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HEPATIC RESPONSE To POSTOPERATIVE SEPSIS

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Hepatic Response to Postoperative Sepsis

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List of Abbreviations

ALF: Acute Liver Failure

ALI: Acute Lung Injury

AoCLF: Acute on Chronic Liver Failure

APACHE: Acute Physiology and Chronic Health Evaluation

APC: Activated Protein C

ARDS: Acute Respiratory Distress Syndrome

ARF: Acute Renal Failure

ASA: American Society of Anesthesiologists

BAL: Bio-Artificial Liver

BBB: Blood Brain Barrier

BiPAP: Bi-Level Positive Airway Pressure

CAD: Coronary Artery Disease

CO: Cardiac Output

CPAP: Continuous Positive Airway Pressure

CRP: C-Reactive Protein

CVP: Central Venous Pressure

CXC: Cytotoxic

DIC: Disseminated Intravascular Coagulation

DO_2: O_2 Delivery

EIHF: Early Isovolemic Hemofiltration

ELAD: Extra-Corporeal Liver Assist Device

FF: Filtration Fraction

GFR: Glomerular Filtration Rate

ICAM: Inter Cellular Adhesion Molecule

ICU: Intensive Care Units

IL: Interleukin

IL: Interleukin

IL-1ra: IL-1 Receptor Antagonist

iNOS: Inducible Nitric Oxide Synthase

LOD: Logistic Organ Dysfunction

LPS: Lipo Poly Saccharide

MAP: Mean Arterial Pressure

MARS: Molecular Absorbent Re circulating System

MIF: Macrophage Migration Inhibitory Factor

MODS: Multiple Organ Dysfunction

MRI: Magnetic Resonance Imaging

NMBAs: Neuromuscular Blocking Agents

NO: Nitric Oxide

NOS: Nitric Oxide Synthase

PBW: Predicted Body Weight

PCT: Procalcitonin

RAAS: Renin-Angiotensin Aldosterone System

RBF: Renal Blood Flow

RCT: Randomized Controlled Trial

ROS: Reactive Oxygen Species

RRT: Renal Replacement Therapy

$ScvO_2$: Central Venous Oxygen Saturation Measured In Superior Vena

SIRS: Systemic Inflammatory Response Syndrome

SOFA: Sequential Organ Failure Assessment

SPAD: Single-Pass Albumin Dialysis

STREM: Soluble Triggering Receptor Expressed On Myeloid Cells

SVR: Systemic Vascular Resistance

TLR: Toll-Like Receptors

TLR4: Toll-Like Receptor 4

TNF: Tumor Necrosis Factor

TNF: Tumor Necrosis Factor

VAP: Ventilator-Associated Pneumonia

VO_2: O_2 Consumption

Abstract

Sepsis, a host response to infection, is a complex physiological disease characterized by the release of many pro-inflammatory, anti-inflammatory, anticoagulants and anti-clotting response to pathogens. One can identify three stages, namely sepsis and acute poisoning (when acute organic failure is due to sepsis), and septic shock (low blood pressure requiring increased vascular tension). More than 40 million major surgeries are performed annually in the United States, and complications can occur in 800,000 to 2 million cases through surgical infections. Surgery patients are the most common cases of poisoning, resulting in building damage, body breakdown, circulatory system, and immune system. The liver participates in sepsis by protecting the body and repairing tissues through hepatic cells, which controls most of the blood clotting and inflammation in the body. When this control is not sufficient, hepatic impairment may occur, which may sometimes lead to the extension of bacterial products, promote coagulation and inflammation, and in turn, many organs fail and die. The death rate from septic shock is high and the systemic inflammatory response that occurs is severe. The result of this shock is the exit of the anti-inflammatory reactions. Regular inflammatory signs are used to help diagnose patients with septic shock and to identify patients at risk at an early stage of the disease. A combination of signs of systemic inflammation and immunosuppression may be useful when choosing between activation and immunosuppression in treatment. Reducing deaths from acute poisoning requires a structured process that ensures early detection of infection and coordinated application of evidence-based treatment practices.

Introduction

Sepsis is the leading cause of death in non-coronary intensive care units (ICUs) and the 10th leading cause of death in the United States overall. The incidence of severe sepsis in the United States is between 650,000 and 750,000 cases [1]. More than 70% of these patients have underlying comorbidities and more than 60% of these cases occur in those aged 65 years and older. When patients with human immunodeficiency virus (HIV) are excluded, the incidence of sepsis in men and women is similar. A greater number of sepsis cases are caused by infection with gram-positive organisms than gram-negative organisms and fungal infections now account for 6% of cases [2].

In 2004, an international group of experts in the diagnosis and management of infection and sepsis, representing 11 organizations, published the first internationally accepted guidelines that the bedside clinician could use to improve outcomes in severe sepsis and septic shock. These guidelines represented Phase II of the Surviving Sepsis Campaign (SSC), an international effort to increase awareness and improve outcomes in severe sepsis. Joined by additional organizations, the group met again in 2006 and 2007 to update the guidelines document using a new evidence-based methodology system for assessing quality of evidence and strength of recommendations [3].

Hepatic injury has been investigated mainly in critically ill and septic patients. In sepsis, the liver participates in host defense and tissue repair through hepatic cell cross-talk that controls most of the coagulation and inflammatory processes. When this control is not adequate, a secondary hepatic dysfunction may occur and may sometimes lead to bacterial products spillover, enhanced pro coagulant and inflammatory processes, and in turn, multiple organ failure and death [4].

Successful management of the critical care stage of sepsis requires support of affected organs. If a causative organism is identified (20% of patients with sepsis have negative cultures), then the antibiotic regimen should be narrowed to decrease the likelihood of the emergence of resistant organisms. In addition to antibiotic treatment, source control by means of removing or draining septic foci is also a priority in the management of patients with sepsis. The use of corticosteroids, vasopressin and intensive insulin therapy requires further study. Later in the course of sepsis, appropriate management necessitates organ support and prevention of nosocomial infection [5].

Chapter 1 - Part A

Sepsis

Pathophysiology

Sepsis remains a critical problem with significant morbidity and mortality even in the modern era of critical care management. Multiple derangements exist in sepsis involving several different organs and systems, although controversies exist over their individual contribution to the disease process. Septic patients have substantial, life threatening alterations in their coagulation system. Previously, it was believed that sepsis merely represented an exaggerated, hyper inflammatory response with patients dying from inflammation-induced organ injury. More recent data indicate that substantial heterogeneity exists in septic patients' inflammatory response, with some appearing immuno-stimulated, whereas others appear suppressed [6].

Sepsis is defined as the presence or presumed presence of an infection accompanied by evidence of a systemic inflammatory response. This response is a complex cascade of events that encompasses pro inflammatory, anti-inflammatory, humoral, cellular, and circulatory involvement. Clinical features of sepsis may include fever or hypothermia, leukocytosis or leucopenia, and tachypnea or raised minute ventilation [7].

Systemic Inflammatory Response Syndrome (SIRS) can be diagnosed when any two of the following criteria exist:

a. Body temperature <36C or >38C, heart rate >90beats/min

b. Respiratory rate>20breaths/min or PCO_2<4.3kPa (32mmHg)

c. White cell count<4000/mm^3 or >12000/mm^3 or the presence of greater than 10% immature neutrophils [8]

Severe sepsis: Sepsis with evidence of organ dysfunction or tissue hypo perfusion [8].

Septic shock: Sepsis-induced hypotension which persists despite adequate fluid resuscitation [8].

Cellular changes continue the theme of heterogeneity. Some cells work too well such as neutrophils that remain activated for an extended time. Other cellular changes become accelerated in a detrimental fashion including lymphocyte apoptosis [6].

Metabolic changes are clearly present, requiring close and individualized monitoring. At this point in time, there's no single mediator/system/pathway/pathogen drives the patho physiology of sepsis [6].

Two major consensus conferences have defined sepsis. The first, in 1992, put forth the concept of the Systemic Inflammatory Response Syndrome (SIRS), recognizing that lethally altered pathophysiology could be present without positive blood cultures [9].

The 2001 International Sepsis Definitions Conference modified the model of SIRS and developed an expanded view of sepsis after revisiting the literature. This conference developed the concept of a staging system for sepsis based on four separate characteristics designated by the acronym PIRO. P stands for the predisposition, indicating pre-existing co-morbid conditions that would reduce survival. I is the insult or infection, which reflects the clinical knowledge that some pathogenic organisms are more lethal than others. R represents the response to the infectious challenge, including the development of SIRS. The last letter O stands for organ dysfunction and includes organ failure as well as the failure of a system such as the coagulation system [10].

Opinions on the causes and potential therapies for sepsis have evolved over time and the following will focus on some of the current thoughts concerning the basic mechanisms of the septic process:

Dysregulated coagulation

Normal hemostasis exists as a finely tuned balance where the blood typically remains liquid to allow free flow within the vessels yet clots appropriately to control bleeding. Under normal conditions the clotting cascade is extremely complex [11].

During inflammatory situations such as sepsis, significant alterations occur at multiple levels within both the coagulation system and the cells that regulate this system [12].

Septic patients frequently manifest disseminated intravascular coagulation (DIC) with consumption of platelets and prolongation of clotting times. In addition, the altered hemostasis allows blood to clot when it should not, clogging blood vessels and reducing blood flow. Because the liver produces fixed quantities of pro-coagulant factors, and the bone marrow releases a defined number of white blood cells into the circulation, local effects modulate the systemic coagulopathy. In other words, although the coagulopathy is systemic, the bleeding typically occurs in select sites, where dysfunctional vasculature provides the necessary environment for bleeding to occur at that site [13]. Sepsis lowers levels of protein C, protein S, anti-thrombin III, and tissue factor–pathway inhibitor [14]. Lipopolysaccharide and TNF-α decrease the synthesis of thrombomodulin and endothelial protein C receptor, impairing the activation of protein C and increase the synthesis of plasminogen-activator inhibitor 1, thus impairing fibrinolysis.

Aberrant Mediator Production

The inflammatory response represents an important, central component of sepsis because elements of the response drive the physiological alterations that become manifest as the SIRS. An appropriate inflammatory response eliminates the invading microorganisms without causing damage to tissues, organs, or other systems.

Hyper inflammatory Response: Several years ago, many basic science investigators and clinicians believed that the problem of sepsis was directly related to the exuberant production of proinflammatory molecules. The problem seemed rather simple: inflammation was excessive. The solution was easy: blunt inflammation, and save lives. This concept was driven by four pieces of information. First, septic patients with increased levels of specific mediators such as tumor necrosis factor (TNF) are at increased risk for death [15]. Second, injection of TNF molecules into experimental animals results in wide spread inflammatory alterations [16] and tissue injury [17] similar to that observed in septic patients. Third, experimental animals injected with lethal doses of endotoxin display elevated levels of the same mediators.

Finally, inhibition of these specific mediators improves survival in endotoxin shock models [18]. Together, these observations launched a series of clinical trials aimed at blocking TNF or interleukin (IL)-1 (Tables 1 & 2) [19].

Table 1: Clinical Trials Using the Interleukin-1 Receptor Antagonist to Treat Sepsis. None of the trials demonstrated an improvement in survival [5].

Year	No. of Patients	Out Come
1994	893	No reduction in 28- day mortality [138]
1995	26	Reduction in surrogate activation Markers [139]
1997	696	No improvement in survival [45]

Table 2: Clinical Trials with TNF Inhibitors. A meta-analysis of all of the trials together indicates that there is a survival advantage when using the TNF inhibitors [5].

Year	No. of Patients	Inhibitor	Outcome
1991	42	Humanized antibody	Safety study. Treatment resulted in a reduction in circulating cytokines [140]
2001	944	Antibody fragment	Patients stratified by plasma IL-6 levels, no improvement in survival [14]
2004	2634	F(ab_)2 monoclonal antibody	Patients stratified by IL-6 levels, TNF inhibition resulted in improved survival [141]
2006	81	Sheep antibody	No reduction in 28-day mortality, decreased circulating TNF and IL-6 [142]

In traditional thinking, a mediator must be elevated and detectable to be implicated in the pathogenesis of disease. In septic patients with poor survival, TNF was elevated, and this provided a portion of the rationale on why it should be blocked [15]. However, it must be borne in mind that cytokines may have significant effects at the local level such that detectable plasma levels may not be necessary for the cytokine blockade to be effective. This was shown dramatically in a recent clinical trial of neonatal onset multisystem inflammatory disease where children treated with the IL-1 receptor antagonist demonstrated a remarkable improvement in both objective and subjective criteria. This dramatic improvement occurred even though IL-1 was not detectable in the plasma. As one index of improvement, IL-6 levels were significantly decreased with IL-1 receptor antagonist treatment [20].

