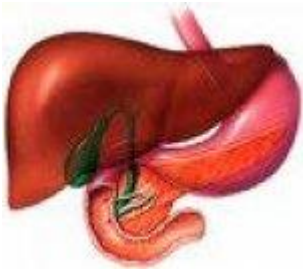
- Diabetes mellitus
- Lymphoproliferative diseases
- Liver cirrhosis
- Burns
- Invasive procedures
- Artificial valves...
- Drugs that cause neutropenia

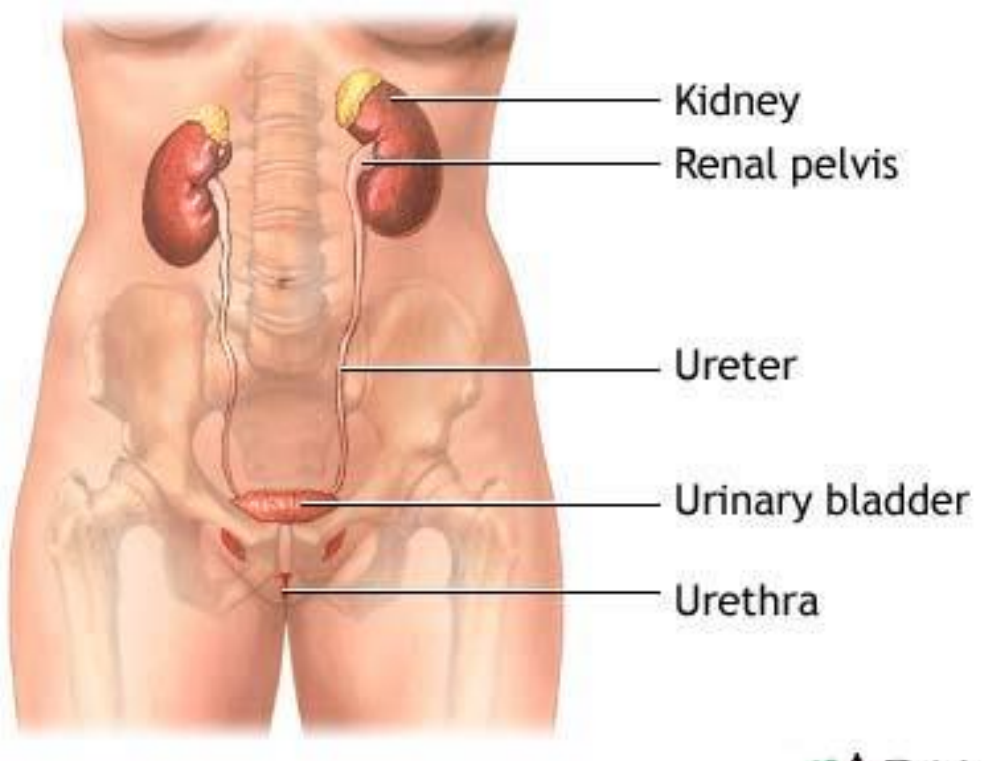
Risk factors for Gram+ bacteremia:

- Venous catheters
- Burns
- Intravenous drug addiction
- Artificial valves...

Pathogenesis

- A local infection in the urogenital tract, biliary tract, lungs, skin or digestive system can spread to the bloodstream.





