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Exhaustion of the immune system by Group A Streptococcus necrotizing fasciitis: the occurrence of late secondary infections in a retrospective study

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ABSTRACT

Background Necrotizing fasciitis is a potentially lethal condition for which early and adequate treatment with surgical debridement and broad-spectrum intravenous antibiotics are essential for survival. It is hypothesized that Group A Streptococcus (GAS) necrotizing fasciitis causes exhaustion of the immune system, making these patients more susceptible for late secondary infections.

Methods A retrospective study was conducted of all patients with necrotizing fasciitis between 2002 and 2016. Patients with necrotizing fasciitis based on macroscopic findings, positive Gram staining, culture or fresh frozen section of fascia biopsies were included. Patients with necrotizing fasciitis were divided into two groups based on the presence of GAS. Of both groups, clinical course, outcome and occurrence of late secondary infections were analyzed. For the occurrence of secondary infections, pneumonia was chosen as reference for late secondary infections.

Results Eighty-one patients with necrotizing fasciitis were included of which 38 (47%) had GAS necrotizing fasciitis and 43 (53%) had non-GAS necrotizing fasciitis. Patients with GAS necrotizing fasciitis were younger (50 vs. 61 years, p=0.023) and more often classified as ASA I (45% vs. 14%, p=0.002) compared with patients with non-GAS necrotizing fasciitis. In-hospital mortality rate for necrotizing fasciitis was 32%. Patients with comorbidities were more likely to die of necrotizing fasciitis compared with patients without comorbidities (OR 7.41, 95% CI 1.58 to 34.63). Twelve patients (39%) with GAS necrotizing fasciitis developed pneumonia compared with four patients (13%) with non-GAS necrotizing fasciitis (p=0.017; OR 4.42, 95% CI 1.124 to 15.79). Median time from diagnosis to development of pneumonia in patients with GAS necrotizing fasciitis was 10 days (IQR 9).

Conclusion Patients with GAS necrotizing fasciitis have an increased risk to develop late secondary infections during initial treatment for necrotizing fasciitis compared with patients with necrotizing fasciitis without involvement of GAS. This suggests exhaustion of the immune system after severe GAS infection.

Level of evidence III

BACKGROUND

Necrotizing soft tissue infections (NSTI or 'necrotizing fasciitis') are rare, severe and potentially lethal conditions for which early and adequate treatment with surgical debridement and broad-spectrum intravenous antibiotics are essential for survival.[1] Necrotizing fasciitis is associated with significant morbidities such as organ dysfunction and amputations.[2–4] Delay in diagnosis is associated with higher morbidity and mortality, but diagnosis can be challenging, as no early pathognomonic symptoms are known.[5–7] When necrotizing fasciitis is suspected, triple diagnostics—based on peroperative macroscopic findings, Gram staining and analysis of fresh frozen sections—is proposed for fast and early conformation of the diagnosis and thus to reduce treatment delay.[8]

All NSTIs (including necrotizing fasciitis, myonecrosis and necrotizing cellulitis) are commonly classified according to microbiologic findings, dividing it in type I (polymicrobial) and type II (monomicrobial).[4 9] The organism isolated in type II necrotizing fasciitis is frequently Group A Streptococcus (GAS), but other streptococcal species or staphylococcal species can also be found.[4 10] Evident differences in clinical course and outcome between both types have not yet been clearly described in current literature. However, differences in patient demographics have been previously reported, stating that patients with type II necrotizing fasciitis tend to be healthier and younger compared with type I.[11 12]

As a result of its often complicated disease course, necrotizing fasciitis is known to impose a high burden on the surgical and critical care and thus on the patient.[11 13] Specifically, GAS causes an excessive inflammatory response, and might induce a damaged and dysregulated immune system.[11] The fulminant course of GAS necrotizing fasciitis is due to the amplified systematic immune response caused by the release of GAS exotoxins (also known as superantigens), which can lead to toxic shock syndrome.[11] It is hypothesized that the massive release of proinflammatory cytokines causes exhaustion of the patient and the immune system, making these patients more susceptible for secondary infections.[14]

The aim of this study was to assess the occurrence of late secondary infections, with pneumonia as reference, in patients hospitalized for initial treatment of GAS necrotizing fasciitis compared with patients with necrotizing fasciitis without involvement of GAS.

