The Systemic Mediator-Associated Response Test Identifies Patients in Failed Sepsis Clinical Trials Among Whom Novel Drugs Reduce Mortality

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Background: Clinical trials using American College of Chest Physicians/Society of Critical Care Medicine Consensus sepsis definitions as entry criteria fail to reduce septic mortality. We hypothesized that the systemic mediator-associated response test (SMART) methodology could match sepsis therapies biologically to individual patients by relating baseline data statistically to outcomes and treatment effects. This article reports the SMART analyses of four failed sepsis investigations.

Methods: Databases from the E5 antiendotoxin antibody, North American Sepsis Trial (NORASEPT) and NORASEPT II anti-tumor necrosis factor antibody (TNFMAb), interleukin (IL)-1ra, and platelet-activation factor acetylhydrolase (PAF-AH) sepsis clinical trials were evaluated with SMART using multivariate logistic regression. From baseline data, within each study, mortality prediction models were built separately for the placebo and active drug populations. Subjects among whom each drug's effects were greatest were then identified by excluding from efficacy analysis subjects predicted by SMART to survive on placebo or to expire on active drug. Finally, prerandomization data from patients in each study were entered into SMART models, and placebo or active drug treatment effects were evaluated for parent populations and SMART cohorts.

Results: E5—consensus mortality: 27.4% placebo, 26.2% E5; SMART mortality: 17.1% placebo, 8.0% E5 ($p < 0.01$). NORASEPT—consensus mortality; 33.4% placebo, 29.5% TNFMAb; SMART mortality: 47.2% placebo, 34.7% TNFMAb ($p = 0.03$). IL-1ra—consensus mortality: 33.9% placebo, 29.8% IL-1ra; SMART mortality: 55.6% placebo, 34.9% IL-1ra ($p < 0.001$). PAF-AH—consensus mortality: 22.4% placebo, 23.9% PAF-AH; SMART mortality: 17.7% placebo, 28.9% PAF-AH ($p = 0.039$).

Conclusions: Using prerandomization clinical trial data, SMART identifies septic patients whose host-inflammatory responses can benefit from specific drugs. SMART also predicts ineffective drugs and patients whom they might harm.

Key Words: Severe sepsis, Shock, Clinical trials, Outcomes.

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Since 1982, clinical trials of new drugs for sepsis have used, virtually unaltered, the entry criteria from the Solu-Medrol (methyprednisolone sodium succinate) study.[1] The Solu-Medrol definitions were first published in the report of that clinical trial's results.[1] Then, the placebo results were reported as sepsis syndrome.[2] Later, they were codified into medical culture by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference on sepsis.[3] Since the ACCP/SCCM Consensus Conference, sepsis definitions were published,[3] and they have been used almost exclusively as the entry criteria for sepsis clinical trials. Unfortunately, in every sepsis clinical trial that has enrolled patients under those definitions, the study drug has failed to reduce septic mortality. Even the large investigations of an anti-tumor necrosis factor (TNF) antibody[4] and recombinant-activated protein C (Xigris),[5] while statistically significant, did not reduce septic mortality to levels that changed standards of care. The anti-TNF antibody was not approved by the Food and Drug Administration (FDA), and Xigris has been underutilized in the medical market.

Prospective, randomized, double-blind, placebo-controlled clinical trials are accepted universally as the highest level of scientific testing for potentially therapeutic molecules in sepsis. From the accumulated sepsis clinical trial data, then, the reasonable conclusion would be that the new drugs studied simply had no beneficial effects. However, it is also possible that novel sepsis therapies have failed to reduce septic mortality because they were not tested in a study population that was responsive to their biological effects. One might speculate that clinical trial entry criteria based on the ACCP/SCCM Consensus Conference publications and other clinical definitions of sepsis could have allowed such large numbers of patients to be enrolled in sepsis studies, whose host-inflammatory responses to infection were unable to benefit from the test compound that their treatment effects were lost within a nonspecific clinical trial population. The true target population for each sepsis drug, then, could be diluted to into invisibility by the overwhelming numbers of nonresponders enrolled. As a result, potentially life-saving drugs for sepsis and septic shock may not have received a fair chance to prove their efficacy but still were deemed ineffective because they were evaluated in what were otherwise thought to be well-designed clinical trials.

We developed the systemic mediator-associated response test (SMART) to prognosticate clinical events in

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sepsis. Preliminary SMART models predicted organ failure days, and even weeks, in advance.[6–8] On the basis of this experience, we hypothesized that, in sepsis clinical trials, the SMART statistical modeling approach might be able to analyze databases of completed studies and then to develop equations that predicted which patients would benefit from the study drug and which would not. This study tested this hypothesis on sepsis clinical trials that used consensus definitions as entry criteria, in which the study test molecule failed to reduce septic mortality.

