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Review

Biomarkers of sepsis in burn injury: an update

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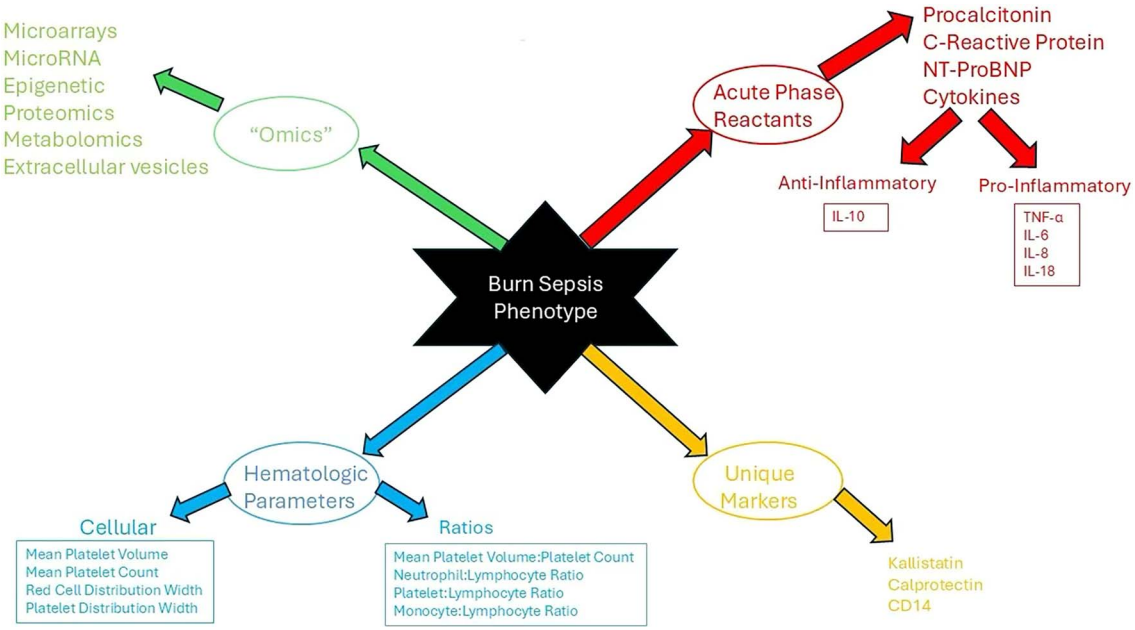
Abstract

Sepsis, a dysregulated response to infection, is a leading cause of death after burn injury. Changes in the immune response as well as the loss of the skin, the primary barrier to infection, contribute to the increased risk for infection and sepsis in burn patients. This higher risk is further compounded by the development of the systemic inflammatory response and hypermetabolic state, which limit the utility of commonly used infection markers. As such, the development of sepsis biomarkers after burn injury is an imperative. A sepsis biomarker would facilitate earlier diagnosis and treatment of sepsis, thus decreasing length of stay, morbidity, and mortality after burn injury. Numerous different biomarkers, ranging from acute phase reactants, cytokines, and inflammatory markers to omics analyses and extracellular vesicles have been assessed as potential biomarkers in burn sepsis. To date no single biomarker has proven useful as the sole indicator for sepsis. The future of burn sepsis biomarkers will likely require a panel of biomarkers from all categories. The purpose of this review article is to list the various biomarkers that have been studied in burn sepsis and describe their clinical utility and future use in patients with burn injury.

Graphical Abstract



Keywords: Sepsis; Burn injury; Biomarkers; Infection; Diagnosis

Highlights

- Identification of sepsis biomarkers after burn injury is essential to improve patient outcomes.
- A biomarker panel consisting of various indicators of sepsis, including acute phase reactants, cytokines (both inflammatory and anti-inflammatory), epigenetic markers and other novel biomarkers ranging from calprotectin to kallistatin could contribute to earlier sepsis diagnosis.
- Patient sepsis phenotype may influence the composition of sepsis biomarker panels.

