Academic lectures for general medicine – 3rd year
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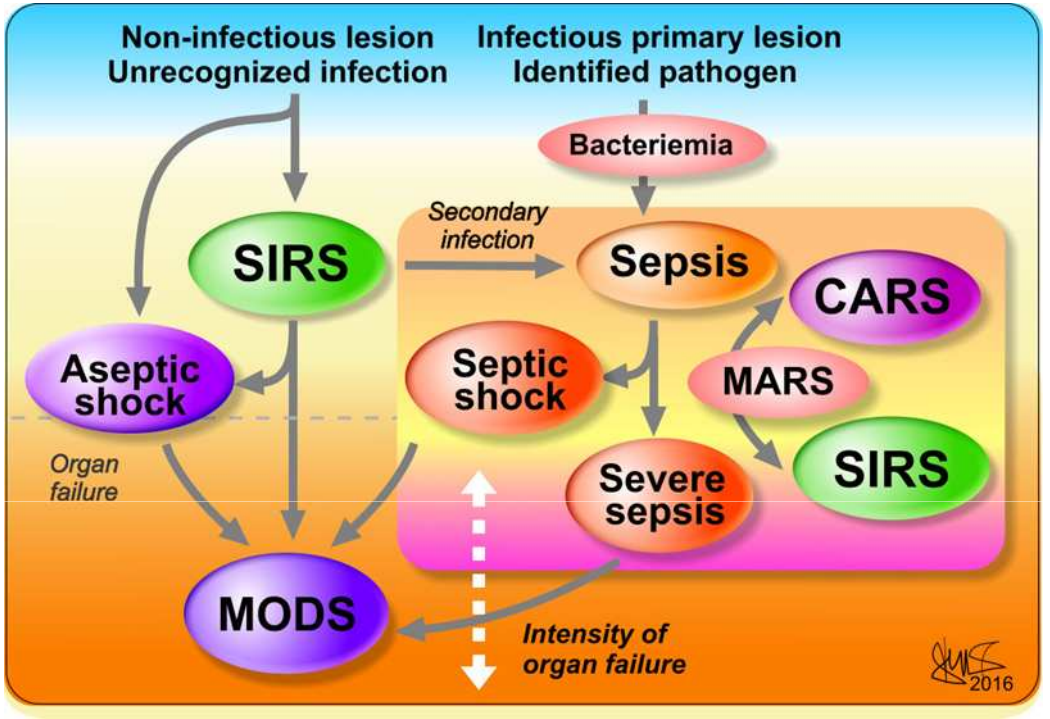
GENERAL PATHOPHYSIOLOGY

CRITICAL OUCOMES OF INFLAMMATION

R. A. Benacka, MD, PhD
Department of Pathophysiology
Medical faculty, Safarik University, Košice

Repetitorium of terms

- **SIRS (systemic inflammatory response syndrome) =** systemic alterative inflammatory state (cytokine storm) to non-infectious or infectious (but nor proven, measured or apparent) conditions (napr.: acute pancreatitis, polytrauma, burning injuries).
- **Sepsis** = serious state characterized by systemic infection (polytopic or metastatic spread of infection from locus (septocaemia, bacteriemia). Today it is sometimes noted as **septic SIRS.**
- **Severe sepsis:** sepsis with sepsis-induced organ dysfunction or tissue hypoperfusion
- **Septic shock:** sepsis-induced hypotension persisting despite adequate fluid resuscitation
- **Compensatory anti-inflammatory response syndrome (CARS)** adapative active supression of immunological activity during sepsis
- **Mixed antagonist response syndrome (MARS)** concurrent manifestations (baboratory findings of pro-inflammatory response and anti-inflammatory response, both SIRS and CARS can be lethal.



Multiple organ dysfunction syndrome (MODS) end stage progressive dysfunction of two or more organ systems resulting from an uncontrolled inflammatory response to a severe illness or injury.

