TRAUMA

Trauma-related sepsis and multiple organ failure: Current concepts in the diagnosis and management

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Summary  Like other critical illnesses, severe traumatic injury is closely associated with the onset of a systemic inflammatory response, sepsis and progressive multiple organ dysfunction, which is the leading cause of death in intensive care units. Increased insight into the complex pathogenesis of this disease process has resulted in the development of a number of therapeutic interventions. This article outlines key mechanisms in the onset of sepsis and multiple organ dysfunction syndrome, as well as a more recent concept of treatment aimed at preventing the progress of those complications and decreasing mortality.

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Introduction

Traumatic injuries are the leading cause of death in persons aged under 30, and the third highest in the total population, following coronary and malignant diseases.1 Mortality of the traumatised has a tri-modal distribution,2 although this has recently been challenged. Thus, 45% of the injured die immediately in the first few minutes at the accident site. With the development of resuscitation procedures and the introduction of damage control operations that decrease the problems of hypothermia, acidosis and coagulopathy,3 mortality in the first 24h has been decreased. However, mortality in the following days and weeks from the effects of sepsis and multiple organ insufficiency remains high (45%). There is a close relationship between trauma, hemorrhagic shock, Systemic Inflammatory Response Syndrome (SIRS), sepsis and Multiple Organ Dysfunction Syndrome (MODS). Despite better management of the traumatised and some understanding of the pathogenesis of sepsis and the etiology of MODS, mortality due to those latter complications is still high. In recent years, several therapeutic interventions have been shown to reduce mortality but population heterogeneity and the generalised definitions of inflammatory response and sepsis, which are currently under review,4 have constituted a major problem.

Pathophysiology

Two patterns of MODS can emerge. A massive traumatic insult may lead to severe systemic
hyperinflammation and early MODS (one-hit model or primary MODS), or progressive MODS may follow sequential insults (two-hit model, secondary MODS). The second insult is presumed to be any untoward event or added stress that overpowers the host’s capacity to generate an appropriate response. The exact mechanisms for dysfunction are unknown. Progressive dysfunction of increasing numbers of organs correlates with mortality by approximately 20% for each additional organ dysfunction. Two types of cell death have been identified—necrosis and apoptosis. Necrosis occurs in response to direct trauma and/or hypoperfusion/reperfusion injury. The expression of apoptosis is altered in all critical illnesses. Apoptosis of lymphocytes and gut epithelial cells is increased, whereas that of neutrophils is delayed. Excessive apoptosis has been implicated as a cause of liver, kidney, and cardiac dysfunction. Much organ dysfunction in patients with sepsis can be explained by “cell hibernation” or “cell stunning”. Sepsis is the most common cause of progression of MODS.

In the post-resuscitation stage, patients with severe trauma go through phases of uncontrolled hyperinflammation and immunosuppression with dysregulation in relation to SIRS/Compensatory Anti-inflammatory Response Syndrome (CARS). The response type is determined by the intensity of the trauma and numerous other factors constituting predisposition: age, previous state and coexisting diseases, genetic factors, virulence of pathogenic organisms and inoculum size.

In the hyperinflammation stage, proinflammatory mediators are released from activated monocytes and the complex of leukocytes and endothelial cells. The released cytokines (tumour necrosis factor-alfa (TNFa) and interleukins IL-2, IL-6, IL-8, coagulation factors and activated complement) stimulate the production of secondary mediators. The action of these mediators leads to a hyperdynamic, hypermetabolic state with diffuse microvascular lesions, formation of microthrombi and the loss of vasoregulation in microvascular vessels.

Trauma patients are very susceptible to the development of infectious complications. This susceptibility is increased by the breached host defences and changes in host response from broken skin and mucosal surfaces (from devitalised tissue), splanchnic ischaemia and translocation of intestinal bacteria, indwelling catheters, drains, intravascular lines, endotracheal intubation, advanced age and co-morbidity (Table 1).

