Validation of a clinical trial composite endpoint for patients with necrotizing soft tissue infections

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OBJECTIVE: Our objective was to develop and validate a composite endpoint for patients with necrotizing soft tissue infections that incorporates: local tissue injury, systemic organ dysfunction, and mortality.

METHODS: The Necrotizing Infection Clinical Composite Endpoint (NICCE) was defined as follows:(i) alive at day 28, (ii) three or less debridements before day 14, (iii) no amputation beyond first debridement, (iv) modified sequential organ failure assessment score score (mSOFA) at day 14 ≤ 1. To be considered a success, all individual criteria must be met. Several data sets were used to assess validity: (i) a retrospective data set of 198 patients treated during 2013 at 12 US trauma centers; (ii) a subset with high disease acuity, admission mSOFA score of 3 or higher (n = 69); and (iii) 40 patients from a multicenter, phase 2 randomized trial of a CD28 immunomodulator (AB103). Clinical success based on each parameter and the composite score was assessed.

RESULTS: Using the retrospective data set for all patients and those with high disease severity (respectively), survival rates were 92% and 84%; day 14 mSOFA 1 or lower score was 69% and 51%; three or less debridements was 84% and 77%; and no subsequent amputations were 96% and 94%. Overall, the percent meeting all success criteria for NICCE was 58% (all patients) and 33% (mSOFA > 3). NICCE success was also associated with reduced utilization of health care resources, intensive care unit–free days were median (interquartile range) of 25.3 (21.9–28) and 19.6 (4.3–25.1) days (one-sided Wilcoxon $p < 0.001$) and ventilator-free days were 28 (26–28) versus 25 (14–28) ($p < 0.001$) for NICCE success versus failure, respectively. Using the phase 2 data set, the treated group (0.5 mg/kg, n = 15) demonstrated a NICCE success rate of 73.3% versus 40% for placebo (n = 10).

CONCLUSION: These data demonstrate internal consistency of the components and face and criterion validity of the NICCE endpoint. NICCE offers an opportunity to demonstrate a clinically relevant treatment effect for patients enrolled in clinical trials for necrotizing soft tissue infection. (*J Trauma Acute Care Surg.* 2017;83: 622–627. Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Prognostic/Epidemiological, level III; Therapeutic, level IV.

KEY WORDS: Necrotizing soft tissue infection; Fournier's gangrene; clinical trial; composite endpoint.

Necrotizing soft tissue infections (NSTIs) represent a spectrum of deep soft tissue infections with tissue necrosis. NSTI is a devastating disease process, which carries a high morbidity for the patient due to the need for extensive surgical debridement and in some cases amputation. In addition, affected patients suffer systemic toxicity and organ dysfunction as a result of sepsis and the consequences of potent bacterial toxins. This toxicity and organ dysfunction results in prolonged intensive care unit (ICU) and hospital stays and multiple operations for serial debridement. Although mortality has classically been reported as high as 30% to 40%, recent studies suggest this is improving with current mortality rates of 10% to 15% in major referral centers.[1–4]

Standard of care for this disease is broad-spectrum antibiotics, emergent wide surgical debridement of all necrotic tissue, and supportive care for organ dysfunction.[5] The diagnosis of NSTI can be challenging as an extensive deep tissue infection may have limited skin changes. Difficulty in accurate and timely diagnosis leads to delays in intervention with an associated increase in morbidity and mortality.[6,7] Adjunctive therapies, including hyperbaric oxygen and intravenous immunoglobulin G, have been reported as possible interventions, but limited data are available to support their use.[8–12]

In general, randomized controlled trials for NSTI interventions are lacking, and these patients have been excluded from the majority of sepsis trials. In 2011, we sought to design the first randomized controlled trial in this patient population to investigate a new drug that showed promise in preclinical models of NSTI. AB103 is a CD28 mimetic octapeptide that selectively inhibits the direct binding of superantigenic exotoxins to the CD28 costimulatory receptor of T helper 1 lymphocytes.[13–17] This multicenter, phase 2a study randomized 40 patients to receive a one of two doses of the drug or placebo within 6 hours of NSTI clinical diagnosis.[18] This study demonstrated safety of the drug and feasibility of conducting a randomized controlled trial in this patient population. In addition, we observed a statistically significant improvement in organ dysfunction scores in the treated patients 14 days after admission.

