SURGICAL INFECTIONS
Volume 22, Number 1, 2021

DOI: 10.1089/sur.2020.297

Sepsis Definitions in Burns

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Abstract

Background: Sepsis is the leading cause of death in burns. Despite its importance, sepsis lacks a proper definition. An established definition will lead to early and accurate diagnosis, prompt treatment, and a reduced mortality rate. The aim of this work is to discuss current definitions and to look ahead at novel definitions with clinical implications.
Method: A review of the current understanding of sepsis definitions in burns.
Results: Adaptation of sepsis definitions in the general population and specific burn definitions have gotten better but still need improvements and, potentially, incorporation of molecular, laboratory, patient-specific, and clinical factors. This work includes the history, evolution, and predictive value of current definitions of sepsis in burns. A review of current and future markers of sepsis and potentially useful definitions are presented.
Conclusions: Sepsis definitions have evolved over the last decades and will continue to do so. We believe the best definition in burn patients is the Sepsis-3 that was developed originally for critically ill patients. However, there are several studies investigating more specific definitions with better sensitivity and specificity.

Keywords: burns; definitions; diagnosis; history; sepsis

Sepsis and septic shock have evolved as the leading cause of death in severely burned patients. Despite the general recognition of sepsis and its deleterious outcomes, the definition of sepsis remains vague. This uncertainty represents a significant problem, as missed identification will not allow adequate diagnosis and initiation of treatment or permit personalized treatment developments.

In general, *sepsis* refers to a systemic host response to an infecting pathogen that cannot be controlled and overwhelms the system, resulting in severe stress leading to single or multi-organ dysfunction and perhaps death [1,2]. The pathobiology of sepsis is complex and not entirely clear. Sepsis involves a plethora of cascades including pro- and anti-inflammatory cytokine responses and stress hormone releases and affects the vascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation pathways [3,4]. The host response to sepsis differs individually and thus demonstrates significant heterogeneity, depending on inherent host factors such as genetics, age, sex, ethnicity, comorbid conditions, concurrent injuries, and the source and type of infection [5].

The importance of sepsis is clearly delineated, and it is concerning that sepsis and septic shock, the leading causes of burn-related deaths, are not well defined. Currently, there is no test or diagnostic criterion that identify sepsis in critically ill patients, let alone burn patients. Sepsis certainly is more challenging to diagnose in the burn population, as many signs are present ubiquitously after injury, even in the absence of sepsis. For example, a burn by itself can cause tachycardia, leukopenia, leukocytosis, hypermetabolism, coagulopathy, hypothermia, hyperthermia, and metabolic alterations, just to name a few. Despite these challenges, the diagnosis of sepsis is essential, as early identification and treatment of infection and sepsis have been associated with improved survival. Therefore, the diagnosis of sepsis is the focus of numerous studies around the globe [6]. Although attempts have been made to adjust the diagnostic criteria to the specific needs of the burn population, the diagnosis of sepsis in burns still requires a precise definition [7,8]. To overcome the delay of diagnosis and treatment, sensitive indicators, quicker methods of microbial identification, and alternative personalized biomarkers have been proposed [9]. The aim of this review is to describe

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the history of sepsis and sepsis indicators, as well as to give a perspective of current and potentially future sepsis indicators and definitions.

History

History of sepsis definitions in critically ill patients

The term *sepsis* has been used since ancient cultures. In ancient Greek, *sepsis* meant decomposition of animal or plant-based organic materials, by what we now call bacteria. Hippocrates used the word ''sepidon'' to describe sepsis, which represented ''distortion, dissolution of a web structure.'' The same term was used by Aristotle, Plutarch, and Galen [9].

The definition of sepsis changed in 1992 when the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) established the systemic inflammatory response syndrome (SIRS), or Sepsis-1, criteria [10]. In 2001, the SCCM, the European Society of Intensive Care Medicine (ESICM), the ACCP, the American Thoracic Society, and the Surgical Infection Society held the second consensus meeting (Sepsis-2) and expanded the signs and symptoms of sepsis [11].

