NON-ANTIBIOTIC MANAGEMENT OF THE
PATIENT WITH SEPSIS

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Patients with sepsis present frequently with dysfunction of vital organ systems in early or subsequent phases of septicemia. When the source of systemic infection can not be eliminated within hours or days, organ failure requiring specific support is common. The purpose of this short overview is to discuss briefly the therapeutic possibilities to correct or improve vital organ dysfunction in septic patients.

CARDIOCIRCULATORY STABILISATION

Sepsis is associated with systemic vasodilatation, an increased pulmonary vascular resistance and an extravasation of fluid and protein resulting in hypovolemia. In addition, it has been shown that significant dilatation of the left ventricular cavity exists in patients with sepsis, improving gradually with time in survivors. It is interesting to note that the increase in ventricular volume was more marked in survivors than nonsurvivors, independently of preexisting ischemic heart disease. In survivors, these abnormalities will normalize within a week or two. Right ventricular volume is also increased, mainly in those patients presenting with adult respiratory distress syndrome (ARDS) and severe pulmonary hypertension. Left and right ventricular ejection fraction can be decreased in sepsis, and a growing number of elements suggest that a circulating myocardial depressant factor plays an important role in the myocardial failure seen in many patients with sepsis.

The therapeutic strategy for cardiocirculatory dysfunction in sepsis must take into consideration the pathophysiologic elements cited above.

First, adequate intravascular volume replacement has to be carried out. The preferred type of fluid is still much debated, possibly meaning that this is not the most important factor for prognosis. Studies in animals and in humans have shown consistently that two or three times more crystalloids than colloids are required to restore hemodynamic stability in hypovolemic states. In contrast to hypovolemia after trauma or surgery, sepsis is however associated with an early capillary permeability defect. Protein losses from the circulation and edema formation can be a serious problem. The need for a rapid restoration and maintenance of nutrient blood flow to the tissues, and oxygen...
supply to the cells could be hampered by interstitial edema, contributing to cellular hypoxia. Improved restoration of plasma volume and oxygen availability with the application of colloids has been shown in patients after trauma or surgery, but no such comparison has been done in septic patients. Similarly hypertonic saline solution has been used in the resuscitation of experimental hypovolemic shock, resulting in improved survival, but this has not been examined in sepsis.

In conclusion, the choice of fluid is probably not important if an adequate amount is given, but colloid solutions will theoretically remain for a longer time period within the vascular space, allowing faster restoration of circulating blood volume and tissue perfusion.

Though the lungs appear protected by a relatively tight capillary membrane and an efficient lymphatic drainage system, interstitial fluid accumulation can occur and must be minimized if possible. A precise control of microvascular pressure as low as possible may help to achieve this. For other organs, this may be even more important to reduce interstitial edema: in the intestinal tract and the liver capillary membranes are less tight and lymphatic drainage more limited.

Second, these patients have a cardiac output above normal, once adequately resuscitated. Treatment with inotropes and/or vasoactive may however be indicated, because myocardial performance may still be inadequate for the increased metabolic demands in sepsis or because of maldistribution of systemic perfusion. The reasons for an inappropriate cardiac output are probably numerous. One explanation could be ischemic myocardial dysfunction due to coronary hyperperfusion. However, in human septic shock both myocardial blood flow and lactate extraction are preserved. In the study of Cunnion et al., the oxygen content difference between arterial and coronary sinus blood was found to be narrowed, with a decreased fractional extraction of arterial oxygen. This suggests a pathologic coronary blood flow distribution analogous to the pattern in the systemic circulation, but no ischemic myocardial dysfunction. A second mechanism postulated and investigated is the presence of a circulating myocardial depressant factor (MDF). Several investigations were able to present evidence for such a factor in human sepsis.

The myocardial dysfunction as an “inappropriate” cardiac output can be treated by inotrop positive agents or vasodilators to increase systemic blood flow and oxygen transport. On the other hand, the decreased systemic vascular resistance may require vasoconstricting agents, if systemic arterial pressure is too low to ensure adequate perfusion pressure of vital organs. Which one of these 2 therapies is more important for ultimate prognosis is unknown at this moment, because:

a) transport dependant oxygen consumption has been reported in sepsis. This led to the hypothesis that an oxygen debt or a cellular oxygen uptake disturbance exists in this condition — making a maximisation of oxygen transport desirable. Systemic oxygen transport can be increased efficiently by increasing cardiac output, either by inotrop positive agents or vasodilators. On the other hand, vasoconstricting agents may decrease cardiac output and thereby systemic oxygen availability.

b) Vasoconstricting drugs such as noradrenaline (norepinephrine) are efficient in septic shock for increasing systemic blood pressure and perfusion pressure of vital organs. Depending on the myocardial condition, cardiac output and oxygen transport will increase, remain stable or decrease. Renal function can be improved by low dose dopamine infusion and, if perfusion pressure is low, norepinephrine.
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It is current practice to maintain in sepsis an appropriate cardiocirculatory function with a combination of fluid therapy and, if necessary, small doses of dopamine and norepinephrine.

RESPIRATORY SUPPORT

Sepsis is frequently associated with gas exchange disturbances, either secondary to pulmonary edema due to increased capillary permeability, or respiratory muscle fatigue due to low systemic arterial pressure and muscle perfusion. The aim of respiratory support techniques are an improvement of pulmonary gas exchange, systemic oxygen availability and carbon dioxide (CO₂) elimination.