METHODS

The database from the second phase III clinical trial of the E5 antiendotoxin antibody in sepsis[9] was supplied by Patrick Scannon, MD, PhD (XOMA LLC, Berkeley, CA). Data from the Synergen 0509 clinical trial of interleukin (IL)-1ra in sepsis[10] were supplied by Michael Bevilaqua, MD (Amgen, Inc., Thousand Oaks, CA). Data from the North American Sepsis Trial (NORASEPT) and NORASEPT II clinical trials[11,12] were supplied by Dr. Deborah Church and colleagues from the Bayer Corporation (West Haven, CT). Data from the COntrolled Mortality trial of human Platelet-activating factor Acetylhydrolase for treatment of Severe Sepsis (COMPASS) clinical trial of PAF-AH in sepsis[13] were supplied by John Pribble, PharmD (ICOS Corporation, Seattle, WA). Their generosity is appreciated. Details of each of these clinical trials are summarized in Table 1.

No patient-identifying information was included. The NORASEPT and NORASEPT II studies were sequential multiinstitutional studies of TNFMAb in severe sepsis and septic shock. All investigations were prospective, randomized, double blind, placebo-controlled phase III clinical trials. In the E5 study, the primary end point was a 30-day all-cause mortality.[9] The primary end point in the NORASEPT and NORASEPT II, Synergen 0509, and COMPASS studies was 28-day all-cause mortality.[10–13] Details of these studies were thoroughly described in the articles that reported their results.[9–13]

In NORASEPT, septic mortality was slightly reduced, but not significantly, among patients with shock at baseline who received the 7.5 mg/kg TNFMAb dosage.[11] In NORASEPT II, therefore, the investigators decided to randomize only patients with septic shock at baseline to either placebo or 7.5 mg/kg TNFMAb.[12] Because the enrollment criteria were otherwise identical, we considered the two studies sufficiently similar to use patient data from NORASEPT II to validate the SMART models developed on NORASEPT.

In the E5, NORASEPT, IL-1ra, and the preinterim analysis cohort of COMPASS, on Health Insurance Portability and Accountability Act compliant, prerandomization clinical information from patients in each study for whom complete data sets were available, using multivariate, stepwise logistic regression with all ways elimination (simultaneous forward and backward elimination of nonweighted independent variables), SMART survival models were separately developed for the placebo and active drug groups. For the E5 study, SMART models also predicted drug effects on organ failure or death. Statistical significance at $p < 0.10$ identified potential independent variables and was the threshold for testing them in the final equations, with, conversely, $p > 0.10$ being the threshold for excluding a potential independent variable. These separate survival models for each study, generated separately from the placebo and from the active drug baseline, prerandomization databases, made it possible to test two possible probabilities for each individual patient: the probability of survival for that patient receiving the active study drug and placebo. After the modeling process was completed, prerandomization data from every patient in that study were entered into both equations, and lengthy explorations into the relationship between the placebo and active drug models and their interactions with treatment effects were undertaken to analyze optimum cutoffs for each drug. Beginning with the original consensus definition patient population, this process tested study drug treatment effects in progressively smaller subpopulations, incrementally excluding, always at prerandomization baseline, from each study's efficacy analysis patients whom SMART predicted would survive if they were to receive placebo or who would expire if they were to receive the active drug. This exploration was performed for each clinical trial on a theoretically infinite number of cutoff points, with efficacy in reducing septic mortality tested for each study drug in cohorts having mortality rates ranging from 0% to 100%. As patients who were excluded from efficacy analysis at each cutoff point were identified before randomization, the resulting placebo and active drug subgroups were, by definition, equal. With this approach, only subjects who were identified by the SMART models for each study as responsive to the treatment arm were included in outcomes statistics, thereby giving each drug a fair chance to prove its efficacy. Survival-treatment effects were evaluated separately among patients enrolled under consensus definitions and among patients predicted by SMART to respond to each sepsis drug. Mortality was analyzed by Kaplan–Meier

TABLE 1. Summary of Clinical Trials Analyzed by SMART

Clinical Trial	Sponsor	Study Drug	Entry Criteria	Year Study Ended
E5	XOMA	E5 antiendotoxin-modified antibody	Sepsis syndrome	1991
NORASEPT	Bayer	TNFMAb antitumor necrosis factor monoclonal antibody	Sepsis syndrome	1993
NORASEPT II	Bayer	TNFMAb	Septic shock	1998
0509	Synergen	IL-1ra	Modified Sepsis syndrome	1994
COMPASS	ICOS	PAF-AH	Modified ACCP/SCCM consensus definitions of sepsis	2004

statistics,[14] as were the E5 results for drug treatment effects on end-organ dysfunction. The E5 and Synergen 0509 results were retrospective, because the Synergen 0556 study database[15] was not released, and the third phase III clinical trial of E5 versus placebo in sepsis had insufficient data to support the SMART models.[16]

As prospective validation of the SMART models for the TNFMAb molecule, and of the efficacy of the drug, baseline information from NORASEPT II subjects was entered into SMART models from NORASEPT. Then, treatment effects of TNFMAb were assessed among consensus NORASEPT II patients, and, separately, in the SMART cohort.

