Systemic inflammatory response syndrome – SIRS

and

Multiple organ dysfunction syndrome – MODS

Jan Janota

Systemic inflammatory response syndrome – SIRS and Multiple organ dysfunction syndrome – MODS

1 Response to the pathogenic factors

2 Definition of the inflammation

3 Systems responsible for inflammatory response

3.1 Endothelial cells

3.2 Platelets

3.3 Leucocytes

3.4 Plasmatic hemocoagulation system

3.5 Complement

4 Local inflammatory response

5 Systemic inflammatory response

6 Systemic inflammatory response syndrome (SIRS)

7 Multiple organ dysfunction during SIRS – primary and secondary MODS

8 Pathophysiology of SIRS

9 Diagnosis of SIRS

10 Relationship between SIRS and sepsis

1 Response to the pathogenic factors

- Reaction to the stimulus - basic activity of the living organisms.
- Jeopardizing stimulus - defensive reaction.
- Defensive systems:
  - *Stress reaction - global neurohumoral defensive changes*
  - *Inflammation - partially autonomous defense of vascularized tissue*

2 Definition of the inflammation

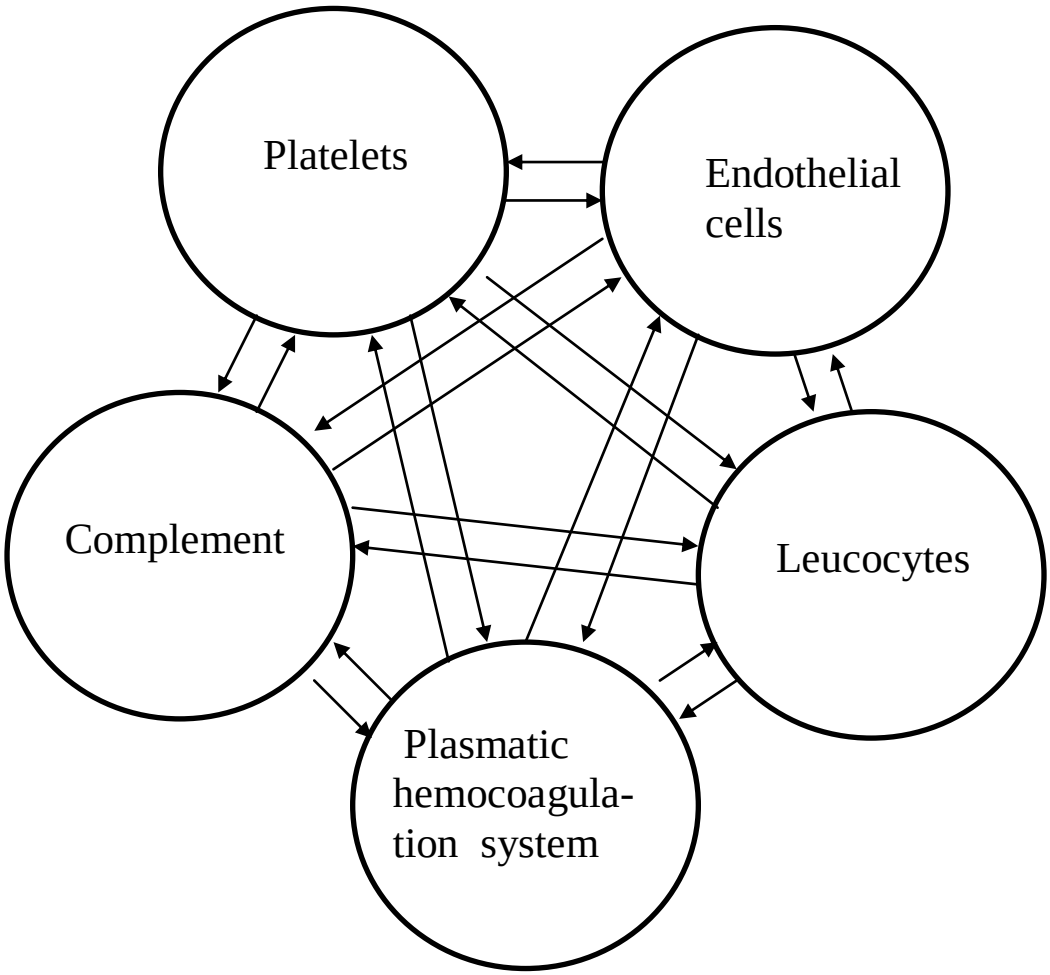
Inflammation is system of the defensive reactions of the vascularized tissues of the organism to the pathogenic insult of different origin. The goal of inflammation is to eliminate the cause, to eliminate destructed tissue and, through regeneration or repair, to restore metabolism and function of the organs to the state of dynamic balance.

