Liver Impairment in Septic Shock

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Septic Shock and Liver Dysfunction

• Mortality in septic shock is around 30-50%
• Complex interaction of immune system, coagulation, apoptosis
• Microcirculatory collapse is central
• Liver dysfunction at baseline or developing within first 7 days does influence prognosis (PROWESS trial, NEJM+CCM 2003)

• Prevalence of Liver dysfunction 1.3% (Angus et al CCM 2004) to 20% (Bakker et al. 2004)

• Definition – Liver dysfunction in severe sepsis/shock
  • Bilirubin: disputed, most use single cut off (21 μmol/L or 34 μmol/L, or 70 μmol/L.)
  • Indocyanine Green (organic anion, eliminated by liver) clearance rate ($PDR_{ICG}$) - but – not associated to histological damage and no change at acute liver damage !!!
“….nevertheless, the incidence of liver dysfunction [in severe sepsis] remains imprecise, probably because current diagnostic tools are lacking, notably those that can detect the early liver insult.”

“…neither static nor dynamic tests can be considered a GOLD standard.”

“…despite this important clinical issue, recent trials on severe sepsis neglected to report specific data about liver function.”

Conclusion (Jensen 2015): We have a problem of diagnostic, prognostic and therapeutic dimensions - very few answers
Septic shock pathogenesis – immune dysregulation

**Endotoxin/Exotoxin**
- NF-κB activation
- TNFα, IL-1β, INFγ, IL-6, IL-8, IL-12, IL-18

**iNOS-activation**
- NO-release

**F-VII → F-VIIa**
- Tissue Factor

**F-X → F-Xa**
- Coagulation cascade
- Pro-Thrombin → Thrombin

**Microcirculation breakdown**
- Vascular stiffness
- RBC stiffness
- Organ Dysfunction

**Fibrin Thrombus**
- Mitochondrial dysfunction
- Apoptosis

**Chemotaxis, opsonization**
- TNFα, IL-1β, INFγ, IL-6, IL-8, IL-12, IL-18
Liver dysfunction in Septic shock – core pathophysiological steps

- Major role in endotoxin and bacterial clearance
  - In dysfunction: probably increased endotoxinaemia
- Synthesis of general blood proteins
  - In dysfunction: hypoalbuminaemia, oedemas, reduced scavenging function
- Synthesis of acute phase proteins (CRP, IL-6, PCT etc)
  - In dysfunction: Immune dysregulation – not just I-paresis
- Glucose metabolic homeostasis maintenance
  - In dysfunction: hyper-glycaemia – significance obscure /probably negative
- Coagulation regulation
  - In dysfunction: Protein C down regulation → hyper-coagulation → hypo-coagulation
- Cytochrome p450 – endo+xenobiotic elimination
  - In dysfunction: Reduced elimination of toxic compounds
Septic shock pathogenesis – immune dysregulation

"Organ crosstalk"?

Or: "Immune homeostasis" involving: Liver, bone-marrow, lymph nodes/spleen, blood cells, CNS, gut, endothelial cells etc

In septic shock: "Organ mis-understanding" when one or more of the components involved in "Immune homeostasis" is hit?
Acute Liver Damage (ALIDA) study – based on The Procalcitonin And Survival Study cohort
- Hyaluronic Acid measurements

- 1200 intensive care patients: RCT 2006-2010 - GCP
- >80% infected, predominantly bacterial and fungal
- 37% severe sepsis/septic shock
- 30-day survival 69%
- 67 years median age
- Plasma and serum frozen (-70°C) from every day – 9915 sample-days
- Hyaluronic acid (HA) measured for all days – 1125 patients with enough material
- HA produced in many tissues – primary elimination: liver
- HA established as a potent independent prognostic marker in chronic liver disease (Peters et al 2011, 2013, 2014)
Survival – liver failure defined as HA-quartiles – PASS

Hyaluronic Acid - day 1 in trial

Hyaluronic Acid - day 2 in trial

P<0.0001, log rank

Days after inclusion in PASS
## Cox regression - multivariable

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<th>Variable</th>
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Thank you for listening!
And thanks to
Jens D. Lundgren – inspiration and scientific input

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