In preparation for a phase 3 study, we then conducted a multicenter, retrospective study to better understand the progression of organ dysfunction in this patient population using the same enrollment criteria as was used in the phase 2a trial.[19] Given the relatively low mortality in recent series, we sought a composite endpoint that would incorporate mortality together with important local and systemic manifestations of this disease and would be suitable to define efficacy in a phase 3 study. The use of a composite endpoint would capture an overall assessment of the total burden of the disease and is expected to achieve a higher event rate in a critically ill and difficult to recruit patient population. This article seeks to assess the performance of this endpoint using the data from the phase 2a and retrospective studies to validate the impact on resource utilization. Our hypothesis was that we could develop a composite endpoint that would characterize clinically important outcomes in NSTI and that this endpoint would perform consistently across data sets and correlate with increased resource utilization.

METHODS

Definition of a Composite Endpoint

In collaboration with the US Food and Drug Administration (FDA) the endpoint that was developed is known as the Necrotizing Infection Clinical Composite Endpoint (NICCE) and was defined as follows:(i) alive at day 28, (ii) three or less debridements before day 14, (iii) no amputation beyond first debridement, (iv) modified SOFA score (mSOFA) at day 14 of 1 or less. The modified SOFA refers to the SOFA score without the liver component and is used due to the infrequency of serial bilirubin analysis in clinical practice. Our precious study demonstrated that the mSOFA score performed as well as SOFA in predicting outcome.[19] Data analysis based on the composite endpoint is a responder analysis, and to be considered a success, all individual criteria must be met.

The following describes the rationale of the criteria chosen for the composite endpoint, and the justifications for the threshold selected. (i) Survival at day 28: as a life-threatening disease,

TABLE 1. Baseline Characteristics

	Phase 2 Cohort (n = 40)	Retrospective Cohort (n = 198)	Retrospective Cohort mSOFA ≥ 3 (n = 69)
Age: mean (SD), y	51 (15)	52 (15)	54 (15)
Sex (% male)	65%	62%	64%
Admission weight: mean (SD), kg	100 (24)	92 (28)	99 (29)
Site of infection, N (%)			
Extremity	15 (37.5%)	84 (42%)	39 (56%)
Perineum	12 (30%)	40 (20%)	15 (22%)
Other	13 (32.5%)	74 (38%)	15 (22%)
Admission mSOFA, median (IQR)	2 (1–3)	1 (0–3)	4 (3–7)

mortality should be followed. Since most deaths occur before day 14, monitoring mortality until day 28 is appropriate. (ii) Number of debridements: excising all the necrotic tissue is critical to control the disease, and the number of debridements is a measure of disease progression. Based review of the literature, the average debridement per patient is three, and thus patients needing three or more debridements to control the infection by day 14 are considered a failure. (iii) Amputations beyond first debridement: Amputation is a marker of advanced disease and is considered a failure to control the infection. However, if performed at the first debridement, it is part of disease presentation and thus not likely be impacted by the intervention being studied. (iv) mSOFA at day 14 ≤ 1: One of the major pathological consequences of NSTI is the development of impaired organ function leading to organ failure. SOFA score is a measure of organ dysfunction/failure, and has been shown to be a good indicator of prognosis in sepsis.[20,21] Day 14 was selected for monitoring recover of organ function based on the phase 2 study results, which indicated that by this time point a good separation existed between treatment groups.[18] In addition, a previous study demonstrated good correlation between resource utilization and resolution of organ dysfunction at this time point.[19] A score of 1 or less was selected as a threshold to identify patients having minimal organ impairment, not requiring critical care intervention, and without risk of deterioration.