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Background

Burn injury is a unique form of trauma that primarily affects the skin but also disrupts the function of key physiological systems, including the immune system. Following a burn, immunosuppression occurs, characterized by upregulation of adaptive immunity, downregulation of innate immunity, apoptosis-induced lymphopenia, and decreased expression of monocyte human leukocyte antigen-DR. [1–3] This immune dysregulation makes burn patients highly susceptible to infection and sepsis, with sepsis being one of the leading causes of death after burn injury [4]. Furthermore, diagnosing infection in burn patients is particularly challenging. The hypermetabolic response after a burn injury results in elevated core temperature, tachycardia, tachypnea, and altered white blood cell and platelet counts, all of which are ubiquitous and make traditional markers of infection unreliable [5]. This can lead to delays in diagnosis which further contributes to the high incidence (3–30%) of sepsis in patients with severe burns [6]. The use of prophylactic antibiotics in burn injury is not recommended due to the increased risk of antibiotic resistance associated with prolonged hospital stays, multiple infections, and the compromised skin barrier. However, early antimicrobial therapy is critical in sepsis treatment, emphasizing the need for methods that enable earlier identification and treatment of infection. The current standard of care relies on cultures and microbial sensitivity testing techniques that have remained largely unchanged for 50 years, with diagnosis delayed several days, thus further impeding definitive diagnosis and treatment.

Biomarkers, commonly defined as measurable substances whose presence is indicative of some phenomenon in an organism, may enable early identification of patients with sepsis, thus facilitating earlier diagnosis and treatment. The ideal sepsis biomarker would not only assist in earlier and more accurate identification of sepsis, but also help direct antibiotic therapy, risk-stratify sepsis patients, and be clinically measurable [7]. Unfortunately, to date no single biomarker meets these criteria. The biomarkers thus far studied in burns vary widely, but generally fall into the following categories: acute phase reactants, damage-associated molecular patterns, hematologic parameters (cell counts), metabolic markers, pathogen-associated molecular patterns, and organ dysfunction markers. The purpose of this review article is to list the various biomarkers that have been studied in burn sepsis; describe the biologic rationale behind their current and future clinical use in patients with burn injury; and discuss promising methodologies for new burn sepsis marker development.

Review

Acute phase reactants

Acute phase reactants, including procalcitonin (PCT), c-reactive protein (CRP), and cytokines are among the most studied sepsis biomarkers in burns. Each acute phase reactant has unique characteristics that both facilitate and limit its utility as a burn sepsis biomarker.

Procalcitonin

PCT, a 116-aminoacid produced primarily by thyroid neuroendocrine cells, has been used for over 20 years as a biomarker of sepsis in critical care and burns [8,9]. The production of PCT is regulated by the CALC-1 gene, which is normally suppressed in nonendocrine tissues. However, CALC-1 gene transcription is stimulated by bacterial infection, leading to increased PCT production anywhere from 3–20 h after bacterial infection. Because PCT has a relatively short half-life of 25–30 h, once the bacterial infection is cleared, PCT levels decrease by half every day [10]. Higher levels of PCT have also been correlated with greater sepsis severity in medical intensive care patients [11]. These features make it a viable candidate for a bacterial infection biomarker. Unfortunately, PCT has not been validated as a biomarker for viral infections.

Although there is evidence that PCT is superior to CRP in non-burn critically ill sepsis patients, the evidence is less clear in burns [11–14]. A recent meta-analysis of PCT reported a moderate sensitivity of 73% (CI 53–87) and specificity of 75% (CI 66–82) [15]. Because peak PCT levels have been associated with burn size, a PCT cutoff of 1.5 ng/ml has been proposed as a trigger for initiation of antibiotics for sepsis in burn patients [16]. This has led to the suggestion that PCT trends over time may be more valuable in sepsis detection than isolated PCT levels [17]. A final potential use for PCT in burns may be the de-escalation of antibiotics for treatment of bacterial infections, particularly in those with respiratory infections. ICU studies have reported a reduction in antibiotic exposure by >3 days by using PCT decreases to terminate antibiotic use [16]. However, further studies are warranted prior to incorporating this practice into patient care. Finally, PCT provides limited information on viral or fungal infections. Hence, sepsis from those infectious etiologies is possible even in the face of normal PCT levels.

C-reactive protein

A second acute phase reactant that has been considered as a potential marker of sepsis in burn injury is CRP, which is thought to bind to the phospholipid components of pathogens and damaged cells to promote macrophage-mediated removal [18]. CRP is notable for increasing in the early stages of infection and inflammation; however, it does not distinguish between mild and severe infections and remains elevated throughout the time course of infection. As such, CRP cannot be used to evaluate the adequacy of therapy or enable the early discontinuation of antibiotic therapy [19]. CRP and its relationship to sepsis was examined in a cohort of 918 pediatric burn patients. CRP was noted to correlate with burn size, but not with infection or sepsis [20]. Interestingly, CRP was lower in burn survivors. Elevated CRP has also been associated with sepsis in elderly burn patients [21].