In the COMPASS clinical trial platelet-activation factor acetylhydrolase sepsis (PAF-AH), modeling was conducted on the 600 patients enrolled for the interim analysis. Then, PAF-AH versus placebo treatment effects were tested prospectively by entering data from the 623 subjects in the second COMPASS interim analysis cohort into the SMART models built upon the first interim group's data.

The χ^2 equation[14] was used to ensure that the distribution of baseline discrete variables was equal within each study for placebo versus active drug populations.

RESULTS

Baseline parameters that were screened as possible independent variables for SMART models that were developed from the E5, TNFMAb, IL-1ra, and PAF-AH clinical trial databases are listed in Table 2. Nearly, all these demographic, physiologic, clinical, and hospital laboratory data points were captured at prerandomization baseline in each study, always within 24 h or less before administrations of the study drug. Nearly, all the variables listed were measured at prerandomization baseline in every patient, pursuant to FDA safety-monitoring requirements.[9–13]

Independent variables that were weighted components of the SMART models built on the NORASEPT sepsis study are displayed in Table 3. TNFMAb versus placebo treatment effects on 28-d all-cause mortality are displayed in Table 4. For the 623 patients in NORASEPT, mortality was 33.4% placebo and 29.5% TNFMAb (3.9% absolute reduction; 11.7% relative to placebo; $p = 0.20$). In the SMART cohort, placebo mortality was 47.3% and 34.7% TNFMAb (12.6% absolute; 26.9% relative to placebo; $p = 0.03$). For NORASEPT II, mortality was 43.9% placebo and 41.0% TNFMAb (2.9% absolute; 6.6% relative to placebo; $p = 0.15$). In the NORASEPT II SMART cohort, 28-d mortality was 49.6% placebo and 42.4% TNFMAb (7.2% absolute and 14.5% relative to placebo; $p = 0.02$).

Independent variables in SMART models for E5 anti-endotoxin antibody are displayed in Table 5. Treatment effects on 30-day all-cause mortality for E5 versus placebo are displayed in Table 6. In the consensus E5 population, placebo mortality was 27.4% and E5 26.2% (1.2% absolute; 4.4% relative to placebo; $p = 0.747$). In the E5 SMART cohort, placebo mortality was 17.1% and E5 8.0% (9.1% absolute; 53.2% relative to placebo; $p < 0.01$).

Independent variables of SMART models from the Synergen 0509 clinical trial of IL-1ra in sepsis are displayed in Table 7. Treatment effects of IL-1ra versus placebo on 28-day all-cause mortality are displayed in Table 8. In sepsis syndrome patients (n = 877), mortality was 33.9% placebo, 32.1% for 1.0 mg/kg/h IL-1ra (1.8% absolute; 5.3% relative; $p = 0.6178$), and 29.8% for IL-1ra 2.0 mg/kg/h (4.1% absolute; 12.1% relative; $p = 0.2824$). In one SMART cohort (59.2%/62.6% of placebo/IL-1ra consensus populations), placebo mortality was 48.3%, versus IL-1ra, at 2.0 mg/kg/h, 36.5% (11.8% absolute; 24.4% relative; $p = 0.024$). In a more IL-1ra-specific SMART cohort (44.6%/42.6% of placebo/IL-1ra consensus populations), placebo mortality was 55.6% versus 35.0% IL-1ra (20.6% absolute; 37.1% relative; $p < 0.001$). In a third SMART cohort (25.8%/24.9% of placebo/IL-1ra consensus populations), placebo mortality was 67.5% versus 40.3% IL-1ra (27.2% absolute; 37.1% relative; $p < 0.001$).

For IL-1ra 1.0 mg/kg/h, in a SMART cohort (56.7%/56.9% of placebo/IL-1ra consensus populations), placebo

TABLE 2. Baseline Observations Screened as Possible Significant Independent Variables for SMART Modeling in Sepsis Clinical Trial Databases

