American Burn Association Consensus Conference to Define Sepsis and Infection in Burns

The American Burn Association Consensus Conference on Burn Sepsis and Infection Group; David G. Greenhalgh, MD,* Jeffrey R. Saffle, MD,† James H. Holmes, IV, MD,‡ Richard L. Gamelli, MD,§ Tina L. Palmieri, MD,* Jureta W. Horton, PhD,¶ Ronald G. Tompkins, MD,‖ Daniel L. Traber, PhD, David W. Mozingo, MD,†† Edwin A. Deitch, MD,‡‡ Cleon W. Goodwin, MD,§§ David N. Herndon, MD,** James J. Gallagher, MD,** Art P. Sanford, MD,** James C. Jeng, MD,¶¶ David H. Ahrenholz, MD,‖‖ Alice N. Neely, PhD,*** Michael S. O'Mara, MD,* Steven E. Wolf, MD,††† Gary F. Purdue, MD,¶ Warren L. Garner, MD,‡‡‡ Charles J. Yowler, MD,§§§ Barbara A. Latenser, MD¶¶¶**

Because of their extensive wounds, burn patients are chronically exposed to inflammatory mediators. Thus, burn patients, by definition, already have "systemic inflammatory response syndrome." Current definitions for sepsis and infection have many criteria (fever, tachycardia, tachypnea, leukocytosis) that are routinely found in patients with extensive burns, making these current definitions less applicable to the burn population. Experts in burn care and research, all members of the American Burn Association, were asked to review the literature and prepare a potential definition on one topic related to sepsis or infection in burn patients. On January 20, 2007, the participants met in Tucson, Arizona to develop consensus for these definitions. After review of the definitions, a summary of the proceedings was prepared. The goal of the consensus conference was to develop and publish standardized definitions for sepsis and infection-related diagnoses in the burn population. Standardized definitions will improve the capability of performing more meaningful multicenter trials among burn centers. (J Burn Care Res 2007;28:776–790)

Large burns (>20% total body surface area) lead to the most profound response to injury. Hypermetabolism developing after burn injury leads to an increase in caloric needs that may double normal resting energy expenditure. No other injury or illness approaches this degree of perturbation. As in other critical illnesses, burn patients are at high risk for infection and sepsis. The major cause of death, if the burn patient survives the first 24 hours, is multiple

*From the *Department of Surgery, University of California, Davis and Shriners Hospitals for Children Northern California, Sacramento, California; †Department of Surgery, University of Utah, Salt Lake City, Utah; ‡Department of Surgery, Wake Forest University School of Medicine, Winston-Salem, North Carolina; §Department of Surgery, Loyola University, Maywood, Illinois; ¶Department of Surgery, University of Texas, Dallas, Texas; ‖Department of Surgery, Massachusetts General Hospital and Shriners Hospitals for Children Boston, Massachusetts; **Department of Surgery, University of Texas Medical Branch and Shriners Hospitals for Children Galveston, Texas; ††Department of Surgery, University of Florida, Gainesville, Florida; ‡‡Department of Surgery, University of Medicine and Dentistry, New Jersey Medical School, Newark, New Jersey; §§Department of Surgery, North Colorado Medical Center, Greeley, Colorado; ¶¶Department of Surgery, The Burn Center at Washington Hospital Center, Washington, DC; ‖‖Department of Surgery, Regions Hospital, Saint Paul, Minnesota; ***Shriners Hospitals for Children Cincinnati and Department of Surgery, University of Cincinnati, Ohio; †††Department of Surgery, University of Texas Health Science Center—San Antonio, Texas; ‡‡‡Department of Plastic Surgery, University of Southern California Medical Center, Los Angeles, California; §§§Department of Surgery, Metro Health Medical Center/Case Western Reserve University, Cleveland, Ohio; and ¶¶¶Department of Surgery, University of Iowa, Iowa City, Iowa.*

This study was supported by the American Burn Association.

Proceedings of the Consensus Conference to Define Sepsis and Infection in Burns, Loew's Ventana Canyon Resort, Tucson, Arizona, January 20, 2007.

Address correspondence to David G. Greenhalgh, MD, Department of Surgery, University of California, Davis and Shriners Hospitals for Children Northern California, 2425 Stockton Blvd., Sacramento, California 95817.

1559-047X/2007

DOI: 10.1097/BCR.0b013e3181599bc9

organ dysfunction syndrome (MODS). There are excellent criteria for the diagnosis of infection and sepsis in most patients, but the standard diagnoses for infection and sepsis really do not apply to burn patients. Burn patients lose their primary barrier to microorganism invasion so they are constantly and chronically exposed to the environment. In response to this exposure, inflammatory mediators that change the baseline metabolic profile of the burn patient are continuously released. The baseline temperature is reset to about 38.5°C, and tachycardia and tachypnea persist for months in patients with extensive burns. Continuous exposure leads to significant changes in the white blood cell (WBC) count, making leukocytosis a poor indicator of sepsis. Burn physicians have learned to use other clues as signs of infection or sepsis, such as increased fluid requirements, dropping platelet counts, altered mental status, worsening pulmonary status, and impaired renal function. So, although excellent standards exist for other diagnoses, standardized definitions for infection and sepsis in burn patients have never been developed.

A major method of standardizing definitions has been through Consensus Conferences. Members of the American Burn Association realized that standardized definitions were required for burn patients. As the American Burn Association has developed a Multicenter Studies Group with a goal of creating level-one evidence for treating burns, it became clear that standardized definitions would be necessary to ensure uniformity in patient accrual in these studies. Since most burn patients fit the current criteria for having systemic inflammatory response syndrome (SIRS) throughout their hospital stay, different definitions would need to be developed for burns. This requirement is reinforced by the fact that most trials dealing with sepsis have eliminated or minimized burns via their inclusion criteria. Consequently, a Consensus Conference to Define Sepsis and Infection in Burns took place on January 20, 2007 in Tucson, Arizona, where several experts in the management or research of burns met to define sepsis and infection in burns. The results of these proceedings are recorded in this review.

METHODS

The Consensus Conference was modeled after similar such conferences reported by the Society of Critical Care Medicine.[1–4] The lead author (D.G.G.) chose 23 experts in the field of burn care and/or research as rapporteurs. Two rapporteurs were assigned to review the current literature of each of the listed topics (see below). They were also encouraged to seek any advice or opinions of other experts in the field. The rapporteurs were asked to send a brief definition (to D.G.G.) before the meeting for placement on a PowerPoint presentation. All members then met on January 20, 2007, in Tucson, Arizona. This brief definition was presented to the experts for discussion. The definition was then adjusted until consensus was met. The final version of the definition was then sent to each rapporteur to create a brief rationalization for that definition. All members of the team could also make suggestions for revisions during this time. All of the definitions and rationalizations were then collated and placed in a manuscript for review by all participants. The final version is presented here.

Consensus Conference Summary of Burn Sepsis and Infection Definitions

Systemic Inflammatory Response Syndrome

Patients with large burns are in a state of chronic systemic inflammatory stimulation; therefore, SIRS is of little value as a discriminating diagnosis in burns. SIRS should not be applied to burn patients.

Rationalization. The term "SIRS" stands for "Systemic Inflammatory Response Syndrome." The concept was developed as a result of studies in the 1980s demonstrating that postinjury MODS resulted from an exaggerated and dysfunctional perturbation of the normal and beneficial inflammatory response to injury which can precede sepsis, and/or exist in the absence of infectious causes.[5] SIRS can vary in severity depending on several factors, including the magnitude and duration of initial tissue injury and shock, and host response factors which are partially determined by genetic variations in the magnitude of inflammation. This proinflammatory state initiates a corresponding counter–anti-inflammatory response syndrome, which is associated with immune suppression and predisposition to infection.[6]

The current definition of SIRS was created by a consensus conference of critical-care and trauma physicians more than a decade ago.[1] SIRS is considered to be present when a patient demonstrates two or more of the following:

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. WBC count >12,000/mm^3 or <4,000/mm^3, or left shift defined as >10% bands.