Insult

- biologic (microorganisms)
- physical (mechanical insult, radiation)
- chemical (poisons, acids)
- metabolic (hypoxia, malnutrition)
- immunologic (autoimmune diseases)
- endogenic disorders of neurohumoral regulation

3 Systems responsible for inflammatory response

- 5 systems



Cooperation of the most important inflammatory response systems.

Localization of the inflammation

- local
- systemic

Regulation of the inflammation

- defensive
- autoaggressive

Defensive inflammation

- localization
- regulation

Autoaggressive inflammation

- dysregulation
- delocalization

3.1 *Endothelial cells*

Physiological conditions

- antithrombogenic vessel wall
- local regulation of vascular tension
- permeability of the vascular wall

During defense after insult

- changes in vessel tension
- adhesion of cells and proteins
- thrombogenic potential for hemostasis
- increase permeability of the vessel wall for proteins
- regulation of leucocyte migration to interstitium

Vasodilatatory and antithrombotic mediators

- NO
- prostacycline (PGI_2)

Vasoconstrictive and prothrombotic mediators

- endothelin-1
- thromboxan A2

Levels of the endothelium dysfunction

- Stimulation - fast, reversible process - endothelial contraction
- Activation (during inflammation) - through (TNF-α a IL-1β), irreversible changes

3.2 *Platelets*

Physiological conditions

- creation of primary hemostatic plug if vessel integrity broken
- platelet surface and mediators - reactions of plasmatic hemocoagulation system

Platelets after activation

- discoid to spheric shape
- pseudopodia
- adhesion and aggregation
- release of mediators

3.3 *Leucocytes*

3.3.1 Mononuclear phagocytes

- monocytes of peripheral blood
- tissue macrophages

Both able to perform phagocytosis.

Macrophages - main producers of TNF-α a IL-1β.

3.3.2 Polymorfonuclear leucocytes

- concentration in the site of insult
- adhesion to stimulated endothelial cells
- penetration to interstitium

.

Phagocytosis

Cytotoxic potential

- reactive oxygen intermediates
- hydrolytic enzymes
- antibacterial proteins

3.3.4 Histiocytes, basophils

3.3.5 Eozinophils

3.3.6 Lymfocytes T and B, Natural killer cells (NK-cells)

Regulatory function of the leucocytes

Role in the inflammatory response

- executive
- signal
- regulatory

Communication among inflammatory systems

- surface membrane receptors
- mediators

Mediators

Cytokines

Proteins (released by different cells), which through interactions with specific receptors regulate functions of target cells.

During inflammation

- proinflammatory cytokines IL-1β a TNF-α. released by activated mononuclear cells
- antiinflammatory cytokines IL-4, IL-10 a IL-13

3.4 *Plasmatic hemocoagulation system*

- activation via tissue factor expressed by activated mononuclear cells and endothelial cells

3.5 *Complement*

4 Local inflammatory response

Symptoms of the local inflammation

- rubor (color)
- calor (temperature)
- tumor (edema)
- dolor (pain)
- functio laesa (dysfunction)

