

# Systemic inflammatory response syndrome

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## A: Local inflammatory response

Inflammation is a stereotypic, mostly local response of the organism followed by systemic signs of different intensity, induced by tissue damage or destruction. Its ultimate goal is to liquidate, dilute or eliminate of the provoking noxas or to sequestrate and disengage affected tissue followed by reparation of the defect.

### There are several possibilities how to classify inflammation

according the time course – acute, per acute, chronic

according the main manifestation of the inflammation – alterative, exudative, proliferative

according the extent of the damage – superficial, deep, bounded or spreading into the surroundings, etc.

Inflammatory reaction consists of:

**vasodilatation** – dilatation of the blood vessels – to allow increased blood supply into the target tissue and enhance the supply of the inflammatory cells, mediators, factors necessary for the optimal course of inflammatory process

**increased permeability of the capillary wall** – allowing glide for the diffusible components of the inflammatory response into the target tissue

**transmigration of the cells (macrophages, lymphocytes, neutrophiles) into the target tissue**

- infiltration is caused and regulated based on chemotaxic stimuli

**changes of biosynthetic, metabolic, and catabolic profiles of many organs** /liver, spleen, lymphatic tissue/

**activation of immune system** – including cells as well as enzymatic system in the plasma /complement, coagulation/, this activation is as strong as the tissue damage seriousness

The local signs of inflammation – calor, rubor, tumor, dolor, functio laesa - are consequences of these abovementioned changes

## B: Acute phase reaction

Eukaryotic organisms have developed defensive and adaptive mechanisms necessary for the maintenance of homeostasis of internal environment after impairment of its integrity. These physiological processes of defensive and reparative nature elicited by tissue damage, infectious causes, nociceptive insults (burns, trauma, hemolysis, excessive physical activities) are termed as acute phase reaction.

**The acute phase reaction** is innate uniform adaptive response to disturbing if the integrity of organism. Acute phase is a group of reactions elicited by humoral factors, especially proinflammatory cytokines (IL-1, IL-2, IL-6, TNF  $\alpha$ ) and axis hypothalamus- pituitary gland-adrenal cortex- stress reaction. Acute phase reaction involves immune processes (production of proinflammatory cytokines, activation of innate nonspecific immunity), changes of hormonal and metabolic profile at systemic level (change of the metabolic profile of liver cells, change of plasmatic level of zinc, iron, insulin resistance, muscle catabolism), **synthesis of acute phase proteins** (C reactive protein CRP, serum amyloid A SAA, haptoglobin), change of water and ions balance (activation of RAA system) and pyretic reaction. The acute phase reaction is time limited – proinflammatory cytokines are cleaved from plasma within several hours, APP are present in the serum for at least 48 hours). The main goal of the acute phase reaction is:

- maintenance of water, ion and temperature homeostasis,
- antiinfectious processes
- perception of pain as a signal of tissue damage
- elimination of irreversibly damaged tissue
- adequate energy supply
- adequate supply of structural molecules, mainly amino acids for the production of antibodies, hormones, regenerative and reparative processes

## **C: Systemic inflammatory response syndrome**

In 1992, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) introduced definitions for systemic inflammatory response syndrome (SIRS), sepsis, sepsis induced hypotension, septic shock, and multiple organ dysfunction syndrome (MODS). The idea behind defining SIRS was to define a clinical response to a nonspecific insult of either infectious or noninfectious origin. SIRS is defined as 2 or more of the following variables:

- Fever of more than 38°C or less than 36°C
- Heart rate of more than 90 beats per minute
- Respiratory rate of more than 20 breaths per minute or a PaCO<sub>2</sub> level of less than 32 mm Hg
- Abnormal white blood cell count (>12,000/ $\mu$ L or <4,000/ $\mu$ L or >10% bands)

Extreme of ages (both young and old) may not manifest as typical criteria for SIRS; therefore, clinical suspicion may be required to diagnosis a serious illness (either infectious or noninfectious). Patients receiving a beta-blocker or a calcium channel blocker are likely unable to elevate their heart rate and, therefore, tachycardia may not be present.

Although blood pressure is not one of the 4 criteria, it is still an important marker of possible progression of disease.

SIRS is nonspecific reaction elicited by acute body danger, defensive reaction of the human body with the goal to localize and eliminate of endogenous or exogenous insults. **SIRS is more complex and more intensive reaction when comparing to the acute phase reaction.** SIRS might lead to complex disturbance of homeostasis with potentially destructive action the body is affecting itself due to its defensive reaction.

SIRS is nonspecific and can be caused by ischemia, inflammation, trauma, infection, or a combination of several insults. SIRS is not always related to infection. Therefore it is important to define several terms related to these problems.