In light of advances in sepsis epidemiology and management, in January 2014, the ESICM and the SCCM convened a task force of 19 critical care, infectious disease, surgical, and pulmonary specialists to redefine sepsis in critically ill patients. This task force created the Sepsis-3 Consensus Definition for Sepsis and Septic Shock; this definition emphasizes organ dysfunction and recognizes sepsis as a syndrome (Table 1) [1].

History of sepsis definitions in burn patients

Adaptation of sepsis criteria for the burn population has been attempted. In the Sepsis-1, Sepsis-2, and Sepsis-3 meetings, burn patients were excluded from the studied population because of the complexity of their injuries. In 2007, burn experts were invited for a conference to come up with a consensus definition: The American Burn Association (ABA) burn-specific criteria for the diagnosis of sepsis [7]. In 2013, Mann-Salinas et al. evaluated the predictability of the ABA sepsis criteria in burns and developed a model for prediction in this specific population [8]. It became evident that neither definition is ideal, and to date, the definition of sepsis in the critically ill and burn populations remains in evolution and awaiting prospective studies, further validation of current criteria, and establishment of reliable markers, among others.

Table 1. Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)[a]

Suspected or documented infection
qSOFA ≥2 • Respiratory rate ≥22 breaths/min • Altered mentation • Systolic blood pressure ≤100 mm Hg
SOFA ≥2 • PaO_2/FiO_2 ratio • Glasgow Coma Scale • MAP • Vasopressor requirements • Serum creatinine or urine output • Bilirubin • Platelet count
Septic Shock Despite adequate fluid resuscitation, 1. Vasopressors required to maintain MAP ≥65 mm Hg AND 2. Serum lactate concentration >2 mmol/L

MAP = mean arterial pressure; qSOFA = quick SOFA; SOFA = Sequential [sepsis-related] Organ Failure Assessment.
[a]Adapted from Singer et al. [1].

History of multi-organ dysfunction in sepsis

Eiseman et al. in 1977 were the first to use the term *multiple organ failure* (MOF) as derived from 42 post-operative patients receiving mechanical and pharmacologic support for two or more severe vital organ systems dysfunctions. In this cohort, sepsis was of etiologic significance and of high mortality rate [12]. Fry and colleagues elucidated the role of uncontrolled infection as the leading cause of MOF in 1980 [13].

Moore et al. and Sauaia et al. investigated potential mediators of SIRS responsible for end-organ modulation and found several contributors linking an association between interleukin (IL)-6 concentrations and death [14,15].

Marshall et al. developed the Multiple Organ Dysfunction Score (MODS) as an outcome measure and emphasized an early phase of organ dysfunction before overt failure occurred. The authors further indicate that patients at risk of developing MODS have a better outcome if they receive early and adequate treatment [16]. Thus, the goal of treating acutely ill patients with a higher risk of MODS should be stopping SIRS from progressing, improving organ function, and preventing MOF [17].

In 1994, the ESICM created the Sepsis-related Organ Failure Assessment (SOFA) score [18] to quantify the degree of organ failure objectively in patients over time, improve the understanding of the natural history of MOF, and evaluate the effect of therapies on its course. Initially, it was not intended to be an outcome predictor but rather to describe the sequence of complications in the critically ill. Nowadays, it is well known that the SOFA score predicts outcome and correlates with death [1,18].

Definitions of Sepsis

Sepsis-1 criteria

The ACCP/SCCM Consensus Conference Committee defined sepsis as a systemic response to an infection [10]. For a systemic inflammatory response to be present, two of the following criteria are required:

1. Temperature above 38°C or below 36°C;
2. Heart rate >90 beats per minute (bpm);
3. Respiratory rate >20/min or maintenance of $PaCO_2$ <32 mm Hg;
4. White blood cell (WBC) count >12,000/mm or <4,000/mm or left shift defined as >10% bands [10].

Infection was said to be present in the presence of a positive culture, identification of a pathological tissue source, or clinical response to antibiotics [2].

Sepsis and its sequelae were divided into clinical stages based on the severity:

Severe sepsis: Sepsis with associated organ dysfunction or hypoperfusion abnormalities;

Sepsis-induced hypotension: Presence of systolic blood pressure <90 mm Hg or its reduction by ≥40 mm Hg from baseline in the absence of other causes of hypotension;

Septic shock: Sepsis-induced hypotension persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction [10].

