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The Burn Wound Exudate – an under-utilized resource

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Abstract

Introduction—The burn wound exudate represents the burn tissue microenvironment. Extracting information from the exudate relating to cellular components, signaling mediators and protein content can provide much needed data relating to the local tissue damage, depth of the wound and probable systemic complications. This review examines the scientific data extracted from burn wound exudates over the years and proposes new investigations that will provide useful information from this underutilized resource.

Method—A literature review was conducted using the electronic database PubMed to search for literature pertaining to burn wound or blister fluid analysis. Key words included burn exudate, blister fluid, wound exudate, cytokine burn fluid, subeschar fluid, cytokine burns, serum cytokines. 32 relevant article were examined and 29 selected as relevant to the review. 3 papers were discarded due to questionable methodology or conclusions. The reports were assessed for their affect on management decisions and diagnostics. Furthermore, traditional blood level analysis of these mediators was made to compare the accuracy of blood versus exudate in burn wound management. Extrapolations are made for new possibilities of burn wound exudate analysis.

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Results—Studies pertaining to burn wound exudate, subeschar fluid and blister fluid analyses may have contributed to burn wound management decisions particularly related to escharectomies and early burn wound excision. In addition, information from these studies have the potential to impact on areas such as healing, scarring, burn wound conversion and burn wound depth analysis.

Conclusion—Burn wound exudate analysis has proven useful in burn wound management decisions. It appears to offer a far more accurate reflection of the burn wound pathophysiology than the traditional blood/serum investigations undertaken in the past. New approaches to diagnostics and treatment efficacy assessment are possible utilizing data from this fluid.

Burn wound exudate is a useful, currently under-utilized resource that is likely to take a more prominent role in burn wound management.

INTRODUCTION

Exudate is a liquid produced by the body in response to tissue injury. In general wound management, much information has been gleaned from the wound exudate, particularly related to chronic wounds. In fact, new approaches to the treatment of chronic wounds have been directed at the wound exudate to influence wound healing [1]. The wound exudate is regarded as a reflection of the wound bed physiology. In much the same way, the burn wound, the ultimate inflammatory injury, creates an exudate that represents the burn tissue microenvironment. Extracting information from the exudate relating to cellular components, signaling mediators and protein content can provide much needed data relating to the local tissue damage, depth of the wound and probable systemic complications. In this regard the exudate may be the first indicator of possible systemic complications to which the patient with significant burn injury is predisposed. Systemic inflammatory response syndrome (SIRS) and subsequent multiorgan failure is thought by many authors to be related to the outpouring of cytokines from the burn wound into the blood stream [2–10](added more references here). Thus, the burn wound exudate should be the logical area for early analysis of cytokine levels.

The exudate examination is likely to provide a more accurate reflection of the burn injury than the traditional analysis of blood levels, which we view as a lagging indicator. The limited literature pertaining to burn exudate analysis already provides useful information for burn assessment and management, but the explosion of molecular biological knowledge should enable us to glean significantly more relevant data from this useful resource. This review examines the scientific data extracted from burn wound exudates over the years and proposes new investigations that will provide very useful information extracted from this underutilized resource.

METHODOLOGY

A literature review was conducted using the electronic database PubMed to search for literature pertaining to burn wound or blister fluid analysis. Key words used for the search included – burn fluid; burn wound exudate; blister fluid; burn cytokines; sub eschar fluid; Thirty two papers relevant to the search topic were selected and analyzed based on the fact that they specifically utilized burn wound exudate as their diagnostic or testing resource.

Additionally some studies that utilized traditional blood/serum investigations of pathophysiologic markers were selected as a basis of comparison with exudate diagnostics. These reports were assessed for their affect on management decisions and diagnostics. Furthermore, traditional blood level analysis of these mediators was made to compare the accuracy of blood versus exudate in burn wound management. Extrapolations are made for new possibilities of burn wound exudate analysis

RESULTS: HISTORICAL DATA GLEANED FROM BURN WOUND FLUID/ EXUDATE

Data accumulated from the study of burn wound fluid has had an important influence on management decisions pertaining to burn injuries. Early investigations on this exudate that accumulates below the eschar demonstrated toxic, immunosuppressive and pro-inflammatory traits that may have reinforced surgeons decisions to perform early escharotomy/escharectomy [11]. In contrast, other studies showed protective and positive wound healing effects of this fluid, particularly in early blisters [12]. Merging current knowledge with the experiences of the past, we seek to develop a logical narrative and explore possible new useful burn wound exudate diagnostics. First, it is relevant to explore the historical data that have formed a basis for exudate analysis in varying contexts of burn wound management.

