Novel Predictors of Sepsis Outperform the American Burn Association Sepsis Criteria in the Burn Intensive Care Unit Patient

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The purpose of this study was to determine whether systemic inflammatory response syndrome (SIRS) and American Burn Association (ABA) criteria predict sepsis in the burn patient and develop a model representing the best combination of novel clinical sepsis predictors. A retrospective, case-controlled, within-patient comparison of burn patients admitted to a single intensive care unit from January 2005 to September 2010 was made. Blood culture results were paired with documented sepsis: positive-sick, negative-sick (collectively defined as sick), and negative-not sick. Data for all predictors were collected for the 72 hours before blood culture. Variables were evaluated using regression and area under the curve (AUC) analyses. Fifty-nine subjects represented 177 culture periods. SIRS criteria were not discriminative: 98% of the subjects met criteria. ABA sepsis criteria were different on the day before ($P = .004$). The six best-fit variables identified for the model included heart rate > 130 beats per min, mean arterial pressure < 60 mm Hg, base deficit < −6 mEq/L, temperature < 36°C, use of vasoactive medications, and glucose > 150 mg/dl. The model was significant in predicting positive-sick and sick, with an AUC of 0.775 ($P < .001$) and 0.714 ($P < .001$), respectively; comparatively, the ABA criteria AUC was 0.619 ($P = .028$) and 0.597 ($P = .035$), respectively. Usefulness of the ABA criteria to predict sepsis is limited to the day before blood culture is obtained. A significant contribution of this research is the identification of six novel sepsis predictors for the burn patient. (J Burn Care Res 2013;34:31–43)

Sepsis is a significant problem for burn patients. It is a systemic infection that overwhelms the body's immune system, triggering an exaggerated inflammatory response. The infectious process may progress to septic shock, multiple organ failure syndrome (MODS), and ultimately to death.[1,2] Infection has been demonstrated to precede multiple organ failure syndrome in 83% of burn patients, and reported mortality in this population increased from 12 to 33% in the setting of sepsis.[2,3] Reported attributable mortality of sepsis in the burn patient ranged from 28 to 65%.[4,5]

International critical care groups developed criteria for the identification of systemic inflammatory response syndrome (SIRS) associated with sepsis for the general intensive care unit (ICU) population.[6] Demonstrated or suspected infection coupled with two or more of the following clinical SIRS findings comprise the American College of Chest Physicians/Society of Critical Care Medicine sepsis criteria: temperature > 38°C or < 36°C; HR > 90 beats per min; respiratory rate (RR) > 20 breaths per min or arterial carbon dioxide tension < 32 mm Hg; or

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white blood cell (WBC) count < 4000 or > 12,000 cells/mm.[6] However, burn patients are different; sustained hypermetabolism and impaired immune function result in SIRS criteria serving as a baseline for the thermally injured patient.[7] The American Burn Association (ABA) developed burn-specific consensus sepsis criteria, which when present with known or suspected infection should "trigger" suspicion for sepsis. Presence of three or more of the following criteria coupled with suspected infection or response to antibiotics comprise the ABA sepsis criteria: temperature >39°C or <36.5°C; progressive tachycardia >110 beats per min; progressive tachypnea >25 breaths per min or minute ventilation > 12 L/min; thrombocytopenia <100,000/mcl; hyperglycemia: untreated plasma glucose > 200 mg/dl or intravenous glucose requirement >7 u/hr or > 25% increase in insulin requirement over 24 hours; or enteral feeding intolerance: abdominal distension pr gastric residuals more than two times feeding rate or diarrhea >2500 ml/d.

Identification of sepsis is further complicated by the lack of an accepted standard diagnostic method. Bacteremia with a pathogenic organism combined with clinical suspicion for sepsis is a reliable measure. However, Vincent et al[8] reported that 40% of multicenter ICU patients (n = 1177) treated for sepsis had no growth on blood cultures. Further, the specific variables associated with sepsis in the burn patient have not been formally evaluated. Changes in white blood cell or neutrophil count and temperature fluctuation have not been reliably associated with prediction of sepsis in the burn patient.[9] A recent study of the ability of the ABA criteria to predict burn sepsis demonstrated poor performance. However, the inclusion criteria were based on bacteremia (positive blood culture), not coupled with a clinical suspicion of sepsis; only elevated heart rate (HR) and temperature were found to correlate with bacteremia in this study.[10]

Prompt intervention is associated with improvement in outcomes[11]; yet, clinical expertise varies greatly among clinicians. Because of the differences in education and training, knowledge of indicators of sepsis differs among nurses who serve as filters, providing critical information to the treating providers.[12,13] Generally, a collection of subtle clinical changes is present in the early stages of infection and sepsis,[6] but compiling trends is difficult for busy clinical staff. The purpose of this study was 2-fold: 1) to determine the ability of the SIRS and ABA criteria to predict sepsis (defined as bacteremia coupled with clinical suspicion of sepsis) in the burn patient, and 2) to identify a model representing the best combination of clinical predictors associated with sepsis in the same population.

METHODS

The institutional review board approval for this study was granted by the appropriate committees for the protection of human subjects.

Design

This study was a case-controlled, within-patient comparison using a retrospective medical record review of critically ill, burned patients from a single regional burn center, admitted to the ICU from January 2005 through September 2010. Subjects served as their own controls by comparing the 72-hour period before three specific blood culture periods for each subject to represent the culture group: 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).

Population

The burn center cares both for adult civilian burn patients from the central Texas region and active-duty military casualties, generally transported from military conflicts overseas. Despite differences in severity of injury and extended duration of military transportation, no differences in outcomes or survival between the two patient groups have been previously reported.[14]

Subject Selection

Subjects were selected on the basis of the following inclusion criteria: adult patients (>18 years) with a thermal injury of at least 10% TBSA, use of intravenous insulin during ICU stay, and at least three reported blood cultures including at least one with bacterial growth. The inclusion of insulin as a primary inclusion criterion was based on the use of glycemic resistance in the ABA sepsis criteria and our local observations of an apparent association of increasing insulin requirements before sepsis diagnosis. Furthermore, use of a computer decision support system to provide hourly insulin titration recommendations provided an insulin resistance factor unique to each patient; this hourly marker was hypothesized to correlate with the onset of sepsis. Pregnancy, prisoner status, or nonthermal injury (dermatologic disease or electrical injury) were cause for exclusion. On the basis of blood culture results, working backward from September 2010, medical records were screened for patients meeting all inclusion criteria, and these were sequentially enrolled. The inclusive study period of January 2005 to September 2010 was

selected because of the relative consistency among clinical practices and providers, as well as complete electronic medical records (EMRs). Before 2005, the EMR lacked comprehensive documentation that curtailed the collection of study information.

