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Clinical Differences in Patients Infected with *Fusobacterium* and Antimicrobial Susceptibility of *Fusobacterium* Isolates Recovered at a Tertiary-Care Hospital in Korea

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Background: *Fusobacterium* species are obligately anaerobic, gram-negative bacilli. Especially, *F. nucleatum* and *F. necrophorum* are highly relevant human pathogens. We investigated clinical differences in patients infected with *Fusobacterium* spp. and determined the antimicrobial susceptibility of *Fusobacterium* isolates.

Methods: We collected clinical data of 86 patients from whom *Fusobacterium* spp. were isolated from clinical specimens at a tertiary-care hospital in Korea between 2003 and 2020. In total, 76 non-duplicated *Fusobacterium* isolates were selected for antimicrobial susceptibility testing by the agar dilution method, according to the Clinical and Laboratory Standards Institute guidelines (M11-A9).

Results: *F. nucleatum* was most frequently isolated from blood cultures and was associated with hematologic malignancy, whereas *F. necrophorum* was mostly prevalent in head and neck infections. Anti-anaerobic agents were more commonly used to treat *F. nucleatum* and *F. varium* infections than to treat *F. necrophorum* infections. We observed no significant difference in mortality between patients infected with these species. All *F. nucleatum* and *F. necrophorum* isolates were susceptible to the antimicrobial agents tested. *F. varium* was resistant to clindamycin (48%) and moxifloxacin (24%), and *F. mortiferum* was resistant to penicillin G (22%) and ceftriaxone (67%). β-Lactamase activity was not detected.

Conclusions: Despite the clinical differences among patients with clinically important *Fusobacterium* infections, there was no significant difference in the mortality rates. Some *Fusobacterium* spp. were resistant to penicillin G, ceftriaxone, clindamycin, or moxifloxacin. This study may provide clinically relevant data for implementing empirical treatment against *Fusobacterium* infections.

Key Words: *Fusobacterium nucleatum*, *Fusobacterium necrophorum*, *Fusobacterium* species, Clinical difference, Antimicrobial susceptibility, Korea

INTRODUCTION

Fusobacteria are obligately anaerobic, non-spore forming, gram-negative bacilli that inhabit the oral, gastrointestinal, and vaginal mucosa as part of the normal microbiota [1]. The genus *Fusobacterium* currently includes 20 species and subspecies iso-

lated from both human and animal sources [2]. Fusobacteria are increasingly recognized as emerging pathogens that cause multiple diseases in humans. *F. necrophorum* is mostly implicated in the pathogenesis of peritonsillar abscesses, adult sinusitis, and Lemierre's syndrome, whereas *F. nucleatum* is mainly associated with periodontal disease, obstetric complications, bacteremia during prolonged neutropenia, and colorectal cancer (CRC) [3-10]. *F. varium* frequently resides in the human gut and may cause acute colitis [11].

The Clinical and Laboratory Standards Institute (CLSI) suggests that antimicrobial susceptibility testing (AST) of *Fusobacterium* spp. should be considered when highly virulent strains are found and when the susceptibility of an isolate to commonly used antimicrobial agents cannot be predicted [12]. Carbapenems, β-lactam/β-lactamase inhibitor combinations, metronidazole, clindamycin, and moxifloxacin are used in clinical practice for infections caused by *Fusobacterium* spp. [13]. Increasing resistance of *Fusobacterium* spp. to several anti-anaerobic agents has been recently reported [14-16]. However, AST data for *Fusobacterium* spp. are rather limited worldwide [17-19].

We investigated the clinical differences, including mortality and associated malignancies, among patients with clinically important *Fusobacterium* infections and determined the antimicrobial susceptibility patterns of *Fusobacterium* isolates recovered from patients at a tertiary-care hospital in Korea.

MATERIALS AND METHODS

Patient and clinical data

Fusobacterium spp. were isolated from clinical specimens, including blood, sterile body fluids, abscesses, and aspirates, obtained from 86 patients at Severance hospital, Seoul, Korea between 2003 and 2020. Clinical data, including sex, age, Charlson comorbidity index (CCI) score, white blood cell count, C-reactive protein, type of specimen, current cancer diagnosis, antimicrobials prescribed during admission, performed surgeries, date of discharge, and mortality, were retrospectively obtained from electronic medical records and laboratory information system database. The Institutional Review Board (IRB) of Severance Hospital, Yonsei University, Korea, approved this study (approval number: 2020-3978-001) and waived the need for informed consent from patients. All methods were performed following the guidelines and regulations of the IRB.

