INTRODUCTION

Despite recent advances in burn care, sepsis still remains a major cause of burn morbidity and mortality. Five factors determine the seriousness of a burn: depth, size, area(s) of involvement, age and general health of the burn victim (1). Burns are classified as partial-thickness (first or second degree) or full-thickness (third or fourth degree) burns. Partial-thickness burns are characterized by superficial injury to varying portions of the epidermis, which may be produced by sunburn and scalds. Full-thickness burns involve injury to the entire dermis, including appendages (sweat glands, hair follicles, etc.) and may extend into the fat and muscle tissues. These burns are produced by flame, chemical contact or electrical current.

Initial treatment of the burn patient is aimed at relief of respiratory distress, initiation of fluid resuscitation, and prevention of burn shock (2). After initial treatment, the patient is admitted for further non-operative treatment including resuscitation, nutrition, infection control, ventilation and other burn wound management techniques. Improved resuscitation, early debridement and grafting, nutrition and critical care have improved outcomes in patients with burn injuries; however, sepsis and multiple organ dysfunction still remain as major causes of burn-related deaths (3).

Remote Consequences of Thermal Injury

Thermal injury may cause damage to multiple organs distant from the original burn wound and may lead to multiorgan failure (4). After a major thermal injury, there is extravasation of intravascular fluids into the injured site, which, without adequate fluid resuscitation, leads to hypovolemia, shock, and death. However, generalized tissue inflammation is present in uninjured organs within hours of injury, even in the absence of shock.

Localized thermal injury triggers an acute pathophysiologic response that incorporates vasodilatation to aid dissipation of the heat and activation of afferent nerve signals, which cause pain. Burn injury also causes the local release of oxidants and arachidonic acid metabolites, which initiate burn wound edema (5, 6). In addition, the activation of a number of systemic mediator cascades, e.g., a complement activation, arachidonic acid release and cytokine production, result in a generalized neutrophil sequestration and most importantly a "priming" of both local and systemic neutrophils and macrophages. The release of mediators and activation of cascade mechanisms are in proportion to the total body surface area burned (6). In severe cases, systemic, neurohumoral and inflammatory reaction peaks at 5-7 days after the burn incident.

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Tissue response to thermal injury

Burn causes the increase of microvascular permeability due to direct effect of heat on endothelial cells and due to chemical mediators of inflammation such as histamine and prostaglandins (7). The increased microvascular permeability allows fluid leakage into the interstitium which results in hypovolemia.

Reactive oxygen metabolites (ROMs) have been implicated as a primary cause of both local progressive skin necrosis and distant organ injury in burns (8, 9). It has been proposed that the source of ROMs could be neutrophils sequestered in systemic organs as a result of the systemic inflammatory reaction to a local burn insult. Organ injury remote to the region of thermal trauma is now known to be due to intravascular activation of complement which results in activation of intravascular neutrophils and heads to the formation of toxic oxygen products (10). The contention that neutrophils play an important role in the development of remote organ injury is supported by the findings which show that postburn intravascular hemolysis as well as lung injury of the skin were largely prevented by neutrophil depletion in experimental animals (11). Thus, since sequestration of metabolically active neutrophils induces tissue injury, therapies that block postburn leukosequestration may improve clinical outcomes by limiting remote tissue injury. In addition to this, antioxidants have been shown to attenuate mortality and morbidity in a number of sepsis models (12).

Lipid peroxidation due to ROMs is one deleterious consequence of burn injury. Increased circulating lipid peroxidases have been demonstrated in humans and burn animal models (13, 14). In addition to inflammation, lipid peroxidation in lung, liver, kidney and other tissues is seen in the early postburn period (14, 15). An increase in distant organ inflammation, as well as tissue oxidant-induced lipid peroxidation, particularly in the liver, occurs within hours after a body burn, even in the absence of shock (14). It has been shown that early lipid peroxidation is successfully prevented by infusion of the iron chelator deferoxamine during the resuscitation period (16). Moreover, the immunosuppressive agent FK506 is of some benefit in the reduction of systemic neutrophilic injury and related lipid peroxidation in rats following burn insult. It was found to be effective in reducing lipid peroxidation and neutrophil infiltration especially at 24 h postinjury in lung, liver and kidney (17).

