

Original articles

Validation of necrotising infection clinical composite endpoint in a retrospective cohort of patients with necrotising soft tissue infections

Victoria Bion¹, Dylan Jape², Rachel Niesen², Margaret Angliss³, Frank Bruscino-Raiola³, Biswadev Mitra^{4,5}, Bridget Devaney^{1,4,5}

¹ Department of Intensive Care and Hyperbaric Medicine, Alfred Health, Melbourne, Australia

² School of Medicine, Monash University, Melbourne, Australia

³ Plastics, Hand and Faciomaxillary Surgery Unit, Alfred Health, Melbourne, Australia

⁴ School of Public Health and Preventative Medicine, Monash University, Melbourne, Australia

⁵ Emergency and Trauma Centre, Alfred Health, Melbourne, Australia

Corresponding author: Dr Bridget Devaney, Head of Hyperbaric Medicine, Alfred Health, 55 Commercial Road, Melbourne, VIC 3004, Australia

ORCID: [0000-0001-6521-418X](https://orcid.org/0000-0001-6521-418X)

b.devaney@alfred.org.au

Keywords

Fournier's gangrene; Hyperbaric research; Necrotising fasciitis; Necrotising infections; Organ dysfunction scores

Abstract

(Bion V, Jape D, Niesen R, Angliss M, Bruscino-Raiola F, Mitra B, Devaney B. Validation of necrotising infection clinical composite endpoint in a retrospective cohort of patients with necrotising soft tissue infections. *Diving and Hyperbaric Medicine*. 2024 30 September;54(3):155–161. [doi: 10.28920/dhm54.3.155-161](https://doi.org/10.28920/dhm54.3.155-161). PMID: 39288918.)

Introduction: Rapidly progressive necrotising soft tissue infections (NSTIs) are associated with high mortality and morbidity. Low incidence and disease heterogeneity contribute to low event rates and inadequately powered studies. The Necrotising Infections Clinical Composite Endpoint (NICCE) provides a binary outcome with which to assess interventions for NSTIs. Partly with a view towards studies of hyperbaric oxygen treatment in NSTIs we aimed to validate NICCE in a retrospective cohort of NSTI patients.

Methods: Eligible patients were admitted between 2012 and 2021 to an adult major referral hospital in Victoria, Australia with surgically confirmed NSTI. The NICCE and its constituents were assessed in the whole cohort ($n = 235$). The cohort was divided into two groups using the modified sequential organ failure assessment (mSOFA) score, with an admission mSOFA score ≥ 3 defined as high acuity.

Results: Baseline characteristics of the whole ($n = 235$), the high ($n = 188$) and the low acuity cohorts ($n = 47$) were similar. Survival rates were high (91.1%). Patients with an admission mSOFA ≥ 3 were less likely to meet NICCE criteria for 'success' compared to the lower acuity cohort (34.1% and 64.7% respectively). Meeting NICCE criteria was significantly associated with lower resource utilisation, measured by intensive care unit days, ventilator days, and hospital length of stay for all patients and for those with high acuity on presentation.

Conclusions: The NICCE provides greater discriminative ability than mortality alone. It accurately selects patients at high risk of adverse outcomes, thereby enhancing feasibility of trials. Adaptation of NICCE to include patient-centred outcomes could strengthen its clinical relevance.

Introduction

Necrotising soft tissue infections (NSTI) are a group of severe, rapidly progressive infections of subcutaneous tissue, fascia or muscle associated with high mortality and morbidity. Incidence varies globally with rates as high as 15 per 100,000 in Thailand¹ and as low as 0.3 per 100,000 in high income countries such as the USA² and Norway.³ The majority of published mortality rates vary between 20–30% with 15% of patients experiencing disability, sequelae and amputation.⁴ At the Alfred Hospital, a quaternary hospital in Melbourne, Australia, the mortality rate for patients with

a diagnosis of NSTI at hospital discharge was reported to be 14%.⁵

Standard treatment of NSTI involves empiric antimicrobials, early and repeated surgical debridement of non-viable tissue, intensive care support, and use of adjuvant therapies.⁶ Patients may require amputation in the early phase of the disease, followed by complex reconstructive procedures and extensive rehabilitation in nearly half of survivors.⁷ Whilst early surgical intervention has been shown to reduce mortality and the number of operations required to control the disease,^{8–10} there is limited high level evidence for any treatment modality for NSTI.¹¹