Blunted Inflammatory Response: Another viewpoint would argue that septic patients failed to control the bacterial infection and died as a result of immuno suppression rather than immuno stimulation. A study has shown that intensive care unit patients have reduced production of both TNF and IL-6 in response to endotoxin stimulation [21]. Another study demonstrated that although TNF was reduced, IL-10 production was not impaired in patients with sepsis [22]. These studies would indicate that the proinflammatory response could not be initiated, whereas the anti-inflammatory response continued unabated, producing the equivalent of a blunted inflammatory response. Patients with severe burns and sepsis exhibit defects in their T lymphocytes because the cells fail to proliferate in response to mutagenic stimuli and also fail to produce IL-2 or -12 [23].

Table 3: Diagnostic Criteria for ALI and ARDS [143].

ALI Criteria	ARDS Criteria
Acute Onset	Acute Onset
$PaO_2/FiO_2 \leq 300mmHg$	$PaO_2/FiO_2 \leq 200mmHg$
Chest Radiograph: Bilateral Infiltrates	Chest Radiograph: Bilateral Infiltrates

Because blocking the inflammatory response with specific inhibitors was not tremendously effective (Tables 2 & 3), the possibility was raised that the patients required immuno stimulation. However, in the clinical trial using granulocyte colony-stimulating factor to treat 701 patients with pneumonia and severe sepsis, there was no improvement in survival [24]. The blunted monocyte response observed in septic patients has been reversed with interferon-gamma and systemic therapy successfully cleared sepsis in eight of nine patients. A larger clinical trial with 416 trauma patients indicated that interferon-gamma therapy did not reduce infections or overall mortality but did reduce deaths due to infections [25].

Cellular Dysfunction

Many cellular aspects become dysfunctional in sepsis and may be characterized as either excessive activation or depressed function. Excessive activation refers to cells that are primed such that they respond in a very vigorous manner to a second stimulus. An example of excessive activation would be neutrophils generating excess toxic products that cause damage to nearby cells .An example of depressed function would be neutrophil failure to phagocytize and clear invading pathogens [26].

One of the current areas of active investigation concerning cellular function is the induction of cellular apoptosis or necrosis apoptosis may contribute to the pathogenesis of sepsis by delayed removal of those cells that should be removed, i.e., neutrophils, and early removal of those cells that should not be removed, i.e., lymphocytes [27].

Lymphocyte apoptosis: Lymphocytes are critical cells in the response to sepsis, and the interactions between the innate and adaptive immune system are becoming increasingly important. These apoptotic lymphocytes were observed in virtually all lymphoid organs including the obvious locations, such as the spleen and thymus, but also in the gastric associated lymphatic tissue and essentially wherever collections of lymphocytes exist. In septic patients, there is a combination of apoptotic and necrotic cell death [27].

Neutrophil hyperactivity: Neutrophils are critical components of the innate immune response to infectious challenges. Neutropenic patients, regardless of the cause of the neutropenia, and patients with neutrophil dysfunction are at increased risk for the development of infectious complications [28]. There is no question that an appropriate, robust neutrophil response benefits the patient and helps to eradicate an infectious focus. The difficulty lies in attempting to define an appropriate response versus a hyperactive response [29] as illustrated in

Figure 1. Patients who have suffered traumatic injury are at increased risk for the development of multisystem organ failure, and neutrophils recovered from such patients demonstrate increased chemotactic responses to cytotoxic (CXC) chemokines [30]. However, neutrophils isolated from septic patients demonstrate decreased chemo taxis toward IL-8 and depressed expression of CXCR2. These results were further explored in a article showing that high CXCR2 function correlates with the development of organ injury, i.e., acute respiratory distress syndrome, whereas low function predisposes to pneumonia and sepsis [31]. These studies aptly demonstrate the heterogeneity of the septic response in that some patients have an excessive response, whereas others have a blunted response.

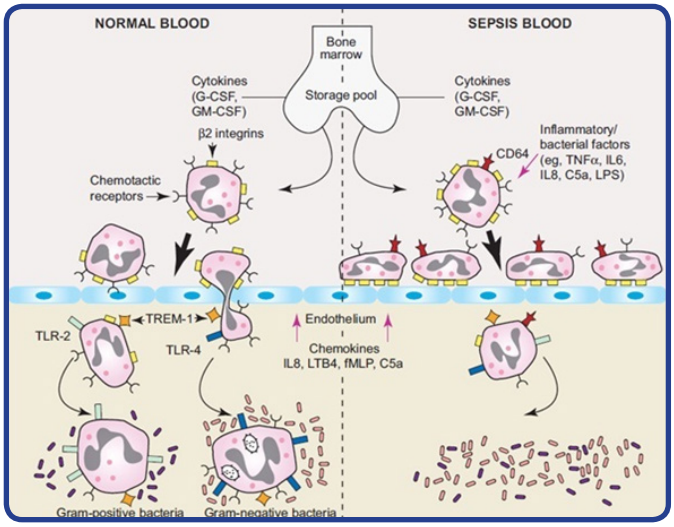


Figure 1: Proposed model for dysregulation of neutrophil recruitment to bacterial infection in nonpulmonary tissue under normal conditions (left) and in sepsis (right) [29].

Modulating the recruitment of neutrophils to the site of inflammation has potential benefits, but this should be via specific modulation rather than global inhibition of neutrophil function. Recently, a class of immuno modulatory compounds termed pepducins, which are cell-penetrating lipopeptides, have been used to target CXC chemokine receptors [32]. These compounds were able to block neutrophil chemo taxis to CXC chemokines without affecting neutrophil responses to other stimulants such as the formyl peptides. Another significant issue concerns inappropriate apoptosis of neutrophils in the septic patients. Neutrophils in the circulation typically have a very short lifespan of approximately 24 hours. However, patients with sepsis have a delay in their neutrophil apoptosis, causing them to persist longer in the bloodstream. As a result, the septic patient has increased numbers of activated cells with the potential to cause organ injury. However, it must be borne in mind that these activated neutrophils are also the precise defenders that are critical in the innate immune response to clear an infection [33].

Endothelial cell failure and apoptosis in other cells: Endothelial cells reside at the critical interface between the blood and tissue. Intact endothelial cells exhibit anticoagulant properties through elaboration of anticoagulant molecules such as protein C. These cells also serve as a barrier between blood products and pro-coagulant molecules, such as heparin, residing in the extra-cellular matrix. Endothelial disruption comes about because of increased expression of adhesion molecules on the endothelial cells, resulting in attachment of white blood cells. It has also become increasingly clear that abundant cross talk exists between the coagulation system and the inflammation system in sepsis [34].

Endothelial cells will undergo apoptosis in response to several mediators *in-vitro*, including some infectious agents. However, endothelial cells are relatively resistant to the effects of endotoxin and several investigators have failed to demonstrate convincing evidence of endothelial cell apoptosis during sepsis [35]. Although it is strongly suspected that endothelial cells are dysfunctional in septic patients, clear-cut documentation during *in-vivo* settings has been difficult to obtain.

Other cells within the body also fail to function normally, and it has been demonstrated that increased apoptosis of dendritic cells, macrophages/monocytes, and mucosal epithelial cells, among other cells, are present in septic patients [36].

Chapter I, Part B

Effect of sepsis on different body organs

Sepsis and the Brain

The impairment of brain function resulting from sepsis is often associated with severe infectious disease. The effects of sepsis on the brain are detectable in previously healthy brains but are amplified in cases with concomitant brain injury, as after traumatic brain injury or subarachnoid hemorrhage. Previous injuries, in fact, increase brain vulnerability to the complex cascade of events known as "septic encephalopathy" [37].

Inflammation and the brain

Sepsis at the outset causes a hyper inflammatory reaction, followed by a counter active anti-inflammatory reaction. Pro- and anti-inflammatory cytokines are initially up regulated. Despite its anatomical sequestration from the immune system by the BBB, the lack of a lymphatic system, and a low expression of histo-compatibility complex antigens, the brain is not isolated from the inflammatory processes occurring elsewhere in the body. The circumventricular organs lack a BBB, and through these specific brain regions blood-borne cytokines enter the brain. The circumventricular organs are composed of specialized tissue and are located in the midline ventricular system. They consist of the organum vasculosum, the pineal body, the sub-commissural organ, and the sub-fornical organ. They also express components of the immune system (Toll-like receptors [TLR]), and receptors for cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α).

A further mechanism by which the brain can detect systemic inflammation is through afferent vagal fibers ending in the nucleus tractus solitarius, which senses visceral inflammation through its axonal cytokine receptors. In response to the detection of systemic inflammation, behavioral, neuro endocrine and autonomic responses are generated including expression of immune receptors and cytokines, inducible nitric oxide synthase (iNOS) and prostaglandins leading to oxidative stress, mitochondrial dysfunction, and apoptosis [38].

Effects of sepsis on the blood-brain barrier , the vascular endothelium and the oxidative stress

The BBB, established by the tight junctions of the endothelial cells in interaction with astrocytic foot processes and pericytes, is responsible for a tightly regulated microenvironment in the brain. It prevents circulating noxious substances from entering into the brain and regulates brain capillary blood flow [39]. In sepsis, cerebral endothelial cells are activated by lipopolysaccharide (LPS) and pro-inflammatory cytokines, including bradykinin, IL-1β, and TNF-α; TNF-α also activates iNOS [40]. These changes in the cerebral microcirculation are associated with the up regulation of mRNA for local production of IL-1β, TNF-α, IL-6, and NO by induction of iNOS. Furthermore, leukocytes stick to the wall of blood vessels and enter the brain, mediated by adhesion molecules. The expression of one such adhesion molecule, the intercellular adhesion molecule (ICAM), is increased in septic rats. These local factors can promote endothelial dysfunction and result in BBB breakdown leading to an increased permeability of the blood-brain barrier and to peri-vascular edema, as has been demonstrated in several animal models of sepsis. The former facilitates the passage of neurotoxic factors, while the latter impairs the passage of oxygen, nutrients, and metabolites. The increased diapedesis of leukocytes and the peri-vascular edema decrease microcirculatory blood flow in the brain capillaries [41].

In a recent magnetic resonance imaging (MRI) study in nine humans with septic shock and brain dysfunction, sepsis-induced lesions could be documented in the white matter suggesting BBB break down [42].

Finally, another mechanism by which the brain is affected in sepsis is the generation of reactive oxygen species (ROS) by activated leukocytes. Exposed to these radicals, erythrocyte cell membranes become less deformable and may be unable to enter the brain microcirculation, thus aggravating the cerebral hypo perfusion seen in sepsis. The brain itself with its high oxygen consumption and low anti-oxidant defense is susceptible to damage by ROS. Generation of ROS may alter oxidative phosphorylation and cytochrome activity in the mitochondria and impair cerebral energy production [43].

Sepsis and the Cardiovascular System

Myocardial global ischemia

An early theory of myocardial depression in sepsis was based on the hypothesis of global myocardial ischemia; however, septic patients have been shown to have high coronary blood flow and diminished coronary artery-coronary sinus oxygen difference. As in the peripheral circulation, these alterations can be attributed to disturbed flow auto-regulation or disturbed oxygen utilization [44]. Coronary sinus blood studies in patients with septic shock have also demonstrated complex metabolic alterations in septic myocardium, including increased lactate extraction, decreased free fatty acid extraction, and decreased glucose uptake [45].

The manifestation of myocardial ischemia due to coronary artery disease (CAD) might even be facilitated by the volatile hemodynamics in sepsis, as well as by the generalized micro vascular dysfunction which is frequently observed in sepsis [46]. Additional CAD aggravating factors encountered in sepsis encompass generalized inflammation and the activated coagulatory system. Furthermore, the endothelium plays a prominent role in sepsis, but little is known of the impact of preexisting, CAD-associated endothelial dysfunction in this context [47].

Myocardial Depressant Substance

A circulating myocardial depressant factor in septic shock was first proposed more than 50 years ago. Recently, Mink et al., demonstrated that lysozyme c, a bacteriolytic agent believed to originate mainly from disintegrating neutrophilic granulocytes and monocytes, mediates cardio depressive effects during Escherichia coli sepsis and, importantly, that competitive inhibition of lysozyme c can prevent myocardial depression in the respective experimental sepsis model. Additional potential candidates for myocardial depressant substance include other cytokines, prostanoids, and nitric oxide (NO) [48].

