The Pathogenesis of Burn Wound Conversion

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Objective: Burn wound progression is a poorly understood process by which certain superficial partial-thickness burns spontaneously advance into deep partial-thickness or full-thickness wounds. Progression of an injury into deeper tissue is an important phenomenon in the treatment of thermal injury due to the fact that burn wound depth may be a significant determinant of morbidity and treatment. This article reviews current knowledge of the pathogenesis, molecular and cellular mechanisms, local and systemic factors, and treatment modalities related to wound conversion.

Data Sources and Study Selection: All peer-reviewed, original, and review articles published in English-language literature relevant to the topic of burn wound conversion on animals and human subjects were selected for this review.

Data Extraction and Synthesis: After assessing data relevance, independent extraction by a sole reviewer was performed. Data were tabulated according to the following categories: pathogenesis, mechanisms, local and systemic factors, and treatment.

Conclusions: Burn wound progression is complex and caused by additive effects of inadequate tissue perfusion, free radical damage, and systemic alterations in the cytokine milieu of burn patients, leading to protein denaturation and necrosis. Even though insufficient evidence exists for causal inferences, infection, tissue desiccation, edema, circumferential eschar, impaired wound perfusion, metabolic derangements, advanced age, and poor general health play important roles. Although consensus-building research is ongoing, current mainstays of treatment include adequate fluid resuscitation, nutritional support, and local wound care, with an emphasis on topical antimicrobial agents and biosynthetic dressings. Identifying early indicators by elucidating possible interacting or synergistic mechanisms and by developing preventative strategies will enhance prevention and treatment.

Key Words: wound conversion, burn wound, burn progression

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Decision making in the treatment of burns remains a challenge despite improved assessment techniques and treatment procedures.[1] In the United States, approximately 2 million people are burned, 80,000 are hospitalized, and 6500 die every year. The initial response to thermal injury involves direct heat-induced protein denaturation and cell death. This is followed by inflammation and ischemia-induced injury, which cause burns of varying skin depth.

The ability of the skin to heal largely depends on the dermis. The contained macrophages produce growth factors, fibroblasts, and extracellular matrix, which control epidermal regeneration. Since the highest concentration of cells and matrix resides in the upper aspect of the dermis, it follows that the deeper the burn, the less rapidly healing will occur. Thus, superficial burns involving the epidermis and papillary dermis tend to regenerate epithelium from sufficient unburned epithelial appendages to allow spontaneous healing with minimal scarring.[1] Deeper burns, involving reticular dermis or full-thickness injuries, are slow to heal, with resultant unstable skin and hypertrophic scarring.

The depth of burn wounds is not entirely static, however, and multiple factors, each acting via a variety of pathophysiologic mechanisms, can promote the deepening of a burn wound. In a subacute time frame of 3–5 days, burns originally assessed to be superficial partial thickness have been observed to progress into deep partial-thickness or full-thickness burns.[2] This process of progressive damage to initially unburned tissue surrounding a burn wound is referred to as burn wound progression, which remains clinically important but poorly understood.

Jackson originally described 3 concentric zones of tissue injury in burn wounds: irreversibly damaged tissue in the zone of coagulation, hypoperfused tissue in the zone of stasis, and edematous tissue in the zone of hyperemia.[3] According to his theory, although tissue in the zones of stasis and hyperemia is at risk for necrosis, it is potentially salvageable, given optimal intervention that preserves perfusion of these zones. Conversely, in the face of suboptimal treatment, partial-thickness burns may readily convert to full-thickness via necrosis of the zone of stasis.

Burn wound progression is clinically relevant not only because it confounds categorization of burn wound depth but also because it may affect morbidity and treatment. As the extent of wound advancement increases, so too does the likelihood of hypertrophic scarring, contractures, need for surgical excision and grafting, burn wound

infection, sepsis, shock, and possibly death.[4] Although technologic advances such as laser Doppler imaging have aided in the assessment of burn wound depth, accurately assessing which burns will convert and determining how to prevent burn wound conversion remain a clinical challenge.[1] The purpose of this article is to outline the current ideology behind burn wound progression and the existing strategies used for prevention.