Pathogenesis

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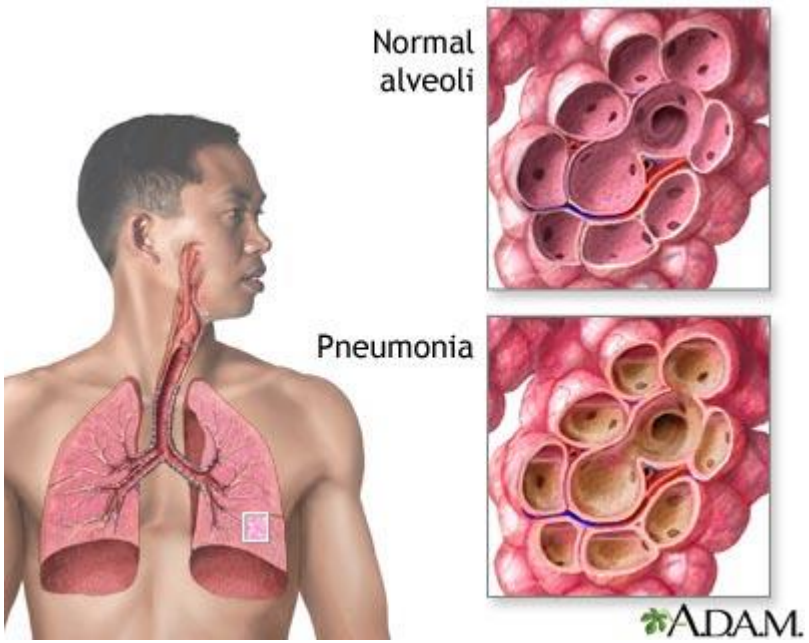
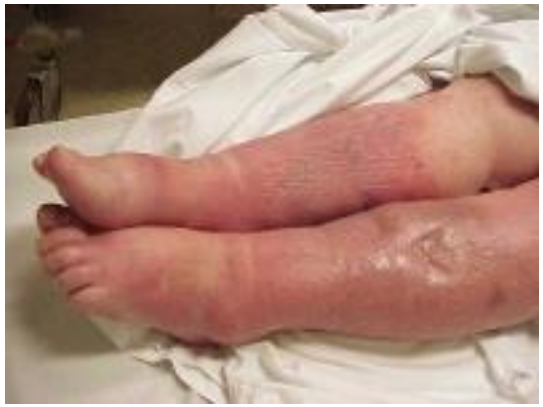
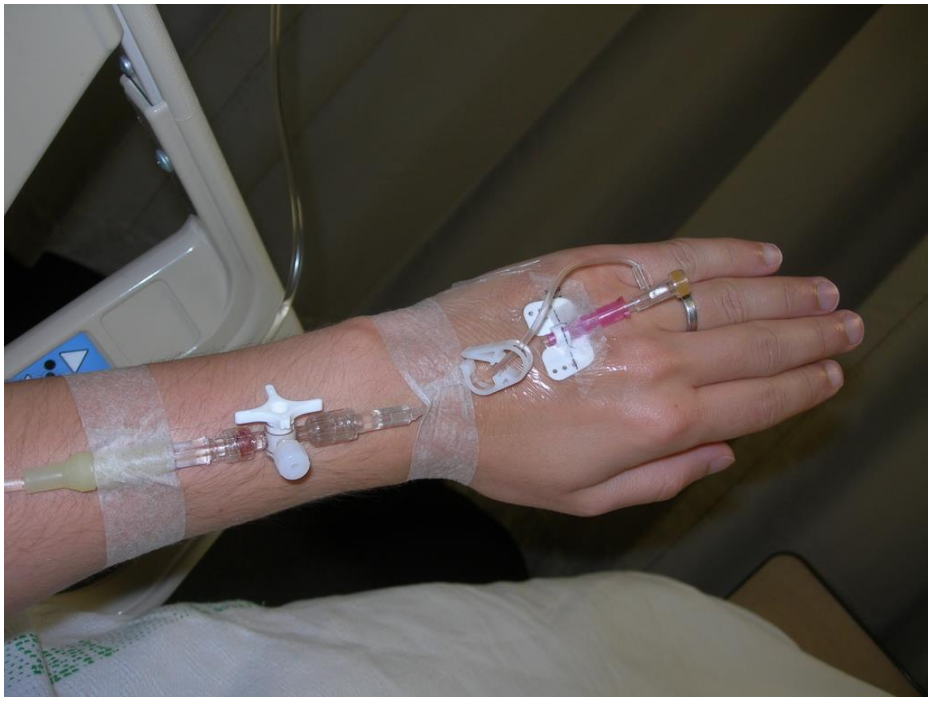




Pathogenesis

- Microorganisms can be introduced directly into the bloodstream.
- In a small number of cases, there are no visible sites of primary infection.



- The penetration of microorganisms into the bloodstream is not decisive for the onset of sepsis. Systemic spread of micro-organism products also causes sepsis.

Pathogenesis

- The host's immune system recognizes certain molecules of microorganisms as foreign.
- Lipopolysaccharide (**LPS**) is a product of Gram- bacteria and a very powerful stimulator of the immune response.
- Peptidoglycan and lipoteichoic acid of Gram+ bacteria, certain polysaccharides and exotoxins cause a similar effect to LPS. The immune response to these molecules is less well studied.

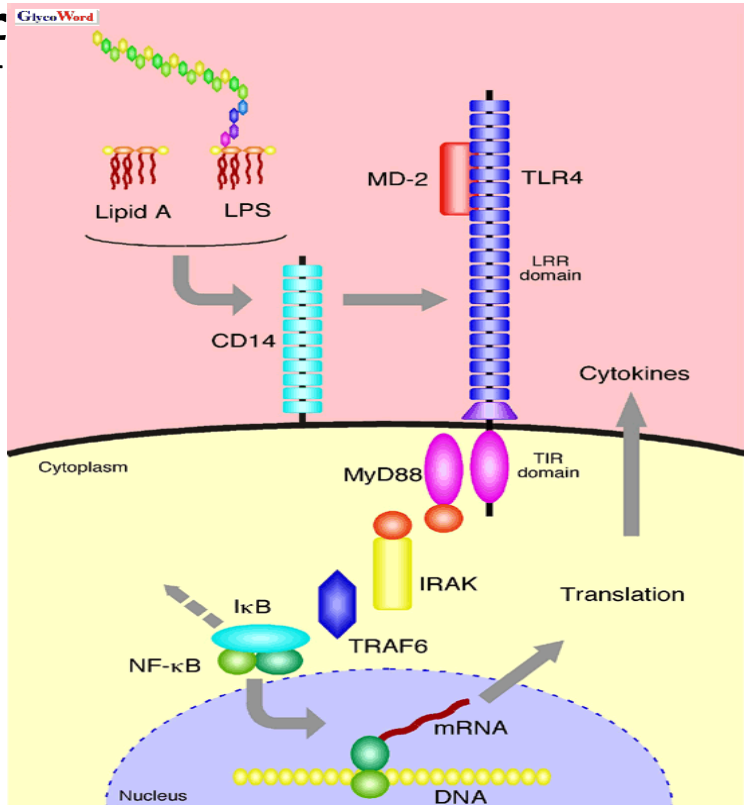
Pathogenesis

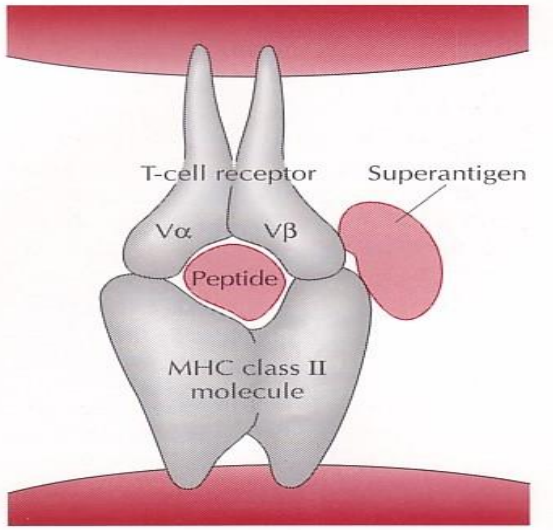
- LPS is a potent activator of macrophages. It binds to CD14 and TLR4 receptors on macrophages and dendritic cells.