5 Systemic inflammatory response

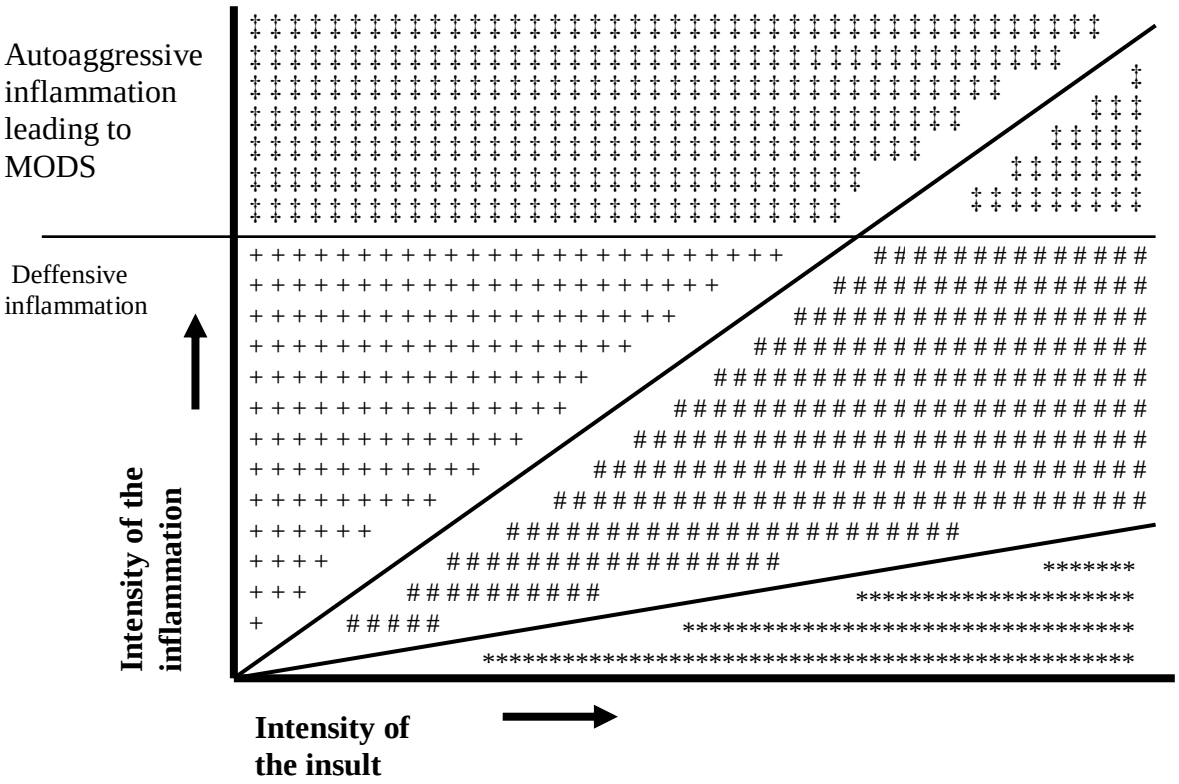
- Systemic insult leads to systemic inflammatory response.
- Systemic inflammatory response may not be necessarily autoaggressive.
- Inflammatory processes are delocalized, if dysregulation is than added - autoaggressive inflammation starts.

