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14. ABSTRACT

Purpose: The purpose of this study was twofold: 1) determine the ability of the SIRS and ABA criteria to predict sepsis in the burn patient; and 2) develop a model representing the best combination of clinical predictors associated with sepsis in the same population. **Design**: A retrospective, case-controlled, within-patient comparison of burn patients admitted to a single intensive care unit from January 2005 to September 2010. **Methods**: Blood culture results were paired with clinical condition: "positive-sick"; "negative-sick", and "screening-not sick". Data for predictors were collected for the 72 hours prior to blood culture. **Sample**: Fifty-nine adult, thermally-injured burn subjects were included in the study, representing 177 culture periods. **Analysis**: Significant dichotomized predictor variables were evaluated using logistic regression, Generalized Estimating Equations and ROC AUC analyses to assess model predictive ability. Bootstrapping methods evaluated potential model over-fitting. **Findings**: SIRS criteria were not associated with culture type, with an average of 98% of subjects meeting criteria in the 3 days prior. ABA sepsis criteria were significantly different among culture type only on the day prior ($p = 0.004$). The model variables identified included: heart rate>130, mean blood pressure<60 mmHg, base deficit<-6 mEq/L, temperature<36°C, use of vasoactive medications, and glucose>150 mg/dl. The model was significant in predicting "positive culture-sick" and sepsis state ("sick"), with AUC of 0.775 ($p < 0.001$) and 0.714 ($p < .001$), respectively; comparatively, the ABA criteria AUC was 0.619 ($p = 0.028$) and 0.597 ($p = .035$), respectively. **Implications for Military Nursing**: ABA criteria performed well, but only for the day prior to positive blood culture results. A combination of novel predictors is superior to individual variable trends and may allow the bedside nurse to better identify the septic patient up to 48 hours prior to clinical detection. Algorithms or computer support will be necessary for the clinician to find such models useful.

15. SUBJECT TERMS

burn patient, SIRS criteria for trauma-related sepsis

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Abstract

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Methods: Blood culture results were paired with clinical condition: "positive-sick"; "negative-sick", and "screening-not sick". Data for predictors were collected for the 72 hours prior to blood culture.

Sample: Fifty-nine adult, thermally-injured burn subjects were included in the study, representing 177 culture periods.

Analysis: Significant dichotomized predictor variables were evaluated using logistic regression, Generalized Estimating Equations and ROC AUC analyses to assess model predictive ability. Bootstrapping methods evaluated potential model over-fitting.

Findings: SIRS criteria were not associated with culture type, with an average of 98% of subjects meeting criteria in the 3 days prior. ABA sepsis criteria were significantly different among culture type only on the day prior ($p = 0.004$). The model variables identified included: heart rate>130, mean blood pressure<60 mmHg, base deficit<-6 mEq/L, temperature<36°C, use of vasoactive medications, and glucose>150 mg/dl. The model was significant in predicting "positive culture-sick" and sepsis state ("sick"), with AUC of 0.775 ($p < 0.001$) and 0.714 ($p < .001$), respectively; comparatively, the ABA criteria AUC was 0.619 ($p = 0.028$) and 0.597 ($p = .035$), respectively.

Implications for Military Nursing: ABA criteria performed well, but only for the day prior to positive blood culture results. A combination of novel predictors is superior to individual variable trends and may allow the bedside nurse to better identify the septic patient up to 48 hours prior to clinical detection. Algorithms or computer support will be necessary for the clinician to find such models useful.

TSNRP Research Priorities that Study or Project Addresses

Primary Priority

Force Health Protection:	☐ Fit and ready force ☐ Deploy with and care for the warrior ☒ Care for all entrusted to our care
Nursing Competencies and Practice:	☐ Patient outcomes ☐ Quality and safety ☐ Translate research into practice/evidence-based practice ☐ Clinical excellence ☐ Knowledge management ☐ Education and training
Leadership, Ethics, and Mentoring:	☐ Health policy ☐ Recruitment and retention ☐ Preparing tomorrow's leaders ☐ Care of the caregiver
Other:	☐

Secondary Priority

Force Health Protection:	☐ Fit and ready force ☐ Deploy with and care for the warrior ☐ Care for all entrusted to our care
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Other:	☐

Progress Towards Achievement of Specific Aims of the Study or Project

Findings related to each specific aim, research or study questions, and/or hypothesis:

Study Question: To what extent can a multivariate predictive model using clinical variables (temperature, HR, respiratory effort, platelet count, insulin resistance, feeding intolerance, blood pressure (BP), UOP, vasoactive agent requirement, and white blood cell count) and biomarkers (lactate, CRP) detect the presence of septicemia in adult burn patients sooner than routine clinical assessment prompts collection of blood cultures for suspected infection?