Problems With SIRS in Burn Patients. Although the concept of SIRS is widely accepted, a number of problems exist with application of the current defini-

tion in clinical practice,[7] and this is particularly true in burn patients. These issues include:

1. *The definition is so inclusive as to be meaningless.* SIRS describes minor perturbations in physiology, which occur extremely frequently in trauma patients even in the absence of infection. As such, the definition has been widely criticized as being far too inclusive and nonspecific.[2,8] In some studies, SIRS criteria were documented in well over half of intensive care unit (ICU) and trauma admissions, having no correlation with outcome,[9,10] whereas other studies have found that the magnitude of SIRS at admission and over time is associated with increased morbidity and mortality in trauma patients.[11,12] Burn patients have never been systematically evaluated, but almost all patients with moderate to major burn injuries undoubtedly manifest SIRS. No studies of the epidemiology and time-course manifestations of SIRS in burn patients have been performed.
2. *When should SIRS be defined*? A transient manifestation of SIRS is part of the normal stress response and may have no predictive value in burns. Persistence of SIRS for ≥3 days was associated with a significantly increased risk of MODS and mortality in trauma patients,[13] while persistence of SIRS was found to be characteristic of burn patients who ultimately died.[14] However, the hypermetabolism of burn injury results from both hormonal and inflammatory influences[15]; even after acute inflammation has subsided, persistence of tachycardia and increased metabolic demands persist for days to weeks even in the absence of clinical complications or infections. No study has demonstrated that there is a time point in the course after burn at which SIRS criteria become clinically valuable.
3. *SIRS does not reflect the severity of the disease process.* In critically ill populations, SIRS criteria have been used to develop other measurements of inflammation and organ dysfunction, including Acute Physiology and Chronic Health Evaluation APACHE-II and APACHE-III.[16,17] None of these scoring systems have been validated in burn patients, who were specifically excluded from their development. In contrast, burns are uniquely quantifiable injuries; burn size has been repeatedly shown to correlate closely with every important clinical parameter in acute care.[18,19] No modification of SIRS has been proposed based on burn size, and no studies have evaluated SIRS criteria in patients with burns of different sizes. It has been suggested that increasing the temperature component of SIRS to 38.3°C would increase its specificity,[20] but confirmation of this awaits a clinical trial.
4. *SIRS may detract from the search for infection.* Although SIRS criteria are manifested by most infected patients, their presence does not mean an infection is present. Conversely, infection can obviously exist in the absence of one or more SIRS criteria. Thus, awareness of the ubiquity of SIRS may distract clinicians from responding to meaningful changes in patient status, and permit occult infections to persist.
5. *SIRS does not help in clinical trials.* One important use of definitions such as SIRS is for stratifying patients into homogenous groups for clinical trials. However, because SIRS has not been found to be useful for this purpose, we need further data in order to declare SIRS not useful in burns.
6. *SIRS is an adult system.* SIRS criteria were developed for adults, and do not apply to pediatric patients who comprise about one third of the hospitalized burn population. Though definitions of sepsis and organ failure have been developed for children, SIRS was not systematically defined in pediatric patients until 2005 (Table 2).[4] This conference increased the temperature component of SIRS to 38.5°C, defined age groups for pediatric patients, and specified vital sign values to establish a diagnosis of SIRS for a number of age groups. However, these definitions remain as irrelevant to pediatric burn patients as do those in adults, and are equally inclusive. Children are more susceptible to alterations in vital signs due to stress, fear, pain, and environmental factors, which may further obviate these criteria in children.

Alternative Definitions for SIRS. In recent years, a number of markers of shock and inflammation have been identified which could be useful in defining ongoing inflammation. During acute resuscitation, the presence of a base deficit and/or lactic acidosis correlates with severity of injury and mortality in burn and trauma patients.[5,21,22] However, it remains unclear whether the absolute value of these abnormalities is as important as their persistence over time. The correlation of "oxygen debt" with outcome in a variety of ICU populations has stimulated interest in "goal-directed" resuscitation therapy.[23] However, while this remains an accepted technique in sepsis,[24] its value in the routine management of burn patients remains unproven,[25] and unquestionably this "goal-directed" approach requires far more fluid administration than predicted by the Parkland formula, with

a corresponding increase in the risk of abdominal compartment syndrome.[26]

A number of other biochemical markers of inflammation have also been correlated with outcome. These include C-reactive protein,[27] procalcitonin,[28] tumor necrosis factor-α,[29] interleukin-6, and others.[30–33] Many of these proteins are elevated early in the course of injury, and taper gradually over time; they are influenced by a number of metabolic events, and do not appear to correlate adequately with prognosis in burn patients.[34]

At present, the efficacy of cytokine "profiles" to quantify systemic inflammation, or to diagnose sepsis in burn patients has not been proven. These markers are not routinely measured, and their interpretation remains unclear. It is likely that in the future the most likely use of these monitors may be in stratifying patients for clinical trials, and for defining more completely the variations in individual response to injury and infection.

Recommendation. The SIRS is a ubiquitous consequence of acute burn injury; the magnitude, time course, and significance of which remain undetermined. Current diagnostic criteria for SIRS are too nonspecific to be clinically useful in prognosis, or in stratifying burn patients for clinical trials. Modified criteria for defining SIRS in burns have been proposed; however, this approach mandates validation via an epidemiologic outcomes study utilizing SIRS scores in burn patients. Until such studies have been completed, routine use of SIRS in burn patients should be abandoned.

Sepsis

Sepsis is a change in the burn patient that *triggers* the concern for infection. It is a presumptive diagnosis where antibiotics are usually started and a search for a cause of infection should be initiated. While there is need for clinical interpretation, the diagnosis needs to be tied to the discovery of an infection (defined below). The definition is age-dependent with adjustments necessary for children.

The trigger includes at least three of the following:

I. Temperature >39° or <36.5°C
II. Progressive tachycardia
  A. Adults >110 bpm
  B. Children >2 SD above age-specific norms (85% age-adjusted max heart rate)
III. Progressive tachypnea
  A. Adults >25 bpm not ventilated
    i. Minute ventilation >12 l/min ventilated
  B. Children >2 SD above age-specific norms (85% age-adjusted max respiratory rate)
IV. Thrombocytopenia (will not apply until 3 days after initial resuscitation)
  A. Adults <100,000/mcl
  B. Children <2 SD below age-specific norms
V. Hyperglycemia (in the absence of pre-existing diabetes mellitus)
  A. Untreated plasma glucose >200 mg/dl or equivalent mM/L
  B. Insulin resistance—examples include
    i. >7 units of insulin/hr intravenous drip (adults)
    ii. Significant resistance to insulin (>25% increase in insulin requirements over 24 hours)
VI. Inability to continue enteral feedings >24 hours
  A. Abdominal distension
  B. Enteral feeding intolerance (residual >150 ml/hr in children or two times feeding rate in adults)
  C. Uncontrollable diarrhea (>2500 ml/d for adults or >400 ml/d in children)

In addition, it is *required* that a documented infection (defined below) is identified

  A. Culture positive infection, or
  B. Pathologic tissue source identified, or
  C. Clinical response to antimicrobials

Rationalization. Sepsis is one of the leading causes of morbidity and mortality in critically ill patients. Several consensus conferences have been held to define sepsis in critically ill adults and children.[1–4] The applicability of these definitions to burn patients becomes problematic due to the altered metabolic, physiologic, and immunologic changes that accompany burn injury. These changes, such as increases in temperature, heart rate, respiratory rate, and blood pressure, would, by current guidelines, result in the diagnosis of sepsis in virtually all major burn injuries. The burn sepsis definition must therefore distinguish changes in patient status as the result of infection due to a microbial entity from the alterations secondary to the burn injury itself or associated events (such as inhalation injury).

Several of these global changes are based on the fact that patients with extensive burns develop a hypermetabolic state that surpasses that of any other patient group. It has been documented that the metabolic rate may approach twice that of the normal state. This hypermetabolic state persists for months after the burn wound has healed. As a manifestation of the hypermetabolic state, patients with large burns "reset" their baseline temperature to around 38.5°C. Therefore, fevers are not considered a sign of sepsis until they reach at least 39°C. Hypothermia, however, is as concerning to the burn doctor as for any other intensivist. The increased metabolism also leads to tachycar-

dia and tachypnea. Therefore, higher values are required to initiate a workup for infection or sepsis.