Markers

Pro-inflammatory cytokines + other markers	Anti-inflammatory cytokines + other markers
IL-1β, TNFα, IL-6, IL-11, IFNγ, IL-8 + chemokines	IL-10, TGFβ, IL-1Ra, sIL-R, IL-4
PDGF, GM-CSF, VEGF, IL-7 IL-17, IL-18, PAF, EDRF	sTNF-Ra, IL-13. IL-11,IL-18BP
Procalcitonin, C-reactive protein	

Abb. tumour necrosis factor receptor (sTNF-R), IL-1 receptor antagonist (IL-1Ra), transforming growth factor-β (TFGβ) , interleukin (IL)

SIRS

- Defintion: generalized acute quasi-inflammatory immunological response with intense but unballanced immune response in *predisposed people* (e.g. genetic, immunological imballance - autoimmunity, hypersensitivity, chronic organ disorders) which may start by local injury or has no local origin. Term was coined as non-infection alternative to more cannonical term sepsis, which was colloquially known as systemic spread of infection from well known primary locus (e.g. post-surgery, open fractures, etc)
- SIRS is not a generalisation of classical inflammation, it is **abnormal, delocalized, non-protective, uncontrolled autoagressive process**, which lead to **damage of distant healthy tissues,** organs.
- Causes: mechanical injury (crush damage), acute radiation injury, burning injury (UV, hot wapors, chemical damage, heavy metals, biological (biological toxins, venoms, etc.), damage to organs (acute pancreatitis), hypoxemia, ischemia, blast syndrome, incompatible transfusion
- Laboratory data.: excessive production of a large number of pro-inflammatory cytokines, incl. IL-1β, TNFα and IL-6, IL11, activation of neutrophiles, activation of inflammatory and thrombotic cascade
- Symptoms: Arbitrary: 1. Fever or hyperthermia > 38 or < 36 C, 2. Tachycardia > 90 beat / min, 3. ´Hyperventilation, tachypnoea > 20/min , 4. $PaCO_2$ < 4,3 kPa, 5. WBC > 12,000 or < 4,000 x 10^9 /L
- Other manifest. are nonspecific, similar to those in inflammation, tiredness, headache, changes in nervous., gastrointestina, cardiovascular, respiratory sy.,
- As a rule, primary „non infective SIRS“ can easily turn into infective sepsis after break of intestinal mucosal barrier → spread of bacterial infection, spead of toxins from cell debris

Sepsis

- Defintion: systemic inflammation (SIRS) with disseminated microbial infections caused by Gramm positive or negative bacteria, polybacterial, fungi, anaerobic bacteria. Lethality 30-40%.
- Causes: infection of skin, sub dermal soft tissues, infections and inflammation of GIT, urogenital system, pneumonias (bacterial, atypical, influenza), meningitis, meningoencephalis, iatrogenic nosocomial infections higher resistance top ATB than common flora (via breathing, skin openings – infusions, injections, nasogastric probes , urinary catheters, invasive diag. and therap. procedures.
- primary sepsis - microbes enter directly blood (illegal abortions, puerperal sepsis, drug addiction, .
- secondary sepsis – posttraumatic, pyelonephritis, peritonitis, pneumonia, thrombophlebitis, meningitis
- Manifestations: Two or more of SIRS criteria

1. Fever or hyperthermia > 38 or < 36 C , 2. Heart Rate > 90 beat / min, 3. Respiratory rate > 20/min , 4. $PaCO_2$ < 4,3 kPa, 5. WBC > 12,000 or < $4{,}000.10^9$ /L, 6. Evidence of infection: locus, blood culture (bacteriemia), 7. BP normal or low : refractory hypotension cannot be reversed by fluid infusion therapy SBP < 90 mHg MAP < 70 mmHg drop in SBP 40mmHg f5rom baseline

- **Severe sepsis** = a major health problem with an overall hospital mortality rate of about 30%, which remained nearly stable during the last two decades
- **Sepsis-induced hypotension:** a systolic blood pressure (SBP) less than 90mmHg or mean arterial pressure less than 70mm Hg, or an SBP decrease of greater than 40mm Hg or greater than 2 SD less than normal for age in the absence of other causes of hypotension
- **Sepsis-induced tissue hypoperfusion:** septic shock, lactate elevation beyond the upper limits of normal or oliguria

Compensatory anti-inflammatory response syndrome (CARS)