6 Systemic inflammatory response syndrome (SIRS)

Definition

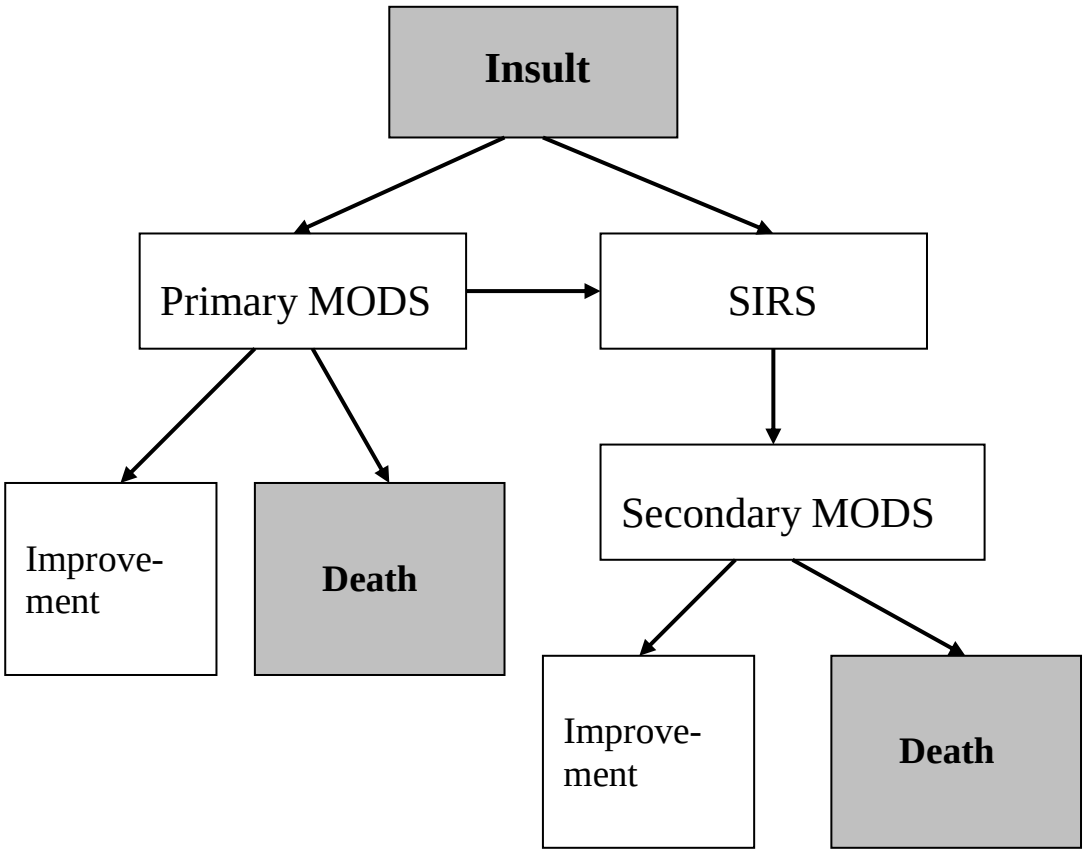
Delocalized and dysregulated inflammation process of high intensity. It leads to disorders of microcirculation, organ perfusion and finally to secondary organ dysfunction.

- This secondary dysfunction is **not due to primary insult**, but due to autoaggressive systemic inflammatory response of the organism to the primary insult.
- This systemic inflammatory response syndrome (SIRS), leads without therapeutic intervention to multiple organ dysfunction syndrome (MODS) and death.



#	- normal reactivity
*	- decreased reactivity
+	- increased reactivity
‡	- autoaggressive systemic inflammation

7 Multiple organ dysfunction during SIRS – primary and secondary MODS



8 Pathophysiology of SIRS

Insult

- hypoxic-reperfusion damage
- infection (endotoxin, other microbial toxins or microorganisms)
- primary mediators (histamin, anaphylatoxins /C3a, C5a /)
- complexes antigen-antibody
- thrombin a plasmin (DIC)

Defensive reactions

First detected signs of defense after insult are local and generalized hemodynamic changes (vasodilatation, vasoconstriction).

Regulation of hemodynamic changes

- systemic sympathic-adrenal activation (changes in organ blood distribution of minute volume)
- local microcirculatory changes - mediators produced by endothelial cells and other inflammatory systems (NO, PGI_2 x endothelin-1, thromboxan A2)

Endothelial cells reaction

Endothelial stimulation

Key process in development of microcirculatory disorders

- release of protective mediators (vasodilatatory and antithrombotic)
- contraction of endothelial cells and P-selectin expression (adhesion of neutrophils)
- aged endothelial cells desquamation, intracellular gaps, disturbances of endothelial surface
- release of vasoconstrictive and prothrombotic mediators

Result of stimulation process - thrombogenic vascular intima with increased permeability.

Reversibility

Fast stimulation of endothelium by primary mediators and development of acute inflammatory response is process not dependent on proteosynthesis. Endothelial cells are rapidly active, however, this activation without further stimulation disappears within few minutes.

