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Monomicrobial gram-negative necrotizing fasciitis: An uncommon but fatal syndrome

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ABSTRACT

This study aimed to characterize patients with monomicrobial gram-negative necrotizing fasciitis in three university hospitals in Korea. In this study, of the 115 patients with community-acquired necrotizing fasciitis, 67 (58%) had monomicrobial infections: 31 (27%) in the gram-negative group and 36 (31%) in the gram-positive group. The majority of patients in the gram-negative group were infected with *Escherichia coli* followed by *Klebsiella pneumoniae* and *Vibrio vulnificus*. More patients in the gram-negative group showed liver cirrhosis than those in the gram-positive group (39% vs. 14%, $P = 0.02$). In a multivariable logistic regression analysis, liver cirrhosis (adjusted odds ratio [aOR], 13.7; 95% confidence interval [CI], 2.9–67.0), treatment with antibiotics without surgery (aOR, 10.2; 95% CI, 2.1–48.3), and lower level of albumin (aOR 4.9; 95% CI, 1.6–14.9) were associated with 30-day mortality. Our findings suggest that gram-negative necrotizing fasciitis is more often associated with liver cirrhosis and has poorer outcomes than gram-positive necrotizing fasciitis.

1. Introduction

Necrotizing fasciitis (NF) is a serious bacterial skin infection resulting in rapidly fatal infections and disability. Traditionally, NF has been classified into three groups according to microbial etiology: type I infection refers to polymicrobial infections, and type II infection refers to monomicrobial infection caused by predominantly *Streptococcus pyogenes* and/or *Staphylococcus aureus*, followed by other less common microbial etiologies such as *Vibrio vulnificus*, *Aeromonas hydrophila*, and *Enterobacteriaceae* (Giuliano et al., 1977).

Outcomes are very diverse even among the same type of NF due to the heterogeneity of populations from different regions, comorbidity, and specific pathogens (Kao et al., 2011; Park et al., 2009). In the microbiological analysis of NF, about two-thirds of infections were polymicrobial and one-third were monomicrobial, with the great majority of monomicrobial infections caused by streptococcal isolates (Wong et al., 2003). However, there has been increased attention focused on the monomicrobial gram-negative pathogen in NF (Cheng et al., 2012; Liu et al., 2005; Park et al., 2009), especially gram-negative marine bacteria as the most common pathogen found in patients with infections admitted in certain hospitals near the coastal areas in Korea and Taiwan (Park et al., 2009; Tsai et al., 2012). Furthermore, previous studies suggested that NF caused by gram-negative bacteria was more fatal than that caused by gram-positive bacteria (Choi et al., 2012; Tsai et al., 2012).

Therefore, this study aimed to investigate the clinical characteristics of patients with gram-negative and gram-positive monomicrobial NF and identify the factors associated with mortality.

2. Materials and methods

2.1. Study population

This study was conducted in three referral hospitals located in Seoul, Bucheon and Cheonan, Republic of Korea. We reviewed the records of patients with NF who were treated from February 2001 to December 2015. The following are the diagnostic criteria for NF: evidence of necrotic fascia during surgical exploration and/or characteristic pathologic features (extensive tissue destruction, thrombosis of blood vessels, abundant bacteria spreading along fascial planes, and infiltration of

Abbreviations: aOR, adjusted odds ratio; IQR, interquartile range; MGP, monomicrobial gram-positive; MGN, monomicrobial gram-negative; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NF, necrotizing fasciitis; spp., species.

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acute inflammatory cells) or patients not undergoing surgery and high clinical suspicion based on the clinical findings and demonstration of muscle involvement or gas on imaging studies (Yahav et al., 2014). Patients with hospital-acquired infections including surgical site infection or infections after 2 days of hospitalization were excluded. The local institutional review boards approved this study, and the need for written consent was waived in view of the retrospective and observational nature of the study.