Fusobacterium spp. cultures

Clinical specimens were routinely cultured under anaerobic conditions at 35°C on phenylethyl-blood agar (Becton Dickinson, Sparks, MD, USA) or Brucella agar (Asan, Hwaseong, Korea). *Fusobacterium* spp. were initially identified by conventional methods and using a commercial rapid identification kit (ATB 32A or VITEK ANI; bioMérieux, Marcy l'Étoile, France). Between 2006 and 2009, species were identified using the VITEK II system (bioMérieux). After 2009, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (Bruker Biotyper, Bruker, Germany; Vitek MS, bioMérieux) or 16S rRNA sequence analysis was used. The collected isolates were stored at –80°C in skimmed milk (Difco, Detroit, MI, USA) until analyses. The isolates were finally re-identified at the species level using the Bruker Biotyper, and/or 16S rRNA sequence and *rpoB* gene analysis.

Antimicrobial susceptibility testing

In total, 76 *Fusobacterium* isolates were selected from the collected isolates (two *F. nucleatum* and three *F. necrophorum* isolates were excluded as they failed to survive, and the number of *F. varium* isolates was reduced to match). All isolates were subcultured on Brucella agar prior to AST using the agar dilution method according to the CLSI guidelines [20]. The Brucella agar was supplemented with 5 μg/mL hemin, 1 μg/mL vitamin K_1, and 5% laked sheep blood. The following antimicrobials were tested: penicillin G (Sigma Aldrich, Yongin, Korea), piperacillin and tazobactam (Yuhan Corp., Seoul, Korea), cefoxitin (Merck Sharp & Dohme, West Point, PA, USA), cefotetan (Daiichi Pharmaceutical, Tokyo, Japan), ceftriaxone (Hanmi Pharmaceutical, Seoul, Korea), clindamycin (Pfizer Korea Upjohn, Seoul, Korea), imipenem and metronidazole (JW Pharmaceutical, Seoul, Korea), moxifloxacin (Bayer Korea, Seoul, Korea), and chloramphenicol (CKD Pharmaceuticals, Seoul, Korea). For the piperacillin and tazobactam combination, a fixed concentration of tazobactam (4 μg/mL) was added to twofold serial dilutions of piperacillin-containing media. Cultures containing 10^5 colony-forming units were inoculated onto agar plates using a Steers replicator (Craft Machine Inc., Woodline, PA, USA) and were incubated in an anaerobic chamber (Bactron 600; Sheldon Manufacturing, Cornelius, OR, USA) at 35°C for 48 hours. The minimum inhibitory concentration (MIC) for each antibiotic was defined as the lowest concentration at which a marked reduction in bacterial growth was observed, in the form of a haze, a few tiny colonies, or a few normal-sized colonies instead of confluent growth and was interpreted using the CLSI breakpoints for anaerobic bacteria [12]. *Bacteroides fragilis* ATCC 25285, *Bacteroides thetaiotaomicron* ATCC 29741, and *Clostridioides difficile*

ATCC 700057 were used as controls. β-Lactamase activity was tested using Cefinase disks (Becton Dickinson, Cockeysville, MD, USA), according to the manufacturer's instructions.

Statistical analysis

Differences among patients infected with *F. nucleatum* vs. *F. necrophorum* vs. *F. varium* were analyzed using a chi-square test or ANOVA, as appropriate. All statistical analyses were performed using GraphPad Prism version 5.0 (GraphPad Software, La Jolla, CA, USA). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline demography and clinical characteristics