- Burn wound exudate analysis can prevent misinterpretation of blood results

  Analysis of the burn wound exudate is useful in explaining pathophysiologic phenomena that might have been misinterpreted if blood level analysis alone was considered. A viable example was provided by Prager *et al*. [13], who focused on the burn wound's exudate in 19 burn wound patients with regard to fibrin degradation products (FDPs). Fibronectin fragments in the exudate induce the formation and release of matrix metalloproteinases (MMPs) including collagenase and neutrophil elastases which are responsible, at least in part, for the derangements in extracellular matrix (ECM) deposition seen in acute burn injury. FDPs in the burn wound exudate reflect the response to the burn wound tissue – local tissue breakdown, and fibrinolysis results in increased FDP levels which spill over into the blood. An isolated consideration of blood level FDPs which do not correlate to the burn wound exudate content might lead to an incorrect interpretation of systemic coagulopathy rather than local wound proteolysis.

  In addition, Sosa *et al*. [14]demonstrated that burn wound fluid may contain a significant amount of creatinine with the burn wound acting as an extrarenal site for creatinine loss. This condition rapidly reverses when the burn wound is healed. Nevertheless the creatinine loss within the acute phase might masquerade as a renal dysfunction by producing a falsely normal serum creatinine clearance. Although this study was presented on the basis of only one case report, monitoring of exudate levels could result in a better understanding of the background pathophysiologic process.

- Sub-eschar fluid - potential toxicity of the retained eschar

Burn tissue and edema fluid may act as a reservoir of potent immunosuppressive substances. Dyess *et al.* collected sub-eschar tissue fluid (STF) from the subcutaneous tissue underlying areas of full-thickness burns, and added this fluid to cultures of lymphocytes obtained from healthy donors. The result was a complete attenuation of the lymphocyte proliferative response to mitogens and specific antigens, reflecting a potential immunosuppressive response. The authors suggested that burn surgeons perform an early escharectomy in order to avoid subsequent systemic immunosuppressive effects. This coincided with clinical observations made by surgeons at the time that retaining eschar made patients vulnerable to sepsis and increased catabolism. The hypothesis of STF acting as a 'toxin reservoir' and markedly contributing to the early stage inflammatory phase was also supported by multiple authors [11] [15] These authors showed that the intravascular injection of STF in an animal model produced a systemic organ dysfunction similar to SIRS and demonstrated that STF was suppressive in humoral and cell-mediated immunologic functions. In fact, a gradual reabsorption of STF, rather than an early-stage evacuation, could potentially result in a prolonged immune compromise. Thus, again, these authors suggested early eschar excision for severely burned patients to improve survival rates by decreasing immunosuppression, resultant sepsis and limiting the severe catabolic process that accompanies the body's attempt to discard the eschar.

- Burn exudate and blister fluid - effect on wound and scarring

  The events within the burn wound extracellular matrix (ECM) milieu affect the healing process (and scarring) of the burn wound itself. In particular, the protease/anti-protease profile is known to be closely related to angiogenesis and re-epithelialization. The result of a study by Claufield *et al.* [16] performed on partial thickness burn wounds surface demonstrated that a high protease level-wound environment is associated with a lower VEGF level, a more uniform wound bloodflow, and a well-healed wound with an architecturally normal epidermis. Work by Nissen *et al.* [17] suggests that the endothelial cells at the site of the burn injury experience a very different early environment than endothelial cells at the sites of surgical injuries. Whereas the appearance of a robust proangiogenic stimulus is rapid in surgical wounds, injuries confined to the dermis (as in burns) demonstrate delayed angiogenic activity. The results of the study suggest that the injuries confined to the dermis elicit a less robust initial angiogenic stimulus than deep surgical wounds. This introduces the potential of moderating this environment utilizing angiogenic influencing agents. Thus, it is apparent that a balanced inflammatory, angiogenic wound mileu is desirable to stimulate healing while limiting scarring.

  In this regard Pan *et al.* [12, 18] examined wound blister fluids assessing the release of angiogenin from both deep-partial and superficial-partial thickness burn wound fluids (DPTB-SPTB). The correlation between the levels of angiogenic factors, neovascularization and resultant hypertrophic scarring suggested that neutralizing angiogenin in an early phase could potentially control the clinical

outcome of DPTB and supported the importance of examining burn wound fluid in controlling eventual scar formation.