2.2. Data collection

The following data were collected: (1) demographic information including age and sex, (2) previous medical history (including diabetes, malignancy, use of immunosuppressants, liver cirrhosis, and alcohol) and clinical characteristics (including site of infection, presence of bullae, and duration of hospitalization), (3) laboratory tests (including white blood cell count, hemoglobin, platelet count, sodium, albumin, creatinine, glucose, and C-reactive protein), (4) treatment (including operation and initial appropriate empirical antibiotic therapy), and (5) outcomes including amputation and 7-, 14-, and 30-day mortality. Initial appropriate empirical therapy was defined as initiation of antibiotics within 24 hours and the use of antibiotic treatments matching the in vitro susceptibility of the pathogen (Fraser et al., 2006). Liver cirrhosis was defined by the presence of cirrhotic changes, such as liver parenchymal coarseness or a nodular surface on liver imaging and/or clinical evidence of portal hypertension (e.g. ascites, gastroesophageal varices, or splenomegaly with a platelet count <100,000/mm^3) (Soresi et al., 2014). We extended the definition of alcoholism to patients who had self-reported drinking more than 500 ml of ethanol per week before the admission date (Hernan et al., 2004). The severity of infection at the time of NF diagnosis was assessed based on the laboratory risk indicator for NF (LRINEC) score (Su et al., 2008) and an Acute Physiologic and Chronic Health Evaluation II (APACHE II) score (Knaus et al., 1985).

2.3. Microbiology

The causative organism refers to the pathogen isolated from blood or sterile specimens obtained in the operation room. Tissue specimens were collected in 50-mL sterile conical tubes (Neurex, Seoul, Korea), and swab specimens were placed in Amies transport medium (Copan Diagnostics Inc., CA, USA). Closed abscesses and body fluids were collected in a sterile syringe, with the air expelled and the needle plugged with a rubber stopper. The specimens were transported directly to the laboratory. We included isolated microorganisms as pathogens when the pathogens were obtained from blood or surgical specimens. Specimen identification and antimicrobial susceptibility patterns were determined using two commonly used commercial systems, MicroScan WalkAway 96 (Beckman Coulter Inc., Brea, CA, USA) or VITEK 2 (bioMerieux, Marcy l'Etoile, France) system. Tests were performed according to the manufacturers' protocol.

2.4. Statistical analysis

All analyses were performed using SPSS (version 21.0; IBM Corp., Armonk, NY, USA). Categorical variables were compared using the χ^2 test or Fisher's exact test, while the appropriate and continuous variables were compared using Student's *t*-test or Mann–Whitney *U* test as appropriate. Survival curves were estimated using the Kaplan–Meier method, while the log-rank test was used to determine the significant differences between groups for the time to event. To identify prognostic factors for mortality, univariate and multivariate analyses were conducted using logistic regression models. The shock variable was excluded from the multivariable analysis because of its causal pathway to mortality (Lustberg, 2008). LRINEC and APACHE II scores were excluded in the multivariable analysis to avoid multicollinearity. Factors with a $P < 0.1$ in the univariate analyses were included in the multivariate logistic regression model. The final model was assessed using backward elimination. Variables with a $P < 0.05$ were considered to be statistically significant.

3. Results

3.1. Study population and microbiological etiology

A total of 135 patients were included. Patients with hospital-acquired infections including surgical site infections or infections after 2 days of hospitalization ($n = 20$) were excluded. Among the 115 patients with community-acquired NF, 67 (58.3%) had monomicrobial infection. There were 19 (16.5%) patients with polymicrobial infection and 29 (25.2%) with culture-negative infection. The polymicrobial organisms are shown in Supplemental Table 1. A total of 36 (31.3%) patients had monomicrobial gram-positive NF (MGP-NF), and 31 (27.0%) had gram-negative NF (MGN-NF). For MGN-NF isolates, the predominant pathogens were as follows: *Escherichia coli*, 32.3% ($n = 10$); *Vibrio* spp. (*V. vulnificus* 5 and *Vibrio parahaemolyticus* 2), 22.6% ($n = 7$); and *Klebsiella pneumoniae*, 16.1% ($n = 5$) (Table 1). Marine bacteria such as *Vibrio* spp. or *Aeromonas* spp. were found only in summer and autumn (July to November) (Supplemental Fig. 1). Two isolates of extended-spectrum β-lactamase producing organisms were found in *E. coli*. The 31 MGN-NF isolates susceptible to antibiotic treatment during the study periods are shown in Supplemental Table 2. Approximately 76% (19/25) of isolates were susceptible to ciprofloxacin, 68% (15/22) to cefotaxime, and 76% (16/21) to piperacillin/tazobactam. All isolates were susceptible to imipenem. For MGN-NP isolates, the following were the predominant pathogens: *S. pyogenes* (27.8%), *S. aureus* (25%), and coagulase-negative staphylococci (19.4%).