- Systemic changes in patients with disseminated bacterial infection represent a reaction to cytokines whose production is initiated and stimulated by LPS.

Stimulation of the production of inflammatory mediators

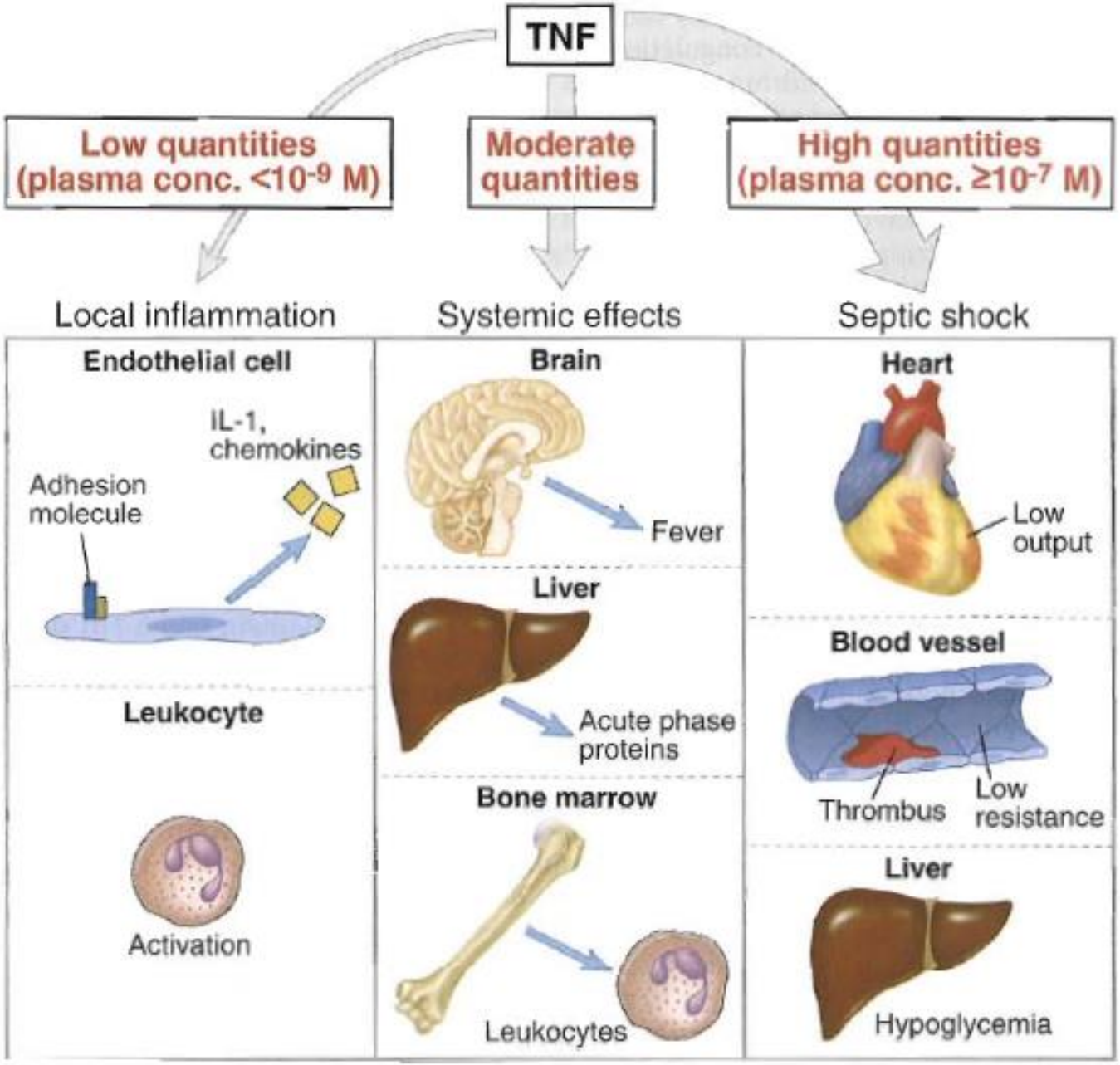
- Lipopolysaccharide or lipid A of Gram- bacteria are among the most potent stimulators of cytokine production
- Another important source of cytokines are T lymphocytes activated by nonspecific binding of superantigens (eg, toxic shock syndrome toxin-1).





Cytokines

- TNF-α is considered a key cytokine in sepsis. The concentration of TNF-α in the serum correlates with the severity of the disease. Intravenous infusion of TNF-α causes most symptoms of sepsis and higher doses shock and death (in animals). Monoclonal antibodies to TNF-α can neutralize the septic response.
- IL-1
- IL-6
- IFN-γ



Abbas AK, Lichtman AH. Cellular and moleculat immunology 6th edition. Elsevier

Interleukin-1 (IL-1)

- Main function of IL-1, similar to TNF
- The main cellular source of IL-1 are activated mononuclear phagocytes. Production is induced by bacterial LPS and cytokines, such as TNF.