METHODS

A study protocol was not registered nor published. This article was written in adherence to the

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement.[15]

Study design

A retrospective observational multicenter study was performed in the University Medical Center Utrecht (UMCU) and St Antonius Hospital, an academic medical center and a large peripheral teaching hospital in the Netherlands, respectively. The institutional review board of both centers provided a waiver. Patients diagnosed with necrotizing fasciitis from August 2002 until September 2016 in either of these centers were identified. In current literature, NSTI is defined as an infection of any of the layers within the soft tissue compartment with necrotizing changes of which necrotizing fasciitis is the most prominent infection.[7 11] Patients who presented at UMCU were identified using the associated ICD-10 code (International Classification of Diseases) for necrotizing fasciitis. As no official ICD-10 code existed for the diagnosis necrotizing fasciitis in the St Antonius Hospital, patients were searched using the search terms 'NSTI', 'fasciitis necroticans/necrotizing fasciitis', Fournier's gangrene' and 'myonecrosis'. To reduce selection bias, this search was performed in multiple databases: (1) rare disease lists kept by the intensive care department, (2) the consulting system of the microbiology department, and (3) the microbiology laboratory information management system with documented positive fascia biopsies. All cases of necrotizing fasciitis from both centers were identified and data were independently collected by three researchers (FN, ECEW, FH). Patients were included if the diagnosis of necrotizing fasciitis (including Fournier's gangrene and myonecrosis) was confirmed by two out of three modalities: (1) macroscopic findings during surgery, (2) positive findings in the fascia fresh frozen section, and (3) positive Gram staining or tissue cultures confirmed by the medical microbiology department. Macroscopic findings indicative for necrotizing fasciitis were lack of tissue resistance, gray necrotic tissue and non-contracting muscles.[8 16 17] Exclusion criteria were patients with a superficial infection (complex cellulitis or erysipelas) and out-of-hospital death before initial presentation at the hospital. For the occurrence of late secondary infections, pneumonia was chosen as reference infection as a result of its evident clinical presentation. Other infectious complications such as multiple organ dysfunction syndrome and bacteremia usually are already present at admission, although it is the second hit that is of interest in the present study. This simultaneous presentation of these complications with necrotizing fasciitis makes it difficult to distinguish them as a primary infection combined with necrotizing fasciitis or as secondary complication with secondary sepsis after a few days.[18] Furthermore, it is challenging to objectively extract details on these complications and secondary infections such as surgical site infections from patient's charts. This is in contrast to the unambivalent description of pneumonia in radiology and microbiology reports, providing a suitable reference infection for late secondary infections.

Data collection

The number of cases found in both hospitals during the study period determined the sample size. For all identified patients, demographic characteristics (sex, age, American Society of Anesthesiologists (ASA) classification, medical history, date and time of presentation, medical microbiology, pathology and operation reports, length of hospitalization, length of intensive care unit (ICU) stay and mortality) were extracted from the hospitals' electronic medical charts. The variable time between first presentation and surgery was categorized in four time categories (within 12 hours, 12–24 hours, 24–48 hours and during 48 hours). Furthermore, of all patients developing pneumonia, the date of pneumonia diagnosis, the causative agent of the pneumonia and antibiotic treatment received for the necrotizing fasciitis were extracted. The length of follow-up was the length of hospital stay for initial treatment of the necrotizing fasciitis. Patients were divided into two groups based on the isolated organism(s) in the fascia biopsy, resulting in a group in which GAS was isolated, either as single organism or as part of a polymicrobial infection. Patients with negative fascia cultures were excluded from the study. The second group consisted of patients in which other organisms than GAS were isolated.

The primary outcome of this study was the rate of late secondary infections during hospitalization for the initial treatment of necrotizing fasciitis, based on the occurrence of pneumonia, in patients with GAS necrotizing fasciitis compared with necrotizing fasciitis without involvement of GAS. Patients with necrotizing fasciitis with (suspected) pneumonia were identified based on their medical charts and discussed in a consensus meeting between three researchers (FN, ECEW, FH) to determine compliance to the a priori defined definition of pneumonia, which was 'an alteration in treatment plan based on pulmonary complaints suspicious for pneumonia combined with supporting radiology finding and/or positive cultures for micro-organisms.'[19 20] This definition was chosen since these results all can be extracted objectively and retrospectively from patients' charts. To assess if there was an association between necrotizing fasciitis and late secondary infections, patients who died within 5 days after diagnosis were excluded from all analyses involving pneumonia, since these patients did not have a chance to develop a pneumonia as a delayed consequence of the necrotizing fasciitis. For all other analyses, all identified patients were included, regardless of mortality within 5 days. A subgroup analysis was performed to assess the baseline characteristics and clinical outcomes of all patients with pneumonia compared with patients without pneumonia.