- APACHE II score
- Body surface area
- Age
- Days since admission
- Underlying comorbidities
  - Cardiovascular
  - Pulmonary disease
  - Autoimmune
  - Hematologic
  - Neurologic
  - Renal or bladder
  - Diabetes mellitus
  - Other endocrine
- Immunosuppressive therapy
- Major surgery/trauma
- Alcoholism
- Source of infection
  - Urinary tract
  - Lungs
  - Intra-abdominal
  - Wound
  - Blood
  - Central nervous system
  - Indwelling catheter
  - Other
  - Causative microorganism
- Diagnostic procedures
  - Estimated sepsis severity
  - Blood pressure: systolic and diastolic
  - Mean
  - Heart rate
  - Respiratory rate
  - Glasgow Coma Scale
- Serum electrolytes
  - Hemoglobin
  - Hematocrit
  - White blood cell count
  - Platelets
  - Arterial blood gas
  - FiO_2
- Cardiac output
- Baseline organ failure
  - Renal
  - Acute respiratory distress syndrome
  - Disseminated intravascular coagulation
  - Hepatobiliary
  - Central nervous system
  - Shock
- Abnormal physical examination
  - Neck
  - Abdomen
  - Skin
  - Extremities
  - Neurologic
  - HEENT
  - Respiratory
  - Cardiovascular

HEENT, head, eyes, ears, nose, throat; FiO_2, fraction of inspired oxygen.

TABLE 3. Independent Variables in the Final SMART Models for NORASEPT and NORASEPT II and Results for Consensus and SMART Cohorts

	Placebo Model		TNFMAb Model	
	p	Odds Ratio	*p*	Odds Ratio
NORASEPT				
APACHE II Score	<0.001	1.089	<0.001	1.116
PTT	0.02	1.016	—	—
RBC	<0.001	0.473	—	—
ROC AUC	0.777		0.737	
NORASEPT II prospectively validated models				
ROC AUC	0.727			
			0.703	

PTT, partial thromboplastin time; RBC, red blood cells; ROC AUC, receiver operating characteristics area under the curve.

SMART models that predicted 28-d all-cause mortality risk were generated separately from the placebo and active drug clinical trial databases, using prerandomization data.

mortality was 46.7% versus 35.0% IL-1ra (10.8% absolute; 23.1% relative; $p = 0.017$). Another SMART cohort (20.5%/18.6% of placebo/IL-1ra consensus populations) had placebo mortality 62.3% versus 25.9% IL-1ra (36.4% absolute; 58.4% relative; $p < 0.0001$).

Independent variables for SMART models from the ICOS COMPASS clinical trial are listed in Table 9. PAF-AH versus placebo treatment effects on 28-day all-cause mortality are displayed in Table 10. In the consensus COMPASS population (COMPASS I), placebo mortality was 22.4% versus 22.9% for PAF-AH (0.5% absolute survival increase; 2.2% relative; $p = 0.924$). The SMART cohort of COMPASS I had placebo mortality 17.7% versus PAF-AH 28.9% (11.2% absolute increase in septic mortality versus placebo; 63.3% relative; $p = 0.039$). The COMPASS I SMART models and PAF-AH treatment effects were tested prospectively on the COMPASS II population that followed COMPASS I up to the second and final interim analysis. In the COMPASS II consensus population (n = 540), placebo mortality was 25.9% versus 25.6% for PAF-AH. In the SMART COMPASS II cohort (n = 244), placebo mortality was 31.9% versus 21.6% for PAF-AH (10.3% absolute reduction in mortality; 32.3% relative; $p = 0.0551$).

There were few weighed independent variables that were common between the four clinical trials in the SMART placebo models. Placebo models from the IL-1ra and E5 studies had disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS) as significantly weighted independent variables. APACHE (Acute Physiology and Chronic Health Evaluation) II score was common to the NORASEPT and COMPASS clinical trials. No other independent variables factored significantly in more than one SMART placebo model.

DISCUSSION

The results of this study illustrate SMART's ability to identify objectively, from prerandomization baseline data, patients within failed clinical trials among whom novel treatments reduce septic mortality. SMART also predicts which sepsis drugs may not be beneficial. Specifically, SMART models uncovered cohorts of septic patients wherein E5, TNFMAb, and IL-1ra improved survival significantly. Furthermore, the SMART models built on the NORASEPT database, and efficacy of the TNFMAb study drug, were validated prospectively in NORASEPT II. Conversely, the failure of PAF-AH to lower septic mortality, and its possible adverse effects, was predicted early in the COMPASS study database by SMART. These results were achieved in clinical trial databases that were uncontrolled for optimal statistical modeling, and through analyzing only ordinary bedside observations and standard hospital laboratory tests, without the potentially valuable contributions of circulating levels of inflammatory response mediators or other sepsis biomarkers. Our review of the literature indicates that this approach to outcomes research has not been reported previously.

