LIVER SUPPORT IN SEPSIS

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SEPESIS

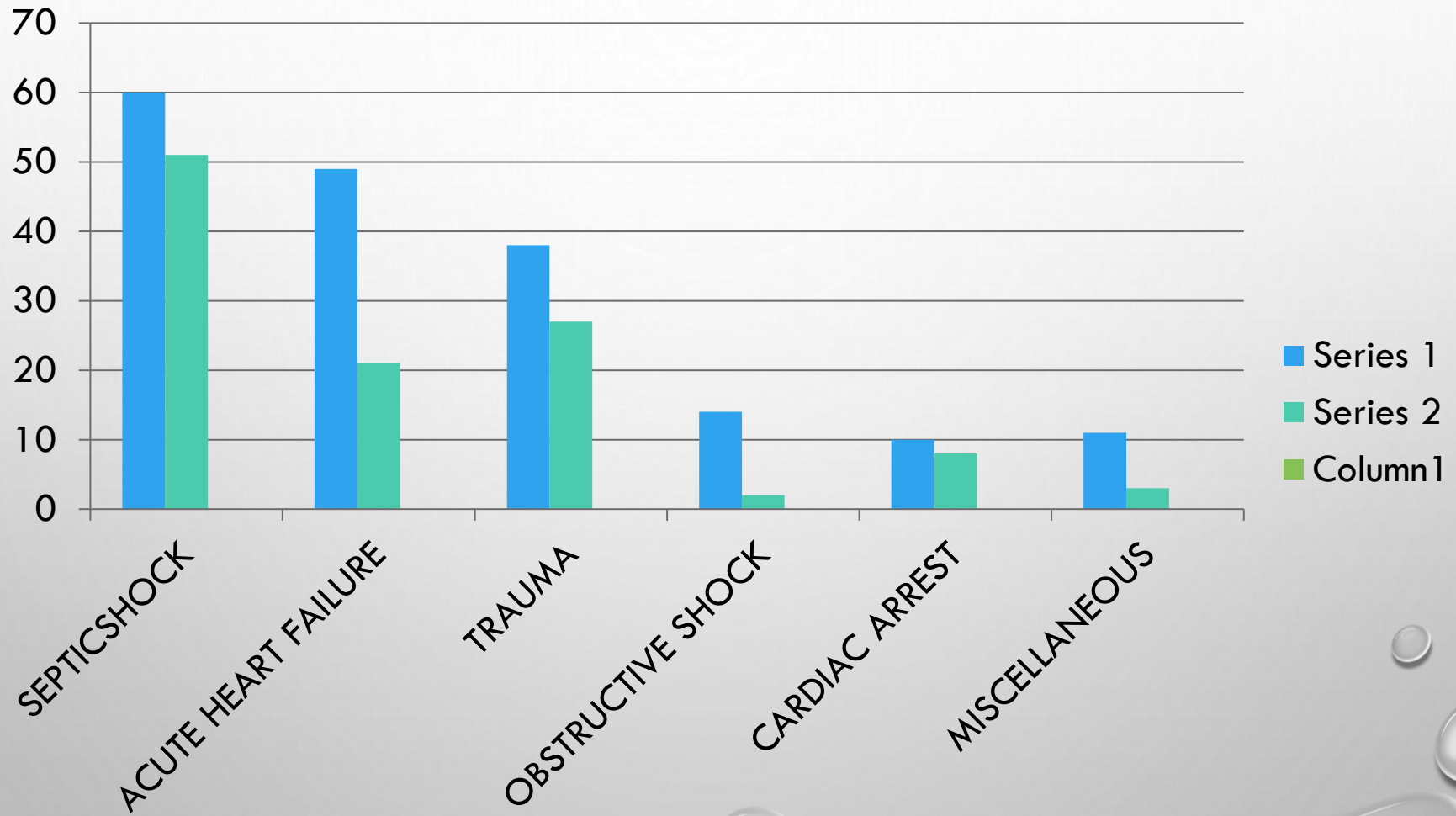
- Sepsis is a complex medical condition starting from an infectious stimulus and resulting in an exaggerated immune response.

- Is the inflammatory response that was initiated to fight the infection ultimately leads to damage in various organs throughout the body and the syndrome known as multiple organ failure.

- Millions of patients worldwide die from sepsis every year, 37.000 people die in the UK.