A second subgroup analysis was performed to assess the association between the ASA classification and the in-hospital mortality rate in patients with GAS necrotizing fasciitis and necrotizing fasciitis without involvement of GAS.

Statistical analysis

Continuous data were presented as means with SD or medians with IQRs. Categorical data were presented as frequencies with percentages. Missing data were handled using pairwise deletion to reduce information bias. ORs were presented with 95% CIs. Normally distributed data were compared using the independent samples t-test for continuous variables or the χ^2 test for categorical variables. The two-tailed Mann-Whitney U test was used to compare not normally distributed continuous variables. The Fisher's exact test for dichotomous variables or the Fisher-Freeman-Halton test, in case of categorical variables with more than two categories, was used when a cell count of five or less was observed. In none of the analysis was adjusted for confounding due to the small sample size. For all analyses, a two-sided p value <0.05 was considered statistically significant. Data were analyzed using SPSS (IBM. Released 2017. IBM SPSS Statistics for Windows, V.25.0).

RESULTS

Patient characteristics

A total of 84 patients with necrotizing fasciitis were identified. Three patients were excluded based on negative fascia cultures, resulting in 81 eligible patients for inclusion. GAS was isolated from fascia cultures in 38 patients (47%) and 43 patients (53%) had fascia cultures without isolation of GAS. The median age of patients with GAS necrotizing fasciitis was 50 (IQR 29), which was significantly younger compared with

Table 1 Baseline characteristics of patients with necrotizing fasciitis

	Total	GAS necrotizing fasciitis	Non-GAS necrotizing fasciitis	
	n=81 (100%)	n=38 (47%)	n=43 (53%)	P value
Age (median, IQR)	56 (27)	50 (29)	61 (20)	**0.023**
Sex				
Male	55 (68%)	25 (66%)	30 (70%)	0.702
Female	26 (32%)	13 (34%)	13 (30%)	
ASA classification				0.017
I	23 (28%)	17 (45%)	6 (14%)	
II	36 (45%)	13 (34%)	23 (53%)	
III	14 (17%)	6 (16%)	8 (19%)	
IV	8 (10%)	2 (5%)	6 (14%)	
Comorbidities*				
Diabetes mellitus	26 (33%)	8 (21%)	18 (42%)	**0.038**
Cardiovascular disease	15 (19%)	6 (16%)	9 (21%)	0.519
Pulmonary disease	9 (11%)	5 (13%)	4 (10%)	0.729
Medical history*				
Malignancy	15 (19%)	7 (18%)	8 (19%)	0.943
Autoimmune disease	12 (15%)	6 (6%)	6 (6%)	0.851
Surgery within 30 days	17 (21%)	7 (18%)	10 (24%)	0.556
Localization necrotizing fasciitis†				
Abdomen	5 (6%)	2 (5%)	3 (7%)	1
Chest and axilla	9 (12%)	8 (21%)	1 (3%)	**0.013**
Head and neck	4 (5%)	4 (11%)	0 (0%)	0.052
Extremity	37 (48%)	17 (45%)	20 (50%)	0.642
Perineum	23 (29%)	7 (18%)	16 (40%)	**0.037**
Time between first presentation and surgery‡				0.414
<12 hours	42 (60%)	21 (62%)	21 (58%)	
12–24 hours	8 (11%)	5 (15%)	3 (8%)	
24–48 hours	14 (20%)	7 (20%)	7 (20%)	
>48 hours	6 (9%)	1 (3%)	5 (14%)	

Bold font denotes significant p value.
*1 (1%) missing case.
†3 (4%) missing cases.
‡11 (14%) missing cases.
ASA, American Society of Anesthesiologists; GAS, Group A Streptococcus.