In the XOMA E5 sepsis clinical trial, SMART discovered patients among whom E5 not only improved survival but also reduced organ failure. Subjects enrolled by consensus definitions alone received only a nonsignificant 1.4% absolute survival benefit from E5. In the SMART cohort, however, which comprised 51% of the consensus population, E5 reduced mortality by 9.1% absolute, 53.2% relative to placebo. In the SMART cohort, placebo mortality was only 17.1%, more than 10% lower than in the parent consensus definition population. Logically, one might expect gram-negative infection to have been a weighted independent variable in SMART models for an antiendotoxin antibody, but infecting bacteriology did contribute to these equations. On the surface, these findings also seem inconsistent with the results of the MEDIC study,[17] which reported strong correlations between increased circulating endotoxin levels and high APACHE II, MOD, and SOFA scores, shock, decreasing partial pressure of oxygen in arterial blood/fractional inspired oxygen ratio, and leucopenia or leukocytosis. The results of this study, specifically the finding of E5 responsive patients in a lower mortality subgroup, presumably, therefore, with low-circulating endotoxin,[17] suggest that endotoxin levels alone might not predict treatment effects for antiendotoxin strategies. It may be that E5 succeeded here by SMART's incorporating the septic pathophysiology of individual patients into the subject selection data mix.

Another interesting observation was that E5 reduced septic mortality only in lower acuity patients, with placebo mortality only 17.1%. This contrasts strikingly with the results of the Phase 2 trial of eritoran tetrasodium (E5564), a toll-like receptor 4 antagonist that interferes with endotoxin signaling.[18] In that investigation, a nonsignificant trend toward lower septic mortality was seen in high-dose eritoran subjects with high APACHE II predicted risk of mortality. These results suggest that for each truly effective molecule in sepsis therapy, there are patients whose host-inflammatory responses to infection are matched biologically to that drug, and who, therefore, are specifically able to benefit from it. Apparently, even different antiendotoxin interventions have different target populations. It follows, logically, then, that

TABLE 4. NORASEPT and NORASEPT II 28-Day Mortality

	Total	Dead	Alive	Mortality (%)	Mortality Reduction vs. Placebo (%) Absolute	Relative	*p*
NORASEPT							
Consensus definition cohort (n = 623)							
Placebo	308	103	225	33.4	3.9	11.7	
TNFMAb	315	93	222	29.5			0.20
SMART cohort (n = 205)							
Placebo	110	52	58	47.2	12.6	26.6	
TNFMAb	95	33	62	34.7			0.03
NORASEPT II							
Consensus definition cohort (n = 1,741)							
Placebo	863	379	484	43.9	2.9	6.6	
TNFMAb	878	360	518	41.0			0.15
SMART cohort (n = 744)							
Placebo	371	184	187	49.6	7.2	14.5	
TNFMAb	373	158	215	42.4			0.02
Non-SMART cohort (n = 997)							
Placebo	492	195	297	39.6	0	0	
TNFMAb	505	202	303	40.0			

SMART cohorts were identified through analysis of interactions between study drug treatment effects and prerandomization placebo and active drug survival models.

TABLE 5. Independent Variables in the Final SMART Models for the E5 Sepsis Clinical Trial and Results for Consensus and SMART Cohorts

Independent Variable	Odds Ratio Estimates—95% Wald Confidence Limits
APACHE II score	1.039–1.144
Urinary tract source of infection	0.222–0.727
Lung source of infection	0.920–4.889
Respiratory rate	1.008–1.071
Diastolic blood pressure	0.951–0.987
DIC	1.344–16.808
Age	1.027–1.067
Neurologic comorbidity	1.341–5.185
Acute central nervous system dysfunction	0.140–0.517
ARDS	3.702–18.304
Hepatobiliary dysfunction	1.734–19.037

SMART models that predicted 28-d all-cause mortality risk were generated separately from the placebo and active drug clinical trial databases, using prerandomization data.

the true target populations for different sepsis therapies should vary significantly, according to the mechanism of action of each molecule. The low mortality therapeutic niche identified here for E5 should be confirmed prospectively, so that thousands of septic patients for whom E5 is not available now can be saved. Unfortunately, the third E5 sepsis investigation did not capture data sufficient to support the E5 SMART models, and the findings here, therefore, could not be validated prospectively.[16] SMART uncovered also a significant E5 treatment effect on organ failure. Although E5 had no significant effects on organ failure or shock in the consensus population, among SMART E5 responders, ARDS, hepatobiliary failure, cerebral dysfunction, DIC, and shock were reduced dramatically.

A clinically significant discovery of this investigation was the unprecedented, extremely high reduction of septic mortality among SMART patients by IL-1ra. Compared with the sepsis syndrome population, in which high-dose IL-1ra reduced mortality by only 4.1% versus placebo, among patients identified by SMART as able to benefit from the study drug, IL-1ra improved survival by from 9% up to 50% absolute, in increasingly IL-1ra-specific cohorts. To the author's knowledge, such dramatically increased septic survival has not been reported for any other drug ever tested in humans. Unfortunately, the Synergen 0556 sepsis clinical trial of IL-1ra,[16] which followed the 0509 study and was nearly identical to it, was not made available to validate prospectively the SMART/IL-1ra models and the IL-1ra efficacy in sepsis seen here. IL-1ra (anakinra) currently is FDA approved for rheumatoid arthritis and marketed by Amgen and its licensees. Considering the life-saving potential of IL-1ra seen here, one hopes that clinical development of this drug for sepsis will be revisited.