Sepsis 2 criteria

For the Sepsis-2 definition, the Sepsis-1 criteria were found to be robust enough to not change the definition in a major way. The list of signs and symptoms were updated, but no major alterations were made. The addition of biomarkers was felt to be premature at that moment. Further studies were required to stage the host response to infection precisely and to develop a system to characterize sepsis [11].

Sepsis-3 criteria

Sepsis-3 was a major re-working of Sepsis-1 and Sepsis-2. Sepsis was defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis should be considered in the presence of a suspected or documented infection and an acute increase of ≥2 in the SOFA score (Table 1 and Table 2). The baseline SOFA score should be assumed to be zero unless the patient is known to have acute or chronic organ dysfunction before the onset of infection. The SOFA score is intended to characterize a septic patient clinically but not as a tool for patient management. This score has a well-validated relation to the mortality risk, as a SOFA score ≥2 correlates with an overall 10% risk of death [1]. It is worth mentioning that failure to meet the 2 points in the SOFA score rule should not defer investigation or early treatment of a severe infection.

Septic shock was described as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are profound enough to increase the mortality rate substantially (see Table 1) [1]. In burns, organ dysfunction should not be considered a result of sepsis before the acute resuscitation phase, approximately three days after initial injury, is completed [7].

ABA criteria

Sepsis was defined by the ABA as any change in the patient's condition based on several clinical signs that triggered the flag for infection plus a confirmed infectious source (Table 3) [7]. Septic shock was considered to be persistent hypotension despite adequate resuscitation, requiring vasopressors, lactate >2–4 mmol (18–36 mg/dL), or both. Septic shock implies profound circulatory and cellular/metabolic abnormalities that carry an increased risk of death (40%) [1,7].

Mann-salinas criteria

Mann-Salinas et al. evaluated the predictability of the previously described sepsis criteria in burns and developed a model of sepsis prediction [8]. Adult subjects were evaluated during the three-day period before blood cultures were taken

TABLE 2. SEQUENTIAL [SEPSIS-RELATED] ORGAN FAILURE ASSESSMENT SCORE[a]

	0	*1*	*2*	*3*	*4*
PaO_2/FiO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 OR Dobutamine (any dose)[b]	Dopamine 5.1–15 OR Epinephrine ≤0.1 OR Norepinephrine ≤0.1b[b]	Dopamine >15 OR Epinephrine >0.1 OR Norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale	15	13–14	10–12	6–9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL/d				<500	<200

[a]Adapted from Singer et al. [1] and Vincent et al. [18].
[b]Catecholamine doses are given as μ/kg/min for at least 1 h.
MAP = mean arterial pressure; qSOFA = quick SOFA; SOFA = Sequential [sepsis-related] Organ Failure Assessment.

Table 3. American Burn Association Sepsis Criteria[a]

The trigger includes at least three of the following:	
I. Temperature	> 39°C or <36.5°C
II. Progressive tachycardia	1. Adults >110 bpm 2. Children >2 SD above age-specific norms (85% age-adjusted max heart rate)
II. Progressive tachypnea	1. Adults >25 bpm not ventilated i. Minute ventilation >12L/min ventilated 2. Children >2 SD above age-specific norms (85% age-adjusted max respiratory rate)
III. Thrombocytopenia (will not apply until 3 d after initial resuscitation)	1. Adults <100,000/μL 2. Children <2 SD below age-specific norms
V. Hyperglycemia (in absence of existing diabetes mellitus)	1. Untreated plasma glucose >200 mg/dLor equivalent mM/L 2. Insulin resistance—examples include: i. >7 units of insulin/h intravenous drip (adults) ii. Significant resistance to insulin (>25% increase in insulin requirements over 24 h)
VI. Inability to continue enteral feedings >24 h	1. Abdominal distension 2. Enteral feeding intolerance (residual >150 mL/h in children or two times feeding rate in adults) 3. Uncontrollable diarrhea (>2,500 mL/d for adults or >400 mL/d in children)
*In addition, it is **required** that a documented infection is identified as:*	
	1. Culture positive, OR 2. Pathologic tissue source identified, OR 3. Clinical response to antimicrobial drug(s)