- The biological effects of IL-1 are similar to those of TNF

- When IL-1 is secreted in low concentrations, it functions as a mediator in local inflammation. It acts on endothelial cells and increases the expression of surface molecules that cause leukocyte adhesion, such as ligands for integrins.
- When secreted in larger quantities, it enters the bloodstream and exerts endocrine effects. It causes high fever, induces the synthesis of plasma proteins in the liver.

- Receptor antagonist for IL-1 (IL-1ra)

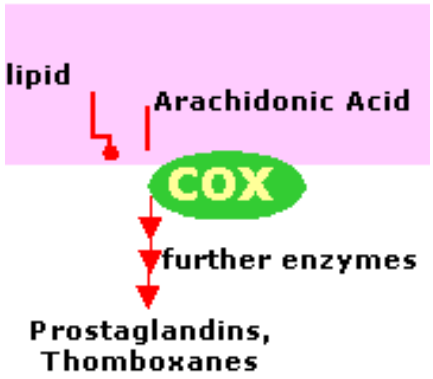
Interleukin-6 (IL-6)

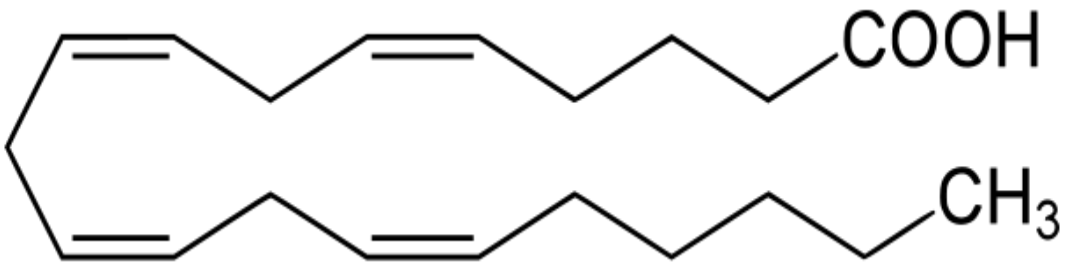
- IL-6 is synthesized by mononuclear phagocytes, vascular endothelial cells, fibroblasts, and other cells in response to other cytokines, particularly IL-1 and TNF.Такође га продукују неки активирани Т лимфоцити.

- IL-6 has several different functions.
- In innate immunity, it stimulates the synthesis of acute phase proteins from hepatocytes and thus contributes to the systemic effect of inflammation.
- It then stimulates the production of neutrophils from bone marrow-derived precursors, usually acting together with cell colony-stimulating factors.

Products of metabolism of arachidonic acid

- Arachidonic acid released from the cell membrane by phospholipase A (cyclooxygenase enzyme) is converted into prostaglandins and thromboxanes.
- Prostaglandin E and prostacyclin cause peripheral vasodilatation, and thromboxane causes vasoconstriction.
- Leukotrienes are products of the lipoxygenase pathway of arachidonic acid metabolism and are potent mediators of ischemia and shock. Leukotriene B is a metabolite of neutrophils and participates in blood vessel damage and thrombosis.





Tissue damage in sepsis

Two central events in the pathogenesis of sepsis are:

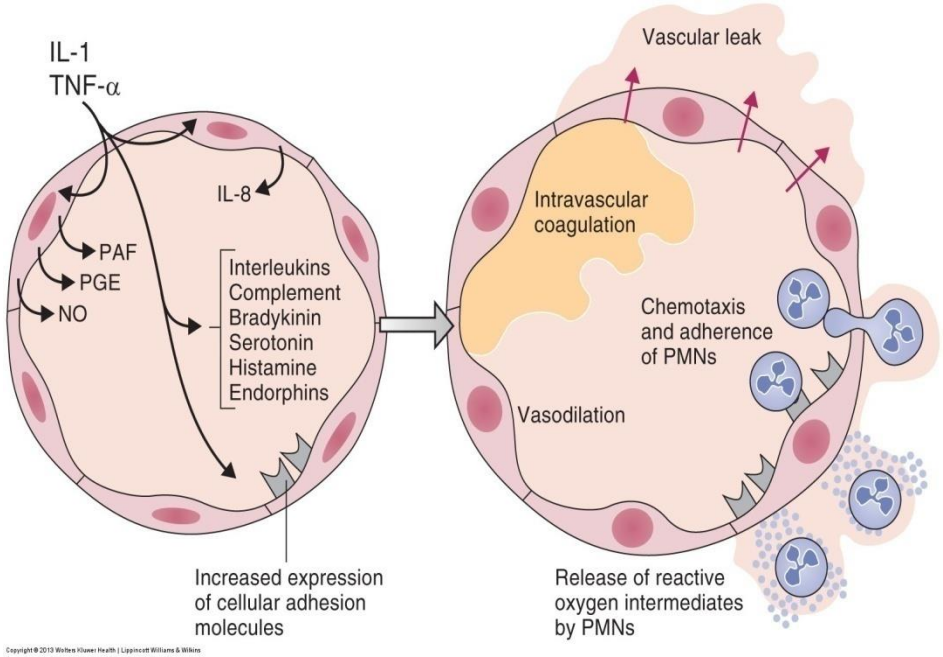
- **hypotension** → dysfunction, necrosis and insufficiency of vital organs (brain, lungs, kidneys, liver and gastrointestinal tract)

- **accumulation of toxic metabolites** (lactic acidosis)

Clinical manifestations of sepsis

Cardiovascular system:

•early dilation of blood vessels (reduced vascular resistance) and extravasation of fluid into the extracellular space, drop in blood pressure and tachycardia