The Alfred Hospital provides a state-wide service for hyperbaric oxygen treatment (HBOT). This has become an established component of NSTI treatment at many centres. Support for HBOT is based on proposed physiological mechanisms, case reports, retrospective case-control studies, and a systematic review and meta-analysis published in 2021 which concluded that HBOT reduced the odds of dying from NSTI (odds ratio 0.44 [95% CI 0.33–0.58]).¹² Research into the efficacy of HBOT in NSTI has continued including a recent Danish nationwide population-based observational study that demonstrated a significant association between HBOT and improved 30 day survival.¹³ There are no randomised controlled trials to support or refute use of HBOT for NSTI. A 2015 Cochrane review cited the following reasons for insufficient randomised controlled trial data; heterogeneity in the disease process, disease severity, anatomical location and management of NSTI, as well as low disease incidence.¹⁴

Given the low incidence of NSTI, randomised controlled trials evaluating interventions should include outcome measures with higher event rates than mortality alone in order to improve the feasibility of successful recruitment and to adequately power future studies. It would also be important to include patient-centered and clinically important outcome measures.¹⁵

In 2017, Bulger et al, developed the Necrotising Infections Clinical Composite Endpoint (NICCE) as a standardised outcome measure to enable comparison between studies and meta-analyses, and as a means of measuring intervention efficacy in future randomised controlled trials.¹⁶ The NICCE criteria incorporate local tissue injury, systemic organ dysfunction and mortality to produce a binary measure of 'success' or not. Whilst other diagnostic composite tools have been developed and assessed with variable success,¹⁷ to our knowledge, the use of a composite outcome score has not been evaluated previously.

The NICCE appears promising in that it demonstrated both internal component consistency as well as face and criterion validity in the US patient cohort in which it was developed and tested. The score has not been validated in an Australian patient cohort to date and if valid would provide a standardised means of assessing NSTI outcomes in future studies. The aim of this study was to validate NICCE in a retrospective cohort of patients with NSTI at an adult major referral hospital in Victoria, Australia.

Methods

The study protocol was reviewed and approval to proceed granted by the Alfred Hospital Human Research and Ethics Committee (Project ID 704/20). The requirement to seek informed consent from patients or persons responsible was waived.

We performed a retrospective cohort analysis of NSTI patients admitted to the Alfred Hospital between 2012 and 2021. Case records were obtained for patients with a diagnosis of NSTI from the intensive care and hyperbaric services' database and plastic surgery databases. Inclusion criteria required patients to have a diagnosis of NSTI confirmed surgically. Cases of clostridial myonecrosis were included. Ambiguous cases were reviewed by a minimum of two authors to ensure that inclusion criteria were met. Cases without a diagnosis of NSTI or where disease control was achieved at the primary hospital prior to transfer were excluded.

Baseline variables, NICCE components, and outcome variables were collected from electronic medical records and entered into a standardised data collection tool using REDCap software. Baseline variables included age, sex, admission weight, site of infection, secondary referral, and admission modified sequential organ failure assessment (mSOFA). A high acuity subset was identified using an admission mSOFA score of three or greater. This subset was analysed in the method described by Bulger et al.¹⁶ We also included data for the low acuity group (mSOFA < 3) for further comparison as high acuity patients were over-represented in the total cohort. Rationale for use of the mSOFA score has been described previously.¹⁶

To simplify the data collection process, given that the public healthcare system in Victoria utilises multiple different electronic medical record systems, we opted to collect admission data from the point of admission to the Alfred Hospital, regardless of transfer status. We expected a large number of cases to have a primary admission elsewhere prior to transfer and therefore included primary hospital debridements in our analysis. All operative findings, including those from the primary hospital, were included where available from the Alfred Hospital medical records. Patients repatriated to their referral hospital with disease controlled and a trend towards recovery, or those that were stepped down were assumed to be alive at day 28. Those that were repatriated to another hospital's intensive care unit were considered to have an inconclusive outcome.

Outcome variables collected included NICCE components (listed below) and resource utilisation as determined by number of intensive care unit days, ventilator days and hospital length of stay. Intensive care unit-free and ventilator-free days were calculated out of 28 for the study period. In addition to following the process used by Bulger et al.¹⁶ we collected data on the use of HBOT and number of hyperbaric treatments completed.

