Therapeutic interventions aimed at preventing MODS

The terms multiple organ failure syndrome (MOFS), multiple systems organ failure (MSOF) and, most recently, multiple organ dysfunction syndrome (MODS) have all been used to describe 'irreversible shock' and organ failure.
Summarised the causes of irreversible shock are:
(1) Haemorrhage uncomplicated by gross trauma; **(2)** burns; **(3)** trauma to large masses of muscle; and **(4)** the re-establishment of circulation in a damaged ischaemic area.

The primary insult

As always, the earliest treatment is most effective and prevention is better than cure. If we assume that the primary insult is unavoidable, has been correctly diagnosed and treated, then all subsequent forms of treatment are aimed at limiting the degree of tissue damage.

Compounding insults

Avoiding tissue hypoxia — simple resuscitation with intravenous fluids

The commonest compounding insult is probably tissue hypoxia as a result of inadequate basic resuscitation. Treating the primary insult is almost a waste of time without restoration of an adequate circulating blood volume. The majority of patients will respond to the administration of intravenous fluids and supplementary oxygen via a face mask.
As one of the central abnormalities in SIRS is thought to be endothelial leak, one might hope that a colloid with a larger molecular weight than albumin might be more effectively retained within the vascular compartment and therefore more likely to maintain microvascular flow and organ perfusion. However, there are no human data that demonstrate that any particular solution (colloid or crystalloid) is better than another in terms of outcome, even though there is approximately a 100-fold price difference between the cheapest and most expensive alternatives. There are, however, good data to suggest that to avoid tissue hypoperfusion you need to give enough of whatever you choose and you need to give it promptly with the appropriate level of monitoring. For rapid restoration of haemodynamic function a colloid does the job more efficiently than a crystalloid. Albumin has no demonstrable advantages over cheaper alternatives such as the modified gelatins.

Treating tissue hypoxia — the global approach

The rationale here is that patients with SIRS are thought to have an occult tissue oxygen debt in spite of apparently normal global cardiovascular variables such as blood pressure and urine output, and that by increasing total body oxygen delivery, commonly by the administration of ionotropes, this debt will be repaid and hypoxic tissue damage will be avoided. In patients undergoing high-risk major surgery and critically ill patients on the intensive therapy unit (ITU) there appears to be a positive correlation between a high oxygen delivery and survival. In patients undergoing high-risk major surgery prophylactically increasing cardiac output and oxygen delivery to predetermined supranormal levels has been associated with a decrease in subsequent organ dysfunc-tion and mortality. However, the same principles when applied to established

critically ill patients on the ITU has met with very limited success. Once a critical degree of tissue hypoperfusion is established then the situation is apparently irreversible.

Avoiding nosocomial infections

Once a patient has some degree of organ dysfunction on an ITU they are thought to be at greater risk from nosocomial infection. In the prevention of secondary infection good hand washing and the avoidance of cross-infection carried by staff probably have the greatest impact. Assuming that such cross-infection is avoided then the patient is his or her own enemy and bacteria carried in the gastrointestinal tract provide the commonest source of secondary infection. Nosocomial pneumonia is thought to occur commonly as a result of spillage from the upper gastrointestinal tract into the lungs. It has been demonstrated that the administration of H2-receptor antagonists with the intention of reducing gastric acidity and avoiding stress ulceration also encouraged the growth of bacteria in the stomach and an increased incidence of nosocomial pneumonias. The use of sucralfate as stress ulcer prophylaxis has the advantage of also being bacteriostatic and has been associated with a decreased incidence of nosocomial pneumonia.

Treating endotoxaemia

Endotoxin is a recognised potent activator of various cellular and humoral pathways involved in the generalised inflam-matory response. Endotoxins are mostly comprised of lipo-polysaccharide, and most of their biological activity resides in the lipopolysaccharide section. The core region of lipopoly-saccharide is nearly identical for most strains of Gram-nega-tive bacterial endotoxins. Supranormal levels of naturally occuring endotoxin core antibodies have been associated with a reduction in organ failure in patients following high-risk surgery and on the ITU. However, in two large multicentre trials of patients with presumed Gram-negative infection, the results of giving donor antibodies against the core region of endotoxin have been inconclusive. Active immunisation would be an attractive alternative for patients scheduled for major surgery, and evidence from animal experiments has been encouraging. However, there is no currently available anti endotoxin vaccine. Other potential anti endotoxin strategies undergoing human testing include bactericidal/permeability-increasing protein (BPI), endo-toxin-neutralising protein and dextran—polymixin B conjugate, all of which have the ability to protect animals from endotoxin-mediated toxicity.

Systemic inflammatory response syndrome

The organo-protective therapeutic regimens cited above seem to work if used prophylactically, as is the case in major surgery. However, the results of adopting similar regimens in established MODS are rather disappointing. This would suggest that once a systemic inflammatory response is unresponsive to cardiovascular manipulations and antimicrobials then if the progression to MODS is to be avoided organ protection must come from a different line of attack. An increased understanding of the host-derived mediators of the tissue destruction seen in MODS has opened up a whole new field of therapeutic agents directed against them. It is hoped that specific manipulation of key mediators will at least halt the tissue damage in its tracks and hopefully be curative.