Pathogenesis of Burn Wound Conversion

Overview of Burn-Induced Tissue Injury

Primary tissue loss in burn injury occurs as a result of protein denaturation secondary to thermal, chemical, electrical, friction, or ultraviolet radiation–induced insults. This process is rapidly followed by activation of toxic inflammatory mediators, especially in the perfused subsurface. Oxidants and proteases further damage skin and capillary endothelial cells, potentiating ischemic tissue necrosis.[2]

Burn wound conversion is also attributed to the secondary consequences of burn injury. Sequelae such as edema, infection, and altered perfusion promote progression of injury beyond the degree of initial cell death. Burn-induced disruption of collagen cross-linking abolishes the integrity of osmotic and hydrostatic pressure gradients, resulting in local edema and larger scale fluid shifts. In addition, damage to cell membranes results in a dynamic cascade of inflammatory mediators that exacerbate already abnormal cell-to-cell permeability, worsening fluid regulation and systemic inflammatory responses.[4]

At the molecular level, both complement activation and intravascular stimulation of neutrophils result in the production of cytotoxic oxygen free radicals. Increased histamine activity, enhanced by the catalytic properties of xanthine oxidase, causes progressive local increases in vascular permeability. Toxic byproducts of xanthine oxidase, including hydrogen peroxide and hydroxyl radicals, appear to directly damage dermal structures.[5]

Mechanisms of Burn Wound Conversion

The pathogenesis of burn wound conversion is related to a multitude of factors (Table 1), many of which are related to the presence of vasoactive and inflammatory mediators in higher-than-normal concentrations. Robson et al[6] suggested the role of vasoconstriction in burn wound conversion. His group described novel prostanoid derivatives involved in burn injury and postulated that an imbalanced ratio of vasodilatory to vasoconstrictive prostanoids can threaten viability of tissue in the zone of stasis. This intriguing hypothesis argues that vasoconstriction compromises the perfusion of perinecrotic partially burned tissue, thereby causing it to advance to full-thickness necrosis.

Vasodilation, too, has been implicated. Up-regulation of inducible nitric oxide synthase (iNOS) may produce peripheral vasodilation that sets off an inflammatory cascade detrimental to the survival of threatened tissue in the zones of stasis and hyperemia.[7] Interestingly enough, up-regulation of transcription factor nuclear factor κB (NF-κB) results in increased downstream production of many inflammatory cytokines. In addition, nitric oxide may react to produce peroxynitrite, an oxygen free radical that causes additional tissue damage.[7]

Free radical injury to the zones of stasis and hyperemia may be involved in the pathogenesis of burn wound conversion. In the setting of acute burns, neutrophil activation and xanthine oxidase activity generate oxygen radicals such as hydrogen peroxide and superoxide. Concomitant decreases in superoxide dismutase, catalase, glutathione, α tocopherol, and ascorbic acid levels impair the body's antioxidant mechanisms.[8] Nagane et al[9] suggest a potential role for antioxidants in the treatment of burn-injury patients, with the goals of both inhibiting free radical formation and scavenging existing free radicals. Increased lipid peroxidation due to cellular oxidative stress may thus contribute to increased necrosis of partial-thickness burns.

Another factor in burn wound progression may be linked to hypoperfusion secondary to edema-related fluid shift. Prostaglandins, histamine, and bradykinin increase in-

TABLE 1. Molecular and Cellular Mechanisms That May Contribute to Burn Wound Conversion

Pathophysiologic Change	Proposed Mechanism	Tissue-Level Consequence	Reference
Vasoconstriction	Decreased level of vasodilatory prostanoids Increased level of vasoconstrictive prostanoids	Insufficient tissue perfusion	Robson et al[6]
Vasodilation	Increased iNOS Increased NF-κB Increased inflammatory cytokines Increased NO	Tissue congestion Free radical damage	Rawlingson et al[7]
Free radical damage	Increased neutrophil and xanthine oxidase activity Decreased levels of superoxide dismutase, catalase, glutathione, α-tocopherol, ascorbic acid	Lipid peroxidation and subsequent cell necrosis	Horton et al[8] Nagane et al[9]
Hypoperfusion	Increased inflammatory cytokines Increased local levels of prostaglandins, bradykinin, and histamine levels	Fluid shifts and edema causing decreased perfusion	Kuo et al[2]
Microthrombosis	Bradykinin may stimulate microthrombosis	Thrombotic perfusion impairment	Nwariaku et al[10] Wirth et al[11]

travascular permeability and promote the passage of fluid in interstitial spaces. As such, local edema translates into both local and systemic fluid shifts that exacerbate hypoperfusion in vulnerable tissue, specifically in the zones of stasis and hyperemia.[2]

