

Managing Tissue Trauma and Inflammation: Noncontaminated Trauma

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In humans, 50% of deaths from extensive traumatic injuries occur immediately, 30% occur within hours, and the remaining 20% occur within days to weeks.¹ The delayed deaths from trauma are associated with the development of sepsis, systemic inflammatory response syndrome (SIRS), and multiple organ dysfunction syndrome (MODS).^{2,3} Proposed causes for the development of SIRS following trauma include shock, ischemia, reperfusion of vital organs (particularly the gastrointestinal tract), depressed immune response secondary to shock and catecholamine release, activation of inflammatory mediators by necrotic tissue, endotoxin, and bacteria. In addition, patient factors such as poor nutritional status, compromised immune function, underlying disease, or drug treatment (particularly glucocorticoids) may predispose certain individuals to SIRS.^{3,4} Specific treatment of SIRS is limited to supportive care. Although several new (and some old) agents are being evaluated for treatment of SIRS and prevention of MODS, the best therapy is prevention. Many of the human patients that progress to MODS are undertreated or misdiagnosed or receive delayed treatment.¹

Once the airway is examined (and secured if indicated), the patient should be evaluated for contraindications to volume loading (e.g., head trauma, severe pulmonary contusions, or preexisting heart disease). Aggressively treating shock with fluid therapy is essential. Therapy consists primarily of hemodynamic support, which is generally initiated with crystalloids administered at 90 ml/kg (one blood volume) to effect. If the animal fails to show improvement with initial resuscitative efforts, it should be evaluated for occult blood loss. Trauma patients with persistent

tachycardia, weak pulses, and low total solids should be checked for intrathoracic or intraabdominal hemorrhage. Percussion, palpation, and paracentesis aid the diagnosis.

Bleeding must be controlled. In patients with persistent signs of shock, fluid therapy should not be limited to 90 ml/kg; blood component therapy should be initiated in cases of ongoing hemorrhage. Synthetic colloids are also a valuable tool for the resuscitation of trauma patients. The potential adverse effects on coagulation must be weighed against the potential benefits. Hypertonic saline (7% NaCl; 3 to 5 ml/kg slow bolus) is an alternative resuscitation fluid and may be useful in cases of head trauma that require volume resuscitation.⁵ In some studies, hypertonic saline has been shown to increase blood loss in uncontrolled hemorrhage. Mazzoni and associates suggest that hypertonic saline provides greater volume expansion despite the increased blood loss.⁶ In cases where hemorrhage can be controlled by pressure (direct abdominal binding) or definitive repair, hypertonic saline remains a valuable fluid choice.

The use of glucocorticoids in the treatment of shock is common in veterinary practice. According to current recommendations for humans, steroids are contraindicated in shock.⁷ The theoretical rationale for steroid use is to block inflammatory mediators (tumor necrosis factor [TNF], eicosanoids). In research studies, steroids are effective only if given *prior* to release of these mediators.^{8,9} In human clinical trials, steroids have not proven advantageous and have been shown to be detrimental in some studies.¹⁰ If steroids are used, they should be administered in conjunction with fluid support, early, and only once; additionally, only short-acting steroids should be used. The potential adverse effects of steroid administration (impairment of immune function, hypercoagulation, impaired gastrointestinal protection, decreased wound healing, and hypotension associated with rapid intravenous injection) must be weighed against the theoretical benefits. Clinical studies to evaluate the efficacy of steroids in traumatic shock in veterinary patients are required to definitively define the role (if any) for their use.

During shock, blood is preferentially shunted to the heart and brain. The resulting decrease in perfusion to other organs causes ischemia. The tissue damage associated with ischemia is amplified by the reintroduction of oxygen (reperfusion),¹¹ which results in release of oxygen free radicals, eicosanoids, and inflammato-

ry mediators. Neutrophils and platelets are also activated, adding to the tissue damage and obstructing small vessels.¹² The villous cells of the intestine slough, and the normal barrier to intestinal flora is compromised. Absorption of bacteria and endotoxin across the gut wall is called *translocation*.¹³

Endotoxin is part of the cell wall of gram-negative bacteria and is a potent stimulus for inflammatory mediator production. TNF, interleukin-1 (IL-1), interleukin-6 (IL-6), platelet-activating factor (PAF), eicosanoids, activated complement, and free radicals are products of the inflammatory cascade initiated by endotoxin. These mediators cause cellular damage (the endothelial cell is a prime target), stimulate the release of stress hormones, produce fever, alter blood flow, increase activation of leukocytes, promote intravascular coagulation, and alter systemic protein and carbohydrate metabolism.^{14,15} It has been proposed that administration of bactericidal antibiotics may increase circulating endotoxin and amplify the inflammatory response. Research studies have shown that endotoxin increases following antibiotic administration, but so does survival.¹⁶ Infection is not the only initiator of the inflammatory cascade in trauma and critical patients—tissue necrosis and inflammation (e.g., pancreatitis) can also trigger this response.¹⁵

Therapy is directed at controlling infection, halting inflammation, and maintaining hemodynamic and organ function. Prevention is the most effective therapy! When patients begin to develop SIRS, it is essential to prevent progression to MODS. Perfusion and oxygen delivery are critical in maintaining organ function. If a source of inflammation can be identified, it should be treated aggressively. The inflammatory response produces a hypermetabolic state and alters normal protein and carbohydrate metabolism. Nutritional support of the patient, especially in terms of efforts to return the gastrointestinal tract to normal, is essential to support the immune response and prevent bacterial translocation.¹⁵

Specific therapy to break the inflammatory cycle continues to be the focus of many research and clinical studies. The timing of interventional therapy is critical. The inflammatory cascade is activated in a predictable fashion in the experimental setting, in which a large dose of endotoxin or bacteria is administered quickly. The clinical situation is more complicated, and it is difficult to determine where the patient

is in the progression of the cascade. As mentioned, glucocorticoids are only useful *prior to* the onset of the cascade. Antiendotoxin antibody pretreatment has shown promise in an experimental setting, but clinical studies failed to demonstrate a benefit. Antibodies to TNF protect experimental animals from the lethal effects of endotoxin or bacterial challenge when given prior to or within 30 minutes of challenge¹⁷ but have failed to demonstrate efficacy in clinical trials. Another type of promising anticytokine agents, IL-1 receptor antagonists, failed clinical trials. Novel therapies continue to be evaluated in clinical trials, which have shown that blocking these factors creates potential hazards and that success in an experimental model does not ensure clinical success. Currently, the best treatment is the prevention of the devastating systemic inflammatory response syndrome through aggressive hemodynamic support.

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