- Definition: (1996, Roger Bone) immunologic phenomenon of systemic deactivation of the immune system duting sepsis; a)enhanced release of anti-inflammatory mediators, e.g. sTNFR, increase of IL10 that supresses TNFa),, IL-1 receptor antagonist (IL-1Ra), transforming growth factor-β (TFGβ), b) de-activation of monocytes, decreased Mo/Mf activation, decrease of HLA DR(+) monocytes.reduction of IL-2/IL-4 production, d) anergy of T lymphocytes, reduction of lymphocytes by apoptosis), and loss of other immune cells by apoptosis, e) plasma of sepsis patients has the capacity to inhibit leukocyte functions, f) anergy to skin test antigen
- CARS can exist separately from SIRS; is not simply the cessation of SIRS contains distinct set of cytokines and cellular responses and may have a powerful influence on clinical outcomes in sepsis.
- SIRS or CARS could predominate in a given patient, and although other authors postulated that CARS follows SIRS in a two-wave process, we rather considered that both events are
- CARS is not a generalized phenomenon that dampens all immune functions, rather an adaptation depending upon the compartments (i.e. blood vs. tissues)
- CARS as standing againts SIRS should not be viewed in any way as sort of anti-inflammatory therapy, or benefitial natural anti-inflammatory mechamism; actually, prevailing CARS has same or more detrimental effect as SIRS; because of immunosuppressive milieu CARS conditions, patient have high susceptibility to nosocomial infections
- Actually sepsis severity is positively correlated with a disproportionate elevation of the anti-inflammatory response relative to the pro-inflammatory response, a pattern reminiscent of TLR-driven responses.

Laboratory findings in CARS

Neutrophile

↓
- TLR2
- TNF & IL-1 receptors
- CXCR2
- Cathepsin D release
- Intracellular microbicidal activity (ROS prod.)
- IL-1β, IL-1Ra prod. in response to LPS
- Apoptosis
- Response to chemoattractant
- Phagocytosis

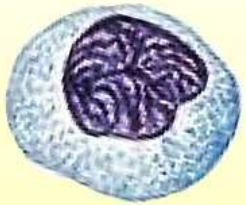
↑
- Fcγ R1 (CD64)
- fMLP-Receptor
- CD66b
- IL-10R1
- PEBF production
- Expression of phospholipase A2
- Elastase release

Lymphocyte

↓
- Proliferation to mitogens
- Cytokine production

↑
- Apoptosis

Monocyte



↓
- HLA-DR
- TNF R p75
- CD14
- Transferrin receptor (CD71)
- Co-activation marker (CD86)
- GM-CSF
- CX3CR
- IL-1β, IL-6, IL-8, IL-12, TNF production in response to LPS

↑
- Fcγ R1 (CD64)
- TNF R p55
- CD40; CD48; CD80
- Fcα R1 (CD89)
- TLR4
- TREM-1
- Tissue factor
- IL-1Ra, MIF production in response to LPS

Reworked & supplemented 2016

Mixed anti-inflammatory response syndrome (MARS)

- **Mixed antagonist response syndrome (MARS)** is more recent concept of not sequential but contemporary **balanced** co-existence of both SIRS and CARS. Intensity of both can be measured by serum inflammatory and anti-inflammatory activities & markers (SIA and SSA) including content of CD8(+) T and CD72(+) B lymphocytes, concentration of IgG and IgA, the production of IL-2 and IL-4, IL-10. MARS is used to either designate temporary homeostasis during the **transition from SIRS to CARS** or the **co-existence of overwhelming inflammation and suppression** of innate and adaptive immunity.
- Based on measures of pro- and anti-inflammatory cytokine production, hyper inflammatory state = systemic inflammatory response syndrome (SIRS) and hypo-inflammatory state = compensatory anti-inflammatory response syndrome (CARS) occur in sepsis :