patients with non-GAS necrotizing fasciitis (61 years (IQR 20), p=0.023). In both groups, most patients were male (66% and 70%). Patients with GAS necrotizing fasciitis were more often classified as ASA I compared with the non-GAS group (45% vs. 14%, p=0.002). At baseline, patients with GAS necrotizing fasciitis had less frequently diabetes mellitus (21% vs. 43%, p=0.038) and tended to have less cardiovascular diseases or recent surgery in their medical history compared with the non-GAS group. The primary site of infection affected most often the extremities in both the GAS (45%) and non-GAS group (50%). In patients with necrotizing fasciitis of the chest or axilla, GAS was significantly more frequently isolated (21% vs. 3%, p=0.013). GAS was less frequently isolated in necrotizing fasciitis of the perineum (18% vs. 40%, p=0.037). In both groups, most patients underwent surgery within 12 hours after presentation (62% in GAS group vs. 58% in non-GAS group). In the non-GAS necrotizing fasciitis group, surgical treatment tends to be more frequently delayed beyond 24 hours after initial presentation (24% vs. 33%). All baseline characteristics are presented in table 1.

Overall outcome characteristics

On average, all patients required 3 (IQR 4) surgical debridements to treat the necrotizing fasciitis, 15 patients (19%) required amputation and 64 patients (84%) were admitted to the ICU with a median length of stay of 5 (IQR 11) days. Total length of hospital stay was 31 (IQR 35) days. The overall rate of late secondary infections, measured as pneumonia rate during initial hospitalization for treatment of necrotizing fasciitis, was 24% among the entire necrotizing fasciitis population (table 2).

The overall in-hospital mortality of necrotizing fasciitis during the inclusion period of this study was 32% (n=26). Subgroup analysis showed that patients classified as ASA I were less likely to die of necrotizing fasciitis compared with patients classified as ASA II–IV (2% vs. 30%, p=0.004) with an OR of 0.16 (95% CI 0.03 to 0.63) for mortality (table 3).

Impact of GAS on outcome

There were no significant differences between the total number of operations, number of amputations, hospital length of stay or ICU admittance between GAS necrotizing fasciitis and non-GAS

Table 2 Clinical outcomes of patients with (non-) Group A Streptococcus necrotizing fasciitis

	Total	GAS necrotizing fasciitis	Non-GAS necrotizing fasciitis	
	n=81 (100%)	n=38 (47%)	n=43 (53%)	P value
Total number of operations (median, IQR)*	3 (4)	2 (2)	2 (1)	0.756
Amputation	15 (19%)	8 (21%)	7 (16%)	0.581
Hospital length of stay (median, IQR)	31 (35)	31 (33)	32 (47)	0.721
ICU admittance	68 (84%)	35 (92%)	33 (77%)	0.06
ICU length of stay (median days, IQR)†	5 (11)	6 (12)	4 (8)	0.406
Pneumonia‡	16 (25%)	12 (39%)	4 (13%)	**0.017**
Time between diagnosis and pneumonia (median days, IQR)	11 (19)	10 (9)	33 (43)	0.063
Mortality	26 (32%)	7 (18%)	19 (44%)	**0.013**
Died within 5 days after necrotizing fasciitis diagnosis	18 (69%)	7 (100%)	11 (58%)	0.439
Time between diagnosis and death (median days, IQR)	3 (9)	1 (2)	4 (14)	0.055

Bold font denotes significant p value.
*1 (1%) missing case.
†13 (16%) missing cases.
‡All patients who died within 5 days after necrotizing fasciitis diagnosis were excluded from this analysis.
GAS, Group A Streptococcus; ICU, intensive care unit.

necrotizing fasciitis. Patients with GAS necrotizing fasciitis were statistically significantly more likely to develop a pneumonia compared with patients with non-GAS necrotizing fasciitis (39% vs. 13%, p=0.017; OR 4.42, 95% CI 1.24 to 15.79). The in-hospital mortality rate of patients with GAS necrotizing fasciitis was significantly lower compared with patients with non-GAS necrotizing fasciitis (18% vs. 44%, p=0.013) (table 2). No significant association was found in the subgroup analysis assessing ASA classification and mortality in patients with GAS necrotizing fasciitis. A significant association between the presence of underlying comorbidities and in-hospital mortality rate was seen in non-GAS necrotizing fasciitis (0% ASA I vs. 44% ASA II–IV, p=0.027) (table 3). Patients with GAS necrotizing fasciitis received immunoglobulins in 40% of the cases (n=14). Analyses showed no association between administration of immunoglobulins and the outcome variables.