Although burn surgeons aggressively attempt to close the burn wound, there are still large areas of open burns or unhealed split-thickness donor sites that contribute to the inflammatory response. As a manifestation of chronic wound exposure, leukocytosis is common and unreliable as an indicator of infection. Thrombocytopenia, however, has been documented to be a reliable sign of sepsis.[35] Due to the large fluid shifts after initial burn shock resuscitation, thrombocytopenia is frequently encountered at 24 to 48 hours after a major burn. At this time, thrombocytopenia is an indicator of hemodilution not sepsis. After approximately 3 days a dropping platelet count is a valuable sign of sepsis.

As for other patients, hyperglycemia, especially in the face of aggressive insulin treatment is a sign of sepsis. Similarly, an inability to tolerate enteral feedings is a common sign of sepsis.[36] Since most burn patients are aggressively supported with enteral nutrition, a change in tolerance is a warning sign to be heeded.

Finally, children have different set points in their vital signs so absolute numbers do not apply. We chose a change in two SD from normal as an indicator of sepsis. There are other indicators of sepsis that are documented in pediatrics that can be used as indicators of sepsis[4] (see appendix 1).

Severe Sepsis

The term *severe sepsis* is dropped.

Rationalization. The term *severe sepsis* has traditionally been defined as sepsis plus MODS. It was the feeling of the committee that it is rare for a burn patient to have an intermediate phase between sepsis and septic shock. Burn patients are chronically expressing signs of SIRS and the focus of clinicians is to seek signs of change due to sepsis. Once sepsis has occurred there is rarely an intermediate step before the onset of signs of shock. Finally, there is no meaningful clinical difference between sepsis and severe sepsis—the term has no relevance for burn-related clinical trials.

Septic Shock

Septic Shock is "sepsis" (defined above) in addition to shock-like hemodynamic parameters defined in "Sepsis Bundles."[37–40] We will not redefine those parameters.

Septic Shock is defined as persistent hypotension despite adequate fluid resuscitation and/or Lactate >4 mmol (36 mg/dl). The indicators of "adequate resuscitation" are described below:

I. The Surviving Sepsis Campaign Resuscitation Goals[37] are the following
   A. Central venous pressure >8 to 12 mm Hg
   B. Mean arterial pressure ≥65 mm Hg
   C. Urine output ≥0.5 $ml \cdot kg^{-1} \cdot hr^{-1}$ [1 $ml \cdot kg^{-1} \cdot hr^{-1}$ for children (this information is not in the Surviving Sepsis Campaign)]
   D. Central venous pressure (superior vena cava) or mixed venous oxygen saturation ≥70%
II. 2001 Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians/American Thoracic Society/Surgical Infection Society International Sepsis Definitions Conference[2]
   A. Adults: "a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes."
      i. Hypotension (despite adequate volume resuscitation)
      ii. Systolic Blood Pressure <90 mm Hg
      iii. Mean Arterial Pressure <60 mm Hg
      iv. Reduction in Systolic Blood Pressure <40 mm Hg from baseline
III. Children >2 SD below normal for age[4]
   A. Tachycardia (may be absent in hypothermia) with signs of decreased perfusion
   B. Decreased peripheral pulses compared to central pulses
   C. Altered alertness
   D. Flash capillary refill or refill >2 seconds
   E. Mottled or cool extremities
   F. Decreased urine output (<1 $ml \cdot kg^{-1} \cdot hr^{-1}$)

Rationalization. It was feeling of the group that redefining the well-established parameters of shock that are already defined in "Sepsis Bundles" is unnecessary and unwise. Hemodynamic instability is similar irrespective of the cause. The definitions utilized in two key publications (Surviving Sepsis Campaign[37] and the 2001 Definitions on Sepsis[2]) appear as references for the "Sepsis Bundles" documents. These definitions are supplied above.

Smoke Inhalation Injury

Smoke inhalation injury is restricted to injury below the glottis caused by products of combustion. The diagnosis requires both of the following:

I. History of exposure to products of combustion
II. Bronchoscopy revealing one of the following *below the glottis*
   A. Evidence of carbonaceous material
   B. Signs of edema or ulceration

Rationalization. There are several types of inhalation injuries that occur after a burn injury. First, there is exposure to poisons such as carbon monoxide and cyanide. While these exposures are clinically relevant they clearly can occur in the absence of smoke inhalation injury below the glottis. Carbon monoxide poisoning is easily diagnosed by measuring carboxyhemoglobin levels. While elevated levels increase suspicion for smoke inhalation injury, both entities can occur independently of each other. The committee felt that smoke inhalation injury (damage from products of combustion below the glottis) should be considered separately.

In a similar light, upper airway and vocal cord injury may occur from exposure to heat or simply as a result of the typical body-wide edema that occurs after a major burn. Upper airway edema is also an important process that frequently requires endotracheal intubation to prevent loss of the airway. Because upper airway injury or swelling may occur in all types of burn injuries, including scalds, it needs to be differentiated from smoke inhalation injury.

There are other signs of smoke inhalation injury that are less reliable or more cumbersome.[41] Flame burns to the face may be associated with increased risk for inhalation injury but not all flame burns to the face result in inhalation injury. For instance, a propane explosion can cause a burn to the face but the exposure is extremely brief and the patient will not have any exposure to the products of combustion below the glottis. In terms of diagnostic tests, Xenon lung scans are diagnostically highly accurate[42] but they require special equipment or a trip to nuclear medicine. Because most units do not have portable equipment and a trip to the nuclear medicine department is cumbersome and potentially dangerous it is rarely performed. Thus, it was the decision of the group that the best and most reliable test should be bronchoscopy. The signs observed below the glottis that indicate smoke inhalation include carbonaceous material, edema, or ulceration. Erythema or carbon staining in the absence of evidence of other signs of injury is *not* an indicator smoke inhalation injury.

There was also discussion about inhalation injury severity scores.[43–45] There are several scores that have been developed and could have potential therapeutic efficacy. It was decided that creating an inhalation injury score would be of considerable value but is beyond the scope of this Consensus Conference. It was agreed, however, that a future Consensus Conference would be dedicated to an inhalation injury severity system.

Multiple Organ Dysfunction Syndrome

The committee decided to use the Marshall MODS Scoring System[46] (as modified by Cook[47]) (Table 1) until a better system is found.

The MODS assessment should not be initiated until acute resuscitation is completed (approximately day 3).

Scores should grade the degree of organ failure over a spectrum of values.

Rationalization. In addition to the 2001 ACCP/SCCM definition,[2] there are many other organ failure scoring systems which use a diverse number of definitions. In general, the scoring systems consist of those in which organ failure is considered to be present or absent, vs. those that use a grading system of organ dysfunction, in which worsening organ dysfunction creates a higher score. Other important differences among these scoring systems are that they evaluate 1) different criteria to define organ failure or organ dysfunction; 2) they use different organs; and 3) that some organ failure/dysfunction systems use the initial or early values, while others use the worst values obtained over the hospital course of the patient.

In the previously published major scoring systems none contained a significant number of burn patients. Additionally, there are relatively few published studies on MODS in burn patients, the number of patients enrolled is small and the definitions vary from study to study. Consequently, it is problematic to use

Table 1. Modified Marshall Scoring System[47]

Organ System	0	1	2	3	4
Cardiovascular (heart rate, inotropes, lactate)	≤120	120–140	>140	Inotropes	Lactate >5
Respiratory, PO_2/FIO_2	>300	226–300	151–225	76–150	≤75
Renal (creatinine, υmol/L)	≤100	101–200	201–350	351–500	>500
Central nervous system (Glascow Coma Scale)	15	13–14	10–12	7–9	≤6
Hepatic (total bilirubin, υmol/L)	≤20	21–60	61–120	121–240	>240
Hematologic (platelet count $\times 10^3$)	>120	81–120	51–80	21–50	≤20

Six domains of the MODS. The scores can range between 0 and 24. The heart rate is defined as beats per minute (bpm). "Inotropes" indicates the need for inotropes more than dopamine >3υg · kg^{-1} · min^{-1}. Lactate is measured in mmol/L.

these studies as the basis for a scoring system in the burn population.