In addition, trauma induces both an immunosuppressive and catabolic state that is unable to clear infection. Initially, sepsis may be characterised by increases in inflammatory mediators; but as sepsis persists, there is a shift towards an anti-inflammatory immunosuppressive state or anergy. Changes in the syndrome are possible at various stages of the disease and differ from patient to patient. The mechanism of immune suppression is a shift to anti-inflammatory cytokines and CARS, due to reduced levels of Th1 cytokines (TNF-alfa, interferon gamma, and interleukin-2) but increased levels of the cytokines (interleukin-4 and interleukin-10) produced by type-2 helper T-cells (Th2). The other mechanism is anergy, a state of T-cell non-responsiveness to antigen, where both Th1 and Th2 subtypes exhibit decreased function and patients with trauma or burns have reduced levels of circulating T-cells. Apoptotic cell death may trigger anergy. One potential mechanism of lymphocyte apoptosis is stress-induced endogenous release of glucocorticoids. The type of cell death determines the immunological function of surviving immune cells. Apoptotic cells induce anergy or anti-inflammatory cytokines that impair the response to pathogens, whereas necrotic cells cause immune stimulation. Moreover, genetic factors and polymorphism in cytokine genes may influence whether a person has a marked hyperinflammatory

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<th>Breeched host defences</th>
<th>Change in host response</th>
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<td>Broken skin and mucous membranes</td>
<td>Co-morbidity</td>
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<td>Devitalised tissue</td>
<td>Advanced age</td>
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<td>Indwelling catheters, drains, intravascular lines</td>
<td>Nutritional deficiency</td>
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<td>Endotracheal intubation</td>
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or hypoinflammatory response. Genetic testing and immunological monitoring could therefore identify early certain groups of patients who may benefit from targeted anti-inflammatory or immunostimulatory therapy.\textsuperscript{18} In these terms, a new classification system named Predisposition, Infection, Response, Organ dysfunction (PIRO) has been proposed\textsuperscript{4,18} (Tables 2 and 3).

### Table 2 Definition of systemic inflammatory response syndrome and sepsis.

The response is manifested by two or more of the following conditions

- Temperature $> 38$ or $< 36$ °C
- Heart rate $> 90$ beats/min
- Respiratory rate $> 20$ breaths/min or PaCO$_2$ $< 32$ Torr ($< 4.3$ kPa)
- WBC $> 12,000$ cells/mm$^3$, $< 4000$ cells/mm$^3$, or $> 10\%$ immature (band) forms

Sepsis is the systemic response to infection


### Table 3 The PIRO concept for staging sepsis.\textsuperscript{4}

<table>
<thead>
<tr>
<th>Domain</th>
<th>Present</th>
<th>Future</th>
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<tr>
<td>Predisposition</td>
<td>Premorbid illness with reduced probability of short-term survival</td>
<td>Genetic polymorphisms in components of inflammatory response (e.g., TLR, TNF, IL-1, CD14)</td>
</tr>
<tr>
<td>Insult infection</td>
<td>Culture and sensitivity of infecting pathogens</td>
<td>Assay of microbial products (LPS, mannan, bacterial DNA)</td>
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<tr>
<td>Response</td>
<td>SIRS, other signs of sepsis, shock, CRP</td>
<td>Nonspecific markers of activated inflammation (e.g., PCT or IL-6) or impaired host responsiveness; specific detection of target of therapy (e.g., protein C, TNF)</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Organ dysfunction as number of failing organs or composite score (e.g., MODS, SOFA)</td>
<td>Dynamic measures of cellular response to insult—apoptosis, cytopathic hypoxia, cell stress</td>
</tr>
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TLR, Toll like receptor; TNF, tumor necrosis factor; IL, interleukin; LPS, lipopolysaccharide; PCT, procalcitonin; SOFA, sepsis related organ failure assessment.