Further evidence of stimulated angiogenesis and potential scarring was provided by Avniel *et al.* [19], who examined the levels of the chemokine CXCL12 and its receptor CXCR4 both in burn blister fluid and in the healthy tissue surrounding burn wounds. CXCL12, also known as stromal derived factor-1 (SDF-1), has been identified as a powerful chemoattractant for immature hematopoietic stem cells and endothelial progenitor cells. The authors demonstrated that CXCL12 levels are markedly increased in burn blister fluid in the early stages, whereas a high expression is detected by surrounding fibroblasts and endothelial cells in a secondary stage, suggesting a short-term skin protecting action after burn injury followed by a possible shift in support of fibrosis in a prolonged secondary phase. The authors thus concluded that a modulation of epithelialization and fibrosis could be achieved through a selective inhibition of CXCR4, leading to faster healing and less scarring following a burn injury. In practical terms, it would appear that a more superficial burn requires less angiogenic stimulus, and if over-stimulated can result in hypertrophic scarring. This appears to be controlled by protease/anti-protease levels in superficial wounds limited VEGF stimulation and hypertrophic scars. However, a deeper burn confined to the dermis exhibits a delay in angiogenesis, overstimulation of protease activity (as with chronic wounds) and decreased endothelial progenitor cells and VEGF release. Monitoring of these levels in the exudate in accordance with the depth of the burn can thus provide important information on healing and scarring and provides opportunity for therapeutic intervention.

The suggestion of a possible role of burn wound fluid constituents and subsequent wound healing/scarring was first addressed by Wilson *et al.* in 1997 [20]. They demonstrated that the addition of burn fluid to culture medium stimulated fibroblasts to contract to a greater degree in the first 24–48 hours. These results suggested the presence of components which promote contraction within the burn blister fluid, contributing to eventual hypertrophic scarring in the end. Furthermore, Inoue *et al.* [10] specifically addressed the presence and level of cytokines within burn blister fluids which play a role in fibroblast proliferation such as platelet-derived growth factor (PDGF), interleukin-6 (IL-6), transforming growth factor-alpha (TGF-α), TGF-β1, IL-1α, and IL-1β. They claimed that the epithelialization proceeded faster if the blister wall was left intact with the cytokines stimulating fibroblast proliferation. Additionally, Ono *et al.* [8]recommended keeping the blister wall intact to allow the blister fluid, filled with cytokines (including IL-α, IL-1β, IL-6, IL-8, TGF-α, TGF-β_1 and TGF-β2) and wound healing factors (EGF, bFGF), to protect and encourage healing of superficial epidermal and superficial dermal burns through a stimulation of keratinocyte proliferation and facilitating the migration of monocytes, neutrophils, macrophages and fibroblasts. These authors suggested that film dressings should be used to dress partial thickness wounds, mimicking the blister wall and thus recreating an optimal healing environment with retention of cytokines. Additional burn fluid cytokine data came from Voronkina *et*

al. and McCarthy *et al.* [21][22]. Voronkina showed that one-to-two percent of burn fluid isolated from dressings helps accelerate the cell proliferation and promotes fibroblast monolayer contraction, all of which help in the healing of the wound. McCarthy identified heparin-binding epidermal growth factor (HB-EGF) as well as platelet-derived growth factor (PDGF) in human burn wound fluid in the early stage; it was also demonstrated that HB-EGF is subject to a re-distribution at the burn wound margins patterned significantly different from that of the non-injured skin, suggesting a healing biological effect for HB-EGF either alone or in combination with PDGF.[22] In addition, Cribbs *et al.* [23] [24]suggested that HB-EGF plays an essential role in the immediate cellular response to burn wounds by stimulating and proliferating the production of other response factors. They demonstrated the strong correlation between keratinocyte proliferation in burn wounds and cell expression of HB-EGF and TGF-α, especially in the epidermal basal layer of the burn site. The study found that keratinocyte and hair follicle epithelial cell proliferation peaked at post-burn day five.

- Blister fluid analysis in other epidermal shedding states

  Blister fluid cellular analysis has been useful in other similar disease profiles such as severe drug induced epidermal shedding. De Araujo *et al.* [25] analyzed blister fluids to measure cellular components that induce keratinocyte necrosis in toxic epidermal necrolysis (TEN). Specifically, soluble death factors such as Tumor Necrosis Factor (TFN-γ), TNF-related apoptosis-inducing ligand (TRAIL), TNF-α and TNF-like weak inducer of apoptosis (TWEAK) proteins were chosen as candidate variables. Most were found to be significantly higher in the blister fluids compared to the healthy subjects suggesting that early treatment and restricting progression should target soluble factors in the local environment of the blister.