General Recommendations and Rationale

1. *Recommendation.* The ACCP/SCCM consensus criteria for sepsis[1] should not be used.
   A. Rationale. Several unique aspects of burn patients and the physiology of a major thermal injury also render certain criteria of organ failure/dysfunction unreliable especially during the initial period of volume resuscitation. These unique issues include criteria based on urine output, lactate levels, WBC and in some case the platelet count.
2. *Recommendation.* Organ dysfunction/failure should not be assessed until the acute resuscitation period is over (approximately day 3 postburn).
   B. Rationale. This strategy would allow treatment-related reversible degrees of organ dysfunction to resolve, and thus would exclude patients with transient evidence of organ stress. During the first 3 days after a major burn there are profound changes due to the massive fluid requirements during resuscitation. Patients literally require dozens of liters of fluid. It is typical for patients to have either early leukocytosis (due to stress) or leukopenia due to dilution and margination. Platelet counts typically drop below 100,000/mcl and then return to normal levels. Clearly, these early changes constitute marked variations in the normal response to injury, not organ failure.
3. *Recommendation.* Organ dysfunction scores should be used which grade the degree of organ failure over a spectrum of values rather than those that define organ failure as present or absent.
   C. Rationale. This recommendation is based on the fact that the magnitude of organ dysfunction appears to be a more important variable than the presence or absence of organ failure. This strategy identifies patients with modest levels of organ dysfunction prior to organ failure. A scoring system used to enroll patients into clinical trials should identify patients as early as possible. Therefore, a graded MODS scoring system, where modest levels of organ dysfunction are used, is likely to be preferable to scoring systems using advanced levels of organ dysfunction/failure. The concept is that early initiation, rather than delayed or late initiation, of a therapeutic strategy is necessary to have the best clinical effect.
4. *Recommendation.* One of the four major MODS scoring systems[46–50] that grade the degree of organ failure should be used.
   D. Rationale. This option would employ a scoring system that has been developed and validated in large patient populations and would allow better extrapolation between results observed in burn patients with those in other critically ill patient populations and vice versa.
5. *Recommendation.* The MODS scoring system used should be simple, use common clinically available criteria and be unlikely to be significantly confounded by the unique characteristics of the burn patient population.
   E. Rationale. Meeting these criteria would allow the chosen MODS scoring system to be clinically facile to use, be generally applicable and reduce the likelihood of misclassification of patients (i.e. especially false positives).
6. *Recommendation.* The initial recommendation was that either the Marshall MODS scoring system[2] as modified by Cook et al[47] or the Sequential Oxygen Failure Assessment scoring system[48] should be used. After discussion among the group, it was felt that the Marshall MODS scoring system should be used for now. The group also recommended that future efforts should be spent on modifying the Marshall MODS score based on findings of the "GLUE" Grant—"Inflammation and the Host Response to Injury" (a grant supported by the National Institute of General Medical Sciences examining the molecular changes of burns and trauma). The system utilized by the Parkland Group to evaluate changes in burn patients should also be evaluated.[51,52]
   F. Rationale. These two MODS scoring systems were chosen for several reasons. First, they are the ones most commonly used and both have been validated in subsequent ICU patient based studies.[47,53,54] Additionally, a modified version of the Marshall MODS score has been used in burn patients.[51,52] Secondly, each of these systems is simple to use and the parameters are easily obtained clinically. Because there is more

experience in burns with the Marshall MODS scoring system, it was chosen.

7. *Unresolved issue 1.* Both the Marshall MODS score and the Sequential Oxygen Failure Assessment system use the Glasgow coma score to assess neurologic function. Although the Glasgow coma score added robustness to the overall accuracy of both of these scoring systems, its measurement can be subjective. Therefore a decision has to be made whether this component of the scoring systems is retained.
8. *Unresolved issue 2.* Depending on how the score is to be used, it may be worthwhile to measure the score over time. If this is done, the score should represent the maximum daily score (ie, the overall worst score). Rationale for a daily score is that this reflects the status of the patient on that day and this could be easily used for enrollment in clinical trials. Rationale for worst cumulative score is that different organs fail at different times and it is the cumulative insult that is important in determining the prognosis of individual patients as well as patient populations.

Pneumonia

I. The clinical diagnosis of *pneumonia* includes two of the following:
   A. Chest x-ray revealing a new and persistent infiltrate, consolidation, or cavitation
   B. Sepsis (as defined above)
   C. A recent change in sputum or purulence in the sputum

II. It also must be remembered that there are diagnoses that may mimic pneumonia (Acute Respiratory Distress Syndrome, tracheobronchitis, chest contusion).

III. Microbiologic Data: the clinical diagnosis can be modified *post hoc* with the microbiologic data into one of three categories
   A. Confirmed: clinical + pathogen isolated
   B. Probable: clinically present without microbiological confirmation
   C. Possible: abnormal chest X-ray with uncertain cause with low or moderate clinical suspicion, but with microbiologic definite criteria met or pathogen identified

IV. Positive Microbiology
   A. Tracheal aspirate: $\geq 10^5$ organisms
   B. Bronchoalveolar lavage (BAL): $\geq 10^4$ organisms (Blind is OK)
   C. Protected bronchial brush (PBB): $\geq 10^3$ organisms (Blind brush is OK)
   D. We recognize that there are other criteria for special organisms that we may not include in the diagnosis
   E. (The burn wound can be a source of the pathogens spread hematogenously)

Rationalization. We concur with the findings of several previous consensus conferences on pneumonia[3,55–57] except that sepsis has been redefined to fit burn patients (see section on Sepsis). There have been papers that have supported these findings in the diagnosis of pneumonia in burn patients. First of all, the group from United States Army Institute of Surgical Research found that there was an increased risk of pneumonia in patients with inhalation injury.[58]

The group from Galveston (Shriners Hospital) examined the accuracy of different methods for isolating bacteria from burn patients with pneumonia.[59–61] Ramzy, in 2003, reported on the correlation of BAL and chest x-ray findings in pediatric burns.[59] A cut off for positive BAL was chosen at 10^3. The usual positive threshold for positive BAL in other (nonburn) patients is 10^4. In this study 80% of the burn patients with inhalation injury had a positive BAL for pneumonia at some time during their hospitalization. The published rate of pneumonia in burn patients with inhalation injury was 38%.[58] This suggests a large number of false positive results. Radiologic abnormalities were evenly distributed between both the BAL positive and BAL negative groups. The conclusion includes the following: "BAL is the best currently available tool and has been useful in directing antimicrobial therapy. It is of paramount importance that the clinician remains vigilant and assimilates BAL findings in the context of the overall clinical picture." Barrett in 1999 looked at BAL vs. PBB sensitivity/specificity for pneumonia diagnosis in pediatric patients with autopsy cultures as the standard for comparison.[60] There was no difference between BAL and PBB. In addition, there was a striking lack of identification of pneumonia both clinically and microbiologically. The premorbid clinical diagnosis of pneumonia was made with the following criteria: SIRS, a positive x-ray, and a sputum sample with pathogenic microorganisms and WBC. Heggars in 1998 looked at culture results of BAL and burn wounds in pediatric patients. About half the time the same organism was found at both sites.[61] In this study BAL was performed for surveillance so no conclusions about the diagnosis of pneumonia can be drawn.

Wahl in 2005 reported on BAL in the diagnosis of ventilator-associated pneumonia (VAP) in burn patients.[62] A prospective examination compared with

historical controls demonstrated a reduction of 21% in the diagnosis of VAP clinically when revised after BAL results returned negative ($\leq 10^4$ cfu). The negative BAL prompted the stopping of antibiotics started for clinical suspicion. None of the six study patients required the reinstitution of antibiotics based on clinical grounds, and there was no other significant change in study endpoints. Pham in 2007 reported on the Clinical Pulmonary Infection Score (CPIS) predicting pneumonia in burn patients.[63] The standard for pneumonia diagnosis was a BAL result of $\geq 10^4$ cfu. The standard parameters for calculating the CPIS were used. The CPIS sensitivity was 30% with a specificity of 80% using the above definitions. It was theorized that low sensitivity could be attributed to a low calculated CPIS from the presence of Acute Respiratory Distress Syndrome in the group of patients. They concluded that, "CPIS poorly predicts VAP in burn patients and that VAP diagnosis should still rely on clinical suspicion verified by quantitative culture results."