The physician's daily progress note served as the primary method of identifying subjects with suspected sepsis. Patient characteristics were collected for all included subjects: age, gender, military status, mechanism of injury, ICU days, hospital days, ventilator days, injury severity score, total %TBSA burned, percentage partial thickness burn, percentage full thickness burn, presence of inhalation injury, and ICU disposition (died or transferred). Bacterial organisms associated with bacteremic episodes were recorded.

Blood Culture Selection

All blood culture results from eligible study subjects were reviewed for the following criteria: 1) culture was obtained at least 72 hours after ICU admission, 2) a review of the physician's progress note revealed that sepsis was suspected as a reason for obtaining blood culture or that the patient was hemodynamically unstable, evidenced by vasoactive medication use or need for continuous renal replacement therapy (CRRT) for refractory shock, 3) at least 72 hours of clinical data were available between any included blood cultures. The periods of documented sepsis associated with a positive or negative culture result were classified as sick. The screening culture period (control) was a negative blood culture associated with a 48-hour period of relative hemodynamic stability and no suspicion of sepsis, designated not-sick. Only blood culture results were considered in this analysis; infection may have been present from other sources.

Variables for Analysis

Predictors associated with sepsis in the burn patient were selected for inclusion based on use in the ABA sepsis criteria (HR, temperature, RR, intravenous insulin requirement, serum glucose level, gastric residual, stool output, and platelet count); SIRS criteria (WBC); and clinical association with organ compromise (mean arterial pressure [MAP], urinary output [UOP], base deficit, and presence of vasoactive support). Confounding variables were collected during the 72-hour period that could conceivably impact the predictor variables (noted in parentheses): operations (vital signs, UOP, insulin, glucose, gastric residual, vasoactive drugs); blood transfusions (vital signs); CRRT (vital signs, UOP, vasoactive drugs), and intravenous steroid administration (insulin, glucose). Values were abstracted directly from the EMR. There was no adjustment of RR for any effect of ventilation support strategies that may have fixed rate. For ABA criteria analysis, enteral feeding intolerance was operationalized as gastric residual >300 ml at any time or stool output of >2500 ml/day. SIRS and ABA criteria were operationally defined as having a required number of criteria variables present in a 24-hour period (≥2 and ≥3, respectively).

Data Management

All available data for each variable were extracted from the EMR (Essentris™, CliniComp, Intl, San Diego, CA) and were compiled using Microsoft™ Excel™. Imputation using means was performed for the missing data for variables collected hourly. Analysis included 72 hourly values prior to each of the three culture groups for every subject. The number of available values for the infrequently collected variables (such as base deficit, platelet count, gastric residuals) ranged significantly among subjects, and imputation for missing values was not done. Every 72-hour period was aggregated into 24-hour periods corresponding to each day before culture draw: day –1, day –2, and day –3. These data sets were further reduced to select the clinically relevant minimum or maximum value for each variable. Ultimately, for all variables, a single value represented each of the 3 days prior to the culture time periods (n = 177 values per subject).

Data Analysis

Quality assurance was conducted to ensure accuracy of database. Evaluation of the continuous variables in the total data set allowed for identification of the bottom 10th and top 90th percentiles for the study population. The maximum sensitivity multiplied by specificity and 95% specificity were identified using receiver operating curves (ROCs). These thresholds were used to identify the most meaningful binary cut-points for the study cohort. Analysis of variance (ANOVA) was performed to identify differences in culture groups, day prior, and the effect of interaction.

Ultimately, various cut-points for each variable were created based on SIRS/ABA criteria for the analysis of predictive ability; other cut-points were created based on routine clinical care (eg, MAP < 60 mm Hg, UOP < 30 ml/hr). Analysis of the continuous variables provided the other likely meaningful cut-points specific to the study population using the process described above.

Further analysis of the identified binary cut-points using a combination of χ^2 analysis, ANOVA with post hoc Bonferroni test, and logistic regression with

ROC area under the curve (AUC) was done to select the most significant variable cut-points associated with the prediction of the culture group. A liberal significance of $P < .2$ was determined a priori as the threshold for including a variable in model development.[15] (For detailed rules for variable selection, see Appendix, Supplemental Digital Content 1, at http://links.lww.com/BCR/A15)

Model Development

Various logistic regression techniques were used to determine the most appropriate variables for inclusion in the final predictive model. The repeated measurement study design mandated the use of generalized estimating equation (GEE) technique, a variant of logistic regression that accounts for repeated measures within subjects. Additionally, to assess adequacy of the model and goodness of fit, binary logistic regression and multinomial logistic regression were used to triangulate the appropriate β values and odds ratios for each included variable. Significance of <0.1 was determined a priori for inclusion of main-effects variables in the final model to avoid overfitting to a limited sample size, yet allow for limitation of the number of predictors. Model variables were then included in the ROC analysis where an AUC of >0.7 was considered a moderate predictive value, >0.8 moderately strong, and >0.9 strongly predictive. One variable for every 10 cases was considered the maximum sustainable for the final model (n = 6).[15] Colinearity among predictors was assessed using Pearson's correlation for the original variables before aggregation into day prior categories; correlation $r \geq .5$ was considered a priori to indicate meaningful relationships among predictors.