The NICCE outcome and resource utilisation measures for both the high acuity (mSOFA \geq 3) and the low acuity (mSOFA < 3) subsets were also compared to the whole cohort.

NICCE VARIABLES COLLECTED

- Alive at day 28
 - Three or less debridements before day 14
 - No amputation beyond first debridement*
 - Modified SOFA** score at day 14 of one or less
- Achievement of the NICCE requires all criteria to be met.
 *debridement was defined as removal of necrotic tissue, not just operative exploration
 **mSOFA components: peripheral oxygen saturation to inspired oxygen fraction (SpO₂/FiO₂) ratio, blood pressure and use of vasopressors or inotropes, Glasgow Coma Scale (GCS), creatinine.

DATA ANALYSIS

Baseline characteristics of the whole cohort and the high and low acuity subsets (mSOFA ≥ 3 or mSOFA < 3 respectively) were summarised using medians and interquartile ranges (IQR). Individual components of NICCE are presented as a percentage of the cohort meeting each criterion, as well as the percentage meeting all NICCE components.

The Wilcoxon rank test was used to compare indicators of resource allocation between cases that met NICCE criteria and those that did not in both the whole cohort and the high acuity subset. Indicators of resource utilisation presented include intensive care unit-free days, ventilator-free days, and hospital length of stay. A result was considered

significant if the *P*-value was less than 0.05. All analyses were conducted using Stata v 15.1 (College Station, TX, USA).

Results

Two hundred and thirty-three cases of NSTI were identified from the hyperbaric database, of which 20 were excluded due to prior disease control at referral centre ($n = 4$), absence of surgical confirmation of disease or alternate diagnosis ($n = 14$) and administrative error ($n = 2$). An additional 23 cases were identified in the plastic surgery database, of which one was excluded for having disease control prior to transfer to our centre.

An mSOFA score of ≥ 3 was observed in 188 (80%) of the cohort, and defined as the high-acuity cohort. Baseline characteristics of the whole cohort ($n = 235$), the high acuity cohort ($n = 188$) and the low acuity cohort ($n = 47$) are presented in Table 1. Age, sex, admission weight, and site of infection were similar between the three groups. Most patients were transferred from other hospitals (89.4%), and 64.3% had an endotracheal tube placed prior to admission at the Alfred Hospital. Transferred patients were admitted to the Alfred Hospital a median of one day after initial presentation to the primary hospital. Two hundred and nineteen patients (93.2%) received HBOT. The median number of HBOT sessions was five (IQR 4–7). Patients who returned to their

Table 1

Baseline characteristics of the study cohort; IQR – interquartile range; mSOFA – modified Sequential Organ Failure Assessment; SD – standard deviation

Variable	Total population ($n = 235$)	Population with initial mSOFA ≥ 3 ($n = 188$)	Population with initial mSOFA < 3 ($n = 47$)
Age (years), mean (SD)	55.2 (15.9)	56.0 (15.9)	51.9 (15.6)
Male	147 (62.5%)	119 (63.3%)	28 (59.6%)
Female	88 (37.5%)	69 (36.7%)	19 (40.4%)
Admission weight (kg) mean (SD)	93.1 (29.0)	93.7 (29.4)	90.4 (27.1)
Site of infection			
Extremity	136 (57.9%)	109 (58.0%)	27 (57.4%)
Perineum	79 (33.6%)	61 (32.4%)	18 (38.3%)
Head and/or neck	9 (3.8%)	7 (3.7%)	2 (4.3%)
Other	43 (18.3%)	37 (19.7%)	6 (12.8%)
Multiple sites	30 (12.8%)	24 (12.8%)	6 (12.8%)
Referred from another hospital	210 (89.4%)	171 (91.0%)	39 (83.0%)
Number of days in primary hospital, median (range)	1 (1–2)	1 (1–2)	2 (1–6)
Intubated on admission	151 (64.3%)	151 (80.3%)	0
Admission mSOFA, median (IQR)	9 (4–12)	10 (7–12)	0 (0–1)

Table 2

Components of NICCE endpoint by cohort; † – data missing for 1 patient; ‡ – complete data available for 173 patients; § – complete data available for 172 patients; mSOFA – modified Sequential Organ Failure Assessment