A modern concept of intensive treatment

**Haemodynamic support**

The haemodynamic profile of a patient with SIRS-sepsis progression is characterised by a hyperdynamic circulation with increased cardiac output and systemic vasodilation. Relative and absolute hypovolemia, biventricular dysfunction and microcirculatory abnormalities result in inadequate tissue perfusion. Signs of inadequate oxygen delivery (DO$_2$) and oxygen debt are hypotension, confusion, oliguria, lactic acidosis, a change in mixed venous oxygen saturation (SvO$_2$) and gastric mucosal acidosis (as measured by gastric tonometry). Haemodynamic support is carried out by volume restitution, vasopressor and inotropic therapies. Various monitoring techniques are used to estimate the type of haemodynamic abnormalities and intensity of tissue hypoxia.\textsuperscript{19} Central venous pressure measurement in mechanically ventilated patients, as well as in those with increased intra-abdominal pressure, is insufficiently accurate. It is also well established that use of a pulmonary artery catheter (PAC) is frequently associated with inaccurate measurements.\textsuperscript{20} Moreover, PAC usage is not associated with a change in mortality rate.\textsuperscript{21} Central haemodynamic monitoring technology continues to advance and less invasive alternatives for the estimation of cardiac output are being made available.\textsuperscript{22} Lactates are not a precise parameter for detection of the intensity of tissue hypoxia in the early stage of progressive SIRS due to maintained
neutralised and recycling mechanisms, although increased lactate clearance has considerable significance in the estimation of a favourable outcome.\textsuperscript{23} Gastric and sublingual tonometries have not been widely used in clinical practice.\textsuperscript{24} The state of SIRS/sepsis is characterised by a pathological dependence on oxygen consumption (VO\textsubscript{2}) and on oxygen delivery, whereas the concept of a necessary supranormal DO\textsubscript{2} increase has not been clinically confirmed in terms of mortality improvement.\textsuperscript{25} It is thought that these interventions occurred too late in the disease process.

That the time is very important was shown by Rivers et al., who found it improved survival in patients with septic shock, while conducting a prospective randomised study investigating early goal-directed therapy within the emergency department.\textsuperscript{26} Monitoring included mean arterial pressure, central venous pressure and urine output and the endpoint was central SvO\textsubscript{2} > 70\%. It was also postulated that appropriate early aggressive resuscitation in trauma patients may reduce the incidence of trauma-induced SIRS and MOF.\textsuperscript{27} Fluid resuscitation may consist of natural or artificial colloids or crystalloids. There is no evidence-based support for one type of fluid over another. As the volume of distribution is much larger for crystalloids than for colloids, resuscitation with crystalloids requires more fluid to achieve the same endpoint and results in more oedema. Clearly, more studies are required in this area.\textsuperscript{28}

Respiratory support

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are spectra of the same syndrome, which occurs upon damage to the alveolo-capillary membrane and is defined by the difference between the intensity of respiratory dysfunction and the intensity of PaO\textsubscript{2}/FiO\textsubscript{2} ratio irregularity.\textsuperscript{29}

The pathogenic substrate may act primarily, directly on the pulmonary epithelium (aspiration, inhalation injuries, pulmonary infection, pulmonary contusion) or secondarily, indirectly, through the pulmonary capillary vasculature (severe trauma with prolonged hypotension, sepsis, multiple transfusions, fat embolism, reperfusion injuries...). Alveolar involvement in ALI/ARDS is heterogeneous, with normal and abnormal alveoli existing in juxtaposition. Compliance is reduced and airflow resistance increases. The increased work of breathing and muscular fatigue may lead to respiratory failure.\textsuperscript{30}

"Protective strategy in mechanical ventilation"

Mechanical ventilation has long been the main support to respiratory function in those states, but since the traditional method (tidal volumes 10–15 m\textsubscript{L}/kg body weight) may itself cause lung injury (ventilator-associated lung injury, ventilator-induced lung injury, ventilator associated systemic inflammation),\textsuperscript{31,32} ventilation strategy in ARDS has recently become the subject of numerous randomised controlled studies. In the biggest study, a limited volume-pressure strategy led to a decrease in mortality by 9\% with a forced expiration volume of 6 m\textsubscript{L}/kg predicted body weight and maintenance of end inspiratory plateau pressures below 30 cm H\textsubscript{2}O.\textsuperscript{33} Smaller randomised studies have shown permissive hypercapnia, aimed at maintaining a limited minute volume of ventilation, to be a safe method.\textsuperscript{34,35} Hypercarbia was limited in patients with already present metabolic acidosis but is contraindicated in patients with increased intracranial pressure. Raising end-expiratory pressure in ALI/ARDS maintains pulmonary units open and leads to an increase in partial oxygen pressure in arterial blood PaO\textsubscript{2}, whether applied through an endotracheal tube or a facial mask.\textsuperscript{36}

