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Sepsis and MODS

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Contents of seminar

1. Sepsis and MODS
2. Meningococcal sepsis
3. Sepsis-like disorders (SIRS)

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Paradoxes of sepsis

- severe and very frequent disorder, meets physicians of most specialities, but rather marginal in the curriculum of medical faculties

- cause of 25 % deaths, bacterial infection, although we have ATB

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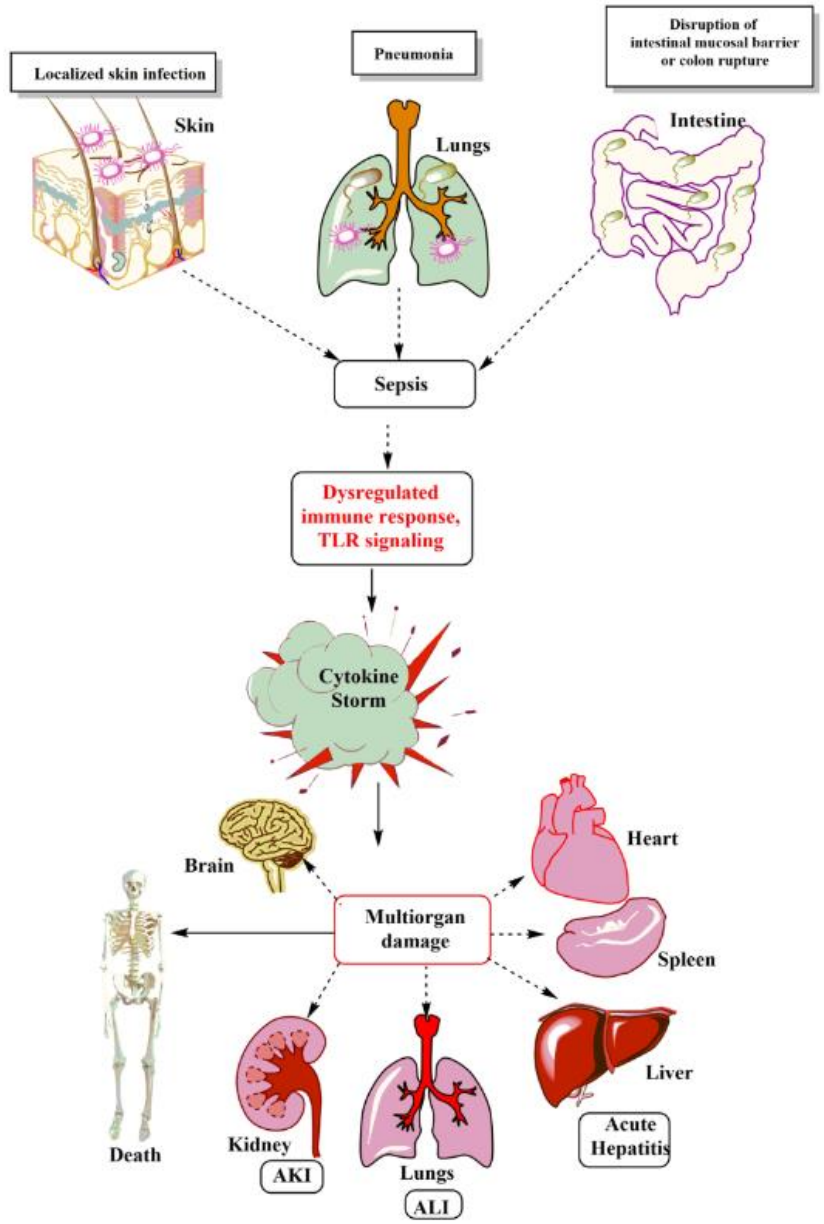
Sepsis „intuitively“

local reaction

- erythema
- swelling
- dysfunction
- fever

systemic reaction

- vasoplegia, shock
- anasarka, hypovolemia
- MODS
- cytokine storm



Definition of sepsis

Bone (1992)

- **SIRS**
  - T > 38°C or < 36°C
  - HR > 90/min
  - BR > 20/min or pCO_2 < 4.3
  - Leu > 12 or < 4
- **sepsis** = infekce + SIRS
- **severe sepsis** = sepse s orgánovou dysfunkcí
- **septic shock** = těžká sepse vyžadující katecholaminy

Consensual conference (2016)

- **sepsis** = life threatening new organ dysfunction due to systemic reaction to infection
- **septic shock** = sepsis with need of catecholamines AND increased lactate

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How does a septic patient look like?

- man 71 yo, anamn. hypertension and nephrolithiasis
- brought to ER because of progressive weakness and back pain for 3 days, sleepy, desoriented
- initially BP 90/50 (chronically 150/90), SR 125/min, clinical signs of dehydration, T 38.4, mild dyspnea, positive tapotement on the left side
- laboratory
  - urea 25 (normal < 8), crea 264 (normal < 100), K 5.2
  - pH 7.22, BE -13, pCO_2 3.5 (normal > 4.6), SaO_2 94%
  - lactate 4.5 (normal < 2)
  - leu 19, CRP 240 (normal < 2), leu in urine 4+
- abdominal US – dilated renal pelvis

Dg.: Sepsis by obstructive pyelonephritis

- crystalloids 1000 ml, but BP decreased to 70/40, NA administered, lactate 5, further 2 l of fluids
- worsening of dyspnea, SaO_2 90%, with 4 l O_2 96 %
- empirical administration of cefotaxim, urological consult.
  - performed nephrostomy of left kidney, drainage of pulurent urine
- oliguria 30 ml/hod, further fluids
- on the nest day urea 30, crea 230, lactate 2.1, normal diuresis, no NA necessary, leu 12, CRP 234
- gradual stabilisation, E. coli sensitive to cefotaxime in urine culture
- later ureterocystoscopy with of concrement removal in plan