- In the early stages of sepsis, blood pressure drops, while cardiac output increases. Due to vasodilation, the skin is red and warm, so this phase is called **warm shock**
- In later stages, cardiac stroke volume decreases, and peripheral vasodilation is replaced by vasoconstriction in order to redistribute blood to vital organs. The skin becomes pale and cold, the hands and feet are livid in color and the patient enters the phase of the so-called **cold shock**

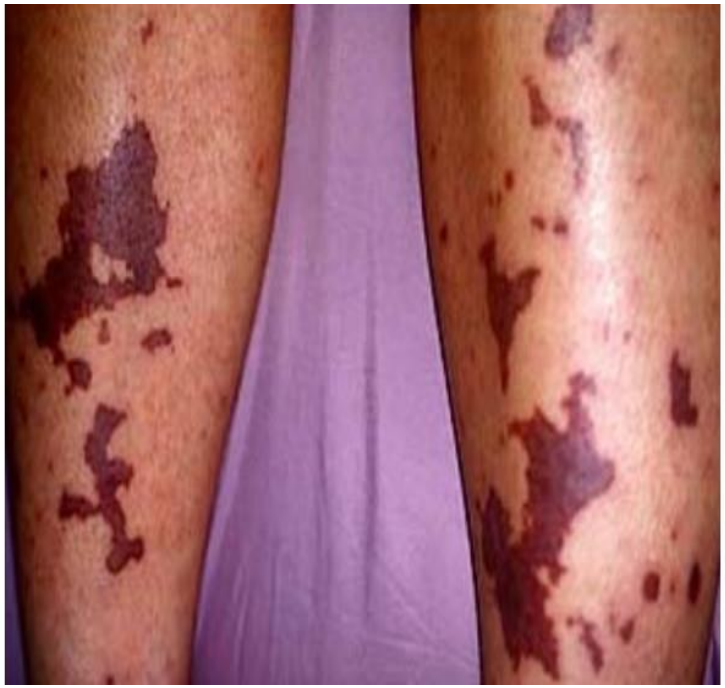
Clinical manifestations of sepsis

- **Brain:** confusion, delirium, stupor and coma
- **Lungs:** fluid extravasation into the interstitium and alveolar space, the lungs become moist and inelastic, which makes gas exchange difficult. This condition is called **acute respiratory distress syndrome (ARDS),** and patients require assisted ventilation
- **Kidneys:** acute tubular necrosis and renal failure
- **Liver:** Liver necrosis, jaundice and liver dysfunction affecting drug metabolism, albumin and coagulation factor synthesis. As a consequence of the lack of albumin, the liquid leaves the vascular system in the tissues, edema occurs, and the blood pressure continues to fall

Clinical manifestations of sepsis

- **Gastrointestinal tract:** ischemia, necrosis and bleeding

- **Coagulation system:** damage to the endothelium is accompanied by extensive microvascular thrombosis (**disseminated intravascular coagulation, DIC**). In the course of DIC, platelets and coagulation factors decreases, which increases the tendency towards bleeding. Thrombosis and bleeding may also be present at the same time. Activation of the fibrinolytic system counteracts thrombosis, which further contributes to the worsening of coagulopathy



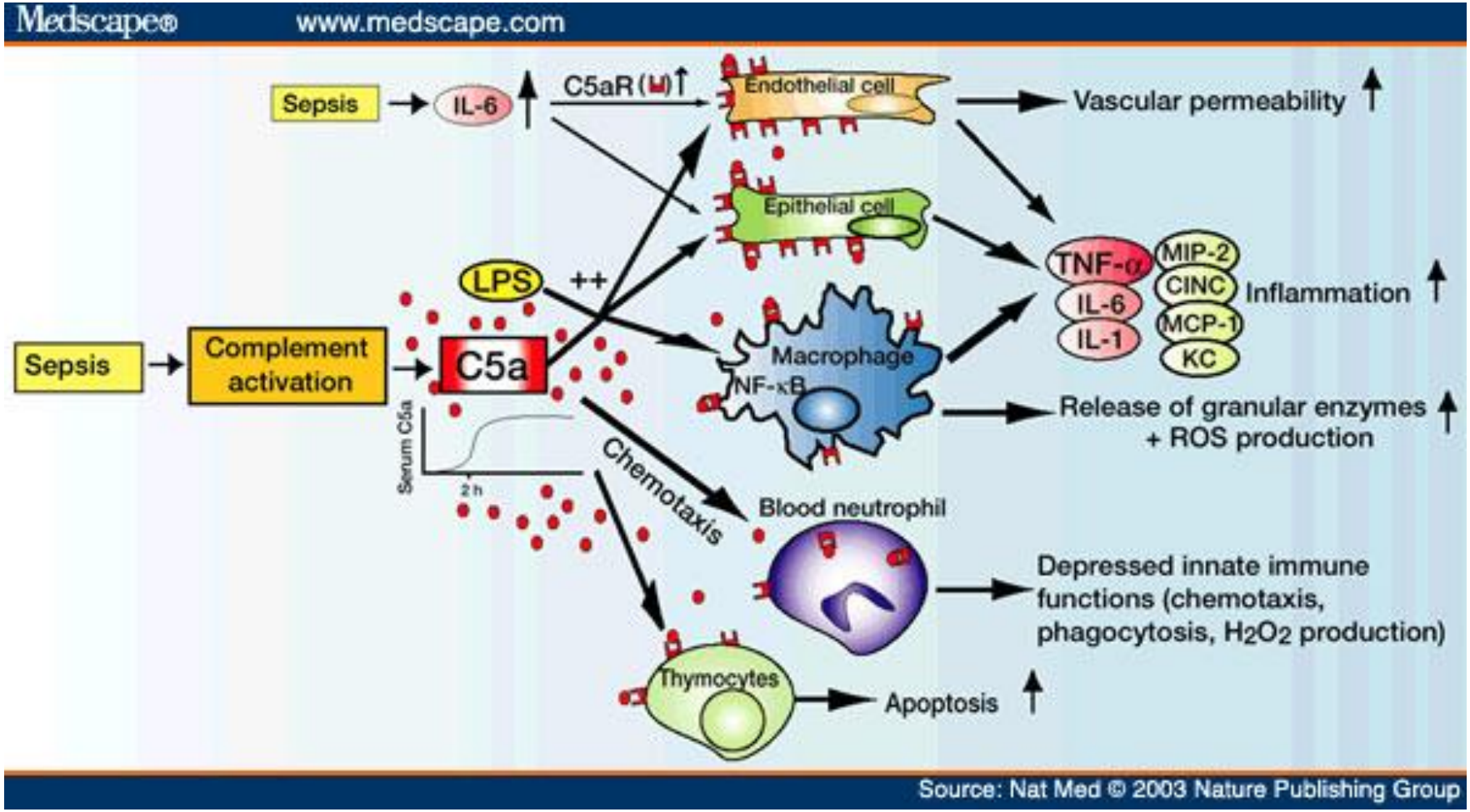
- **Endocrine and metabolic effects**: sepsis is a catabolic state accompanied by massive proteolysis, lipolysis and glycogenolysis. Stress hormones (cortisol, catecholamines, glucagon) are found in high concentrations in the circulation. As a consequence of the difficulty in supplying and taking up oxygen in the tissues, glycolysis takes place in the cells to pyruvate and lactic acid, which accumulates in the tissues - lactic acidosis