Data Sets Used for Assessments

Data were obtained from the phase 2a study of AB103 (n = 40) and the retrospective study (n = 198). In brief, the phase 2a study was conducted at six academic medical centers in the United States from December 2011 to August 2012.[18] This placebo-controlled, randomized trial included two dosing arms for AB103 (0.25 mg/kg and 0.5 mg/kg) administered within 6 hours of the diagnosis of NSTI. Mean time to drug administration was 4 hours. The retrospective study was conducted at 12 academic medical centers in the United States in 2013. Inclusion and exclusion criteria were the same for both studies with the exception of age, which was restricted to age 18 years and older in the phase 2a study and broadened to include ages 12 years to 80 years in the retrospective study. Inclusion was based on surgical confirmation of NSTI. Exclusion criteria included weight greater than 150 kg, pregnant or lactating women, previous debridement for NSTI, HIV with CD 4 count less than 200 mm^3 or less than 14% of all lymphocytes, severe peripheral vascular disease in the involved area, deep venous thrombosis in the involved area within the last month, acute cerebrovascular accident in the last 3 months, cardiac arrest within the past 30 days, patient not expected to survive 28 days based on underlying medical condition, end-stage organ dysfunction, extremis on admission, NSTI after intra-abdominal operation or burns. End-stage organ dysfunction based on pre-existing co-morbidities was defined as follows: congestive heart failure (New York Hear Association class III or IV), chronic obstructive pulmonary disease (GOLD stage III or IV), liver dysfunction (Childs-Pugh class C), renal failure necessitating hemodialysis, hematologic or lymphatic malignant disease. Extremis on admission was defined as follows: (1) inability to maintain a mean systolic blood pressure of 70 mm Hg or higher for at least 1 hour before screening despite treatment with vasopressors and intravenous fluids or; (2) respiratory failure, such that Sa_{O_2} of 80% cannot be achieved or; (3) refractory coagulopathy (INR >3) or thrombocytopenia (platelet count < 50,000/μL) that does not correct to any extent with administration of appropriate factors or blood products. These criteria were chosen to be representative of the patient population likely to be enrolled in a phase 3 randomized controlled trial.

TABLE 2. Components of NICCE Endpoint by Cohort

	Phase 2 Cohort (n = 40)	Retrospective Cohort (n = 198)	Retrospective Cohort mSOFA ≥ 3 (n = 69)
≤3 Debridements	31 (77%)	167 (84%)	53 (77%)
Amputation rate*	0	9/84 (11%)	4/39 (10%)
mSOFA ≤ 1, day 14	30 (75%)	137 (69%)	35 (51%)
28-d survival	36 (90%)	183 (92%)	58 (84%)
NICCE composite endpoint success	22 (55%)	114 (58%)	23 (33%)

*Amputation rate based on subset with extremity infections.

TABLE 3. Relationship Between NICCE Endpoint and Resource Utilization

(A) All Patients (Phase 2 and Retrospective Cohorts)			
	NICCE Success (n = 136)	**NICCE Failure (n = 102)**	***p***
ICU days, median (IQR)	2.7 (0–6.1)	5.4 (1.9–13.6)	<0.0001
ICU-free days, median (IQR)	25.3 (21.9–28)	19.6 (4.3–25.1)	<0.0001
Ventilator days, median (IQR)	0 (0–2)	2 (0–7)	<0.0001
Ventilator-free days, median (IQR)	28 (26–28)	25 (14–28)	<0.0001
Hospital LOS: median (IQR), d	11.5 (7–18)	15.5 (11–28)	0.0002
(B) Retrospective Cohort Admission mSOFA ≥ 3			
	NICCE Success (n = 23)	**NICCE Failure (n = 46)**	***p***
ICU days, median (IQR)	4 (2.9–6.9)	8.4 (2.6–18)	0.05
ICU-free days, median (IQR)	24 (21.1–25.1)	11.5 (0.4–22.4)	0.0002
Ventilator days, median (IQR)	1 (0–4)	4 (0.5–9.5)	0.0069
Ventilator-free days, median (IQR)	27 (24–28)	21 (5.5–26.5)	0.0003
Hospital LOS: median (IQR), d	13 (9–25)	16 (12–28)	0.17

Assessing the NICCE Endpoint

The rates of response to each of the individual component of the composite endpoint were evaluated for each data set, as well as the response rate for composite endpoint as a whole. We evaluated the performance of the endpoint for the population as a whole as well as for those with high disease severity as judged by evidence of organ dysfunction on admission that was defined as mSOFA score of 3 or higher in the emergency department. The relationship between the composite endpoint and resource utilization was also assessed including ICU-free days, ventilator-free days, and hospital length of stay. Free days were calculated out of the 28-day study period. These data are presented as medians with interquartile range (IQR). Statistical comparisons were made using a one-sided Wilcoxon rank test. Significance was considered as p less than 0.05.