Dg.: Septic shock with failure of circulation, kidneys and CNS

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Sepsis versus infection

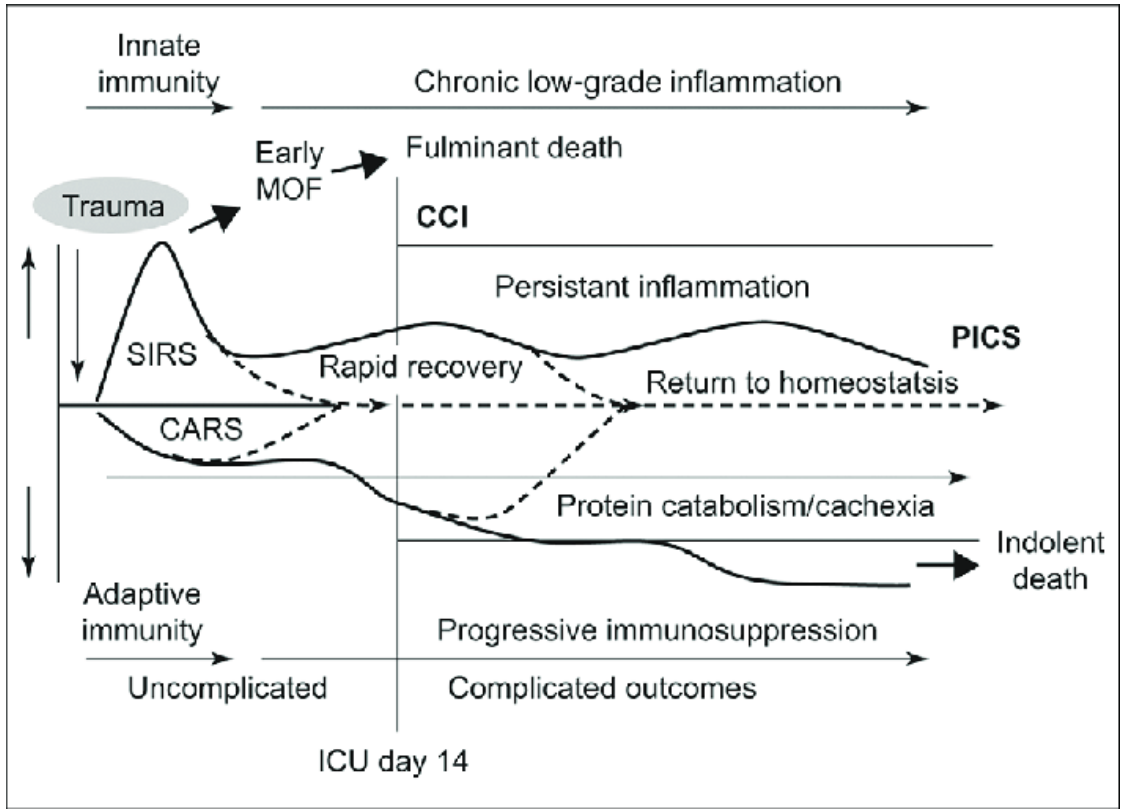
- no clear-cut relation between „size of infection“ and sepsis
  - focal dental infection with sepsis
  - severe cholecystitis without sepsis
- various bacteria and site of infection cause similar sepsis
- usual bacteria sufficient, no „superbacteria“ necessary
- genetic base of tendency to react with sepsis
- etiology
  - **bacterial infection**
  - **candidosis**, aspergillosis, other mycoses usually without sepsis
  - less often viruses or TBC (miliary form, or TBC pneumonia)

Sepsis versus MODS

- sepsis is illness
- MODS = multiple organ dysfunction **syndrom**
- belongs to the picture of sepsis, but not just sepsis
  - polytrauma
  - cardiogenic shock by myocardial infarction
  - …

Immune system in sepsis

- disorder highly complex and multisystemic, no one elegant explanation
- exaggerated imunne response to usual infectious agens??
  - corticosteroids
  - immunosupressive drugs
  - anti-cytokine antibodies (e.g. antiTNF-α)
  - high-volume dialysis eliminating cytokines
  - activated protein C
  - AT-III



Cardiovascular system in sepsis

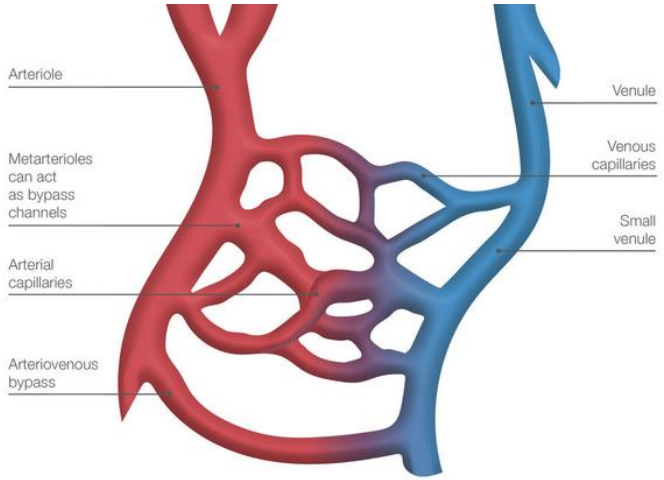
- low peripheral resistance (NO) - vasoplegia
- Leaky endothelium (damaged glycocalyx) – albumin in interstitium, lack of oncotic gradient
  - fluid loss into interstitium – hypovolemia
  - edema, anasarka
  - !!! edemas do not exclude hypovolemia
- change in cardiac output
  - decreased
    - hypovolemia
    - septick cardiomyopathy – both left and right ventricles involved
  - increased
    - hyperdynamic shock – e..g CO above 9 l/min, but increased lactate
      - ➢ problem in microcirkulaci??

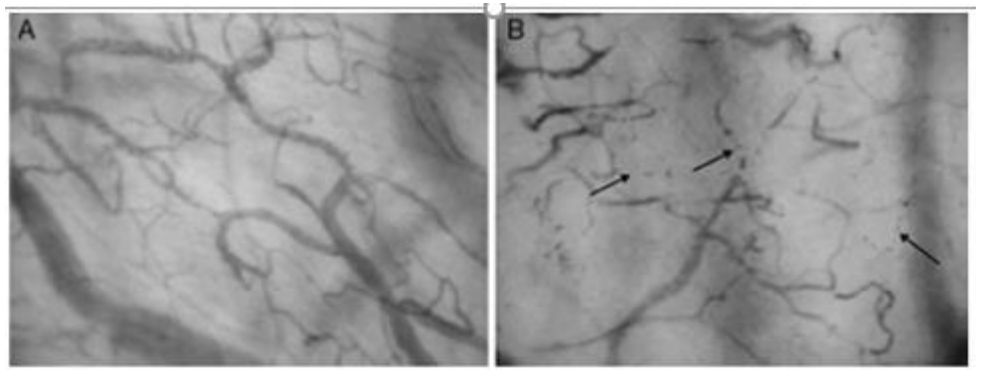
Mikrocirculation in sepsis

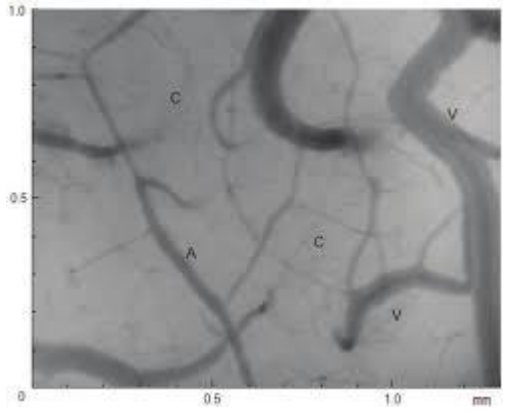
- increased lactate vs. increased cardiac output + high central venous saturation

