

Prognostic factors and outcomes of extremity necrotising fasciitis in Singapore

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Dear Editor,

Necrotising fasciitis (NF) is a rapidly progressive infection that spreads across the fascial planes, leading to tissue necrosis and severe systemic toxicity.¹ In Singapore, Wong et al. conducted a retrospective study on a cohort of 89 patients in 2004 and found that the misdiagnosis rate was 85%, amputation rate was 23% and mortality rate was 21%.^{2,3} However, since these early studies, there has been a paucity of data on NF in the Singapore context, despite changing antimicrobial resistance patterns and evolving management approaches.^{2,3} To address this gap, a 17-year retrospective cohort study was conducted in the National University Hospital (NUH) in Singapore. The aim was to report an update of the clinical/microbiological profile, adverse outcomes (amputation/mortality) rates and identify predictive factors for adverse outcomes in patients with extremity NF.

A total of 167 patients with surgically confirmed NF of the extremities (upper or/and lower limbs) from January 2005 to December 2021 were reviewed. The diagnosis of NF was confirmed intraoperatively by the presence of friable necrotic fascia and “dishwater fluid”, with further confirmatory histopathology performed when in doubt. Tissue cultures were taken in all patients. All patients received empirical antibiotics (i.e. benzylpenicillin, ceftazidime, clindamycin) based on institutional guidelines followed by culture sensitivity-directed antibiotics. Patient demographic variables, comorbidities, clinical presentation, laboratory and microbiological investigation results were recorded. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was calculated. The primary outcomes were amputation and mortality rates during index hospitalisation. Logistic regression was performed to identify independent predictors of amputation/mortality.

The mean age of patients was 57 years, with majority being male (62.3%) and of Chinese (45.5%) or Malay

(39.5%) ethnicity. Diabetes mellitus (56.9%) was the most common comorbidity. Most NF cases involved the lower limbs only (80.2%, 134/167), while 17.3% (29/167) involved upper limbs only and 2.4% (4/167) involved both upper and lower limbs. Only 74.8% (122/167) of patients in the cohort had LRINEC scores of ≥ 6 . Monomicrobial gram-positive NF (56.9%, 95/167) was the most common, followed by polymicrobial (27.5%, 46/167), monomicrobial gram-negative (10.8%, 18/167) and vibrio (3.6%, 6/167) infections. Moreover, 22.2% of patients in this cohort had infections which were not sensitive to empirical antibiotics.

Amputation and mortality rates of patients were 30.5% (51/167) and 25.1% (42/167), respectively. Accurate initial diagnosis of NF was made in 80 (47%) patients, and 55.8% (92/167) of patients were operated within 24 hours. Multivariate logistic regression showed that advanced age, positive blood cultures, bacterial infections not sensitive to empirical antibiotics and hyperlipidaemia (HLD) were significantly associated with amputation (Table 1). Multivariate logistic regression also showed that advanced age, multifocal involvement and end-stage renal failure (ESRF) were significantly associated with mortality (Table 1). The odds ratio (OR) and 95% confidence interval (CI) for all variables mentioned are detailed in Table 1.

Despite increased awareness and the adoption of the LRINEC score, the amputation and mortality rates of patients with NF remain high at 31% and 25%, respectively.^{2,3} While the numbers still lie within global norms, it is still higher than that reported by previous Singapore studies, highlighting the need for improved management strategies.^{2,4}

Wong et al. recommended surgical treatment within 24 hours, however only 55.8% of the patients underwent surgery within 24 hours. Increasingly surgery within 6 hours is recommended, and delayed surgery is associated with poorer outcomes.⁵ Surgical

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Table 1. Multivariate analysis of risk factors for mortality and amputation.

	Variable	Death/amputation, no. (%)	Survival/salvaged, no. (%)	Multivariate analysis ^a	
				OR (95% CI)	P value
Mortality	Age, years (mean ± SD)	62 ± 11	55 ± 14	1.05 (1.01–1.09)	0.021
	Glucose ≥10 mmol/L	23/70 (32.9)	47/70 (67.1)	2.91 (1.17–7.21)	0.021
	Involvement (multifocal)	8/17 (47.1)	9/17 (52.9)	4.80 (1.49–15.50)	0.027
	ESRF (GFR <15 mL/min/1.73 m ²)	9/18 (50.0)	9/18 (50.0)	4.43 (1.19–16.50)	0.09
Amputation	Age, years (mean ± SD)	62 ± 11	54 ± 14	1.04 (1.01–1.08)	0.012
	Positive blood cultures	23/51 (45.1)	28/51 (54.9)	2.53 (1.11–5.79)	0.028
	Sensitivity ^b	18/37 (48.6)	19/37 (51.4)	0.21 (0.078–0.56)	0.020
	Hyperlipidaemia	29/58 (50.0)	29/58 (50.0)	3.68 (1.57–8.60)	0.030

CI: confidence interval; ESRF: end-stage renal failure; GFR: glomerular filtration rate; OR: odds ratio; SD: standard deviation

^aAnalysis used backwards model selection.

^bBacteria were not sensitive to empirical antibiotics used.

Values are expressed in no. (%) unless indicated otherwise.

exploration is recommended even when the diagnosis is not confirmed. While this may result in negative explorations, the benefit of early surgical intervention outweighs the risks associated with delayed surgery.

This study suggests an evolving microbiological landscape for extremity NF in Singapore, with decreasing polymicrobial and increasing gram-positive monomicrobial NF.

Findings reveal that 22% of bacterial isolates were resistant to NUH's empirical antibiotic regime, and methicillin-resistant *Staphylococcus aureus* (MRSA) was the most common resistant organism isolated. Notably, all cases of MRSA in this study occurred in patients with recent hospital admissions (within 3 months).

The Infectious Disease Society of America recommends broader empirical coverage for NF, including vancomycin or linezolid plus piperacillin-tazobactam, a carbapenem or ceftriaxone and metronidazole.⁶ Given that a lack of sensitivity to empirical antibiotics was a significant predictor of amputation, there may be a need to re-evaluate antimicrobial protocols. It may be beneficial to start high-risk patients such as those with recent hospital admission on empirical antibiotics that cover MRSA and resistant gram-negative bacteria.^{6–9} However, these considerations must be balanced with the goals of antimicrobial stewardship.

Advanced age, bacteraemia, lack of microbial sensitivity to empirical antibiotics and HLD were significantly associated with amputation. Advanced age, hyperglycaemia, ESRF and multifocal NF were associated with mortality.

Reported prognostic factors of NF have been largely heterogenous, and this study aims to provide further

clarity to the prognostic factors of NF specific to the Singapore cohort. The factors identified in this study will help clinicians in Singapore to better identify and promptly escalate care for more vulnerable NF patients (e.g. older/bacteraemia/HLD/ESRF). Of note, the LRINEC scores were not predictive of amputation or mortality after multivariate analysis and should be used with caution as a prognostic tool. Sex and ethnicity were also not found to be independent predictive factors for amputation or death.

In conclusion, extremity NF continues to pose a major clinical challenge in Singapore, with persistently high rates of amputation and mortality. Based on the findings, the following recommendations are proposed: (1) identification, appropriate counselling and treatment of patients with identified risk factors for amputation and mortality; (2) early surgical intervention within 6 hours of diagnosis; (3) broadening empirical antimicrobial coverage to include MRSA-active agents (e.g. vancomycin) and carbapenems for gram-negative organisms in patients with recent healthcare exposure of less than 3 months; (4) early engagement of a multidisciplinary team for comprehensive management.

Ethics statement

This study was approved by the National University of Singapore Institutional Review Board (NUS-IRB-2022-00956).

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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