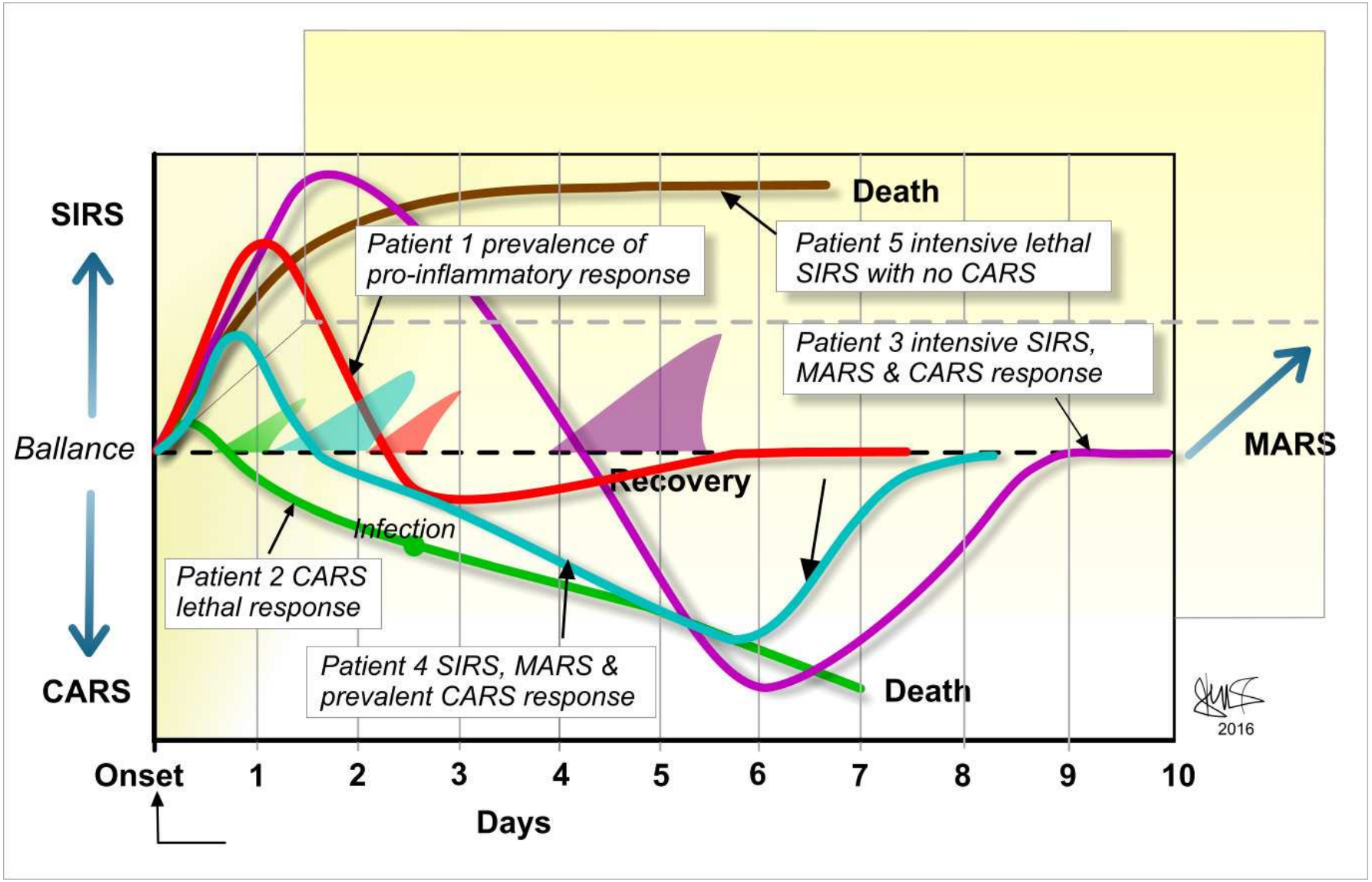
  a) concurrently (or visually sequentially), with prevalence of SIRS usually in early stages and CARS - at the late stage of disease;

  b) concurrently (or sequentially) with brief transient peak of hyper inflammatory response and longer predominance of hypo inflammatory response, i.e. CARS

  c) concurrently, with predominance of neither SIRS nor CARS, i.e. balanced MARS.

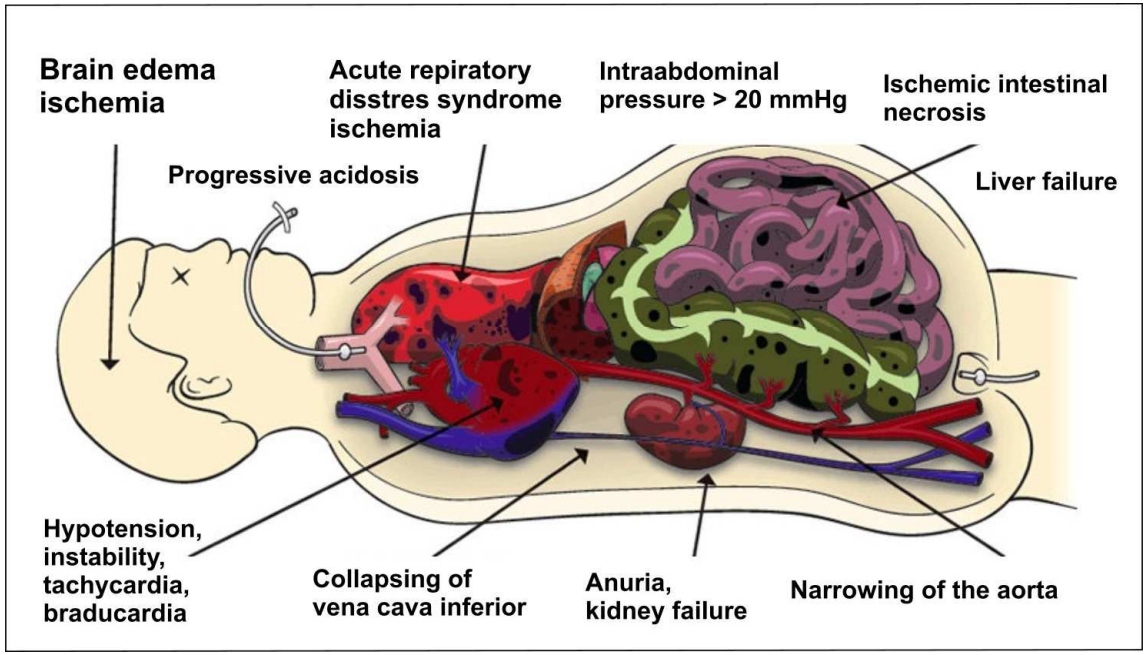
  While overwhelming inflammation may cause organ injury and shock, a prolonged hypo-inflammatory state may lead to immunosuppression and a failure to clear infection