➢ problem in microcirkulaci

  - microthrombi – activated coagulation, DIC
  - functional shortcuts
  - Interstitial edema with diffusion impairment
  - mitochondrial dysfunction



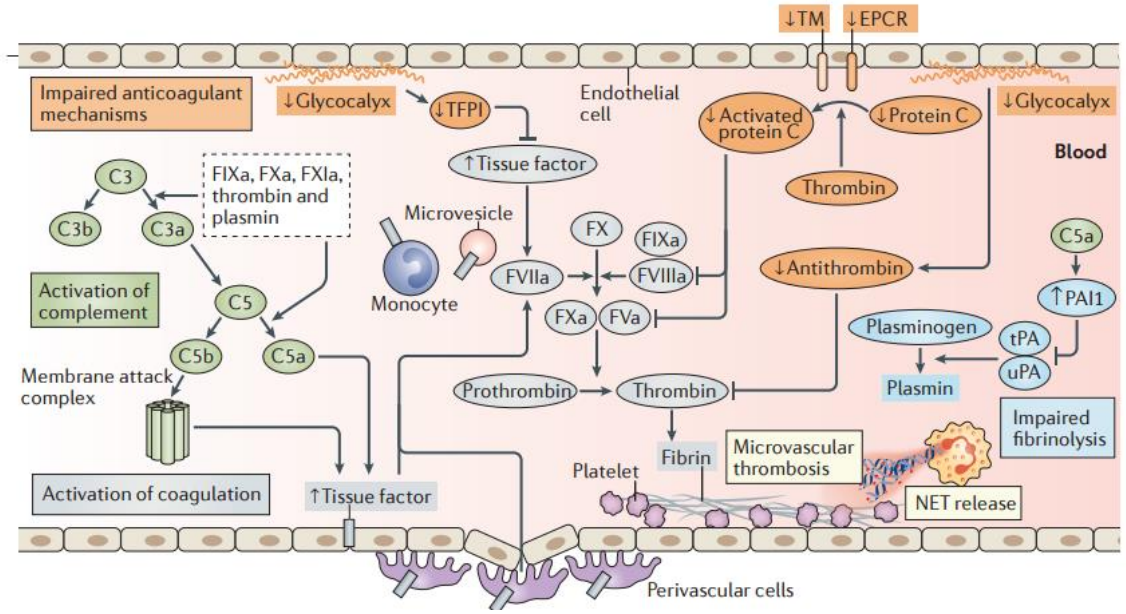


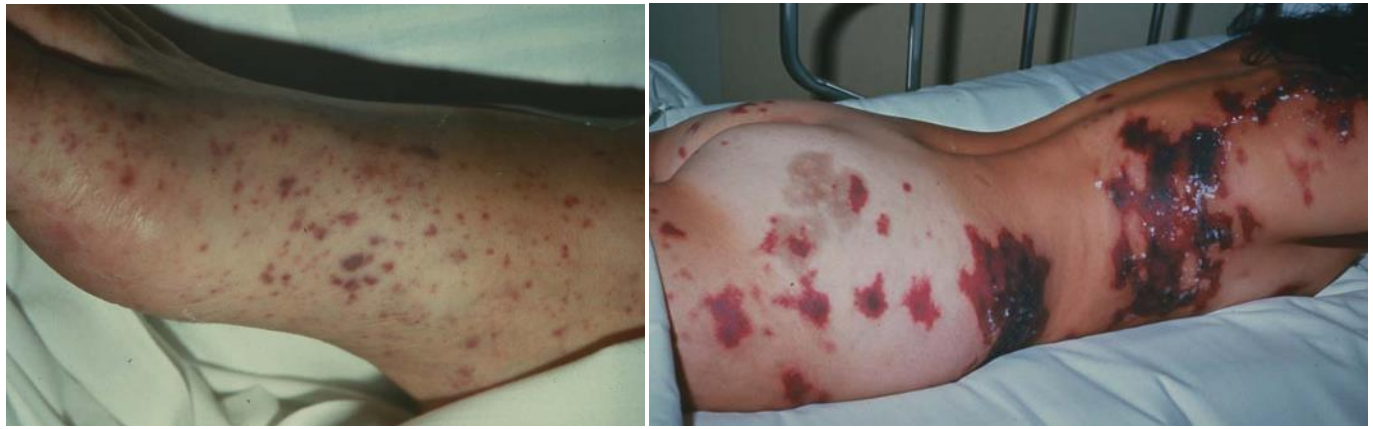


Relationship of oxygen supply-demand in sepsis

Coagulopathy in sepsis

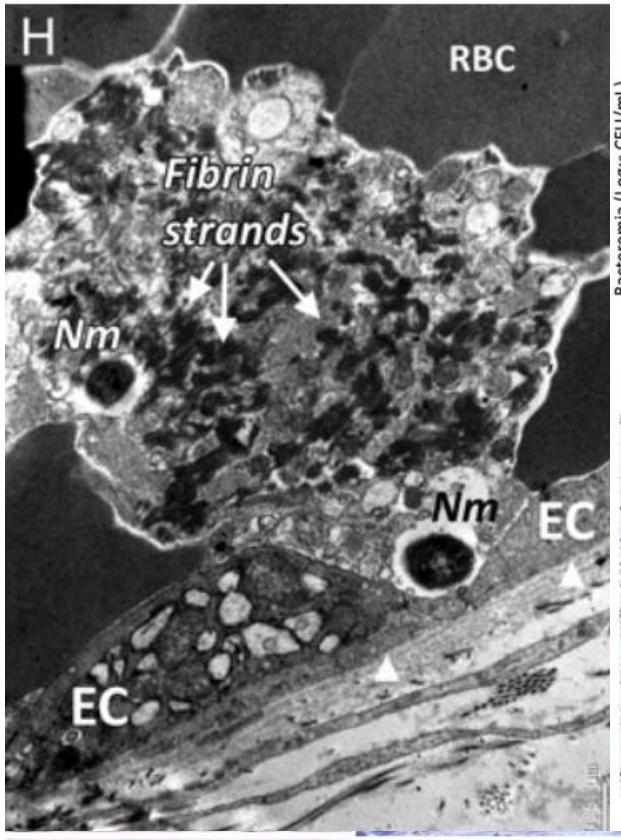
- inflammation end coagulation are interconnected
- low grade DIC
  - more thrombotisation
  - mikrothrombi
  - thrombocytopenia (vs. heparine induced trombocytopenia)
- massive DIC with consumed factors and bleeding is rare
- special is meningococcal sepsis
  - ➢ Purpura fulminans