SIRS	Two or more of: <ol style="list-style-type: none"> <li>1. Temperature &gt; 38°C or &lt;36°C</li> <li>2. Tachycardia &gt; 90 beats/minute</li> <li>3. Respiratory rate &gt; 20 breaths/minute or PaCO<sub>2</sub> &lt; 4.3 kPa</li> <li>4. White blood count &gt; 12 x 10<sup>9</sup>/l or &lt; 4 x 10<sup>9</sup>/l or &gt; 10% immature (band) forms</li> </ol>
Sepsis	SIRS due to severe infection , positive evidence for the presence of bacteria within the bloodstream, confirmed by cultivation
Bacteriemia	presence of bacteria within the bloodstream, but this condition does not always lead to SIRS
Sepsis induced hypotension	the presence of a systolic blood pressure of less than 90 mm Hg or a reduction of more than 40 mm Hg from baseline in the absence of other causes of hypotension
Septic shock	clinical syndrome caused by a sepsis, characterized by persistent hypotension and perfusion abnormalities (mostly in microcirculation), despite adequate fluid and vasopressoric resuscitation
MODS	Multiple organ dysfunction syndrome – dysfunction of kidneys, liver, lungs, heart, GUT caused by a severe hypo perfusion, and other complications of SIRS – physiological derangements in which organ function is not capable of maintaining homeostasis

## D: Causes of SIRS

**The most common causes of SIRS related to infectious disease are as follows:**

bacterial infection, wound infection (burns, surgical wounds, diabetic foot and other infectious complications), cholecystitis, cholangitis, other abdominal infections, pneumonia both nosocomial or community acquired, urogenital infections, meningitis and other less frequent conditions

**Noninfectious causes as underlying conditions for SIRS** involve acute intestinal ischemia, pancreatitis, GUT bleeding, autoimmune diseases, burns, aspiration, cirrhosis, inadequate reaction to drugs, cocaine, amphetamines, teophyllin in high dose, myocardial infarction, trauma and other causes.

## Pathophysiology

SIRS, independent of the etiology, has the same pathophysiologic properties, with minor differences in inciting cascades. Many consider the syndrome a self-defense mechanism. Inflammation is the body's response to nonspecific insults that arise from chemical, traumatic, or infectious stimuli. The inflammatory cascade is a complex process that involves humoral and cellular responses, complement, and cytokine cascades. Bone best summarized the relationship between these complex interactions and SIRS as the following 3-stage process:

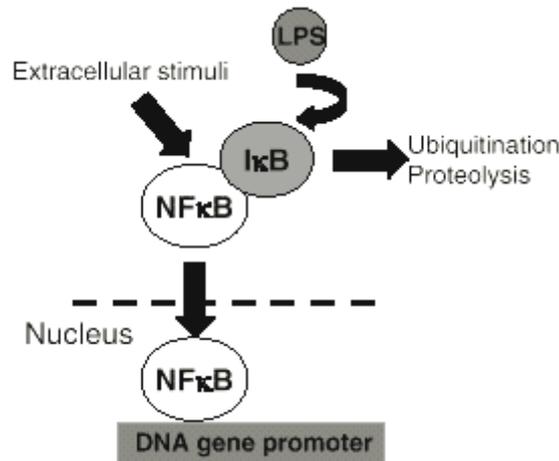
- Stage I: Following an insult, **local cytokine is produced with the goal of inciting an inflammatory response**, thereby promoting wound repair and recruitment of the reticular endothelial system.
- Stage II: **Small quantities of local cytokines are released into circulation to improve the local response**. This leads to growth factor stimulation and the recruitment of macrophages and platelets. This acute phase response is typically well controlled by a decrease in the proinflammatory mediators and by the release of endogenous antagonists. **The goal is homeostasis**.
- Stage III: **If homeostasis is not restored, a significant systemic reaction occurs**. The cytokine release leads to destruction rather than protection. A consequence of this is the activation of numerous humoral cascades and the activation of the reticular endothelial system and subsequent loss of circulatory integrity. **This leads to end-organ dysfunction**.

## E: Initiation of SIRS

Trauma, inflammation, or infection leads to the activation of the inflammatory cascade. When SIRS is mediated by an **infectious insult**, the inflammatory cascade is often initiated by **endotoxin or exotoxin**. Tissue macrophages, monocytes, mast cells, platelets, and endothelial cells are able to produce a multitude of cytokines. The cytokines **tissue necrosis factor- $\alpha$  (TNF- $\alpha$ )** and **interleukin (IL)-1** are released first and initiate several cascades. The release of **IL-1** and **TNF- $\alpha$**  (or the presence of endotoxin or exotoxin) leads to cleavage of the **nuclear factor- $\kappa$  B (NF- $\kappa$  B) inhibitor**. Once the inhibitor is removed, NF- $\kappa$  B is able to initiate the production of mRNA, which induces the production other proinflammatory cytokines. If the SIRS is induced by viral infection the main stimulus is **interferon gamma IFN $\gamma$**  released from cells infected and destroyed by the virus.

