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Clinical Study

Comparison of pyogenic postoperative and native vertebral osteomyelitis

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Abstract

BACKGROUND CONTEXT: Postoperative vertebral osteomyelitis (PVO) after spinal surgery is a clinical challenge. However, there is a paucity of evidence regarding the most likely etiologic organisms to guide the choice of empirical antibiotic therapy, and previous reports of treatment outcomes for PVO are scarce.

PURPOSE: To compare the microbiology, clinical characteristics, and outcomes of pyogenic PVO with native vertebral osteomyelitis (NVO).

STUDY DESIGN: Retrospective comparative study.

PATIENT SAMPLE: Patients with microbiologically proven vertebral osteomyelitis from three university-affiliated hospitals in South Korea between January 2005 and December 2015 with follow-up of at least 12 months after completion of antibiotics or until the patient was transferred. Patients who had a spine operation in the same location within 1 year of diagnosis, and all patients with remnant implants at the time of the vertebral osteomyelitis diagnosis, were defined as having PVO. The remainder of the patients was considered to have NVO. Spinal operations included discectomy, laminectomy, arthrodesis, and instrumentation for stabilization of the spine.

OUTCOME MEASURES: Overall mortality, neurologic outcomes, treatment failure, and relapse of infection.

METHODS: Demographic data, comorbidities, presenting symptoms, microbiological data, radiographic characteristics, laboratory data (including white blood cell counts, erythrocyte sedimentation rate, and C-reactive protein), surgical treatment, and neurologic outcomes for each patient were reviewed from electronic medical records and analyzed. Mortality rate, treatment failure, and relapse of infection were calculated for the two groups. Factors associated with treatment outcome were evaluated using univariate and multivariate logistic regression analyses.

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RESULTS: The study evaluated 104 patients with PVO and 441 patients with NVO. In PVO, the most common isolate was *Staphylococcus aureus* (34%, n=35), followed by coagulase-negative staphylococci (31%, n=32). In NVO, the most common isolates were *S. aureus* (47%, n=206) and streptococci (21%, n=94). Of the staphylococci, the proportion of methicillin-resistant strains was significantly higher in PVO than that in NVO (75% vs. 39%, p<.001). The proportion of patients with gram-negative bacilli was 14% in PVO and 20% in NVO. Pre-existing or synchronous nonspinal infection was observed more frequently in NVO than in PVO (33% vs. 13%, p<.001). Although the duration of antibiotic use was similar in both groups, surgery for infection control was performed more frequently in PVO. The mortality rate was similar in both groups. However, the treatment failure and relapse rates at 12 months were higher in the PVO group (23% vs. 13%, p=.009; 14% vs. 7%, p=.028, respectively). Methicillin-resistant *S. aureus* was significantly associated with treatment failure or relapse via logistic regression (odds ratio 3.01, 95% confidence interval [1.71−5.32], p<.001; odds ratio 2.78, 95% confidence interval [1.40−5.49], p=.003).

CONCLUSIONS: Coverage of methicillin-resistant staphylococci should be considered when prescribing empirical antibiotics for PVO. Although surgery was performed more often in PVO than NVO, the treatment failure and relapse rates at 12 months were higher in PVO.

Keywords: Microbiology; Outcome; Risk factor; Treatment; Spinal surgery; Vertebral Osteomyelitis.

Introduction

Vertebral osteomyelitis (VO) in adults is generally the result of hematogenous seeding, spread from adjacent disc space, or direct inoculation of micro-organisms into the spine caused by trauma or surgery [1,2]. The rate of spine infection after spinal surgery (eg, decompressive laminectomy, discectomy, and fusion) ranges from 0.2% to 9% [2−7]. Sequelae of deep wound infections after spinal surgery are potentially serious, and include failure of fixation, osteomyelitis, and pseudoarthrosis. The increasing trend of using spinal implants may lead to an increase in the incidence of surgical site infection (SSI), which would likely increase the risk of postoperative vertebral osteomyelitis (PVO) [8,9]. Postoperative vertebral osteomyelitis imposes a major burden on both the patient and the health-care system caused by significant morbidity and high costs of treatment [10,11].