Cytokines: Tumor necrosis factor (TNF) is an important early mediator of endotoxin-induced shock.TNF is derived from activated macrophages, but studies have shown that TNF is also secreted by cardiac myocytes in response to sepsis [49]. Although application of anti-TNF antibodies improved left ventricular function in patients with septic shock, subsequent studies using monoclonal antibodies directed against TNF or soluble TNF receptors failed to improve survival in septic patients [50]. IL-1 is synthesized by monocytes, macrophages and neutrophils in response to TNF and plays a crucial role in the systemic immune response. IL-1 depresses cardiac contractility by stimulating NO synthase (NOS) [50]. IL-6, another proinflammatory cytokine, has also been implicated in the pathogenesis of sepsis and is considered a more consistent predictor of sepsis than TNF because of its prolonged elevation in the circulation [51]. Although cytokines may very well play a key role in the early decrease in contractility, they cannot explain the prolonged duration of myocardial dysfunction in sepsis, unless they result in the induction or release of additional factors that in turn alter myocardial function, such as prostanoids or NO [52].

Prostanoids: Prostanoids are produced by the cyclo-oxygenase enzyme from arachidonic acid. Elevated levels of prostanoids such as thromboxane and prostacyclin, which have the potential to alter coronary auto regulation, coronary endothelial function and intra-coronary leukocyte activation, have been demonstrated in septic patients [53]. Early animal studies with cyclo-oxygenase inhibitors such as indomethacin yielded very promising results. Along with other positive results, these led to an important clinical study involving 455 septic patients who were randomized to receive intravenous ibuprofen or placebo [54]. Unfortunately, that study did not demonstrate improved survival for the treatment arm. Similarly, a more recent, smaller study on the effects of lornoxicam failed to provide evidence for a survival benefit through cyclo-oxygenase inhibition in sepsis [55].

Nitric Oxide: NO exerts a plethora of biological effects in the cardiovascular system [56]. It has been shown to modulate cardiac function under physiological and a multitude of pathophysiological conditions. In healthy volunteers, low-dose NO increases LV function, whereas inhibition of endogenous NO release by intravenous infusion of the NO synthase (NOS) inhibitor NG-monomethyl-L-arginine reduced the stroke volume index [57]. Sepsis leads to the expression of inducible NOS (iNOS) in the myocardium, followed by high-level NO production, which in turn importantly contributes to myocardial dysfunction, in part through the generation of cytotoxic peroxynitrite, a product of NO and superoxide. Strikingly, in septic patients, infusion of methylene blue, a nonspecific NOS inhibitor, improves mean arterial pressure, stroke volume, and left ventricular stroke work and decreases the requirement for inotropic support but, unfortunately, does not alter outcome [58].

The peripheral circulation

Vasodilatation of the peripheral (systemic) resistance vessels occurs in severe sepsis, to the extent that the SVR may be reduced to a quarter of the normal value. The vasodilatation is not uniform across tissue beds nor is it simply an increase in the baseline vessel calibre. In severe sepsis, the term `vasoplegia' is often applied to the vasculature, suggesting that rhythmic vasomotion is paralyzed. The vasculature of septic patients becomes progressively less responsive to sympathomimetic pressor agents. Yet the exact cause of this vasodilatation and pressor resistance remains to be determined [59].

In humans, circulating endotoxin binds to the LPS binding protein, and the complex is recognized by CD14 receptors on the surface of immune cells. This in turn triggers an inflammatory cascade, with the release of both pro- and anti-inflammatory mediators and cytokines. This complex network of mediators is responsible for the clinical manifestations of severe sepsis, including the peripheral vasodilatation. The mediator that has received most attention as the `culprit' vasodilator in sepsis is nitric oxide. Excess nitric oxide might also explain some of the other features of severe sepsis. Most patients with severe sepsis develop a lactic acidosis even in the presence of a high cardiac output and other indicators of adequate tissue perfusion, such as a high mixed venous oxygen saturation or content. Although there are several mechanisms by which this could occur, one possible cause could be partial failure of oxidative metabolism in mitochondria. Excess nitric oxide (which binds avidly to a range of metallo proteins) might be inactivating the haem-containing cytochrome enzymes involved in oxidative metabolism [60].

The hypotension of septic shock has been reversed using analogues of L-arginine such as mono methyl arginine (L-NMMA) and nitro arginine methyl ester (L-NAME) as competitive blockers of NOS in both animal studies and human sepsis [61].

Nitric oxide is not the only diatomic gas that binds to metallo proteins. Carbon monoxide's high afinity for hemoglobin is well known, but carbon monoxide also binds to cytochromes; this is thought to be the mechanism behind neurological changes in carbon monoxide poisoning. Carbon monoxide may also cause vascular relaxation by directly activating calcium-dependent potassium channels [62].

Prostaglandins, leukotrienes and thromboxanes are metabolites of arachidonic acid and are known to increase in concentration in the blood of patients with sepsis. They have a range of actions, including vasodilatation, leucocyte activation and damage to vascular endothelial cells, the specific effects depending on the specific prostaglandin. Prostaglandin and thromboxane concentrations correlate with the severity of organ failure in patients with severe sepsis [63].

Sepsis and the Lung

Acute lung injury (ALI) secondary to sepsis is the source of substantial morbidity and mortality in both adult and pediatric [64] populations and is a major contributor to intensive care unit (ICU) costs. ALI and acute respiratory distress syndrome (ARDS) are defined by well-established criteria with sepsis and pneumonia being the two leading etiologies. Endothelial injury in the pulmonary vasculature during sepsis disturbs capillary blood flow and enhances micro vascular permeability, resulting in interstitial and alveolar pulmonary edema. Neutrophil

entrapment within the lung's microcirculation initiates and/or amplifies the injury in the alveolo capillary membrane. The result is pulmonary edema, which creates ventilation-perfusion mismatch and leads to hypoxemia. Such lung injury is prominent during sepsis, likely reflecting the lung's large micro vascular surface area. Acute respiratory distress syndrome is a manifestation of these effects [65].

The adult respiratory distress syndrome (ARDS) has been characterized as a disease state, in which the inflammatory balance is shifted towards tissue injury. Excessive inflammatory reactions and, in particular, neutrophil activation have been implicated in ARDS pathogenesis [66].

Sepsis and the Kidney

Renal haemodynamics in septic patients (Figure 2)

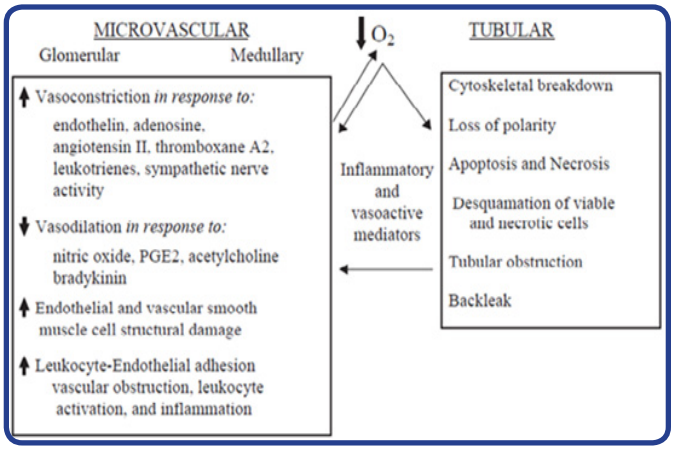


Figure 2: Renal haemodynamics in septic patients [134].

During severe sepsis, in addition to overwhelming production of inflammatory humoral mediators and activation of cellular system, there is activation of sympathico-adrenal axis with increased plasma levels of nor-epinephrine, of renin-angiotensin aldosterone system (RAAS) with elevated levels of angiotensin II and a rise in vasopressin levels are often part of host response. These mechanisms are largely responsible for the clinical manifestations of sepsis, including the haemodynamic alterations that are characterized by vasodilatation, a hyper dynamic circulation and microcirculatory changes contributing to inefficient oxygen extraction.

Global renal blood flow: The effect of sepsis on systemic vasculature is ultimately to cause reduction in mean arterial pressure (MAP). In normal circumstances, when blood pressure falls auto regulation will act to maintain renal blood flow (RBF), increasing the proportion of cardiac output going to the kidneys. When mean arterial pressure falls below the auto-regulatory range in hemorrhagic or cardiogenic shock, renal vasoconstriction will occur. Many studies are done and can be partially reconciled that in early hyper dynamic resuscitated sepsis, RBF increases in parallel with increasing CO, but that when a fall in CO occurs (either from inadequate fluid resuscitation or advancing sepsis with cardiac depression), disproportionate renal vasoconstriction occurs. It would appear that the main determinant of renal blood flow in sepsis is the state of systemic circulation, but there may be relative renal vasoconstriction in some circumstances.

Glomerular changes: The most significant alteration in glomerular function in sepsis is a decrease in glomerular filtration rate (GFR) [67]. In many cases this is determined by a fall in renal plasma flow and glomerular perfusion pressure, in the context of systemic hypotension. However, the renal ischemia is by no means a uniform feature of sepsis. A fall in GFR due exclusively to a reduction in the filtration fraction has been described in experimental sepsis, and may well occur in septic patients. The main determinants of filtration fraction (FF) are the balance between the resistances of the afferent and efferent glomerular arterioles, and the total surface area for filtration. Constriction of the afferent arteriole and/or dilation of the efferent arterioles, will reduce the FF. Vasoactive substances which are released during sepsis, and which cause preferential afferent constriction, include leukotrienes, adenosine, thromboxane A2 and endothelia. The reduction in the surface area for filtration as an effect of vasoactive mediators involved in sepsis, has been described. These include leukotrienes thromboxane A2, and angiotensin II.

Endothelial Injury: In common with vascular beds elsewhere, there is the potential for glomerular capillaries to be affected by acute endothelial injury. This is linked to activation of the coagulation system by endotoxin, release of tissue factor, deposition of platelets and fibrin within capillaries, and reduced fibrinolytic activity in affected capillaries. In addition, activated neutrophils and a range of cytokines, such as IL-Iβ, TNF and platelet activating factor, are also implicated in the pathogenics of endothelial injury [68].

Tubular Injury: Patients with established acute renal failure due to sepsis are generally regarded as suffering from acute tubular necrosis. There is evidence that in many cases, this is indeed true. In addition to renal blood flow, arterial oxygenation and hemoglobin concentration are important determinants of renal oxygen delivery. Renal oxygen extraction may be impaired in a septic patient and renal O2 requirements may be initially high, because of active tubular sodium absorption. Once established, the tubular damage may be perpetuated or worsened by haemodynamic disturbances occurring during the course of acute renal failure, which in some cases may be associated with intermittent dialysis treatment. This observation has underpinned the current trend towards the use of continuous modes of replacement therapy in septic patients [69].

Chapter 1, Part C

Post-Operative Sepsis

Sepsis after major surgery is common in patients admitted to intensive care units (ICU). It is fast becoming the most common cause of mortality in surgical ICU [1]. Recent therapeutic advances have enabled clinicians to reduce early postoperative mortality and/or morbidity [70]. Despite these advances, patients remain at high risk for infection and the associated increased morbidity and mortality. The suppression of the immune system after surgery predisposes the patients to develop sepsis.

The post-surgical immuno suppression may be related to:

- Direct effects of anaesthetic drugs.
- Hormonal changes related to stress.
- Effects of hemorrhage and transfusion.
- Occurrence of ischaemia–reperfusion.
- Extent of surgical trauma.

Table 4: American Society of Anesthesiologists Physical Status Classification. (Practice advisory for preoperative evaluation: A report by the American Society of Anesthesiologists.2002).

ASA 1	Healthy patient without organic, biochemical, or psychiatric disease.
ASA 2	A patient with mild systemic disease, e.g., mild asthma or well controlled hypertension. No significant impact on daily activity. Unlikely to have an impact on anesthesia and surgery.
ASA 3	Significant or severe systemic disease that limits normal activity, e.g., renal failure on dialysis or class 2 congestive heart failure. Significant impact on daily activity. Probable impact on anesthesia and surgery.
ASA 4	Severe disease that is a constant threat to life or requires intensive therapy, e.g., acute myocardial infarction, respiratory failure requiring mechanical ventilation. Serious limitation of daily activity. Major impact on anesthesia and surgery.