[a]Adapted from Greenhalgh et al. [7].

and divided into three groups: (1) Known positive blood cultures with clinical suspicion of sepsis (positive–sick); (2) known negative blood culture with clinical suspicion of sepsis (negative–sick); and (3) known negative screening blood culture with clinical stability (screening–not sick). Using the studied population, Mann-Salinas et al. identified six novel predictors of sepsis (Table 4). This model was significant in predicting positive sick and sick with an area under the curve (AUC) of 0.775 and 0.714, respectively [8].

Novel definitions and predictors

Hill et al. analyzed data from 198 blood cultures taken from burn patients with sepsis in a single center retrospective review. Forty variables were found to be statistically significant predictors of sepsis in these patients. The top ten variables by odds ratio considered sepsis predictors were mean arterial pressure <60 mm Hg, lactate ≥2 mmol/L, temperature maximum >39°C, WBC count <4,000/mm^3, heart rate >130 bpm, temperature minimum <36°C, mean arterial pressure decrease 10%, gastric residual volume twice the feeding rate, temperature maximum increase at least 0.5°C, and temperature maximum >38.6°C [19].

Although not yet published, a screening tool using common laboratory, clinical, and patient features to assist in early identification of blood stream infection (BSI) was developed at the Ross Tilley Burn Centre and validated in an adult burn population within 10 days of injury. The odds of bacteremia were determined with an equation that included platelet vitality, temperature, full- and partial-thickness burn areas, and maximum heart rate. The sensitivity, specificity, accuracy, false-positive rate, false-negative rate, and positive and negative likelihood ratios (LR) of this model were 89%, 98%, 96%, 2%, 11%, 53%, and 0.11%, respectively (Walker et al. Development and validation of a screening tool for early identification of bloodstream infection in acute burn injury patients. In press.)

A novel and innovative technique that focuses on the immune response at the site of injury called the Sepsis Predictor Index will be discussed in the new and prospective markers section below [20].

Table 4. Mann-Salinas et al. Novel Predictors of Sepsis[a]

1. Heart rate >130 bpm
2. Mean arterial pressure <60 mm Hg
3. Base deficit <−6 mEq/L
4. Temperature <36°C
5. Use of vasoactive medications
6. Serum glucose >150 mg/dL

[a]Adapted from Mann-Salinas et al. [8].

Special Considerations

Sepsis definitions in adult patients

The definition of sepsis in critically ill patients and especially burn patients remains controversial. Current definitions are in evolution, and no gold standard exists. Burn patients, especially after a major injury, are in a chronic hyperinflammatory state. This inflammatory response differs depending on the magnitude, duration, and location of the initial tissue injury and intrinsic host factors such as genetics and immunosuppression. Multiple factors associated with a burn injury such as inhalation injury, pain, compartment syndromes, carbon monoxide poisoning, and graft donor areas also activate a ''non-infectious'' inflammatory response [7]. Although never systematically studied, the Sepsis-1 criteria are not specific to infection in burns and are considered of little value when investigating sepsis in the burn population. A retrospective review of 282 blood cultures from 196 burn

patients in the intensive care unit (ICU) found the SIRS criteria to be overly present in this population and did not correlate with bacteremia [21]. Mann-Salinas's retrospective case-controlled, within-patient review from a single burn center compared the 72-hour period before blood cultures were drawn and divided this cohort into three groups as previously mentioned. This study demonstrated that the SIRS criteria for sepsis were inappropriate for use in the chronically hypermetabolic burn patient in the ICU, as >95% of subjects met the SIRS criteria at all times during the study period whatever group they were assigned to, even when there was no clinical suspicion of sepsis [8].