**IL-6, IL-8, and interferon gamma** are the primary proinflammatory mediators induced by NF- $\kappa$  B. In vitro research suggests that glucocorticoids may function by inhibiting NF- $\kappa$  B. TNF- $\alpha$  and IL-1 have been shown to be released in large quantities within 1 hour of an insult and have both local and systemic effects. In vitro studies have shown that these 2 cytokines given individually produce no significant hemodynamic response but cause severe lung injury and hypotension when given together. TNF- $\alpha$  and IL-1 are responsible for fever and the release of stress hormones (norepinephrine, vasopressin, activation of the renin-angiotensin-aldosterone system).

The figure shows activation of NF $\kappa$ B, primary transcription factor preexisting in the cytoplasm like an inactive molecule linked to the inhibitor complex subunit. The answer to external stimuli or presence of lipopolysaccharide is the cleavage of the inhibitory subunit, transport into the nucleus and initiation of transcription of target genes.



Other cytokines, especially IL-6, stimulate the release of acute-phase reactants such as **C-reactive protein (CRP)**. Of note, infection has been shown to induce a greater release of TNF- $\alpha$  than trauma, which induces a greater release of IL-6 and IL-8. This is suggested to be the reason **higher fever is associated with infection rather than trauma**.

The proinflammatory interleukins either function directly on tissue or work via secondary mediators to activate the coagulation cascade, complement cascade, and the release of nitric oxide, platelet-activating factor, prostaglandins, and leukotrienes.

Numerous proinflammatory polypeptides are found within the complement cascade. Protein **complements C3a and C5a** have been the most studied and are felt to contribute directly to the release of additional cytokines and to **cause vasodilatation and increasing vascular permeability**. **Prostaglandins and leukotrienes incite endothelial damage, leading to multiorgan failure**.

The **correlation between inflammation and coagulation** is critical to understanding the potential progression of SIRS. IL-1 and TNF- $\alpha$  directly affect endothelial surfaces, leading to the expression of tissue factor. Tissue factor initiates the production of thrombin, thereby promoting coagulation, and is a proinflammatory mediator itself. **Fibrinolysis is impaired** by IL-1 and TNF- $\alpha$  via production of plasminogen activator inhibitor-1. Proinflammatory cytokines also disrupt the naturally occurring anti-inflammatory mediator's antithrombin and activated protein-C (APC). If unchecked, this coagulation cascade leads to complications of microvascular thrombosis, including organ dysfunction. The complement system also plays a role in the coagulation cascade. Infection-related procoagulant activity is generally more severe than that produced by trauma. The cumulative effect of this inflammatory cascade is an unbalanced state with inflammation and coagulation dominating.

## F: Signs and symptoms of SIRS – mechanisms involved

### fever

- the effect of pyrogens onto the hypothalamus
- the central thermostatic point is converted to the higher point of body temperature
- mechanism responsible for the heat production are enhanced, but heat loss is inhibited to conserve heat - reach this new temperature
- production and loss of heat are regulated at this increased point until the level of pyrogens is decreased spontaneously, by action of immune system or by an action of treatment

**hypotension** – is a consequence of the drop of peripheral vascular resistance due to vasodilatation induced by cytokines and other proinflammatory agents, and partially is a consequence of the cardio inhibitory effect of proinflammatory molecules

### **tachykardia**

- drop of blood pressure inhibits the firing activity of baroreceptors in the arcus aortae
- therefore natural high activity of sympathetic centre within the brainstem becomes dominant
- the effects of sympathetic system on the heart involve **increased heart rate – tachycardia** and **increased strength of myocardial contractions**
- apart from these mechanism, also another could be involved – fever increase the metabolic rate therefore the tissue oxygen requirements are increased to enhance oxidative processes
- tachycardia is one of the powerful compensatory mechanisms able to increase oxygen tissue supply

### **increased breathing rate and hypocapnia**

- stimulation of breathing is a **complex process**, with many of possible mechanism involved in it
  - example – fever – **increased oxygen consumption** therefore it is necessary to increase ventilation **to take more oxygen**
  - change of PaCO<sub>2</sub> depends strongly on the **type of breathing pattern employed**
  - example – panting as a thermoregulatory response is characterized by rapid shallow breathing with re breathing / ventilation of death space within the airways - there is no hypocapnic response
  - but hyperventilation - when alveolar space is ventilated – hypocapnia is common sign
- respiratory alkalosis may be a consequence of hypocapnia