Arterial hypoxemia can usually be improved by providing supplemental oxygen by mask or nasal prongs. Systemic oxygenation can be further enhanced in most circumstances by application of a positive airway pressure over a tight fitting face mask or an endotracheal tube. When respiratory acidosis is present, alveolar ventilation should be increased by partial ventilatory support, for instance intermittent mandatory ventilation (IMV) or inspiratory pressure support (PS). In severe forms of acute pulmonary parenchymal failure such as the adult respiratory distress syndrome (ARDS), full ventilatory support with positive end-expiratory pressure (PEEP) may be necessary to ensure adequate pulmonary oxygen uptake and CO₂ elimination. The respiratory requirements, i.e., oxygen consumption and CO₂ production, are frequently above normal in sepsis (similar to the hyperdynamic cardiocirculatory function). This can represent an important burden in patients with limited respiratory reserves, and part of the ventilatory work must be taken over by mechanical means in this situation.

Unfortunately, mechanical ventilatory support has it's own secondary effects which can be dangerous in the septic patients:

first, positive pressure application to the airway and the lung slows down the resorption of interstitial lung edema by the lymphatics;

second, cardiac output can be decreased by positive intrathoracic pressure, secondary to an impaired venous return and ventricular filling; systemic oxygen transport can decrease by this mechanism;

third, endotracheal intubation carries a high risk for secondary bronchopulmonary infection; the incidence of this complication can be decreased by strict aseptic handling of the artificial airway, prevention of stress ulcer bleeding by sucralfate rather than histamine-2 blocking agents, and possibly selective digestive decontamination.

In conclusion, the respiratory function of the patient with sepsis requires close monitoring and appropriate intervention if necessary. The incidence of side effects can be kept low by adequate measures.

SUPPORT OF RENAL FUNCTION

Sepsis can cause acute renal failure through renal vasoconstriction by endotoxin and/or by the cardiovascular impairment due to sequestration of fluids, resulting in
a decrease in renal perfusion pressure. The association of acute renal failure and sepsis is accompanied by a high mortality, overall in the presence of acute respiratory failure. Conventional hemodialysis is not an ideal support technique for acute renal failure complicated by respiratory failure in sepsis. In contrast, a relatively new method, hemofiltration, can eliminate efficiently excess fluid and low molecular weight solutes. Continuous arteriovenous or veno-venous hemofiltration is based on the principle of ultrafiltration which is directly proportional to the filtration pressure and the blood flow through a special low volume filter. A blood pump can increase the ultrafiltrate volume. Concerning permeability, this method is similar to normal glomerular filtration, but is less efficient than hemodialysis regarding the clearing of blood urea.

Gotloib et al. reported a series of 5 patients with ARDS secondary to sepsis in which hemofiltration has been used for excess fluid removal. The technique permitted the gradual weaning from the ventilator in all cases.

In summary, hemofiltration is an efficient treatment of an impaired renal function in sepsis for removing solutes and management of fluid balance.

METABOLIC SUPPORT

The most important goal of metabolic support and nutrition is a positive nitrogen balance without providing excess calories, and specific correction of deficient elements. Energy expenditure is increased during sepsis, reflected in increased oxygen consumption and carbon dioxide production. The amount of calories provided by enteral or intravenous route should not exceed 30 total calories/kg body weight/day, and for glucose not more than 4-5 g/kg/day. An excess of total calories or glucose has been shown to have important side effects: fatty liver degeneration, plasma hyperosmolality, increased CO₂ production and oxygen consumption. Stimulation of catecholamine release and increased lactate formation. Up to 30% of daily calories can be given as fat, if plasma clearance of triglycerides remains normal. Aminoacids at doses of 1.5-2 g/kg/day are appropriate in most cases. Modified aminoacid solutions (i.e. with an increased proportion of branched-chain forms) may be interesting in sepsis to improve nitrogen balance. In addition to these nutritional needs, septic patients require administration of phosphate, magnesium and minimal amounts of other trace elements and vitamins. Whenever possible, the enteral route is the preferred way for supply of nutrients.

Assessment of nitrogen balance, oxygen consumption and CO₂ production every 4-6 days can help to improve the metabolic management of these patients and avoid the administration of excess calories. Applied in this way, metabolic support is an efficient part of the treatment of sepsis.

MULTIPLE ORGAN FAILURE (MOF) SECONDARY TO SEPSIS

Sepsis can be complicated by significant dysfunction of several vital organ systems. This evolution represents probaby (either) the systemic response of a generalized "malignant" inflammatory response, or a consequence of organ ischemia after a low perfusion state. MOF can also be seen in critically ill patients without proven septicemia, overall in the context of severe polytrauma or after a period of circulat-
ory shock of another origin. Because liver function is central to host-defense homeostasis, hepatic function is an important moderator of the generalized inflammatory response, determining the expression and prognosis of MOF.

Therapies of sepsis and vital organ failures that do not eradicate the primary process and prevent dysfunction of other systems can not be expected to reduce the mortality in these patients. Current prevention and treatment of MOF is aimed at supportive care. Secondary infection, hypotension and hypoxemia will exacerbate organ dysfunctions and must be avoided. Today no efficient pharmacological therapy is available which could interfere with mediator release or prevent their harmful effects on organ function. Although anti-inflammatory agents and prostacyclines have shown short term beneficial effects on pulmonary gas exchange, oxygen transport and CO₂ extraction, no improvement in prognosis was observed with these agents.

In conclusion, MOF is a frequent cause of death in the patient with sepsis. Efficient therapy includes prevention and prompt treatment of hypotension, low flow states, hypoxemia and secondary infection. Therapy of each individual organ dysfunction remains supportive.

References