3.2. MGN-NF vs. MGP-NF

The MGN-NF group had several distinguishing findings compared to the MGP-NF group (Table 2). Four patients in the MGN-NF group had a history of seafood intake or exposure to the sea, and eight patients were considered alcoholics. However, only one patient in the MGP-NF group was considered alcoholic. Liver cirrhosis as an underlying disease was more common in the MGN-NF group than in the MGP-NF group. Patients with MGN-NF were more likely to have bacteremia (52% vs. 28%, $P = 0.04$) and shock (42% vs. 19%, $P = 0.05$). In contrast, fever

Table 1
Causative organisms of monomicrobial necrotizing fasciitis in 67 patients.

Gram stain	Pathogen	Number of patients
Gram positive ($n = 36$)	*Streptococcus pyogenes*	10
	Staphylococcus aureus	9 (MRSA 4, MSSA 5)
	Coagulase-negative staphylococci	7
	Viridans streptococci[a]	5
	Streptococcus agalactiae	2
	Group F *streptococcus*	2
	Streptococcus dysgalactiae	1
Gram negative ($n = 31$)	*Escherichia coli*	10
	Klebsiella pneumoniae	5
	Vibrio vulnificus	5
	Aeromonas hydrophila	2
	Vibrio parahaemolyticus	2
	Serratia marcescens	2
	Pseudomonas aeruginosa	2
	Prevotella loescheii	1
	Yersinia enterocolitica	1
	Enterobacter spp.	1

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

[a] Viridans streptococci included *Streptococcus constellatus*[2], *Streptococcus mitis/oralis*[1], *Streptococcus sanguinis*[1], and *Streptococcus gordonii*[1].

Table 2
Baseline characteristics of patients with gram-positive and gram-negative monomicrobial and polymicrobial necrotizing fasciitis.

Variable	Gram-negative ($n = 31$)	Gram-positive ($n = 36$)	Polymicrobial ($n = 18$)	P value[a]
Age (median, IQR)	59 (52–68)	53 (46–70)	49 (43–72)	0.18
Male (n, %)	30 (97)	23 (64)	13 (72)	0.03
Underlying disease				
Diabetes	12 (39)	18 (50)	9 (50)	0.35
Malignancy	6 (19)	4 (11)	1 (6)	0.50
Immunosuppressant	1 (3)	2 (6)	0	1.00
Liver cirrhosis	12 (39)	5 (14)	4 (22)	0.02
HBV	5 (16)	3 (8)	2 (11)	0.46
HCV	2 (6)	3 (9)	0	1.00
End-stage renal disease	5 (16)	5 (14)	3 (17)	1.00
Site of infection				
Lower extremity	18 (58)	18 (50)	11 (61)	0.35
Upper extremity	4 (13)	6 (16)	1 (6)	0.74
Trunk	5 (16)	8 (22)	4 (22)	0.53
Head and neck	0	4 (11)	1 (6)	0.12
Perineum	4 (13)	3 (8)	2 (11)	0.40
Presence of bullae	12 (33)	13 (36)	5 (28)	0.85
LRINEC score, median (IQR)	5 (3–8)	6 (3–8)	6 (4–10)	0.41
APACHE II score, median (IQR)	13 (10–17)	8 (5–13)	11 (6–16)	0.001
Bacteremia	16 (52)	10 (28)	5 (28)	0.04
Fever ≥38°C	3 (10)	11 (31)	6 (33)	0.04
Shock	13 (42)	7 (19)	6 (33)	0.05
Laboratory findings				
White blood cell, $10^3/\mu L$	8.1 (3.5–16)	15.3 (9.3–22.2)	18.0 (10.9–22.5)	0.004
Hb, g/dL	11.3 (9.8–12.9)	12.3 (11.0–13.7)	11.0 (8.6–12.7)	0.04
Platelet, $10^3/\mu L$	96 (34–206)	182 (118–301)	161 (99–292)	0.004
Sodium, mmol/L	136 (131–139)	136 (131–140)	135 (126–140)	0.39
Albumin, mg/dL	2.4 (2.0–2.7)	3.3 (2.4–3.9)	2.5 (1.6–3.0)	0.002
Cr, mg/dL	1.6 (1.0–2.3)	1.2 (0.8–1.8)	1.1 (0.6–2.6)	0.07
Glucose, mg/dL	122 (74–171)	169 (116–239)	122 (97–168)	0.02
C-reactive protein, mg/dL	13.4 (8.8–21.2)	24.4 (10.5–32.0)	17.9 (7.6–26.7)	0.02

Abbreviation: HBV, hepatitis B virus; HCV, hepatitis C virus; LRINEC, laboratory indicators for necrotizing fasciitis; APACHE, Acute Physiologic and Chronic Health Evaluation.
[a] P value for the comparison between the gram-negative monomicrobial necrotizing fasciitis group and gram-positive monomicrobial necrotizing fasciitis group.