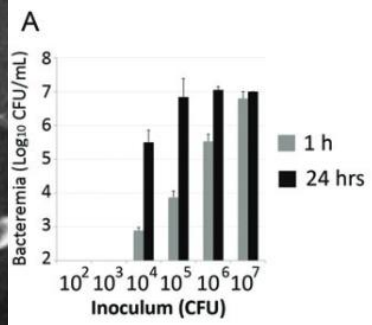


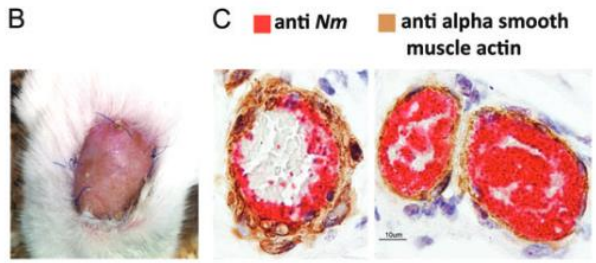


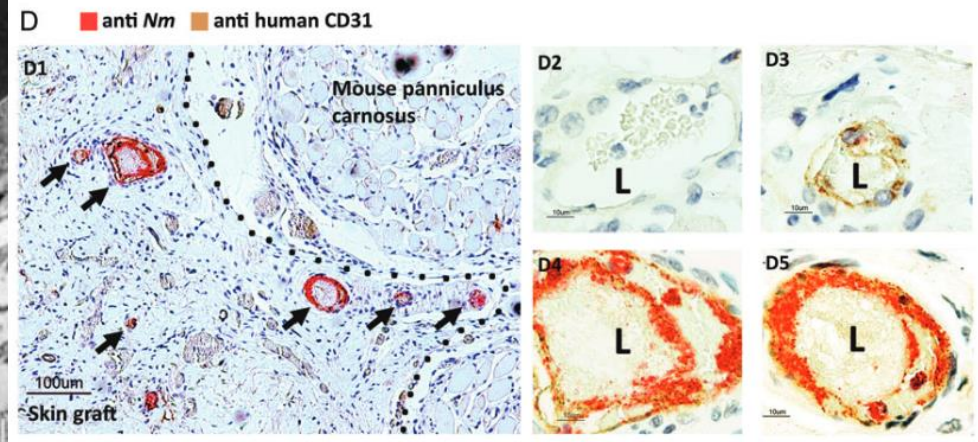
Meningococcal sepsis and purpura fulminans

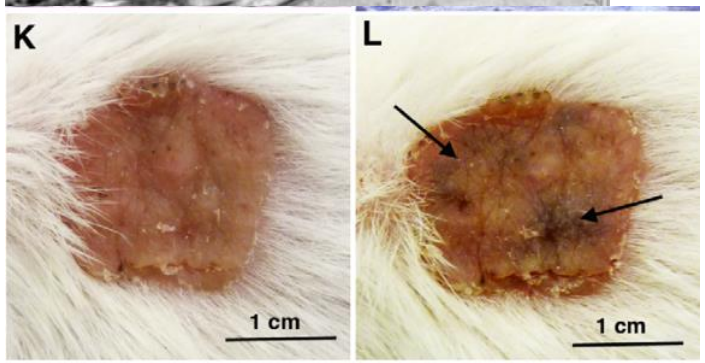
- G- diplococcus
- most often associated with PF
- often even without DIC
- many factors
  - AT-III and protein C deficit
  - meningococcal endotoxin is more prothrombotic than with other bacteria
    - Shwartzman reaction
  - **adhesion of meningococci to human endothelium**

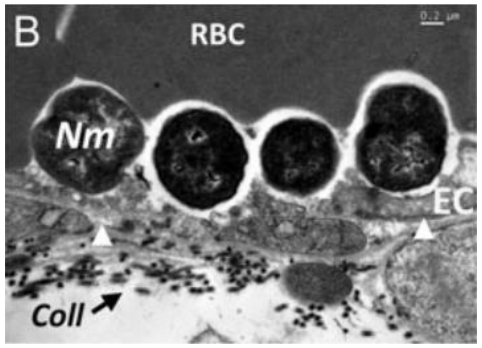












Melican K,(2013) PLoS Pathog 9(1): e1003139

Olivier Join-Lambert, The Journal of Infectious Diseases 2013;208:1590–7

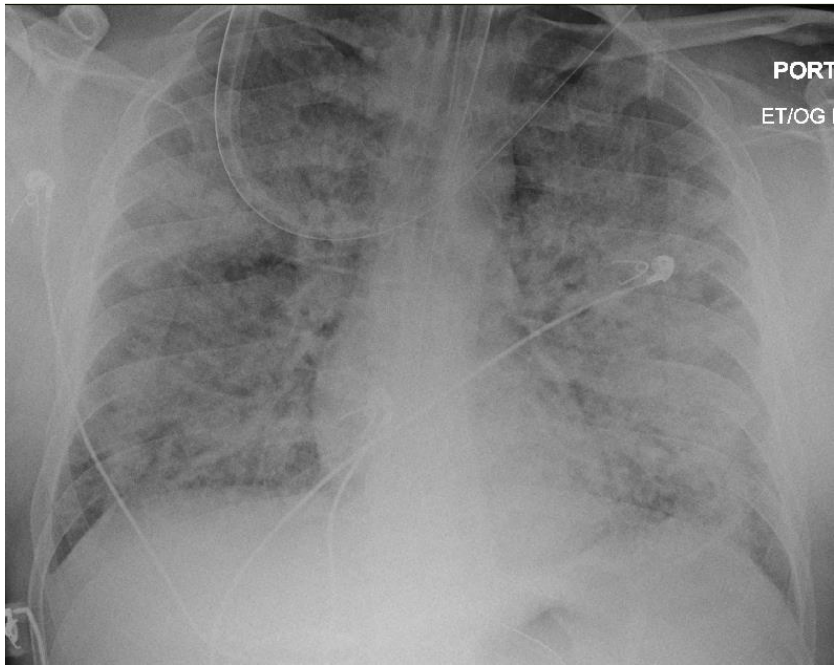
Kidneys in sepsis

- significant mortality **association and causality** of AKI (acute kidney injury)
- oliguria is one of first symptoms
- functional, often full recovery, but slowly
- after improvement/partial reparation often non-oliguric renal failure, recovery of tubular functions is slower
- **Pathogenesis**
  - mechanism is NOT ischaemic tubular necrosis - no necrosis on histology
  - minimal changes identified early post mortem
  - **alteration of microcirculation (glomerulus, peritubular capillaries)**
  - **metabolic „shutdown“ of tubular cells**