Model Validation

To ensure the model was not overfit to the relatively limited sample, a variant of bootstrapping analysis was performed. The predictive value of the entire cohort using logistic regression was first calculated, reported as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The predictive values were then calculated using randomly selected subsets comprising 10% of the population (n = 12). Analysis of convergence was performed from 50 to 1000 iterations at increments of 50. Examination of the difference in the group means and subpopulation means with 95% confidence intervals (CIs) was performed to evaluate convergence. Failure to converge at 1000 iterations was a priori evidence of overfitting the original model.

Statistical Analysis

Descriptive statistics were used to describe the patient characteristics. ANOVA test with post hoc Bonferroni test was used to determine whether the subjects differed in age, military status, presence of inhalation injury, requirement for CRRT, or degree of full thickness injury based on disposition (died in ICU, transferred to ward, or transferred to another ICU).

Investigation of the discrimination of the SIRS/ABA criteria and combined model variables to correctly predict culture group was performed using ROC AUC analysis, crosstabulation, and χ^2 tests. Analysis was performed using SPSS v.18 (PASW, SPSS Inc., Chicago, IL), and statistical significance was accepted at $P < .05$ (unless otherwise noted).

RESULTS

From a total of 4141 burn center admissions during the study period, 246 subjects were determined eligible for screening of the EMR; 59 subjects met inclusion criteria (Figure 1A, 1B). The characteristics of the study subjects are presented in Table 1. No differences in mortality were identified among included subjects regarding age, military status, inhalation injury, or full thickness burn size based on ICU disposition status (died in ICU or transferred to ward). A total of 73 culture results were obtained; 14 subjects had two organisms recovered from a single sample. Gram-negative organisms predominated (88%) with *Klebsiella sp.* (21/73; 29%) and *Pseudomonas aeruginosa* (17/73; 23%) the most prevalent; *Staphylococcus aureus* was the most common Gram-positive organism recovered (6/73; 8%) (Figure 2).

SIRS and ABA Sepsis Criteria

Categorical analysis of the presence of SIRS criteria for the day before each blood culture demonstrated no difference between culture group for any day (day –3: $P = .17$; day –2: $P = .6$; day –1: $P = .36$) with an average of 98.3% of subjects meeting SIRS criteria by culture group (positive-sick: 99.4%; negative-sick: 98.9%; screening-not sick: 96.6%; Table 2). Details of subjects with each SIRS variable present are displayed in Figure 3A.

Similar analysis of ABA criteria demonstrated a difference in meeting sepsis criteria between culture group only for day –1 (for positive-sick vs screening-not sick; day –3: $P = .07$; day –2: $P = .23$; day –1: $P = .004$) with an average of 71.9% subjects meeting ABA criteria by culture group on

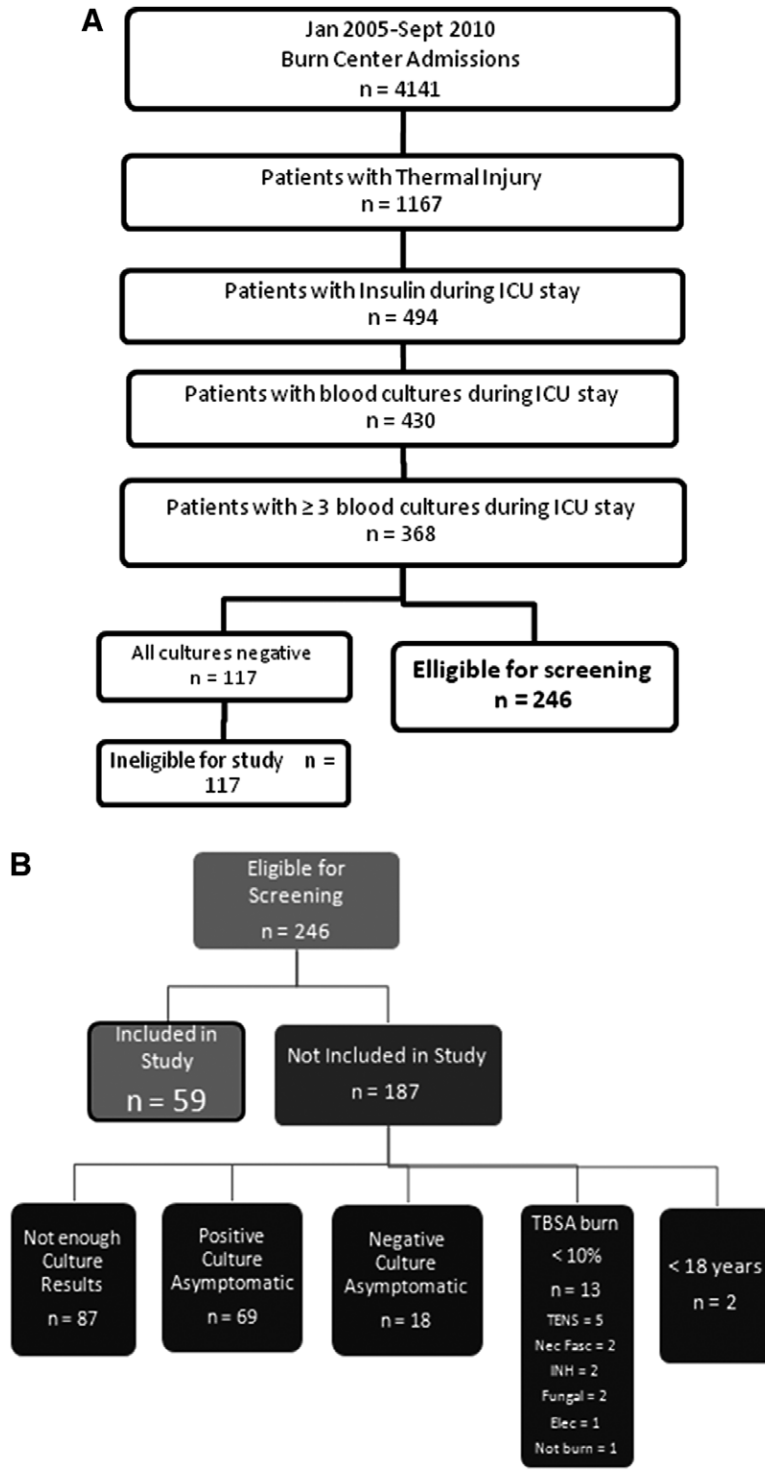

Figure 1. A, Consort diagram of subjects selected for manual record review. B, Consort diagram of subjects enrolled with indications for exclusion from study. ICU, intensive care unit.

day –1 (positive-sick: 80.8%; negative-sick: 73.5%; screening-not sick: 61.6%; Table 2). The number of patients with each of the ABA criteria variables is provided in Figure 3B.