Microthrombosis of viable tissue proximal to frankly necrotic tissue appears to be important. Elevated bradykinin levels not only increase vascular permeability but also act to promote coagulation. In combination with the procoagulant properties of thermal energy, bradykinin may stimulate microthrombosis in the zone of stasis and, as such, contribute to the progression of superficial burns to deeper ones.[10] Preliminary data in animal models suggest a possible role for bradykinin antagonists in preventing sequelae of burn injury.[11]

Factors Affecting Burn Wound Conversion

Local Factors

Several factors act locally to predispose partial-thickness burns to progress to deeper wounds (Table 2). Most notable are infection, tissue desiccation, collateral wound edema, and circumferential eschar in the extremities.[12]

Bacterial infection contributes to the process and is decreased by topical antimicrobial agents. In a retrospective study of 342 patients with 10%–50% total-body-surface-area burns, Sawhney et al[13] demonstrated that topical 1% silver sulfadiazine decreased both the conversion rate and the healing time of deep partial-thickness burns. The bacterial load of predominant surface microorganisms, specifically *Staphylococcus aureus*, *Pseudomonas* species, and *Klebsiella* species, was also decreased.

Silver-coated barrier dressings have also been shown to be effective in burns closed with cultured skin substitutes. Supp et al[14] demonstrated the utility of one such dressing, Acticoat, in decreasing wound infection and conversion in an animal model of athymic mice treated with cultured skin substitutes.

It must be noted, however, that antibiotic overuse in the context of burn injury has been implicated in the increased prevalence of multidrug resistance in nosocomial pathogens. Multidrug-resistant bacteria, including *Pseudomonas aeruginosa*, methicillin-resistant staphylococci, and vancomycin-resistant enterococci, are associated with high wound morbidity.[15]

Edema, desiccation, and circumferential eschar are local factors that increase rate of burn wound progression by decreasing tissue perfusion. Local hyperemia and desiccation compromise perfusion via shifts in intravascular and interstitial fluid volumes. Both processes decrease intracellular fluid volumes, altering hemostasis in a manner that ultimately decreases intravascular volume and inhibits oxidative metabolism of partially burned tissue. Circumferential eschar in the extremities acts mechanically, compromising distal tissue perfusion when escharotomy is delayed.[12]

Systemic Factors

Systemic factors can be considered as those that impair wound perfusion, those that predispose to infection, those related to metabolic derangements, and those that are related to general health status (Table 3).

Impaired wound perfusion often occurs secondary to shock, hypoxia resultant from pulmonary insufficiency, and massive wound sepsis.[12] A number of studies have demonstrated that inadequate fluid resuscitation exacerbates the tendency toward burn wound deepening. Using a rat model of fluid resuscitation, Kim et al[16] illustrated that conversion of partial- to full-thickness burns is hastened when fluid resuscitation fails to provide adequate flux, or perfusion, to burn wounds. Similarly, in a review of pediatric burn resuscitation, Carvajal[17] argued that restoring and maintaining perfusion pressures maximally oxygenates injured and noninjured tissues and, as such, promotes spontaneous healing while minimizing wound conversion and bacterial colonization. These

TABLE 2. Local Factors That May Contribute to Burn Wound Conversion

Proposed Mechanism	Contributing Factors	Tissue-Level Consequence	Reference
Impaired wound perfusion	Shock	Bacterial virulence factors causing cell death	Matouskova et al[12]
	Hypoxia		Kim et al[16]
	Massive wound sepsis	Inflammation causing cell death	Carvajal et al[17]
	Inadequate fluid resuscitation		
Infection predisposition	Decreased IL-12	Cytokine alterations increase susceptibility to wound infection	O'Sullivan et al[18]
	Increased TH-2 cells		Bjornson et al[19]
	Decreased C3 conversion		
Metabolic derangements	Depressed glucose uptake	Metabolic insufficiency	Turinsky et al[21]
	Depressed lactate release		
	Increased metabolic need		
General health status	Advanced age	Less robust healing, immune function, and tissue perfusion	Ward et al[22]
	Vascular pathology, including atherosclerosis, coagulopathy, and peripheral vessel disease		
	Diabetes mellitus		
	Immunosuppression		