- Note: initially often hyperfiltration – high dose of ATB necessary

Respiratory system in sepsis

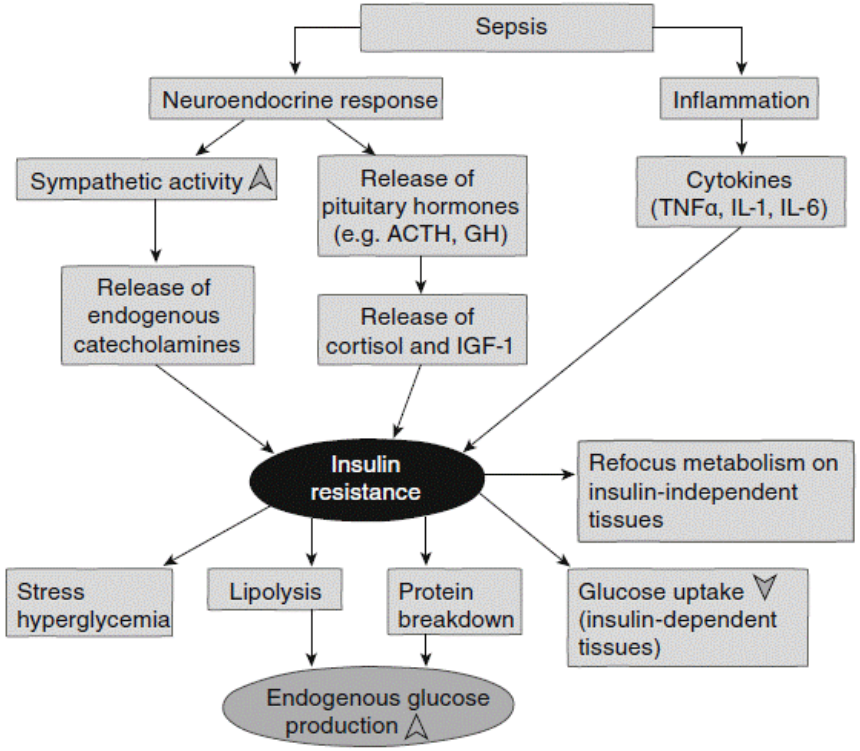
- ARDS
  - non-cardiac pulmonary edema
  - diffuse lung involvement
  - many other causes than sepsis/SIRS (e.g. COVID-19)
  - shock lung after non-pulmonary trauma – so was ARDS discovered
- often combined with primary pneumonia
  - community bacteria – pneumococcus, hemophilus, staphylococcus, E.coli …
- often secondary pneumonia due to the immunodeficiency
  - nosocomial bacteria – PSAE, KLPN, acinetobacter, enterobacter, aspergillus, HSV reactivation
- weakness of respiratory muscles, extubation impossible
  - tracheostomy
  - danger of re-infection



Metabolism in sepsis

- Low T3 syndrome – conversion of T4 to rT3, low T3, normal TSH
- catabolism, severe proteolysis
  - snaha zajistit AA a glukozu pro imunitní systém (cytokiny, adrenalinu, kortikoidy)
  - inzulinorezistence - hyperglykémie
  - Up to 250 g protein/day = 1 kg musles/day
- hypoalbuminemia – positive acute phase protein – high turnover, low level
- high need of cortisol, sometimes substitution necessary fpr relative hypocorticalism (CAVE: chronic hypocorticalism or longterm use of corticosteroids)

- Muscles
  - ICU acquired weakness
  - sarcopenia (atrophy, proteolysis)
  - Critical illness polyneuromyopathy (CIP, CIM)