### **changes of the leucocytes (WBC) count**

- due to action of proinflammatory cytokines the white blood cell population within the bone marrow is stimulated to proliferate and mature thus providing optimal immune defense
- if stimulation of the WBC is strong, then younger „un matured“ cells are released from the bone marrow into the blood stream – bands

**decreased count** – mechanisms of rolling, adhesion and transmigration into the tissue are responsible for the progressive decreasing of WBC count in the blood

this blood pool is not adequately completed from the marrow pool – proliferation and maturation might be not so strong enough to stabilize normal WBC count

## **G: The balance between inflammatory and anti-inflammatory response**

The intensity and time course of SIRS is influenced by a balance in action of proinflammatory and anti-inflammatory systems at the local and systemic level. To counteract the acute inflammatory response, the body is equipped to reverse this process via **counter inflammatory response syndrome (CARS)**. This antagonistic system is induced by the same stimuli like the SIRS is, and both processes **are running simultaneously**. CARS represent the system of negative feedbacks in cytokine and endocrine network (including the

axis hypothalamus- pituitary gland-adrenal cortex) and limits extend and duration of systemic inflammatory response syndrome. **The balance between the SIRS and CARS course represents the balance between optimal inflammatory response and the extent of immunosuppression.**

IL-4 and IL-10 are cytokines responsible for decreasing the production of TNF- $\alpha$ , IL-1, IL-6, and IL-8. The acute phase response also produces antagonists to TNF- $\alpha$  and IL-1 receptors. These antagonists either bind the cytokine, and thereby inactivate it, or block the receptors.

**Counter inflammatory response involves:**

- cytokines with anti-inflammatory action IL-4 and IL-10 - responsible for the decrease of TNF- $\alpha$ , IL-1, IL-6, and IL-8 production
- production of receptor site antagonists for TNF- $\alpha$ , and IL-1. These antagonists could be bounded directly to the molecule of cytokine and inactivate it, or could be bounded to the receptor resulting into the block of the cytokine induced biological signal
- activation of the axis hypothalamus-pituitary gland-adrenal cortex with overproduction of glucocorticoids – their action is inhibition of cytokine release, therefore immunosuppressive effect

Comorbidities and other factors can influence a patient's ability to respond appropriately. The balance of SIRS and CARS determines a patient's prognosis after an insult. Some researchers believe that, because of CARS, many of the new medications meant to inhibit the proinflammatory mediators may lead to deleterious immunosuppression.

As it was described above, both SIRS and CARS are induced at the same time, and the main idea of these antagonistic reactions is to maintain a balance within the cytokine network, therefore to maintain the balance in action of proinflammatory and anti-inflammatory cytokines. The disturbed balance might result into two extreme situations:

1. **excessive activity of proinflammatory cytokines leads to severe SIRS with potential risk of organ dysfunction and death**
1. **excessive anti-inflammatory response leads to immunosuppression and risk of increased mortality later phases of clinical course**

## **E: Organ dysfunction as a consequence of severe SIRS**

Multiorgan dysfunction could be a consequence of inconvenient clinical course of SIRS; the dysfunction is mostly related to the kidneys, liver, lungs, central nervous system and heart.

Mechanisms responsible for the development of organ dysfunction

1. vasodilatation – abnormal distribution of circulating volume - tissue hypoperfusion
2. increased vascular permeability - impairment of Starling's mechanisms – displacement of fluids into the interstitial space
3. endothelial damage with expression of cell adhesion molecules and small thrombi in microcirculation - disseminated intravascular coagulation
4. production of reactive oxygen species by neutrophils
5. production of proteases by neutrophils
6. production of NO by inducible NO synthase – refractoriness in vasodilatation

## **Respiratory Dysfunction**

Pulmonary dysfunction is common in the patient with SIRS and is manifested as tachypnoea, hypoxaemia and respiratory alkalosis. When severe it may progress to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). The primary pathological process is pulmonary capillary endothelial dysfunction resulting in interstitial and alveolar oedema of protein and phagocytic immune cell rich exudative fluid. Endothelial permeability is increased in response to pro-inflammatory cytokines with progression to alveolar denudation and basement membrane destruction. Another mechanisms employed are destruction of pneumocytes type I, destruction of surfactant molecules, and onset of microatelectatic areas in lungs.

