Clinical Infectious Diseases

BRIEF REPORT

High Mortality of Non-Fournier Necrotizing Fasciitis With Enterobacteriales: Time to Rethink Classification?

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This cohort study describes mortality predictors of necrotizing fasciitis (NF). Higher age, chronic kidney disease, and higher Charlson score increased the mortality rate. Mortality was >3 times higher in monomicrobial gram-negative NF than in type I or type II NF. Highest mortality was found with Enterobacteriales in non-Fournier NF.

Keywords. necrotizing soft tissue infection; Fournier gangrene; microbiology; Enterobacteriaceae; outcome.

Necrotizing fasciitis (NF) is a highly aggressive and life-threatening infection with a reported mortality of 16%–34% [1, 2]. NF has been classified microbiologically as type I (polymicrobial) or type II (monomicrobial streptococcal or *Staphylococcus aureus*) [3]. A further type caused by *Vibrio* species or *Aeromonas* species has been proposed but is not widely used [4]. The nomenclature does not cover all microbiological entities and there is still a lack of consensus among experts [3]. Applying an anatomical distinction, NF developing in the region of the perineum has been named Fournier gangrene [5]. The goal of our study was to describe and classify NF and to determine improved predictors of mortality.

METHODS

We performed a retrospective single-center cohort study including all consecutive patients hospitalized with NF from January 2011 through March 2017 at the University Hospital Basel, an 855-bed tertiary care center. Patients were identified by a hospital-wide database screening for NF-related *International Classification of Diseases, Tenth Revision* codes, full-text search of the hospital electronic database, and written reports of the Division of Infectious Diseases and Hospital Epidemiology. Diagnosis of NF was verified by documentation of consistent clinical and intraoperative findings such as grayish necrotic fascia and/or by histological analysis. Intraoperative specimens were sent immediately for microbiological analysis to the in-house laboratory. All specimens were cultured aerobically and anaerobically. Mainly, matrix-assisted laser desorption/ionization–time of flight mass spectrometry was used for species identification (Microflex, Bruker, Germany). Antibiotic resistance testing was either performed using Etest and/or VITEK2 (both bioMérieux, France). Demographic data, length of hospital stay, comorbidities, results of microbiological and laboratory analysis, and surgical and antibiotic treatment were recorded. Infections were grouped anatomically in Fournier NF occurring in the region of the perineum and non-Fournier NF developing in any other region. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score was calculated [6]. Primary outcome was in-hospital mortality. Type I NF consisting of polymicrobial infections was differentiated from type II NF with monomicrobial infections with *Streptococcus pyogenes*, another *Streptococcus* species, and/or *Staphylococcus aureus*. Categorical variables were analyzed by χ^2 or Fisher exact test as appropriate. Nonnormally distributed continuous variables were analyzed by the Mann-Whitney *U* test. Time-dependent data were plotted by Kaplan-Meier curves, and comparisons were performed using the log-rank test and Cox regression analyses. Two-tailed *P* values < .05 were considered significant. Analyses were performed using Stata version 14.0 software (StataCorp, College Station, Texas).

RESULTS

Sixty-one patients were identified (Table 1). Median age was 66 years (interquartile range [IQR], 51–75 years) with 61% male. Patients were hospitalized for a median of 27 days (IQR, 15–43 days). NF was polymicrobial (type I) in 47% (28/60 patients), monomicrobial with *Streptococcus* species/*S. aureus* (type II) in 38% (23/60), and monomicrobial with gram-negative bacteria in 15% (9/60), most of which were Enterobacteriales (78% [7/9]). Fournier NF was found in 31% (19/61) and non-Fournier NF in 69% (42/61). Type I NF was correlated in 64% (18/28) with Fournier gangrene, whereas non-Fournier NF was predominant in type II (96% [22/23]) and monomicrobial gram-negative infections (100% [9/9]) (*P* < .001). The LRINEC score would have categorized 34% (21/61) as low risk, 21% (13/61) as intermediate, and 44% (27/61) as high risk for NF at initial presentation.

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Table 1. Characteristics of Survivors and Nonsurvivors With Necrotizing Fasciitis