- Sever sepsis and septic shock remain a thorny issue in ICU as their mortality rate between 30% and 50% (Blanco,2008)

NUMBER OF PATIENTS WITH H.H (BLUE) AND NUMBER OF NONSURVIVORS(GREEN). (RAURICH ET AL,2011,ANAESTHESIA)



THE SURVIVING SEPSIS CAMPAIGN (SSC)

- An initiative of the ***European Society of Intensive Care Medicine***, the *International Sepsis Forum*, and the **Society of Critical Care Medicine** (SCCM), was launched with the goal to reduce mortality by 25% through publicity of evidence-based treatments.
- Originally published in 2004,[4] the SSC guidelines were recently revised because of the continuing evolution of sepsis knowledge

- Making the diagnosis of sepsis is critically important for both timely and appropriate therapy. The earliest therapies to be instituted in sepsis focused on eradication of the infectious focus and fluid resuscitation.

Early initiation of appropriate antibiotics is associated with higher survival rate.

Kumar et al. 2006,suggested that each hour of delay decreased SURVIVAL by7.6%.

- To achieve early and appropriate therapy, sepsis must be diagnosed empirically, before culture results are known, and thus the diagnosis must be based on suspicion of the source and type of infection.
- Cultures should be taken from every suspected source, and diagnostic studies (ie, x-rays, CT scan, lumbar puncture) should be performed to identify the source and causative organism.

SITES OF INFECTION AND TYPES OF MICROORGANISMS

The most common infection is patients with liver cirrhosis are:

- Spontaneous bacterial peritonitis (SBP), followed by
- Urinary tract infection
- Pneumonia
- Bacteraemia following a therapeutic procedure
- Cellulitis
- Spontaneous bacteraemia

THE LIVER IN SEPSIS

- SEPTIC LIVER DYSFUNCTION
- HYPOXIC HEPATITIS
- MANAGEMENT OF SEPSIS GENERALLY, AND IN PATIENTS WITH LIVER IMPAIRMENT.

- The liver has a role in endotoxin and bacteria scavenging, detoxification, synthesizing proteins for metabolic, immune and coagulation functions.

- Several cells are involved in these processes: hepatocytes (HCs), **Küpffer cells** (KCs), and sinusoidal endothelial cells (SECs).

- Liver perfusion represents 25% of the cardiac output mainly by portal venous blood flow.

- Hepatic arterial buffer response to compensate for reduction in portal flow(Lautt 1985)

Küpffer cells

- Key cells involved in scavenging bacteria and endotoxins.
- Produce pro-inflammatory mediators (TNF-α)
- Systemic inflammatory response syndrome (SIRS)
- The enhancement of hepatic acute-phase proteins
- Production of nitric oxide (NO) (Fong,1990)
- KCs interact with blood cell components (platelets, erythrocytes, and Leukocytes), promoting neutrophil recruitment in the sinusoids and enhancing the pro-inflammatory response (Dhainaut, 2001)

HEPATOCYTES

- Shift their metabolic pathway toward upregulation of the inflammatory response
- Increase in the synthesis of acute-phase proteins mediated predominantly by interleukin 6 (IL-6)
- Increases in C-re active protein, α-1-antitrypsin, fibrinogen, prothrombin, and haptoglobin levels,
- Decrease in production of albumin, transferring, and antithrombin
- Inhibits the protein C pathway

HEPATOCYTES

- Liver hypermetabolism, such as increased amino-acid uptake
- Glucose metabolism is significantly altered
- Decrease in biotransformation liver function, especially a reduction in cytochrome P450 activity.
- Decrease in Hepcidin levels
- Up regulate Endothelin-1

EFFECTS OF CYTOKINES DURING LIVER SEPSIS

Cytokines	Effects of cytokines	
TNF-α	Pro-inflammatory response and stimulation of IL-6 production by HCs	
IL-6	Pro-inflammatory response, stimulation of acute-phase proteins, and activation and release of TGF-β	
IL-1β	Pro-inflammatory response and synergistic action with TNF-α	
TGF-β	Anti-inflammatory response and counteracting of the extension of inflammatory response	
IL-18	LPS-induced liver toxicity and secretion of IFN-γ	
IFN-γ	HC apoptosis, elevation of TNF-α, and upregulation of CD14	
IL-10	Anti-inflammatory response and downregulation of LPS-induced IL-6 release	

HC, hepatocyte; IFN-γ, interferon-gamma; IL, interleukin; LPS, lipopolysaccharide; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha. Nesseler et al. Critical Care 2012

SEPTIC LIVER DYSFUNCTION

- The precise incidence of sepsis liver dysfunction remains difficult to establish because of the lack of a precise and consensus definition and the various observation times.