Patients with pneumonia

No significant differences were found in baseline characteristics of patients with necrotizing fasciitis developing pneumonia and those who did not. Patients who developed pneumonia were most often classified as ASA II (56%). Pneumonia was diagnosed at a median of 11 days (IQR 19) after start of treatment for necrotizing fasciitis, which was 10 days (IQR 9) in the GAS group and 33 days (IQR 43) in the non-GAS group. The most commonly isolated organism associated with pneumonia was the *Pseudomonas aeruginosa*, other frequent organisms isolated from sputum cultures were *Candida albicans* and *Klebsiella oxytoca* (table 4). All patients with pneumonia were admitted to the ICU at some point during their treatment for the necrotizing fasciitis (100% vs. 75%, p=0.027). The group with a pneumonia required more frequent amputations (50% vs. 15%, p=0.014) and required more surgical debridements (5 (IQR 4) vs. 3 (IQR 3), p=0.015). Patients who developed pneumonia had a longer length of hospital stay (62 days (IQR 44) vs. 23 days (IQR 22), p<0.001) and ICU stay (24 days (IQR 24) vs. 5 days (IQR 7), p<0.001).

DISCUSSION

This study found that patients with GAS necrotizing fasciitis are more likely to develop pneumonia during hospitalization compared with patients with necrotizing fasciitis without involvement of GAS. Notably, pneumonia became clinically evident 10 days after the necrotizing fasciitis diagnosis in the GAS group, compared with 33 days in patients without involvement of GAS. Furthermore, patients with GAS necrotizing fasciitis were significantly younger and had less comorbidities. The clinical course of GAS necrotizing fasciitis was more prolonged, especially in patients developing a late secondary infection, with more surgical debridements and more frequently an indication for amputation.

Table 3 Association between ASA classification and mortality in patients with (non-) Group A Streptococcus necrotizing fasciitis

	Total			GAS necrotizing fasciitis			Non-GAS necrotizing fasciitis		
	n=81 (100%)			n=38 (47%)			n=43 (53%)		
	Died	Survived		Died	Survived		Died	Survived	
	n=26 (32%)	n=55 (68%)	P value	n=7 (18%)	n=31 (82%)	P value	n=19 (44%)	n=24 (56%)	P value
ASA classification			**0.004**			0.427			**0.027**
I	2 (2%)	21 (26%)		2 (5%)	15 (39%)		0 (0%)	6 (14%)	
II+III+IV	24 (30%)	34 (42%)		5 (13%)	16 (42%)		19 (44%)	18 (42%)	

Bold font denotes significant p value.
ASA, American Society of Anesthesiologists; GAS, Group A Streptococcus.

Table 4 Pathogens associated with development of pneumonia in patients with necrotizing fasciitis

Case No	Days until onset pneumonia (days)	Necrotizing fasciitis-associated microorganism found	Pneumonia-associated isolated organism	Antibiotic treatment given for necrotizing fasciitis
1	2	GAS	Yeast	Benzylpenicillin, clindamycin
2	3	GAS	*Candida albicans*	Benzylpenicillin, clindamycin
3	6	GAS	No cultures, diagnosis based on chest X-ray	Meropenem
4	6	GAS	*Aspergillus fumigatus*	Benzylpenicillin, clindamycin, gentamicin
5	7	GAS	*Enterobacter cloacae*	Benzylpenicillin, clindamycin
6	10	GAS	*Enterobacter cloacae complex, Stenotrophomonas maltophilia*	Benzylpenicillin, clindamycin
76	10	GAS	*Klebsiella oxytoca, Escherichia coli*	Cefuroxime
8	11	GAS	*Candida albicans, Pseudomonas aeruginosa, Klebsiella oxytoca*	Benzylpenicillin, clindamycin
9	14	GAS	*Proteus mirabilis, Candida albicans*	Benzylpenicillin, clindamycin, gentamicin
10	15	GAS, *Escherichia coli*	*Pseudomonas aeruginosa*	Cefuroxime, clindamycin, gentamicin, metronidazole
11	21	GAS	*Pseudomonas aeruginosa, Candida albicans*	Benzylpenicillin, clindamycin, gentamicin
12	26	GAS	*Klebsiella oxytoca, Serratia marcescens, Streptococci*	Benzylpenicillin, clindamycin, gentamicin
13	7	*Streptococcus pneumoniae, Staphylococcus aureus*	*Pseudomonas aeruginosa*	Benzylpenicillin, clindamycin, gentamicin
14	26	GGS, *Staphylococcus aureus*	No cultures, diagnosis based on chest X-ray	Benzylpenicillin, clindamycin, gentamicin
15	40	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	Piperacilline, tazobactam
16	60	*Morganella morganii*	No cultures, diagnosis based on clinical presentation	Meropenem