In addition to oxidants, the cytokines are also involved in a number of major responses to burn injury. These include hemodynamic changes, tissue inflammation, wound healing, immune defenses, hypermetabolism, and catabolism. Continued increased activity of some of these agents, particularly TNF-α, is felt to be responsible for the organ failure syndrome seen with a persistent sepsis syndrome. The major cytokines involved with the response to burn trauma, include TNF-α, interleukin-1 (IL-1), IL-2, IL-6, and interferon-α. The role of TNF-α in the septic response to endotoxemia is evident by the fact that pretreatment with TNF-α antibodies prevents the systemic response (18). TNF-α has been shown to be increased in the plasma of burn patients, but almost always in septic patients or patients who soon died (19). The specific role of IL-1 in the various aspects of burn injury is not well defined. This cytokine is most certainly involved in the later response of postburn sepsis and hypermetabolism (6). On the other hand, both IL-2 production and IL-2 action are well documented as decreasing after burn injury (20). The decreased IL-2 correlates with increased mortality after a septic challenge in burn animals (21). It is therefore clear that a deficiency of this cytokine plays an important role in the decreased resistance to infection in the burn patient. Another cytokine released very rapidly into the circulation in response to circulating endotoxin is IL-6. Serum levels of IL-6 are markedly increased in burn patients with peak response beginning about 1 week postburn (22). Circulating IL-6 levels appear to correspond with endotoxin levels and large increases appear to correspond with mortality.

Arachidonic acid metabolites are definitely involved both in the early and late responses after thermal injury (23). Arachidonic acid is released from cell membranes after any significant septic event. It is now well established that there is a massive release after burn of both the vasodilator prostanooid, namely prostacyclin (PGI2) and the vasoconstrictor prostanooid, thromboxane A2 (TxA2), as detected in burn edema and plasma (23). The characteristic blood
flow maldistribution seen with sepsis appears to be related with excessive production of TxA2 or PG12 in various vascular beds (24). Early thromboxane release is considered to be at least in part responsible for a persistent decrease in burn tissue blood flow (25). The local increase in TxA2 has also been reported to stimulate platelet aggregation and neutrophil margination in the burn microcirculation. It has been demonstrated that thromboxane concentrations are markedly increased in patients immediately after burn injury and during septic episodes (26). Pretreatment of pigs with the specific thromboxane inhibitor OKY046 attenuated the increase in mesenteric vascular resistance and restored the decrease in gut blood flow (27). All these findings indicate that the TxA2 is involved in the systemic hemodynamic response after burn insult. PGI2 is a potent vasodilator and is therefore known to accentuate vascular leak by an increase in local blood flow. The lipooxygenase pathway products, leukotrienes B4, C4 and D4 are shown to be involved in the later postburn response than any of the early changes (28). To date, however, there have been variable responses reported with the use of lipooxygenase inhibitors and leukotriene antagonists in burn sepsis.

Nitric oxide (NO) which is important in numerous physiological and pathophysiological events shows dramatic increases in plasma and urine after thermal injury (29). Thermal injury induces the production of inducible NO synthase (iNOS) in gut mucosa. iNOS activity increases 24 h after the injury and up to a maximum of twofold 2 days after burn and decreases thereafter (30). The increase in iNOS activity in gut mucosa has been found to correlate well with the increase in intestinal permeability, an index for barrier failure (30). According to these studies, the change in mucosal iNOS activity after the burn occurs mainly in the enterocytes rather than in the macrophages (30). Suppression of intestinal mucosal iNOS activity prevents barrier failure as demonstrated by a decrease in bacterial translocation occurrence and intestinal permeability (30). NOS inhibitors administered as therapeutic treatment were also effective in suppressing vascular permeability 1 and 6 hours postburn (31). On the other hand, it has been suggested that venule constriction, which is observed 5 h after thermal injury, is related to decreased NO production by endothelial cNOS (32). Dietary arginine supplementation decreases the mRNA expression of inflammatory cytokines (i.e. TNF-α, interferon-α, IL-1 beta and IL-6) in the spleen, thymus, lung and liver after thermal injury in rats and improves the survival rate (33). It has been observed that burn injury in humans is also associated with excess NO production (34). However, NO production was not proportional to burn area, and seemed to be further enhanced in septic patients (34).