Variable	Total population (n = 235)	Population with initial mSOFA ≥ 3 (n = 188)	Population with initial mSOFA < 3 (n = 47)
≤ 3 debridements	158 (67.2%)	121 (64.4%)	37 (78.7%)
Amputation beyond first debridement †	14 (6.0%)	12 (6.4%)	2 (4.3%)
mSOFA ≤ 1, day 14 ‡	104 (44.3%)	72 (38.3%)	32 (68.1%)
28-day survival	214 (91.1%)	169 (89.9%)	45 (95.7%)
NICCE composite endpoint – all criteria met §	69 (40.1%)	47 (34.1%)	22 (64.7%)

Table 3

Relationship between NICCE and resource utilisation; data are median (interquartile range); ICU – intensive care unit; LOS – length of stay; mSOFA – modified Sequential Organ Failure Assessment

Groups / parameters	All NICCE criteria met	Did not meet all NICCE criteria	P-value
All patients	(n = 69)	(n = 103)	
ICU days, median	4 (3–8)	14 (8–19)	< 0.001
ICU free days, median	24 (20–25)	14 (9–20)	< 0.001
Ventilator days, median	3 (0–6)	9 (5–13)	< 0.001
Ventilator-free days, median	25 (22–28)	19 (15–23)	< 0.001
Hospital LOS, median, days	21 (17–28)	33 (2–555)	< 0.001
Admission mSOFA ≥ 3		(n = 91)	
ICU days, median	6 (4–9)	15 (9–23)	< 0.001
ICU free days, median	22 (19–24)	13 (6–19)	< 0.001
Ventilator days, median	4 (3–7)	9 (6–14)	< 0.001
Ventilator-free days, median	24 (21–25)	19 (14–22)	< 0.001
Hospital LOS, median, days	21 (18–28)	34 (25–57)	< 0.001

primary hospital either after reconstruction had begun, or with ward level care (79 patients) were assumed not to have any further debridements or amputations, and to have survived to day 28, whilst two patients repatriated with ongoing intensive care unit-level care were considered to have insufficient data to determine all NICCE criteria. This only resulted in missing data for 11 patients.

Individual NICCE components and those achieving overall NICCE criteria for ‘success’ are displayed in Table 2. Patients with initial mSOFA ≥ 3 were less likely to meet all NICCE criteria compared to the lower acuity cohort (34.1% and 64.7% respectively). The differences observed between the low and high acuity groups for all NICCE criteria as well as the individual component of mSOFA at day 14 were substantially larger than the individual components of debridement, amputation, or 28-day survival.

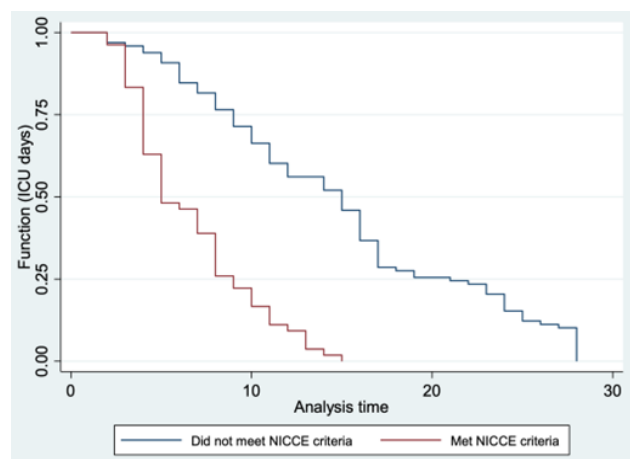
Meeting all NICCE criteria was associated with lower resource utilisation for all patients as well as for those with high acuity at baseline (Table 3). Meeting all NICCE criteria was associated with reduced intensive care unit length of stay, fewer ventilator days, and reduced hospital stay (Figures 1–3). This remained significant when comparing ICU-free and ventilator-free days which would account for deaths prior to the 28-day study period.