GAS, Group A Streptococcus; GGS, Group G Streptococcus.

This is, to our knowledge, the first study assessing the clinical course and occurrence of late secondary infections focusing on necrotizing fasciitis with involvement of GAS. Previous studies have assessed the differences between type I and type II necrotizing fasciitis, but no evident differences in clinical course or outcome were reported.[21 22] However, the microbiologic classification is still used since the specific pathophysiologic mechanisms of the disease often depend on the specific properties of the by-products produced by the bacteria involved, resulting in significant differences in patient populations and clinical presentation.[11 23 24] Type I necrotizing fasciitis occurs more frequently in immunocompromised hosts and affects typically the perineum and trunk, whereas patients with type II necrotizing fasciitis tend to have no comorbidities and typically have necrotizing fasciitis of the extremities or trunk.[3 11 12 23 25] All these studies assessed GAS necrotizing fasciitis as part of type II, combined with all other monomicrobial necrotizing fasciitis, which limits the ability to provide firm conclusions about the clinical course of solely GAS necrotizing fasciitis. The exact incidence of GAS as isolated organisms in necrotizing fasciitis is unknown, incidences varying from 9% up to 56% have been reported.[3 21 26–28] This study found a relatively high number (47%) of positive fascia biopsies with GAS. Such high incidences are mainly seen in Europe and the USA.[28]

This study found that patients with GAS necrotizing fasciitis were significantly younger and were more often classified as ASA I, indicating a healthier patient population. These findings are in line with previously conducted studies.[3 11 12] Therefore, it seems contradictory that especially these patients are more susceptible for late secondary infections. The most plausible explanation for this finding can be found in the pathophysiology of GAS infections. GAS produce a broad array of virulence factors, such as the M protein and pyrogenic exotoxins.[23] The M proteins permit tissue adherence, evasion of phagocytosis and bypass of the typical antigen presentation pathway. Pyrogenic exotoxins act as superantigens by binding directly to and activating a large number of T helper cells, resulting in an amplified activation of the inflammatory cascade, including a massive release of proinflammatory cytokines, leading to systemic toxicity and the development of toxic shock syndrome.[11 23 29–31] Furthermore, the produced exotoxins are known to damage neutrophils, prevent phagocytosis and bacterial clearance by fluid secretion, and break down hyaluronic acid in connective tissues facilitating spread along deep tissue planes.[11 23 32] These virulence factors and exotoxins make GAS a highly potent microorganism, which can effectively evade the immune system of even a previously healthy patient.[23 31] The same response is seen in severe trauma patients, in which a reduced responsiveness of polymorphonuclear neutrophils and a state of immune paralysis due to dysregulation of the proinflammatory and anti-inflammatory response is seen. This contributes to an elevated incidence of infectious complications on day 7–14 after trauma.[33 34] This theory could be extrapolated to our cohort in which the GAS infection can be considered equal to severe trauma. Both result in a massive immune response with an amplified proinflammatory response and subsequent dysregulation, resulting in exhaustion of the immune system followed by severe infectious complications by opportunistic microorganisms. Even the timeline for development of late secondary infections due to depletion of the immune system caused by GAS is in line with the theory of the dysregulated immune system seen in polytrauma patients, with pneumonia occurring a median of 10 days after diagnosis of necrotizing fasciitis.[33 34]

A compromised immune system makes patients more susceptible to normally non-virulent bacterial and fungal infections.[35] Patients with necrotizing fasciitis without involvement of GAS developed pneumonia 33 days after diagnosis, making it very unlikely that the pneumonia in this group was a direct consequence of a dysregulated immune system such as seen in GAS necrotizing fasciitis, but more likely the result of illness in patients with multiple comorbidities during a prolonged hospital stay.