Management of PVO is multidisciplinary, and strategies differ among institutions and countries. Favorable outcomes to PVO depend on the antibiotic therapy used, as well as adequate surgical interventions such as debridement or implant removal. Several studies have described the microbiology of infections after spinal surgery [12,13]. A small number of studies have examined the incidence and the clinical outcomes of infections after spinal surgery. However, these studies have limited utility for general application in clinics, because results varied greatly caused by small sample sizes [14,15], and study populations were restricted to patients with SSI, implant associated spine infection [16,17], or mixed study populations of superficial wound infection and deep seated infection [13−17]. Furthermore, although PVO seems to result in poorer outcomes than native vertebral osteomyelitis (NVO), studies comparing PVO and NVO are scarce [18]. Appropriate guidance on the treatment of PVO is limited by this paucity of data on the etiologic organism of PVO and treatment outcomes.

In light of these knowledge gaps, the purpose of this study was to compare and contrast the microbiology, clinical characteristics, and outcomes of pyogenic PVO compared with NVO.

Methods

Study design

We conducted a retrospective cohort study between January 2005 and December 2015 at three university-affiliated teaching hospitals in South Korea. We retrospectively collected the medical records of patients ≥18 years of age with VO. Only culture-confirmed patients with pyogenic VO were included. Patients with VO caused by *Brucella* species, *Mycobacterium tuberculosis*, or fungi were excluded. We collected demographic data, comorbidities, presenting symptoms, microbiological data, radiographic characteristics, laboratory data (including white blood cell counts, erythrocyte sedimentation rate, and C-reactive protein), surgical treatment, neurologic outcomes, and mortality. The presence of the following predisposing factors was also documented: pre-existing or synchronous infection, previous bacteremia within 1 year, previous spine operation within 1 year, and presence of remnant spine instrumentation. Clinical outcomes such as mortality and neurologic outcomes were evaluated at 3 and 12 months after treatment completion. The Institutional Review Boards of the three participating hospitals approved this study. A waiver for consent was granted, given the retrospective nature of the study.

Definitions

Pyogenic VO was diagnosed when all of the following conditions were satisfied: (1) presence of clinical signs or symptoms such as fever, back pain, etc, (2) radiological evidence of VO with or without discitis, and (3) presence of micro-organisms identified from bone, spinal, or paraspinal tissues, or blood cultures that were performed at the time of diagnosis of VO. When common skin contaminants (eg, coagulase-negative staphylococci, *Bacillus* sp., *Corynebacterium* sp., or *Micrococcus* sp.) grew in blood cultures, they were considered to be pathogens only when the same organism was isolated in at least two separate sets of blood cultures. When common skin contaminants grew in tissue cultures, they were considered to be pathogens when the same organism was also grown in the blood culture or in two or more tissue samples according to previous definition [19]. Patients with remnant implants at the time of the VO diagnosis or who had had a spinal operation performed in the same location as the infection within 1 year of the diagnosis of VO were defined as having PVO. For example, a cervical spine operation performed 6 months before a lumbar VO did not qualify as PVO. Spinal operations included discectomy, laminectomy, arthrodesis, and instrumentation for stabilization of the spine. Pre-existing or synchronous infection was defined as a documented infection at a site other than the spine within 30 days before or at the diagnosis of VO [20]. Surgical site infection was defined by an infection occurring within 1 year postoperatively that was related to the operative procedure, or by the diagnosis of SSI by an attending physician [21]. Patients with SSI after spinal surgery were identified through an in-hospital note or a transfer note from another hospital. Severe sepsis was defined as sepsis with at least one sign of organ dysfunction.

Outcomes were evaluated based on overall mortality, neurologic outcomes, treatment failure, and relapse. Treatment failure was defined as patients (1) requiring repeated surgical debridement before cessation of antibiotic treatment caused by uncontrolled infection or (2) having persistent intractable pain with a reduction in CRP of less than 25% from the baseline measurement despite more than 1 month of appropriate treatment [17,18]. Relapse at 12 months after treatment was defined as patients who received a second course of parenteral antibiotic treatment for the initial pathogen responsible for VO, caused by recurrent signs and symptoms after completion of the first antibiotic treatment [22].