Improvement in laboratory testing has led to the ability to measure CRP at much lower levels and detect smaller changes in CRP over time. This so called, high-sensitivity CRP (hsCRP), test has been traditionally used to diagnose cardiovascular disease, but has also been proposed as a more specific predictor of sepsis. A study of hsCRP in individuals residing in the community suggested that elevated baseline hsCRP could be used to predict those at increased risk for future sepsis [22]. Another study comparing hsCRP to PCT in the elderly reported that hsCRP was not inferior to PCT in the diagnosis of sepsis and septic shock [23]. Unfortunately, the use of hsCRP as a predictor of sepsis in burn patients has not been demonstrated in a prospective study. However, one potential use for CRP as a burn sepsis biomarker is to combine

Table 1. Cytokines in sepsis.

Pro-inflammatory	Function	Role in Sepsis
TNF-α	Cytokine production, apoptosis cell proliferation, tumor necrosis anti-infection	Biomarker survival, progression
Il-6	Cytokine production, cell differentiation/growth	Biomarker, survival, severity
IL-8	Angiogenesis, chemotaxis	Biomarker mortality
IL-12	IFNγ, TNF-α production	Unknown
IL-17	Production cytokine/chemokine Autoimmunity	Unknown
IL-1β	Cell apoptosis, differentiation, proliferation	Unknown
IL-18	IFNγ, anti-microbial immunity	Biomarker disease severity
IFN-γ	Anti-infection, auto-immunity	Unknown
GM-CSF	Cell survival, growth, autoimmunity Development granulocyte, monocyte	Unknown
Other proinflammatory cytokines with possible sepsis role: High-mobility group box-1 (HMGB1), MCP-1, MIP-1β (macrophage inflammatory protein)		
Anti-inflammatory		
TGF-β	Inhibits proinflammatory cytokines, Apoptosis, cell proliferation, migration	Unknown
IL-1RA	IL-1-α, β inhibitor	Unknown
IL-4	Cell proliferation	Unknown
IL-10	Pro-inflammatory cytokine inhibitor	Biomarker severity, mortality
IL-11	Induction Th2 Inhibition Th1 cytokine production	Unknown
IL-13	Pro-inflammatory cytokine inhibitor	Unknown

IL interleukin, *IFN* interferon, *TNF* tumor necrosis factor, *GM-GCSF* granulocyte-macrophage colony-stimulating factor, *Th* T helper cells, *RA* receptor antagonist, *HMGB1* high-mobility group box-1, *MCP-1* monocyte chemoattactant protein-1, *MIP-1β* macrophage inflammatory protein

it with PCT. CRP could be used for early detection, while PCT would enable early termination of antimicrobials. However, this requires further prospective evaluation.

Plasma N-terminal prohormone of brain Naturetic peptide (NT-proBNP)

Plasma N-terminal prohormone of brain naturetic peptide (NT-proBNP) is traditionally used as a biomarker for cardiac dysfunction, as it is released by cardiac myocytes in response to volume expansion and wall stress [24]. However, NT-proBNP levels are also influenced by sepsis and shock by less well understood mechanisms [24,25]. The cardiac insufficiency and acute ventricular dilatation that accompany sepsis and shock cause elevation of NT-proBNP. As such, NT-proBNP could serve as a biomarker for sepsis in burn patients. Unfortunately, cardiac insufficiency in sepsis is not an early phenomenon, which may restrict the utility of NT-proBNP. Early studies of NT-proBNP in burn sepsis report a 89.7–96% sensitivity and 62.5–100% specificity [26,27]. Although promising, NT-proBNP utility is yet to be proven and may also be limited by test availability, turnaround times, and patient comorbidities such as preexisting cardiac dysfunction.