At cellular level, thermal injury induces programmed cell death with a concomitant loss in cellular mass and absorptive surface area in the gut (35). Thermal injury induces intestinal atrophy and causes marked alterations in the morphology, growth, and function of the small intestinal epithelium (36, 37). Post-thermal atrophy of the intestinal mucosa was based on a decrease in the mucosa weight and a reduced intestinal cell proliferation, as demonstrated by diminished DNA and protein synthesis (37). Cutaneous thermal injury causes a transient suppression of mitosis as well as induction of apoptosis in the small intestinal crypt (38). Similarly, it induces hepatic cell apoptosis and proliferation which associates with an increase in hepatic NF-kB expression and a decrease in hepatic protein concentration (39) (Fig. 1).

![Fig. 1](image-url) - A brief summary of the pathophysiological events that appear to be associated with remote consequences of local skin burn.
Burn-Induced Alterations In Gastrointestinal Functions

Although the pathophysiological basis of remote organ injury remains unclear, understanding the effects of thermal injury on the gastrointestinal system is important for the physician involved in nutrition of the patient. Adynamic ileus, gastric dilatation, increased gastric secretion and ulcer incidence, gastrointestinal hemorrhage, local and general redistribution of the blood flow with a decrease of mesenteric blood flow are among the effects of thermal injury on the gastrointestinal system (40). Relative intestinal ischemia resulting from decreased splanchnic blood flow many result in the activation of neutrophils and tissue-bound enzymes such as xanthine oxidase. These factors impair gut mucosal barrier and result in bacterial translocation.

The gastrointestinal barrier is normally highly effective in containing its flora. However, subsequent to the stress of thermal injury, the barrier breaks down and leads to the passage of inert particles and microorganisms across the intestinal wall, a condition termed "translocation". Endotoxin, a lipopolysaccharide derived from the outer membrane of gram-negative bacteria, translocates across the gastrointestinal tract barrier within 1 hour of thermal injury (41). Although the burn wound is sterile initially, plasma endotoxin concentration reaches to a peak at 12 h and 4 days postburn (42). Bacterial by-products including endotoxin are potent activators of the macrophages and neutrophils. This leads to the release of massive amounts of oxidants, arachidonic acid metabolites, proteases, etc., which cause further local and systemic inflammation, induced tissue damage (6).

The terminal ileum is an area of the intestine particularly vulnerable to ischemia during splanchnic vasoconstriction. A 30% body surface area burn in rats causes a marked increase in lipid peroxidation in the terminal ileum within 24 h after thermal injury (43). Aggressive fluid resuscitation, pretreatment with the xanthine oxidase inhibitor allopurinol or with an anti-inflammatory agent that inhibits neutrophil degranulation azapropazone are effective interventions for preventing bacterial translocation and ileal lipid peroxidation (43).

Additionally, diets rich in glutamine-the most plentiful intracellular amino acid and the major fuel of enterocyte- and fiber have been found to decrease the degree of intestinal bacterial translocation (44).

Chen et al. (45) demonstrated that the decrease in intestinal and colonic motility in the rat following burn injury was accompanied by a delay in gastric emptying. In contrast, Hu et al. showed that the kinetics of gastric emptying was not affected by thermal injury (46). In a study performed in our laboratory, we observed a significant delay in intestinal transit in both early and late phases after burn injury in rats (47). Another interesting finding of this study was the reversal of this effect by bombesin, a peptide essential in the maintenance of gut integrity, intestinal motility and proliferation of gut mucosa. This finding supports the previous studies in which bombesin was found to prevent intestinal mucosal atrophy with a concomitant decrease in bacterial translocation after thermal injury (48).

**CONCLUSION**

Most of the studies cited here use animal models which are then extrapolated to the clinical setting. The advantages in using an animal model include complete control of burn size, severity and area of involvement. However, the validity of using an animal model in burn research has never been established, nor is it clear whether one animal species is superior to another in terms of extrapolation to humans.

It is obvious that modulation of the inflammatory response has tremendous potential for benefit. Parenteral or topical nonsteroidal anti-inflammatory drugs, anti-endotoxin antibodies, antioxidants blockers of cytokine action are all agents currently available. In addition to these interventions, new therapeutic modalities may become available to protect and/or treat impaired gastrointestinal barrier in the near future. The key point is that it is essential for the clinician to choose the right pharmacological manipulation in order to be able to optimally utilize these future advances.
REFERENCES

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