Various combinations of SIRS, CARS + MARS



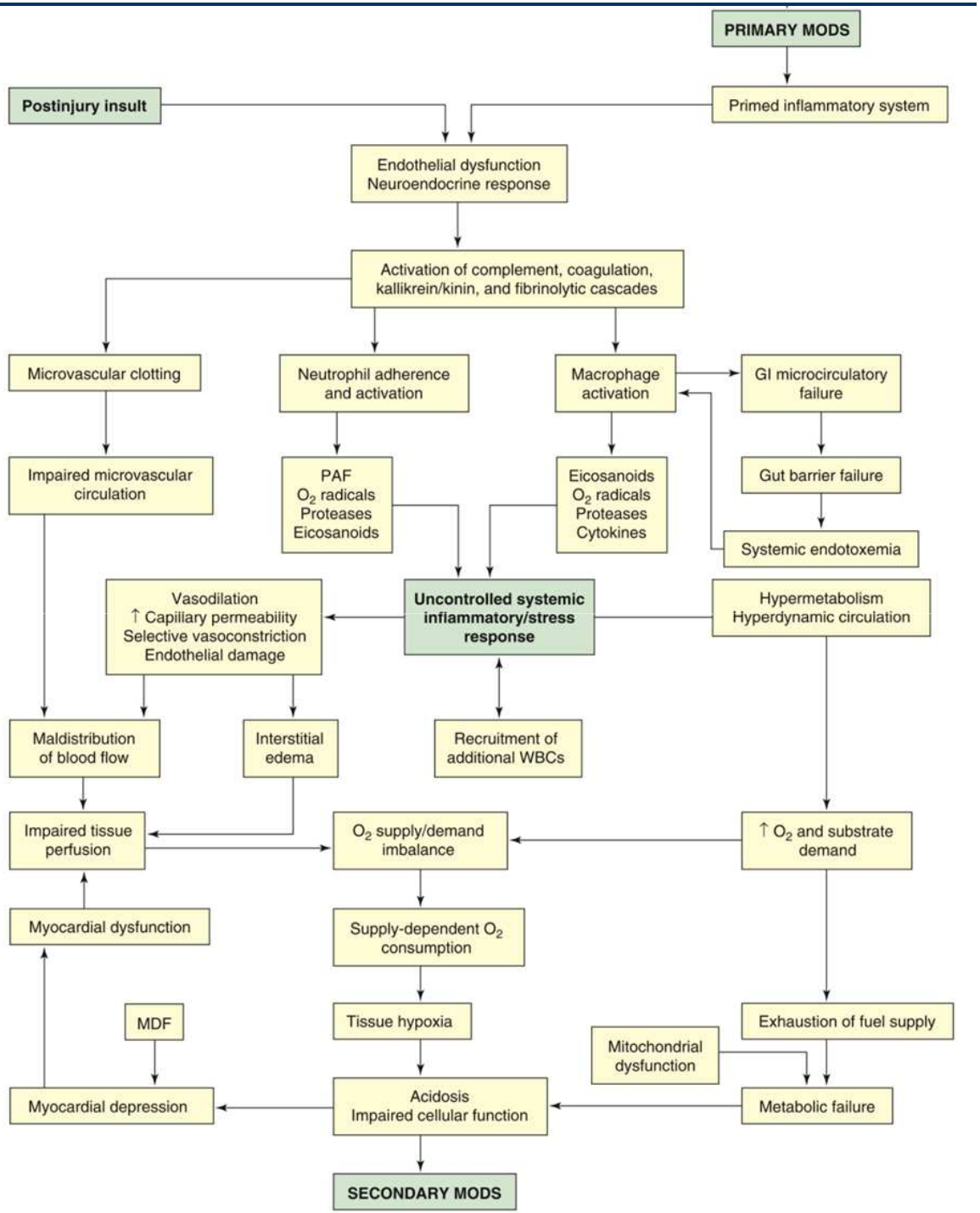
Multiple organ dysfunction syndrome (MODS)