≥38°C was less common in the MGN-NF group (10% vs. 31%, $P = 0.04$) upon admission. Treatments (surgery and appropriate empirical antibiotic therapy) were not different in both groups. Patients in the MGN-NF group and NGP-NF group underwent surgery for a median of 1 day (interquartile range [IQR], 0–4 days) and 1.5 (IQR 1–3) days ($P = 0.31$), respectively (Table 3).

3.3. Risk factors associated with 30-day mortality

A total of 23 (34.3%) patients died within 30 days, including 15 (48%) patients in the MGN-NF group and eight (22%) patients in the MGP-NF group. Amputation was performed in three patients, that is, one patient (3%) from the MGN-NF group and two patients (6%) from the MGP-NF group. All amputated patients survived without sequelae. In a univariate logistic regression analysis, the odds of dying within 30 days were more than three times greater among patients with MGN-NF than among those with MGP-NF (odds ratio [OR], 3.61; 95% CI, 1.17–11.18), besides liver cirrhosis, lower extremity location, presence of bullae, treatment with antibiotics without surgery, bacteremia, white blood cell count, albumin, and platelet count. The Kaplan–Meier survival analysis at 30 days, showed that there was a significant difference in survival between the MGN-NF group and MGP-NF group ($P = 0.02$) (Fig. 1). In a multivariable logistic regression analysis, liver cirrhosis (adjusted odds ratio [aOR], 13.7; 95% CI, 2.9–67.0), treatment with antibiotics only without surgery (aOR, 10.2; 95% CI, 2.1–48.3), and lower albumin level (aOR 4.9; 95% CI, 1.6–14.9) were significantly associated with 30-day mortality (Table 4).

4. Discussion

We presented the causative organisms with antibiotic susceptibility and the clinical characteristics of patients with NF admitted to three referral hospitals. These hospitals were located in different urban areas in Korea. About two-thirds of patients with NF had a monomicrobial infection. Among 67 patients with monomicrobial NF, 46% (31/67) had MGN-NF. Liver cirrhosis as an underlying disease, bacteremia, higher APACHE II score, and shock were common among patients with MGN-NF than among those with MGP-NF. Moreover, patients with MGN-NF

Table 3
Treatment and outcomes of patients with gram-positive and gram-negative monomicrobial and polymicrobial necrotizing fasciitis.

Variable	Gram negative ($n = 31$)	Gram positive ($n = 36$)	Polymicrobial ($n = 18$)	P value[a]
Operation	23 (74)	31 (86)	14 (78)	0.22
Interval from diagnosis to operation, median (IQR)	1.0 (0–4.0)	1.5 (1.0–3.0)	6 (1–9)	0.31
Amputation	1 (3)	2 (6)	1 (6)	0.65
Appropriate empirical antibiotic therapy	23 (74)	25 (69)	13 (72)	0.63
Hospital days, median (IQR)	20 (3–53)	34 (15–52)	44 (11–72)	0.12
7-day mortality	10 (32)	4 (11)	4 (22)	0.004
14-day mortality	10 (32)	7 (19)	5 (28)	0.07
30-day mortality	15 (48)	8 (22)	5 (28)	0.02

Abbreviation: IQR, interquartile range.
[a] P value for comparison between the gram-negative monomicrobial necrotizing fasciitis group and gram-positive monomicrobial necrotizing fasciitis group.