TABLE 3. Systemic Factors That May Contribute to Burn Wound Conversion

Pathophysiological Change	Proposed Mechanism	Tissue-Level Consequence	Reference
Infection	Overwhelms metabolic capacity of tissue	Bacterial virulence factors causing cell death	Sawhney et al[13]
		Inflammation causing cell death	Supp et al[14]
Edema	Fluid shifts decrease intracellular and intravascular fluid, thereby compromising cellular respiration	Decreased tissue perfusion	Kuo et al[2]
Tissue desiccation	Decreased intracellular and intravascular fluid compromises cellular respiration	Decreased tissue perfusion	Kuo et al[2]
Circumferential eschar in the extremities	Mechanically decreases vessel caliber, compromising flow to distal tissue	Decreased tissue perfusion	Matouskova et al[12]

2 vibrant studies demonstrate the harmful effect, even at the tissue level of a suboptimal resuscitation in thermal injuries.

Impaired infection control is a cytokine-mediated process that affects most patients that suffer large burns. Alterations in the cellular milieu have been suggested by O'Sullivan et al,[18] who nicely demonstrated increased levels of T helper-2 lymphocytes and decreased levels of interleukin-12 in an animal model of trauma and burn injury. According to their work, these systemic alterations are associated with a decreased resistance to infection. Abnormal complement activity has also been demonstrated postburn. Specifically, Bjornson et al[19] showed a decreased rate of alternative complement pathway-mediated C3 conversion in the serum of 18 burned patients, as compared with 25 controls. Decreased C3 conversion in burn patients was associated with large burns, full-thickness burns, and infectious complications such as bacteremia and pneumonia. The underlying implication is that systemic alterations in the cytokine and cellular milieu worsens burn injury and predisposes to infection.

Metabolic and nutritional derangements can also exacerbate progression of burn depth.[20] The basal energy expenditure of burned patients may be 3 times normal values.[21] Failure to provide adequate nutrition, replete electrolyte deficits, and correct lactic acidosis may thus contribute to ischemia of viable tissue surrounding partial-thickness burns, thereby promoting wound conversion.

Patient-Dependent Factors

Other patient-dependent factors such as advanced age, poor general health, and predisposition to systemic infection may underlie increased tendency toward burn conversion.[22] Disorders that compromise the vasculature, including atherosclerosis, coagulopathy, and peripheral vessel disease of other etiologies, may impair tissue perfusion. In addition, conditions such as diabetes and immunosuppression impair a host's ability to fight systemic infection.

Prevention of Burn Wound Conversion

Broadly stated, the goal of treating partial-thickness burn wounds is to promote healing while minimizing scarring and contracture. Because superficial wounds are likely to spontaneously heal with good cosmetic outcome, the clinician's underlying goal is to prevent wound progression (Table 4).

Systemic Intervention

Fluid resuscitation is essential to maintain tissue perfusion.[16] Adequate nutritional status should be maintained, using enteral feeding if necessary, to prevent metabolic derangements that could compromise cellular tissue respiration.[20] Anti-inflammatory agents have been shown to decrease edema and increase perfusion of burned tissue, although their clinical effectiveness is not confirmed.[23]

Local Wound Care: Antibiotics, Dressings, and Bioactive Agents

The common ground is to reduce continuing damage by inflammation stimulated by the initial injury. Careful wound debridement removes surface eschar, bacteria, and neutrophils, reducing oxidant activity and decreasing proteases known to deactivate locally released growth factors.

Appropriate for clean partial-thickness burns, occlusive dressings maintain a moist wound environment that hastens epithelialization and closes a wound to contamination. For limited superficial partial-thickness burns, infection is uncommon, and fine-mesh petrolatum gauze, Xeroform, or Mepitel is an alternative that hastens healing as well.[24] Bacitracin, bacitracin plus polymyxin B sulfate, may be added and is suitable for use on the face. For deeper burns, topical antibiotics, usually twice daily silver sulfadiazine or a nanocrystalline silver delivery system (Acticoat), are indicated to decrease microbial load and prevent infection.[25] Mafenide acetate is also prescribed where greater eschar penetration is required.