A number of studies in the pediatric and adult burn literature used the ABA definition to characterize sepsis in burns. It became evident that these criteria have a limited ability to discriminate between patients with sepsis, bacteremia, and no infection at all [21]. In the aforementioned retrospective review of 282 blood cultures from 196 burn patients in the ICU, meeting more than three of six ABA sepsis criteria did not correlate with bacteremia [21]. The retrospective single burn center review by Mann-Salinas et al. demonstrated a significant difference in meeting ABA sepsis criteria only on day one, before blood cultures were drawn, between the positive–sick group and the screening–not sick group. In this cohort, the ABA criteria were unable to differentiate patients suspected of sepsis who had a negative blood culture from the other two groups [8]. Because of the low sensitivity of blood cultures, this latter finding leads to a high proportion of sepsis-positive burn patients being unclassified. At the Ross Tilley Burn Centre, a cohort of 418 adults believed prospectively to have sepsis was analyzed. The findings were not promising, as the predictive validity of the ABA criteria for sepsis for patients with 10%–20% TBSA burns was only 58% and for patients with ≥20% TBSA burns was 60% [22].

The Mann-Salinas model has multiple limitations, such as being extrapolated from a single burn centre with a small cohort of patients and defining sepsis as clinical suspicion with a positive blood culture and not including sepsis from a different source such as pneumonia, tissue infection, lines, etc. When this model was tested prospectively against other models, its sensitivity for sepsis in patients with 10%–20% TBSA burns was 27% and in patients with ≥20% total body surface area (TBSA) burns was 29%, which is a poor performance compared with the ABA and Sepsis-3 criteria [22].

At present, we propose that Sepsis-3 criteria outperform the Sepsis-1, Sepsis-2, ABA, and Mann-Salinas definitions [22,23]. These criteria simplify the definition of sepsis and focus on multi-organ failure syndrome rather than the inflammatory response alone. Although burn patients were excluded in the development of Sepsis-3, the sensitivity for sepsis in patients with 10%–20% TBSA burns was 82% and for ≥20% TBSA burns was 87% [22], by far outperforming other definitions. But Sepsis-3 still is not ideal [1]; the SOFA score calculation does not take into account the skin and the gastrointestinal system in its measurements. Death in burn patients is strongly related to the extent of body surface area affected. Therefore, not considering the skin dysfunction may represent a limitation in this specific population [24]. A retrospective review of 1,185 adult burn patients concluded that the Sepsis-3 criteria were not superior to and had a lower specificity than the ABA criteria in burn sepsis. This study also concluded that for the SOFA score to predict death in burns, a value greater than or equal six is necessary [25].

Predictive models in sepsis seem promising but require further validation in larger populations and prospective trials [22].

Sepsis in pediatric burn patients

Children account for as many as one-third of burn-unit admissions, and burn injuries represent the fifth leading cause of unintentional injury-related death in the pediatric population. Although there now is better survival of burns, sepsis remains the leading cause of death in pediatric burn units [26,27].

It is important to recognize that sepsis in children should not be considered equivalent to sepsis in the adult population. In pediatric burn patients, there is a deficiency in oxygen delivery rather than in oxygen extraction related to a low cardiac output and impaired systemic vascular resistance. Furthermore, children have higher heart and breathing rates, and their overall physiology mimics even more of the signs of infections and sepsis [2].

A prospective multi-center cohort study, part of the Inflammation and the Host Response to Injury Glue grant, conducted in six major burn centers in North America, included 573 patients with >20% TBSA burns, of whom 226 were children. Children had a higher incidence of burn wound infection (93.8% versus 55%), a greater number of infections, less pneumonia, and less sepsis (2% versus 10%) than the adults. In this prospective cohort, children and adults had a similar incidence of MOF (27%), but children had a lower mortality rate (8% versus 55%). These data suggest that pediatric patients have the ability to compartmentalize infections and tolerate and survive severe organ dysfunction better than adults. This is attributable to differences in their immune system and in organ reserve [28].

Both the ABA and SIRS criteria include the pediatric population, although further evaluation of their validity is required [29]. Pediatric guidelines provide principles called *home-grown bundles,* which involve a recognition bundle containing a trigger tool for rapid identification of patients in septic shock, a resuscitation and stabilization bundle for early treatment, and a performance bundle to monitor, improve, and sustain adherence. Better survival in pediatric and neonatal sepsis has been achieved with these rapid diagnosis and early treatment protocols [30].