Characteristic	Nonsurvivors (n = 17)		Survivors (n = 44)		*P* Value
Fournier necrotizing fasciitis	2	(11.8)	17	(38.6)	.064
Non-Fournier necrotizing fasciitis	15	(88.2)	27	(61.4)	
Age, y, median (IQR)	72	(67–76)	55	(47–72)	**.004**
Male sex	7	(41.2)	30	(68.2)	.079
Charlson comorbidity score, median (IQR)	4	(3–5)	2	(1–4)	**.011**
Risk factor					
Diabetes mellitus	4	(23.5)	14	(31.8)	.755
Smoking	4	(23.5)	20	(45.5)	.150
Chronic kidney disease	12	(70.6)	9	(20.5)	**.001**
Chronic liver disease	4	(23.5)	8	(18.2)	.723
Obesity (BMI >30 kg/m^2)	6	(35.3)	15	(34.1)	1.000
Immunosuppression	4	(23.5)	13	(29.6)	.757
Neoplasia	6	(35.3)	9	(20.5)	.320
Prior hospitalization (last 6 mo)	6	(35.3)	8	(18.2)	.154
Recent antibiotics (last 6 mo)	4	(23.5)	9	(20.5)	.793
Time from admission to surgery, h, median (IQR)	4.4	(3.4–6.4)	7.6	(3.6–22.1)	.084
Time from admission to antibiotic, h, median (IQR)	1.75	(0–2.6)	1.69	(0.76–3.95)	.692
Amputation (genital/extremity)	2	(11.8)	7	(15.9)	1.000
Tissue culture positive with:					
Streptococcus pyogenes	3	(17.7)	14	(31.8)	.350
Staphylococcus aureus	2	(11.8)	8	(18.2)	.711
Enterobacteriales	11	(64.7)	14	(31.8)	**.024**
Enterococcus spp	3	(17.7)	6	(13.6)	.699
Nonfermenting bacteria	3	(17.7)	2	(4.6)	.127
Anaerobic bacteria	3	(17.7)	19	(43.2)	.079
Blood culture positive with:					
Any species	9	(56.2)	11	(28.2)	.050
Streptococcus pyogenes	2	(12.5)	4	(10.3)	1.000
Enterobacteriales	6	(37.5)	2	(5.1)	**.005**

Data are presented as No. (%) unless otherwise indicated. Values in bold indicate statistical significance ($P < .05$).

Abbreviations: BMI, body mass index; IQR, interquartile range.

Overall mortality was 28% (17/61). Death occurred after a median of 15 days (IQR, 2–18 days) after hospitalization. Higher age, chronic kidney disease, and higher Charlson score were associated with mortality (Table 1). Patients with low LRINEC score (≤5 points) had lower mortality (9.5% [2/21]) than those with the highest LRINEC score (≥8 points; mortality of 37% [10/27]) ($P = .044$). Patients with Fournier NF died in 10.5% of cases (2/19) whereas non-Fournier NF led to death in 35.7% (15/42) ($P = .06$). Empirical antibiotic therapy was effective against the identified pathogens in 93.3% (56/60). Genital or limb amputation was necessary in 14.7% (9/61) but did not change mortality rate (Table 1). Mortality was highest in monomicrobial gram-negative NF (66% [6/9]), followed by type I (21% [6/28]) and type II NF (17% [4/23]) ($P < .001$; Figure 1A). Interestingly, Enterobacteriales were significantly associated with mortality in univariable analysis ($P = .02$; Table 1) and multivariable Cox regression analysis (hazard ratio [HR], 2.82 [95% confidence interval {CI}, 1.02–7.81]; $P = .046$), adjusting for age (HR, 1.00 [95% CI, 1.00–1.00]; $P = .763$) and Charlson score (HR, 1.26 [95% CI, .98–1.62]; $P = .066$). Enterobacteriales led to death in 71% (10/14) if associated with non-Fournier NF but only in 9% (1/11) of patients with Fournier NF ($P = .004$). Concordantly, mortality in patients with non-Fournier NF (n = 42) was much higher if caused by Enterobacteriales (71% [10/14]) compared to other pathogens (18% [5/28]) ($P = .001$; Figure 1B). In the subgroup of non-Fournier NF, patients with Enterobacteriales (33% [14/42]) were older (median, 74 years [IQR, 68–82 years] vs 56 years [IQR, 51–72 years]; $P = .018$), had a higher rate of chronic kidney disease (85.7% [12/14] vs 21.4% [6/28]; $P < .001$), and had a higher Charlson score (median, 4 [IQR, 4–5] vs 1 [IQR, 0–3.5]; $P = .002$). However, Enterobacteriales stayed significantly associated with mortality in non-Fournier NF (HR, 3.90 [95% CI, 1.09–13.96]; $P = .036$) after adjusting for age and Charlson score. Moreover, we found a higher rate of simultaneously positive tissue and blood cultures with Enterobacteriales in non-Fournier (43% [6/14] tissue cultures with Enterobacteriales) than in Fournier NF (9% [1/11]) ($P = .09$).