Discussion

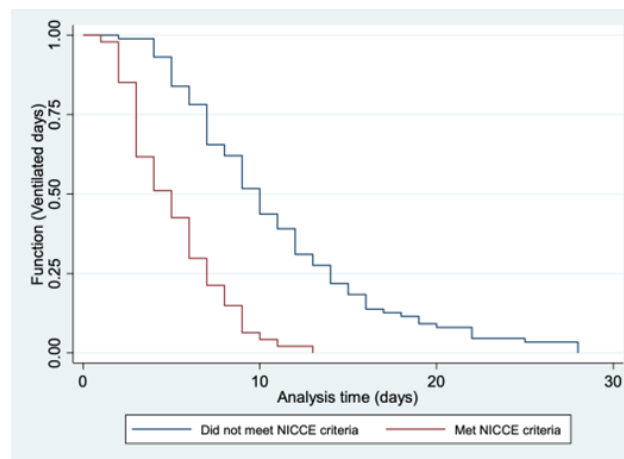
The NICCE demonstrated good discriminative ability in comparison to the individual components of debridement, amputation, or 28-day survival. In our analysis, mSOFA score at day 14 appears as discriminative as the overall NICCE outcome, suggesting that this component may perform as well as the composite measure. This could

Figure 1

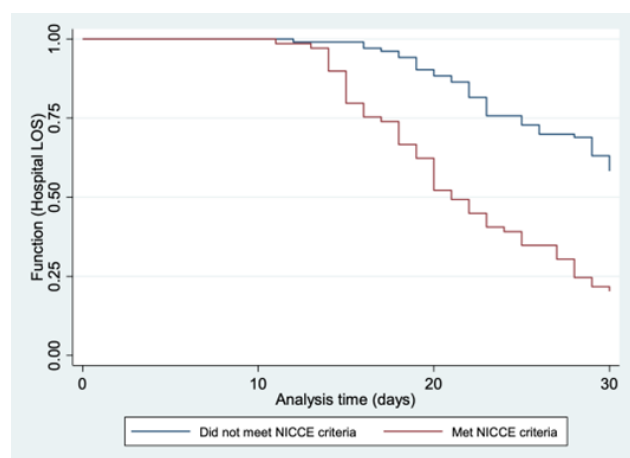
Intensive care unit (ICU) length of stay (days) among patients who met NICCE criteria compared to those that did not in the whole cohort

**Figure 2**

Number of days requiring invasive ventilation out of 28-day period among patients who met NICCE criteria compared to those that did not in the whole cohort

**Figure 3**

Hospital length of stay (LOS) (days) among patients who met NICCE criteria compared to those that did not in the whole cohort



indicate that mSOFA at day 14 could provide a less complicated, and as effective an endpoint compared to NICCE. Conversely, mSOFA at day 14 is likely to be seen as less important to patients than other components such as operations, amputation, and survival. Among patients with mSOFA ≥ 3 , the proportion of patients meeting NICCE criteria in our cohort was similar to that reported elsewhere (33%).¹⁶ The NICCE composite endpoint provided greater discriminative ability than mortality alone.

The number of cases included from the Alfred Hospital was similar to the cohort reported by Bulger et al.¹⁶ (235 and 238 respectively). Eighty percent (188/235) of the Alfred Hospital cohort had an admission mSOFA score ≥ 3 compared with 35% in the Bulger cohort (69/198), indicating a higher acuity cohort at the Alfred Hospital. High acuity cases in the Bulger cohort were identified from one of the

trial datasets, not both, resulting in the smaller denominator above.

The study by Bulger et al.¹⁶ utilised data from two pre-existing trial datasets with extensive predetermined exclusion criteria, including two different age cut-offs, comorbidities such as human immunodeficiency virus (HIV) infections and end stage organ dysfunction, as well as extremis on admission. These criteria exclude patients with high acuity on admission. Whilst the Bulger dataset included multiple centres, the extensive exclusion criteria limits applicability in NSTI cohorts, who often present with organ dysfunction in septic shock. Despite being a single-centre study, it is likely that with fewer exclusion criteria, our study more accurately reflects a real-world NSTI population and is more generalisable.

For patients transferred from other centres, the Alfred Hospital admission data does not represent the first time-point of their clinical admission and occurred a median of one day after primary admission. To be considered for transfer to our quaternary centre, patients would generally be required to demonstrate haemodynamic instability and/or progressive necrosis, and commonly require intensive care unit admission. The Alfred Hospital surgical teams generally recommend primary debridement of suspected NSTI at the referring centre prior to transfer where possible. Whether intubated to facilitate resuscitation or routinely at the time of primary surgical intervention at the referring hospital, these patients often remain intubated for transfer. Presence of an endotracheal tube raises the mSOFA score, and may over-estimate the acuity level of our cohort. On the other hand, having received initial treatment with surgery and antibiotics at the primary hospital and gaining a degree of source control, the use of Alfred admission data may under-estimate the initial acuity of transferred patients. The use of the intensive care and hyperbaric services and

the plastics surgery databases for identification of patients may have resulted in a number of Alfred NSTI patients not being included in the study sample, including those with NSTI of the trunk (general surgery or urology) or head and neck, who required neither intensive care support nor reconstructive surgical intervention. This may result in an over-estimate of the acuity level of our cohort. These factors did not appear to have a significant impact on the results, which remained consistent with those reported in the original NICCE validation study.