Activation of other inflammation components

If insult persists

Activation of endothelial cells, platelets, neutrophils, plasmatic hemocoagulation system, and complement

- Endothelial activation
    - persisting insult (hours)
    - activation of mononuclear cells - release of TNF-α a IL-1β
    - adhesive receptors on mononuclear cells and tissue factor release
    - endothelial cells activated by cytokines - release of adhesive receptors, tissue factor expression
    - endothelial cytoskeleton rebuilding
    - irreversible active state
- chemotaxis of neutrophils - activation (reactions worsening hypoxia)
- interstitial edema and microthrombotization
- edema compresses lymphatic and blood stream
- anaerobic metabolism of tissue cells (decrease of pH - optimal for hydrolytic enzymes)
- hypoxia and organ dysfunction

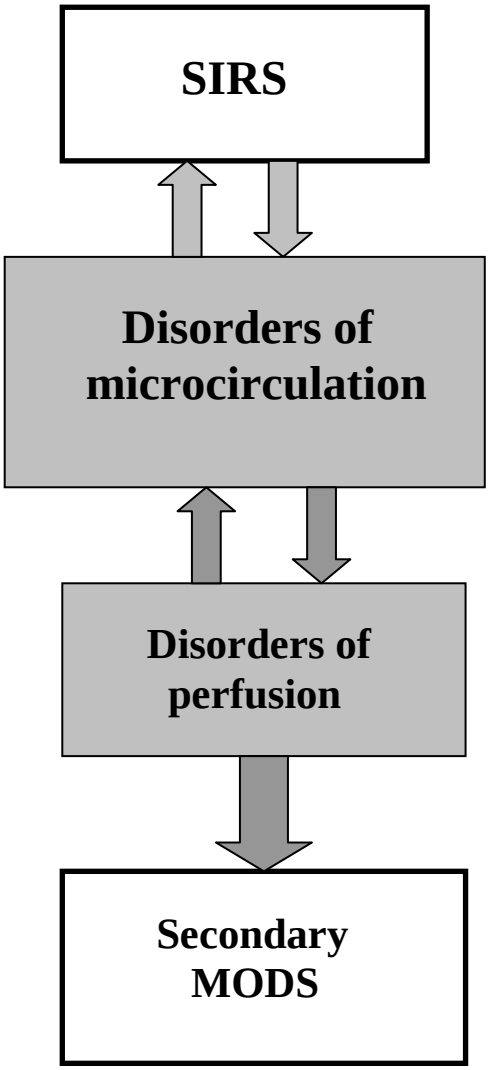
Reversibility

Activation of mononuclear cells and release of TNF-α a IL-1β is inhibited by corticosteroids released after activation of hypothalamic-adrenal stress reaction. Those acute microcirculatory disorders can be reversible, if the insult is eliminated and appropriate intensive care started.

Tissue damage

The degree of reversibility of secondary MODS is influenced by:

- necrotic tissue damage
- changes of vessel wall caused by proinflammatory cytokines
- during chronic process - proliferation of less valuable cells (fibroblasts)
- apoptosis (induced during SIRS)


SIRS
Disorders of microcirculation
Disorders of perfusion
Secondary MODS

9 Diagnosis of SIRS

Diagnostic criteria - weak part of SIRS theory.

Official diagnostic criteria SIRS (Tab.) are not able to cover dynamics and degree of SIRS.

Symptoms	Assessed factors
Body temperature	>38°C or <36°C
Pulse rate	>90 /min
Rate of breathing or PCO2 (arterial blood)	Frequency of breathing >20 /min $PaCO_2$ <32 mm Hg
White blood count or I/T ratio	>12 000/mm^3 or <4 000/m^3 >10%

SIRS diagnosis

Presence of SIRS indicated by presence of minimum 2 described signs. (Bone et al., 1992).

- intensive care - tachycardia and tachypnea pharmacologically influenced
- published SIRS criteria - low level inflammatory response (may not be autoaggressive)
- goal: diagnostic criteria of autoaggressive SIRS

10 Relationship between SIRS and sepsis

Developed noninfectious SIRS usually proceeds into sepsis.

Sepsis is most frequent example of severe SIRS caused by infectious insult.

Sepsis is a part of SIRS (Pic.).

Causes of sepsis development:

- disorders of intestinal wall microcirculation during SIRS - translocation of endotoxin and bacteria
- invasion of microorganisms to damaged tissues