### **Cardiovascular Dysfunction**

Both the heart and the blood vessels are sensitive to the effects of pro-inflammatory cytokines as well as vasoactive substances present in excessive amounts in SIRS. Nitric oxide is synthesized by inducible nitric oxide synthase (iNOS) from L-arginine in the vascular endothelium and smooth muscle in response to pro-inflammatory cytokines. Nitric oxide is the vasodilator mediator responsible for the fall in systemic vascular resistance underlying the hypotension in SIRS. This hypotension may be refractory to treatment with fluids, inotropes and conventional vasoconstrictors.

The response to the fall in blood pressure is an increase in cardiac output. Baroreceptors mediate a pronounced tachycardia and stroke volume increases due to decreased afterload but hypovolaemia may decrease preload and thus cardiac output. Independent of the effects of preload and afterload intrinsic myocardial depression is present within 24 hours of the onset of SIRS. Endotoxin and pro-inflammatory cytokines have both been shown to induce myocardial depression. These effects are probably mediated through nitric oxide. Constitutive NO in the heart is responsible for leucitropy, the ability of the myocardium to relax, thus maximizing end diastolic filling and coronary artery perfusion. Inducible NOS is expressed in cardiac myocytes in response to cytokines and increases NO production. Nitric oxide reduces myocardial contractility and responsiveness to  $\beta$ -adrenergic agents mediated through increased cGMP.

### **Renal Dysfunction**

Several mechanisms have been proposed for the pathogenesis of acute renal failure occurring in SIRS. In normal states, the kidney maintains renal blood flow and glomerular filtration through autoregulation dependent on the tone of the afferent and efferent arterioles, an autoregulation is disturbed in SIRS. The cytokine-induced systemic vasodilatation and relative hypovolaemia in SIRS are responsible for renal hypoperfusion. Therefore, it is difficult to predict renal blood flow from systemic blood pressure parameters. The kidney produces intrinsic vasoconstrictors in response to cytokines and the renin-angiotensin-aldosterone system. In particular, the arachidonic acid metabolites of thromboxane and leukotrienes both reduce renal blood flow and antagonists of these substances have been shown to have renal protective effects. In common with other tissues, the kidney is susceptible to leucocyte mediated tissue injury with neutrophil aggregation in response to chemokines and production of proteases and ROSs.

### **GIT**

Gastrointestinal system suffers from hypoperfusion too; and the barrier function of the intestinal wall is compromised due to hypoperfusion. After that a translocation of intraluminal bacteria or their endotoxin might occur – worsening the hemodynamic parameter primarily disturbed due to SIRS. There is a possibility for the development of septic complication in patients with SIRS as a response to no infection causes – based on the mechanisms of bacterial translocation across the impaired intestinal barrier from the lumen into the internal environment.

### **Metabolic Disturbances**

The alteration in haemodynamic regulation produces inappropriate distribution of perfusion and arteriovenous shunting resulting in tissue hypoxia and lactic acidosis. Many of the current therapeutic approaches aim to optimize oxygen delivery to the tissues by improving perfusion and avoiding hypoxemia. The cellular hypoxia is confounded due to impaired cellular oxygen extraction. Evidence suggest this is at a mitochondrial level mediated through NO which blocks the mitochondrial electron transfer chain at its terminal receptor of cytochrome oxidase. This then causes cellular hypoxia and an increase in mitochondrial derived ROS concentrations.

### **Haematological Dysfunction**

SIRS is often associated with a disorder of coagulation secondary to the cytokine-mediated activation of the coagulation pathways. This disseminated intravascular coagulation (DIC) produces both bleeding and microvascular thrombi which have been proposed as mechanisms of multiorgan dysfunction. The cytokine-mediated activation of coagulation in SIRS occurs via the tissue factor dependent extrinsic pathway. Tissue factor is the activator of and cofactor for factor VIIa activation of factors IX and X of the extrinsic pathway.

Monocytes and endothelial cells express tissue factor in response to endotoxin, complement fractions, IL-6 and IL-8. Attenuation of the anticoagulant systems furthers the procoagulant state. Antithrombin III (ATIII) is an inhibitor of the serine proteases responsible for coagulation clotting factors IXa, Xa, XIa and XIIa and thrombin. Thrombomodulin is an endothelial cell derived inhibitor of clotting and activator of fibrinolysis. It acts as a thrombin binding protein, reducing the effects of thrombin. The thrombin-thrombomodulin complex has further anti-coagulant properties as an activator of protein C which, with cofactor protein S, inactivates factors V and VIII. In sepsis, the production of thrombomodulin by endothelial cells is downregulated by pro-inflammatory cytokines and circulating free levels of protein S are reduced.