Meeting NICCE criteria of 'success' was associated with resource utilisation, and was consistent across all measures (ventilator-days, ICU-days, length of hospital stay). The NICCE could therefore be used in future studies to assess cost-efficacy of study interventions. Once surgical control and haemodynamic stability are achieved, and hyperbaric treatment is complete, patients often return to their primary hospital resulting in missing data for subsequent time-points in our analysis. This study demonstrates that NICCE is a feasible endpoint to measure with minimal missing data.

The NICCE does not apply weighting to its components. The debridements measure provides equivalent value to the survival measure, although it seems likely that patients and clinicians would place much higher value in the latter component. Similarly, NICCE does not measure long term comorbidity or functional status to provide a quality-of-life measure. The NICCE may therefore not be a good tool for the study of patient-centered outcomes. The NICCE was developed without patient consultation and future developments of NSTI outcome scoring might usefully include establishment of a patient advisory group to guide the inclusion of patient reported outcome measures.

The mortality rate presented in this study of 8.9% at 28 days appears at first glance to be an improvement from the overall mortality of 14.4% reported in a 2015 study at the same centre,⁵ and to our knowledge is the lowest published mortality rate for NSTI outside of large-scale registry-based studies. This six percent improvement in survival needs to be interpreted with caution, however, as survival data was not collected beyond 28 days in this study (as required by NICCE), whereas in the previous study all known deaths at the time of data collection were included. Survivors of NSTI are known to have an ongoing increased risk of mortality subsequent to the early phases of the disease, as evidenced by all-cause mortality rates of 19% at 30 days, 25% at 90 days and 30% at one year reported in a recent, large, prospective multi-centre study.¹⁸ A further potential limitation to the survival estimate in our study is the assumption that participants who were repatriated to their referring hospital with ward level care prior to 28 days survived. If inaccurate this would falsely elevate the survival rate. A follow up study at our centre could clarify this trend toward improved survival over time, which may be attributed to better awareness and management of sepsis, high performing intensive care support, and consolidation

of expertise in a high-volume centre. The routine use of HBOT in NSTI patients at our centre may also contribute to the high survival rates. This hypothesis is strengthened by a contemporary (2023) study which demonstrated almost identical mortality rates to ours of 9% in a group receiving HBOT,¹³ but this is an area which requires further research. Current reporting of survival in NSTI is inconsistent.¹⁹ A 2021 meta-analysis found that whilst mortality outcomes were universally reported, the time from admission to death was not.¹² It is critical that a Core Outcome Set for NSTI is developed for consistent reporting.⁵

The restriction of study populations to higher severity cases could further enable assessment of efficacy. In modern critical care medicine, improved outcomes of patients have paradoxically increased the degree of difficulty to demonstrate statistically significant outcomes for individual interventions.²⁰ One strategy has been development of large, multicentre trials that provide high quality evidence for the primary outcomes, but may be affected by limited generalisability and exploration of secondary outcomes. For example, the CRASH-2 trial enrolled over 20,000 patients to demonstrate a relative mortality benefit of 9% in favour of patients receiving tranexamic acid after trauma.²¹ However, restricting the population to a clinically relevant cohort of patients with acute traumatic coagulopathy enabled power to detect a similar relative difference in outcomes using a sample size of 1300 patients.²² Similarly, the population of patients with mSOFA ≥ 3 would seem to represent the more clinically important cohort as evidenced by differences in endpoints (Table 2).

Conclusion

The NICCE endpoint of 'success' provides a higher event rate than mortality alone, particularly among patients with higher disease severity as measured by the mSOFA score on admission. The resultant higher discriminative ability of NICCE should enable more accurate identification of patients who had higher risk of adverse outcomes, thereby enhancing the feasibility of interventional trials. The NICCE endpoint should be considered for future studies in the NSTI population. Adaptation of the weighting of components with patient input should be considered and evaluated alongside addition of specific patient-centered outcome measures to further improve correlation of a useful research outcome measures with clinically meaningful outcomes.