If they are to be considered as more than mere conjecture, results of SMART retrospective, post hoc analyses in sepsis, and the efficacy of successful drugs, must be validated prospectively in populations of like patients who were not included in the equation-building process. This was accomplished in this study for SMART models based on NORASEPT. In the post hoc phase, survival benefits of TNFMAb in NORASEPT were improved from 3.9% in consensus patients, to 12.6% in the SMART-identified cohort. Then, baseline raw data from NORASEPT II patients was entered into the SMART equations from NORASEPT. In the SMART cohort of NORASEPT II,

TABLE 6. 30-Day Mortality and Organ Failure in Severe Sepsis and Septic Shock in the E5 Clinical Trial

	30-Day Mortality					
					Mortality Reduction vs. Placebo (%)	
	Total	Dead	Alive	Mortality (%)	Absolute	Relative
Consensus definition cohort (n = 759)						
E5	390	102	288	26.2	1.2%	4.4%
Placebo	369	101	268	27.4	$p = 0.747$	
SMART cohort (n = 388)						
E5	201	16	185	8.0	9.1%	53.2%
Placebo	187	32	155	17.1	$p = 0.006$	

	Organ Failure/Death in Severe Sepsis and Septic Shock					
	ARDS	Hepatobiliary	Renal	Centra Nervous System	DIC	Shock
E5 vs. Placebo p values						
Consensus cohort (n = 759)	0.43	0.65	0.81	0.20	0.54	0.97
SMART cohort (n = 388)	0.01	0.03	0.22	0.02	0.002	0.04

SMART cohorts were identified through analysis of interactions between study drug treatment effects and prerandomization placebo and active drug survival models.

TABLE 7. Independent SMART Variables for the Synergen 0509 Sepsis Clinical Trial and Results for Consensus and SMART Cohorts

Independent Variable	Odds Ratio Estimates—95% Wald Confidence Limits
Placebo model results (n = 302)*	
ARDS	0.169–0.621
DIC	0.135–0.616
Mean arterial pressure	1.007–1.047
Temperature	1.082–1.634
Arterial pH	1.673–5.427
BUN	0.967–0.990
FiO_2	0.990–0.999
High-dose IL-1ra model results (n = 293)†	
Cardiovascular	0.264–0.934
Age	0.965–0.998
Systolic blood pressure	1.003–1.034
Respiratory infectiozan	0.288–0.895
Urinary tract infection	1.993–25.933
BUN	0.978–0.998
Low-dose IL-1ra model results (n = 298)‡	
ARDS	0.193–0.738
DIC	0.138–0.595
Acute Renal Failure	0.215–0.708
Vasco	0.274–0.872
Age	0.956–0.989
HEENT abnormal	0.214–0.717
Abdomen abnormal	0.328–1.124
Neurological abnormal	0.361–1.119
Extremities/joint abnormal	0.320–1.009

BUN, blood urea nitrogen; FiO_2, fraction of inspired oxygen; Vasco, peripheral vascular disease; HEENT, head, eyes, ears, nose, throat; ROC AUC, receiver operating characteristics area under the curve.

* ROC AUC = 0.822.

† ROC AUC = 0.762.

‡ ROC AUC = 0.776.

SMART models that predicted 28-d all-cause mortality risk were generated separately from the placebo and active drug clinical trial databases, using prerandomization data.

TNFMAb lowered septic shock mortality significantly, as it had done in NORASEPT SMART group. These results validated prospectively the predictive power of SMART models from NORASEPT and established TNFMAb efficacy in reducing septic mortality. Our review of the literature indicates that the objective identification of septic patients among whom a novel therapy reduced mortality, followed by prospective validation of the predictive process and of drug efficacy, observed here with SMART and TNFMAb, have not been reported previously.

SMART prognostic models from the population of the first interim analysis of the COMPASS study of PAF-AH in sepsis also were validated prospectively, using the second and final interim analysis cohort of that clinical trial. Septic mortality was increased significantly compared with placebo among active PAF-AH subjects in the SMART modeling cohort of COMPASS. When data from subjects of the second COMPASS interim analysis group were entered into the SMART models, increased PAF-AH mortality was not confirmed, but, conversely, neither was a significant beneficial effect identified. One might speculate that application of the SMART approach to the first interim analysis data of COMPASS would have resulted in termination of that investigation earlier, with significant savings of research dollars, and, possibly, of adverse drug effects among study subjects.