Proinflammatory cytokines (Table 1)

Innumerable cytokines have been proposed as potential biomarkers for sepsis [28]. For the purposes of this review, we will focus on those pro- and anti-inflammatory cytokines that have a clear link to sepsis. Proinflammatory cytokines, including tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and interleukin-8 (IL-8) as well as the anti-inflammatory cytokine interleukin-10 (IL-10) have been proposed as markers for sepsis in burn injury due to their relationship to the immune response to infection and tissue-associated damage [29]. Unfortunately, cytokine levels are influenced by numerous factors, including organ dysfunction, comorbidities, genetic variability, and the timing of sampling [18]. This limits their utility as the sole method of sepsis identification.

Tumor necrosis factor alpha

TNF-α, a central mediator of inflammation, is the subject of numerous investigations focusing on sepsis biomarkers. TNF-α is generated in response to a variety of stimuli including hypoxemia, ischemia/reperfusion, endotoxin and other bacterial products as well as in response to complement activation and other cytokines. TNF-α plays a key role in activation of natural killer cells as well as monocytes and macrophages, induction of apoptosis, vasodilatation via nitric oxide production, promotion of neutrophil chemotaxis, and activation of both the fibrinolytic and prothrombotic pathways [30,31]. TNF-α is elevated after burn injury; however, burn patients with sepsis have even more pronounced increases in TNF-α [2,32].

Il-6

IL-6, like TNF-α, is elevated in both burns and sepsis. IL-6 is an inducible pleiotropic cytokine expressed in leukocytes, liver, spleen and kidney with a variety of immune functions ranging from induction of fever to stress hormone production stimulation and immune cell activation [33]. Studies have confirmed that an IL-6 > 500 pg/ml helps discriminate sepsis from non-infectious Systemic Inflammatory Response Syndrome, which could be particularly helpful in the patient with major burn injury [34]. Finally, IL-6 has comparable diagnostic value to PCT, with a 78% specificity and 68% sensitivity [35]. As such, IL-6 is a promising biomarker for burn sepsis.

Il-8

IL-8, a proinflammatory cytokine that promotes migration and activation of neutrophils, is produced by macrophages, monocytes, and endothelial cells [17]. Elevations in IL-8 after burn injury are common immediately after injury and peak levels have been correlated with increased mortality and sepsis [36,37]. One study in 468 pediatric patients with burns with greater than 30% TBSA confirmed that a second peak of IL-8 of at least 234 pg/ml was associated with sepsis and

organ dysfunction in burn injury [37]. Elevated IL-8 was also present in patients with multiple organ failure. IL-8 as a biomarker for sepsis is limited by the discriminating factors for survival, including inhalation injury, burn size, and other infectious complications [37]. Nonetheless, IL-8 use as a sepsis biomarker in conjunction with other cytokines remains intriguing.

Il-18

IL-18 is a proinflammatory Th1 cytokine produced by macrophages that may stimulate the release of IFN-γ (type II interferon) which further activates macrophages. Although IL-18 levels are increased at 48 h in moderately burned patients, IL-18 correlation with burn sepsis is not known [38]. In non-burn populations, IL-18 levels are both elevated in patients with sepsis and associated with adverse outcomes in sepsis [39]. Interestingly, IL-18 concentrations have been used to distinguish gram positive from gram negative sepsis in non-burn populations [40]. Further studies of IL-18 in burn sepsis are needed.

Anti-inflammatory cytokines

Il-10

Although numerous anti-inflammatory cytokines have been identified, few have known functions in sepsis. IL-10 is one of the key mediators in the anti-inflammatory response. IL-10 inhibits the production of proinflammatory cytokines TNF-α, IL-1, IL-6, IL-8, IL-12, GM-CSF, MIP-1α, and MIP-2α in multiple different cell types [41]. In contrast to TNF-α, IL-6, and IL-8, IL-10 is an anti-inflammatory cytokine that regulates immune cells, including macrophages, NK cells, and B cells [42]. IL-10 is initially elevated but progressively decreases after burn injury except when the patient is developing sepsis. Hence, it has been proposed as a marker of sepsis and/or increased mortality after burn injury [43]. IL-10 levels are elevated in sepsis and correlate with sepsis severity as well as mortality. Overexpression of IL-10, i.e. presence of profound immunosuppression, is a risk factor for mortality in sepsis [44]. Hence, using IL-10 in isolation as a biomarker of sepsis is problematic. The dynamic interplay of sepsis, immunosuppression, and IL-10 release in burns requires further study.