SEPTIC LIVER DYSFUNCTION

- Sands and colleagues (1997) Liver failure was present in 12% within 28 days of the onset of disease .
- Angus and colleagues(2001) observed hepatic failure in only 1.3%.
- Bakker and colleagues (2004) Liver failure was reported in 20%
- French EPISEPSIS (EPIdemiology of SEPSIS) study group reported incidences of liver dysfunction (hepatic score of greater than 0) and liver failure (hepatic score of 3 or 4) of 46.6% and 6.3%, respectively

SEPTIC LIVER DYSFUNCTION

- Microcirculatory changes in the liver sinusoids, neutrophil sequestration, and platelet activation and adhesion are main contributors to known hepatic dysfunction parameters

- Cholestasis, steatosis, hepatocellularinjury, impaired cellular regeneration and impaired hepatic mitochondrial respiration are factors implicated in the clinical septic hepatic dysfunction.

- Clinical **jaundice** is usually associated with severe infections such as pneumonia, Gram-negative bacterial sepsis, or septic shock

SEPTIC LIVER DYSFUNCTION

- Liver histological studies in patients with bacteraemia jaundiced showed a predominant ant intrahepatic cholestasis (Moseley 2004)

- Bile and bile acids transport and excretion into the canalicular duct are highly dependent on energy and Oxygen.

- Bile and bile acids are involved mainly gut barrier integrity (Assimakopouls 2007)

- The reduction of bile flow or the absence of intraluminal bile can lead to intestinal mucosal atrophy and then deprives the gut of its bacteriostatic neutralizing effects and promotes an increase of endotoxin blood levels This endotoxin release participates in direct bile flow reduction and thus might enter the liver in a vicious circle promoting MODS.

HYPOXIC HEPATITIS (ISCHEMIC LIVER)

DEFINITION

- A clinical setting of circulatory shock or arterial hypoxemia.
- Early rapid but reversible rise in serum aminotransferase level (more than 20-fold the upper limit)
- Exclusion of other potential causes of increased aminotransferases (Fuhrmann 2009)

HYPOXIC HEPATITIS ; SHOCK LIVER; ISCHEMIC LIVER

- Due to Centrilobular nercrosis
- Triad of biochemical abnormalities involves profound fall in Prothrombin time and altered renal function
- Incidence : 1% to 12% of ICU population
- Mortality : 61.5% but up to 83.3% in septic shock and 77.7% in cardiac shock
- Prolonged INR ,Septic Shock need for Renal replacement therapy and duration of hypoxic hepatitis are predictors of high mortality

HYPOXIC HEPATITIS ; SHOCK LIVER; ISCHEMIC LIVER

- Septic shock ; splanchnic blood flow and cardiac output are increased but not sufficient to counterbalance the high demands for oxygen and the inability of liver cells to extract oxygen .
- Moreover, vascular mechanisms of defence against portal blood flow reduction are altered, especially the hepatic arterial
- cardiogenic shock, HH is secondary to decreased cardiac output and oxygen delivery.
- Glucose monitoring is of central interest in critically Ill patients, spontaneous hypoglycaemia in 14% of all patients with HH

THERAPEUTIC CONSIDERATIONS IN SEPTIC LIVER DYSFUNCTION

- Goal-directed therapy
- Early antibiotic therapy and infection source control
- Fluid resuscitation, and Vasopressor support to restore perfusion in the liver and other organs as well as
- Support for the associated organ failure)
- Corticosteroid induces hepatobiliary transporters and restoration of bile transport

EARLY GOAL-DIRECTED THERAPY, FLUID RESUSCITATION AND MANAGEMENT

- INTRAVENOUS FLUIDS ,INTRAVENOUS FLUIDS , INTRAVENOUS FLUIDS ,INTRAVENOUS FLUIDS , INTRAVENOUS FLUIDS , INTRAVENOUS FLUIDS , INTRAVENOUS FLUIDS , INTRAVENOUS FLUIDS , INTRAVENOUS FLUIDS , INTRAVENOUS FLUIDS

AND INTRAVENOUS FLUID

NEW FLUID RESUSCITATION RECOMMENDATIONS

- **Crystalloids** like normal saline as the **initial fluid resuscitation** for people with severe sepsis.
- further advise that the initial fluid challenge should be 1L or more of crystalloid, and a minimum of 30 mL/kg of crystalloid (2.1 L in a 70 kg) in the first 4-6 hours.