Several minor studies, as well as one major one, have shown that a "prone" position can improve oxygenation in most ventilated patients with ALI/ARDS.\textsuperscript{37,38} The big multi-centre trial did not prove this but post-hoc analysis detected improvement in patients with the most severe hypoxemia.\textsuperscript{39}

The incidence of pneumonia during mechanical ventilation is decreased by 45\% with elevation of the headrest.\textsuperscript{40}

Sedation and analgesics decrease the intensity of stress and sympathetic stimulation; but mechanically ventilated patients with continuous daily sedation spend a significantly longer time with ventilation support and in special intensive care units.\textsuperscript{41} More effective treatment is carried out with intermittent administration of sedatives and/or daily interruptions and proper titration of continuous sedative drips. This also decreases the necessity of tracheotomies. The use of intermediate and long-acting neuromuscular blockers contributes to prolonged weakness of the skeletal musculature.\textsuperscript{42} To avoid this risk, it is necessary to limit their use maximally.

Other methods of respiratory support have also been tested: high-frequency ventilation, high-frequency oscillatory ventilation, non-invasive ventilation, extracorporeal membrane oxygenators, extracorporeal membrane removal of carbon dioxide, NO inhalation, surfactant and partial liquid ventilation. So far, there are no relevant data on their effectiveness. Further research on this is in progress.
Infection-diagnosis and management

Most often, it is difficult to distinguish between post-traumatic non-infective SIRS and the beginning of infection and sepsis. The probability of infection is increased with the advance of clinical symptoms contained in the definition of SIRS, as well as with progressive organ dysfunctions but the clinical signs may be very subtle initially. However, effective, aggressive therapy is very necessary. A delay in instituting appropriate sepsis therapy can result in an increased mortality rate. Nevertheless, the use of long-term prophylactic antibiotics following trauma is not recommended.

Among the laboratory parameters, the level of C-reactive protein (CRP) is most widely employed but the data clearly demonstrate that procalcitonin is a better marker of sepsis. Infection probability score is a simple score to predict infection and the variables can be obtained routinely. Many studies in the last few years have dealt with the relevance of cytokine profiles. Proinflammatory markers combined with anti-inflammatory cytokine profiles, may be an option for the future. They should be used in conjunction with other modalities rather than in isolation.

Targeted clinical, imaging and bacteriological examinations aimed at foci detection as well as timely drainage and surgical procedures for the removal of abscesses, local infection foci and necrotic tissue are of great significance. When an infective complication of SIRS of unknown source is suspected, it is reasonable to replace the vascular catheters.

Intravenous antibiotics should be administered from the very beginning, in the first few hours, immediately after diagnosing sepsis and taking specimens for microbiological analysis. The initial selection of an empirical antimicrobial regimen should be broad enough covering all likely pathogens, until the cause is determined. Then, further treatment is targeted depending on the antibiogram. This method of administration decreases the incidence of superinfections as well as bacterial resistance.

Nutritional support

Sepsis results in profound alteration in metabolism, a catabolic state, or “auto-cannibalism”, with increased morbidity. What type of nutrition is required and by which route it should be given to critically ill patients are objects of debate. Parenterally administered nutrition is easier but the benefits of total parenteral nutrition (TPN) are undermined by complications related to central venous access and bowel inactivity, with its attendant translocation of gut bacteria and infections. Early administered enteral nutrition in trauma and other surgical patients maintains a better microcirculatory flow in the gastrointestinal region. Thus, meta-analysis of clinical tests has shown a decrease in the infection incidence and in the length of hospital treatment in comparison to TPN. However, a large multi-centre controlled study did not show many beneficial effects of early enteral immunonutrition (EN+L-arginine, omega-3 fatty acids, vitamin E, beta carotene, zinc, selenium) in patients with severe sepsis in comparison to TPN. Glutamine-enriched TPN decreases infective complications and endotoxaemia-induced intensification of inflammatory and coagulatory cascade processes, as well as the progress of MODS. Be it as it may, the concept of immunonutrition is still the subject of many studies both in terms of method of administration and in terms of favourable immunomodulatory effects of certain additives.