The baseline characteristics of the patients with *Fusobacterium* infections are presented in Table 1. The median age of the patients with *F. nucleatum*, *F. necrophorum*, and *F. varium* infections was 59, 27, and 59 years, respectively, and the majority were males (68%, 75%, and 84%, respectively). *F. nucleatum* was mainly isolated from blood (58%), whereas *F. necrophorum* and *F. varium* were mainly isolated from aspirate specimens of the head and neck (75%) and peritoneal fluid (88%), respectively. Malignancy was the most common comorbidity in all patients (42/86, 49%), but differed significantly among patients with *F. nucleatum* vs. *F. necrophorum* vs. *F. varium* infections (53% vs. 13% vs. 67%; $P < 0.001$). Two or more comorbidities were present in 13 patients with *F. nucleatum* infection, two patients with *F. necrophorum* infection, and 38 patients with *F. varium* infection (68% vs. 13% vs. 88%; $P < 0.001$). Hematologic malignancy and hepatobiliary cancer were common in patients with *F. nucleatum* infection (16% each), whereas CRC was common in patients with *F. varium* infection (51%). Anti-anaerobic agents were more commonly used for the treatment of *F. nucleatum* and *F. varium* infections than for *F. necrophorum* infections (63% and 95% vs. 29%, respectively). We found no significant differences in 7-day, 30-day, and 12-month mortality rates among the patients infected with the different *Fusobacterium* species.

Antimicrobial susceptibility of *Fusobacterium* isolates

The MICs of the antimicrobial agents and the antimicrobial susceptibility of the *Fusobacterium* isolates to the 10 antimicrobials tested are shown in Table 2. All *F. nucleatum* and *F. necrophorum* isolates were susceptible to all antimicrobial agents tested, whereas *F. varium* and *F. mortiferum* isolates showed variable

resistance to penicillin G, ceftriaxone, clindamycin, and moxifloxacin. The resistance rates of *F. varium* isolates to clindamycin and moxifloxacin were 48% and 24%, respectively. The resistance rates of *F. mortiferum* isolates to penicillin G, ceftriaxone, and moxifloxacin were 22%, 67%, and 11%, respectively. One of the two *F. periodonticum* isolates was resistant to moxifloxacin (MIC=16 μg/mL). All isolates were susceptible to metronidazole, piperacillin-tazobactam, cefoxitin, imipenem, and chloramphenicol. β-Lactamase activity was not detected among the isolates that were non-susceptible to β-lactam agents.

DISCUSSION

The patient age distribution differed significantly according to the *Fusobacterium* species. Patients infected with *F. necrophorum* were generally younger (median age, 27 years) than those infected with *F. nucleatum* and *F. varium* (median age, 59 years each; $P < 0.001$). Patients were predominantly male (N=67, 78%). These findings are similar to those in previous reports [23, 24]. The majority of *Fusobacterium* bacteremia cases were caused by *F. nucleatum* (61%), with *F. necrophorum* accounting for 25% of cases [25]. *F. necrophorum* has been identified as a primary cause of head and neck infections [3]. These infection patterns were similar to those in our study.

The presence of diabetes mellitus, coronary artery disease, malignancy, and metastasis in patients with comorbidities differed significantly among the *Fusobacterium* species. Several studies have reported an association between *F. nucleatum* bacteremia and hematologic malignancies [26, 27]. We also observed hematologic malignancies in three out of 11 patients with *F. nucleatum* bacteremia. A significant association between *F. nucleatum* bacteremia and subsequent diagnosis of CRC has also been reported [28]. However, we did not observe CRC in patients with *F. nucleatum* bacteremia. We are currently investigating whether the presence of *F. nucleatum* is a cause or a consequence of CRC. However, 51% (22/43) of the patients with *F. varium* infection were diagnosed with CRC. Postoperative infection by *F. varium* may have resulted in the isolation of this species from peritoneal fluid after gastrointestinal surgery, implying that most of these infections would have been independent of CRC.

The treatment of anaerobic infections is complicated by the slow growth of the organisms, their polymicrobial nature, and their growing resistance to antimicrobial agents [14]. Penicillin and amoxicillin are generally appropriate for the treatment of non-β-lactamase-producing fusobacterial infections. Clindamy-

Table 1. Clinical characteristics of patients with *F. nucleatum*, *F necrophorum*, or *F. varium* infections