Sepsis-3 criteria were validated in a retrospective single-center cohort of 6,303 critically ill patients under the age of 21 years who presented to a pediatric intensive care unit. The SOFA score criteria were adapted to accepted pediatric cut-offs (pSOFA). The pSOFA criteria performance was compared with established organ failure criteria. The optimal pSOFA cut-off to discriminate mortality risk was a score greater than eight points. The ability of the pSOFA score at discriminating hospital death likelihood was similar to or better than the performance of other common pediatric organ dysfunction scores [31].

In burns, thrombocytopenia, hyperglycemia, and enteral feeding intolerance have been associated with sepsis. Often, these signs are used to establish the diagnosis of sepsis because of the limited sensitivity and time-requiring nature of microbial cultures. In a retrospective cohort of 91 seriously

burned (>80% TBSA) children surviving longer than five days, enteral feeding intolerance was found to be associated with bacteremia and fungemia and to be a subtle indicator of sepsis. In this study, enteral feeding intolerance was defined as the inability to tolerate enteral feedings because of abdominal distention, high gastric residual volumes (>150 mL/h), uncontrollable diarrhea (>2.5 L/d), or all three with discontinuation of enteral feedings for more than 24 hours [32].

Sepsis in elderly and frail burn patients

Similar to pediatric and adult burn patients, there is no universally accepted definition of sepsis in elderly (age ≥65 years) patients or those who have high frailty scores (poor physical condition before injury). Although we recognize that the pre-injury frailty measures are not always known, frailty is an important consideration because chronologic age does not always reflect biological age or the effects of frailty [33–35].

It is well documented that elderly patients have a different response after the initial burn injury than younger adult patients. These differences are numerous; some of which are an acute-phase response characterized by cardiac depression and hypoinflammation [36], impaired inflammatory and metabolic response [37,38], delayed wound healing [39,40], and decreased survival [28,41]. The burn injury itself and the risk of sepsis are compounded by the physiological effects of aging such as thinning skin, compromised immune systems, and, often, chronic co-morbidities [42]. The ABA's Committee on Elderly Burn Care recently published a paper outlining the ''State of the Science Burn Research: Burns in the Elderly'' [42]. There is recognition by many in the burn community that there is a dearth of treatment guidelines or protocols specifically geared toward the special needs of elderly patients [42,43]. Any future definitions of sepsis after burn injury should incorporate the important factors of age and frailty.

Novel Approaches to Diagnose and Predict Sepsis

Biomarkers

Biomarkers are a fascinating aspect in the approach of personalized medicine to identify pathology or even predict responses and diseases. It would be desirable to develop or find a biomarker that can not only identify but further discriminate sepsis from a non-infectious critical illness such as a burn injury. Numerous biomarkers for sepsis have been investigated, but unfortunately, none of the current ones seems ideal to diagnose or predict sepsis [44,45].

C-reactive protein (CRP). This is an acute-phase reactant synthesized by the liver. A plasma concentration >8 mg/dL has been reported to distinguish inflammatory responses from other types of inflammation. Synthesis of CRP is mediated by IL-6, IL-1, and tumor necrosis factor (TNF)-α. The protein is secreted within 4–6 hours after stimulation, has a doubling time of 8 hours, peaks at 36–50 hours, and has a half-life of 19 hours [46]. Although a large body of work has been done on the topic of CRP and burns, there is no clear signal whether CRP can be used as a biomarker for the prediction of sepsis. A large cohort study showed that CRP cannot predict sepsis in burn patients; however, a significant correlation was found with burn size, gender, and survivability on day two post-admission [47]. A meta-analysis of nine studies with 495 patients in the sepsis group and 873 patients in the non-sepsis group demonstrated an AUC for CRP in sepsis of 0.73 (95% confidence interval [CI] 0.69–0.77), a sensitivity of 0.80 (95% CI 0.63–0.90), and specificity of 0.61 (95% CI 0.50–0.72). In this meta-analysis, a moderate degree of value of CRP in sepsis definition was indicated [48]. A prospective single-center study of 43 patients compared the severity of organ dysfunction with the values of PCT and CRP in three increasing SOFA score groups. It was concluded that CRP concentrations were higher in the sepsis group than in the SIRS (not infected) and the negative group of patients. It also was concluded that CRP concentrations did not differ at low SOFA scores and had significantly higher values only in patients with a SOFA score greater than or equal to nine [49]. In summary, CRP use as a biomarker for sepsis in burns is controversial. The use of CRP is preferred in some burn centers but not all, as it is a non-specific biomarker with limited evidence for its value as a diagnostic tool for infection