Table 5: Charlson co-morbidity index. Assigned weights for each condition that a patient has the total equals the score. Example: chronic pulmonary disease (1) and lymphoma (2) = total score of 3 (BJA 2005).

Assigned Weights for Diseases	Conditions
1	Myocardial infarction; Congestive heart failure; Peripheral vascular disease; Cerebrovascular disease; Dementia
2	Chronic pulmonary disease; Connective tissue disease; Ulcer disease; Mild liver disease; Diabetes; Hemiplegia
3	Hemiplegia; Moderate or severe renal disease; Diabetes with end-organ damage; Any tumour; Leukaemia
6	Lymphoma; Moderate or severe liver disease; Metastatic solid tumour; AIDS

The underlying illness, co-morbidity, and factors like age or gender also play a pivotal role in modulating the immune system [71]. The postoperative period is characterized by development of SIRS. SIRS, sepsis, severe sepsis, and septic shock represent a clinical continuum, with an increasing mortality from SIRS to septic shock [71]. The early identification of markers to this progression may reduce postoperative morbidity and mortality. Many tools like Charlson co-morbidity index, American Society of Anesthesiologists (ASA) physical status [72] and logistic organ dysfunction (LOD) system can be used to determine the outcome of patients undergoing surgery [73] (Table 4 & 5).

Epidemiological features of postoperative sepsis and septic shock

Incidence: Post-operative sepsis and septic shock are major healthcare problems with a reported incidence of 66-132 per 100,000 populations in the USA and UK, respectively. Severe sepsis occurs in 1-2% of all hospitalizations and accounts for as much as 25% of intensive care unit (ICU) bed utilization. It is common in elderly, immuno compromised and critically ill patients and is a major cause of death in ICUs worldwide. Sepsis is the second leading cause of death in non-coronary ICU patients. Mortality remains high at 30-50% despite improved care in the past 10-15 yr [74].

Micro-organisms: (Table 6)

Table 6: Operations and Likely Surgical Site Infection Pathogens [144].

Operations	Likely Pathogens
Placements of all grafts, prostheses or implants	*Staphylococcus aureus*; coagulase negative *Staphylococci*
Cardiac	*St. aureus*; coagulase negative *Staphylococci*
Neurosurgery	*St. aureus*; coagulase negative *Staphylococci*
Breast	*St. aureus*; coagulase negative *Staphylococci*
Ophthalmic	*St. aureus*; coagulase negative *Staphylococci; Streptococci;* gram-negative bacilli
Orthopedic: Total joint replacement Closed fractures/ use of nails, bone plates, other internal fixation devices, Functional repair without implant/device, Trauma	*St. aureus*; coagulase negative *Staphylococci; Streptococci*; gram-negative bacilli
Non-Cardiac Thoracic: Thoracic (lobectomy, pneumonectomy, wedge resection, other noncardiac, mediastinal procedures), Closed tube thoracostomy	*St. aureus*; coagulase negative *Staphylococci; Streptococci*; *Streptococcus pneumoniae;* gram-negative bacilli
Vascular	*St. aureus*; coagulase negative *Staphylococci; Streptococci;* gram-negative bacilli
Appendectomy	Gram-negative bacilli; Anaerobes
Biliary Tract and Colorectal	Gram-negative bacilli; Anaerobes
Gastroduodenal	Gram-negative bacilli; *Streptococci*; oropharyngeal anaerobes (eg, peptostreptococci)
Head and neck (major procedures with incision through oropharyngeal mucosa)	*St. aureus; Streptococci*; oropharyngeal anaerobes (eg, peptostreptococci)
Obstetric and gynecologic	Gram-negative bacilli; Enterococci; Group B streptococci; anaerobes
Urologic	Gram-negative bacilli

Potential risk factors for developing post-operative sepsis

Age of the patient: The aged were more likely to develop sepsis and severe sepsis after surgery and had a higher mortality rate after developing sepsis. Older persons are more prone to infections due to the effects of aging, comorbidities, use of invasive devices and problems associated with institutionalization. The diagnosis of sepsis in this population can be difficult, as older patients may have atypical responses to sepsis and may present with delirium or falls, thus delaying therapeutic interventions that may influence their outcome [75]. Aging patients account for 40–50% of all cases of sepsis, and the overall case fatality rate for older patients with bacteremia ranges from 40-60% or higher when Gram-negative organisms are involved [2].

Gender of the patient: gender differences were confirmed in human sepsis with a significantly better prognosis for women, which may be related to increased levels of anti-inflammatory mediators. The hypothetical different ratio of proinflammatory and anti-inflammatory mediators may be important for further therapeutic interventions in sepsis [76].

Patient body weight: Epidemiological data support the hypothesis that obesity can affect immune function in humans. Findings from hospitalized, obese patients have been reviewed by several groups. Briefly, in the hospital setting, obese patients are more likely to develop secondary infections and complications such as sepsis, pneumonia, bacteremia, and wound and catheter-related infections. Patients with increased body mass index (BMI) and adiposity also present a higher incidence of surgical site infections, which have been associated with increased risk of other wound complications, increased length of stay and increased risk of death. Obesity negatively affects pulmonary function, and hospitalized obese patients have been shown to be at increased risk for pulmonary aspiration and community-related respiratory tract infections. Obesity is an extremely multi-factorial disease and numerous pathways and processes are altered by obesity, which could potentially alter the immune response. Aside from leptin, factors such as altered immune cell metabolism and even epigenetic alterations could influence the immune response to infectious disease in the obese host [77].

Presence of preoperative co-morbidities: Patients with more co-morbidities on admission had a greater risk of postoperative complications and increased mortality. Cardiovascular disease and chronic lung disease predispose patients to the most common and serious postoperative complications. These patients may be a target group for specialist preoperative medical assessment. To reduce mortality, attention must focus on optimizing health status preoperatively, preventing postoperative complications, and, when these complications develop, providing optimal specialist medical care [78].

Length of pre-operative stay: A prolonged preoperative stay with exposure to hospital environment and its ubiquitous diagnostic procedures, therapies and micro flora have been shown to increase the rate of surgical site infection and postoperative sepsis. Kowli found an infection rate of 17.4% when preoperative stay was 0-7 days and an infection rate of 71.4% with a pre-operative stay of more than 21 days [79].

Duration of the operation: It has been observed that postoperative sepsis rate is influenced by duration of the operation. With increase in duration of surgery the rate of infection and post-operative sepsis increased in direct proportion [80].

Use of prophylactic antibiotics: Anti-microbial prophylaxis is used to reduce the incidence of post-operative wound infections and sepsis. Patients undergoing procedures associated with high infection rates, those involving implantation of prosthetic material, and those in which the consequences of infection are serious should receive peri-operative Antibiotics. The goal of prophylactic antibiotics is to reduce the incidence of post-operative wound infection. It is important to recognize the difference between prophylactic and empiric therapy. Prophylaxis is indicated for procedures associated with high infection rates, those involving implantation of prosthetic material, and those in which the consequences of infection are serious. The antibiotic should cover the most likely contaminating organisms and be present in the tissues when the initial incision is made. Therapeutic concentrations should be maintained throughout the procedure. Empiric therapy is the continued use of antibiotics after the operative procedure based upon the intra-operative findings. Inappropriate prophylaxis is characterized by unnecessary use of broad-spectrum agents and continuation of therapy beyond the recommended time period. These practices increase the risk of adverse effects and promote the emergence of resistant organisms [81].

Type of the procedure: Each year, as many as two million operations are complicated by surgical site infections all over the world, and surgical patients account for 30% of patients with sepsis. Sepsis and death were more likely after non-elective than elective surgery. Esophageal, pancreatic, and gastric procedures represented the greatest risk for the development of sepsis, but mortality for patients developing sepsis was found to be the greatest following thoracic, adrenal and hepatic procedures [82].

Causes of sepsis

Table 7: Aetiology of sepsis [145].

Infective causes	Non-infective causes
CNS infections	Severe trauma
CVS infections	Haemorrhage
Respiratory infections	Complication of surgery
Renal infections	Complicated aortic aneurysm
GIT infections	Myocardial infarction
Skin and soft tissue infections	Pulmonary embolism
Bone and joint infections	Cardiac tamponade
	Subarachnoid haemorrhage Burns
	Acute pancreatitis Drug overdose/toxicity
	Diabetic ketoacidosis
	Adrenal insufficiency
	Anaphylaxis

Severe sepsis may have infective and non-infective causes (Table 7). Infections are common and amenable to treatment; therefore, in patients presenting with clinical signs of systemic inflammation (SIRS), an infective cause should be actively sought. Community-acquired infections in previously well patients are easier to recognize than nosocomial infections in debilitated hospitalized patients. Infections leading to sepsis include central nervous system (CNS) infections, for example, meningitis or encephalitis, cardiovascular infections (e.g. infective endocarditis), respiratory infections (e.g.pneumonia), gastrointestinal infections (e.g. peritonitis), or urinary tract infections (e.g. pyelonephritis). Although bacterial infections are the most common infective cause, viruses and fungi can also cause septic shock. Non-infective causes include severe trauma or hemorrhage and acute systemic disease, including myocardial infarction, pulmonary embolus, and acute pancreatitis [83].

Chapter 2

Effect of Post-Operative Sepsis on Liver

The liver plays a major role in modulating the systemic response in severe sepsis because it contains most of the macrophages of the body (Kupffer cells) able to clear the endotoxin and bacteria that may stimulate the systemic inflammatory response [84]. Hepatocytes synthesize the acute phase proteins and the enzymes required to modulate the inflammatory response [85]. Additionally, during bacterial translocation from the gut, the liver limits the access of proinflammatory substances into the systemic circulation [86].

Modifications of Hepatic Hemodynamics in Sepsis

Hepatic vessels and cells

The liver has a dual blood supply. Approximately two thirds of the blood perfusing the liver is venous and is supplied by the portal vein draining the splanchnic vascular bed, which collects the blood coming from the digestive tract below the diaphragm, the spleen, and the pancreas. One third of the blood perfusing the liver is arterial and is provided through the hepatic artery. Within the liver, the portal vein and the hepatic artery branch in parallel. After a number of divisions, terminal branches of these vessels supply blood to the hepatic capillaries or sinusoids, which are organized in a dense network. In sinusoids, several types of cells have been identified: endothelial cells, Kupffer cells, and stellate cells [87].

Endothelial cells are perforated by large fenestrate and are not surrounded by a basal lamina. Thus, the porosity of the sinusoids enable the dispersion of plasma into the space of Disease (which separates sinusoids and hepatocytes). Endothelial cells have a high endocytic activity and produce various mediators, such as thromboxane and prostaglandins. Stellate cells store intra-cytoplasmic fat droplets containing vitamin A and synthesize collagen and other constituents of the extracellular matrix. After acute or chronic hepatic injury, stellate cells undergo activation, a process characterized by the conversion to a myofibroblastic phenotype with de novo expression of the cytoskeletal protein smooth muscle α-acting. Thus, during sepsis, stellate cells undergo contractile properties and, similar to endothelial cells, participate to the modifications of hepatic blood flow [87].

Kupffer cells are hepatic macrophages and represent 80%-90% of all resident macrophages of the body. They play a major role in the uptake and destruction of bacteria and endotoxin. After activation by endotoxin, they secrete cytokines, lipid mediators such as leukotrienes and prostaglandins, O_2-derived radicals, and lysosomal enzymes. Hepatocytes, which represents 60% of hepatic cells, have numerous metabolic functions, including gluconeogenesis and glycogenolysis, protein synthesis (albumin, fibrinogen), urea synthesis, bile formation, and drug biotransformation by cytochrome P450 enzymes which are important during sepsis [87].

Estimation of hepatic blood flow in human septic shock

Ruokonen, et al. [88] found that hepatosplanchnic blood flow is higher in hyper dynamic septic patients than in patients after uncomplicated cardiac surgery. Because the cardiac index is also higher in these patients, the ratio between hepatosplanchnic blood flow and cardiac output remains constant (approximately 25%) [88].

Dahn, et al. [89] compared the hepatosplanchnic blood flow in critically ill patients with or without sepsis and found similar results. These studies suggest that hepatosplanchnic blood flow increases proportionately to the cardiac index in patients with sepsis and that the fractional hepatosplanchnic blood flow remains constant [89].