A mild form of sepsis

- *Neutrophilia.* Bone marrow response to circulating cytokines, primarily G-CSF. Increased production and release of neutrophils that replace those used in the inflammatory reaction.
- *Elevated temperature.* LPS (exogenous pyrogen) stimulates leukocytes to produce the cytokines IL-1 and TNF-α (endogenous pyrogens) which enhance cyclooxygenase-2 enzyme activity and increase prostaglandin synthesis from arahidonic acid in vascular and perivascular cells of the hypothalamus, which raises temperature.
- *Acute phase proteins.* Plasma proteins synthesized primarily in the liver. In response to LPS, their plasma concentration increases.
  - **C-reactive protein**
  - **Fibrinogen**
  - **Serum amyloid A**

The synthesis of these molecules is regulated by IL-6, IL-1 and TNF-α

Fibrinogen - erythrocyte sedimentation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Vascular permeability
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LPS
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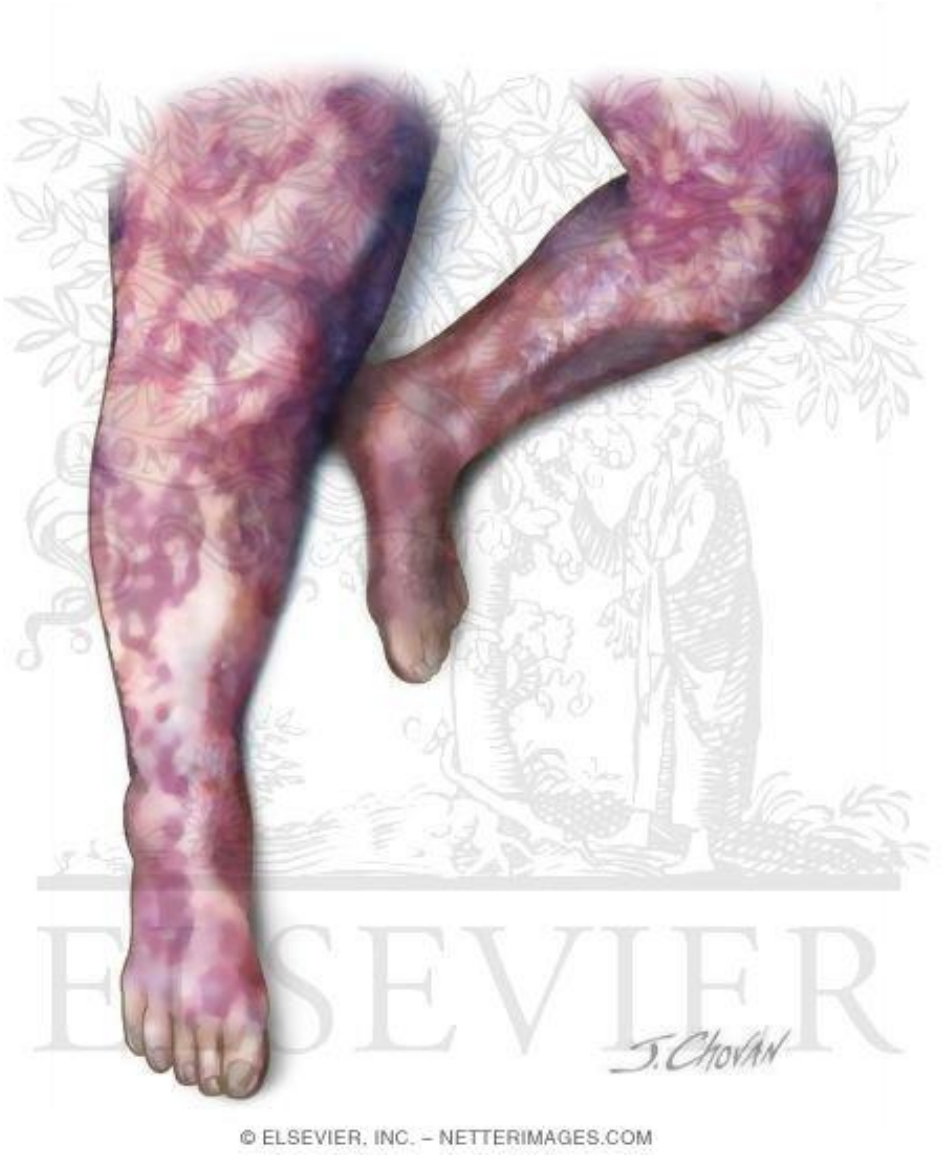
TNF-α
IL-6
IL-1
MIP-2
CINC
MCP-1
KC
Inflammation
Sepsis
Complement activation
C5a
Macrophage
NF-κB
Release of granular enzymes + ROS production
Serum C5a
2 h
Chemotaxis
Blood neutrophil
Depressed innate immune functions (chemotaxis, phagocytosis, H2O2 production)
Thymocytes
Apoptosis
Source: Nat Med © 2003 Nature Publishing Group