Cytokines

Protein cytokines play an important part in the mobilisation, localisation and subsequent activity of leucocytes in the inflammatory reaction. Tumour necrosis factor alpha (TNF-a) and the interleukins (IL) have emerged as prime targets for experimental manipulation. In animal models of septic shock, treatment with monoclonal antibodies to TNF-alpha and various interleukins (e.g. IL-1) have improved survival. There are ongoing trials of inhibitors of both TNF-alpha and IL in human sepsis. Unfortunately, the early reports have been inconclusive.

Decreasing cytokine synthesis and secretion

Corticosteroids reduce TNF-alpha mRNA translation in response to a stimulus and thus reduce secretion. Numerous studies have demonstrated the protective effects of corticosteroids in animal models of septic and haemorrhagic shock. The use of low-dose dexamethasone has been shown to improve outcome in paediatric patients with meningitis. From a purely hypothetical viewpoint, steroids should be the answer to the treatment of SIRS. However, two large multicentre, randomised trials of high dose dexamethasone used in the treatment of septic shock failed to demonstrate any improvement in survival.

Nitric oxide

In 1987 it was reported that the endothelium-derived relaxant factor was identical to the free radical nitric oxide (NO). NO is synthesised from r-arginine by a constitutive enzyme present in the endothelium, which has a physiological role in the control of blood pressure, and by an inducible nitric oxide synthase, which is expressed in vessel walls and phagocytic cells in response to endotoxin or cytokines. NO has a myriad of actions but is predominantly a vasodilator and can modify the neutrophil—platelet interactions that may result in the microvascular occlusion seen in MODS. These effects create a therapeutic dilemma. Should you give NO in an attempt to restore microvascular flow or block its effects to restore the blood pressure in septic shock? In patients with severe acute respiratory distress syndrome inhaled NO has been demonstrated to reduce pulmonary artery pressure and improve pulmonary oxygenation without affecting systemic vascular resistance. However, it has also been demonstrated that blocking the production of NO from its precursor L-arginine is possible by the administration of arginine analogues such as NG-monomethyl-r.-arginine (L-NMMA). In animal studies the administration of NO antagonists has been shown to restore the vascular response to catecholamines and improve survival.

Arachidonic acid metabolites

There is a multitude of animal and human evidence to suggest that metabolites of arachidonic acid play key roles in the pathogenesis of MODS, both protective (e.g. prostaglandin E2) and deleterious ones (e.g. leukotrienes and thromboxane). Cyclo oxygenase inhibitors such as ibuprofen or indomethacin, which are nonsteroidal anti-inflammatory drugs, have been shown to reduce tissue damage and improve survival in animal models of sepsis.

Neutrophils

Degranulating neutrophils as part of a systemic inflammatory response are said to cause microvascular injury and promote organ dysfunction by the release of destructive enzymes and the generation of oxygen free radicals. Free radical scavengers such as superoxide dismutase, allopurinol and even vitamin C are universally successful in

reducing the tissue damage seen in septic and haemorrhagic shock models. Provisional reports from at least two human studies claim success from free radical scavenging.

Contact, coagulation and complement activation

A common clinical feature of SIRS is a coagulopathy. Histologically the microvascular abnormality seen in MODS is not unlike clot. This has led to the assumption that there is a disturbance of the balance between procoagulant and anticoagulant pathways in SIRS that can manifest itself most vividly in the disseminated intravascular coagulation seen in meningococcal meningitis. There are preliminary results suggesting that the administration of clinical concentrates of inhibitors of the contact system such as antithrombin III and C1 -esterase inhibitor may modify the outcome in established SIRS.

Endogenous anti-inflammatory agents

It is now recognised that most proinflammatory acute-phase reactants are balanced by the production of endogenous anti-inflammatory acute-phase reactants. For example, antago-nists to soluble IL-1 and TNF-alpha are produced by hepatocytes and released into the circulation, thereby reducing the inflammatory response. The anti-inflammatory cytokine IL-10 is a potent macrophage-deactivating factor, and injection of recombinant IL-10 has been shown to protect mice from endotoxic shock. IL-10 is thought to regulate the effects of other cytokines (e.g. TNF-alpha), rather than block them completely, and therefore has the potential for maintaining optimal balance in the inflammatory system.

Multiple organ dysfunction syndrome

There are no animal or human data to suggest that fully established MODS is treatable. This does not mean that all patients who have MODS die. However, the small percentage who survive have probably done so because supportive care has given them a chance to get better.

Conclusion

Prevention of MODS by the prompt diagnosis and treatment of the primary insult coupled with cardiovascular resuscitation and supportive care has an extremely high success rate in patients who have some hope of long-term survival. However, once the same group of patients has established organ failure the outlook is extremely gloomy.

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