Study Aims:

a) Develop a multivariable predictive model for detection of bacteremia in the burned ICU patient using 12 clinical measures associated with presence of infection (temperature, heart rate, respiratory rate, platelet count, insulin resistance, feeding intolerance, BP, UOP, vasoactive agent requirement, WBC count and available biomarkers (lactate, CRP); Hypothesis: Sepsis will be predicted with a combination of clinical measures;

b) Compare the ability of the systemic inflammatory response syndrome (SIRS) criteria, the ABA sepsis criteria, and the multivariate model to predict a positive blood culture; Hypothesis: Prediction of a positive blood culture in the burn patient is maximized with the multivariate predictive model compared to clinical suspicion or the ABA sepsis criteria;

c) Validate the multivariate sepsis prediction model on an independent group of burn ICU patients during periods of documented sepsis and absence of infection; Hypothesis: A multivariate prediction model will accurately differentiate between sepsis and absence of infection in an independent group of burn ICU patients.

Results: From a total of 4141 ICU admissions during the study period, 246 subjects were determined eligible for manual screening of the EMR; 59 subjects met inclusion criteria. The demographic profile of the study subjects is presented in Table 1. No differences in outcome were identified among subjects regarding age, military status, inhalation injury or full thickness burn size based on ICU disposition status.

Table 1. Demographic profile of study subjects (n = 59) (CI = 95% confidence interval; CRRT = continuous renal replacement therapy; ICU = intensive care unit; ISS = injury severity score; SD = standard deviation; TBSA = total body surface area)

	Study Subjects n = 59			
	Mean	SD	CI mean	Range
*Age	40.3	18.8	35.1-44.9	19-86
ICU Day	81.6	64.3	65-98.4	14-427
Hosp Day	102.3	74.1	83-121.7	24-427
Vent Day	60.2	61.8	44.1-76.3	1-427
ISS	29.3	13	25.9-32.7	9-75
TBSA	49.3	19.5	49.2-54.4	16-94
*Full Thickness	33.8	24.8	27.3-40.3	0-90
Partial Thickness	15.5	15.1	91.6-19.5	0-62

	%
Male	88.0%
*Military	42.4%
MOI: trauma	57.6%
Died ICU	49.2%
*Inhalation	37.3%
*CRRT	54.20%

*No difference based on disposition status
(Death, Ward, ICU transfer)

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A total of 73 positive blood 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; *Staphlococcus aureus* was the most common Gram positive organism recovered (6/73; 8%). All quality assurance measures demonstrated accuracy of the database items: Teleform™ data was 100% accurate, inter-rater reliability had a 0.4% error rate, and intra-rater reliability was 100% accurate.

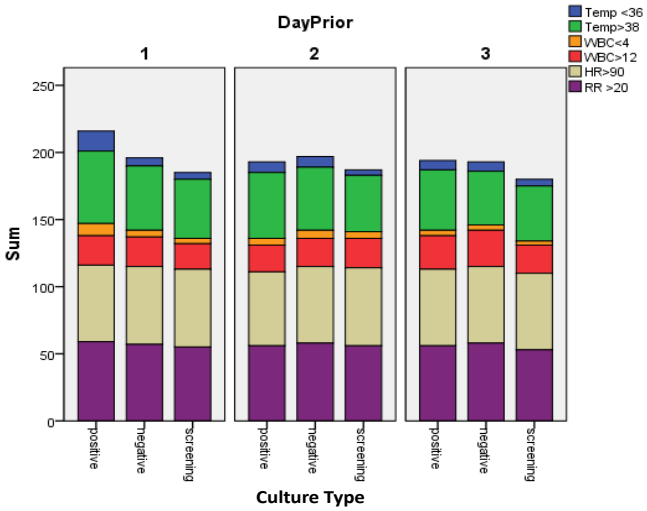
SIRS and ABA Sepsis Criteria

Analysis of the presence of the SIRS criteria for day prior to blood culture demonstrated no difference between culture type for any day (day -1: $p = 0.36$; day -2: $p = 0.6$; day -3: $p = .17$) with an average of 98.3% of subjects meeting SIRS criteria by culture type (positive-sick: 99.4%; negative-sick: 98.9%; screening-not sick: 96.6%) (Table 2). Details of the number of patients with each SIRS variable present are displayed in Figure 1.

Table 2. Percent of SIRS (Levy, et al., 2003) and ABA sepsis criteria (Greenhalgh, et al., 2007) met by culture type and day prior to culture acquisition. (ABA = American Burn Association; SIRS = systemic inflammatory response syndrome)