More severe form of sepsis

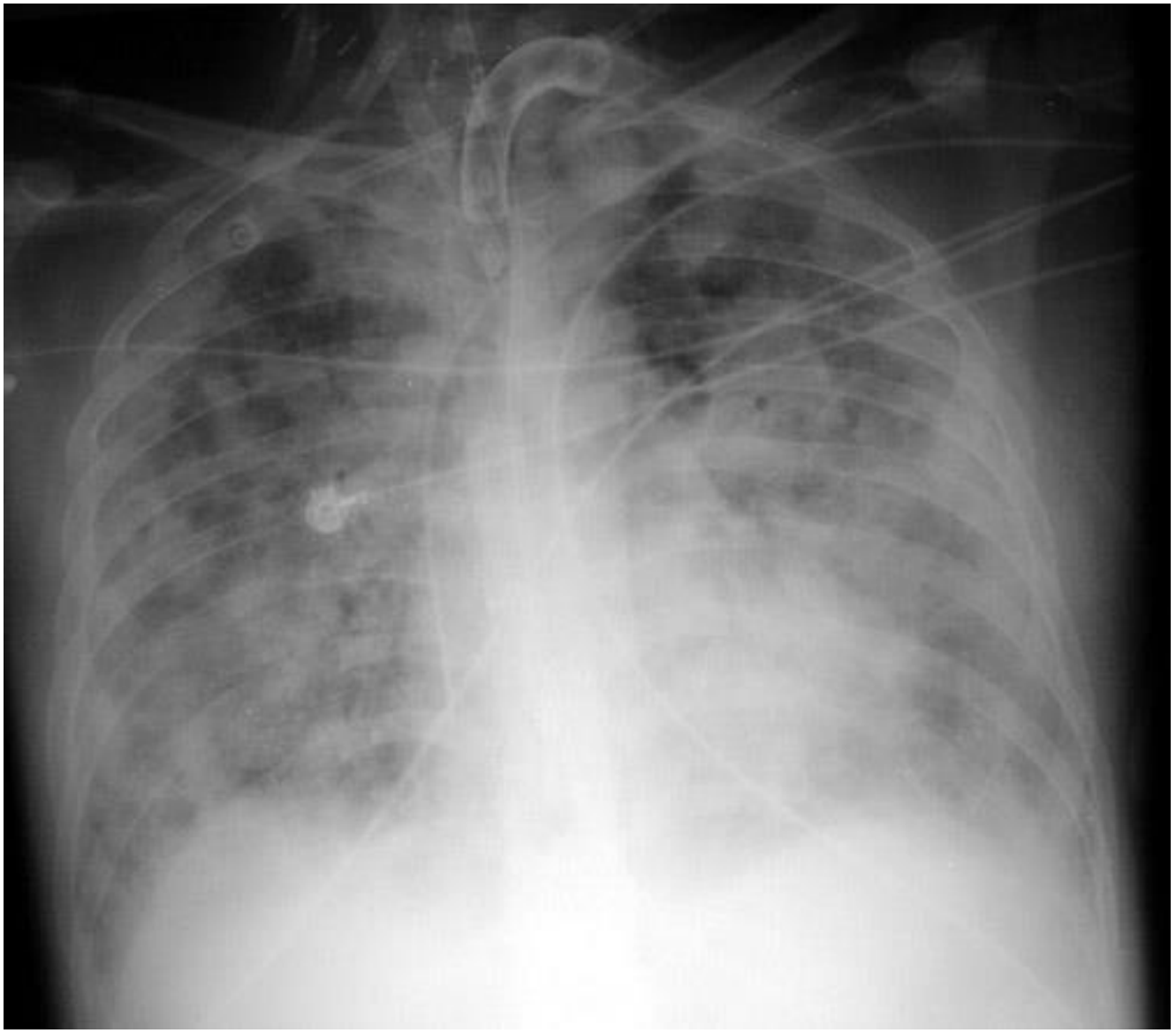
- *Disseminated intravascular coagulation.* Increased expression of pro-coagulant proteins (tissue factor) and decreased anti-coagulant activity of endothelial cells (consequence of TNF-α). Inflammation and intravascular thrombosis develop in many organs.

- *Tissue destruction.* Activation of neutrophils before exiting the vascular bed damages endothelial cells and reduces blood flow. The lungs and liver are particularly sensitive. Neutrophilic damage of the lung endothelium allows fluid to escape from the blood vessels into the air space of the lungs - ARDS (Acute Respiratory Distress Syndrome). Liver damage leads to reduced gluconeogenesis and a drop in glycemia.