References

- 1 Khamnuan P, Chongruksut W, Jearwattananok K, Patumanond J, Tantraworasin A. Necrotizing fasciitis: epidemiology and clinical predictors for amputation. *Int J Gen Med*. 2015;8:195–202. doi: 10.2147/IJGM.S82999. PMID: 25999758. PMCID: PMC4437611.
- 2 Endorf FW, Klein MB, Mack CD, Jurkovich GJ, Rivara FP. Necrotizing soft-tissue infections: differences in patients treated at burn centers and non-burn centers. *J Burn Care*

- Res. 2008;29:933–8. doi: [10.1097/BCR.0b013e31818ba112](https://doi.org/10.1097/BCR.0b013e31818ba112). PMID: 18997557. PMCID: PMC3042354.
- 3 Naseer U, Steinbakk M, Blystad H, Caugant DA. Epidemiology of invasive group A streptococcal infections in Norway 2010–2014: a retrospective cohort study. *Eur J Clin Microbiol Infect Dis*. 2016;35:1639–48. doi: [10.1007/s10096-016-2704-y](https://doi.org/10.1007/s10096-016-2704-y). PMID: 27311458.
 - 4 Stevens DL, Bryant AE. Necrotizing soft-tissue infections. *N Eng J Med*. 2017;377:2253–65. doi: [10.1056/NEJMra1600673](https://doi.org/10.1056/NEJMra1600673). PMID: 29211672.
 - 5 Devaney B, Frawley G, Frawley L, Pilcher DV. Necrotising soft tissue infections: the effect of hyperbaric oxygen on mortality. *Anaesth Intensive Care*. 2015;43:685–92. doi: [10.1177/0310057X1504300604](https://doi.org/10.1177/0310057X1504300604). PMID: 26603791.
 - 6 Giuliano A, Lewis F Jr, Hadley K, Blaisdell FW. Bacteriology of necrotizing fasciitis. *Am J Surg*. 1977;134:52–7. doi: [10.1016/0002-9610\(77\)90283-5](https://doi.org/10.1016/0002-9610(77)90283-5). PMID: 327844.
 - 7 Endorf FW, Supple KG, Gamelli RL. The evolving characteristics and care of necrotizing soft-tissue infections. *Burns*. 2005;31:269–73. doi: [10.1016/j.burns.2004.11.008](https://doi.org/10.1016/j.burns.2004.11.008). PMID: 15774280.
 - 8 Bucca K, Spencer R, Orford N, Cattigan C, Athan E, McDonald A. Early diagnosis and treatment of necrotizing fasciitis can improve survival: an observational intensive care unit cohort study. *ANZ J Surg*. 2013;83:365–70. doi: [10.1111/j.1445-2197.2012.06251.x](https://doi.org/10.1111/j.1445-2197.2012.06251.x). PMID: 22989238.
 - 9 Boyer A, Vargas F, Coste F, Saubusse E, Castaing Y, Gbikpi-Benissan G, et al. Influence of surgical treatment timing on mortality from necrotizing soft tissue infections requiring intensive care management. *Intensive Care Med*. 2009;35:847–53. doi: [10.1007/s00134-008-1373-4](https://doi.org/10.1007/s00134-008-1373-4). PMID: 19099288.
 - 10 Kobayashi L, Konstantinidis A, Shackelford S, Chan LS, Talving P, Inaba K, et al. Necrotizing soft tissue infections: delayed surgical treatment is associated with increased number of surgical debridements and morbidity. *J Trauma*. 2011;71:1400–5. doi: [10.1097/TA.0b013e31820db8fd](https://doi.org/10.1097/TA.0b013e31820db8fd). PMID: 21768906.
 - 11 Hua C, Bosc R, Sbidian E, De Prost N, Hughes C, Jabre P, et al. Interventions for necrotizing soft tissue infections in adults. *Cochrane Database Sys Rev*. 2018;5(5):CD011680. doi: [10.1002/14651858.CD011680.pub2](https://doi.org/10.1002/14651858.CD011680.pub2). PMID: 29851032. PMCID: PMC6494525.
 - 12 Hedetoft M, Bennett MH, Hyldegaard O. Adjunctive hyperbaric oxygen treatment for necrotising soft-tissue infections: A systematic review and meta-analysis. *Diving Hyperb Med*. 2021;51:34–43. doi: [10.28920/dhm51.1.34-43](https://doi.org/10.28920/dhm51.1.34-43). PMID: 33761539. PMCID: PMC8081587.