In summary, investigations of burn wound exudate have fashioned treatment choices and provided clues for burn wound conversion, healing and scarring. These early studies demonstrated that collections of sub-eschar fluid beneath necrotic tissue could have immunosuppressive effects with risks of sepsis. Early escharectomy, was thus logical. Cytokine profiles were seen to be both beneficial and detrimental to good healing. Thus cytokine bursts within the exudate appear to need a form of control as yet undefined; the correct balance of growth factors and inflammatory cytokines appear to promote a healing environment. However, overstimulation of angiogenic factors may result in exuberant granulation, vascularity and hypertrophic scarring. Additionally, as with new chronic wound strategies, the wound exudate may provide a therapeutic target at the wound interface that would ultimately affect the wound-healing trajectory. This has been suggested in TEN, but may well be applicable to thermal injury in general.

BLOOD/SERUM MEASUREMENT OR BURN WOUND EXUDATE ANALYSIS?

Traditionally, investigations of inflammatory mediators, growth factors and cytokine responses have been measured in the blood. However, is this an accurate refection of the wound physiology? Does the wound exudate offer a more accurate representation of the local burn wound tissue and its potential systemic effects?

Mikhal'chik *et al.* compared the cytokine levels in the blood plasma with that in the exudate in pediatric burn wounds [26]. The study analyzed 27 cytokines in nineteen children with severe burns. Cytokine levels in the plasma and the exudate were compared over 18 days. The study revealed that the cytokine levels were higher in the exudate over the entire duration of the 18 days compared to the blood. The cytokine levels were measured 2–5 days after the injury occurred, and before any surgical treatment of the wound. High levels of cytokines in the exudate can potentially spill over into the blood, which causes systemic complications such as SIRS. The higher levels of cytokines in the exudate compared to the blood can be expected due to high levels of chemokines that are present in the wound area. Certain proinflammatory cytokines such as IL-1, IL-2, IL-6, IL-8, TNF-α, and TNF-γ can activate neutrophils which generate oxygen radicals and proteases. The overproduction of free radicals by activated neutrophils leads to oxidative tissue damage as well as multi-organ failure [26].

Macrophages, lymphocytes, fibroblasts, keratinocytes, and endothelial cells are essential to the healing process of the burn wound. These cells are regulated by cytokines present in the exudate of burn blisters. Spontaneous deepening of the burn wound may follow generation of oxygen radicals and proteases. Secondary necrosis can be prevented through regulation of neutrophil activity. Hyperactivation and impairment in neutrophil apoptosis can be prevented through surgical cleaning of the wound and skin autografting in order to achieve accelerated wound healing through balanced neutrophil activity [26]

Findings of this study indicate that IL-8 concentration in wound exudate exceeded that in the plasma, which is consistent with previously published data [8, 27, 28]. The concentrations of IL-1β, IL-1ra, IL-8, MCP-1, MIP-1α, TNF-α, and GM-CSF in the exudate were higher than in blood plasma at all periods of the study. By contrast, the concentrations of IL-2, IL-6, IL-10, G-CSF, IFN-γ, PDGFbb, and VEGF in blood plasma were higher than in wound exudate. Increases in IL-8, MCP-1, and TNF-α in blood plasma is associated with the risk of serious complications, possibly via over stimulation of radical production by neutrophils, which results in oxidative damage to various organs [26].

The authors conclude that the systemic inflammatory response after severe burns is characterized by a significant increase in the concentrations of IL-6, IL-8, and MCP-1. The development of serious complications is associated with an increase in the content of IL-ra, IL-6, IL-8, IL-10, TNF-α, IFN-γ, MCP-1, and G-CSF in blood plasma. The concentrations of IL-1β, IL-8, MCP-1, TNF-α, MIP-1α, and GM-CSF in burn wounds of patients with systemic complications are much higher than in the plasma. These differences occur for at least 18 days after injury (period of active surgical treatment) [26]. This study convincingly demonstrates the importance of measuring cytokine levels in the exudate to accurately reflect the wound bed status and to anticipate blood level increases from 'spill over' from the wound itself.

DISCUSSION (future directions)

It is evident that useful information has been obtained from burn wound exudate that could potentially influence treatment decisions. At this stage, the explosion of molecular biological knowledge opens doors to new analyses and diagnostics using the wound exudate.

Among the important considerations in burn wound therapy today, early objective diagnosis of the burn wound depth, burn wound conversion influences and the ability to manipulate mediators and cytokines within the exudate are all new possible strategies that would make excellent use of the burn wound exudate as a useful resource.