Biologic dressings such as xenograft and allograft have shown improved healing of partial-thickness wounds as compared with silver sulfadiazine.[26,27] Recombined human/pig skin (RHPS), which is composed of allogeneic keratinocytes cultured on cell-free pig dermis, is a hybrid biologic product that allows wound coverage while promoting epithelialization from adnexal remnants in the wound bed.[28]

The biologic strategy for the use of temporary skin substitutes is to provide a contact between the wound and a bioengineered dermal matrix. Epithelial cells are known to migrate along matrix proteins, and this approach is very effective for a superficial mid-dermal or indeterminate burn. The outer synthetic layer is also protective against environmental insults.[29] Biosynthetic dressings such as Biobrane, a silicon film with enmeshed nylon and collagen, promotes

TABLE 4. Treatment Measures That May Prevent or Reduce Burn Wound Conversion

Treatment Measure	Avoided Consequence	Reference
Fluid resuscitation	Tissue hypoperfusion	Kim et al[16]
	Shock	
NSAIDS	Local tissue edema	Tan et al[23]
	Tissue hypoperfusion	
Nutritional support	Metabolic derangements	Pasulka et al[20]
	Depressed cellular respiration	
Topical antibiotics	Infection	Stern et al[25]
	Sepsis	
Occlusive wound dressings: biological, biosynthetic, nonbiologic, and vacuum-assisted	Wound desiccation Delayed epithelialization Wound contamination	Vloemans et al,[26] Chatterjee et al,[27] Konigova et al[28] Barret et al,[30] Gotschall et al,[24] Morykwas et al[32]
Local bioactive agents for enzymatic debridement and growth factor elution	Necrotic tissue burden	Hansbrough et al,[35] Shapira et al[36]
	Infection	Brown et al[37]
	Sepsis	
	Decreased local growth factor levels	
Early surgical excision and grafting	Necrotic tissue burden	Kao et al[2]
	Infection, sepsis	Konigova et al,[28] Engrave et al[38]
	Hypertrophic scarring	
	Requirement for late grafting	
	Delayed healing	
Correction of patient-dependent pathologic factors	Tissue hypoperfusion (in the setting of vascular pathology, including atherosclerosis, coagulopathy, and peripheral vessel disease)	Ward et al[22]
	Infection predisposition (in the setting of diabetes mellitus and immunosuppression)	

epithelialization and has been shown to be very effective in superficial scalds and avoids painful dressing changes in children.[30]

Though used much less frequently in burns than occlusive dressings, negative-pressure bandages (Vacuum Assisted Closure [VAC] devices) may also be effective. Although not proven in human subjects, a swine model demonstrated decreased burn depth of partial-thickness burns that received subatmospheric pressure dressings within 6 hours of burn injury.[31] In a porcine wound model, the VAC has been shown to increase blood supply and reduce the incidence of infection.[32] The major mechanism of action of the VAC device is the reduction of tissue edema through the application of subatmospheric pressure.[33] Secondly, it is hypothesized that the application of mechanical force to wounds induces tissue deformation at the level of individual cells, in turn altering gene expression, inducing cell proliferation and angiogenesis, and hence promoting wound healing. The cells which are stretched can divide and proliferate in response to soluble growth factors, whereas unstretched cells assume a more spherical shape, are cell-cycle arrested, and tend to undergo apoptosis.[34,35] In addition, there is increased granulation tissue production and decreased bacterial levels.

Recent studies have introduced the concept of treating burn wounds with bioactive agents that may promote healing and decrease wound conversion. Topical enzymatic debridement with collagenase has been shown to speed healing of partial-thickness wounds, relative to silver sulfadiazine ointment.[35] Enzymatic debridement with papain has also been studied, although results are equivocal.[36] In addition, addition of growth factors may promote healing, as evidenced by Brown et al,[37] who demonstrated that epidermal growth factor (EGF) decreases healing time in partial-thickness burns

CONCLUSION

The progression of depth of partial-thickness burns (Fig. 1) is a complex and fascinating topic. Hypotheses based on animal and human subjects hint at several potential underlying mechanisms likely rooted in the additive effects of inadequate tissue perfusion, free radical damage, and systemic alterations in the cytokine milieu of burn patients.