	F. nucleatum (N=19)	*F. necrophorum* (N=24)	*F. varium* (N=43)	P
Sex				0.376
Male	13 (68)	18 (75)	36 (84)	
Female	6 (32)	6 (25)	7 (16)	
Age in years	59 (35–76)	27 (19–66)	59 (40–73)	<0.001
WBC count, ×10^9/L	7.53 (0.48–13.15)	14.66 (7.60–19.39)	9.93 (5.27–16.14)	<0.001
Clinical specimen type				<0.001
Blood	11 (58)	3 (13)	1 (2)	
Aspirate from head and neck	4 (21)	18 (75)	0 (0)	
Peritoneal fluid	2 (11)	2 (8)	38 (88)	
Others*	2 (11)	1 (4)	4 (9)	
Comorbidity				
DM	4 (21)	1 (4)	6 (14)	0.004
Renal failure	2 (11)	0 (0)	9 (21)	0.077
Heart failure	1 (5)	0 (0)	1 (2)	0.257
Coronary artery disease (myocardial infarction)	0 (0)	0 (0)	5 (12)	0.002
Cerebrovascular disease	0 (0)	0 (0)	1 (2)	0.564
Chronic pulmonary disease	0 (0)	0 (0)	2 (5)	0.102
Malignancy	10 (53)	3 (13)	29 (67)	<0.001
Metastasis	2 (11)	1 (4)	6 (14)	0.066
CCI 0/1/≥2	4/2/13 (21/11/68)	19/2/3 (79/8/13)	4/1/38 (9/2/88)	<0.001
CRP, mg/L	69.45 (10.21–252.88)	51.59 (3.97–145.87)	94.9 (20.5–204.62)	0.096
Current cancer diagnosis	10 (53)	3 (13)	29 (67)	<0.001
Hematologic malignancy	3 (16)	0 (0)	0 (0)	
Stomach cancer	1 (5)	2 (9)	3 (7)	
Colorectal cancer	1 (5)	1 (4)	22 (51)	
Hepatobiliary cancer	3 (16)	0 (0)	3 (7)	
Other cancer type[†]	2 (11)	0 (0)	1 (2)	
Surgery	7 (37)	5 (21)	38 (88)	<0.001
GI tract surgery	3 (16)	2 (8)	32 (74)	
Head and neck surgery	2 (11)	3 (13)	0 (0)	
Other type of surgery	2 (11)	0 (0)	6 (14)	
Antimicrobials prescribed	15 (79)	22 (92)	42 (98)	0.045
Anti-anaerobic agents used	12 (63)	7 (29)	41 (95)	<0.001
Days in hospital	16.5 (7–46)	4 (2–14)	28 (9–74)	<0.001
Mortality				
Seven days	1 (5)	1 (4)	0 (0)	0.739
30 days	2 (11)	1 (4)	3 (7)	0.186
12 months	3 (16)	2 (8)	6 (14)	0.255

Data are presented as number (%) or median (10–90%-tile).
F. nucleatum isolated from head aspirate and pleural fluid (N=1, each); *F. necrophorum* isolated from a deep foot wound; *F. varium* isolated from buttock aspirate, perianal abscess, pleural fluid, and foot tissue (N=1, each). [†]*F. nucleatum*, ovarian cancer and oral cavity cancer; *F. varium*, prostate cancer.
Abbreviations: CCI, Charlson comorbidity index; CRP, C-reactive protein; DM, diabetes mellitus; GI, gastrointestinal; WBC, white blood cell.

Table 2. Antimicrobial susceptibility of the 76 *Fusobacterium* isolates tested in this study