- **Incremental fluid boluses** should be continued as long as patients continue to improve hemodynamically (in blood pressure, delta pulse pressure, or both) .
- They weakly recommended adding **albumin** to initial fluid resuscitation with crystalloid for severe sepsis and septic shock.
- Do **not use hetastarches/hydroxyethyl starches**.
- You may use Gelofusine which is a 4% w/v solution of succinylated gelatine

INOTROPIC SUPPORT

- **NOREPINEPHRINE**
- **VASOPRESSIN** 0.03 UNITS / MINUTE
- **DOPAMINE** was only recommended in highly selected patients whose risk for arrhythmias was felt to be very low and who had a low heart rate and/or cardiac output.

DOBUTAMINE is strongly recommended (by itself or in addition to a vasopressor) for patients with cardiac dysfunction as evidenced by high filling pressures and low cardiac output, or clinical signs of hypoperfusion after achievement of restoration of blood pressure with effective volume resuscitation

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CORTICOSTEROID RECOMMENDATIONS

- Authors suggest **not providing** intravenous corticosteroid therapy to patients with septic shock for whom fluid resuscitation and vasopressors can restore an adequate blood pressure. For those with vasopressor-refractory septic shock, they recommend IV hydrocortisone in a continuous infusion totaling 200 mg/24 hrs

ADRENAL INSUFFICIENCY (HEPATO-ADRENAL SYNDROME)

- Adrenal insufficiency has been identified in a significant proportion of septic patients and warrants treatment with hydrocortisone to lower mortality.
- Adrenal insufficiency has been recognized in acute decompensation of chronic liver disease with a prevalence of 51–62%.
- It has been described as the hepato-adrenal syndrome (Marik et al,2005)

VENTILATION

- Ascites, chest wall oedema and pleural effusions may decrease thoracic compliance. Lung compliance is decreased in patients with pulmonary oedema complicating liver failure

- Permissive hypercapnia may exacerbate acidemia it is usually well tolerated. A key exception is the patient with ALF and increased cerebral blood flow for whom hypercapnia may dramatically increase intracranial pressure.

NUTRITION

- Early enteral feeding is a recommended standard of care
- Postpyloric feeding tube placement.
- Early enteral feeding is a recommended standard of care
- Monitoring of glycaemic levels.(hypergylcemia is problematic)
- Formula containing eicosapentaenoic acid and g-linolenic acid showed an absolute mortality reduction of 19.4% in septic patients.(Pontes et al, 2006)
- Branched-chain amino acid-enriched formulae may allow adequate protein supplementation for the patient with refractory hepatic encephalopathy.

RENAL FAILURE

- Due to Acute tubular necrosis / Hepatorenal syndrome
- The renin–angiotensin–aldosterone system is activated and antidiuretic hormone secretion is inappropriately high leading to volume overload and free water excess.
- Paracentesis with reduction of intraabdominal pressure also offers benefit if intravascular volume is maintained
- Isovolemic Hemofiltration (EIHF) is of benefit. It improves recovery in gas exchange, urine production, earlier weaning form mechanical ventilation, decreases ICU length of stay and increases 28-day survival (55 vs. 27.5%)

DIAGNOSTIC AND PROGNOSTIC BIOMARKERS

- Differentiating sepsis from non-infectious triggers of the systemic inflammatory response syndrome (SIRS) is difficult, especially in critically ill patients who may have SIRS for other reasons

- PROCALCITONIN (PCT) has emerged as the most studied and promising sepsis biomarker. For diagnostic and prognostic purposes in critical care, PCT is an advance on C-reactive protein and other traditional markers of sepsis, but is not accurate enough for clinicians to dispense with clinical judgement. There is stronger evidence, however, that measurement of PCT has a role in reducing the antibiotic exposure of critical care patients. For units intending to incorporate PCT assays into routine clinical practice, the cost-effectiveness of this is likely to depend on the pre-implementation length of an average antibiotic course and the subsequent impact of implementation on emerging antibiotic resistance.

- When no infection can be found during empiric antibiotic therapy, consider using a low procalcitonin level as a supportive tool for the decision to stop antibiotics

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