



Monomicrobial necrotizing fasciitis in a single center: the emergence of Gram-negative bacteria as a common pathogen



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SUMMARY

Background: Necrotizing fasciitis (NF) is a life-threatening soft tissue infection. It is usually caused by *Streptococcus pyogenes* and other Gram-positive bacteria. Several reports, however, emphasize the importance of Gram-negative rods in this infection.

Methods: We retrospectively studied all cases of monomicrobial necrotizing fasciitis hospitalized in our center during the years 2002–2012. We compared clinical characteristics and outcomes of patients with Gram-negative versus Gram-positive infection.

Results: Forty-five cases were reviewed, 19 caused by Gram-negative organisms, 10 of them *Escherichia coli*, and 26 caused by Gram-positive organisms, 10 of them *S. pyogenes*. Compared to Gram-positive infections, patients with Gram-negative infections were more likely to have a baseline malignancy (9/19, 47.4%) or to have undergone recent surgery (4/19, 42.3%). The 30-day mortality was higher among Gram-negative infected patients (8/19, 42.1% vs. 8/26, 30.8%). Creatine phosphokinase (CPK) was elevated in a minority of patients with Gram-negative necrotizing fasciitis, and its absolute value was lower than in Gram-positive necrotizing fasciitis.

Conclusions: In our center, 42% of monomicrobial necrotizing fasciitis cases were found to be caused by Gram-negative organisms, mostly *E. coli*. These infections usually appeared in immunocompromised or postoperative patients, often presented with normal CPK levels, and were associated with high mortality rates.

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1. Introduction

Necrotizing fasciitis (NF) is a life-threatening soft tissue infection.¹ The estimated mortality from necrotizing soft tissue infections is 12–35%,² with lower rates described in more recent series. Approximately 20% of patients require amputations and 30% experience functional limitations after discharge.³ The most important determinants of mortality are timing and adequacy of debridement.⁴

Approximately 80% of NF cases are type I (polymicrobial infections), approximately 15% are type II (monomicrobial

infections, classically caused by *Streptococcus pyogenes*), and <5% are type III (clostridial infections).⁵ The US Centers for Disease Control and Prevention (CDC) report 600–800 cases annually of *Streptococcus pyogenes* NF in the USA.⁶

Monomicrobial NF is usually attributed to Gram-positive organisms. In recent years, however, reports of monomicrobial infection by Gram-negative rods have been increasing. In a recent report from Taiwan, approximately half of monomicrobial NF cases were caused by Gram-negative rods, mostly *Klebsiella pneumoniae*.⁷ Other series have demonstrated *Escherichia coli*, *Klebsiella spp.*, and *Pseudomonas spp.* as causes of monomicrobial NF.^{3,8,9} Additional Gram-negatives reported were *Proteus spp.*, *Acinetobacter spp.*, *Vibrio spp.*, and *Aeromonas spp.* In a retrospective cohort study from the USA, 1% of monomicrobial NF was caused by *Klebsiella spp.* and 6% by *Pseudomonas spp.*¹⁰

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Pathogenic mechanisms suggested for *Klebsiella* NF, other than direct inoculation, are hematogenous spread from other septic foci and bacterial translocation. In addition, once NF is established, *Klebsiella spp* has a propensity to spread and involve other organ systems.^{7,11} Cheng et al. compared monomicrobial *S. pyogenes* NF with *Klebsiella* NF and demonstrated a significantly higher risk for bacteremia, concomitant distant abscesses, and underlying immunosuppression in patients with *Klebsiella* NF.⁷ Data on *E. coli* NF are scarce.¹²

Recently, we reported several cases of *E. coli* monomicrobial NF from our hospital.¹³ The aims of this study were to document the causative pathogens of monomicrobial NF in our hospital for the period 2002 to 2012 and to compare Gram-negative with Gram-positive infections.

2. Methods

The charts of all hospitalized adult patients with a discharge diagnosis of necrotizing fasciitis were reviewed retrospectively for the period January 2002 to December 2012. We found 45 cases of monomicrobial necrotizing fasciitis. The diagnostic criteria for necrotizing fasciitis are summarized in Table 1. Two independent investigators examined the data and determined whether the infection could be classified as necrotizing fasciitis or not. In cases of disagreement, a third investigator was involved in the decision. The study protocol was approved by the local ethics committee.

2.1. Statistical analysis

Dichotomous variables were compared using the Chi-square test. Continuous data were expressed as the mean \pm standard deviation (SD) or median and interquartile range (25th–75th percentiles, IQR), as appropriate, and compared using the *t*-test. Due to the rarity of the infection, the study sample size was small and we did not expect to show statistical significance in the results.