- Def: progressive dysfunction of two or more organ systems resulting from an uncontrolled inflammatory response to a severe illness or injury. The organ dysfunction can progress to organ failure and death (alt. multiple organ failure (MOF), total organ failure (TOF) or multisystem organ failure (MSOF))
- Etio: uncontrolled inflammatory response; sepsis (severe sepsis) is the most common cause in operative and non-operative patients; . in absence of infection, a sepsis-like disorder is termed **systemic inflammatory response (SIRS**);
- Common course: SIRS - Sepsis - Severe sepsis – Septic shock – MODS



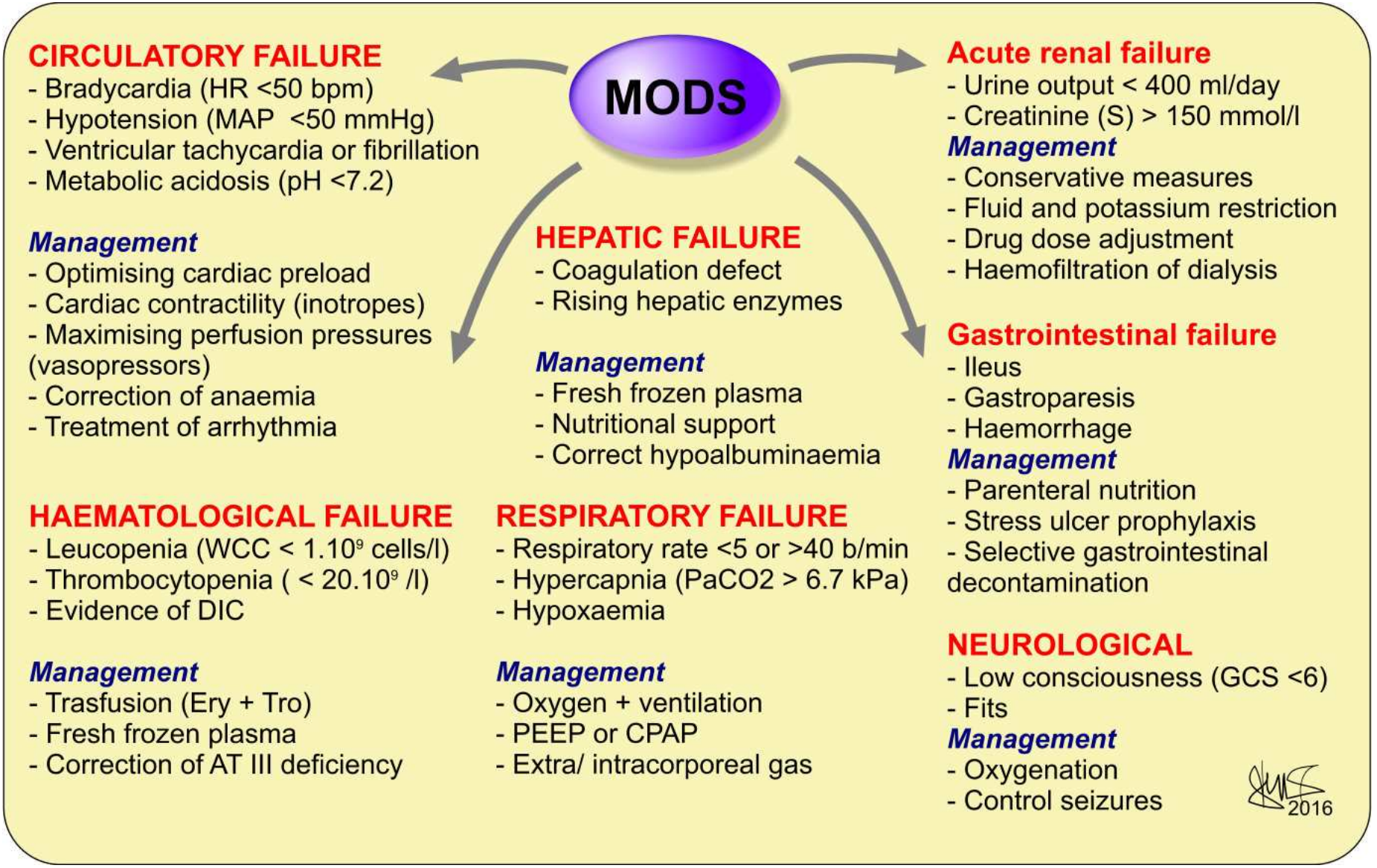
Pathogenesis of MODS

- Endothelial dysfunction ⟶ activation of com-plement, coagulation, kallikrein kinin cascade ⟶ microtrobi ⟶ hypperfusion, hypoxia, hypo-xia, lactic acidosis, constrictive efects on precapilary sphincters
- Neurophile & macropahge adherence to endothe-lium and their activation ⟶ PAF, prostaglandins, O2 radicals, proteases, cytokines, ⟶ uncotrolled systemic response ; global vasodilation vs. local slective constriction , capillary permeability, endotheleial damage, edema, maldistribution of blood
- Hypermaetabolic state, hyoerdynamic state vs. tiisue hypoxia, low O2 supply, metabolic failure; micro- and macronecrosis.



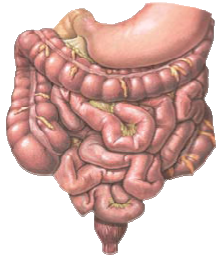
GI, Gastrointestinal; MDF, myocardial depressant factor; MODS, multiple organ dysfunction syndrome; PAF, platelet-activating factor; WBCs, white blood cells.

Manifestations of MODS

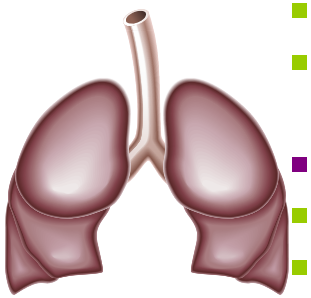


Clinical manifestation of MODS