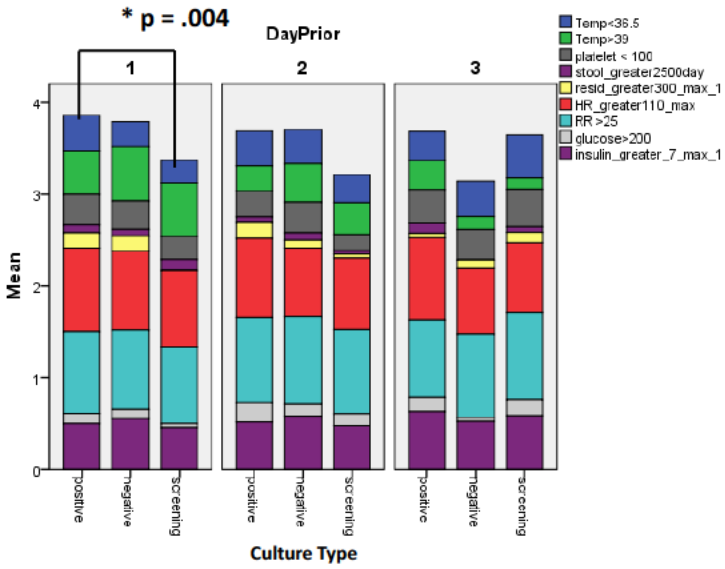
Day Prior	Culture Type: Positive "sick"	Negative "Sick"	Screening "not sick"	Total
SIRS Criteria				
-1	100.0%	98.3%	96.6%	98.3%
-2	98.3%	100.0%	98.3%	98.9%
-3	100.0%	98.3%	94.9%	97.7%
Total	99.4%	98.9%	96.6%	98.3%
ABA Criteria				
-1	91.5%	83.1%	67.8%	80.8%
-2	78.0%	74.6%	64.4%	72.3%
-3	72.9%	62.7%	52.5%	62.7%
Total	80.8%	73.5%	61.6%	71.9%

Figure 1. Number of subjects with each SIRS criteria(Levy, et al., 2003) variable by culture type and day prior. (HR = heart rate; RR = respiratory rate; SIRS = systemic inflammatory response syndrome; temp = temperature; WBC = white blood cells)



Similar analysis of ABA criteria demonstrated a difference in meeting sepsis criteria between culture type only for day -1 (day -1: p = .004, for “positive-sick versus screening-not sick”; day -2: p = .23; day -3: p = .07) with an average of 71.9% subjects meeting ABA criteria by culture type on day -1 (positive-sick: 80.8%; negative-sick: 73.5%; screening-not sick: 61.6%) (Table 2, above). The number of patients with each of the ABA criteria variables is provided in Figure 2.

Figure 2. Number of subjects with each ABA sepsis criteria (Greenhalgh, et al., 2007) variable by culture type and day prior. (ABA = American Burn Association; HR = heart rate; resid = gastric residual; RR = respiratory rate; temp = temperature; WBC = white blood cells)



Variable Selection

The eight strongest variable cut-points associated with culture type and included in model development were: HR > 130 beats/min, MAP < 60 mmHg, BD < -6 mEq/L, stool output > 1000ml, temperature > 36°C, RR > 20 breaths/min, use of vasoactive medications, and serum glucose > 150 mg/dL. The only potentially confounding variables found to be associated with blood culture type were operations and blood transfusions; these variables were included in the model development process.

Day prior to blood culture acquisition was found not to be associated with culture type and universally reduced overall significance of all variables concerning prediction of culture type. Further ROC AUC analysis revealed diminished ability of the combined model variables to predict sick status (positive and negative culture types = "sick"; screening culture type = "not sick") when all three days prior to blood culture acquisition were compared to only day -1 (AUC 0.64 [95% CI 0.59, 0.69]; $p < 0.001$ versus 0.721 [95% CI 0.64, 0.8]; $p < 0.001$; respectively). Additionally, comparison of the combined eight selected variables on day -1for "sick versus not sick" with "positive-sick versus screening-not sick" also demonstrated a reduced predictive ability (AUC 0.721 [95% CI 0.642, 0.8]; $p < 0.001$versus 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" versus "screening-not sick".

Model Development Initial GEE analysis of the ability of the top eight variables and 2 confounders to predict culture type excluded RR < 20 breaths/minute ($p = 0.201$) and stool output > 1000 ml ($p = 0.759$) although the overall model was significant in predicting "positive-sick" ($p < 0.001$) and "negative-sick" ($p < 0.001$) culture types using "screening-not sick" as the reference category. All subsequent model development was performed with the remaining six variables: HR > 130 bpm ($p = 0.027$), MAP < 60 mmHg ($p = 0.016$), temperature < 36°C ($p = 0.047$), glucose > 150 mg/dL ($p = 0.016$), base deficit <-6 mEq/L ($p = 0.095$), and vasoactive medications ($p = 0.004$). When the potentially confounding variables of operations and blood

transfusions were removed from the model no change resulted in the beta 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 collinearity among predictor variables was noted, all correlations were < r = 0.35.

Comparison of the top six variables in various regression methods revealed the absolute values of beta coefficients and odds ratios remained the same across all comparisons (Table 3).

Table 3. Model development: results of comparing logistic regression with Generalized Estimating Equations. Outcome variable is "sick versus not-sick". Note that beta coefficient absolute values and odds ratios (some are reported as inverse ratios depending on the value of the predictor variable) remain the same across models. Significance for individual predictors remains consistent between logistic and GEE models.