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences ver. 22.0 (IBM, Armonk, NY, USA). Data are presented as means with standard deviation or as numbers with percentages. Categorical variables were compared using chi-squared or Fisher's exact tests, and continuous variables were compared using Student's *t* test. Univariate and multivariate logistic regression analyses were used to identify risk factors associated with treatment failure or relapse. Variables with $p<.10$ after univariate analysis were included in multivariate analysis. Significance tests were two-tailed, and p values$\leq$.05 indicated statistical significance.

Results

During the study period, 104 patients with PVO and 441 patients with NVO were identified. Of the 104 patients with PVO, 59 (56.7%) had spinal instrumentation. Among the 59 patients with instrumentation, 45 patients had instrumentation for 2 years or less, 9 patients between 2 and 10 years, and 5 patients over 10 years.

Etiologic micro-organisms

Table 1 shows the causative organisms of PVO and NVO. In the PVO group, *Staphylococcus aureus* was the most commonly isolated organism (n=35, 34%), followed by coagulase-negative staphylococci (n=32, 31%),

Table 1
Micro-organisms identified in patients with postoperative or native pyogenic vertebral osteomyelitis

	PVO N=104 (%)	NVO N=441 (%)	p value
Gram-positive cocci			
Staphylococcus aureus	35 (34)	206 (47)	.016
Methicillin-sensitive	13 (13)	130 (30)	<.001
Methicillin-resistant	22 (21)	76 (17)	.349
Coagulase-negative staphylococci	32 (31)	20 (5)	<.001
Methicillin-sensitive	4 (4)	7 (2)	.234
Methicillin-resistant	28 (27)	13 (3)	<.001
Enterococcus species	4 (4)	12 (3)	.522
E. faecium	1(1)	2 (1)	.471
E. faecalis	3(3)	9 (2)	.708
E. gallinarium	0	1	.999
Streptococcus species	11 (11)	94 (21)	.012
S. pneumoniae	0	6 (1)	.601
S. agalactiae	3 (3)	18 (4)	.779
Viridans streptococci	7 (7)	61 (14)	.049
Other streptococci	1 (1)	9 (2)	.696
Gram-negative bacilli	15 (14)	86 (20)	.231
Citrobacter koseri	0	1	.999
Escherichia coli	6 (6)	50 (11)	.092
Enterobacter cloacae	2 (2)	3 (1)	.244
Klebsiella pneumoniae	1 (1)	18 (4)	.145
Klebsiella oxytoca	0	1	.999
Pseudomonas aeruginosa	4 (4)	8 (2)	.256
Serratia marcescens	2 (2)	2 (1)	.166
Salmonella (nontyphoidal)	0	2 (1)	.999
Proteus mirabilis	0	1	.999
Anaerobes	1 (1)	7 (2)	.999
Polymicrobial	5 (5)	9 (2)	.109
Other	1 (0)[3]	7 (2)[4]	.999

PVO, postoperative vertebral osteomyelitis; NVO, native vertebral osteomyelitis; *Lactococcus garvieae*(1); *Neisseria* species(1), *Burkholderia cepacia*(1), *Stenotrophomonas maltophilia*(1), *Listeria monocytogenes*(1), *Campylobacter fetus*(1), *Ralstonia mannitolilytica*(1), *Moraxella* species(1).

Streptococcus species (n=11, 11%), and gram-negative bacilli (n=15, 14%). Among the *Staphylococcus* species, methicillin-resistant strains (75%) were more prevalent than methicillin-sensitive strains (25%, p<.01). Staphylococci were isolated in 73% (n=43) of 59 patients with spinal implants. In the NVO group, *S. aureus* was the most commonly isolated organism, accounting for 47% (n=206) of isolates; *Streptococcus* species (n=94, 21%) were the second most common isolates. Methicillin-resistant *Staphylococci* comprised 20% (n=89) and gram-negative bacilli constituted 20% (n=86) of all isolates in the NVO group. Polymicrobial infection was more common in PVO, but this difference was not statistically significant (p=.109).