Blood Stream Infection

One of two criteria must be met for a blood stream infection (BSI)

1. Patient has a recognized pathogen (defined as a microorganism *not* usually regarded as a common skin contaminant, ie, diphtheroids, *Bacillus* species, *Propionibacterium* species, coagulase-negative Staphylococci, or micrococci) cultured from two or more blood cultures, or one positive blood culture, in the presence of sepsis (as defined above).
2. Patient has a common skin contaminant cultured from two or more blood cultures drawn on separate occasions (including one drawn by venipuncture) and the patient has clinical signs of sepsis.

If the microbe cultured from the blood has not caused an infection at another site on the patient, then the BSI is termed a primary BSI. If the microorganism cultured from the blood has caused infections at other sites on the patient, then the BSI is termed a secondary BSI.

There are instances when some of these criteria may not apply

- Culture techniques may miss infections
- Patients on antibiotics (cultures may be negative)
- The role of single positive blood cultures needs to be clarified
- Some organisms act differently in BSI

Rationalization. This definition concurs with the blood stream infection definition published in 2005 by "The International Sepsis Forum Consensus Conference on Definition of Infection in the Intensive Care Unit."[3] Their definition requires that a microorganism be recovered from the bloodstream to confirm the diagnosis. This is similar to the definition of "laboratory-confirmed BSIs" published in 1988[64] by the Centers for Disease Control and Prevention (CDC) in Atlanta.

We require at least one positive blood culture to confirm a BSI in a burn patient. We recognize it is possible to have, as with all laboratory tests, a false negative result, especially if the patient is receiving antimicrobial agents or the levels of microbes in the blood are low. Conversely, false positive culture results can occur if the blood was contaminated during the blood draw. Also, manipulation of a patient, for example during a dressing change, could cause a transient, but not clinically relevant, bacteremia. The definition requires two or more blood draws and that signs of sepsis be present. This should reduce the possibility of misidentifying a BSI in the burn patient. Specific techniques to decrease the incidence of a false positive or a false negative blood culture result are included in the Appendix.

Catheter-Related Infection

A central venous catheter is a vascular access device that terminates close to the heart or in one of the great vessels in the venous system.

A *central venous catheter should be considered the source of an infection* if one is in place at any time in the 48 hours before the infection occurs, even if said catheter has been removed in the intervening time period. Any patient who has signs of an infection or sepsis, and has the central venous catheter removed, with no other documented source of infection, and the signs resolve with 24 hours after removal, should be considered to have had an infection originating with the catheter.[65]

Localized Catheter Colonization. This is the significant growth of a microorganism (>15 colony-forming units) from the catheter tip, subcutaneous segment of the catheter, or from the catheter hub.[66]

Exit Site Inflammation. Any erythema or induration that occurs within 2 cm of the catheter exit site is, by this definition, not an infection.[67] No bloodstream infection, signs of sepsis, or localized purulence may be present.

Exit Site Infection. Tenderness, erythema, or undue induration more than 2 cm from the catheter exit site is an exit site infection.[68] Also, purulence or necrosis at the exit site is an exit site infection. These both assume absence of a blood stream infection or signs of sepsis.

Central Venous Catheter Infection. For the diagnosis of Central Venous Catheter Infection (CVCI), the following will be required

Any bacteremia or fungemia in a patient with an intravascular catheter with the microbial growth from at least one blood culture obtained from a vein or artery separate from the catheter site, clinical signs of infection (as noted elsewhere), and no other documented source of the infection or one of the following:

1. Any bacteremia or fungemia in a patient with an intravascular catheter with greater than 15 colony-forming units (>15 cfu) per catheter segment on semiquantitative culture analysis[66] or greater than 10^3 colony-forming units ($>10^3$ cfu) per catheter segment on quantitative culture analysis[69,70] with the same organism (species and antimicrobial sensitivity) isolated from a blood culture from a separate vein or arterial sample is a CVCI.
2. Simultaneous quantitative blood cultures drawn from both the central venous catheter and a separate venous or arterial site with a greater than 5:1 catheter vs. other site ratio is a CVCI.[71,72]
3. If a differential period of culture growth occurs with catheter blood growing pathogenic organisms more than 2 hours before a separate site, then a CVCI is present.[73]

Rationalization. Central venous catheters remain a source of infection in burn patients. They are often a source of bacteremia and sepsis. An approach needs to be applied that is inclusive of all infections that could be from the catheter. Central venous catheters that are in place when a suspected or documented infection is present, by these definitions, should be treated as infected catheters for all clinical purposes. A stricter definition, requiring the infection to be documented, should be used for research protocols.

Central venous catheters have become a mainstay of therapy in burn care. They have also become a primary source of infection and sepsis in the burn patient, with rates of infection sometimes exceeding 20 catheter-related blood stream infections per 1000 catheter days,[74] as defined by the CDC[64] and the National Nosocomial Infection Surveillance System.[75] Due to the high rate of bacteremia and bloodstream contamination in burn patients, there is a dilemma as to how many of the infections that are attributed to central venous catheters truly are central venous catheter infections.[76,77] The reality and nomenclature of infections associated with central venous catheters in burn patients thus has the potential to be confusing. A simplified mechanism of description is therefore offered, with a detailed description of the methods of diagnosis.

Conclusions. A fairly strict set of definitions should be used to define an infection as a CVCI, but any infection in a burn patient should be considered to be from the central venous catheter until proven otherwise. Any catheter fitting the aforementioned definitions is infected. The noted diagnostic tests should be run, and infections treated according to the organism and patient, but in all cases of suspected CVCI or exit site infection the catheter should be removed and new access sought. These definitions do not preclude existing surveillance definitions, but those definitions are inadequate in the burn patient population and this refinement allows a more directed approach to infections attributable to central venous catheters in burn patients.

Burn Wound Infection

Wound Colonization. Bacteria present on the wound surface at low concentrations. No invasive infection. Pathologic diagnosis: $<10^5$ bacteria/g tissue

Wound Infection. Bacteria present in the wound and wound eschar at high concentrations. No invasive infection. Pathologic diagnosis: $>10^5$ bacteria/g tissue

Invasive Infection. "Presence of pathogens in a burn wound at concentrations sufficient in conjunction with depth, surface area involved and age of patient to cause suppurative separation of eschar or graft loss, invasion of adjacent unburned tissue or cause the systemic response of sepsis syndrome."