O_2 Delivery and O_2 consumption in the hepatosplanchnic region

Hepatosplanchnic O_2 delivery (Do_2) and O_2 consumption (Vo_2) were also measured in clinical studies. However, the contribution of the liver to the whole hepatosplanchnic Vo_2 is impossible to determine because no sample can be collected from the portal vein [90]. Hepatosplanchnic Vo_2 is significantly higher in septic patients ($1.9\pm0.5 ml.min\text{-}1.kg^{-1}$) than in non-septic patients ($1.3\pm0.4 mL.min\text{-}1.kg^{-1}$), whereas systemic Vo_2 is similar in both groups. Both hepatosplanchnic Vo_2 and systemic Vo_2 are significantly increased in septic patients and postoperative patients [88]. In healthy volunteers, hepatosplanchnic Vo_2 is 66+/-5mL/min before endotoxin administration and increases 120min (10 +/-13 mL/min) and 240min (90+/-12mL/min) after endotoxin administration. Hepatosplanchnic Vo_2 returns to baseline by 360 min [91].

Moreover, Do_2 is higher in septic shock patients treated with norepinephrine than in patients with severe sepsis who do not receive norepinephrine [92]. This finding contrasts with the common knowledge that norepinephrine infusion decreases hepatosplanchnic blood flow [90]. It is likely that the vascular hypo responsiveness to norepinephrine observed in the mesenteric circulation during experimental sepsis is an explanation for this finding [93].

In septic patients, most of the increased hepatosplanchnic Vo_2 is attributed to an increased hepatic glucose production resulting from increased substrate delivery. Hepatic amino acid uptake and other hepatic pathways, such as tumor necrosis factor-a (TNF-a) and free fatty acid production, are also increased in volunteers injected with endotoxin [89].

Hepatic Cell Functions in Sepsis

Hepatic injury

Hepatic injury has been investigated mainly in critically ill patients, but few studies have included only septic patients.

Criteria used to define hepatic injury are:

I. Jaundice with hyperbilirubinemia

II. Increase of plasma concentrations of transaminases, alkaline phosphatase, or lactate dehydrogenase

III. Decrease of serum albumin concentration

IV. Prolonged PT.

A disproportionate increase in plasma concentration of total bilirubin, compared with that in alanine transaminase and aspartate transaminase, is found in septic patients [94].

Prothrombin time has been proposed by Le Gall et al. and Smail et al. [95,96] as an early criterion of hepatic injury. They suggest that prothrombin time may be abnormal even when the plasma concentration of bilirubin remains within normal limits. To quantify the degree of hepatic injury, scores with a severity grading have also been proposed (Table 8). These scores measure the worst values observed during the disease. An important limitation is that they do not take into consideration the duration of hepatic injury. These scores are similar to those measured in chronic hepatic diseases. The occurrence of hepatic injury varies markedly among studies. One reason might be that low-grade hyperbilirubinemia and increased hepatic enzyme go unnoticed in many patients without clinical jaundice. When defined by low-grade hyperbilirubinemia and mild hepatic enzyme increase, hepatic injury is as common as pulmonary and renal failure. Hepatic dysfunction is usually mild during septic shock. It can occur 5.7 to 7.6 days after surgery, after pulmonary failure but before cardiovascular failure. In septic patients without preexisting hepatic disease, the plasma bilirubin concentration may become abnormally increased 1 week after the initial injury [97]. Compared with other organ dysfunction, the effect of hepatic injury on mortality rate in intensive care unit patients is controversial. It can be lower or higher than the mortality rate associated with other organ failure [98].

Table 8: Criteria for Hepatic Dysfunction in Multiple Organ Dysfunction Syndrome: Severity Grading Score [147].

					Seventy Grading Some	
Studies	**Patients**	**0**	**1**	**2**	**3**	**4**
Gotb, el al.	92 KU patkitts	ASAT < 25 U/L and ttihrubln <31 prnol/L	25 U/L s ASAT <SO U/1. or s bdirubin <103 pm01/1.	ASAT x993 U/L or		
Carrico, et al. [146]			CheTkal jaundke ClWeal uundke Encephalopathy			
Dellell CI, et al.		13dirubln z 31-51 pin01/1. or liver tests ld Nice normal values IdEsnancionl	Clinical jaundice with bdirubin z137-171 AM01/ I. (as awed failure)			
Saud, et al.	163 trauma patknt.	IdEsnancionl ltshrotnn pmol/L•	68 < Inlirubins 137 'Amin, PT > 2 over control	>137 is mol/1.	PT >4 over control	
Slarshall, et al.	NIEULINE database	Bdirubin 7;20 pn101/L	21 s blllrubin s 60 tonola		61 s Ninitirt s 121 s 133 prnol/L	
Le Call, et al.	FNAS dauhase	Billrubbs <34 prno1/1 and PT s 3F	34 r." Nimbi° < 68 017101/1. and PT > 3s over control		.-t68 pinol/L	
VinCerll, et al.	1440 KU patient	over control Bihrubln -:20 prno1/1.	21 s bfilrubin s 32 prno1/1.		It s biltrubin 101 M/1.	102 tv bilout4n s 204 prnol/1
Stevens, et al.	30 septic patients	LINT and ASAT increascd, normal biluutnn	21 <1,41nobin 7.. 41 pn101/1.		43 -= NOUNS% r; 82 prno1/1.	<billrubm r. B 137 pmo1/1.

Besides the role of hepatic injury on the mortality rate in septic patients, the importance of preexisting normal hepatic function for the survival rate of these patients is emphasized by the fact that underlying hepatic dysfunction is an important risk factor for prognosis. For example, the mortality rate was 100% in a group of cirrhotic patients requiring mechanical ventilation for septic shock [99].

Modifications of hepatic function in sepsis

During experimental sepsis, hepatic plasma concentrations of proteins such as C reactive protein, α_1-antitrypsin, and fibrinogen increase [100]. These acute phase proteins modulate the immunologic functions, repair tissue injury, and have a protective effect on endotoxin- and TNF-α-induced injury [85]. An increased transport of amino acids in hepatocytes is necessary to increase the synthesis of these proteins, and endotoxin has been shown to increase hepatic glutamine [101] and arginine transport. In contrast, concentrations of albumin and transferrin decrease. Hepatic production of urea is also activated in experimental sepsis by the increased uptake of amino acids after the catabolism of proteins in peripheral tissues [102].

Glycogenolysis is increased during sepsis by catecholamines, prostaglandins, and glucagon [103]. Gluconeogenesis initially up regulated by the increased availability of amino acid and lactate is soon reduced because the activity of the limiting enzyme of the pathway (phosphoenolpyruvate carboxykinase) is down-regulated by endotoxin [104]. Consequently, as glucose becomes limited, severe hypoglycemia may occur. Glucose availability may also modify the inflammatory response of the liver because, in Kupffer cells, the release of interleukin-1 (IL-1) is lower when cells are incubated in a glucose-deficient medium than in a normal medium [105].

The reduction of drug biotransformation is another modification encountered during sepsis [106]. Cytokines and NO have been shown to decrease the activity of most cytochrome

P-450 enzymes. Decreased bile flow and diminished bile excretion impair the elimination of various compounds (Moseley RH 1997) (Table 9).

Table 9: Modifications of Hepatic Functions in Sepsis [147].

Hepatic Cells	Function	Modifications
Hepatocytes	Acute phase protein response	Increased
	Amino acid transport	Increased
	Urea production	Increased
	Glycogenolysis	Increased
	Gluconeogenesis	Increased (early sepsis) and decreased (late sepsis)
	Drug biotransformation	Decreased
	Bile formation	Decreased
Kupffer Cells	Endotoxin, cytokine, and bacteria scavenging	Overwhelmed
	Cytokine production	Increased (TNF-α, IL-1, IL1-ra, IL-6)
	O_2-derived radical production	Increased

The liver is also a site of cytokine release, as well as a potent scavenger for extra-hepatic cytokines [86]. In conscious dogs injected with endotoxin, the liver is a major site of TNF-alpha production [107]. Besides TNF-α, endotoxin injection increases the production of IL-1 in Kupffer cells [108]. In the intact liver, IL-1α/β mRNA significantly increases 1-2 h after endotoxin injection, whereas the IL-1 receptor antagonist (IL-1ra) mRNA peaks 2-4 h later [109]. Thus, Kupffer cells produce both pro and anti-inflammatory cytokines. The liver also participates in cytokine clearance. Thus, this organ plays a key role in the inflammatory response during sepsis by both producing and clearing cytokines. During sepsis, oxygen-derived radicals are released by the hepatic macrophages. These radicals are involved in microbial killing but may also induce tissue injury. Superoxide anion release by the liver is enhanced after the IV administration of endotoxin [110].

Thus, numerous hepatic cell functions are modified in experimental sepsis. Whether these modifications are beneficial or deleterious on outcome is speculative. On one hand, acute-phase protein response, bacteria and endotoxin scavenging, and cytokine clearance might be beneficial by decreasing systemic inflammation. On the other hand, decreased biotransformation and hypoglycemia might have deleterious consequences [107].

Oxidative stress after development of post-operative sepsis

Oxidative stress has been studied in patients with systemic inflammatory response syndrome (SIRS), sepsis, and multi-organ failure (MOF). Several studies confirm severe oxidative stress in patients with SIRS as demonstrated by reduced values of plasma total radical-trapping antioxidant parameter (TRAP) and its components (uric acid, protein SH groups, unconjugated bilirubin, vitamin C, vitamin E, and plasma unidentified antioxidants); elevated levels of thiobarbituric acid-reactive substances (TBARS), especially in patients who developed MOF and increased levels of malondialdehyde and 4-hydroxynonenal. Patients with sepsis show an increase in lipid peroxides, malondialdehyde, TBARS and xanthine oxidase activity [73]. Conversely, they present reduced levels of α-tocopherol, selenium, vitamin A,B-carotene, and lycopene and ascorbic acid. Higher levels of lipid peroxidation products and lower plasma selenium and ascorbic acid levels were associated with higher incidence of MOF and worse prognosis [111]. Moreover, plasma antioxidant potential values increased to normal or even supranormal values in patients who survived, whereas they did not in patients who died [112]. TNF-α induced oxidative stress occurs as a result of bacterial or endotoxin translocation under conditions of reduced reticuloendothelial system (RES) function in various disease states. In addition, the intracellular Ca^+ or Zn levels may participate, at least in part, in free radical formation in endotoxin poisoned mice [113] (Figure 3).