3. Results

Forty-five cases of necrotizing fasciitis were included in the analysis; 19 were caused by Gram-negative pathogens and 26 by Gram-positive pathogens (Table 2). Most patients in the two groups had community-acquired infections and were either immunocompromised (malignancy or immunosuppressive therapy) or diabetic.

Baseline characteristics of the patients in the two groups are presented in Table 3. Four out of 19 (21%) patients in the Gram-negative group had undergone a surgical procedure during the previous 30 days before the infection, compared with 11 out of 26 (42%) patients in the Gram-positive group.

Almost all patients in the Gram-negative group (89.5%) were either immunocompromised or diabetic (or both). Ten patients

Table 2

Pathogens associated with necrotizing fasciitis

Gram stain	Pathogen	Number of patients
Gram-positive	<i>Streptococcus pyogenes</i>	10
	<i>Streptococcus anginosus</i>	1
	Streptococcus group G	2
	Streptococcus group F	1
	Streptococcus viridans	1
	Streptococcus group B	1
	<i>Staphylococcus aureus</i>	7 (MRSA 3; MSSA 4)
	<i>Enterococcus spp</i>	3
	Total	26
	Gram-negative	<i>Pseudomonas aeruginosa</i>
<i>Escherichia coli</i>		10 (ESBL 2)
<i>Enterobacter cloacae</i>		1
<i>Proteus mirabilis</i>		2
<i>Serratia marcescens</i>		1
<i>Acinetobacter baumannii</i>		1
<i>Aeromonas hydrophila</i>		2
Total		19

MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; ESBL, extended-spectrum beta-lactamase.

were diabetic, two received steroids, five had a hematological malignancy, and four had a solid organ malignancy. In the Gram-positive group, 64.5% were either immunocompromised or diabetic (or both). Fifteen patients were diabetic, two had solid organ malignancies, and two had a hematological malignancy.

3.1. Outcomes

The 30-day mortality was 42.1% in the Gram-negative group (8/19 patients) and 30.8% in the Gram-positive group (8/26 patients) ($p = 0.433$). The 90-day mortality was 57.9% in the Gram-negative group (11/19 patients) and 53.8% in the Gram-positive group (14/26) ($p = 0.787$).

Sixty percent (6/10) of patients with *S. pyogenes* infection died within 90 days, as did 60% (6/10) of patients with *E. coli* infection. All deaths among the *E. coli* group occurred during the first 30 days.

Limb amputation was performed within 30 days in 11.5% (3/26) of Gram-positive infections and 5.3% (1/19) of Gram-negative infections ($p = 0.634$). No amputations were performed beyond 30 days.

Nineteen patients in the Gram-negative group were operated on 42 times; 23 patients in the Gram-positive group were operated on 66 times within 90 days. One patient with *Streptococcus viridans* infection had distant abscesses documented by day 30.

There was no significant difference in the duration of hospitalization among Gram-negative (median 28 days, IQR 8–48) and Gram-positive patients (median 23 days, IQR 15–42). Thirteen patients (68%) from the Gram-negative group and 21 (81%) from the Gram-positive group were hospitalized in intensive care units (ICUs) within 30 days of infection. The median duration of ICU stay was 3.0 days (IQR 0.0–11.0) in the Gram-negative group

Table 1

Criteria for diagnosing necrotizing fasciitis

A single pathogen cultured from blood or infected soft tissue (obtained surgically, by skin biopsy or swab from exudate) AND
Evidence of necrotic fascia during an operation and/or characteristic pathologic features (extensive tissue destruction, thrombosis of blood vessels, abundant bacteria spreading along fascial planes, and infiltration of acute inflammatory cells)
OR
Patients not undergoing surgery with the above monomicrobial culture and high clinical suspicion based on clinical findings including high fever, systemic toxicity, soft tissue involvement with severe pain, crepitus, rapid progression of clinical manifestations, elevated serum creatine kinase level, and demonstration of muscle involvement or gas on imaging studies

Table 3

Baseline characteristics of patients by Gram stain group

	Gram-negative	Gram-positive	<i>p</i> -Value
Total, <i>n</i>	19	26	
Male sex, <i>n</i> (%)	9 (47.4)	15 (57.7)	0.493
Age, years, mean \pm SD	59.7 \pm 14.2	58.0 \pm 18.5	0.818
Community-acquired, <i>n</i> (%)	15 (78.9)	20 (76.9)	0.872
Immunosuppression or diabetes mellitus, <i>n</i> (%)	17 (89.5)	17 (65.4)	0.086
Surgical procedure in previous 30 days, <i>n</i> (%)	4 (21.1)	11 (42.3)	0.203

SD, standard deviation.

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