Pathogen present in the wound at high concentrations (frequently $>10^5$ pathogens/g tissue)
Invasion or destruction of unburned skin/tissue
Invasive infection may occur with or without sepsis
Many burn wound invasive infections, however, are life threatening and need urgent treatment (usually wound excision)

Cellulitis

Bacteria present in the wound and/or wound eschar at high concentrations
Examination of surrounding tissue reveals advancing erythema, induration, warmth, tenderness
Sepsis must be present
(Redness around the wound may not require treatment)

Necrotizing Infection/Fasciitis. Aggressive, invasive infection with underlying (beneath the skin) tissue necrosis

Diagnosis of Wound Infection

I. Objective
   A. Quantitative biopsy (can be used to confirm but is not reliable. It may help with identifying the organism)
   B. Quantitative swab (poor test but may help with identifying organism)
   C. Tissue histology
II. Subjective
   A. Pain, erythema, color changes

B. Unexpected change in the appearance or depth of the wound
C. Systemic changes
D. Premature separation of burn eschar

Rationalization. A key point is that all skin surfaces and wounds have bacteria present. The presence of bacteria alone does not indicate an infection. The patient/bacterial interaction is a more important factor than the presence of bacteria. The wound needs constant surveillance since the major method of detecting an infection is from observing a significant change in the wound appearance. The changes may be subtle but any change should prompt further investigation. The wound may change color, have increased exudate, have increased pain or appear to increase in depth. The classic definition suggests that there is early separation of the burn eschar. An eschar is the tough coagulated protein covering a deep burn. Superficial burns develop an exudate [scab] that forms from fibrin, cellular debris, and the residue of topical antimicrobial agents. This sometimes called pseudoeschar. The normal process of eschar separation is the result of bacteria digestion of nonviable tissue away from the underlying viable tissue. Early separation indicates an invasive infection. Today, early separation is rare because most burn surgeons excise a deep burn followed by skin grafting long before bacterial invasion.[78–82]

A frequent burn wound colonizer, *Pseudomonas aeruginosa*, tends to produce a yellow/green exudate.[83] This is not an invasive infection. Invasive *Pseudomonas* is a surgical emergency. This invasive infection produces purple-black and "punched-out" areas of the wound. The invasion frequently destroys both deep and superficial wounds. Split-thickness donor sites and even unwounded skin are sometimes involved. The patient has severe signs of sepsis. Treatment involves both systemic antibiotics and injection (clysis) of antibiotics beneath the wound. Most importantly, these wounds need aggressive surgical debridement and excision.

Other pathogens in addition to bacteria can cause disease. Yeast and molds are significant causes of burn wound invasion.[84–86] In a superficial wound, Candida may present with small papules of purulence. Aspergillus is manifested as gray-brown plaques that can be scooped out of the wound. Herpes simplex is a not uncommon cause of breakdown in a superficial wound where it is characterized by punched out lesions in the wound.

Urosepsis

Modified CDC criteria[3,64.]

1. One of the following: fever (>39.5°C and no other source of the fever), urgency, frequency, dysuria or suprapubic tenderness, and a urine culture $\geq 10^5$ cfu/ml (cfu = colony forming units) with no more than two species of organisms or
2. Two of the following: fever (>39.5°C), urgency, frequency, dysuria or suprapubic tenderness, and any of the following:
   a. positive dipstick for leukocyte esterase and/or nitrate
   b. pyuria ($\geq$10 WBC/μl or $\geq$3 WBC/high-power field of unspun urine)
   c. organisms seen on Gram stain of unspun urine
   d. two urine cultures with repeated isolation of the same uropathogen with $\geq 10^2$ cfu/ml in a nonvoided specimen
   e. two urine cultures with $\leq 10^5$ cfu/ml of single uropathogens in a patient being treated with appropriate antimicrobial therapy.

Rationalization. Urosepsis is not a major contributor to sepsis in the burn population.[87] It should be sought out as a source of high fever and systemic signs of sepsis. Most burn patients have Foley catheters in place to monitor urine output. Thus, the bladder is usually empty, so stasis, a key factor in urosepsis, is usually not present. The presence of the foreign body (Foley catheter) also makes the interpretation of positive cultures difficult. Treatment of a positive urine culture first involves changing the Foley catheter. These positive findings are usually treated with antibiotics. A more challenging problem is candiduria. It is not uncommon to find candida in the urine of burn patients. The finding of $>10^4$ cfu/ml, sepsis and no other source of infection may prompt an action. Sometimes, changing the Foley is all that is needed. Occasionally, antimicrobial treatment is initiated. The correct treatment is unknown.

CONCLUSION

This symposium is the first attempt to create standard definitions for sepsis and infection in the unique burn population. The major goal is to publish definitions so that future research can be performed using criteria agreed upon by all participants. By having standard definitions, future studies will have greater relevance to all burn centers. It is expected that multicenter trials will clarify and refine these definitions over time. For now, standardized definitions will allow for consistent diagnoses of infection and sepsis and facilitate multicenter trials in burn patients.

APPENDIX 1

Table 2. Physiologic parameters consistent with SIRS/sepsis in pediatrics based on age[4]

Age Group	Tachycardia	Bradycardia	Respiratory Rate	Leukocyte Count	SBP
0 d–1 wk	>180	<100	>50	>34	<65
1 wk–1 mo	>180	<100	>40	>19.5 or <5	<75
1 mo–1 yr	>180	<90	>34	>17.5 or <5	<100
2–5 yr	>140	NA	>22	>15.5 or <6	<94
6–12 yr	>130	NA	>18	>13.5 or <4.5	<105
13–<18 yr	>110	NA	>14	>11 or <4.5	<117

SBP, systolic blood pressure.

APPENDIX 2

Table 3. Blood volumes suggested for culture

Patient Weight (lbs)	Total Blood Volume (ml)	Recommended Volume/ Culture (ml)		Total Volume Cultured (ml)	Total Blood Volume (%)
		Culture 1	Culture 2		
4.5–27	>200	4	2	6	3
28–80	>800	10	10	20	2.5
>80	>2200	20–30	20–30	40–60	1.8–2.7

Reprinted from (Baron EJ, Weinstein MP, Dunne WM Jr, et al. In: Baron EJ, coordinating editor. Blood Cultures IV. Washington (DC): ASM Press; 2005, with permission.

Table 4. Results of studies to determine the number of blood draws needed to detect bacteremias and fungemias in adult patients

No. Patients	Blood Volume/Draw (ml)	Bacteremias and Fungemias Detected (%)				Reference
		1 Draw	2 Draws	3 Draws	4 Draws	
80	20	80	88	99	—	[9]
282	15	91	>99	—	—	[10]
163	20	65	80	96	100	[11]

Additional Information About Blood Stream Infections

Techniques for Culturing Patients Receiving Antimicrobials. Antimicrobials decrease the number and/or growth rate of microbes. Therefore, whenever possible, blood samples should be drawn before the patient is placed on antimicrobial therapy. If this is not possible, then a blood culture system designed to remove or inactivate antimicrobials from the blood sample should be used. Consult your in-house or reference microbiology laboratory for recommendations regarding these commercially available containers.

Comments About Blood Culturing

The following techniques are suggested to reduce the incidence of false negative or false positive blood culture results. A false negative result is more likely if there are few microorganisms in the bloodstream. The larger the blood sample, the greater will be the possibility of detecting the microbe.[88–92] Clearly there is a limit to the blood volume that can safely be drawn, especially from children. Kellogg et al[92] established that a maximum of 4.0 to 4.5% of the patient's total blood volume can safely be taken. Table 3 lists the suggested blood specimen volume for cultures from infants to adults, based on weight. None of the

total volumes exceed 3% of the patient's blood volume. Whenever possible, the frequency of repeat cultures should be limited to prevent iatrogenic anemia.

Studies in adults have also shown that the recovery of microorganisms from the blood is increased when more than one blood sample is obtained.[93] Table 4 summarizes the results of three studies that were conducted with adults who were bacteremic or fungemic.[94–96] These studies suggest that at least two, but not more than four blood specimens, should detect most common organisms in the blood. Optimally these draws should be from more than one site, and specimens obtained by venipuncture are preferable to those from indwelling lines. Specimens from at least two separate sites are recommended, because multiple draws increase the sensitivity of the assay, and reduce the risk of contamination as a confounding factor.