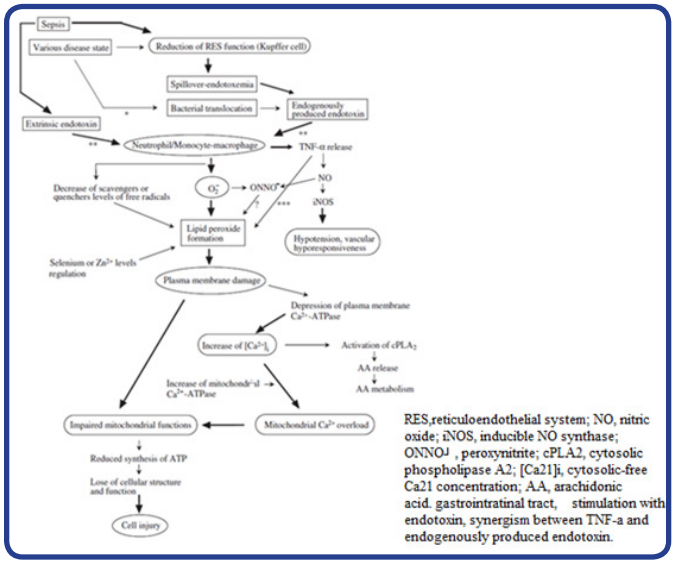
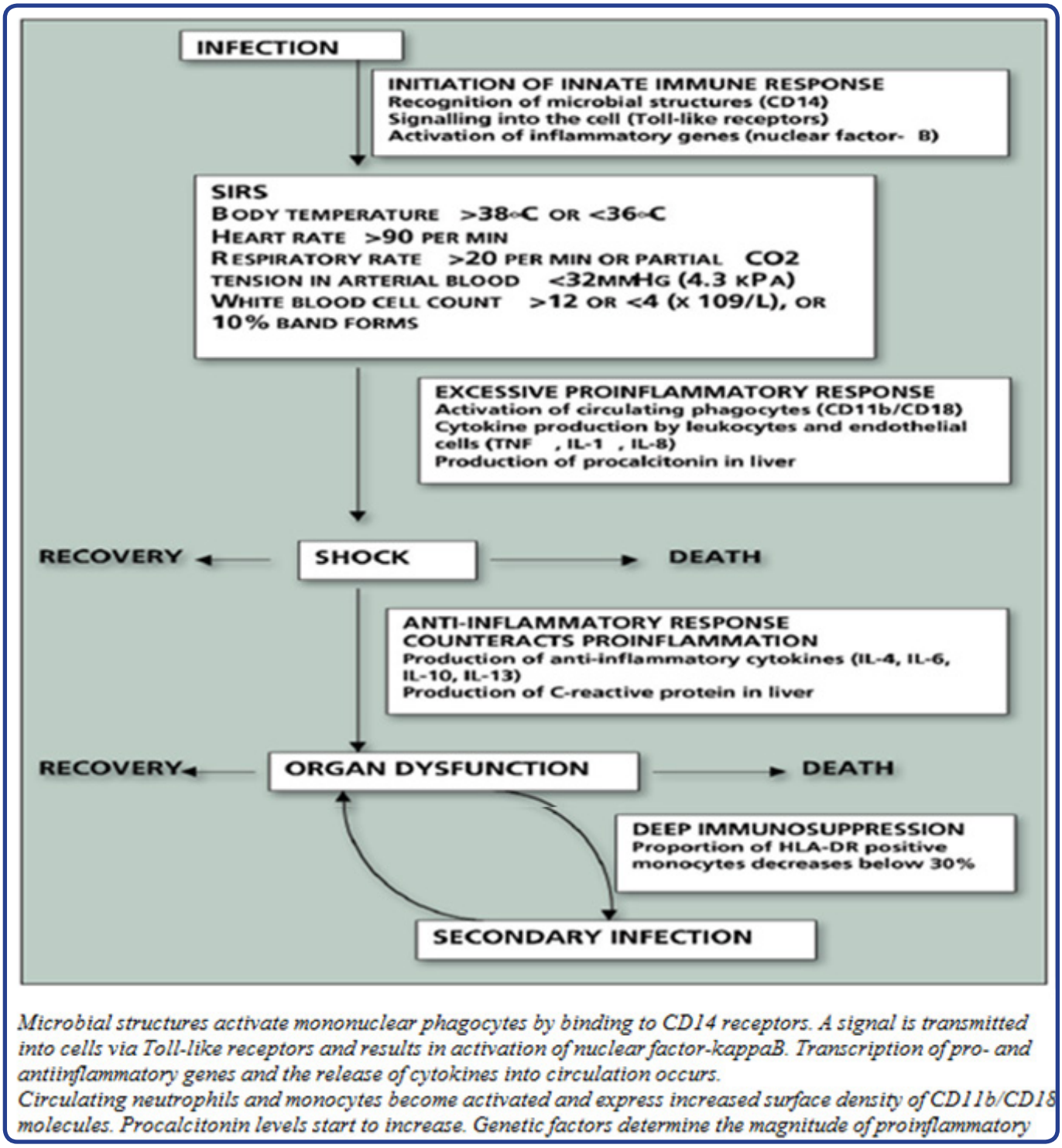


Figure 3: Hypothetical schematic of endotoxin induced oxidative stress in the liver [135].

Chapter 3

Management of Post-Operative Sepsis & Liver Support



Microbial structures activate mononuclear phagocytes by binding to CD14 receptors. A signal is transmitted into cells via Toll-like receptors and results in activation of nuclear factor-kappaB. Transcription of pro- and antiinflammatory genes and the release of cytokines into circulation occurs.
Circulating neutrophils and monocytes become activated and express increased surface density of CD11b/CD18 molecules. Procalcitonin levels start to increase. Genetic factors determine the magnitude of proinflammatory

Figure 4: Clinical events in the evolution of a complicated course of sepsis and concurrent steps in activation of the innate immune system [136].

Host response to local tissue injury includes identification, isolation, neutralization and elimination of the offending agent, and subsequent repair and healing. Inflammatory cells are recruited and activated as a consequence of cytokines. This process may become exuberant if tissue is extensively injured. A systemic inflammatory response may develop and is associated with stereotypic changes in multiple organ systems function, and is known as the systemic inflammatory response syndrome (SIRS). An older term 'sepsis' applies most specifically when the systemic inflammatory response is triggered by infection. Severe SIRS is associated with shock and is called 'septic shock'. Sepsis is the most common cause of ICU mortality [1]. The liver contains a large concentration of fixed tissue macrophages (Kuppfer cells). When the liver is injured, cytokines are released. Ongoing injury results in fibrosis and may eventuate in cirrhosis. Portal blood flow, draining the mesentery and the spleen, and representing

nearly 25% of the cardiac output, is diverted into the systemic circuit as a consequence of high intra-hepatic resistance. Thus, the filtration function of the liver is compromised and eventually lost. This results in systemic circulation of endotoxin and cytokines that are usually cleared by the liver. Liver injury results in SIRS, sepsis Multiple organ system dysfunction includes the brain and peripheral nervous system (hepatic encephalopathy), cardiovascular impairment (four-chamber enlargement with decreased ejection fraction, loss of arterial tone), acute lung injury (ALI)/adult respiratory distress syndrome (ARDS), acute renal failure [hepatorenal syndrome (HRS)], bone marrow suppression and depressed infection surveillance with increased susceptibility to infection [114].

Clinical Features of Sepsis

SIRS characterized by the presence of two or more of the following:

- Fever (>38 °C) or hypothermia (<35 °C).
- Tachycardia (heart rate>90 beats/min).
- Tachypnea (respiratory rate>20 breaths/min).
- Leukocytosis>12 or leucopenia <4(×10^9/L).
- Tension in arterial blood < 32mmHg.

With progression to SEVERE SEPSIS, there are features of compromised end organ perfusion (Figure 4).

Severe sepsis (one or more of the following) (Figure 5)

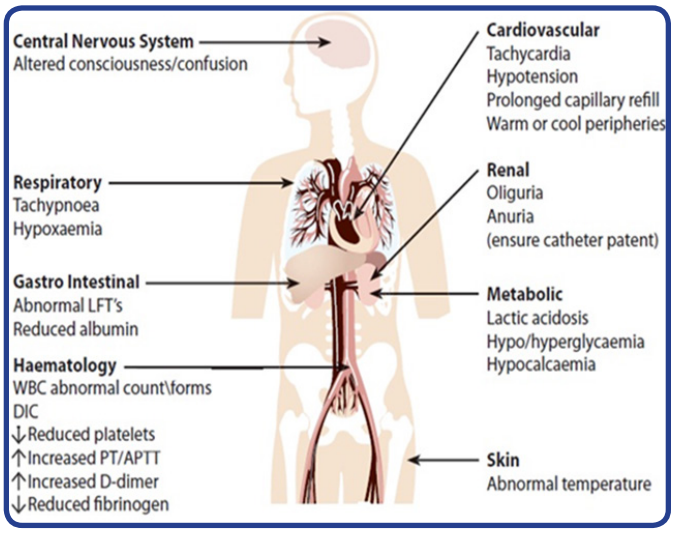


Figure 5: Findings in severe sepsis [136].

a) Neurological manifestations: altered sensorium, irritability, agitation, confusion, unresponsiveness or coma.

b) Respiratory manifestations: tachypnea, increase breathing effort, apnea/respiratory arrest, cyanosis (late sign).

c) Renal manifestations: oliguria less than 0.5ml/kg per hour

- Mottled skin.
- Impaired capillary refill (0.3 s).
- Hyperlactacemia (>2mmol/l).
- Thrombocytopenia (<100,000 platelets/ml).
- Disseminated intravascular coagulation.
- Cardiac dysfunction.

d) Septic shock: features of warm or cold shock [115]:

Warm shock	Cold shock
Peripheries	warm, flushed
Capillary refill	< 2 sec
Pulse	bounding
Heart rate	tachycardia
Blood pressure	relatively maintained
Pulse pressure	widened

e) Refractory septic shock: Normotension requires high-dose vasopressor infusion despite fluid resuscitation [115]

Sepsis biomarkers

A multitude of biomarkers has been proposed in the field of sepsis, many more than in other disease processes [116]. This large difference in the numbers of biomarkers for sepsis is likely to be related to the very complex pathophysiology of sepsis, which involves many mediators of inflammation, but also other pathophysiological mechanisms. Coagulation, complement, contact system activation, inflammation and apoptosis are all involved in the sepsis process, and separate markers for each (part of each) system have been proposed [117].

Additionally, the systemic nature of sepsis and the large numbers of cell types, tissues and organs involved expand the number of potential biomarker candidates, compared with disease processes that involve individual organs or are more localized. Additionally, as the sepsis response varies with time, the exact time period during which any specific biomarker may be useful varies, and this is difficult to assess reliably in experimental models. Moreover, as there is no 'gold standard' for the diagnosis of sepsis, the effectiveness of a biomarker needs to be compared with current methods used to diagnose and monitor sepsis in everyday clinical practice, i.e., by the combination of clinical signs and available laboratory variables; experimental models cannot be used for this purpose. The diagnosis of sepsis is a challenge. Clinical and standard laboratory tests are not very helpful because most critically ill patients develop some degree of inflammatory response, whether or not they have sepsis. Even microbiological assessment is unreliable because many culture samples do not yield microorganisms in these patients [118]. However, biomarkers have also not been shown to be a great asset in the diagnosis of sepsis. Indeed, relatively few biomarkers have been evaluated as diagnostic markers [118].

C-reactive Protein and Procalcitonin

Perhaps the most widely used markers at present are C-reactive protein (CRP) and procalcitonin (PCT). CRP was first described in the early 1930s, and CRP levels are widely used as a relatively non-specific marker of inflammation. Many studies have demonstrated increased CRP levels in patients with sepsis;

increasing or persistently high levels suggest a poor prognosis, while declining values are associated with a more favorable prognosis [119]. PCT was described more recently and is not routinely measured in all hospital laboratories. PCT levels have been shown to correlate with the severity of sepsis as measured by the acute physiology and chronic health evaluation (APACHE) II or sequential organ failure assessment (SOFA) scores [120], and a recent meta-analysis reported that PCT was more sensitive and specific than CRP for differentiating bacterial from non-infective causes of inflammation In addition, PCT is produced and cleared more rapidly than CRP, making it potentially more useful for identifying infection early and for following the progress of disease [121]. Using a new sensitive and rapid PCT assay, Christ-Crain, et al. [121] have shown that PCT-guided therapy can reduce total antibiotic exposure and antibiotic treatment duration in patients with community-acquired pneumonia [122].

Cytokines

Another group of potential markers is the cytokines. As key mediators of the sepsis response, the cytokines would seem to be ideal candidates, and many have been proposed, including tumor necrosis factor (TNF) and several interleukins, including interleukin (IL)-6, IL-8 (CXCL8), IL-10, and IL-18. However, although the concentrations of these cytokines are raised in patients with sepsis and have been correlated with outcome, none of these cytokines is specific for sepsis, being raised in other inflammatory disease processes. In addition, the degree to which levels increase varies over time, making implementation as a marker less useful. In addition, measurement techniques for individual cytokines are usually time-consuming and expensive [123].

CD64

CD64 expression on the neutrophil membrane is up regulated in response to pro inflammatory cytokines, and neutrophil CD64 expression has been reported to have good sensitivity and specificity for a diagnosis of sepsis in several studies [124].

Soluble Triggering Receptor Expressed on Myeloid Cells

Expression of soluble triggering receptor expressed on myeloid cells (sTREM)-1 is up regulated in the presence of bacteria or fungi, but not in non-infectious inflammatory diseases, and levels of sTREM-1 are elevated in patients with sepsis [125]. Gibot, et al. [126] showed that sTREM-1 was more sensitive and specific for infection than other markers, including CRP, PCT, TNF, and IL-1β. In addition, a decrease in STREM-1 levels over time was associated with a favorable outcome, suggesting a potential place in tracking response to therapy [126].

Macrophage Migration Inhibitory Factor

Macrophage migration inhibitory factor (MIF) is a mediator of sepsis, which induces the production of various pro-inflammatory mediators by modulating the expression of toll-like receptor 4 (TLR4) [127]. MIF levels are raised in patients with sepsis and correlate with outcome, and higher levels have been associated with development of sepsis after cardiac surgery [128]. However, MIF levels are also raised in non-septic, critically ill patients, and in non-infectious inflammatory diseases [129].