The optimal use of cytokines as sepsis biomarkers may well require simultaneous examination of cytokine profiles consisting of both proinflammatory and anti-inflammatory cytokines. For example, one study compared the ratio of the pro-inflammatory cytokine TNF-α to the anti-inflammatory cytokine IL-10 in 34 patients with >20% TBSA, within 48 h of admission. The TNF-α to IL-10 ratio was inversely correlated with burn severity, and a lower ratio was associated with hyper susceptibility to infections (>3 infection episodes) [45]. Hence, a sepsis cytokine panel may well be a useful 'biomarker' of sepsis.

Other potential biomarkers of sepsis in burns

CD14

One of the most promising biomarkers for burn sepsis is CD14. The CD14 receptor for the lipopolysaccharide (LPS)-Lipopolysaccharide Binding Protein (LBP) complex may activate inflammatory cascades and signal transduction pathways leading to systemic inflammatory response syndrome (SIRS), which is ubiquitous in burn injury. CD14 exists in both a soluble (sCD14) and membrane-bound (MCD14) forms. sCD14 can be cleaved by proteases to generate presepsin, which has better specificity and sensitivity in distinguishing sepsis than many other biomarkers [46]. A subtype of the soluble CD14, produced by monocytes and macrophages, presepsin, shows promise as a marker for sepsis in burn injury. Presepsin, in conjunction with endotoxin, helps to activate the inflammatory cascade [47]. Presepsin has been reported to have better sensitivity and specificity in sepsis diagnosis than PCT, IL-6, and CRP. Further studies, including a meta-analysis, report that values ranging from 317–719 pg/ml indicated the presence of sepsis [46,48]. In one study of sepsis in burn patients presepsin elevation preceded PCT, CRP, and WBC count changes by 1 day [49]. Administration of antibiotics a day earlier would likely improve sepsis outcomes significantly. However, because inflammation occurs in states other than sepsis, presepsin cannot be used in isolation for the diagnosis of sepsis in burn injury [50]. Clinical trials of presepsin and CD14 are needed to confirm its utility.

Complete blood count (CBC) parameters

Virtually every patient with a major burn injury has blood analyzed for complete blood count (CBC) and its associated ratio markers. Recently there has been increased interest in using these parameters to identify sepsis. The advantage of cell counts, cell properties and cell ratio markers is their ready availability, cost-effectiveness, and common use in clinical medicine. Several ratios have become increasingly prominent: Neutrophil-to-Lympohocyte Ratio, Platelet-to-Lymphocyte Ratio, and Monocyte-to-Lymphocyte Ratio [51,52]. Kim et al investigated RDW (Red Cell Distribution Width), MPV (Mean Platelet Volume), PDW, and MPVPR these biomarkers as predictors of sepsis in 1806 burn patients [53]. They report a hazard Ratio of >1 for sepsis for RDW, MPV, PDW, and MPVPR. Platelet count, PDW (Platelet Distribution Width), and MPVPR (Mean Platelet Volume/Platelet Count ratio) were predictive for septic shock and associated with sepsis and mortality, with an area under the curve (AUC) of >0.65 in an unadjusted generalized estimating equations model. The findings of this single center retrospective study, although suggestive, will require further confirmation in a multicenter prospective study.

Kallistatin is a human serine proteinase inhibitor with pleiotropic effects including anti-apoptosis, anti-inflammation, anti-angiogenesis, and antioxidation. These anti-apoptotic properties may influence outcomes in sepsis. In addition, kallistatin could be used as a biomarker for sepsis. Lin et al reported in septic ICU patients that kallistatin levels were lower in septic shock compared to severe sepsis; mortality was inversely related to kallikrein level [54]. Hence, kallikrein could be either a biomarker for sepsis or potentially a new treatment for sepsis. In pediatric burn sepsis combined treatment with simvastatin and kallistatin inhibited human endothelial cell apoptosis, suggesting that this combination may be a potential therapeutic strategy for pediatric burn patient sepsis [55]. Further studies are needed to validate these promising findings.

Calprotectin, found in neutrophil cytosol, is a calcium-binding protein that has demonstrated diagnostic value in sepsis, including sepsis-associated encephalopathy, sepsis-associated kidney injury as well as neonatal sepsis prediction [56]. Calprotectin is released by neutrophils in response to bacterial infection or endotoxin within hours [57]. A recent study comparing calprotectin to PCT reported that

calprotectin was superior to PCT in distinguishing sepsis in ICU patients (AUC 0.79 calprotectin, 0.49 procalcitonin) [57]. The use of calprotectin for predicting burn sepsis, however, requires validation.