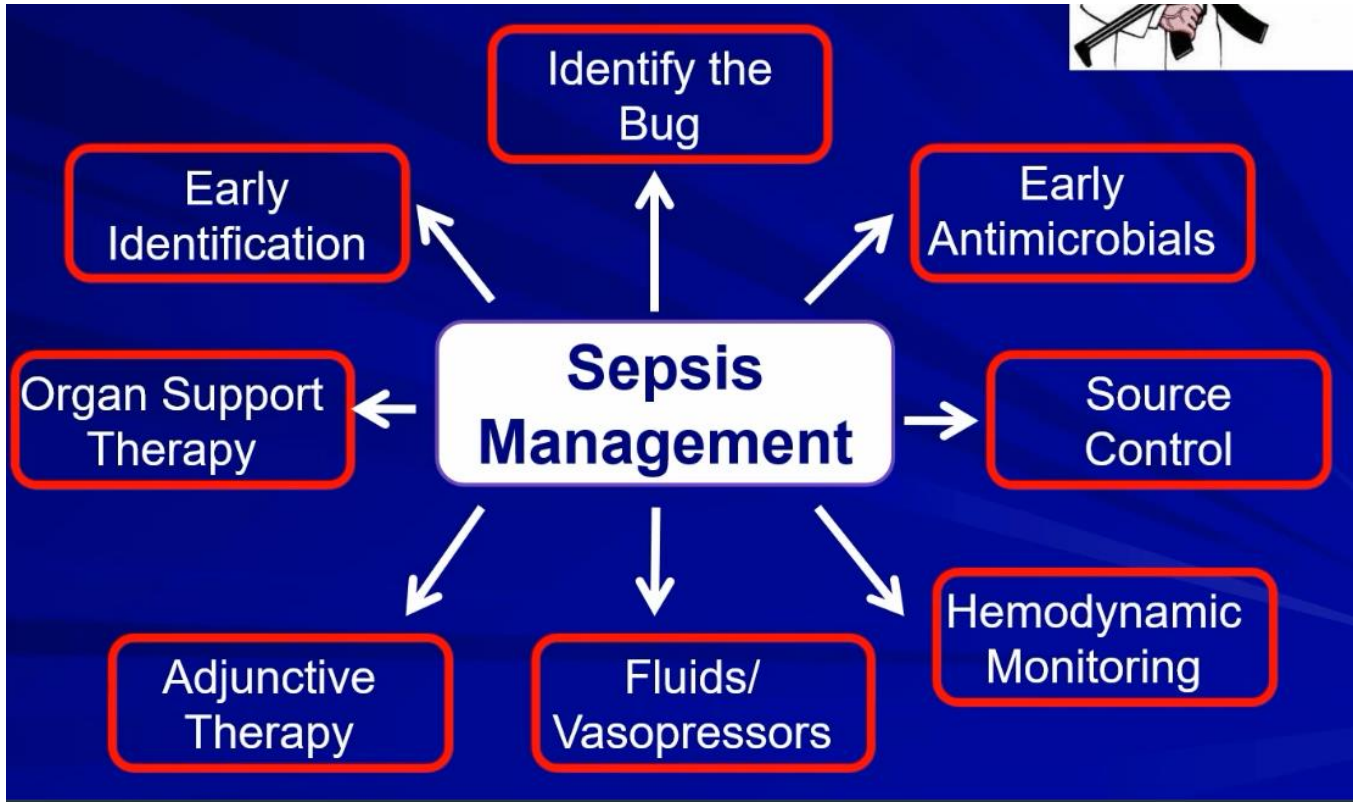


Other systems in sepsis

- GIT
  - disordered continuity of microvilli
    - translocation of bacteria - second hit, motor of MODS
    - enteral feeding for nutrition of microvilli („trophical nutrition“)
  - selective decontamination did not bring any significant effect
  - liver – cholestasis, higher transaminase, usually unimportant
- Brain
  - septic encefalopathy
    - delirium up to coma – more expressed at older patients
    - sometimes admitted as neurological disorder (apoplex?, but normal brain CT)

Principles of sepsis treatment

- source elimination – ATB, surgery, as fast as possible
- blood culture, microbiology – targeted ATB
- circulatory optimization
  - fluids, NA, vasopressin, corticosteroids
- symptomatic treatment of other problems
  - cardiac dysfunction – dobutamine, levosimendan
  - MV
  - dialysis
  - enteral/parenteral nutrition
  - RHB
  - correction of metabolic abnormalities
  - treatment of DIC – heparine, fibrinogen substitution, AT3 substitution, thrombocytes



Sepsis-like disorders – SIRS, SIRS shock

- non-infectious antigens start the same immune response (SIRS) as by sepsis
  - tissue damage results in release of DAMPs (HMGB1, protein S100, ATP, DNA, RNA)
  - both PAMPs and DAMPs bind to the same receptors of immune cells callled PRR (pattern recognition receptors, e.g. Toll-like receptors)
- cause is different, but systemic response incl. MODS is the same
- similar clinical signs, can be difficult to distinguish

Sepsis-like disorders

- acute pancreatitis
- status after CPR
- major trauma
- severe burns
- large operations
- massive transfusion (TRALI)
- ischemic-reperfusion damage
- anaphylaxis?

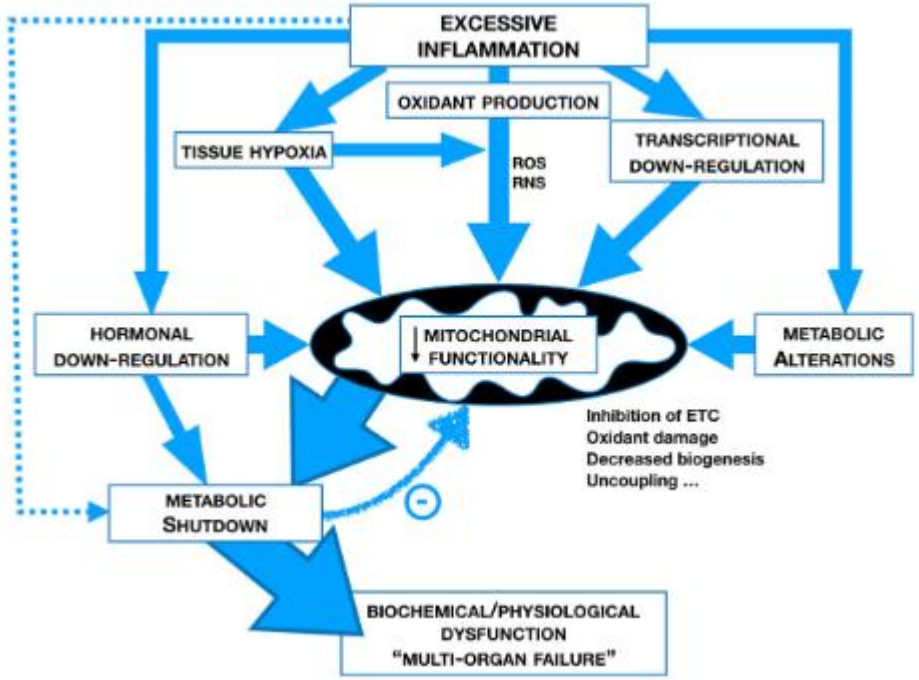
- all other shocks – SIRS is secondary
  - massive bleeding
  - cardiogenic shock
  - massive pulmonary embolism
  - …
- instestinal ischemia
- Endotoxin shock
  - worsening after ATB initiation
  - Jarisch-Herxheimer reaction (syphylis treatment)

MODS as adaptation?

- MODS, but
  - bez dramatic pathology on section, early post-mortem histology almost normal
  - usually full recovery of function
  - usually adequate oxygen supply

➢ adaptation, metabolic shutdown, similar to hibernation

  - hibernating myocardium known from cardiology
  - but hibernation proved also in septic cardiomyopathy (expressior of similar genes as in hibernatng animals)
  - low T3 syndrome
  - decrease in number of mitochondria