DISCUSSION

This cohort study reports a relevant proportion of monomicrobial gram-negative NF associated with an increased mortality

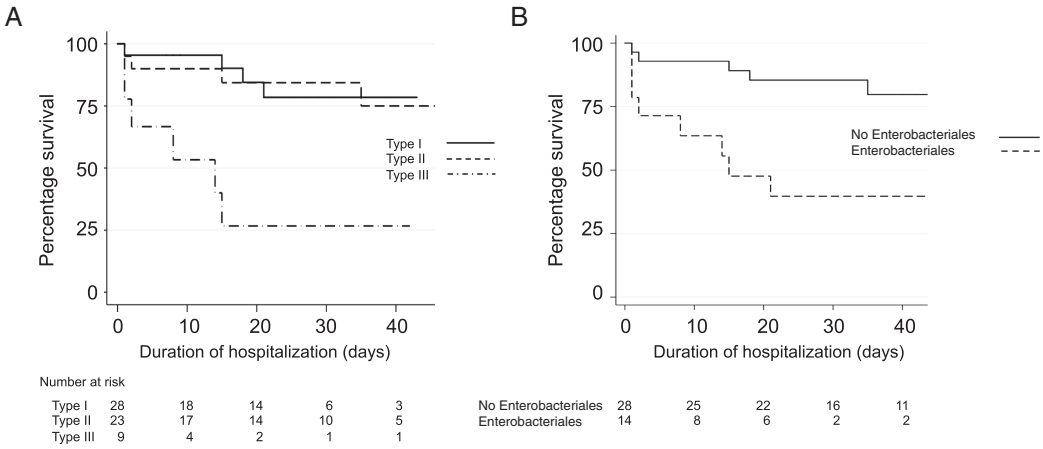

Figure 1. *A,* Kaplan-Meier survival curve according to type of necrotizing fasciitis (NF). Type I: polymicrobial; type II: monomicrobial with *Streptococcus* species and/or *Staphylococcus aureus*; proposed type III (this study): monomicrobial gram-negative bacteria. *B,* Kaplan-Meier survival curve for patients with non-Fournier NF with and without Enterobacteriales.

of 66%, which was markedly higher than the overall mortality of 28%. Enterobacteriales—classically associated with Fournier gangrene—even led to an unexpected high mortality of 71% if occurring in a non-Fournier NF. There may be several reasons for this association. On the one hand, patients developing non-Fournier Enterobacteriales infections were older and had more comorbidities, potentially leading to a higher risk for gram-negative infections and for fatal outcome; however, our finding remained significant after respective adjustment. On the other hand, we may see the result of an increasing rate of highly virulent gram-negative bacteria, which are able to cause infections at the extremities without the need of the postulated synergism with anaerobes. Recent smaller cohort studies have shown similar trends and some have found exceptionally high mortality, in particular with monomicrobial gram-negative infections [7–9]. The rate of multidrug resistance in Enterobacteriales is low at our institution (eg, 11% and 9% for extended-spectrum β-lactamase–producing *Escherichia coli* and *Klebsiella pneumoniae*, respectively), and our standard empirical treatment with a carbapenem for NF covered all retrieved Enterobacteriales. However, resistance rates may be considerably higher in other settings and regions of the world, making our results even more worrisome. We propose to add a new type of NF consisting of monomicrobial gram-negative bacteria, which could be named type III NF. This adapted classification would directly reflect the risk of mortality in our cohort (Figure 1A). However, before introducing it in clinical practice, the validity of this classification would need to be verified in further studies.

Time from hospitalization until surgical debridement was short for all our patients, thus explaining why we did not find an association with mortality in our cohort (Table 1). Early and broad empirical antibiotic treatment was initiated in all patients and covered the detected pathogens in almost all of them. Although earlier case studies have shown a mortality of 20%–40% in Fournier NF, more recent, large population-based cohorts found a marked lower mortality of 7.5%–16%, consistent with our data [5]. The LRINEC score, originally developed to differentiate nonnecrotizing soft tissue infections from necrotizing infection, did not perform well in our retrospective analysis, categorizing more than one-third as low risk for NF at initial presentation. This limited predictive value of the LRINEC score is consistent with the results of a recent meta-analysis [6]. However, patients with a high-risk LRINEC score had a significantly higher mortality than those with a low risk, underscoring its utility as a potential tool for outcome prediction.

Our study has several limitations. Due to its retrospective design, we cannot exclude selection bias and missing single cases of NF. However, due to manifold search strategies including different in-hospital databases and search terms, we believe selection bias to be minimal. Furthermore, we may have missed relevant factors contributing to mortality but not sufficiently documented in the records. As a single-center cohort, our findings may not be transferable to all hospital settings. However, our cohort covers a typical patient population of a tertiary care center including medical and surgical patients.

The strength of our study lies in the rigorous and standardized microbiological procedures including anaerobic culture, the high standard of care, and the wide range of patients.

In conclusion, NF is still associated with high mortality requiring rapid and aggressive surgical and medical treatment. The exceedingly high mortality of monomicrobial gram-negative infections as identified in this cohort may reflect a so far underappreciated type of NF occurring in non-Fournier NF, potentially due to virulent pathogens encountering a more susceptible population. This will be increasingly important in light of the aging Western population with accumulating comorbidities and in awareness of the growing rate of antibiotic resistance

in gram-negative bacteria. We therefore suggest introducing a new type of NF for monomicrobial gram-negative infections.

Notes

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