Disseminated intravascular coagulation



ARDS



Septic shock

- Severe disseminated infections sometimes lead to a potentially fatal clinical syndrome called septic shock.

- *Increased production of nitrogen oxides.* Cytokines trigger increased production in cardiomyocytes and endothelial cells. Perfusion pressure drop and hemodynamic shock.

- *Disseminated intravascular coagulation.*
- *Hypoglycemia.*
- *Cardiovascular collapse.*

Presentation of a patient with sepsis

Presentation of a patient with sepsis

- I.I., a 35-year-old journalist, was healthy all his life. A few days after a surgical intervention in the oral cavity, he noticed frequent fatigue, sleepiness, muscle pain and loss of appetite. He did not consult a doctor. The next day, he developed a high fever, rapid breathing and a disturbance of consciousness.

- Sepsis is easily suspected in a patient with a **local infection** who suddenly develops a **fever**.
- **Hyperventilation** is often a useful clue to diagnosis even though its cause is not clear enough.
- **Disorientation** and other signs of encephalopathy can also be early signs of sepsis.

Presentation of a patient with sepsis

- I.I. then reports to the doctor. During the examination, the doctor confirmed a high temperature, rapid breathing and a disturbance of consciousness, but he also discovered a rapid heartbeat and a drop in blood pressure. He also noticed skin lesions.

- Hypotension and disseminated intravascular coagulation create **ischemic necrosis of peripheral tissues**. Bacterial toxins can spread hematogenously and cause **diffuse skin changes**. Skin lesions can sometimes point to a specific causative agent.

Presentation of a patient with sepsis

- The doctor asks the patient if he has had nausea, vomiting or other gastrointestinal complaints.

- Gastrointestinal manifestations (nausea, vomiting, diarrhea, ileus, ulcer, cholestatic jaundice) may precede other signs of sepsis. In most cases, it is a hepatocellular disorder. Prolonged or severe hypotension can cause acute liver damage.

Presentation of a patient with sepsis

- Laboratory findings: thrombocytopenia, increased lactates, hypoglycemia, increased C-reactive protein, fibrinogen, complement components, accelerated sedimentation.

- Serum **lactates** are elevated primarily due to incomplete hepatic clearance. Impaired gluconeogenesis leads to **hypoglycemia**. Cytokines IL-6, IL-1 and TNF-α induce the synthesis of acute phase proteins in the liver: **C-reactive protein, fibrinogen, complement components**. **Thrombocytopenia** suggests DIK.

Presentation of a patient with sepsis

- Blood was taken for microorganism isolation and final diagnosis. A Gram-causative agent of the infection was discovered, which spread into the bloodstream.

- Sepsis can quickly kill the patient. Successful treatment requires prompt treatment of local infection, ensuring hemodynamics of the cardiovascular system and treatment of other sepsis symptoms.

Sepsis therapy

- *Antibiotic therapy.* It should be started immediately after taking blood and appropriate local samples for analysis. The choice of initial therapy is based on knowledge of the likely pathogens at the site of infection. Symptoms caused by different microorganisms should also be taken into account.

- While waiting for culture results, empiric antimicrobial treatment should cover Gram+ and Gram- pathogens.

- The maximum recommended doses of antibiotics should be given intravenously, taking into account possible impaired renal function.

Antimicrobial therapy

- Cefotaxime or ceftazidime together with gentamicin is an appropriate initial empiric regimen.
- Vancomycin should be added if the patient has an venous catheter or is an intravenous drug user.
- Clindamycin or metronidazole should be added if the source of infection in the oral or abdominal cavity is suspected.
- Removal and drainage of the focus, which is the source of sepsis, is essential.

Hemodynamic support

- Maintaining the integrity of the cardiovascular system enables the supply of tissues with oxygen and substrates.
- Because of the drop in blood volume, initial treatment should include intravenous fluids, usually 1-2 liters of solution over 1-2 hours.
- Continuous infusion should maintain diuresis (use of diuretics).
- In a third of patients, hypotension responds well to fluid replacement. Maintain pressure above 90/60mmHg.
- The most commonly used drug to raise blood pressure is dopamine.

Antiendotoxin therapy

- The toxic part of endotoxin is called lipid A.
- An antibody specific for lipid A was produced.
- Trials with polyclonal antisera against lipid A appeared promising, but in placebo-controlled studies two monoclonal antibodies to lipid A did not prevent death in patients with Gram-bacterial sepsis.

- Neutrophil proteins that neutralize endotoxin, as well as non-toxic lipid A analogs that inhibit the immune response to endotoxin, are also being tested.

Antimediator therapy

- The goal is to control the immune response regardless of the causative agent.
- Most of the attention is paid to corticosteroids.
- Two large-scale randomized clinical trials of septic patients treated with high-dose methylprednisolone indicate that such treatment does not prevent death or arrest shock. Therefore, the treatment of sepsis with high doses of corticosteroids is not currently recommended.

Anticytokine therapy

- The goal is to control the immune response regardless of the causative agent.
- Monoclonal antibodies to **TNF-α** can reverse the septic response and prevent the death of the test animal after exposure to endotoxin.
- Recombinant **IL-1** receptor antagonists and IL-1 monoclonal antibodies can protect animals from endotoxic death.
- Monoclonal antibodies to **IL-6** may also be protective.

- As TNF-α, IL-1 and IL-6 play a beneficial role in the host's response to invading microorganisms, anticytokine therapy could have both beneficial and adverse effects on patients with sepsis.