From this study, one could envision SMART facilitating clinical development of new therapeutic molecules for sepsis, such as other anti-TNF strategies,[4,19] antiendotoxin interventions,[9,18,20] PAF interventions[21,22] or restoring coagulation homeostasis,[5] among others. SMART equations derived from Phase II databases could facilitate protocol development for Phase III clinical trials of novel therapies. Similarly, SMART evaluation of completed Phase III investigations could assist in confirmatory study design. Ultimately, SMART interactions with novel drugs may be able to guide bedside management of septic patients,

TABLE 8. 0509 Clinical Trial of IL-1ra in Sepsis—28-Day All-Cause Mortality

					Mortality Change vs. Placebo (%)		
	Total	Dead	Alive	Mortality (%)	Absolute	Relative	*p*
Consensus definition cohort							
Placebo	298	101	197	33.9%			
Low dose	290	93	197	32.1	1.8	5.3	0.618
High dose	289	86	203	29.8	4.1	12.1	0.282
SMART cohort high dose							
Placebo	176	85	91	48.3			
High dose	181	66	115	36.5	11.8	24.4	0.024
Placebo	133	74	59	55.6			
High dose	123	43	80	35.0	20.6	37.1	0.0009
Placebo	77	52	25	67.5			
High dose	72	29	43	40.3	27.2	40.3	0.0008
SMART cohort low dose							
Placebo	169	79	90	46.7			
Low dose	165	56	109	35.9	10.8	23.1	0.017
Placebo	61	38	23	62.3			
Low dose	54	14	40	25.9	36.4	58.4	<0.0001

SMART cohorts were identified through analysis of interactions between study drug treatment effects and prerandomization placebo and active drug survival models.

TABLE 9. Independent Variables in the COMPASS Clinical Trial of PAF-AH in Sepsis and Results for Consensus and SMART Cohorts

Independent Variable	95% Wald Confidence Limits
Placebo*	
Mechanical ventilator	0.066–0.412
APACHE II score	1.049–1.171
Multiple organ dysfunction score	1.006–1.306
Eosinophil count	0.004–0.062
PAF-AH†	
Mechanical ventilation	0.066–0.412
Multiple organ dysfunction score	1.006–1.171

* ROC AUC = 0.708.
† ROC AUC = 0.788.
SMART models that predicted 28-d all-cause mortality risk were generated separately from the placebo and active drug clinical trial databases, using prerandomization data.

supplemental to clinical judgment and consensus sepsis definitions screening.

Considering the multiple clinical trials testing IL-ra, antiendotoxin, and anti-TNF regimens that have failed to reduce septic mortality,[4,9–13,19] the results of this investigation suggest that enrollment criteria for such studies should be reconsidered. Certainly, the concept of designing a confirmatory clinical trial on the basis of subgroup analysis from a previous study has been discredited. This is evidenced in the failure of NORASEPT II,[12] wherein shock was added at entry, based on a nonsignificant trend toward anti-TNF efficacy observed in the preceding NORASEPT investigation,[11] In the sequential clinical trials of the E5 antibody, a trend toward efficacy among patients without shock in the first study led to excluding shock in the second study.[9,20] The second IL-1ra sepsis clinical trial[16] added organ failure and increased APACHE III risk of death as entry criteria, because post hoc analysis suggested a correlation between them and drug treatment responses. All three studies failed to reduce septic mortality. Similarly, severity of illness scores, including APACHE II scoring,[5,18] and/or the presence of DIC[11] or ARDS,[23] while attractive as single, commonly understood screening measurements, also have not panned out as patient identification tools for predicting anti-TNF and antiendotoxin treatment responses. Even though APACHE II was an independent variable in SMART survival models for both the E5 and TNFMAb populations, and DIC, and ARDS figured in the E5 SMART modeling, they contributed only to building the tools that identified individual septic pathophysiology. None of these factors directly predicted treatment response. Therefore, as the CytoFab anti-TNF molecule[19] and eritoran tetrasodium[18] move from Phase II studies to Phase III confirmatory clinical trials, their sponsors should consider supplementing patient identification with alternatives such as SMART if standard clinical definitions of sepsis, severity of illness, shock, DIC, or ARDS are to be entry criteria.

SMART may identify also patients for whom sepsis study drugs are ineffective, or even detrimental. During the current study, this was manifested in the preinterim analysis cohort of the COMPASS clinical trial[13] wherein PAF-AH increased septic mortality significantly among a SMART-predicted group. One might speculate that if SMART had been applied to the Phase II PAF-AH database, or even at the first Phase III interim analysis, then COMPASS could have been ended earlier, saving hundreds of subjects from the risk of possible adverse clinical effects.