	Log Regress (sick = 1) Pred = 1				**Multinom Log Regress** (sick = 1) Pred = 0				**GEE Multinom** (sick = 0) Pred = 1				**GEE Multinom** (sick = 1) Pred = 1				**GEE Binom** (sick = 1) Pred = 1			
	B	Wald	sig	OR	B	Wald	sig	OR	B	Wald	sig	OR	B	Wald	sig	OR	B	Wald	sig	OR
Intercept					4 315	20 814	**< .001**	na												
Constant	-0 732	4 345	**0.036**	0 981																
Threshold									0 732	4 772	**0.029**	2 08	-0 732	4 772	**0.029**	0 481	-0 73	4 772	**0.029**	0 481
HR> 130	0 89	5 369	**0.02**	2 434	-0 89	5 369	**0.02**	0 411	0 89	5 548	**0.018**	2 434	-0 89	5 548	**0.018**	0 411	0 89	5 548	**0.018**	2 434
MAP < 60	0 791	4 968	**0.026**	2 206	-0 791	4 968	**0.026**	0 453	0 791	4 857	**0.028**	2 206	-0 791	4 857	**0.028**	0 453	0 791	4 857	**0.028**	2 206
BD < -6	0 942	2 37	0 124	2 566	-0 942	2 37	0 124	0 39	0 942	2 218	0 136	2 566	-0 942	2 218	0 136	0 39	0 942	2 218	0 136	2 566
Glu > 150	0 769	4 834	**0.028**	2 158	-0 769	4 834	**0.028**	0 463	0 769	4 97	**0.026**	2 158	-0 769	4 97	**0.026**	0 463	0 769	4 97	**0.026**	2 158
T < 36	0 765	1 808	0 179	2 148	-0 765	1 808	0 179	0 465	0 765	1 414	0 234	2 148	-0 765	1 414	0 234	0 465	0 765	1 414	0 234	2 148
Vaso Bin	0 89	3 456	0 063	2 435	-0 89	3 456	0 063	0 411	0 89	3 397	0 065	2 435	-0 89	3 397	0 065	0 411	0 89	3 397	0 065	2 435
Omnibus	< 001	Ovarall significant																		
Model fit					< 001	Overall significant			All compare "sick" vs "not sick" (sick = pos and neg; not sick = screening)											
Hos-Lem	0 505	Adequate fit																		
Good -fit					102 11	adequate fit														
sens	95 8				95 8															
spec	23 7				23 7															
R2	0 142				0 142															
R2	0 197				0 197															
R2					0 12															

The significance values were very similar between the logistic regression methods and the GEE models; therefore it was concluded that significant relationships were not present as a result of the repeated measures study methodology. This allowed for application of the additional information reported in the logistic regression to the overall model when the outcome "sick versus not-sick" was employed (e.g. Omnibus test: $p < 0.001$, indicating overall significance; goodness-of-fit analysis: $p > 0.05$, indicating adequate fit; and sensitivity 95.8%, specificity 23.7%, PPV 71.5% and NPV 73.6%). The variables HR > 130 bpm (p = 0.02), MAP < 60 mmHg (p = 0.026), and glucose > 150 mg/dL (p = .028) were independent predictors of "sick" outcome.

The model of the top 6 predictors using the outcome "positive-sick versus screening-not sick" was then further compared to a reduced model, sequentially dropping the least significant predictor variable (Table 4a and 4b).

Table 4a. Multinomial logistic regression models (outcome variable culture type, reference category = "screening".

	Multinomial Log Regress																							
	Culture Type (ref = screen)																							
	Pred = 0																							
	Top 6								drop BD <-6								drop HR >130							
	Positive				**negative**				**Positive**				**negative**				**positive**				**negative**			
	B	Wald	sig	OR	B	Wald	sig	OR	B	Wald	sig	OR	B	Wald	sig	OR	B	Wald	sig	OR	B	Wald	sig	OR
Intercept	4.73	19.68	**<.001**		2.49	5.59	**0.018**		3.88	19.59	**<.001**		1.78	3.97	**0.046**		3.31	17.32	**< .001**		1.26	2.29	0.13	
HR> 130	-0.954	4.371	**0.037**	0.385	-0.856	4.167	**0.041**	0.425	-0.829	3.46	0.063	0.437	-0.76	3.39	0.066	0.469								
T < 36	-1.25	3.97	**0.046**	0.286	-0.264	0.16	0.689	0.768	-1.34	4.61	**0.032**	0.262	-0.34	0.268	0.605	0.713	-1.29	4.36	**0.037**	0.277	-0.29	0.197	0.657	0.75
map < 60	-1.11	6.74	**0.0009**	0.33	-0.545	1.929	0.165	0.58	-1.01	6.74	**0.009**	0.333	-0.55	1.96	0.162	0.579	-1.03	6.07	**0.014**	0.357	-0.48	1.54	0.214	0.62
BD < -6	-1.042	2.34	0.126	0.353	-0.887	1.766	0.184	0.412																
Glu > 150	-1.031	5.78	**0.016**	0.357	-0.59	2.345	0.126	0.554	-1.03	5.834	**0.016**	0.385	-0.6	2.43	0.119	0.551	-0.96	5.24	**0.022**	0.384	-0.55	2.132	0.144	0.576
Vaso Bin	-1.44	7.495	**0.006**	0.238	-0.304	0.307	0.58	0.738	-1.55	8.92	**0.003**	0.213	-0.4	0.536	0.464	0.673	-1.68	10.67	**0.001**	0.187	-0.52	0.932	0.332	0.596
Model fit	**<.001**								**< .001**								**< .001**							
Good -fit	**0.272**								**0.075**								**0.249**							
	0.236								**0.104**								**0.152**							
R2	0.22								0.21								0.19							
R2	0.25								0.23								0.21							
R2	0.11								0.11								0.09							
class +	54.20%								52.5								52.5							
class -	44.1								35.6								15.3							
class scr	59.3								62.7								69.5							
overall %	52.5								50.3								45.8							