Variable Selection

The eight strongest variable cut-points associated with the culture group and included in model development

Table 1. Patient characteristics of study subjects (n = 59)

	Mean	SD	CI Mean	Range
*Age	40	18.8	35.7–44.9	19–86
ICU day	81	64.3	65–98.4	14–427
Hospital day	102	74.1	83–121.7	24–427
Ventilator day	60	61.8	44.1–76.3	1–427
TBSA	49	19.5	49.2–54.4	16–94
*Full thickness	34	24.8	27.3–40.3	0–90
Partial thickness	16	15.1	9.6–19.5	0–62
Male, %	88.0			
*Military, %	42.4			
MOI: trauma, %	57.6			
Died ICU, %	49.2			
*Inhalation, %	37.3			
*CRRT, %	54.20			

CI, 95% confidence interval; *CRRT*, continuous renal replacement therapy; *ICU*, intensive care unit; *MOI*, mechanism of injury.
*No difference based on disposition status (death, ward, ICU status).

were HR >130 beats per min, MAP <60 mm Hg, base deficit <–6 mEq/L, stool output >1000 ml, temperature <36°C, RR >20 breaths per min, use of vasoactive medications, and serum glucose >150 mg/dl. The only potentially confounding variables found to be associated with the culture group were operations and blood transfusions; these variables were included in the model development process.

The day prior to blood culture acquisition was found not to be associated with the prediction of the culture group; this lack of association universally reduced the overall significance of all variables with regard to prediction of culture group when all 3 days prior were analyzed. Further, ROC AUC analysis revealed diminished ability of the combined model variables to predict sick status (positive and negative culture groups associated with sepsis = sick; screening culture group with no sepsis = not sick) when all 3 days prior to blood culture acquisition were compared with only day –1 (AUC 0.64 [95% CI, 0.59–0.69]; $P < .001$ vs .721 [95% CI, 0.64–0.8]; $P < .001$, respectively). Additionally, comparison of the combined eight selected variables on day –1 for sick vs not sick with positive-sick vs screening-not sick also demonstrated a reduced predictive ability (AUC 0.721 [95% CI, 0.642–0.8]; $P < .001$ vs AUC 0.781 [95% CI, 0.7–0.86]; $P < .001$, respectively). Therefore, subsequent analyses were performed using only day –1 data with all ROC binary predictive states reflecting positive-sick vs screening-not sick.

Model Development

Initial GEE analysis of the ability of the top eight variables and two confounders to predict culture group excluded RR <20 breaths per min ($P = .201$) and stool output >1000 ml ($P = .759$), although the overall model was significant in predicting positive-sick ($P < .001$) and negative-sick ($P < .001$) culture groups using screening-not sick as the reference category. All subsequent model development was performed with the remaining six variables: HR > 130 beats per min ($P = .027$), MAP < 60 mm Hg

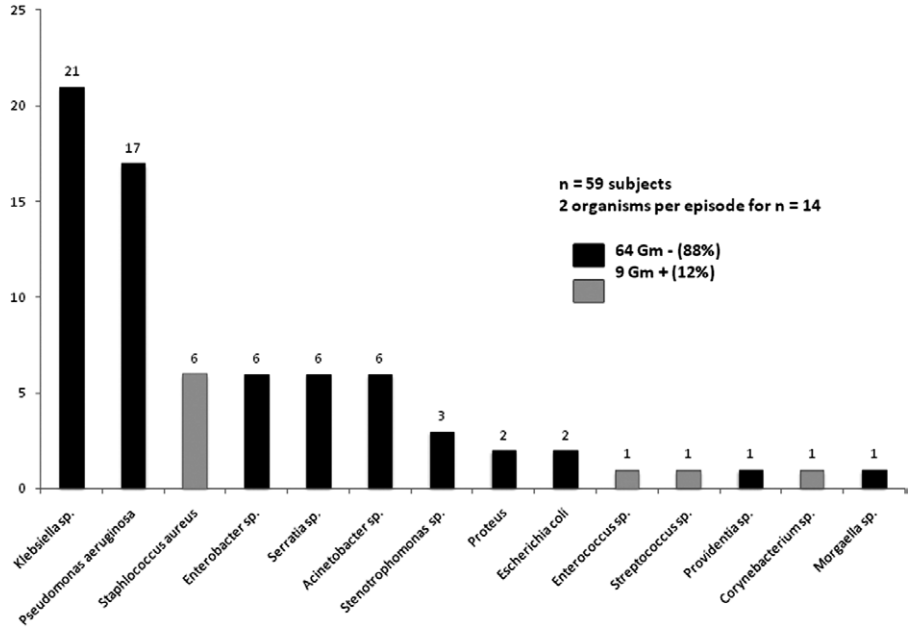

Figure 2. Organisms associated with positive blood culture results in the presence of suspected sepsis.

Table 2. Percentage of SIRS[6] and ABA sepsis criteria[7] met by culture group and day prior (–1, –2, –3) to culture acquisition

Day Prior	Positive-Sick (%)	Negative-Sick (%)	Screening-Not Sick (%)	Total (%)
SIRS criteria				
–1	100.0	98.3	96.6	98.3
–2	98.3	100.0	98.3	98.9
–3	100.0	98.3	94.9	97.7
Total	99.4	98.9	96.6	98.3
ABA criteria				
–1	91.5	83.1	67.8	80.8
–2	78.0	74.6	64.4	72.3
–3	72.9	62.7	52.5	62.7
Total	80.8	73.5	61.6	71.9

ABA, American Burn Association; *SIRS*, systemic inflammatory response syndrome.