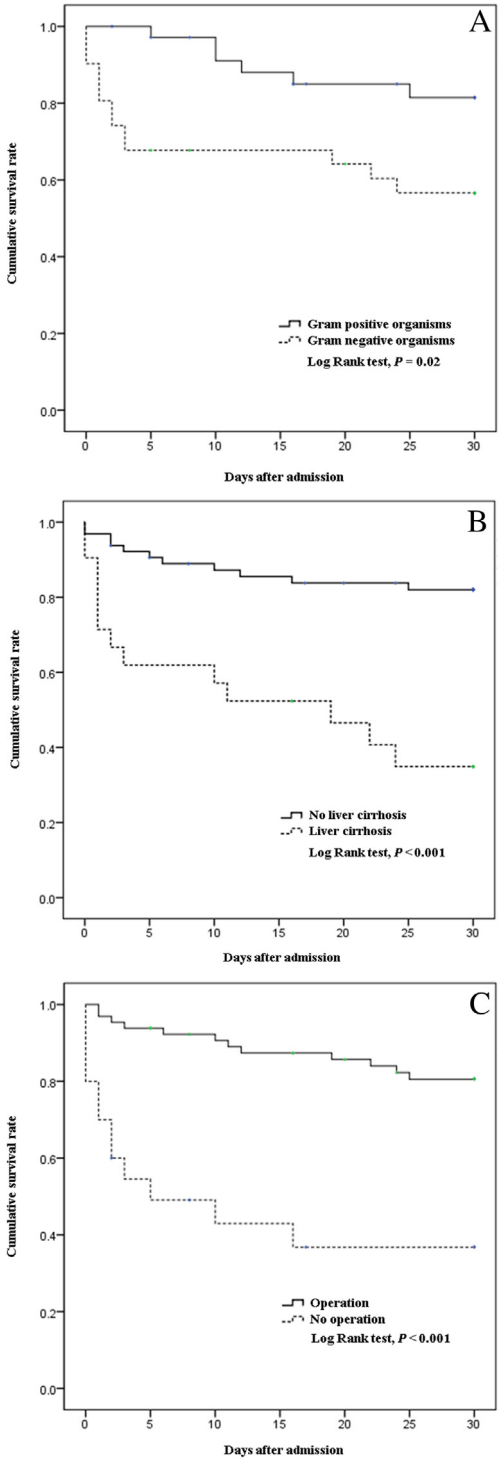

Fig. 1. Thirty-day Kaplan–Meier survival curves of patients with monomicrobial necrotizing fasciitis caused by gram-positive and gram-negative organisms (A), with or without liver cirrhosis (B), and with or without surgery (C).

had lower WBC, platelet count, albumin, glucose, and C-reactive protein levels than those with MGP-NF. Liver cirrhosis, antibiotic treatment without surgery, and lower albumin levels were significantly associated with 30-day mortality.

NF has been known to be a polymicrobial infection caused by normal microbial flora of adjacent organs (Brook and Frazier, 1995). However, previous studies showed that the causative organism of NF is more diverse. Several studies have highlighted that gram-negative organisms are the possible causative pathogens of monomicrobial NF. Geographic

Table 4
Thirty-day mortality for patients with gram-negative monomicrobial necrotizing fasciitis compared with gram-positive monomicrobial necrotizing fasciitis.

Variable	Univariate analysis		Multivariate analysis	
	Unadjusted odds ratio (95% CI)	*P*	Adjusted odds ratio (95% CI)	*P*
Gram-negative organisms	3.61 (1.17–11.18)	0.03	1.14 (0.23–5.61)	0.87
Liver cirrhosis[a]	9.63 (2.76–33.58)	<0.001	13.71 (2.85–66.95)	0.001
Lower extremity	3.04 (0.95–9.78)	0.06		
Presence of bullae	3.00 (0.99–9.01)	0.05		
Treatment with antibiotics only without surgery	6.26 (1.71–22.94)	0.006	10.16 (2.14–48.29)	0.004
Bacteremia	3.03 (1.01–9.05)	0.04		
Diabetes	1.06 (0.40–2.83)	0.90		
White blood cell count	3.23 (1.00–10.41)	0.05		
Albumin	4.46 (1.90–10.53)	0.001	4.93 (1.62–14.93)	0.005
Platelet	1.00 (1.00–1.00)	0.003		
Sodium	1.00 (0.97–1.03)	0.94		

Abbreviation: CI, confidence interval.
[a] The total number of patients with liver cirrhosis with gram-negative or gram-positive monomicrobial infection was 17 (25.4% [17/67]). The 30-day mortality rate for liver cirrhosis was 64.7% (11/17) and that of patients without liver cirrhosis was 16% (8/50).

location can be helpful in predicting the causative organism of NF. In coastal areas, gram-negative marine bacteria were the most common organisms found in patients with NF with seasonal predominance (Park et al., 2009; Tsai et al., 2012). Not only the location but also the underlying disease should be considered in the selection of empirical antibiotics and prediction of outcomes. Monomicrobial gram-negative infection is common in patients with an underlying disease such as hematologic malignancy or hepatic dysfunction (Foo et al., 2015; Park et al., 2009).