Genomic considerations

Analysis of the genome may have utility in identification of patients at increased risk for sepsis. Several studies have implicated specific polymorphisms associated with burn sepsis, including IL-6-174G, PAI-1 4G/4G, TLR4 + 896G-allele, TNFα-308 A-allele [58–60]. Unfortunately meta-analyses evaluating the association of SNPs with sepsis have not corroborated these initial findings [18]. The complex nature of genome interactions and translation increase the difficulties in isolating single gene markers for sepsis. Hence, further clinical study is needed to determine which polymorphisms are associated with sepsis development in burn injury and whether identification of these polymorphisms can be effectively employed clinically to prevent sepsis.

Microarrays

Expression profiling, primarily via microarray transcriptome technology from a variety of different sources (skin, skeletal muscle, etc.) may help to reveal the underlying genomic and transcriptomic activities that accompany sepsis. Microarrays and real time quantitative reverse transcription polymerase chain reaction (qRT-PCR) analysis have been used to examine potential mRNA and cytokine receptors associated with sepsis. One multicenter prospective study identified a set of 42 molecular biomarkers related to key innate/adaptive immune function, cell cycling, WBC differentiation, extracellular remodeling and immune modulation pathways could be used in conjunction with clinical findings for early sepsis detection [61]. Further clinical validation is needed prior to adopting this methodology.

MicroRNA

MicroRNAs, consisting of noncoding RNAs 21–26 nucleotides, regulate gene expression via post transcriptional repressors [62]. MicroRNAs exist in numerous body fluids, including serum, plasma, whole blood, urine, cerebrospinal fluid, and sweat, participating in the cross talk between innate immunity, apoptosis, and mitochondrial function [63,64]. MicroRNA expression profiling in nonburn sepsis patients reveals a correlation between microRNA dysregulation and clinical signs of sepsis [65]. Both upregulation and downregulation of microRNA have been identified in sepsis patients, with downregulation in miR-499-Sp, miR-25, miR-150 and upregulation in miR16, MiR-223, 27a, 133a, 155, 34a, and 143. microRNA have been posited as a biomarker of sepsis in burn patients. For example, in burn sepsis microR495 downregulated as well as negatively correlated with PCT and CRP [66]. Two other types of RNA have been investigated in sepsis: IncRNAs (long non-coding RNAs) and circular RNAs (circRNAs). IncRNAs, >200 nucleotides in length, have diverse cellular functions, including mRNA translation regulation, protein transport and RNA processing. In sepsis, they help regulate proinflammatory cytokines and other immune pathways such as Nuclear Factor-κB signaling pathway [67,68]. Likely a panel of microRNAs consisting of microRNAs, IncRNAs, and circRNAs will be needed to serve as a burn sepsis biomarker. microRNA technology requires extensive clinical testing prior to employing it as a biomarker for sepsis in burn injury.

Epigenetic markers

Epigenetics plays a pivotal role in the interaction of genes with the environment. By definition, epigenetics consists of regulatory mechanisms governing gene expression excluding changes caused by DNA sequence alterations [69]. Examples of epigenetic modification include DNA methylation, histone modifications, and non-coding RNAs. DNA methylation shows promise a biomarker for bacterial sepsis: demethylation of key genes responsible for the response to bacteria and for inflammation are present in neonates with sepsis [70]. Definitively linking epigenetic markers with clinical outcomes has proven to be problematic, as association and causation must be clarified. The clinical study of epigenetic biomarkers in burn sepsis is limited. Much work still needs to be done.

Proteomics and metabolomics

The use of proteomics and metabolomics as biomarkers for burn sepsis is under intense investigation. Proteomics employs high-throughput protein expression analysis to identify proteins associated with sepsis. Elevations in proteins (lipocalin 2, YKL40), downregulated proteins (vitamin D-binding protein, retinol-binding protein), and dysregulated proteins (antithrombin-III, CLUSterin, serum amyloid A-1) have all been identified in non-burn sepsis [71,72]. Metabolomics differs from proteomics in that it analyzes metabolites with relationship to biochemical events. Metabolomics is particularly intriguing in the burn-injured patient, whose metabolism is fundamentally altered due to injury. Thus far the use of metabolomics in burn injury has focused on lipidomics to explain the crosstalk between muscle wasting and fatty liver infiltration [73]. Further work is needed to determine if these methodologies will prove useful in developing sepsis biomarkers.