($P = .016$), temperature < 36°C ($P = .047$), glucose >150 mg/dl ($P = .016$), base deficit <–6 mEq/L ($P = .095$), and vasoactive medications ($P = .004$). When the potentially confounding variables of operations and blood transfusions were removed from the model, no change resulted in the β coefficients or significance of any of the variables. Therefore, it was determined that these confounders had no impact on the model main effect variables and were subsequently dropped from further model development. No colinearity among predictor variables was noted (correlations < $r = 0.35$).

Comparison of the top six variables in various regression methods revealed the absolute values of β coefficients, and odds ratios remained the same across all regression methods. The significance values were very similar between the logistic regression methods and the GEE models; therefore, it was concluded that the repeated measures study methodology did not have a confounding effect and further GEE analysis would not be contributory. This allowed for the use of standard logistic regression analysis with the added benefit of additional information (eg, omnibus test: $P < .001$, indicating overall significance; goodness-of-fit analysis: $P > .05$, indicating adequate fit; and sensitivity 95.8%, specificity 23.7%, PPV 71.5%, and NPV 73.6%). Using logistic regression, the variables HR > 130 beats per min ($P = .02$), MAP < 60 mm Hg ($P = .026$), and glucose > 150 mg/dl ($P = .028$) were independent predictors of sick outcome.

The model of the top six predictors using the outcome positive-sick vs screening-not sick was then further compared with a reduced model, sequentially dropping the least significant predictor variable. The full model maintained a significant omnibus test ($P < .001$) with good fit ($P > .05$); sensitivity 72.9%, specificity 69.5%, PPV 70.5%, and NPV 72%. In the GEE model, MAP < 60 mm Hg ($P = .022$), glucose > 150 mg/dl ($P = .048$), and vasoactive medications ($P = .009$) were independent predictors of positive-sick outcome; this can be interpreted to mean that the odds of predicting the outcome of sepsis with positive blood culture group in the presence of one of these significant variables is 2.7, 2.5, or 4.8 times, respectively, greater than when those particular variables are not present. Comparison of the variables among the culture group reveals a significant difference in day –2 ($P = .026$; difference between positive-sick and screening-not sick) and day –1 ($P < .001$; difference between positive-sick and negative-sick and positive-sick and screening-not sick) with the percentage of subjects having at least one variable present of 35% positive-sick, 18.6% negative-sick, and 16.9% screening-not sick (Table 3). The number of subjects with each model variable present by day prior to blood culture and culture type are presented in Figure 4.

Despite achieving a parsimonious model with four predictors, the original six predictors achieved better overall performance and avoided overfitting to a small sample. ROC AUC analysis reveals the model incorporating the sum of the top six predictors to perform better than the top 5, top 4, or the 6 ABA sepsis criteria in predicting positive-sick vs screening-not sick or sick vs not sick (Table 4). When two or more of the top six model predictors are present, the ROC AUC remains >0.7, indicating a moderate ability to predict the sick patient with a positive blood culture group. Note that the ability to discriminate between the positive-sick and negative-sick groups and the negative-sick and screening-not sick groups fails to achieve an AUC >0.7 for any model.

Model Validation

Evaluation of the results of the validation process revealed an overall decrease in the 95% CI around the mean difference in the group means for sensitivity, specificity, PPV, and NPV. The decrease was evident at 500 iterations and continued the downward trend through 1000 iterations. This analysis supports the premise that 59 cases were adequate for the final six predictor model.

DISCUSSION

Identification of appropriate indicators of sepsis in the burn patient is critical to facilitate prompt intervention. This study has provided evaluation of sepsis criteria currently used in the burn population (SIRS and ABA sepsis criteria) and variables identified in