Table 4b. Binomial logistic regression and Generalized Estimating Equations evaluating least significant variables. Outcome variable is "positive-sick versus screening-not sick". Note that HR is dropped second in binomial regression and temperature is dropped in GEE model.

	Binomial Log Regress												**GEE Binomial**											
	Positive vs Screen (ref scr)												Positive vs Screen (ref scr)											
	Pred 1												Pred 1											
	Top 6				Drop BD < -6				drop HR > 130				Top 6				drop BD < -6				drop T < 36			
	B	Wald	sig	OR	B	Wald	sig	OR	B	Wald	sig	OR	B	Wald	sig	OR	B	Wald	sig	OR	B	Wald	sig	OR
Intercept													-1.864	17.169	**<.001**	0.155	-1.828	16.885	**<.001**	0.161	-1.644	12.51	**<.001**	0.193
Constant	1.864	15.55	**<.001**	0.645	1.828	15.29	**<.001**	6.22	1.485	13.69	**<.001**	4.14												
HR> 130	-0.856	3.34	0.068	0.425	-0.816	3.08	0.079	0.442					0.856	3.404	0.065	2.353	0.816	3.07	**0.08**	2.26	0.812	3.18	0.075	2.253
BD < -6	-0.596	0.732	0.392	0.551									0.596	0.782	0.377	1.815								
T < 36	-1.15	3.23	0.072	0.318	-1.162	3.35	0.067	0.313	-1.16	3.39	0.065	0.313	1.145	2.27	0.132	3.142	1.162	2.45	0.118	3.195				
MAP < 60	-0.992	3.861	**0.049**	0.371	-1	5.41	**0.02**	0.368	-0.96	5.155	**0.023**	0.383	0.992	5.254	**0.022**	2.696	1	5.431	**0.02**	2.72	1.006	5.664	**0.017**	2.736
Glu > 150	-0.876	3.86	**0.049**	0.417	-0.911	4.22	**0.04**	0.402	-0.78	3.304	0.069	0.46	0.876	3.903	**0.048**	2.4	0.911	4.208	**0.04**	2.49	0.844	3.557	0.059	2.326
Vaso Bin	-1.46	7.51	**0.006**	0.232	-1.56	8.99	**0.003**	0.209	-1.66	10.39	**0.001**	0.19	1.46	6.914	**0.009**	4.305	1.565	8.76	**0.003**	4.78	1.63	10.654	**0.001**	5.119
Omnibus	<.001				<.001				<.001															
Hos-Lem	0.865				0.717				0.717															
R2	0.25				0.25				0.23															
R2	0.34				0.33				0.3															
sens	72.9				71.2				69.5															
spec	69.5				71.2				69.5															
Overall %	71.2				71.2				69.5															
QIC/QICC													305.225 / 304.445				299.087 / 298.264				278.167 / 278.274			

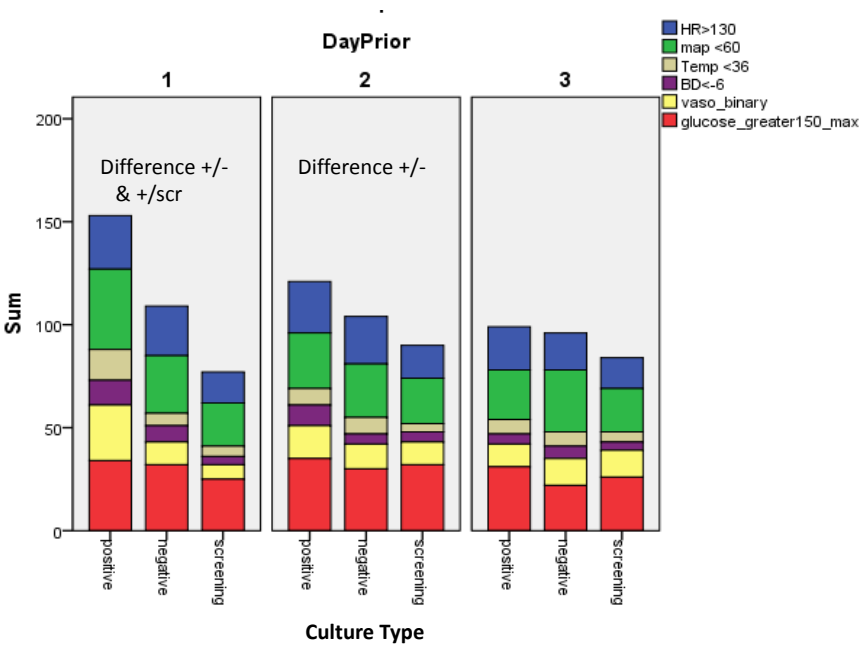
The full model maintained a significant omnibus test ($p < 0.001$) with good fit ($p > 0.05$) with sensitivity 72.9% specificity 69.5%, PPV 70.5%, and NPV 72%. In the GEE model, MAP < 60 mmHg (p = 0.022), glucose > 150 mg/dL (p = .048) and vasoactive medications (p = 0.009) were independent predictors of "positive-sick" outcome; this can be interpreted to mean that the odds of predicting the outcome of sepsis with positive blood culture in the presence of one of these significant variables is 2.7, 2.5, or 4.8 (respectively) times greater than when those particular variables are not present. Comparison of the variables among culture type reveals a significant difference in day -1 ($p < 0.001$; difference between "positive-sick and negative-sick" and "positive-sick and screening-not sick") and day -2 ($p = 0.026$; difference between "positive-sick and negative-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 5). The number of subjects with each model variable present is presented in Figure 3.