Extracellular vesicles

Extracellular vesicles (EV) are emerging as a potential biomarker for sepsis. In brief, EV are nonreplicating small, lipid-coated particles containing proteins (chemokines, cytokines, heat shock proteins), microRNA, and DNA [74]. EV particles are released by cells and exist in blood, urine, saliva, and other body fluids. EV may alter cell function, metabolism, and life span of the targeted cells after release via both their membrane-bound and internal biomolecular contents [75]. In general, there are three types of EV: exosomes (endocytic origin, 30–150 nm in size, contain endosome-associated proteins), microvesicles (budding plasma membrane origin, 100–800 nm, contain CD63, CD81, annexin V), and apoptotic bodies (from cell apoptosis) [76]. EV can both induce and be a biomarker for sepsis [74]. The cellular origin of EV (leukocyte, macrophage, platelet, granulocyte) varies, providing a diverse range of potential biomarkers for sepsis, and EV transport some of the classic markers of sepsis, including CRP [77]. Finally, the cargo content of EV may have utility in sepsis diagnosis [78]. EV are generated from leukocytes and endothelial cells and decrease progressively after burn injury. In addition, EV production correlates with injury severity (burn size and depth) and sepsis [79]. The use of EV in burn sepsis is promising: Raman spectroscopy, in conjunction with plasma

derived EVs, achieved a 97.5% sensitivity and 90% specificity in one study of burn patients with sepsis [80]. Although these results are promising, further work is needed to confirm the utility of EV as a sepsis biomarker.

Sepsis phenotypes

No review of sepsis biomarkers would be complete without a discussion of sepsis phenotypes. Sepsis is unique in that there is significant heterogeneity in presentation between individuals. Sepsis phenotypes, in which patients are characterized by their physiologic and immunologic responses as well as demographics, may help to differentiate patients with sepsis. Seymore identified four phenotypes for sepsis (α, β, γ, and δ) based on physiology, treatment, and response to therapy in a cohort of 20 189 patients who met Sepsis-3 criteria within 6 h of presentation [81]. This cohort was validated in 43 086 patients. The α phenotype was most common (33%), including patients with the lowest vasopressor need; the β phenotype (present in 27%) consisted of older patients with more chronic illness and renal dysfunction, the γ phenotype (27%) had more inflammation and pulmonary dysfunction, and the δ phenotype (13%) had more liver dysfunction and septic shock as well as the highest mortality. Simulation modeling of the four phenotypes for outcomes based on randomized controlled trials demonstrated that patient outcome varied widely based on phenotype (range from >33% chance of benefit to >60% chance of harm). This suggests that biomarker efficacy in predicting sepsis and septic shock may be related to the patient's sepsis phenotype. Hence, use of the biomarkers described above may require further validation based on sepsis phenotype.

Conclusions

Sepsis is an important cause of both morbidity and mortality after burn injury. The diagnosis of sepsis is confounded by the extreme inflammatory response, complex immunologic changes, and clinical course of burn injured patients. Proposed biomarkers for burn sepsis range from commonly measured laboratory tests such as CBC to acute phase reactants, inflammatory markers, omics techniques, and extracellular vesicles. Due to the complexity of sepsis and burn injury, the 'ideal' biomarker for sepsis in burns will likely be a panel of tests with representation from each of the major categories of biomarkers. Furthermore, the use of biomarkers will likely be refined by identifying patient sepsis phenotypes. Advanced informatic techniques in conjunction with machine learning and artificial intelligence that can combine the vast genomic, proteomic, metabolomic, acute phase reactants with patient clinical data will likely be the key to improving the diagnosis and early treatment of sepsis in burn injury. The journey has just begun.

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Authors' contributions

Dr Palmieri wrote the paper, collated references, edited final draft, and developed the key concepts.

Dr Heard helped edit the paper, provided references, and contributed to content (additional references and text).

Tina L. Palmieri (Conceptualization [lead], Formal Analysis [Lead], Resources [lead]), Jason Heard (Conceptualization [supporting], Investigation [supporting], Methodology [equal], Validation [equal]).

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Conflict of interest

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Data Availability

None declared.

Consent for publication

None declared.

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