Microarrays and multiplex panels

It is increasingly recognized that, given the complexities of the sepsis response, the likelihood of finding a single 'magic bullet' marker of sepsis is remote. However, sampling of multiple individual markers is time-consuming and requires considerable amounts of blood from the patient. An alternative approach to the combination of individual diagnostic markers and measures is, therefore, the use of microarrays and multiplexes. Genomic and proteomic techniques have advanced hugely in the last few years, enabling microarrays for multiple proteins, DNA probes, and antibodies to be multiplexed onto miniaturized diagnostic assays. Using small samples of blood, the individual patient profiles produced can be translated using bioinformatics into a diagnostic index for that patient [130]. Repeated sampling could assess changes in the profile over time, theoretically allowing treatments to be adapted accordingly [131]. Such systems are already being applied to many disease processes. In addition to continuing to improve the necessary biochemical and bioinformatic technology, challenges for the future will be to determine which specific combinations of biomarkers should be included in multiplexes, and whether adjusting treatment according to multiplex-derived profiles will indeed improve outcomes [132].

Scoring and Staging

Table 10: L The infection propability score [133].

Variable	0	1	2	3	6	8	10
Temperature °C	<37.5		>37.5				
C-reactive protein, mg/dl	<6				>6		
WBC, cells/mm'	5-12	>12		<5			
Heart rate, beats/min	<80					81-140	>140
Respiratory rate, breaths/min	<25	>25					
SOFA	<5		>5				

Peres Bota, et al. [133] devised a so-called infection probability score using statistical logistic regression techniques. The score incorporates five variables routinely associated with the presence of infection (temperature, heart rate, respiratory rate, white blood cell count, and SOFA score) and assigned each a weighted score ranging from 0 to 26 (Table 10). Using a cutoff value of 14 points, the infection probability score had a positive predictive value for infection of 53.6% and a negative predictive value of 89.5%. With a score less than 14, patients had only a 10% chance of having an infection. As new biomarkers and even microarray systems are developed, such scores could be adapted to provide a more accurate probability of infection [133].

Management of Severe Sepsis

Initial resuscitation

During the first 6 hrs of resuscitation, the goals of initial resuscitation of sepsis-induced

hypoperfusion should include all of the following as one part of a treatment protocol :

I. Central venous pressure (CVP): 8–12mm Hg.

II. Mean arterial pressure (MAP) ≥ 65mm Hg.

III. Urine output ≥ 0.5mL.kg^{-1}.hr^{-1}.

IV. Central venous (superior vena cava) or mixed venous oxygen saturation ≥ 70% or ≥ 65%, respectively [83].

Early goal-directed resuscitation has been shown to improve survival for emergency department patients presenting with septic shock in a randomized, controlled, single-center study. Resuscitation directed toward the previously mentioned goals for the initial 6-hr period of the resuscitation was able to reduce 28-day mortality rate [83]. The consensus panel judged use of central venous and mixed venous oxygen saturation targets to be equivalent. Either intermittent or continuous measurements of oxygen saturation were judged to be acceptable. Although blood lactate concentration may lack precision as a measure of tissue metabolic status, elevated levels in sepsis support aggressive resuscitation. In mechanically ventilated patients or patients with known pre-existing decreased ventricular compliance, a higher target CVP of 12–15mm Hg is recommended to account for the impediment to filling. Elevated central venous pressures may also be seen with pre-existing clinically significant pulmonary artery hypertension. Although the cause of tachycardia in septic patients may be multifactorial, a decrease in elevated pulse rate with fluid resuscitation is often a useful marker of improving intravascular filling. Recently published observational studies have demonstrated an association between good clinical outcome in septic shock and MAP ≥ 65mm Hg as well as central venous oxygen saturation (ScvO2, measured in superior vena cava, either intermittently or continuously) of ≥ 70% [134].

During the first 6 hrs of resuscitation of severe sepsis or septic shock, if $SCVO_2$ or SvO_2 of 70% or 65% respectively is not achieved with fluid resuscitation to the CVP target, then transfusion of packed red blood cells to achieve a hematocrit of ≥ 30% and/or administration of a dobutamine infusion (up to a maximum of 20 μg.kg^{-1}.min^{-1}) be utilized to achieve this goal. The protocol used in the study cited previously targeted an increase in SCVO2 to ≥ 70%. This was achieved by sequential institution of initial fluid resuscitation, then packed red blood cells, and then dobutamine. This protocol was associated with an improvement in survival. Based on bedside clinical assessment and personal preference, a clinician may deem either blood transfusion (if Hct is less than 30%) or dobutamine the best initial choice to increase oxygen delivery and thereby elevate $SCVO_2$. When fluid resuscitation is believed to be already adequate. The design of therefore mentioned trial did not allow assessment of the relative contribution of these two components (i.e. increasing O_2 content or increasing cardiac output) of the protocol on achievement of improved outcome [83].

Diagnosis

Obtaining appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay in antibiotic administration. To optimize identification of causative organisms, at least two blood cultures be obtained prior to antibiotics with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently (<48 h) inserted. Cultures of other sites (preferably quantitative where appropriate) such as urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection should also be obtained before antibiotic therapy if not associated with significant delay in antibiotic administration. In patients with indwelling catheters (for 48 h) at least one blood culture should be drawn through each lumen of each vascular access device. Obtaining blood cultures peripherally and through a vascular access device is an important strategy. If the same organism is recovered from both cultures, the likelihood that the organism is causing the severe sepsis is enhanced. Imaging studies be performed promptly in attempts to confirm a potential source of infection. Diagnostic studies may identify a source of infection that requires removal of a foreign body or drainage to maximize the likelihood of a satisfactory response to therapy.

Antibiotic therapy

Intravenous antibiotic therapy should be started as early as possible and within the first hour of recognition of septic shock and severe sepsis without septic shock. Appropriate cultures should be obtained before initiating antibiotic therapy, but should not prevent prompt administration of antimicrobial therapy. In the presence of septic shock each hour delay in achieving administration of effective antibiotics is associated with a measurable increase in mortality [135].

In choosing the antimicrobial regimen, clinicians should be aware that some antimicrobial agents have the advantage of bolus administration, while others require a lengthy infusion. The choice of empirical antibiotics depends on complex issues related to the patient's history including drug intolerances, underlying disease, the clinical syndrome, and susceptibility patterns of pathogens in the community, in the hospital, and that previously have been documented to colonize or infect the patient [136]. Because patients with severe sepsis or septic shock have little margin for error in the choice of therapy, the initial selection of antimicrobial therapy should be broad enough to cover all likely pathogens. There is evidence that failure to initiate appropriate therapy with activity against the pathogen that is subsequently identified as the causative agent correlates with increased morbidity and mortality [137]. All patients should receive a full loading dose of each antimicrobial. However, patients with sepsis or septic shock often have abnormal renal or hepatic function and may have abnormal volumes of distribution due to aggressive fluid resuscitation. Drug serum concentration monitoring can be useful in an ICU setting for those drugs that can be measured promptly. An experienced physician or clinical pharmacist should be consulted to ensure that serum concentrations are attained that maximize efficacy and minimize toxicity [138].

Narrowing the spectrum of antibiotic coverage and reducing the duration of antibiotic therapy will reduce the likelihood that the patient will develop superinfection with pathogenic or resistant organisms such as Candida species, Clostridium difficile, or vancomycin-resistant Enterococcus faecium. However, the desire to minimize superinfections and other complications should not take precedence over the need to give the patient an

adequate course of therapy to cure the infection that caused the severe sepsis or septic shock. the duration of therapy typically be 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, or who have immunologic deficiencies including neutropenia. If the presenting clinical syndrome is determined to be due to a noninfectious cause, antimicrobial therapy be stopped promptly to minimize the likelihood that the patient will become infected with an antibiotic resistant pathogen or will develop a drug related adverse effect [139].

Source Control

All patients presenting with severe sepsis should be evaluated for the presence of a focus of infection amenable to source control measures, specifically the drainage of an abscess or local focus of infection, the debridement of infected necrotic tissue, the removal of a potentially infected device, or the definitive control of a source of ongoing microbial contamination. The principles of source control in the management of sepsis include a rapid diagnosis of the specific site of infection, and identification of a focus of infection amenable to source control measures (specifically the drainage of an abscess, the debridement of infected necrotic tissue, the removal of a potentially infected device, and the definitive control of a source of ongoing microbial contamination) [140]. Foci of infection readily amenable to source control measures include an intra-abdominal abscess or gastrointestinal perforation, cholangitis or pyelonephritis, intestinal ischemia or necrotizing soft tissue infection, and other deep space infection such as an empyema or septic arthritis. Such infectious foci should be controlled as soon as possible following successful initial resuscitation [141], accomplishing the source control objective with the least physiologic upset possible (e. g., percutaneous rather than surgical drainage of an abscess, endoscopic rather than surgical drainage of biliary tree), and removing intravascular access devices that are potentially the source of severe sepsis or septic shock promptly after establishing other vascular access [142]. The selection of optimal source control methods must weigh benefits and risks of the specific intervention as well as risks of transfer .Source control interventions may cause further complications such as bleeding, fistulas, or inadvertent organ injury. Surgical intervention should be considered when lesser interventional approaches are inadequate, or when diagnostic uncertainty persists despite radiological evaluation. Specific clinical situations require consideration of available choices, patient's preferences, and clinician's expertise [142].

Fluid therapy

Previous meta-analyses of small studies of ICU patients had demonstrated no difference between crystalloid and colloid fluid resuscitation [143]. Although administration of hydroxyethyl starch may increase the risk of acute renal failure in patients with sepsis variable findings preclude definitive recommendations. Many studies indicated albumin administration was safe and equally effective as crystalloid [144]. There was an insignificant decrease in mortality rates with the use of colloid in a subset analysis of septic patients. As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same end points and results in more edema. fluid resuscitation initially target a CVP of at least 8 mm Hg (12 mm Hg in mechanically ventilated patients). Further fluid therapy is often required. a fluid challenge technique be applied, wherein fluid administration is continued as long as the hemodynamic improvement (e. g., arterial pressure, heart rate, urine output) continues. Fluid challenge in patients with suspected hypovolemia should be started with at least 1000 mL of crystalloids or 300–500mL of colloids over 30 min. More rapid administration and greater amounts of fluid may be needed in patients with sepsis induced tissue hypoperfusion. The rate of fluid administration should be reduced substantially when cardiac filling pressures (CVP or pulmonary artery balloon-occluded pressure) increase without concurrent hemodynamic improvement. Fluid challenge must be clearly separated from simple fluid administration; it is a technique in which large amounts of fluids are administered over a limited period of time under close monitoring to evaluate the patient's response and avoid the development of pulmonary edema. The degree of intravascular volume deficit in patients with severe sepsis varies. With venodilation and ongoing capillary leak, most patients require continuing aggressive fluid resuscitation during the first 24 hours of management. Input is typically much greater than output, and input/output ratio is of no utility to judge fluid resuscitation needs during this time period [143].

Vasopressors

Vasopressor therapy is required to sustain life and maintain perfusion in the face of life-threatening hypotension, even when hypovolemia has not yet been resolved. Below a certain mean arterial pressure, autoregulation in various vascular beds can be lost, and perfusion can become linearly dependent on pressure. Thus, some patients may require vasopressor therapy to achieve a minimal perfusion pressure and maintain adequate flow [145]. The titration of norepinephrine to as low as MAP 65 mm Hg has been shown to preserve tissue perfusion [146]. In addition, pre-existing comorbidities should be considered as to most appropriate MAP target. For example, a MAP of 65 mm Hg might be too low in a patient with severe uncontrolled hypertension, and in a young previously normotensive, a lower MAP might be adequate. Supplementing end points such as blood pressure with assessment of regional and global perfusion, such as blood lactate concentrations and urine output, is important. Adequate fluid resuscitation is a fundamental aspect of the hemodynamic management of patients with septic shock, and should ideally be achieved before vasopressors and inotropes are used, but using vasopressors early as an emergency measure in patients with severe shock is frequently necessary. When that occurs great effort should be directed to weaning vasopressors with continuing fluid resuscitation. There is no high-quality primary evidence to recommend one catecholamine over another. Much literature exists that contrasts the physiologic effects of choice of vasopressor and combined inotrope/vasopressors in septic shock [147].