Demographics and clinical characteristics

Patient age did not differ between PVO and NVO, but women were more prevalent in the PVO group than in the NVO group (55% vs. 37%, p=.001) (Table 2). Pre-existing or synchronous nonspinal infection (<30 days) was more common in NVO than in PVO (33% vs. 13%, p<.001). The presence of comorbidities was similar in both groups, except that liver cirrhosis was more frequent in the NVO group (p=.029). The lumbar spine was the most frequently involved vertebral level in both groups, and the cervicothoracic region was more frequent in the NVO group. Regarding the initial symptoms, radiating pain was observed more often in PVO than in NVO. The prevalence of sepsis and severe sepsis did not differ between the two groups. Laboratory tests revealed no differences between groups in neutrophil counts or erythrocyte sedimentation rate, but CRP levels were higher in NVO than in PVO (13.5 vs. 10.8 mg/dL, p=.011). The rate of positive blood cultures was higher in NVO, whereas the rate of positive tissue cultures was higher in PVO. Types of pre-existing or synchronous infections associated with gram-negative bacteria are described in Table 3. Genitourinary tract and intra-abdominal infections were significantly more common in VO caused by gram-negative bacilli (p=.001). A total of 23 patients in the PVO group had had SSI after spinal surgery (15 patients with spinal implant, 8 patients without spinal implant).

Treatment methods

Both groups were treated with intravenous antibiotics followed by oral antibiotics. For patients in whom treatment duration was evaluable, the mean duration of intravenous antibiotics was 55±35 days for PVO and 48±38 days for the NVO group (p=.092), and the mean duration of all antibiotics was 78±58 and 72±60 days, respectively (p=.342). The duration of antibiotic treatment did not differ significantly when divided by gram-positive cocci for the PVO and NVO groups (60±3 vs. 61±7, p=.341) and gram-negative bacilli (63±7 vs. 51±13, p=.747). Surgical treatment for VO was more common in the PVO group than in

Table 2
Demographics and clinical characteristics of the patients with postoperative or native pyogenic vertebral osteomyelitis

	PVO N=104 (%)	NVO N=441 (%)	p value
Age (y), mean±SD	66±11	64±13	.233
Female	57 (55)	160 (37)	.001
Presence of preexisting or synchronous nonspinal infection (<30 days)	13 (13)	147 (33)	<.001
Previous bacteremia (<1 year)	7 (7)	48 (11)	.277
Comorbidity			
Cerebrovascular disease	3 (3)	21 (5)	.595
Congestive heart failure	3 (3)	16 (4)	.999
Diabetes mellitus	35 (34)	130 (30)	.408
Chronic kidney disease	7 (7)	45 (10)	.354
Renal replacement therapy	3 (3)	18 (4)	.779
Liver cirrhosis	3 (3)	43 (10)	.029
Solid tumor	10 (10)	57 (13)	.410
Hematologic malignancy	1 (1)	10 (2)	.699
Immunosuppressant	1 (1)	24 (5)	.064
Trauma	2 (2)	8 (2)	.999
Involved vertebral area			
Cervical spine	2 (2)	33 (8)	.043
Thoracic spine	6 (6)	76 (17)	.003
Lumbar spine	68 (65)	241 (55)	.048
Sacrum	1 (1)	3 (1)	.572
Cervicothoracic spine	0	4 (1)	.999
Thoracolumbar spine	4 (4)	33 (7)	.204
Lumbosacral spine	20 (19)	48 (11)	.023
Cervical, Lumbar spine	1 (1)	2	.471
C-T-L-spine	1 (1)	1	.346
T-L-S-spine	1 (1)	0	.191
Number of involved vertebra			
1−2	74 (72)	357 (81)	.044
3−4	27 (26)	63 (14)	.005
≥5	2 (2)	21 (5)	.280
Clinical manifestation at presentation			
Fever	47 (45)	243 (55)	.080
Back pain	97 (93)	414 (94)	.822
Radiating pain	61 (59)	181 (41)	.003
Motor weakness, Sensory deficit	20 (19)	59 (13)	.162
Paralysis	4 (4)	12 (3)	.522
Initial complications			
Epidural abscess	57 (55)	189 (43)	.029
Paravertebral abscess	49 (47)	185 (42)	.379
Psoas abscess	32 (31)	116 (26)	.391
Sepsis	42 (38)	216 (49)	.102
Severe sepsis	17 (16)	69 (16)	.999
Laboratory findings			
WBC (mm^3)	10,947±6,356	12,091±5,543	.067
PMN (%)	70±22	73±24	.324
ESR (mm/h)	73±30	68±31	.235
CRP (mg/dL)	10.8±9.7	13.5±9.5	.011
Positive blood culture (%)	52/85 (61)	319/411 (78)	.002
Positive tissue culture (%)	88/100 (88)	267/352 (76)	.013
Positive blood/tissue culture (%)	39/83 (47)	148/324 (79)	.902