Procalcitonin (PCT). Serum PCT is a protein biomarker that is non-detectable under normal conditions. The concentration increases shortly after a pro-inflammatory stimulus and remains elevated for more than 25–30 hours, which makes it one of the most attractive biomarkers. In severe infections, the serum PCT concentration increases and can be measured. But PCT also increases with a burn injury per se. In addition, variable characteristics of burn patients such as burn size and surgical procedures may influence PCT. The protein has been described as a simple and useful biomarker for the early identification of sepsis in burn patients when combined with clinical criteria and other biomarkers [50,51]

The validity of PCT in the diagnosis of sepsis is controversial. A meta-analysis of 30 studies on its use to distinguish between sepsis and SIRS demonstrated a sensitivity of 0.77 (95% CI 0.72–0.81) and specificity of 0.79 (95% CI 0.74–0.84). More than an isolated value, the trend over time of PCT is recommended in the diagnosis of sepsis [52].

Antimicrobial therapy is advocated when the PCT concentration oscillates between 0.1 and 0.5 ng/mL, as this suggests the presence of infection [53]. An elevated PCT concentration despite treatment is associated with a higher mortality rate [54]. Recommendations are to stop antibiotic treatment when the PCT concentration decreases by 80% or to <0.5 ng/mL. Controversy surrounds this aspect, and the literature is not yet conclusive [54,55].

Despite being the protein biomarker with the highest sensitivity for sepsis and carrying a potential for reduction of antibiotic treatment, PCT is not widely used as a diagnostic biomarker, as false-negative results might lead to a higher mortality rate; and further validation is needed [45].

Cytokines. Cytokines such TNF-α, basic fibroblast growth factor (bFGF), and IL-6, IL-8, and IL-10 are mediators of burn-induced inflammation, infection, and sepsis. Cytokines and pro-inflammatory mediators block and decrease endogenous anabolic agents. Immediately after burn injury, expression of anti- and pro-inflammatory markers, immune mediators, and chemokines increase, particularly IL-6, IL-8, monocyte chemotactic protein (MCP)-1, macrophage inflammatory protein (MIP)-1β, and granulocyte-colony stimulating factor (G-CSF) [56]

Plasma concentrations of cytokines have been shown not only to differentiate sepsis from systemic inflammatory responses but to differentiate survivors from non-survivors. The concerns about cytokines are that these markers are easily affected by other pathophysiologic processes such as individual genetic variability, organ function, environment, and type of dressing, among others [51]. Early after injury (0–6 and 7–14 days), sepsis in the adult patient is associated with significant increases in IL-6, TNF-α, and IL-10 as well as in chemokines and the immune mediators MCP-1, IFN-γ–induced protein 10 (IP-10), granulocyte-macrophage colony-stimulating factor (GM-CSF), FMS-like tyrosine kinase 3 ligand (FLT-3L), and IL-2. In the elderly burn population, significance is found for high concentrations of IL-6, IL-10, and FLT-3L in early sepsis and for high concentrations of TNF-α and IP-10 in late sepsis (>14 days) [38]. The complexity of the cytokine cascade makes interpretation difficult, and a simple increase or decrease is not sufficient to diagnose or predict sepsis.