Table 5. Percent of subjects with at least one of the top six predictors present by culture type and day prior to blood culture acquisition.

Top 6 Predictors				
Day Prior	Culture Type			
	Positive "sick"	Negative "sick"	Screening "not sick"	Total
-1	45.8%	18.6%	13.6%	26.0%
-2	35.6%	15.3%	20.3%	23.7%
-3	23.7%	22.0%	16.9%	20.9%
Total	35.0%	18.6%	16.9%	23.5%

Figure 3. Number of subjects with each of the top six predictors present by culture type for day prior to blood culture. (BD = base deficit; HR = heart rate)



Despite achieving a parsimonious model with four predictors, the original six predictors achieved better overall performance and avoided over-fitting 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 six ABA sepsis criteria in predicting "positive-sick versus screening-not sick" or "sick versus not-sick" (Table 6).

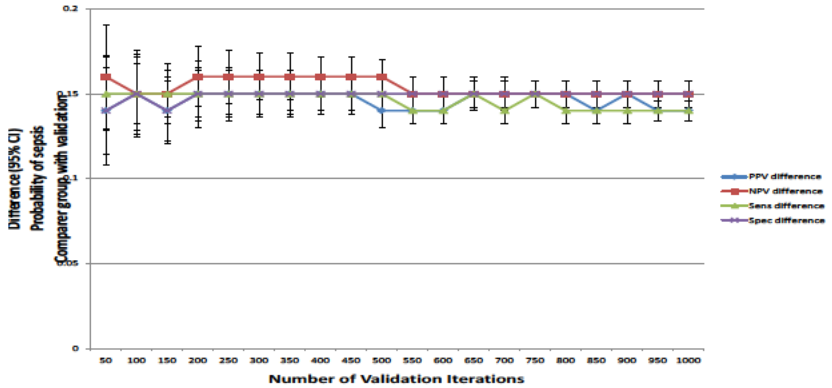
Table 6. Receiver operating curve comparison of generated models and ABA sepsis criteria. (ABA = American Burn Association; AUC = area under the curve)

	Positive-sick vs screen-not sick		Negative-sick vs screen-not sick		Positive-sick vs negative-sick		"sick" vs "not sick"	
	AUC	sig	AUC	sig	AUC	sig	AUC	sig
Top 6	**.775**	**.000**	.653	**.004**	.669	**.002**	**.714**	**.000**
Top_6_crit2	**.712**	**.000**	.636	**.011**	.576	.153	.674	**.000**
Top_6_crit3	.661	**.003**	.525	.634	.636	**.011**	.593	**.043**
Top_6_crit4	.619	**.026**	.517	.751	.602	.057	.568	.142
Top_6_crit5	.542	.427	.500	1.000	.542	.427	.521	.646
Top 5	**.760**	**.000**	.657	**.003**	.647	**.006**	**.709**	**.000**
Top 4	**.741**	**.000**	.625	**.019**	.657	**.003**	.683	**.000**
ABA_sum	.646	**.006**	.626	**.018**	.514	.796	.636	**.003**
ABA_Criteria3	.619	**.026**	.576	.153	.542	.427	.597	**.035**

When 2 or more of the top six predictors are present the ROC AUC remains greater than 0.7 indicating a moderate ability to predict the sick patient with a positive blood culture. 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 of greater than 0.7 for any model.

Model Validation Evaluation of the results of the validation process revealed an overall reduction in the 95% CI around the mean difference in the group means for: sensitivity, specificity, PPV, and NPV. Reduction was evident at 500 iterations and continued the downward trend through 1000 iterations (Figure 4). This analysis supports the premise that 59 cases were adequate for the final six predictor model.