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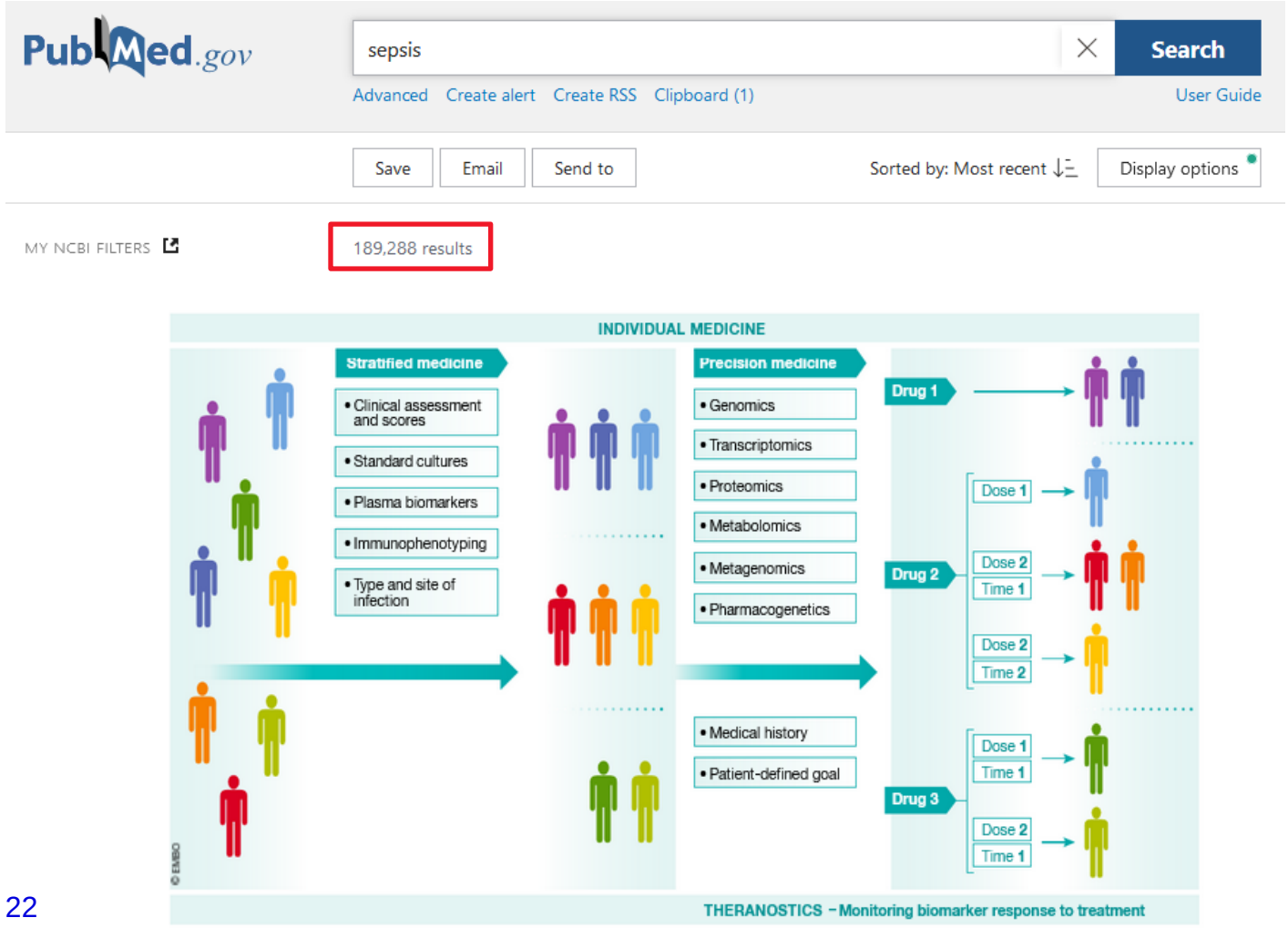
Problems of sepsis research



Sepsis therapies: learning from 30 years of failure of translational research to propose new leads

Jean-Marc Cavaillon[1,*], Mervyn Singer[2] & Tomasz Skirecki[3]

February 2020 | Accepted 17 February 2020 | Published online 16 March 2020
EMBO Mol Med (2020) 12: e10128

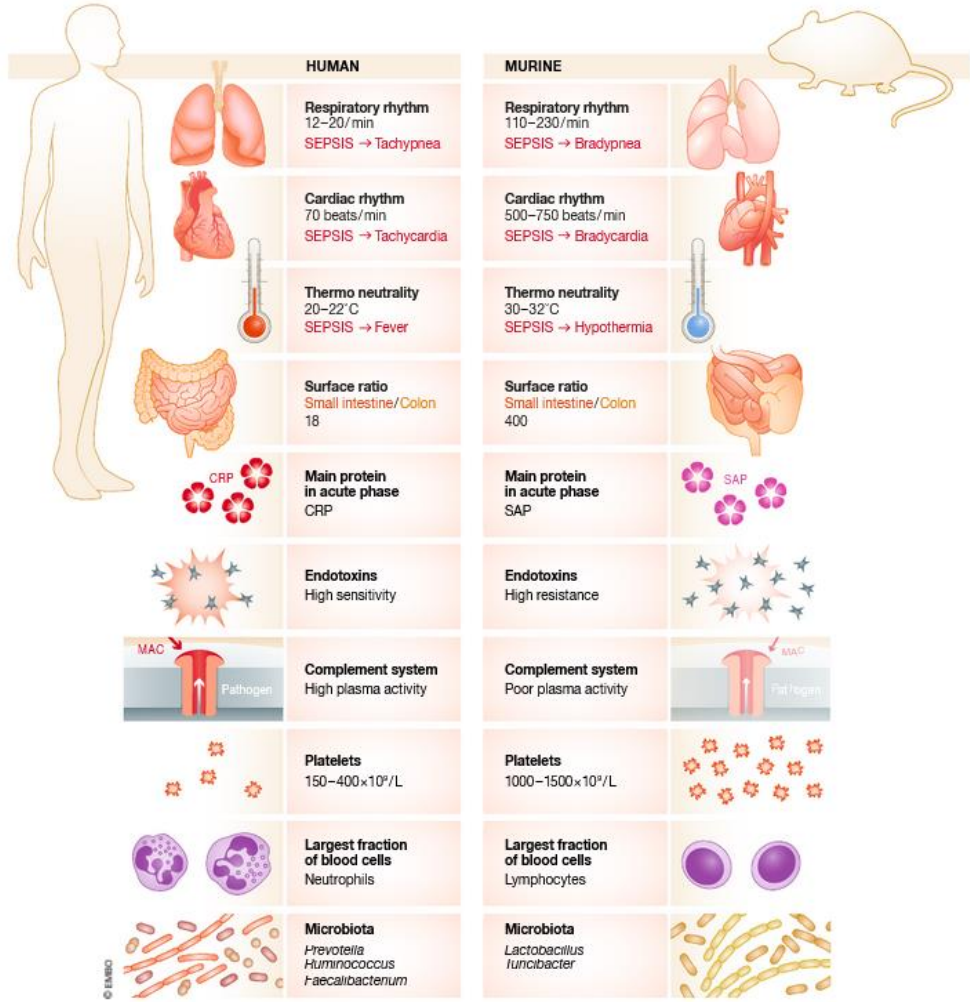


Figure 5. Some keys differences in murine and human physiology that affect the response to sepsis (CRP—C-reactive protein, MAC—membrane attack complex, SAP—serum amyloid protein).