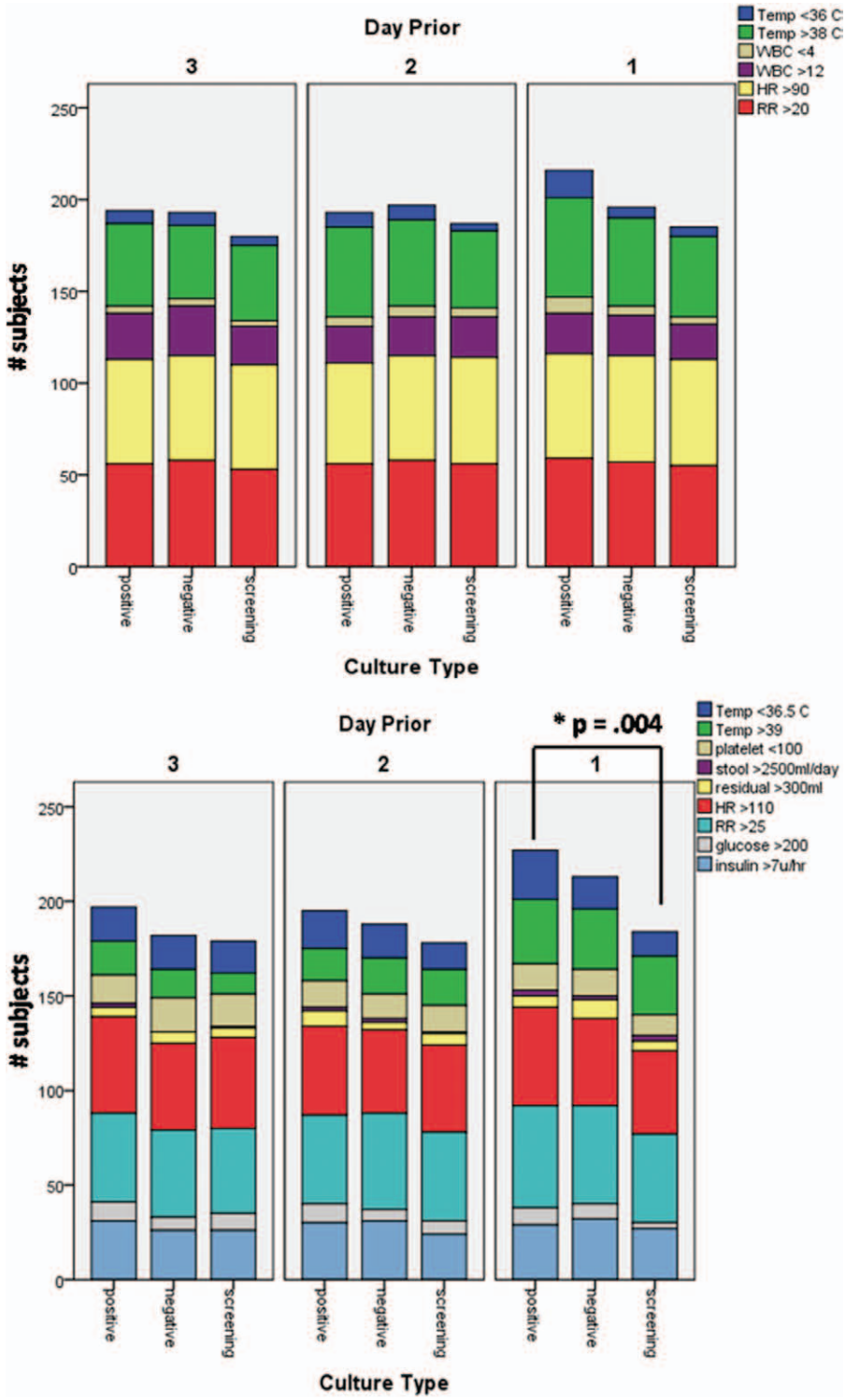

Figure 3. A, Number of subjects with each SIRS criteria[6] variable by culture group for the 3 days before the blood culture. B, Number of subjects with each ABA sepsis criteria[7] variable by culture group for the 3 days before the blood culture. ABA, American Burn Association; HR, heart rate; negative, negative blood culture with sepsis; positive, positive blood culture with sepsis; resid, gastric residual; RR, respiratory rate; screening, negative blood culture without sepsis; temp, temperature; WBC, white blood cell; SIRS, systemic inflammatory response syndrome.

Table 3. Percentage of subjects with at least one of the top six predictors present by culture group and day prior to blood culture acquisition

Day Prior	Positive-Sick (%)	Negative-Sick (%)	Screening-Not Sick (%)	Total (%)
–1	45.80	18.60	13.60	26.00
–2	35.60	15.30	20.30	23.70
–3	23.70	22.00	16.90	20.90
Total	35.00	18.60	16.90	23.50

a known septic population. The subjects represent a very ill group of burn patients, as represented by significant thermal injury and a high rate of mortality. The bacterial organisms most frequently associated with sepsis in the presence of positive blood cultures reflect previous reports of isolates recovered in the same burn center: *P. aeruginosa* and *K. pneumonia*.[16] However, the most common isolate noted by Keen and colleagues[16] in our burn center was *Acinetobacter baumannii*, yet this organism was not noted to be associated with sepsis in this study, nor associated with mortality in our ICU.[17]

This study demonstrated that the SIRS criteria for sepsis are inappropriate for use in the chronically hypermetabolic burn ICU patient. No differences were noted in the presence of SIRS criteria for 3 days prior to known blood culture results coupled with clinical suspicion of sepsis or in the control group. Moreover, >95% of subjects met SIRS criteria at all times during the study period, even during clinical stability. To our knowledge, this is the first report of the omnipresence of SIRS criteria in the burn patient, regardless of clinical status. Results of studies that use the SIRS criteria to identify sepsis in the burn population should be appraised cautiously.[2,3]

This study has also demonstrated a limited ability of the ABA sepsis criteria to discriminate between patients with bacteremia and suspected sepsis from no growth on blood culture with no sepsis. The ABA criteria were unable to differentiate patients suspected of sepsis in the presence of a negative blood culture from the other groups. Finally, only the day immediately before blood culture acquisition demonstrated difference between groups.

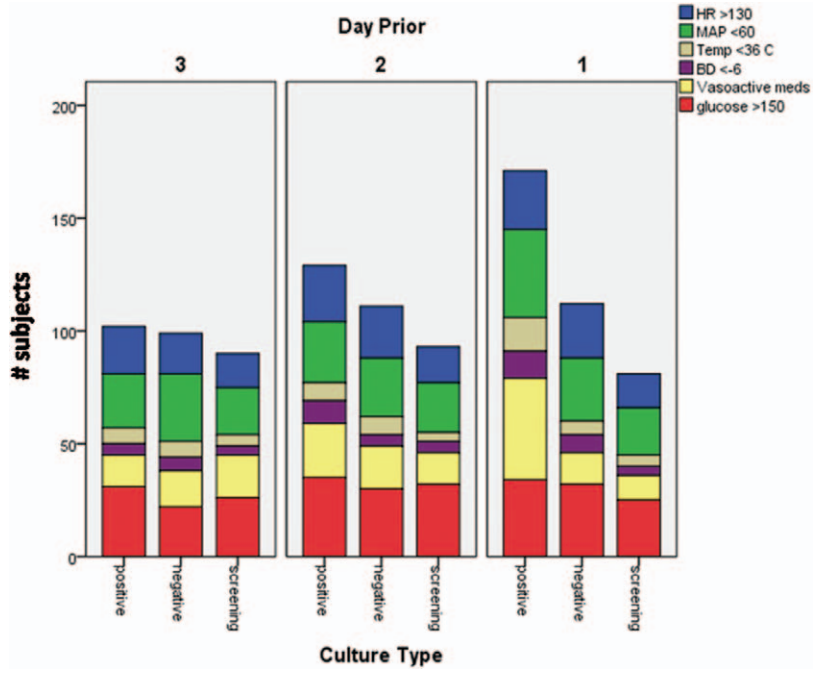

Figure 4. Number of subjects with each of the model top six novel predictors present by culture group for the 3 days before blood culture. BD, base deficit; HR, heart rate; MAP, mean arterial pressure; negative, negative blood culture with sepsis; positive, positive blood culture with sepsis; screening, negative blood culture without sepsis; temp, temperature.