Organism and antimicrobial agent	MIC (µg/mL)			Susceptibility (%)		
	Range	50%	90%	S	I	R
Fusobacterium nucleatum (N=17)						
Penicillin G	≤0.12–0.25	≤0.12	0.25	100	0	0
Piperacillin-tazobactam	≤0.12	≤0.12	≤0.12	100	0	0
Cefoxitin	≤0.12–1	0.25	1	100	0	0
Cefotetan	≤0.12–0.25	≤0.12	0.25	100	0	0
Ceftriaxone	≤0.12–0.5	≤0.12	0.5	100	0	0
Imipenem	≤0.12	≤0.12	≤0.12	100	0	0
Clindamycin	≤0.12	≤0.12	≤0.12	100	0	0
Moxifloxacin	≤0.12–0.25	≤0.12	0.25	100	0	0
Chloramphenicol	0.5–1	1	1	100	0	0
Metronidazole	≤0.12–0.5	≤0.12	0.5	100	0	0
Fusobacterium necrophorum (N=21)						
Penicillin G	≤0.12	≤0.12	≤0.12	100	0	0
Piperacillin-tazobactam	≤0.12–0.25	≤0.12	≤0.12	100	0	0
Cefoxitin	≤0.12–1	≤0.12	1	100	0	0
Cefotetan	≤0.12–2	≤0.12	2	100	0	0
Ceftriaxone	≤0.12–0.5	≤0.12	0.25	100	0	0
Imipenem	≤0.12–1	≤0.12	≤0.12	100	0	0
Clindamycin	≤0.12	≤0.12	≤0.12	100	0	0
Moxifloxacin	0.5–2	1	2	100	0	0
Chloramphenicol	0.25–2	1	2	100	0	0
Metronidazole	≤0.12–1	≤0.12	0.5	100	0	0
Fusobacterium varium (N=25)						
Penicillin G	≤0.12–1	0.25	0.5	96	4	0
Piperacillin-tazobactam	1–16	4	8	100	0	0
Cefoxitin	2–16	4	16	100	0	0
Cefotetan	≤0.12–64	2	16	92	0	8
Ceftriaxone	1–>128	4	8	96	0	4
Imipenem	0.5–2	1	2	100	0	0
Clindamycin	1–>128	4	32	36	16	48
Moxifloxacin	2–32	4	16	24	52	24
Chloramphenicol	2–4	4	4	100	0	0
Metronidazole	≤0.12–1	0.5	0.5	100	0	0
Fusobacterium mortiferum (N=9)*						
Penicillin G	≤0.12–2	1	2	44	33	22
Piperacillin-tazobactam	0.25–8	2	8	100	0	0
Cefoxitin	2–8	4	4	100	0	0
Cefotetan	1–4	2	4	100	0	0
Ceftriaxone	8–>128	64	128	11	22	67
Imipenem	0.5–1	1	1	100	0	0
Clindamycin	≤0.12–0.5	≤0.12	0.5	100	0	0
Moxifloxacin	0.5–2	0.5	0.5	89	0	11
Chloramphenicol	0.5–1	0.5	1	100	0	0
Metronidazole	0.25–1	0.25	0.5	100	0	0

(*Continued to the next page*)

Table 2. Continued

Organism and antimicrobial agent	MIC (µg/mL)			Susceptibility (%)		
	Range	50%	90%	S	I	R
Fusobacterium spp. (N=4)[†]						
Penicillin G	≤0.12	≤0.12	≤0.12	100	0	0
Piperacillin-tazobactam	≤0.12–1	≤0.12	1	100	0	0
Cefoxitin	≤0.12–0.5	≤0.12	0.5	100	0	0
Cefotetan	≤0.12–0.25	≤0.12	0.25	100	0	0
Ceftriaxone	≤0.12	≤0.12	≤0.12	100	0	0
Imipenem	≤0.12	≤0.12	≤0.12	100	0	0
Clindamycin	≤0.12–1	≤0.12	1	100	0	0
Moxifloxacin	≤0.12–16	2	16	75	0	25
Chloramphenicol	0.5–2	0.5	2	100	0	0
Metronidazole	≤0.12–0.5	≤0.12	0.5	100	0	0

F. mortiferum, isolated from blood (N=3), abdomen (N=5), and foot wound (N=1); [†]*Fusobacterium* spp., including *F. canifelinum* (N=1) isolated from perianal abscess aspirate, *F. periodonticum* (N=2) isolated from blood, and *F. ulcerans* (N=1) isolated from abdomen.
Abbreviations: MIC, minimum inhibitory concentration; S, susceptible; I, intermediate; R, resistant.

cin or a combination of a penicillin and a β-lactamase inhibitor can be used to treat dental, oropharyngeal, or pulmonary infection. Metronidazole plus a third-generation cephalosporin can be used for central nervous system infection and bacteremia. Antimicrobial treatment is usually prolonged depending on the site of infection, adequacy of surgical intervention, and host factors [29, 30].

Antimicrobial treatment was given to most patients, albeit more frequently to those with *F. necrophorum* (92%) and *F. varium* (98%) infections than to those with *F. nucleatum* infection (79%; P=0.045). However, patients with *F. nucleatum* and *F. varium* infections more often received treatment with anti-anaerobic agents than those with *F. necrophorum* infection (63% vs. 95% vs. 29%; P<0.001). This may be because *F. nucleatum* and *F. varium* more commonly cause bacteremia and deep tissue infections. Additionally, anti-anaerobic agents were used in 95% of *F. varium* infections, which were most likely associated with complications after gastrointestinal tract surgery, as suggested above.