We presume that the levels of bacteria in blood are not constant. Blood samples should be obtained when signs of sepsis are found, and preferably before antimicrobials are started. In 1988 the American Society for Clinical Pathologists recommended that cultures be taken consecutively if the patient is critically ill and needs to be placed on antimicrobials immediately; otherwise, they arbitrarily recommended 30 to 60 minutes between draws.[97] However, Li el al. have shown no difference in the detection of bloodborne microbes when multiple blood samples were taken synchronously vs. when an interval of an hour or two was used between cultures.[91]

REFERENCES

1. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101:1644–55.
2. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31:1250–6.
3. Calandra T, Cohen J; International Sepsis Forum Definition of Infection in the ICU Consensus Conference. The International Sepsis Forum Consensus Conference on definitions of infection in the intensive care unit. Crit Care Med 2005; 33:1538–48.
4. Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med 2005;6:2–8.
5. Moore F, Moore E, Sauaia A. Postinjury multiple organ failure. In: Mattox K, Feliciano DV, Moore FA, editors. Trauma. New York: McGraw-Hill; 2000. p. 1427–60.
6. Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS Crit Care Med 1996;24:1125–8.
7. Vincent JL. Dear SIRS, I'm sorry to say that I don't like you. Crit Care Med 1997;25:372–4.
8. Marshall JC. SIRS and MODS: what is their relevance to the science and practice of intensive care? Shock 2000;14:586–9.
9. Salvo I, de Cian W, Musicco M, et al. The Italian SEPSIS study: preliminary results on the incidence and evolution of SIRS, sepsis, severe sepsis and septic shock. Intensive Care Med 1995;21 (Suppl 2):S244–S249.
10. Muckart DJ, Bhagwanjee S. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference definitions of the systemic inflammatory response syndrome and allied disorders in relation to critically injured patients. Crit Care Med 1997;25:1789–95.
11. Napolitano LM, Ferrer T, McCarter RJ Jr, Scalea TM. Systemic inflammatory response syndrome score at admission independently predicts mortality and length of stay in trauma patients. J Trauma 2000;49:647–52.
12. Hoover L, Bochicchio GV, Napolitano LM, et al. Systemic inflammatory response syndrome and nosocomial infection in trauma. J Trauma 2006;61:310–16.
13. Gando S, Nanzaki S, Kemmotsu O. Disseminated intravascular coagulation and sustained systemic inflammatory response syndrome predict organ dysfunctions after trauma: application of clinical decision analysis. Ann Surg 1999;229: 121–7.
14. Sheridan RL, Ryan CM, Yin LM, Hurley J, Tompkins RG. Death in the burn unit: sterile multiple organ failure. Burns 1998;24:307–11.
15. Bessey PQ, Jiang ZM, Johnson DJ, Smith RJ, Wilmore DW. Posttraumatic skeletal muscle proteolysis: the role of the hormonal environment. World J Surg 1989;13:465–70.
16. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest 1991;100:1619–36.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–29.
18. Warden G. Fluid resuscitation and early management. In: Herndon D, editor. Total Burn Care. Philadelphia, PA: WB Saunders; 2002. p. 88–97.
19. Saffle JR, Davis B, Williams P. Recent outcomes in the treatment of burn injury in the United States: a report from the American Burn Association Patient Registry. J Burn Care Rehabil 1995;16:219–32.
20. O'Grady NP, Barie PS, Bartlett JG, et al. Practice guidelines for evaluating new fever in critically ill adult patients. Task Force of the Society of Critical Care Medicine and the Infectious Diseases Society of America. Clin Infect Dis 1998;26: 1042–59.
21. Choi J, Cooper A, Gomez M, Fish J, Cartotto R. The 2000 Moyer award. The relevance of base deficits after burn injuries. J Burn Care Rehabil 2000;21:499–505.
22. Jeng JC, Jablonski K, Bridgeman A, Jordan MH. Serum lactate, not base deficit, rapidly predicts survival after major burns. Burns 2002;28:161–6.
23. Bishop MH, Shoemaker WC, Appel PL, et al. Prospective, randomized trial of survivor values of cardiac index, oxygen delivery, and oxygen consumption as resuscitation endpoints in severe trauma. J Trauma 1995;38:780–7.
24. Rhodes A, Bennett ED. Early goal-directed therapy: an evidence-based review. Crit Care Med 2004;32:S448–S450.
25. Kirton OC, Civetta JM. Do pulmonary artery catheters alter outcome in trauma patients? New Horiz 1997;5:222–7.
26. Holm C, Mayr M, Tegeler J, et al. A clinical randomized study on the effects of invasive monitoring on burn shock resuscitation. Burns 2004;30:798–807.
27. Lobo SM, Lobo FR, Bota DP, et al. C-reactive protein levels correlate with mortality and organ failure in critically ill patients. Chest 2003;123:2043–9.
28. Brunkhorst FM, Eberhard OK, Brunkhorst R. Discrimination of infectious and noninfectious causes of early acute respiratory distress syndrome by procalcitonin. Crit Care Med 1999;27:2172–6.
29. Zhang B, Huang YH, Chen Y, Yang Y, Hao ZL, Xie SL. Plasma tumor necrosis factor-alpha, its soluble receptors and interleukin-1beta levels in critically burned patients. Burns 1998;24:599–603.

30. Sherwood E, Traber D. The systemic inflammatory response syndrome. In: Herndon D, editor. Burns. New York: WB Saunders; 2002. p. 257–70.
31. Drost AC, Burleson DG, Cioffi WG Jr, Jordan BS, Mason AD Jr, Pruitt BA Jr. Plasma cytokines following thermal injury and their relationship with patient mortality, burn size, and time postburn. J Trauma 1993;35:335–9.
32. Vindenes HA, Ulvestad E, Bjerknes R. Concentrations of cytokines in plasma of patients with large burns: their relation to time after injury, burn size, inflammatory variables, infection, and outcome. Eur J Surg 1998;164:647–56.
33. Castelli GP, Pognani C, Cita M, Stuani A, Sgarbi L, Paladini R. Procalcitonin, C-reactive protein, white blood cells and SOFA score in ICU: diagnosis and monitoring of sepsis. Minerva Anestesiol 2006;72:69–80.
34. Cannon JG, Friedberg JS, Gelfand JA, Tompkins RG, Burke JF, Dinarello CA. Circulating interleukin-1 beta and tumor necrosis factor-alpha concentrations after burn injury in humans. Crit Care Med 1992;20:1414–19.
35. Housinger TA, Brinkerhoff C, Warden GD. The relationship between platelet count, sepsis, and survival in pediatric burn patients. Arch Surg 1993;128:65–6.
36. Wolf SE, Jeschke MG, Rose JK, Desai MH, Herndon DN. Enteral feeding intolerance: an indicator of sepsis-associated mortality in burned children. Arch Surg 1997;132:1310–4.
37. Dellinger RP, Carlet JM, Masur H, et al. Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 2005;32:858–73.
38. Levy MM, Pronovost PJ, Dellinger RP, et al. Sepsis change bundles: converting guidelines into meaningful change in behavior and clinical outcome. Crit Care Med 2004;32 (Suppl 11):S595–S597.
39. Gao F, Melody T, Daniels DF, Giles S, Fox S. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study. Crit Care 2005;9:R764–R770.
40. Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: secondary analysis of a high quality clinical database, the ICNARC Case Mix Programme Database. Crit Care 2006;10:R42–R51.
41. Heimbach DM, Waeckerle JF. Inhalation injuries. Ann Emerg Med 1988;17:1316–20.
42. Moylan JA Jr, Wilmore DW, Mouton DE, Pruitt BA Jr. Early diagnosis of inhalation injury using 133 xenon lung scan. Ann Surg 1972;138:477–84.
43. Chou SH, Lin SD, Chuang HY, Cheng YJ, Kao EL, Huang MF. Fiber-optic bronchoscopic classification inhalation injury: prediction of acute lung injury. Surg Endosc 2004;18: 1377–9.
44. Isago T, Ooshige K, Nakamura S, et al. Clinical trial of a scoring system for early diagnosis of inhalation injuries. Jpn J Burn Inj 1994;20:238–47.
45. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of adult respiratory distress syndrome. Am Rev Respir Dis 1988;138:720–3.
46. Marshall JC, Cook DJ, Christou NV, Bernard GR, Sprung CL, Sibbald WJ. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. Crit Care Med 1995;23:1638–52.
47. Cook R, Cook D, Tilley J, Lee Ka, Marshall J; Canadian Critical Trials Group. Multiple organ dysfunction: baseline and serial component scores. Crit Care Med 2001;29: 2046–50.
48. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. Intensive Care Med 1996;22:707–10.
49. Bernard G. The Brussels score. Sepsis 1997;1:43–4.
50. Le Gall JR, Klar J, Lemeshow S, et al. The logistic organ dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. JAMA 1996; 276:802–10.
51. Cumming J, Purdue GF, Hunt JL, O'Keefe GE. Objective estimates of the incidence and consequences of multiple organ dysfunction and sepsis after burn trauma. J Trauma 2001; 50:510–15.
52. Fitzwater J, Purdue GF, Hunt JL, O'Keefe GE. The risk factors and time course of sepsis and organ dysfunction after burn trauma. J Trauma 2003;54:959–66.
53. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med 1998;26:1793–800.
54. Moreno R, Vincent JL, Mendonca A, et al. The use of maximum SOFA score to quantify organ dysfunction/failure in intensive care. Results of a prospective, multicenter study. Working group on sepsis related problems of the ESICM. Intensive Care Med 1999;25:686–96.
55. Rello J, Paiva JA, Baraibar J, et al. International Conference for the Development of Consensus on the Diagnosis and Treatment of Ventilator-Associated Pneumonia. Chest 2001; 120:955–70.
56. Hubmayr RD, Burchardi H, Elliot M, et al. Statement of the 4th International Consensus Conference in Critical Care on ICU-Acquired Pneumonia—Chicago, Illinois, May 2002 Intensive Care Med 2002;28:1521–36.
57. National Nosocomial Infections Surveillance System (NNIS). Available from http://www.cdc.gov/ncidod/dhqp/nnis_pubs.html.
58. Rue LW III, Cioffi WG, Mason AD Jr, McManus WF, Pruitt BA Jr. The risk of pneumonia in thermally injured patients requiring ventilatory support. J Burn Care Rehabil 1995;16: 262–8.
59. Ramzy PI, Jeschke MG, Wolf SE, et al. Correlation of bronchoalveolar lavage with radiographic evidence of pneumonia in thermally injured children. J Burn Care Rehabil 2003;24: 382–5.
60. Barret JP, Ramzy PI, Wolf SE, Herndon DN. Sensitivity and specificity of bronchoalveolar lavage and protected bronchial brush in the diagnosis of pneumonia in pediatric burn patients. Arch Surg 1999;134:1243–7.
61. Ramzy PI, Herndon DN, Wolf SE, et al. Comparison of wound culture and bronchial lavage in the severely burned child: implications for antimicrobial therapy. Arch Surg 1998; 133:1275–80.
62. Wahl WL, Ahrns KS, Brandt M-M, et al. Bronchoalveolar lavage in diagnosis of ventilator associated pneumonia in patients with burns. Presented at the 36th American Burn Association, University of Michigan Health Systems, Ann Arbor, 2004.
63. Pham TN, Neff MJ, Simmons JM, Gibran NS, Heimbach DM, Klein MB. The clinical pulmonary infection score poorly predicts pneumonia in patients with burns. J Burn Care Res 2007;28:76–9.
64. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. Am J Infect Control 1988;16:128–40.
65. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers for Disease Control and Prevention. MMWR Recomm Rep 2002;51:1–29.
66. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. N Engl J Med 1977;296:1305–9.
67. Safdar N, Maki DG. Inflammation at the insertion site is not predictive of catheter-related bloodstream infection with short-term, noncuffed central venous catheters. Crit Care Med 2002;30:2632–5.
68. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. Clin Infect Dis 2001;32:1249–72.