Table 4. Receiver operating curve comparison of generated models and ABA sepsis criteria

	Positive-Sick vs Screening-Not Sick		Negative-Sick vs Screening-Not Sick		Positive-Sick vs Negative-Sick		Sick vs Not Sick	
	AUC	*P*	AUC	*P*	AUC	*P*	AUC	*P*
Top 6	0.775	0.000	0.653	0.004	0.669	0.002	0.714	0.000
Top_6_crit2	0.712	0.000	0.636	0.011	0.576	0.153	0.674	0.000
Top_6_crit3	0.661	0.003	0.525	0.634	0.636	0.011	0.593	0.043
Top_6_crit4	0.619	0.026	0.517	0.751	0.602	0.057	0.568	0.142
Top_6_crit5	0.542	0.427	0.500	1.000	0.542	0.427	0.521	0.646
Top 5	0.760	0.000	0.657	0.003	0.647	0.006	0.709	0.000
Top 4	0.741	0.000	0.625	0.019	0.657	0.003	0.683	0.000
ABA_sum	0.646	0.006	0.626	0.018	0.514	0.796	0.636	0.003
ABA_criteria3	0.619	0.026	0.576	0.153	0.542	0.427	0.597	0.035

ABA, American Burn Association; *AUC*, area under the curve.

A significant contribution of this research is the identification of novel sepsis predictors for the burn patient that expand on the parameters of the ABA criteria and add markers of hemodynamic compromise. Predictors associated with sepsis are HR > 130 beats per min, temperature < 36°C, and base deficit < −6 mEq/L; regression methods identified three additional predictors independently associated with sepsis: MAP < 60 mm Hg, serum glucose > 150 mg/dl, and use of vasoactive medications. The ROC AUC for this model of the top six predictors on the day prior to blood culture is 0.775 (95% CI, 0.692–0.858; $P < .001$) to predict positive-sick from screening-not sick. The predictors reflect shock states (tachycardia, low MAP, acidemia, need for hemodynamic support), and failure of temperature and glucose regulation, physiologic states associated with systemic infection. Results of this study show that predicting sepsis is generally confounded when periods of negative-sick are included in the analysis; further, the ability to predict >24 hours from culture acquisition is limited. The model of the top six predictor variables increases prediction time compared with the ABA sepsis criteria, demonstrating discrimination between the positive-sick and screening-not sick groups 2 days prior. Increasing "lead time" may simply be a matter of incorporating the best predictors, be they biomarkers, clinical findings, or interventions to maximize intervention time.

The sensitivity of the top six predictor models to predict sepsis with a positive blood culture was 46% on the day before blood culture compared with 92% for the ABA criteria; however, the false-positive rate was 14% compared with 68%, respectively. Liberal sepsis diagnosis, as evidenced by a high sensitivity in the ABA criteria, may be of benefit to ensure all potentially septic patients are evaluated further. Yet, the high false-positive rate of the ABA criteria may increase risk associated with treatment from antimicrobial therapy. Improving the sensitivity of novel sepsis predictor variables by adding additional variables, while reducing false-positive, may improve the effectiveness of burn sepsis screening. During prospective validation of the developed model, the ABA criteria will also be evaluated to determine clinical significance of the differing sensitivity.

An unexpected finding from this particular analysis is the lack of significance for insulin infusion as a predictor of sepsis.[18,19] Research studies have specifically identified escalation of insulin dosing to treat hyperglycemia to be associated with the onset of sepsis in burn patients.[20,21] The insulin to glucose ratio was evaluated in this analysis but failed to prove useful. Perhaps the thresholds for insulin treatment were inappropriate to identify differences, or perhaps it is a feature of this particular group of patients. The ABA sepsis criteria[7] include glucose intolerance and resistance to insulin but such association was not noted in this study.

Murray and colleagues previously reported a lack of association of leukocyte count or elevated temperature with the presence of bloodstream infection in the burn patient,[9] findings supported by this study. However, this is the first study to demonstrate a relationship between low body temperature and burn sepsis. The recent report of correlation between the ABA sepsis criteria and bacteremia found only association between elevated heart rate and temperature and positive blood culture in burn patients.[10] Clinical presentation (sepsis or hemodynamic instability) was not linked with documented bacteremia in that study, suggesting that the ABA criteria are not strong predictors of bacteremia without associated physiologic response.

Several reasons may explain the difficulty in extending the time period for detection of sepsis

using clinical variables. First, when a patient becomes unstable or organ dysfunction develops, aggressive action is taken to "normalize" the patient. Oftentimes interventions such as vasoactive drips or fluid bolus to increase blood pressure or ventilator support to reduce respiratory rate or improve acid–base balance are employed. At our institution, oral naloxone is administered and feeds held when enteral residuals are excessive because of bowel hypomotility, or insulin infusion rates may be increased to control hyperglycemic episodes. Episodes of thrombocytopenia prompt administration of platelets. Standard of care in many centers directs routine β-blockade that depresses tachycardic episodes. These types of interventions interfere with the ability to trend abnormal clinical measures such as vital signs and laboratory values, yet do provide the possibility of measurement of the "treatment" rather than the "indicator" in future studies. Second, sepsis is a progressive response to overwhelming infection and is potentially compensated for by the body's self-regulating mechanisms. Perhaps there is a threshold where homeostasis is overcome, resulting in a rapid deterioration that is clinically apparent.

Unfortunately, the subtle trends that accompany compensatory response to sepsis are difficult to ascertain, especially by inexperienced clinical staff. Automated assimilation of trending results may prove to be a useful tool to increase the period prior to overt signs of sepsis. Finally, it may be that a sensitive and specific biomarker such as procalcitonin can be incorporated into models of sepsis prediction that could begin to approximate an accepted, standard means of diagnosis while extending the window of opportunity for detection.[22] Procalcitonin may prove to be a valuable addition to a multifactorial model, despite disappointing utility in prompting aggressive antimicrobial therapy.[23]

Another problem noted during the analysis is the perennial difficulty in identifying the septic patient with persistently negative blood cultures. Poor technique in obtaining the culture specimen, an inadequate sample volume, operative or empiric antibiotic coverage, organisms that do not grow in bacterial culture medium, or nonbacteremic septic patients contribute to this problem.[24] It would appear from the results of this study that the variables associated with positive culture and sepsis are not those predictive of negative culture and sepsis. ROC AUC demonstrates no method to achieve the 0.7 threshold for at least moderate predictive ability for this group. Future analysis of biomarkers and other clinical variables should be undertaken to better identify appropriate measures of sepsis identification in this cohort of patients.