Marrying some of the recent advances in molecular biology with those of previous publications is useful. In particular, the earlier discussion on burn scar evolution in relation to wound fluid has been advanced. Van den Broek *et al.* examined burn wound exudates isolated from deep burn wounds [29]. They were found to contain many cytokines, including chemokines and growth factors related to inflammation and wound healing. In particular a skin-specific chemokine CCL27 was investigated in relation to its effect on different cellular subpopulations and ultimately on scar outcome. Thus adipose-derived stem cells (ADSCs) from fatty tissue (deep burn), fibroblasts and keratinocytes were compared in relation to their response to CCL27. A markedly increased response was noted from ADSCs in the form of increased expression of VEGF and IL-6, mediators known to stimulate granulation tissue, explaining the clinically evident hypertrophic scarring seen in the great proportion of deeper burns. The implication of this study was that full-thickness wounds, which penetrate the adipose tissue containing stem cells, responded more vigorously to wound-bed-derived CCL27 than do superficial dermal wounds containing dermal fibroblasts or keratinocytes. This suggested that burn wound exudates may trigger ADSCs more than fibroblasts to produce granulation tissue-forming factors in deeper burns where adipose tissue is exposed. This has profound implications as ADSC mono-cultures that are exposed to burn wounds may be expected to increase scar formation ironically, by promoting unwanted angiogenesis and granulation tissue formation. Thus, this practice that is evolving at present may turn out to be contraindicated in early burn management. This observation may be altered in skin substitute tissue engineering combining different cellular elements (including ADSCs) to promote cross talk and possible synergies. The final word has not been written on this relationship of fatty tissue component interaction and hypertrophic scarring but what is evident is that burn exudate is an important mediator in this cellular cross-talk dynamic.

It is important to note that some of the evidence cited pertains to in vitro testing that may have limitations in reflecting the true thermal injury. However, the only unsupportive data that has yet to be validated concerns the actual volumes and variation on some growth factor elaboration within the burn wound fluid (29). This is a difficult assessment as it varies in timing, is pleiotropic with differing effects on local tissue and is dependent on the particular management of that burn wound. Thus, levels are subject to change and are unlikely to be absolute and defined. In contrast, however, the elaboration of angiogenic markers such as endothelial progenitor cells, levels of certain growth factors such as VEGF, inflammatory signaling mediator/cytokine analysis are all well supported by clinical and laboratory testing

and are likely to be important measurable parameters in future analyses of burn wound status.

An added factor that is important to consider is the method of collection of wound fluid exudate. Differing techniques of wound fluid collection were utilized in the studies cited. The simplest collection technique involved blister fluid aspiration (10,12,14,18,20,25), but that is limited to more superficial wounds and can usually be used only once. Allied to this, some authors have collected fluid under film dressings (17) while the majority of studies have extracted fluid from absorptive dressings, filter papers or collection bags (13,14,16,26). This has only been possible due to the improved accuracy of current technologies and the smaller volumes that can be tested. However this technique does have limitations in terms of potential contamination, accessibility and assessment of timing of fluid elaboration. In this regard, our laboratory has designed a micro-fluidic patch that evenly absorbs fluid into a test tube that can be emptied without violating dressings or interfering with management. This will allows us to standardize fluid collections and timing of analyses. This methodology and analysis of results will be reported on in forthcoming publications.

Finally, it is apparent that in many situations such as the studies noted above, there is non-correlation of cellular signaling mediators with blood levels and wound exudate. Wound exudate would appear to more accurately represent the wound interface and provides a valuable resource for targeting and designing therapies to enhance healing and decrease possible systemic effects resulting from a ‘spill-over’ of these wound derived factors into the blood stream. We believe that monitoring the tissue interface and managing the local situation is likely to positively impact on the systemic situation rather than the converse. Alterations in the wound exudate mirror the state of the underlying wound and may also give insight into the general health of the patient. Therefore, careful monitoring of the exudate could provide valuable information for the application of systemic and local therapies.

CONCLUSION

Analysis of the burn wound exudate has provided useful information over the years. Such information relating to sub-eschar immunosuppression has prompted strategic management changes. However, further information has yet to be gleaned and assessed relating to growth factors and angiogenesis, cellular constituents, inflammatory mediators and other cytokines. Collectively, this information may have great impact on wound depth diagnostics, burn wound conversion, hypertrophic scarring and objective assessment for wound dressings and therapeutics. Burn wound exudate is a useful, currently under-utilized resource that is likely to take a more prominent role in burn wound management.

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Highlights

- This review examines the information gleaned form the burn wound exudate and highlights the usefulness of exudate analysis in management decisions
- Burn wound exudate is likely to be a more accurate reflection of the wound milieu and healing than serum measurements
- Cytokine levels and cellular component analysis of burn wound exudate should prove useful for assessing dressing efficacy and monitoring healing progress