- **Gastrointestinal failure**
- **Paralytic ileus** (Decreased bowel sounds) , Intolerance to enteral feedings,
- **Abdominal distention**, ascites
- **Upper and lower gastrointestinal bleeding**
  Ischemic colitis → Mucosal ulceration,
- **Bacterial overgrowth** in colon (ev in stool) → leak into circulation (G(-) bact.) + Diarrhea

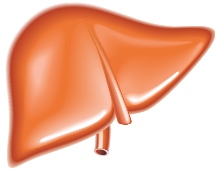


- **Pulmonary**
- Acute respiratory distress syndrome
- (ARDS) type of **respiratory failure** (dyspnea, patchy infiltrates, refractory hypoxemia, respiratory acidosis,
- abnormal PAO_2, PaO_2 $PaCO_2$
- Pulmonary hypertension

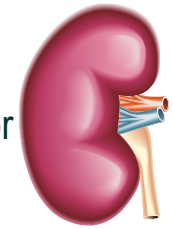


- **Gallbladder**
- Right upper quadrant tenderness or pain
- Abdominal distention, Unexplained fever,
- Decreased bowel sounds

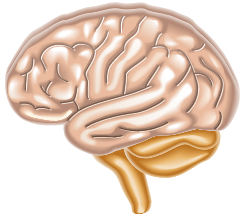
- **Liver**
- ↑ liver enzyme levels (AST, ALT, LDH, ALP (alkaline phosphatase))
- ↑ serum ammonia ,↓ serum transferrin level
- Jaundice, ↑ serum total bilirubin (hyperbilirubi-nemia), Hepatomegaly



- **Renal**
- ↑ serum creatinine and urea nitrogen
- **Oliguria, anuria** with prerenal azotemia or
- Aacute tubular necrosis



- **Central Nervous System**
- Altered consciousness (Stupor)
- Confusion, Lethargy
- Hepatic encephalopathy



Manifestations of MODS

- **Cardiovascular**
- **Hyperdynamic**
  - ↓ pulmonary capillary wedge pressure (CWP)
  - ↓ systemic vascular resistance (SVR)
  - ↓ right atrial pressure (RAP)
  - ↓ left ventricular stroke work index
  - ↑ oxygen consumption
  - ↑ cardiac output (CO), cardiac index (CI), heart rate (HR)