It is apparent that single variables are insufficient to detect sepsis, despite the helpfulness of the independent predictors such as MAP <60 mm Hg, glucose >150 mg/dl, and use of vasoactive medications. For example, analysis of the ABA criteria demonstrates minor differences among the individual predictors, yet when combined, those predictors evaluated collectively are significantly different among culture groups. What remains to be discovered is the exact combination of predictors and in what frequency they are most predictive. For example, the operational definition in this study for SIRS and ABA criteria was determined to be at least one incidence in 24 hours of having the minimum number of criterion present. Perhaps this definition is far too liberal, as evidenced by >95% frequency of SIRS criteria in all groups at all times; half of SIRS criteria were the mean values for 25 to 75% of study subjects (HR > 90 beats per min, RR > 20 beats per min, WBC > 18 cells/mm^3, and temperature > 38°C). A more conservative definition such as meeting criteria at least 3, 6, 9, or 12 hours out of the day may be more helpful, but probably not for SIRS as the parameters fall well within the average range for most critically ill burn patients. For the ABA criteria or the model developed for this study, such analysis may be of use in refining the predictive ability of combinations of variables.

Model development induced numerous subjective decisions, such as determination of values of significance for retaining or rejecting potential predictors. Use of several regression methods improved the reliability of the conclusions: triangulation was achieved among the logistic regression and GEE models with respect to β coefficients, odds ratios, and significance values. Such concordance demonstrated that for future methodology employing within-patient matching of culture results, repeated measures techniques (GEE) do not contribute significantly to interpretation. Logistic regression provides more information on model significance and fit that are useful in comparing models and more widely understood and reported in the literature. The combination of regression methodology and ROC analysis further improves utility of these findings as models incorporating alternative variables can be easily compared and communicated.

Limitations

This study was conducted at a single regional burn center and thus reflects a small cohort of patients with similar treatment regimen. The predictive

variables used in the modeling process were based in part on study population parameters, and hence may not reflect patients elsewhere. The sample size is limited, yet by using carefully matched case-controlled design, the 177 cases (reflecting 59 subjects × 3 conditions) increase the robustness of the analysis and minimize effects of intrapatient variability. Selection of variables for model development was done with as much rigor as possible, yet many other potentially viable predictors were either not considered or ruled out. Such limitations do not diminish the importance of the method that underscores the requirement for a multinomial model to predict such a complex disease process as sepsis. Use of positive blood culture coupled with clinical suspicion of sepsis is a rigorous standard for classifying septic patients. Yet, perhaps the negative blood culture period coupled with clinical suspicion of sepsis represents nonbacterial infection such as fungal elements, or infection secondary to pneumonia, urinary tract, or wound infection; this study was not designed to analyze these potential sources of infection or to identify the effect of empiric antibiotic coverage. The order of positive and negative blood culture was not controlled for in this analysis; there is a potential difference in response to an infection early in the clinical course compared with much later during hospitalization. Finally, retrospective record review is fraught with limitations, yet discernable trends were identified. Quality assurance measures validated the integrity of the extraction of the data from the medical records. The next step is to conduct prospective studies to enhance and validate this initial model.

Despite the retrospective nature of this study, a significant strength of the analysis is the pairing of clinical suspicion of sepsis with blood culture result group and periods of relative stability paired with the negative routine screening culture. Inasmuch as an accepted standard does not exist for the diagnosis of sepsis, this method approximates the currently most useful means of classifying patients for comparison. Caution is warranted when interpreting results from studies where only positive cultures are used without evaluating clinical condition; 69 potential subjects were deemed ineligible in this study because of lack of symptoms during periods of demonstrated bacteremia.

Clinical Significance

Early identification coupled with appropriate aggressive treatment, even by a matter of hours, is associated with improved survival in the septic patient.[25] Yet, many subtle trends may be unappreciated by a novice clinician or a busy nurse. As the "filters" for information are provided to the responsible physician, improving the nurses' appreciation for critical changes associated with sepsis is paramount.[12,13] A role exists for computerized decision support systems to continuously "mine" available data and interpret changes occurring in tandem.[26,27] Clinical alerts have been shown to increase therapeutic and diagnostic interventions in the general ICU population.[28] A computer decision support system has been shown to improve recognition and management of the septic surgical ICU population and is attributed to a decrease in mortality associated with sepsis.[29]

The problem is that we have yet to identify the precise predictors of sepsis that would be of greatest use, particularly for the burn population.[30] The contribution of these study findings is to enhance awareness of the limited time frame in which to recognize sepsis (about 24 hours) and identify some important and readily available clinical variables that may be good predictors of developing sepsis. However, this proposed model is not intended to serve as a diagnostic tool, but rather to heighten the suspicion of the providers, prompt initiation of appropriate treatment, and commence a search for corroborating evidence of severe infection. The expectation is for a more robust predictive model of burn sepsis as an ROC AUC of >0.7 noted in this proposed model is adequate and superior to the ABA sepsis criteria, but could be enhanced with appropriate biomarkers. Perhaps a predisposing factors, infection, response, and organ dysfunction (PIRO) sepsis model that is specific for burn patients will be of use in deciphering this complex presentation.[31,32]

CONCLUSION

SIRS criteria, developed for a general ICU patient population, are clearly not useful in the detection of sepsis in the burn patient. The modified ABA sepsis criteria improve predictive ability, but only for the 24 hours before obtaining blood cultures when sepsis is suspected. A multivariable model containing six readily available clinical variables outperforms the ABA sepsis criteria and is capable of discriminating between septic patients with positive blood cultures and those who are not sick with negative cultures. However, detecting the septic patient without a positive bacterial blood culture remains elusive, and this cohort continues to require careful clinical evaluation and proactive intervention.

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