PVO, postoperative vertebral osteomyelitis; NVO, native vertebral osteomyelitis; SD, standard deviation; WBC, white blood cell; PMN, polymorphonuclear leukocytes; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Table 3
Pre-existing or synchronous infections in 515 patients with monomicrobial vertebral osteomyelitis

	GNB N=101 (%)	GPC N=414 (%)	p value
Postoperative wound infection (nonspinal operation)	0	6 (1)	.603
Postoperative spinal wound infection	4 (4)	19 (5)	1.000
Pneumonia	0	10 (2)	.222
Urinary tract infection	24 (24)	14 (3)	.001
Intra-abdominal infection	17 (17)	5 (1)	.001
Skin and soft tissue infection	1 (1)	20 (5)	0.094
Infective endocarditis	0	24 (6)	.007
Infective arthritis	0	6 (1)	.343
A-V fistula infection	0	2 (1)	>.999

GNB, gram-negative bacilli; GPC, gram-positive cocci; A-V, arteriovenous.

Table 5
Comparison of the outcomes of postoperative and native pyogenic vertebral osteomyelitis

	PVO N=104 (%)	NVO N=441 (%)	p value
Neurologic outcome (post 3 mo)	N=95	N=362	
No residual symptom	30 (32)	155 (43)	.060
Back pain	32 (34)	119 (33)	.903
Nerve root pain	20 (21)	37 (10)	.006
Motor weakness, Sensory deficit	4 (4)	19 (5)	.798
Paralysis	4 (4)	8 (2)	.283
Death	5 (5)	24 (7)	.654
Neurologic outcome (post 12 months)	N=80	N=284	
No residual symptom	37 (46)	150 (53)	.313
Back pain	22 (28)	66 (23)	.461
Nerve root pain	13 (16)	22 (8)	.031
Motor weakness, Sensory deficit	1 (1)	13 (5)	.320
Paralysis	2 (3)	6 (2)	.690
Death	5 (6)	27 (10)	.389
Treatment failure	25/99 (25)	53/413 (13)	.002
Relapse at 12 mo	14/99 (14)	29/402 (7)	.028

PVO, postoperative vertebral osteomyelitis; NVO, native vertebral osteomyelitis.

the NVO group (81% vs. 42%, p<.001; Table 4). Implants were removed for infection control in 47% (n=28) of the 59 patients with spinal implants. Implants were removed in 3 of 15 patients with SSI after spinal surgery. The total duration of antibiotic treatment in the implant retention group was longer than in the implant removal group, but this difference was not statistically significant (69±12 vs. 52±10, p=.803).

Outcomes

Clinical and neurologic outcomes were assessed at 3 and 12 months after the completion of antibiotic treatment (Table 5). There were no significant differences in the proportion of patients with residual pain, sensory deficit, or paralysis between the groups. The overall mortality rate was 5% and 7% in PVO and NVO, respectively, at 3 months (p=.654), and 6% and 10% in each group at 12 months (p=.389). Among the patients in whom treatment failure or relapse were evaluable, the treatment failure and relapse rates at 12 months were higher in the PVO group (25% vs. 13%, p=.002; 14% vs. 7%, p=.028, respectively) than in the NVO group. Among PVO patients with spinal implants, treatment failure and relapse did not differ according to implant retention.

In the multivariate analysis, treatment failure was associated with a history of spinal surgery within 12 months of the diagnosis (odds ratio [OR] 1.94, 95% confidence interval [CI 1.05−3.57], p=.025), severe sepsis on admission (OR 2.19, 95% CI [1.19−4.05], p=.006), and methicillin-resistant *S. aureus* (MRSA) infection (OR 3.01, 95% CI [1.71−5.32], p<.001; Table 6). Methicillin-resistant S. aureus infection (OR 2.78, 95% CI [1.40−5.49], p=.003; Table 6) was the only risk factor associated with relapse.