69. Cleri DJ, Corrado ML, Seligman SJ. Quantitative cultures of intravenous catheters and other intravascular inserts. J Infect Dis 1980;141:781–6.
70. Raad II, Sabbagh MF, Rand KH, Shertz RJ. Quantitative tip culture methods and the diagnosis of central venous catheter-related infections. Diagn Microbiol Infect Dis 1992;15: 13–20.
71. Fan ST, Teoh-Chan CH, Lau KF. Evaluation of central venous catheter sepsis by differential quantitative culture. Eur J Clin Microbiol Infect Dis 1989;8:142–4.
72. Wing EJ, Norden CW, Shadduck RK, Winkelstein A. Use of quantitative bacteriologic techniques to diagnose catheter-related sepsis. Arch Intern Med 1979;139:482–3.
73. Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. Ann Intern Med 2004;140:18–25.
74. Ramos GE, Bolgiani AN, Patino O, et al. Catheter infection risk related to the distance between insertion site and burned area. J Burn Care Rehabil 2001;23:266–71.
75. National Nosocomial Infections Surveillance System. National nosocomial infection surveillance (NNIS) system report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 2004;32:470–85.
76. Sheridan RL, Weber JM. Mechanical and infectious complications of central venous cannulation in children: lessons learned from a 10-year experience placing more than 1000 catheters. J Burn Care Res 2006;27:713–18.
77. Sheridan RL, Weber JM, Peterson HF, Tompkins RG. Central venous catheter sepsis with weekly catheter change in pediatric burn patients: an analysis of 221 catheters. Burns 1995;21:127–9.
78. Peck MD, Weber J, McManus A, Sheridan R, Heimbach D. Surveillance of burn wound infections: a proposal for definitions. J Burn Care Rehabil 1998;19:386–9.
79. Church D, Elsayed S, Reid O, Winston B, Lindsay R. Burn wound infections. Clin Microbiol Rev 2006;19:403–34.
80. Wurtz R, Karajovic M, Dacumos E, Jovanovic B, Hanumadass M. Nosocomial infections in a burn intensive care unit. Burns 1995;21:181–4.
81. Pruitt BA Jr, McManus AT, Kim SH, Goodwin CW. Burn wound infections: current status. World J Surg 1998;22: 135–45.
82. McManus AT, Kim SH, McManus WF, Mason AD Jr, Pruitt BA Jr. Comparison of quantitative microbiology and histopathology in divided burn-wound specimens. Arch Surg 1987;122:74–6.
83. McManus AT, Mason AD Jr, McManus WF, Pruitt BA Jr. Twenty-five year review of Pseudomonas aeruginosa bacteremia in a burn center. Eur J Clin Microbiol 1985;4:219–23.
84. Ballard J, Edelman L, Saffle J, et al. Positive fungal cultures in burn patients: a multicenter review. J Burn Care Res. In press.
85. Mousa HA, al-Bader SM. Yeast infections of burns. Mycoses 2001;44:147–9.
86. Sheridan RL, Weber JM, Budkevich LG, Tompkins RG. Candidemia in the pediatric patient with burns. J Burn Care Rehabil 1995;16:440–3.
87. Weber J, Sheridan RL, Pasternack MS, Tompkins RG. Nosocomial infections in pediatric patients with burns. Am J Infect Control 1997;25:195–201.
88. Szymzcak EG, Barr JT, Durbin WA, Goldman DA. Evaluation of blood culture procedures in a paediatric hospital. J Clin Microbiol 1979;9:88–92.
89. Tenney JH, Reller B, Mirrett S, Wang W-LL, Weinstein MP. Controlled evaluation of the volume of blood cultured in detection of bacteremia and fungemia. J Clin Microbiol 1982;15:558–61.
90. Ilstrupt DM, Washington JA II. The importance of volume of blood cultured in the detection of bacteremia and fungemia. Diagn Microbiol Infect Dis 1983;1:107–10.
91. Li J, Plorde JJ, Carlson LC. Effects of volume and periodicity on blood cultures. J Clin Microbiol 1994;32:2829–31.
92. Kellogg JA, Manzella JP, Bankert DA. Frequency of low-level bacteremia in children from birth to fifteen years of age. J Clin Microbiol 2000;38:2181–5.
93. Baron EJ, Weinstein MP, Dunne WM Jr, et al. In: Baron EJ, coordinating editor. Blood Cultures IV. Washington, DC: ASM Press; 2005.
94. Washington JA. Blood cultures: principles and techniques. Mayo Clin Proc 1975;50:91–95.
95. Weinstein MP, Reller LB, Murphy JR, Lichtenstein KA. The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I. Laboratory and epidemiologic observations. Rev Infect Dis 1983;5:35–53.
96. Cockerill FR, Wilson JW, Vetter EA, et al. Optimal testing parameters for blood cultures. Clin Infect Dis 2004;38: 1724–30.
97. Strand CL. Blood cultures: consensus recommendation in 1988. Microbiology no. MB 88–1 (MB-172). American Society for Clinical Pathologists Check Sample Continuing Education Program. Chicago, IL: American Society of Clinical Pathologists; 1988.