 - 13 Hedetoft M, Madsen MB, Hyldegaard O. Hyperbaric oxygen treatment in the management of necrotising soft-tissue infections: results from a Danish nationwide registry study. *BMJ Open*. 2023;13:e066117. doi: [10.1136/bmjopen-2022-066117](https://doi.org/10.1136/bmjopen-2022-066117). PMID: 36813488. PMCID: PMC9950903.
 - 14 Levett D, Bennett MH, Millar I. Adjunctive hyperbaric oxygen for necrotizing fasciitis. *Cochrane Database Sys Rev*. 2015;1:CD007937. doi: [10.1002/14651858.CD007937.pub2](https://doi.org/10.1002/14651858.CD007937.pub2). PMID: 25879088. PMCID: PMC6516968.
 - 15 Memar MY, Yekani M, Alizadeh N, Baghi HB. Hyperbaric oxygen therapy: antimicrobial mechanisms and clinical application for infections. *Biomed Pharmacother*. 2019;109:440–7. doi: [10.1016/j.biopha.2018.10.142](https://doi.org/10.1016/j.biopha.2018.10.142). PMID: 30399579.
 - 16 Bulger EM, May A, Dankner W, Maislin G, Robinson B, Shirvan A. Validation of a clinical trial composite endpoint for patients with necrotizing soft tissue infections. *J Trauma Acute Care Surg*. 2017;83:622–7. doi: [10.1097/TA.0000000000001564](https://doi.org/10.1097/TA.0000000000001564). PMID: 28538644.
 - 17 Cribb BI, Wang MTM, Kulasegaran S, Gamble GD, MacCormick AD. The SIARI Score: a novel decision support tool outperforms LRINEC score in necrotizing fasciitis. *World J Surg*. 2019;43:2393–400. doi: [10.1007/s00268-019-05061-4](https://doi.org/10.1007/s00268-019-05061-4). PMID: 31214830.
 - 18 Hedetoft M, Madsen MB, Madsen LB, Hyldegaard O. Incidence, comorbidity and mortality in patients with necrotising soft-tissue infections, 2005–2018: a Danish nationwide register-based cohort study. *BMJ Open*. 2020;10(10):e041302. doi: [10.1136/bmjopen-2020-041302](https://doi.org/10.1136/bmjopen-2020-041302). PMID: 33067303. PMCID: PMC7569942.
 - 19 Wackett J, Devaney B, Chau R, Ho J, King N, Grewal J, et al. Reported outcome measures in necrotising soft tissue infections: a systematic review. *Diving Hyperb Med*. 2024;54:47–56. doi: [10.28920/dhm54.1.47-56](https://doi.org/10.28920/dhm54.1.47-56). PMID: 38507909.
 - 20 Hauser CJ, Boffard K, Dutton R, Bernard GR, Croce MA, Holcomb JB, et al. Results of the CONTROL trial: efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic hemorrhage. *J Trauma*. 2010;69:489–500. doi: [10.1097/TA.0b013e3181edf36e](https://doi.org/10.1097/TA.0b013e3181edf36e). PMID: 20838118.
 - 21 CRASH-2 trial collaborators; Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23–32. doi: [10.1016/S0140-6736\(10\)60835-5](https://doi.org/10.1016/S0140-6736(10)60835-5). PMID: 20554319.
 - 22 Mitra B, Bernard S, Gantner D, Burns B, Reade MC, Murray L, et al. Protocol for a multicentre prehospital randomised controlled trial investigating tranexamic acid in severe trauma: the PATCH-Trauma trial. *BMJ Open*. 2021;11(3):e046522. doi: [10.1136/bmjopen-2020-046522](https://doi.org/10.1136/bmjopen-2020-046522). PMID: 33722875. PMCID: PMC7970250.

Conflicts of interest and funding: nil

Submitted: 28 December 2023

Accepted after revision: 28 June 2024

Copyright: This article is the copyright of the authors who grant *Diving and Hyperbaric Medicine* a non-exclusive licence to publish the article in electronic and other forms.