Figure 4. Validation results represent the difference in group mean predict probability of sepsis compared to serial iterations of 50 to 1000 (at 50 iteration increments)



Effect of problems or obstacles on the results: The primary problem encountered based on this study design was the inability to include the predicted number of subjects (n = 90), finding only

a total of n = 59 eligible patients. This shortcoming resulted in the inability to conduct analysis of the predictors on a true validation set. Instead, analysis was performed to ensure there was no over-fitting of the model to a limited sample size. A database managed by the Brooke Army Medical Center Infectious Disease department has been tracking all infectious episodes of all military burned patients treated at the USAISR Burn Center. This database may serve as a surrogate validation set for the proposed model. Another alternative is to conduct prospective validation in the USAISR Burn Center by nursing staff; both of these plans are currently undergoing development.

The results concluded from this retrospective study are intriguing and mark a new direction for clinical recognition of sepsis. Discovery of the best predictors is an iterative process, expected to evolve over time.

Relationship of current findings to previous findings: This is the first study to show that SIRS criteria are omni-present in the burn population and thus not helpful to identify periods of sepsis. This is also the first study to evaluate the performance of the ABA consensus sepsis criteria, demonstrating some usefulness for detecting sepsis in the 24 hours prior to clinical presence of sepsis. Novel predictors and higher thresholds for some of the ABA criteria have been demonstrated to be associated with burn sepsis and will be prospectively validated. Murray and colleagues have previously reported a lack of association of leucocyte count or elevated temperature with presence of bloodstream infection in the burn patient (Murray et al., 2007), findings supported by this study. However, this is the first study to demonstrate a relationship between low body temperature and burn sepsis.

Limitations: The primary limitation of this study involves the retrospective nature of this design. Some of the physiologic biomarkers that are likely associated with sepsis in the burn patient such as serum lactate and CRP are not routinely measured as part of standard care. Therefore, the original intent to use 12 clinical variables for the study were reduced to only ten. A prospective validation study can address this limitation.

Conclusion: 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 patient status for three days prior to known blood culture results coupled with clinical suspicion of sepsis. Moreover, greater than 95% of subjects met SIRS criteria at all times during the study period, even during clinical stability. Results of studies that use the SIRS criteria to identify sepsis in the burn population should be appraised cautiously (Cumming, et al., 2001; Fitzwater, et al., 2003). This study has also demonstrated a limited ability of the ABA sepsis criteria to discriminate between patients with a positive blood culture and suspected sepsis from negative blood culture and no sepsis. However, this difference is noted on the day immediately prior to blood culture acquisition, with no discrimination for patients suspected of sepsis in the presence of a negative blood culture from the other groups.

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 heart rate > 130bpm, temperature < 36°C, and base deficit < -6 mEq/L; regression methods have identified three predictors independently associated with sepsis: MAP < 60mmHg, serum glucose > 150 mg/dL, and use of vasoactive medications. The ROC AUC for this model on the day prior to blood

culture is 0.775 (95% CI 0.692, 0.858; $p < 0.001$) to predict "positive-sick" from "screening-not sick". Results of this study show that predicting sepsis is generally confounded when periods of "negative-sick" are included in analysis. Further, the ability to predict greater than 24 hours from culture acquisition is limited, although the model of the top six identified variables performs better than the ABA sepsis criteria in this respect, 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.

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. At our institution oral naloxone is administered and feeds held when enteral residuals are excessive due to 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 beta-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". 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 hemostasis 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 a "gold-standard" means of diagnosis while extending the window of opportunity for detection (Mann, Wood, & Wade, 2011).

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, or organisms that do not grow in bacterial culture medium contribute to this problem (Keen, Knoblock, Edelman, & Saffle, 2002). 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 MAP < 60 mmHg, glucose > 150 mg/dL and use of vasoactive medications. Analysis of the ABA criteria for example demonstrates minor differences among the individual predictors, yet when combined those predictors evaluated collectively are significantly different among culture types for day prior (Figure 5b). What remains to be discovered is the exact combination of predictors and in what frequency is most predictive. For example, the operational definition in this study for SIRS and ABA criteria was randomly selected 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 greater than 95% frequency of SIRS criteria in all groups at all times; half of SIRS criteria were the mean values for 25-75% of study subjects (HR > 90bpm, RR > 20 bpm, 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 required 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 beta 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.

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 prior to 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 stable with negative cultures. However, detecting the septic patient who fails to produce a produce a positive blood culture remains elusive and this cohort continues to require careful clinical evaluation and proactive intervention. Future use of technology to trend and combine multiple parameters offers the potential to promptly identify this complex disease process and allow for more timely definitive intervention.

Significance of Study or Project Results to Military Nursing

Sepsis is the number one killer of burn patients. Yet knowledge of the clinical variables associated with burn sepsis is unclear within the burn community. Therefore, nurses providing care to critically ill burn patients at the US Army Burn Center, or at military medical facilities in combat Theaters are unaware of what subtle clinical changes to alert providers that could indicate presence of life-threatening sepsis. Moore and colleagues (2009) demonstrated that a simple daily screening of surgical ICU patients for presence of sepsis by the nursing staff resulted in a significant reduction of mortality by approximately 33%. It is rare that nursing interventions can impact patient survival, so the prospect of early identification of burn related sepsis by the bedside nurse offers hope that a simple screening intervention can save lives.