Only Faraklas *et al* have previously reported on the occurrence of pneumonia in a necrotizing fasciitis cohort, which occurred in 7% of all patients, thereby presenting a considerably lower incidence than the 25% in our cohort.[13] Faraklas *et al* did not perform subgroup analysis based on microbiology, therefore the influence of GAS on their percentage is unknown, and thus prevents direct comparison to our cohort.

Almost all patients, including patients eventually developing a pneumonia, received benzylpenicillin and clindamycin at presentation, with or without the addition of a single dose of gentamicin, as initial treatment for necrotizing fasciitis. Benzylpenicillin and clindamycin are both effective against Gram-positive organisms.[4 10 16] Both antibiotics thus exert a selective pressure toward Gram-negative colonization and subsequent nosocomial pneumonia with Gram-negative pathogens. In healthy individuals, the immune system is potent enough to clear these Gram-negative bacteria.[36] This appears not to be the case in patients with necrotizing fasciitis developing pneumonia. The dysfunctional immune system caused by GAS results in an inability to clear Gram-negative organisms and fungi effectively with an opportunistic pneumonia as outcome.

In this cohort, the overall in-hospital mortality was 32%, which is in line with previously reported mortality rates of 14% to 33%.[2 13 21 37] Remarkably, the mortality rate of GAS necrotizing fasciitis was significantly lower compared with the group without involvement of GAS, even though patients with GAS necrotizing fasciitis are more at risk for late secondary infections. Two possible theories could explain this unexpected finding. First, patients with GAS necrotizing fasciitis tend to be younger and have less comorbidities making them more vigilant to severe disease, as ASA classification was the most important factor for mortality. This is in line with previous studies in which the presence of GAS did not influence the mortality, but the presence of pre-existent comorbidities did.[21 24 37 38] Patients classified as ASA II or higher are more at risk to developing necrotizing fasciitis and, when they do, have a worse prognosis. Patients with necrotizing fasciitis with comorbidities, especially patients with necrotizing fasciitis without involvement of GAS, were more likely to die compared with patients without comorbidities. The high frequency of comorbidities found in patients with necrotizing fasciitis without involvement of GAS could (partly) explain the relative high mortality rate in this group compared with patients with GAS necrotizing fasciitis.[3 21 26 37] The second theory is that due to the severity of GAS necrotizing fasciitis, it might be that diagnosis was made more promptly and debridement more aggressive. However, this study was unable to provide rigid data supporting this matter.

These results should be interpreted in the right context. The retrospective nature of this study unfortunately resulted in some degree of information bias due to certain missing variables. Not all variables were reported in the level of detail as desired, such as the exact time of presentation and diagnosis. When possible, time was categorized, which resulted in less missing values. Additionally, the relatively high in-hospital mortality rate within 5 days after diagnosis in patients with necrotizing fasciitis without involvement of GAS could have caused selection bias in our risk assessment of the occurrence of pneumonia, since they might have developed a pneumonia if they had lived longer. Furthermore, there was a difference in the selection process between both hospitals, due to the absence of a corresponding ICD code for necrotizing fasciitis at the St Antonius Hospital. This might have resulted in selection bias. However, the elaborated search of different databases and lists at this hospital limited the risk of missing eligible patients for inclusion. Furthermore, we consider the generalizability of this study to be high, as it is predominantly conceptual in nature and with underlying data obtained from an academic and a peripheral hospital and covering a substantial time period.

CONCLUSION

Patients with GAS necrotizing fasciitis have an increased risk to develop late secondary infections compared with patients with necrotizing fasciitis without involvement of GAS. This increased risk is likely due to the fulminant disease course of GAS necrotizing fasciitis with exhaustion of the immune system caused by the virulent factors of GAS, preventing adequate immunologic response against opportunistic bacteria and fungi.

Contributors FH conceived the study. FN, ECEW, and FH searched and collected data. BJMV, JSKR, JW, LPHL, and FH supervised the conduct of the study. DPJS provided additional statistical advice on study design and methodology. FN analyzed the data and drafted the article. All authors contributed substantially to its revision and approved the final article.

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