Introduction

Definition

Multiple organ dysfunction syndrome is the presence of altered organ function in acutely ill patients such that homeostasis cannot be maintained without intervention. It usually involves two or more organ systems ***(Heard et al.,2006).***

Etiology

The condition usually results from infection, injury (accident, surgery), hypo perfusion and hypermetabolism. The primary cause triggers an uncontrolled inflammatory response. In operative and non-operative patients sepsis is the most common cause. Sepsis may result in septic shock. In the absence of infection a sepsis-like disorder is termed systemic inflammatory response syndrome (SIRS). Both SIRS and sepsis could ultimately progress to multiple organ dysfunction syndrome. However, in one-third of the patients no primary focus can be found ***(Heard et al.,2006).***

Multiple organ dysfunction syndrome is well established as the final stage of a continuum Systemic inflammatory response syndrome + infection →sepsis →severe sepsis →Multiple organ dysfunction syndrome. Currently, investigators are looking into genetic targets for possible gene therapy to prevent the progression to Multiple organ dysfunction syndrome. ***(Matsuda and Hattori.,2006)***

Some have developed a mouse model sepsis via cecal ligation and puncture (CLP). Male Balb/c mice subjected to CLP were given an IL-10-carrying vector or an empty control vector. Lung, Liver and kidney tissue destruction were measured by assessing myeloperoxidase and malonialdehyde activity. These last two are endogenous oxidizing

compounds produced during tissue inflammation. The authors assessed the level neutrophil infiltration in lung and liver tissue. IL-10 protein expression was measured using immunohistochemistry***(Dhainaut et al.,2003)***..

The expression of Tumor necrosis factor-alpha mRNA was measured at 3, 8, and 24 hours after CLP using reverse transcription polymerase chain reaction. Their results show significantly reduced organ damage by IL-10 gene transfer, as quantified by reduced myeloperoxidase activity in the lung, liver, and kidney. The malonialdehyde level was not affected by the transfer into the liver. The livers of the mice infected with the adenoviral vector showed reduced neutrophil activity.

The lung and kidney samples in mice carrying the gene showed lower expression of Tumor necrosis factor-alpha mRNA. The investigators concluded that increased IL-10 expression significantly reduced sepsis-induced Multiple organ injury***(Matsuda and Hattori.,2006).*** .

Pathophysiology

A definite explanation has not been found. Local and systemic responses are initiated by tissue damage. Respiratory failure is common in the first 72 hours after the original insult. Following this one might see hepatic failure (5–7 days), gastrointestinal bleeding (10–15 days), and renal failure (11–17 days) ***(Heard et al.,2006)***.

Gut hypothesis

The most popular hypothesis by Deitch to explain MODS in critically ill patients is the gut hypothesis ***(Kabay et al.,2007)*** Due to splanchnic hypoperfusion and the subsequent mucosal ischaemia there are structural changes and alterations in cellular function. This results in increased gut permeability, changed immune function of the gut and

increased translocation of bacteria. Hepatic dysfunction leads to toxins escaping into the systemic circulation and activating an immune response. This results in tissue injury and organ dysfunction ***(Heard et al.,2006)***.

Endotoxin macrophage hypothesis

Gram-negative infections in MODS patients are relatively common, hence endotoxins have been advanced as principal mediator in this disorder. It is thought that following the initial event cytokines are produced and released. The pro-inflammatory mediators are: tumor necrosis factor-alpha (TNF-α), interleukin-1, interleukin-6, thromboxane A2, prostacyclin, platelet activating factor, and nitric oxide ***(Heard et al.,2006)***.

Tissue hypoxia-microvascular hypothesis

As a result of macro- and microvascular changes insufficient supply of oxygen occurs. Hypoxemia causes organ dysfunction and cell death ***(Kabay et al.,2007)***.

Integrated hypothesis

Since in most cases no primary cause is found, the condition could be part of a compromised homeostasis involving the previous mechanisms ***(Heard et al.,2006)*.**

Diagnosis

The European Society of Intensive Care organized a consensus meeting in 1994 to create the "Sepsis-Related Organ Failure Assessment (SOFA)" score to describe and quantitate the degree of organ dysfunction in six organ systems. Using similar physiologic variables the Multiple Organ Dysfunction Score was developed ***(Heard et al.,2006)*** .

Four clinical phases have been suggested:

- **Stage 1** the patient has increased volume requirements and mild respiratory alkalosis which is accompanied by oliguria, hyperglycemia and increased insulin requirements.
- **Stage 2** the patient is tachypneic, hypocapnic and hypoxemic. Moderate liver dysfunction and possible hematologic abnormalities.
- **Stage 3** the patient develops shock with azotemia and acid-base disturbances. Significant coagulation abnormalities.
- **Stage 4** the patient is vasopressor dependent and oliguric or anuric. Ischemic colitis and lactic acidosis.

Management

At present there is no agent that can reverse the established organ failure. Therapy therefore is limited to supportive care, i.e. safeguarding hemodynamics, and respiration. Maintaining adequate tissue oxygenation is a principal target. Starting enteral nutrition within 36 hours of admission to an Intensive care unit has reduced infectious complications ***(Heard et al.,2006)***.

Human recombinant activated protein C(activated drotrecogin alfa) can reduce 28-day mortality among patients with multiple organ dysfunction syndrome according to a randomized controlled trial ***(Dhainaut et al.,2003).*** The relative risk reduction was 21.8%. For patients at similar risk to those in this study (33.9% had 28-day mortality), this leads to an absolute risk reduction of 7.4%. 13.5 patients must be treated for one to benefit.

Prognosis

Mortality varies from 30% to 100% where the chance of survival is diminished as the number of organs involved increases. Since the 1980s the mortality rate has not changed ***(Heard et al.,2006)***.