The goal of this program of research is to first, prospectively validate these identified sepsis criteria in burn patients at the US Army Burn Center. Next, the criteria will be included in a shift checklist for the bedside nurse to screen for presence of the criteria; should clinical indicators associated with burn sepsis be noted, the nurse will alert the medical resident or Fellow to further evaluate the patient for sepsis risk factors. Then, the USAISR software developers will develop a “smart alarm” to constantly mine the electronic medical record for the pattern of clinical markers associated with burn sepsis. Such a system is currently in use for other clinical conditions such as acute renal failure and burn fluid overload during initial resuscitation. Upon validation of this system of nurse screening or automatic alerts, the process can be projected to combat hospitals where non-burn providers will benefit from knowledge and experience of the burn center in a far-forward environment. A similar process is appropriate for the identification of trauma-related sepsis since the presence of SIRS is also omni-present in the trauma patient (unpublished data, Mann, 2012).

Changes in Clinical Practice, Leadership, Management, Education, Policy, and/or Military Doctrine that Resulted from Study or Project

Currently underway at the USASIR is development of an automated “smart alarm” to constantly screen the electronic medical record (ESSENTRIS) for the pattern of clinical symptoms associated with burn sepsis. This process will be preceded with a paper-based version of the nursing screening tool upon protocol approval by the Medical Research and Material Command Institutional review Board (in process).

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Summary of Dissemination

Type of Dissemination	Citation	Date and Source of Approval for Public Release
Publications in Press	"Novel Predictors of Sepsis Outperform the ABA Sepsis Criteria in the Burn ICU Patient" EA Mann, MM Baun, JC Meininger, JA Aden, C Murray, SE Wolf, CE Wade, in press *Journal of Burn Care and Research* ***(Paper received the Clinical Research Award for non-physician research at the 44th Annual ABA Meeting, 23-27 April 2012, Seattle, WA)***	PAO/OPSEC review approval USASIR 10 FEB 2011
Published Abstracts	"SIRS is not associated with Sepsis in the Burn Patient" , EA Mann, in *Critical Care Medicine* "Novel Clinical Parameters to Predict Burn Sepsis are Superior to ABA Consensus Criteria", EA Mann, MM Baun, JC Meininger, J Aden, SE Wolf, CE Wade, in *Journal of Burn Care and Research*	PAO/OPSEC review approval USAISR 25 AUG 2011 PAO/OPSEC review approval USAISR 25 AUG 2011
Podium Presentations	American Burn Association Annual Meeting 2012, Seattle, WA, 23-27 April 2012: "Novel Clinical Parameters to Predict Burn Sepsis are Superior to ABA Consensus Criteria", EA Mann, MM Baun, JC Meininger, J Aden, SE Wolf, CE Wade PJV Army Nursing Research Course, San Antonio, TX, " Prediction of Sepsis in the Burn Patient: Implications for Nursing", EA Mann, 30 April – 2 May 2012	PAO/OPSEC review approval USAISR 25 AUG 2011 and USASIR 20 APR 2012 USASIR 20 APR 2012

Poster Presentations	Poster Abstract Accepted for AMSUS 2011 Karen A Reider Research/Federal nursing Poster Session, 8 NOV 2011, San Antonio, TX : "Prediction of Sepsis in the Burned Intensive Care Unit Patient" EA Mann, MM Baun, JC Meininger, CE Wade (2nd place award) Society of Critical Care Medicine, Critical Care Congress 4-8 Feb 2012, Houston, TX: "SIRS is not associated with Sepsis in the Burn Patient" , EA Mann, in *Critical Care Medicine*	PAO/OPSEC review approval USAISR 28 June 2011 PAO/OPSEC review approval USAISR 25 AUG 2011
Other: Dissertation	"Prediction of Sepsis in the Burn Intensive Care Unit Patient" accepted May 23, 2011, UT Health – Houston, School of Nursing	

Reportable Outcomes

Reportable Outcome	Detailed Description
Applied for Patent	None
Issued a Patent	None
Developed a cell line	None
Developed a tissue or serum repository	None
Developed a data registry	None

Recruitment and Retention Table

Recruitment and Retention Aspect	Number
Medical or Data Registry Records Available	4141
Medical or Data Registry Records Screened	246
Subjects Ineligible	187
Subjects With Complete Data	59
Subjects with Incomplete Data	0

Demographic Characteristics of the Sample

Characteristic	N = 59
Age (yrs)	40 ± 19
Women, n (%)	7(12%)
Military Service or Civilian	
Military, n (%)	25(42.4)
Civilian, n (%)	34 (57.6)

Final Budget Report

Approval for reallocation of personnel funds was authorized to utilize the support of the research assistance for an additional 2 months since dissertation presentation was delayed. This reallocation allowed for support with final data management prior to data analysis. The remaining travel funds were spent in the Spring of 2012 for project dissemination and was the purpose of the request for a no cost extension. The remaining amount will be returned to TSNRP.