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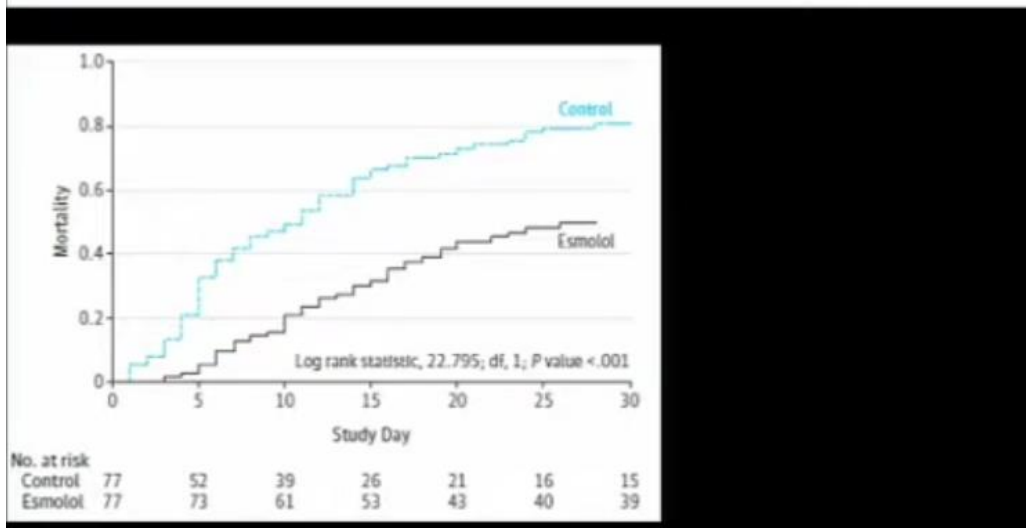
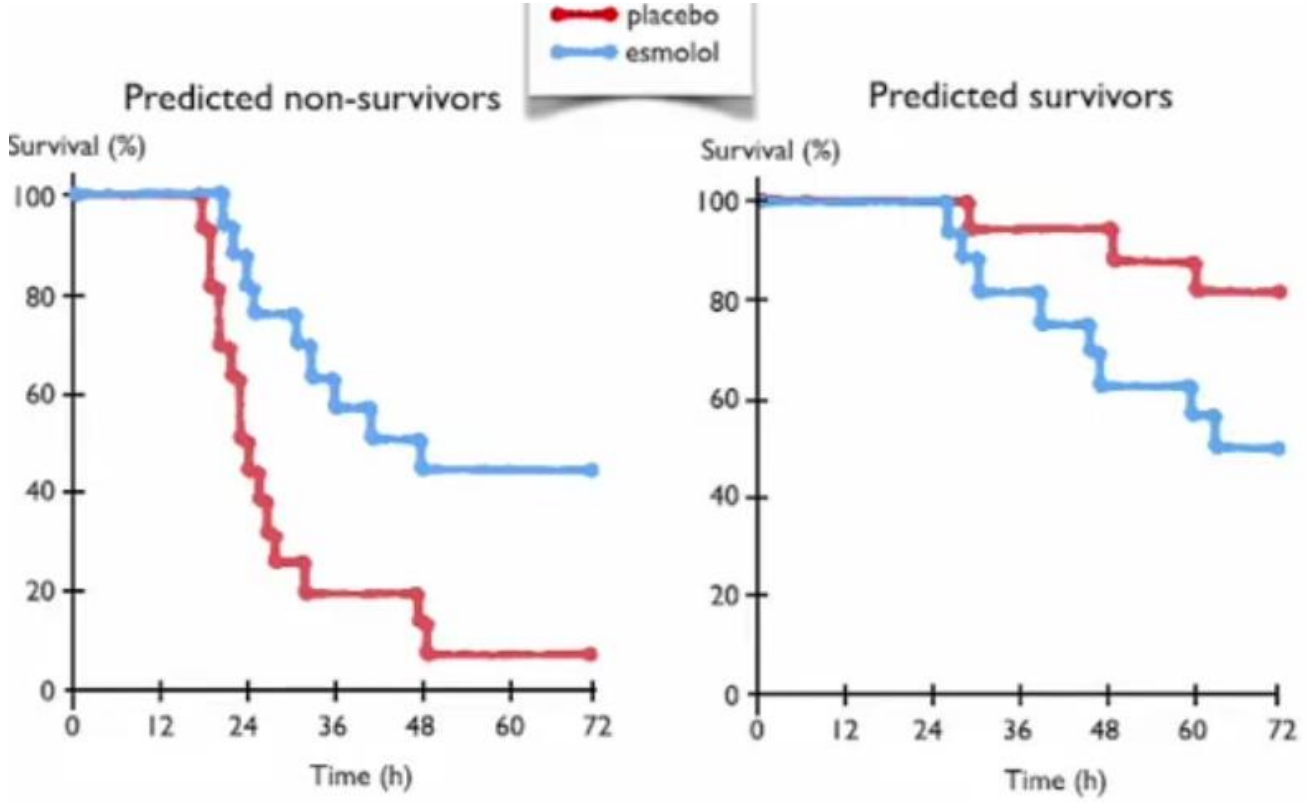
Individualisation

Effect of Heart Rate Control With Esmolol on Hemodynamic and Clinical Outcomes in Patients With Septic Shock

A Randomized Clinical Trial

Andrea Morelli, MD; Christian Ertmer, MD; Martin Westphal, MD; Sebastian Rehberg, MD; Tim Kampmeier, MD; Sandra Ligges, PhD; Alessandra Orecchioni, MD; Annalia D'Egidio, MD; Fiorella D'Ippoliti, MD; Cristina Raffone, MD; Mario Venditti, MD; Fabio Guarracino, MD; Massimo Girardis, MD; Luigi Tritapepe, MD; Paolo Pietropaoli, MD; Alexander Mebazaa, MD; Mervyn Singer, MD, FRCP





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Summary

- life threatening new organ dysfunction due to infection
- „local inflammation everywhere“
- multiple organ dysfunction
  - circulatory failure
  - acute kidney injury
  - ARDS
  - DIC
  - GIT – motor of sepsis
  - metabolism – catabolism and CIPNM
- meningococci – pronounced ability to activate thrombosis
- very similar to other systemic conditions - SIRS