- **Hypodynamic**
- ↑ systemic vascular resistance (SVR)
- ↑ right atrial pressure (RAP)
- ↑ left ventricular stroke work index
- ↓ oxygen delivery and consumption
- ↓ cardiac output (CO) and cardiac index (CI)

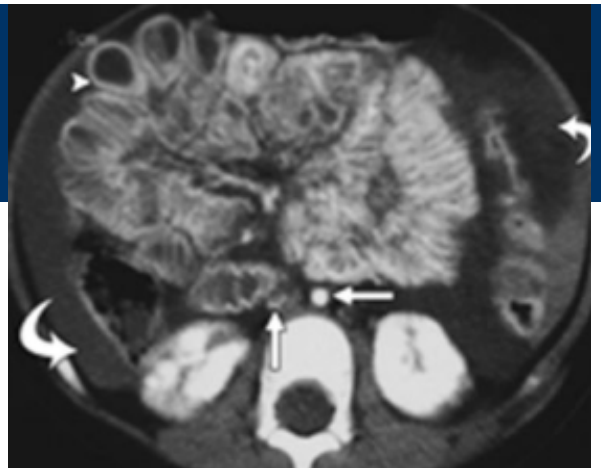
- **Coagulation and Hematologic**
- Thrombocytopenia
- Disseminated intravascular coagulation

- **Immune**
- Infection, Immunodefiency (Anergic inflammation)
- Decreased lymphocyte count

- **Metabolic/Nutritional**
- Decreased lean body mass
- Muscle wasting, Severe weight loss7
- Negative nitrogen balance, Hyperglycemia

Modified from Thelan LA et al: Critical care nursing: diagnosis and management, ed 6, St Louis, 2010, Mosby.

Hypoperfusion complex

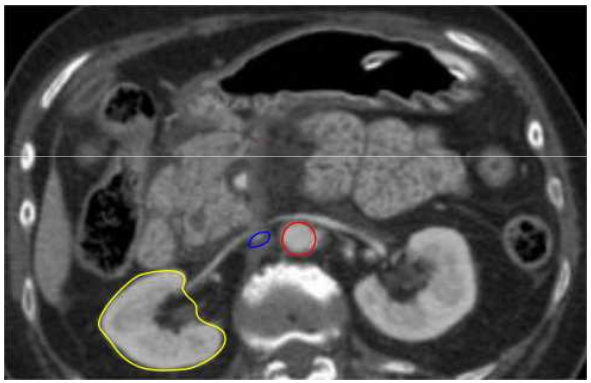


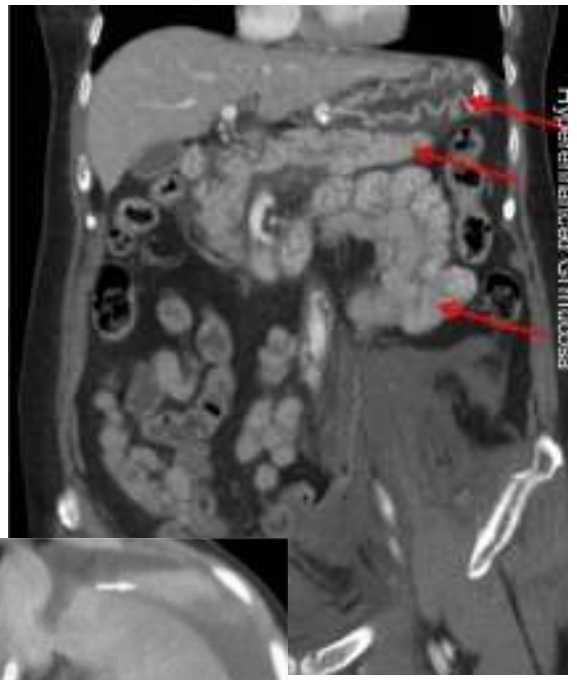
- radiographic feature which occur in the context of profound hypotension.; early abdominal CT scans

- **Vascular Manifestations**

1. Collapsed inferior vena cava: AP diameter <9mm in three consecutive segments; i.e. 20mm both above, below the renal veins

2. “Halo Sign”,
3. *Small calibre aorta*





- **Visceral Manifestations**

1. Abnormal liver enhancement,
2. Splenic hypoperfusion
3. Peripancreatic oedema and hyperenhancement,
4. Intense renal parenchymal enhancement
5. Shock bowel = dilated and fluid-filled with sparin of the colon;
6. Bilateral adrenal gland hyperenhancement = haemorrhagic shock, pancreatitis, sepsis and trauma