Table 4
Treatment durations of postoperative and spontaneous pyogenic vertebral osteomyelitis

	PVO N=104 (%)	NVO N=441 (%)	p value
Treatment method			
Antibiotics only	20 (19)	256 (58)	<.001
Antibiotics+surgery	84 (81)	185 (42)	<.001
Surgery method			
Open surgical drainage	48 (46)	112 (25)	<.001
Drainage+instrumentation	18 (17)	54 (1)	.615
Drainage+autobone graft	18 (17)	19 (4)	<.001
Treatment duration, days			
Total antibiotics	78±58	72±60	.342

PVO, postoperative vertebral osteomyelitis; NVO, native vertebral osteomyelitis.

Discussion

The purpose of this study was to identify micro-organisms and clinical outcomes of PVO as compared with NVO. In this study, among 545 patients with microbiologically confirmed pyogenic VO, 19% had a history of spinal surgery and 11% had spinal instrumentation. In PVO, the most common isolate was *S. aureus*, followed by coagulase-negative staphylococci, and 75% of these staphylococcus strains were methicillin resistant. In NVO,

Table 6
Factors associated with treatment failure or relapse in pyogenic vertebral osteomyelitis

	Univariate analysis		Multivariate analysis	
Factor	OR 95% CI	p	OR 95% CI	p
Treatment failure				
Spinal implant	1.94 (0.98−3.81)	.010		
Spinal surgery within 12 mo	1.84 (1.01−3.32)	.005	1.94 (1.05−3.57)	.025
Severe sepsis	2.03 (1.13−3.66)	.010	2.19 (1.19−4.05)	.006
MRSA	2.96 (1.71−5.12)	<.001	3.01 (1.71−5.32)	<.001
Antibiotics total duration	1.00 (1.00−1.01)	.025		
Relapse				
Spinal implant	2.37 (1.07−5.25)	.033	2.19 (0.97−4.96)	.058
Spinal surgery within 12 mo	1.90 (0.92−3.96)	.078		
Neutrophil count	0.98 (0.98−0.99)	.018		
MRSA	2.92 (1.49−5.74)	.001	2.78 (1.40−5.49)	.003
Antibiotics total duration	1.00 (1.0−1.01)	.032		

OR, odds ratio; CI, confidence interval; MRSA, Methicillin-resistant *Staphylococcus aureus*.

methicillin-susceptible *S. aureus* and streptococci were the most common isolates. Gram-negative bacilli infections were present in 14% of the PVO group, and urinary tract and intra-abdominal infections were identified as risk factors for gram-negative bacilli infection in VO. The duration of antibiotic use was similar in both groups, whereas surgical drainage was performed more frequently in PVO than in NVO. Despite more frequent surgical treatment, the treatment failure and relapse rates at 12 months of follow-up were higher in PVO than in NVO.

Microbiological diagnosis is an important step in the management of VO as it guides long-term antibiotic treatment [23,24]. Often, however, no etiologic organisms are isolated, so antibiotics are chosen empirically. In real clinics, the most frequently used empirical antimicrobial agent is cefazolin, which is active against methicillin-susceptible *S. aureus* and streptococci [25]. In clinical practice, guidelines established by the Infectious Diseases Society of America, in circumstances requiring empirical antimicrobial therapy of NVO (hemodynamic instability, sepsis, septic shock, or progressive or severe neurologic symptoms), the regimen should be directed at *Staphylococcus* species, including MRSA, streptococci, and gram-negative bacilli [26]. Such regimens would consist of vancomycin in combination with a third or fourth generation cephalosporin. Consensus on empirical antibiotics therapy in PVO has not been reached, and clinicians tend to initially choose broad-spectrum combination antibiotics with more than two antibiotics covering both gram-negative and gram-positive organisms [15,27]. In this study, staphylococci were the most common pathogen in PVO, especially in patients with spinal implants. Similar findings have been reported in other studies [16,18,28]. In this study, the proportion of methicillin resistance in *Staphylococcus* species was very high, and methicillin-resistant coagulase-negative staphylococci were significantly more common in the PVO group compared with the NVO group. Most of the etiologic organisms in PVO were monomicrobial infections, with gram-negative bacilli infection occurring in 14% of cases. Previous reports have identified preceding urinary tract and intra-abdominal infections as risk factors for gram-negative bacilli infection in VO [20,29]. Such an association was also found in this study. In other studies, polymicrobial or gram-negative organisms in SSIs after spine surgery have been reported to be associated with intravenous drug use, bladder or fecal incontinence, and sacral surgical intervention [13,30]. However, the number of PVO patients with these risk factors in the present study was too small for statistical analysis (bladder/fecal incontinence [n=4], sacral surgical intervention [n=1], and intravenous drug user [n=0]). The routine use of broad-spectrum combination antibiotics may result in resistant bacterial strains, increased costs, and additional adverse effects. Our study suggests that empirical antibiotics that target mainly gram-positive organisms should be considered in PVO, rather than routine use of broad-spectrum combination antibiotics in patients without risk factors for polymicrobial organisms or gram-negative bacilli.