Human and animal studies suggest some advantages of norepinephrine and dopamine over epinephrine (the latter with the potential for tachycardia as well as disadvantageous effects on splanchnic circulation an hyperlactemia) and phenylephrine (decrease in stroke volume). There is, however,

no clinical evidence that epinephrine results in worse outcomes, and it should be the first chosen alternative to dopamine or norepinephrine. Phenylephrine is the adrenergic agent least likely to produce tachycardia, but as a pure vasopressor would be expected to decrease stroke volume. Dopamine increases mean arterial pressure and cardiac output, primarily due to an increase in stroke volume and heart rate. Norepinephrine increases mean arterial pressure due to its vasoconstrictive effects, with little change in heart rate and less increase in stroke volume compared with dopamine. Either may be used as a first-line agent to correct hypotension in sepsis. Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia and may be more arrhythmogenic [148]. It may also influence the endocrine response via the hypothalamic-pituitary axis and have immunosuppressive effects. Vasopressin levels in septic shock have been reported to be lower than anticipated for a shock state [149]. Low doses of vasopressin may be effective in raising blood pressure in patients refractory to other vasopressors, and may have other potential physiologic benefits [150].

Studies show that vasopressin concentrations are elevated in early septic shock, but with continued shock, concentration decreases to normal range in the majority of patients between 24 and 48 hrs [151]. This has been called "relative vasopressin deficiency" because in the presence of hypotension, vasopressin would be expected to be elevated.

Inotropic therapy

Dobutamine is the first-choice inotrope for patients with measured or suspected low cardiac output in the presence of adequate left ventricular filling pressure (or clinical assessment of adequate fluid resuscitation) and adequate mean arterial pressure. Septic patients who remain hypotensive after fluid resuscitation may have low, normal, or increased cardiac outputs. Therefore, treatment with a combined inotrope/vasopressor such as norepinephrine or dopamine is recommended if cardiac output is not measured. When the capability exists for monitoring cardiac output in addition to blood pressure, a vasopressor such as norepinephrine may be used separately to target specific levels of mean arterial pressure and cardiac output [152].

Corticosteroids

One french multi-center, randomized, controlled trial (RCT) of patients in vasopressor-unresponsive septic shock (hypotension despite fluid resuscitation and vasopressors) showed a significant shock reversal and reduction of mortality rate in patients with relative adrenal insufficiency [153]. Two additional smaller RCTs also showed significant effects on shock reversal with steroid therapy [154]. However, a recent large, European multicenter trial (CORTICUS), which has been presented in abstract form but not yet published, failed to show a mortality benefit with steroid therapy of septic shock [155]. CORTICUS did show a faster resolution of septic shock in patients who received steroids. The use of the ACTH test (responders and nonresponders) did not predict the faster resolution of shock. Importantly, unlike the French trial, which only enrolled shock patients with blood pressure unresponsive to vasopressor therapy, the CORTICUS study included patients with septic shock, regardless of how the blood pressure responded to vasopressors. Although corticosteroids do appear to promote shock reversal, the lack of a clear improvement in mortality-coupled with known side effects of steroids such a increased risk of infection and myopathy-generally tempered enthusiasm for their broad use. There was considerable discussion and consideration by the committee on the option of encouraging use in those patients whose blood pressure was unresponsive to fluids and vasopressors, while strongly discouraging use in subjects whose shock responded well to fluids and pressors. There has been no comparative study between a fixed duration and clinically guided regimen, or between tapering and abrupt cessation of steroids. Three RCTs used a fixed duration protocol for treatment [155], and in two RCTs, therapy was decreased aftershock resolution. In four RCTs steroids were tapered over several days [156], and in two RCTs steroids were withdrawn abruptly. One cross-over study showed hemodynamic and immunologic rebound effects after abrupt cessation of corticosteroids. It remains uncertain whether outcome is affected by tapering of steroids or not [157].

Blood product administration

Although the optimum hemoglobin for patients with severe sepsis has not been specifically investigated, the Transfusion Requirements in Critical Care trial suggested that a hemoglobin of 7–9 g/dL when compared to 10–12 g/dL was not associated with increased mortality rate in adults [158].

Red blood cell transfusion in septic patients increases oxygen delivery but does not usually increase oxygen consumption [159]. This transfusion threshold of 7 g/dL contrasts with the early goal-directed resuscitation protocol that uses a target hematocrit of 30% in patients with low SCVO2 (measured in superior vena cava) during the first 6 hrs of resuscitation of septic shock.

No specific information regarding erythropoietin use in septic patients is available, but clinical trials in critically ill patients show some decrease in red cell transfusion requirement with no effect on clinical outcome [160]. The effect of erythropoietin in severe sepsis and septic shock would not be expected to be more beneficial than in other critical conditions. Patients with severe sepsis and septic shock may have coexisting conditions that do warrant use of erythropoietin.

Although clinical studies have not assessed the impact of transfusion of fresh frozen plasma on outcomes in critically ill patients, professional organizations have recommended fresh frozen plasma for coagulopathy when there is a documented deficiency of coagulation factors (increased prothrombin time, international normalized ratio, or partial thromboplastin time) and the presence of active bleeding or before surgical or invasive procedures [161]. In addition, transfusion of fresh frozen plasma in nonbleeding patients with mild abnormalities of prothrombin time usually fails to correct the prothrombin time [162]. In patients with severe sepsis, platelets should be administered when counts are < 5000/mm3 regardless of apparent bleeding. Platelet transfusion may be considered when counts are 5,000–30,000/mm^3 and there is significant risk of bleeding. Higher platelet counts (≥ 50,000/mm^3 (50 × 109/L) are typically required

for surgery or invasive procedures. Guidelines for transfusion of platelets are derived from consensus opinion and experience in patients undergoing chemotherapy. Recommendations take into account the etiology of thrombocytopenia, platelet dysfunction, risk of bleeding, and presence of concomitant disorders [163].

Supportive Therapy of Severe Sepsis

A. Ventilatory Support

i. Noninvasive ventilatory support

Many patients require more support than a passive O_2 delivery device. Several noninvasive ventilatory interventions can support oxygenation and ventilation, and possibly obviate the need for endotracheal intubation and mechanical ventilation. Intermittent positive pressure breathing aids in clearance of secretions but is labor intensive and, because it is not continuously applied, does not permanently recruit alveoli. Continuous positive airway pressure (CPAP) applied by a tight-fitting mask can maintain and restore functional residual capacity and, therefore, provides a temporary salutary effect on oxygenation as the underlying cause of hypoxia is treated. Bilevel positive airway pressure (BiPAP) also uses a tight-fitting mask, but requires a ventilator to deliver a high airway pressure during spontaneous patient-initiated breaths and a lower baseline pressure during exhalation (like PEEP). It may provide enough assistance to prevent fatigue and stave off endotracheal intubation. Similar to CPAP, BiPAP should be considered a short-term therapy that allows for the identification and treatment of the underlying derangement. Continued close monitoring is necessary for patients on CPAP and BiPAP because their condition may deteriorate precipitously.

ii. Mechanical ventilation

Over the past yrs, several multi-center randomized trials have been performed to evaluate the effects of limiting inspiratory pressure through moderation of tidal volume [164]. These studies showed differing results that may have been caused by differences between airway pressures in the treatment and control groups [165]. The largest trial of a volume and pressure-limited strategy showed a 9% decrease of all-cause mortality in patients with ALI or ARDS ventilated with tidal volumes of 6 mL/kg of predicted body weight (PBW), as opposed to 12 mL/kg, and aiming for a plateau pressure ≤ 30 cm H_2O. The use of lung protective strategies for patients with ALI is supported by clinical trials and has been widely accepted, but the precise choice of tidal volume for an individual patient with ALI may require adjustment for such factors as the plateau pressure achieved, the level of PEEP chosen, the compliance of the thoraco-abdominal compartment and the vigor of the patient's breathing effort. Some clinicians believe it may be safe to ventilate with tidal volumes higher than 6 ml/kg PBW as long as the plateau pressure can be maintained ≤ 30 cm H_2O [166]. The validity of this ceiling value will depend on breathing effort, as those who are actively inspiring generate higher trans-alveolar pressures for a given plateau pressure than those who are passively inflated. Conversely, patients with very stiff chest walls may require plateau pressures higher than 30 cm H_2O to meet vital clinical objectives. No single mode of ventilation (pressure control, volume control, airway pressure release ventilation, high frequency ventilation, etc.) has been consistently shown advantageous when compared with any other that respects the same principles of lung protection. The semirecumbent position has been demonstrated to decrease the incidence of ventilator-associated pneumonia (VAP). Enteral feeding increased the risk of developing VAP; 50% of the patients who were fed en-enterally in the supine position developing VAP [167].

B. Sedation, analgesia, and neuromuscular blockade in sepsis

Although not specifically studied in patients with sepsis, the administration of intermittent sedation, daily interruption, and retitration or systemic titration to a predefined end point have been demonstrated to decrease the duration of mechanical ventilation [168]. Patients receiving neuromuscular blocking agents (NMBAs) must be individually assessed regarding discontinuation of sedative drugs because neuromuscular blocking drugs must also be discontinued in that situation. The use of intermittent vs. continuous methods for the delivery of sedation in critically ill patients has been examined. An observational study of mechanically-ventilated patients showed that patients receiving continuous sedation had significantly longer durations of mechanical ventilation and ICU and hospital length of stay [169].

Similarly, a prospective, controlled study in 128 mechanically-ventilated adults receiving continuous intravenous sedation demonstrated that a daily interruption in the "continuous" sedative infusion until the patient was awake decreased the duration of mechanical ventilation and ICU length of stay (Figure 6) [170].

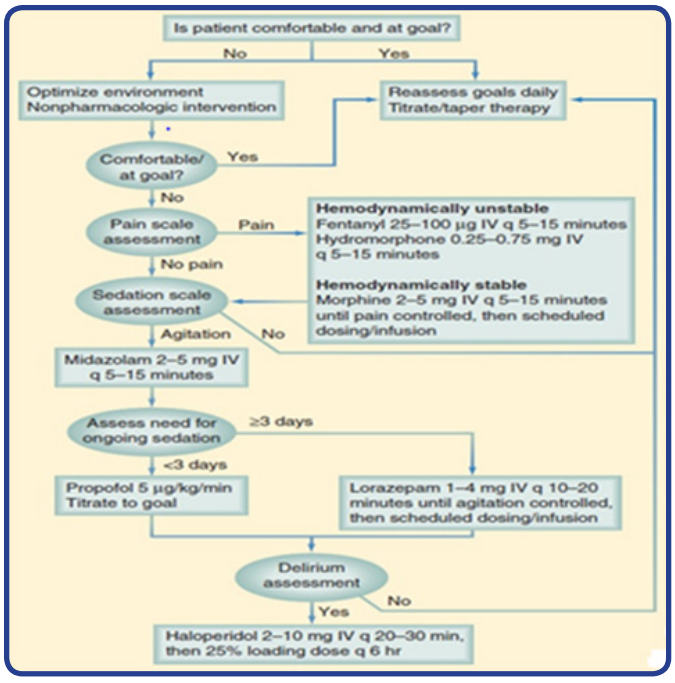


Figure 6: Algorithm for analgesia and sedation in the ICU [137].

Summary

Sepsis, which is the host response to infection, is a complex pathophysiological state characterized by the release of many proinflammatory and anti-inflammatory and pro-coagulant and

anticoagulant substances in response to pathogens. One can identify three stages of severity, namely sepsis, severe sepsis (when acute organ failure is attributed to sepsis) and septic shock (when refractory hypotension requires the use of vasopressor agents).

More than 40 million major surgical operations are performed annually in the United States of which 800,000 to two million are complicated by surgical site infections. Surgery patients can be defined as a high risk group for developing sepsis, as procedures evoke substantial metabolic, hematologic, and immunologic responses.

In sepsis, the liver participates in host defense and tissue repair through hepatic cell cross-talk that controls most of the coagulation and inflammatory processes. When this control is not adequate, a secondary hepatic dysfunction may occur and may sometimes lead to bacterial products spillover, enhanced pro coagulant and inflammatory processes, and in turn, multiple organ failure and death.

The mortality due to septic shock is high. Intense systemic inflammatory response, and anti-inflammatory reaction induced by it, co-occur and contribute to poor prognosis of patients with septic shock. The use of markers of systemic inflammation may help to identify patients at risk of a complicated course of sepsis at an early stage of disease. A combination that includes markers of both systemic inflammation and immune suppression would be useful when choosing between suppressive and stimulatory immunotherapies.

Reducing mortality due to severe sepsis requires an organized process that guarantees early recognition and consistent application of evidence-based practices.

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