We found that liver cirrhosis along with antibiotic treatment without surgery and lower albumin levels was a prognostic factor that contributed to the 30-day mortality. In addition, patients with MGN-NF presented more fatal infections according to the results of the Kaplan–Meier analysis. Specific groups of populations had a high risk of acquiring gram-negative bacterial infection. It was different according to each study (diabetics, immunocompromised, or hepatic dysfunction) (Cheng et al., 2015; Choi et al., 2012; Foo et al., 2015; Liu et al., 2005;Park et al., 2009; Tsai et al., 2012). Considering the scarcity of NF, previous studies showed that patients with NF caused by gram-negative bacteria have the tendency to experience a more fatal clinical course (Park et al., 2009; Tsai et al., 2012). In a retrospective multicenter study of 103 patients with NF, gram-negative infections were associated with in-hospital mortality with an adjusted odds ratio of 437 along with the presence of solid tumor, shock, and bacteremia (Choi et al., 2012). This study reported that the most common underlying diseases were diabetes and liver cirrhosis. Patients with liver cirrhosis have about 11 times the odds of death within 30 days than those without liver cirrhosis after adjusting for other variables. Patients with liver cirrhosis underwent surgery at a similar rate to those without liver cirrhosis (76.2% [16/21]). However, the median time from admission to surgery was significantly longer than that in patients without liver cirrhosis (median 4 days vs. 1 day, $P = 0.04$). Delay in the decision to perform surgery can adversely affect the prognosis in patients with liver cirrhosis.

Previous studies showed that skin and soft tissue infection in liver cirrhosis are mostly caused by gram-negative organisms with a 4–24% mortality rate. Even for cellulitis, patients with liver cirrhosis have poorer outcome (Pereira et al., 2012; Sanglodkar et al., 2018). In this study, a total of 21 (24.7%, 21/85) patients had liver cirrhosis as an underlying disease. The higher mortality rate observed in the study (39%) compared with previous studies could be due to the confined study population comprising patients with radiologically or operatively confirmed NF. The LRINEC score can be used in distinguishing severe cellulitis/abscess vs. NF using C-reactive protein, white blood cell

count, hemoglobin, sodium, creatinine, and glucose. However, in our study, MGN-NF showed lower levels of sodium, glucose, and white blood cell count. Considering these results, we suggest that a clinician should be cautious in differentiating NF from cellulitis/abscess even in those patients with low LRINEC score who have an underlying disease such as liver cirrhosis caused by gram-negative organisms.

It is important to know the local susceptibility data for the selection of empirical antibiotic treatment. During the study periods (2001 to 2015), 76% of the MGN-NF isolates were susceptible to ciprofloxacin, while 68% were susceptible to third-generation cephalosporins. From 2009 to 2015, their susceptibility rates to ciprofloxacin and third-generation cephalosporins were 73% and 75%, respectively. However, their susceptibility rate to aminoglycoside was above 90% (amikacin 93% and gentamicin 91%). Considering the severity of NF, aminoglycoside combination regimen may be one of the remaining effective strategies during the initial empirical antibiotic treatment. There were only seven patients with *S. aureus* infection, four of whom had methicillin-resistance. Although community-acquired methicillin-resistant *S. aureus* infection in the Republic of Korea has a negligible incidence, with a substantial limitation of the number of *S. aureus* NF cases itself, infection with methicillin-resistant *S. aureus* should still be considered.

Our study has the following strengths. This study described the detailed characteristics (including susceptibility and severity) of patients with MGN-NF using a large sample size ($n = 115$) in a multicenter study, with a 15-year follow-up. However, only four anaerobe isolates were found in the present study. Anaerobic-specific transfer media were not used after the acquisition of surgical specimens. Therefore, a polymicrobial infection could be misclassified as monomicrobial infection. In our study, MGN-NF had different characteristics and outcomes compared with MGP-NF. Furthermore, when compared with polymicrobial infection, the clinical features and outcomes of MGN-NF were different from those of polymicrobial-NF (Supplemental Tables 3 and 4). Based on those findings, we conclude that MGN-NF has distinct clinical characteristics with higher severity and poor outcomes even though preexisting anaerobes were not found in real-world practice.

Our data suggest that gram-negative organisms should be considered as a major pathogen of NF, especially in patients with liver cirrhosis. Patients with MGN-NF have an increased risk of developing bacteremia with higher disease severity. Patients with gram-negative NF seem to have poor prognosis. Patients with liver cirrhosis as an underlying disease have poorer outcomes.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diagmicrobio.2018.12.013.

Declarations of interest

None.

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