In NVO, antimicrobial treatment duration of at least 6 weeks and surgical treatment in progressive VO has been recommended [26]. The management of PVO can be more challenging than NVO, especially in cases of spinal implant infection, in which successful treatment requires chronic oral antibiotics or removal of the implant [17]. In previous studies, relapse and treatment failure of PVO appeared to be uncommon. Relapse rates ranged from 0% to 4% [18,31] and no significant difference was observed in treatment failure rate between PVO (3%) and NVO (4%) [18]. However, recent reports of treatment failure rates in PVO are much higher than previous reports, ranging from 16% to 29% [14,16,17,32]. Our results are in line with those of recent studies. Moreover, outcomes of PVO were significantly worse than NVO in terms of treatment failure and relapse. These findings emphasize the importance of appropriate management of PVO. Although there has been no standard recommendation in the management of PVO, surgical debridement with or without implant removal has been considered as an important factor in the successful treatment of PVO, along with the prolonged use of antibiotics [12,16,17,33]. Studies on the use of antibiotics to manage PVO have exhibited antibiotic treatment duration of at least 6 weeks, although most studies have been of case reports or small numbers of patients [17,27,34,35]. In this study, both groups of patients received antibiotics treatment of at least 6 weeks, as well as surgical drainage as needed, as decided by the clinician. Despite these measures, the clinical outcome of PVO was poor, and multivariate analysis revealed that MRSA infection was the only factor that was significantly associated with both treatment failure and relapse in pyogenic VO. In this study, the small number of cases of relapse in PVO meant that no associated factors could be identified. Methicillin-resistant *S. aureus* is reported to be a risk factor for relapse in hematogenous VO [22]. The role of MRSA in the outcome of spine SSI is uncertain. Recently, Bilieres et al. reported that *S. aureus* infection was not associated with remission in PVO [28]. Rifampin-based combination treatments existed the protective effects on recurrence of patients with *S. aureus* spinal implant infections [36]. Infection caused by MRSA was one of the four validated variables for multiple surgical debridements in the treatment of PVO [37]. Based on these findings, we suggest that successful treatment of MRSA infection may require more prolonged antibiotics usage or more aggressive debridements, including implant removal, especially in PVO.

Several limitations should be considered when interpreting our results. First, the present study has missing variables, and the complete individual history of risk factors for PVO such as previous wound status were not available caused by the retrospective nature of data collection. However, we believe that the sample size was large enough to overcome the possible limitation caused by missing variables. Future prospective studies are warranted to confirm our results. Second, since the data were collected from three university-affiliated hospitals, which serve as a tertiary referral site for complex spinal infections, it is possible that the study population was weighted toward more severe and complicated patients. Third, we classified patients with remnant implants as having PVO, regardless of the duration of the instrumentation. Although there might be differences in etiologic organisms according to the duration of instrumentation, we could not evaluate this caused by the small number of patients having instrumentation over 2 years. This needs to be studied further with a larger number of patients with various durations of instrumentation. Last, patient treatment strategies were not randomly chosen, and thus, uncontrolled selection bias could have occurred.

In conclusion, *Staphylococcus* species comprised over two-thirds of all isolates, and methicillin-resistant staphylococci were dominant in PVO. We suggest that monotherapy targeting gram-positive cocci as empirical antibiotics may be sufficient in noncritically ill patients for PVO. In the management of VO, aggressive surgical debridement should be considered along with medical treatment, and patients with MRSA infection may require close monitoring for signs of treatment failure or relapse.

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