The results of this study reiterate that the traditional definitions of severe sepsis and septic shock,[1–3] when used as entry criteria for clinical trials, do not match responsive patients with study drugs that are biologically appropriate to

TABLE 10. COMPASS Clinical Trial of PAF-AH in Sepsis—28-Day All-Cause Mortality

					Mortality Change vs. Placebo (%)		
	Total	Dead	Alive	Mortality (%)	Absolute	Relative	*p*
COMPASS I consensus definition cohort (n = 587)							
Placebo	304	68	236	22.4	0.5	2.2	0.921
PAF-AH	283	65	218	22.9			
SMART cohort I (n = 251)							
Placebo	130	23	107	17.7	11.2	63.3	0.039
PAF-AH	121	35	86	28.9			
COMPASS II consensus definition cohort (n = 540)							
Placebo	255	66	189	25.9	0.3	1.1	1.000
PAF-AH	285	73	212	25.6			
SMART cohort II (n = 244)							
Placebo	119	38	81	31.9	10.3	32.3	0.0551
PAF-AH	125	27	98	21.6			

SMART cohorts were identified through analysis of interactions between study drug treatment effects and prerandomization placebo and active drug survival models.

their host pathophysiologies. Therefore, under consensus definition enrollment, new therapies for sepsis are denied a fair chance to prove their efficacy. So many patients are enrolled who would recover on placebo, and who would expire even on active drug, that the true treatment effects of even the most potent sepsis drugs are diluted to invisibility. Good drugs fail because they are studied in the wrong patients. Then, they are abandoned by the pharmaceutical industry and never reach biologically appropriate patients whom they might save. After nearly three decades of clinical trials that failed because patients were entered through consensus definitions of sepsis, clearly an alternative approach to selecting subjects for these studies should be considered. The results of this study suggest that SMART should at least be interviewed for the job.

SMART is an analytic approach that uses conventional statistical techniques and is applicable universally across the gamut of sepsis clinical trials. However, it is not a single-fixed formula or a one-size-fits-all clinical generalization. In current practice, SMART is most readily applied as a supplement to consensus sepsis definitions. This is a practical consideration, because of the prevalence of consensus criteria in sepsis clinical trials. Because each novel intervention for sepsis has it own unique mechanism of action, it follows that the host biology of treatment-responsive patients also is unique for each molecule. Therefore, weighted independent variables in the SMART models for E5, for example, are not the same as those for TNFMAb, IL-1ra, or PAF-AH. In addition, clinical factors that would seem to have obvious relevance to sepsis or to a specific drug, such as age, illness acuity, shock, or microbiology, might not pan out as significant independent variables in SMART modeling. Rather, by avoiding preconceived notions of which parameters might predict treatment success, SMART allows the host-inflammatory response to infection of each patient to interact with study drug mechanism of action, thereby building predictive models that match patients to drugs, accurately and objectively. Thus, by the very nature of the SMART approach, a single entity known as "the SMART model" cannot exist, because SMART is a dynamic process that ferrets out the important temporal interactions within each clinical trial database. The preliminary results of this study suggest that the SMART approach works across a variety of therapeutic agents in sepsis clinical trials.

Interestingly, the independent variables for the placebo survival models also varied considerably among the clinical trials analyzed in this study. One might expect, logically, that, at least the placebo patients from different sepsis investigations would be similar, statistically. However, one must realize that sepsis clinical trial entry criteria, while similar in concept, were not uniform in specifics among the studies analyzed here. Thus, NORASEPT, E5, IL-1ra, and COMPASS placebo survival models required varying independent variables, secondary to actual clinical differences in the study populations.

A deficiency of this study is the absence of prospective validation of each SMART model in a second population of septic patients identical to the group studied by SMART. Even the NORASEPT II clinical trial did not fill this void perfectly for the NORASEPT or SMART predictions because NORASEPT included severe sepsis and septic shock, whereas all patients in NORASEPT II had septic shock.[11,12] Similarly, first interim analysis data from COMPASS revealed a negative drug effect that could have predicted an ineffective final result of that study. Prospective testing of those results confirmed a lack of efficacy in reducing septic mortality. Unfortunately, no opportunity for prospective validation was possible for the other therapeutic molecules, because the final Phase III E5 sepsis study[15] did not have enough baseline data to support SMART, and the Synergen 0556 investigation, sequential to the 0509 clinical trial of IL-1ra in sepsis[19] was not available to us. Ultimately, SMART models developed on a completed sepsis clinical trial of an effective drug must be tested prospectively in real time on a study population that is enrolled under identical clinical entry criteria.

The results here clarify SMART's ability to identify objectively patients who can benefit from novel interventions in severe sepsis and septic shock, using readily available prerandomization clinical information, The logical next step for SMART is to develop predictive models for patients who can respond to molecules that currently are in active clinical development. Whether those models are built on Phase II databases, or as retrospective analyses of completed Phase III clinical trials, when they are used in subsequent confirmatory investigations, the hope is that SMART will give good drugs a fair chance to demonstrate efficacy in sepsis. Thereafter, when these treatments come into clinical use, SMART may be able to guide physicians at the bedside, supplemental to consensus sepsis definition screening and to clinical judgment, toward optimizing their efficacy among septic patients in real time.

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