Low-dose corticosteroids

Steroids have been used following trauma (spinal cord injury, head injury) for a number of years with mixed results. Corticosteroids have a range of anti-inflammatory actions and therefore might be expected to be of benefit to patients with sepsis. Despite favourable results obtained in experimental studies on animal models, clinical studies have remained without confirmation of a beneficial effect of short-course high-dose corticosteroids; whereas a meta-analysis indicated the possibility of increased mortality due to immunosuppression and nosocomial infection. The finding that patients in the progressive stage of sepsis have relative adrenal insufficiency has led to a new method of clinical examination. Thus, a significant reduction of mortality has been achieved with small doses of hydrocortisone (100 mg 2–3 times a day for 7 days) in patients who, in addition to restitution of intravascular volume, also need vasopressor therapy for maintenance of blood pressure. There is no proof that low-dose steroids improve the non-shock forms of sepsis.

Intensive insulin therapy

Hyperglycaemia and insulin resistance are frequent in the states of critical illness. A large prospective clinical trial has demonstrated the significant effect of proper glycaemic control in the prevention of
progressive MODS in severe sepsis through administration of a continuous insulin drip. The best results were achieved in the group of patients with glycaemia values maintained at 80–110 mg/dl (4.4–6.1 mmol/l). Subsequent analysis showed that an improvement in survival was also obtained at 8.3 mmol/l and, by maintaining glycaemia at this value, the risk of hypoglycaemia was easier to avoid. Exogenous glucose is administered in parallel, with frequent determination of glycaemia (each hour or even more often at the beginning of insulin administration). Proper control of blood glucose concentration appears to be more important than the amount of insulin infused. The precise mechanisms involved in the prevention of MODS progress through satisfactory control of glycaemia are unknown. The phagocytic function of neutrophils is impaired in patients with hyperglycaemia, and correcting hyperglycaemia may improve bacterial phagocytosis. Another potential mechanism involves the antiapoptotic effect of insulin.

Immunomodulating strategies

Adjunctive therapy in sepsis is an attempt to interrupt or modify the systemic response. Recent studies investigating anti-inflammatory therapy as immunostimulatory have not shown a dramatically improved outcome. Major criticisms regarding incorrect hypotheses, errant study designs, inappropriate target groups and uncontrolled variables have arisen. However, further studies examining the use of combined and more targeted treatments are awaited.

Coagulation modulating therapy

The tight link between inflammation and coagulation is almost universal in patients with severe sepsis, which has led to the development of an anticoagulant strategy for treating patients in this condition.

A multi-centre randomised controlled trial did not confirm the efficiency of recombinant tissue factor pathway inhibitor (TFPI), which is a physiological inhibitor of the extrinsic coagulation pathway. Antithrombin (AT) is a natural inhibitor of thrombin and other serine proteases. In patients with sepsis, AT levels are reduced and low levels have been correlated with a poor outcome. Administration of antithrombin III has not achieved any favourable effects in decreasing mortality, with the possible exception of a subgroup of patients who did not receive heparin. Protein C is a potent anticoagulant that inhibits factors Va and VIIa, activates fibrinolysis and inhibits thrombin production. This natural endogenous anticoagulant has additional anti-inflammatory effects in comparison to TFPI and AT III, including an anti-apoptotic action. Inactivation of thrombin generation during the deregulated inflammatory response decreases inflammation by inhibiting platelet activation, neutrophil recruitment, and mast cell degranulation but also inhibits cytokine production and leukocyte-endothelium adhesion. Another multi-centre, randomised controlled trial demonstrated that activated protein C could decrease mortality in patients with severe sepsis.

Conclusions

Progressive organ dysfunction syndrome of trauma patients is most often a consequence of septic complications. There has been an advance in diagnosis and treatment of such patients and it has been shown that simple but timely therapeutic procedures (early aggressive resuscitation, early enteral nutrition, infection control, tight glucose control), when used in combination, may prevent progressive complications and improve the outcome. In any case, sepsis is still a subject of extensive research.

References