Despite the clinical differences among patients with *Fusobacterium* infections, there were no significant differences in the 30-day mortality rate among patients infected with *F. nucleatum* (11%) vs. *F. necrophorum* (4%) vs. *F. varium* (7%; P=0.186). Similarly, the 30-day mortality rates of *F. nucleatum* and *F. necrophorum* infections in a study in Denmark were 9% and 3% (P=0.11), respectively [31]. A study in Taiwan reported that *F. nucleatum* bacteremia was associated with a high 30-day mortality rate (47.4%) [32]. The 30-day mortality rate (1/11, 9%) in

the patients with *F. nucleatum* bacteremia in our study was substantially lower than that in Taiwan.

All *F. nucleatum* and *F. necrophorum* isolates were susceptible to the 10 antimicrobial agents tested. In a previous study, *F. nucleatum* and *F. necrophorum* isolates showed low-level resistance to penicillin G (9% and 6%, respectively) [25]. Piperacillin-tazobactam, cefoxitin, imipenem, chloramphenicol, and metronidazole were active against all isolates tested. Resistance rates of *Fusobacterium* spp. to clindamycin and moxifloxacin are geographically variable [33, 34]. In our study, the resistance rate (48%) of *F. varium* to clindamycin was higher than the rates reported in Singapore, Taiwan, and the USA (33%, 31%, and 4%–10%, respectively). The 24% resistance rate of *F. varium* to moxifloxacin was similar to that in Taiwan (25%), but higher than that in the USA (10%–12%), and lower than that in Singapore (44%) [33, 35]. *F. canifelinum* is intrinsically resistant to fluoroquinolones [36]. Interestingly, we found one *F. canifelinum* strain susceptible to and one *F. periodonticum* strain resistant to moxifloxacin. We found penicillin G resistance in 22% of *F. mortiferum* isolates, which is higher than the 9% and 12.1% reported for *Fusobacterium* spp. in USA and Canada, but substantially lower than the 45% reported in Taiwan [15, 16, 18].

Resistance to β-lactams in *Fusobacterium* spp. mainly involves the production of β-lactamases. Other mechanisms, such as alterations in penicillin-binding proteins and decreased outer membrane permeability are less strongly related to resistance to β-lactams [37]. In general, 41% of *Fusobacterium* isolates produce β-lactamases; however, positivity rates are unevenly dis-

tributed among species; 76% of *F. mortiferum*, 50% of *F. varium*, 22.7% of *F. necrophorum*, and 21.4% of *F. nucleatum* isolates in the USA produce these enzymes, whereas only 3.1% of *F. nucleatum* isolates from Taiwan are β-lactamase producers [19, 32]. However, we did not detect β-lactamase production in any of the *F. mortiferum* or *F. varium* isolates, which were non-susceptible to β-lactam agents, including penicillin G, cefotetan, and ceftriaxone. In *F. nucleatum*, resistance to β-lactam agents is primarily due to penicillinase production, whereas *F. varium* and *F. mortiferum* may have other mechanisms for penicillin resistance [29]. The production of β-lactamases by *Fusobacterium* spp. has not been investigated in Korea. Further studies are necessary to understand the resistance mechanism of *Fusobacterium* spp. to β-lactam agents.

The major limitations of our study were that the data were collected from a small number of patients in a single medical center and that we could not analyze any antimicrobial usage data, which may be correlated with antimicrobial susceptibility, for the isolates tested.

In summary, *F. nucleatum* was commonly isolated from patients with bacteremia and *F. necrophorum* was prevalent in head and neck infections in patients admitted to a tertiary-care hospital in Korea. Despite the variability in the clinical characteristics of patients infected by different *Fusobacterium* spp., there was no significant difference in the mortality rates. Piperacillin-tazobactam, cefoxitin, imipenem, chloramphenicol, and metronidazole were active against the *Fusobacterium* isolates tested. Some *Fusobacterium* spp. were resistant to penicillin G, ceftriaxone, clindamycin, or moxifloxacin. This study may provide clinically relevant data for the implementation of empirical therapies against *Fusobacterium* infections.

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AUTHOR CONTRIBUTIONS

Lee H and Lee K designed the study; Kim M conducted the experiments and Yun SY investigated the clinical data of patients; Kim M and Lee Y performed the experiments and analyzed the results; Yong D commented on the manuscript. All authors reviewed and approved the manuscript.

CONFLICTS OF INTEREST

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