RESULTS

The baseline characteristics of each study cohort are shown in Table 1. There was no difference in age, sex, or admission weight among the cohorts. Patients with a higher mSOFA on admission were more likely to have an extremity infection than other anatomic sites. The median mSOFA (IQR) on admission was similar between the Phase 2 study cohort and the retrospective cohort (2 [1–3] vs. 1 [0–3]). As expected, the median admission mSOFA for the group selected based on admission mSOFA score greater than 3 was higher (4 [3–7]).

Success rate for the individual components of the composite score and the overall success rates for the NICCE endpoint are shown in Table 2. For all data sets, the response to all the individual components trended in the same direction.

Using the retrospective data set for all patients and those with high disease severity at baseline (respectively), survival rates were 92% and 84%; day 14 mSOFA 1 or less score was 69% and 51%; three or less debridements was 84% and 77%; and no subsequent amputations were 96% and 94%. Similar success rate among all data sets were observed for number of debridements. Success rate of SOFA score at day 14 was similar between the phase 2 cohort and the full retrospective cohort (75% vs. 69%), but was much lower for patients with high mSOFA score at baseline (51%).

The overall success rate for the composite endpoint was similar between the phase 2 and retrospective cohorts (55% vs. 58%) as were each component of the endpoint (Table 2). The subset of patients with greater organ failure on admission was less likely to meet success (33%) on the composite endpoint, and this difference was largely driven by higher mortality and higher rates of persistent organ dysfunction. When assessed by treatment group within the phase 2 study, the high-dose AB103 group (0.5 mg/kg, n = 15) demonstrated a NICCE success rate of 73.3% versus 40% for placebo (n = 10).

There was a significant association between resource utilization and NICCE success for all patients and those with higher organ dysfunction on admission (Table 3*A* and *B*). NICCE success was associated with significantly fewer ICU days, ventilator days, and hospital days. These differences persisted when assessed by ICU-free and ventilator-free days, which take into account early deaths.

DISCUSSION

NSTI remains a rare disease with an estimated incidence of only four cases/100,000 people/year in the United States.[22] As a result, it has been designated an orphan disease by the US FDA. Traditionally, these infections have been associated with mortality rates of 30% to 40%. However, with rapid surgical intervention and advances in critical care, current series report mortality rates of 10% to 20%, which although lower than past historical data, remains a poor outcome in light of the mean age of 52 years in these series.[1–4] Despite the reduction in mortality, these patients continue to suffer significant morbidity as a result of the tissue loss associated with serial debridement and organ dysfunction that develops as a result of systemic manifestations of the disease. In addition, they require considerable resource utilization with multiple operative procedures and prolonged ICU and hospital stays. The combination of a low incidence and a low mortality makes clinical trial design particularly challenging as it is not feasible to enroll enough patients

to adequately power a study for mortality as the primary endpoint. As a result, we sought to develop a composite endpoint that would reflect the clinically relevant outcome parameters of this disease and allow for efficacy studies of novel interventions.

The NICCE endpoint is a composite endpoint that requires each individual criterion to be successfully met to establish a beneficial outcome for the patient. The components of the NICCE endpoint were selected to reflect both the local and systemic manifestations of the disease. The local progression is assessed by the number of debridements required and the rate of amputation after the first operation for patients with extremity infection. A debridement was strictly defined as the removal of necrotic tissue, not just operative exploration. We considered a parameter to assess the size of the debridement or the amount of additional tissue removed over time; however, given the variable anatomy at presentation and the difficulty in standardizing measurement of a three-dimensional debridement, this was determined impractical. Although the rate of amputation is low and thus does not contribute to the endpoint in most cases, progression to amputation limits the number of debridements and has major impact on patient quality of life so should be considered a failure.