In our experience, the risk of progression mainly correlates with a patient's total body surface area (tbsa) of burn. Anecdotally, we have found larger burns have more of a tendency to deepen compared with smaller burns. We feel there is a relationship with the amount of fluid resuscitation required with the probability of a wound progressing from superficial partial thickness to deep partial thickness. For example, a patient who has a 40% (tbsa) burn of intermediate depth will have a stronger possibility of the wound progressing deeper compared with a patient who sustains a 5% (tbsa) burn of the identical depth. As shown in this review, there are

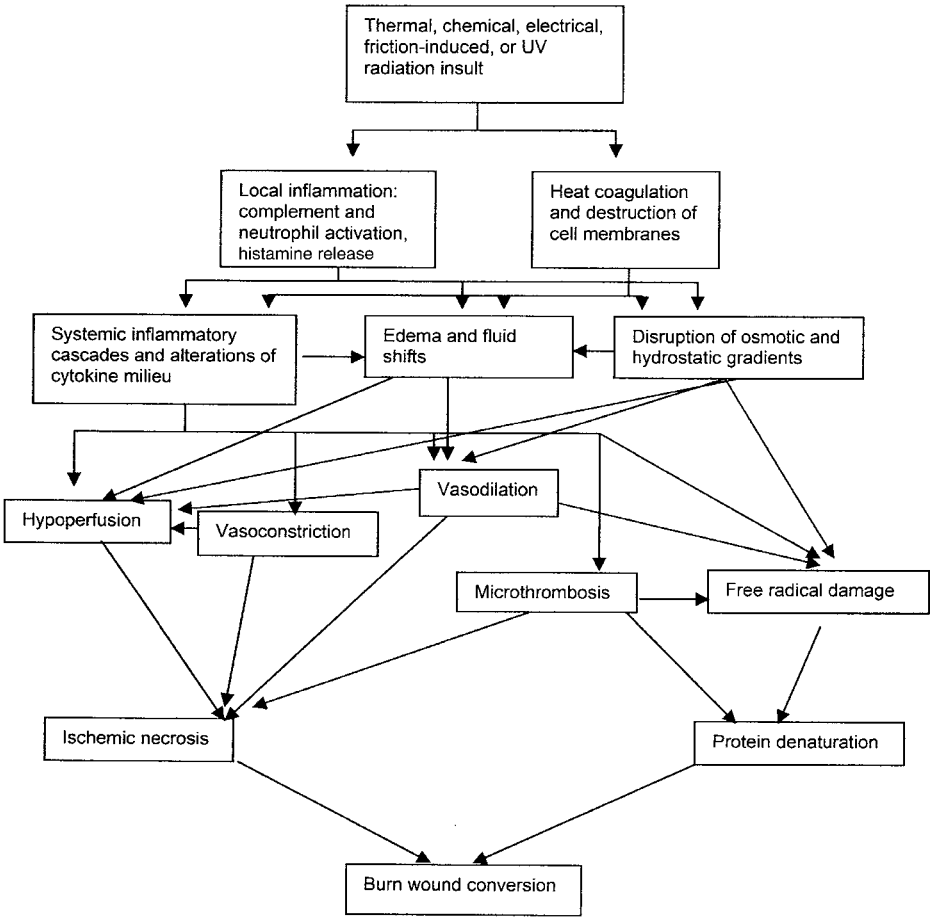

FIGURE 1. Schematic of burn conversion.

a number of treatment modalities used to prevent progression, but there continues to be no absolute method to thwart this phenomenon.

Current mainstays of the treatment of partial-thickness burn wounds include adequate fluid resuscitation, nutritional support, and local wound care, with an emphasis on topical antimicrobial agents and biosynthetic dressings. Consensus-building research is ongoing. Future directions in the care of partial-thickness burns will likely focus on the development of biosynthetic dressings, bioactive treatments such as enzymatic debridement and growth factor inoculation, and imaging modalities that may better predict burn wound depth.

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