Neutrophil dysfunction. Neutrophils are the first-line protectors against bacterial and fungal infections. The antimicrobial function of neutrophils encompasses phagocytosis, toxic intracellular intermediates, and neutrophil extracellular traps (NETs). The NETs are composed of granule-derived peptides, enzymes, and histones and are able to ensnare and eliminate extracellular bacteria directly [57]. Impairments in neutrophil function have been related to the presence of sepsis, as neutrophils derived from patients with sepsis show a different phenotype from those from patients without sepsis. In a cohort of severely burned patients, circulating neutrophils and immature granulocyte counts were elevated, showing decreased neutrophil activity [58]. Neutrophil oxidative burst capacity is reduced after burn injury, leading to a greater risk of infection. Differences in immature granulocyte count, phagocytic activity, and circulating free DNA (cfDNA) have been found in septic and non-septic burn patients [58]. Therefore, they have potential use as biomarkers for sepsis in burns. In the prospective cohort described earlier, this combination showed good discriminatory power to predict later development of sepsis as early as day one after the injury. In addition, the revised Baux score was included in any combination of one or two of these parameters leading to an even better discriminatory power (area under the receiver operating characteristic curve [AUROC] 0.986 (95% CI 0.955–1.000)] [58]

Investigational markers. Omics technology is novel and exciting and seeks to characterize and quantify molecules involved in the structure, function, and dynamics of an organism. These molecules consist of DNA (genomics and epigenetics), RNA (transcriptomics), proteins (proteinomics), and metabolites (metabolomics) [45]. The use of RNAs as biomarkers (transcriptomics) is attractive, as these molecules have the advantage of being easily accessible in polymerase chain reaction-based bedside tests. Sepsis affects the genomic response in WBCs with a subsequent change in RNA transcripts compared with healthy individuals. Analysis of these transcriptomes has shown differences between infection and non-infectious acute disease and between different causative pathogens and allows stratification of patients into risk groups correlating with outcome measures such as death [59]

Sepsis Predictor Index (SPI). Collecting and analyzing white adipose tissue samples from the site of injury and plasma from 37 severely burned adult patients (> 20% TBSA) within 96 hours of injury led to the development of the Sepsis Predictor Index (SPI). This tool identifies the percentage of IL-1β produced by leukocytes/macrophages in the stromal vascular fraction of the adipose tissue. Compared with non-septic patients, the site of injury in septic burn patients shows a higher concentration of IL-1β, a pro-inflammatory cytokine, and a lower number of macrophages. An SPI ratio >0.5 was present in all septic patients, whereas all non-septic patients had an SPI <0.5. Sepsis occurred within 12 days after injury in patients with SPI ratios >1, and patients with SPI values between 0.5 and 1 had sepsis onset later than 12 days after injury. The SPI is a novel technique that not only identifies susceptibility to sepsis, but also predicts its onset by creating an immunological profile based on samples from the injured tissue. The SPI is a promising tool for sepsis prediction, although it requires further validation in multi-center trials and larger samples [20]

Conclusions

Burn patients, especially after a major injury, are in a chronic hyperinflammatory state. This state mimics SIRS and certainly sepsis or even septic shock. This is the fundamental challenge of developing a sepsis definition in burn patients. Hence, the definition of sepsis in critically ill and burn patients remains to be improved and needs to be adjusted to novel findings. New prospective studies must further validate current criteria and examine reliable markers and precise predictors. In clinical practice, sepsis definition relies frequently on expert opinion. The new Sepsis-3 Consensus Definition published in 2016, although not originally developed for burn patients specifically, outperformed the other burn-specific sepsis criteria at predicting the onset of sepsis [22,23].

Sepsis in the pediatric population is different from sepsis in the adult population. Similarly, there is no tailored sepsis definition for patients considered to be elderly (aged ≥65 years) or those who have high frailty scores. The systemic response to sepsis differs in these two populations compared with younger adults.

A biomarker that can discriminate sepsis from a non-infectious cause is strongly required. Newer technologies seem attractive and promising, but at this time, there is not a single factor that can identify or predict sepsis. The recently introduced SPI may be a novel avenue to be used along with clinical information to identify and define sepsis early allowing interventions to improve the outcomes of burn patients suffering from sepsis. We believe there is potential utility in a combination of clinical and novel immune biomarker data for the early prediction and diagnosis of sepsis.

Acknowledgments

The authors thank the Ross Tilley Burn Centre staff for their support.

Funding Information

The authors received no specific funding for this work. Some funding came from the Canadian Institutes of Health Research #123336, National Institutes of Health #R01GM087285,

National Institutes of Health #R01GM133961, and the Ontario Institute of Regenerative Medicine.

Author Disclosure Statement

The authors have no disclosures to report.

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