The systemic manifestations of the disease include mortality as well as the development and subsequent recovery from systemic organ dysfunction. Even though mortality in modern series is only 10% to 15%, mortality must be included in the endpoint as a poor outcome. To better understand the progression of organ dysfunction in this patient population, we undertook a retrospective study of NSTI patients presenting to 12 academic medical centers in the United States in 2013.[19] This study used a modified-SOFA score which is based on the traditional SOFA score but excludes the hepatic component (total bilirubin) which is frequently not serially assessed.[23] This study demonstrated a rise in mSOFA from admission to day 1 which likely reflects the initial surgical intervention and then a decline over time.[19] The persistence of organ dysfunction over time as evidenced by an mSOFA score greater than 1 at day 14 was associated with increased resource utilization. This study also suggested that the mSOFA at admission could be used to define a population of patients with greater disease severity and significantly worse outcome. We considered several different approaches to the assessment of organ dysfunction for the endpoint including change in mSOFA over time. This approach was not appropriate given the normal progression of the mSOFA score in these patients, which peaks on day 1 after the first surgical intervention. Thus, the change in SOFA from admission does not reflect the true impact of the therapy and measuring change from day one involves use of a post-randomization variable. We also considered the individual components of the mSOFA score, but the score as a whole performed better in a responder analysis.

Although the NICCE composite endpoint was accepted by the US FDA and European Medicines Agency for the phase 3 trial of AB103 that is currently enrolling, (clinicaltrials.gov ID: NCT02469857), this study seeks to validate its performance in a contemporary NSTI patient population. Our results show that this endpoint and its components performed consistently across the phase 2 and retrospective data sets. Furthermore, restricting the population to those with organ dysfunction on admission (mSOFA $\geq$ 3) demonstrated even greater discrimination and lower success rates. This lower success rate provides a greater opportunity to demonstrate a therapeutic effect of the intervention. In addition, there was internal consistency of the components, and the significant association with increased resource utilization reflects face criterion validity of the NICCE endpoint.

There are limitations to this study. The patients included in the data sets evaluated were based on inclusion/exclusion criteria for clinical trials and thus may not be representative of the entire population of NSTI patients. The retrospective data set required retrospective calculation of the mSOFA score, which is subject to some missing data at specific time points. Further validation of this endpoint should be conducted for studies enrolling a broader population of NSTI patients.

In summary, NSTI is a devastating disease that has a significant unmet need for novel therapeutic approaches. We have demonstrated that conducting a randomized clinical trial with early intervention is feasible in this patient population, and the NICCE endpoint should be considered for future efficacy trials.

AUTHORSHIP

E.B., W.D., A.M., A.S., and G.M. all contributed to study design and development of the composite endpoint. G.M. performed the statistical analysis. E.B. drafted the article. All authors were involved in data interpretation and critical revision of the article.

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DISCLOSURE

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EDITORIAL CRITIQUE

I would like to commend Dr. Bulger and her group for their successful investigation of a composite endpoint for necrotizing soft tissue infections (NSTI). NSTI is a devastating condition with significant morbidity and mortality even after early recognition and treatment. Although mortality has improved somewhat in the setting of improved delivery of critical care, disease-specific therapies are still lacking.

In this study, the authors developed and validated a Necrotizing Infection Clinical Composite Endpoint (NICCE) for demonstrating a clinically relevant treatment effect in further efficacy studies. The main advantages supporting the use of a composite outcome are that it increases statistical efficiency because of higher event rates, thereby avoiding an arbitrary choice between multiple important outcomes that refer to the same disease process. However, the chosen endpoints may not be of equal clinical importance. To me, survival seems more important than the number of debridements required before day 14. In addition, the need for further debridement or amputation may be a subjective decision and not necessarily a marker of disease progression or failure to control infection. I wonder if the use of weighted endpoints, assigning different values to different outcomes within a composite endpoint, rather than treating all outcomes as statistically the same would have yielded the same results. While I applaud the authors on their selection of endpoints that accurately reflect the local and systemic manifestations of NSTI, I am curious to know if there is also a significant association between functional outcome and NICCE success. Current research suggests that functional outcomes, including health-related quality of life may be better overall measures for patients with NSTI, especially when a significant number of survivors have severe functional limitation even at the time of hospital discharge.

Congratulations to Dr. Bulger and her colleagues for this informative study that comes at a particularly relevant time, as novel adjuncts and pharmacologic therapies for this complicated disease are being developed. I look forward to seeing the results of future studies from this prolific group of authors.