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Factors associated with sequelae after treatment of hematogenous pyogenic vertebral osteomyelitis

Yu-Mi Lee [a], Oh-Hyun Cho [b], Seong Yeon Park [c], Chisook Moon [d], Yong Pil Chong [e], Sung-Han Kim [e], Sang-Oh Lee [e], Sang-Ho Choi [e], Mi Suk Lee [a], In-Gyu Bae [b], Yang Soo Kim [e], Jun Hee Woo [e], Kyung-Chung Kang [f], Jung-Hee Lee [f], Ki-Ho Park [a,*]

[a] Division of Infectious Diseases, Department of Internal Medicine, Kyung Hee University Hospital, Kyung Hee University School of Medicine, Seoul, Republic of Korea
[b] Department of Internal Medicine, Gyeongsang National University School of Medicine, Jinju, Republic of Korea
[c] Division of Infectious Diseases, Department of Internal Medicine, Dongguk University Ilsan Hospital, University of Dongguk College of Medicine, Goyang-si, Republic of Korea
[d] Department of Infectious Diseases, Busan Paik Hospital, Inje University College of Medicine, Busan
[e] Department of Infectious Diseases, Asan Medical Center, University of Ulsan college of Medicine, Seoul, Republic of Korea
[f] Department of Orthopaedic Surgery, Kyung Hee University Hospital, Kyung Hee University School of Medicine, Seoul, Republic of Korea

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ABSTRACT

Objectives: Functional disability may persist after completing treatment for hematogenous pyogenic vertebral osteomyelitis (HPVO). The objective of this study was to identify factors associated with residual sequelae after treatment of HPVO.

Methods: We conducted a retrospective study of patients diagnosed with HPVO at 5 tertiary-care hospitals between January 2005 and December 2012. Sequelae were defined as an inability to walk without assistance, bladder/bowel incontinence, and/or unresolved pain that required analgesic therapy at 12 months after completing the HPVO treatment.

Results: Of the 279 patients with microbiologically proven HPVO, 79 (28.3%) had sequelae at 12 months posttherapy. Independent risk factors for sequelae were neurologic deficit (adjusted odds ratio [aOR], 3.38), recurrence within 12 months (aOR, 2.45), age ≥ 65 years (aOR, 2.05), C-reactive protein level ≥ 10 mg/dL (aOR, 2.01), and epidural/paravertebral abscess (aOR, 2.00). Among 58 patients with neurologic deficit, sequelae rates differed according to the surgical strategy, as follows: 28.6% (early surgery [<48 h]), 55.0% (delayed surgery [≥48 h]), and 66.7% (no surgery) ($P = 0.03$). Among the 170 patients with abscess, early drainage (<72 h) was an independent protective factor for sequelae (aOR, 0.35). The 12-month recurrence rates differed according to the total duration of antibiotic treatment, as follows: 20.5% (4–6 weeks), 18.4% (6–8 weeks), and 5.2% (≥8 weeks) ($P < 0.001$).

Conclusions: A substantial proportion of patients with HPVO experienced sequelae after completing treatment. Early surgery for neurologic deficit, early drainage of abscess, and antibiotic therapy of appropriate duration to reduce recurrence may prevent development of sequelae in patients with HPVO.

1. Introduction

The prevalence of pyogenic vertebral osteomyelitis (VO) has increased recently, perhaps because of longer life expectancy, availability of improved diagnostic tools, and increased prevalence of chronic diseases (Aagaard et al., 2016; Akiyama et al., 2013; Kehrer et al., 2014; Murillo et al., 2014). Healthcare-associated infections, such as catheter-related and procedure-related bloodstream infections, also increase the risk of pyogenic VO (Pigrau et al., 2015). Pyogenic VO typically has an indolent clinical course and a low mortality rate but frequently also a poor functional outcome (Mylona et al., 2009). Despite medical and surgical treatment, some patients with pyogenic VO have residual disability, such as motor weakness, bowel or bladder dysfunction, and persistent pain (Mylona et al., 2009). Residual disability reportedly occurs in 31–52% of pyogenic VO patients and can seriously affect their quality of life (McHenry et al., 2002; Priest and Peacock, 2005).

Limited data are available on the optimal management of patients with pyogenic VO in terms of improving functional outcomes. Surgical therapy may reduce the frequency of sequelae after treatment of pyogenic VO (Hadjipavlou et al., 2000; Lemaignen et al., 2017), but the patient populations who are at high risk of sequelae and who would benefit from surgical intervention are unclear. We hypothesized that early identification of at-risk patients will facilitate timely intervention

* Corresponding author. Tel.: +82-2-958-2966; fax: +82-2-968-1848.
E-mail address: parkkiho@hotmail.com (K.-H. Park).

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and reduce the risk of sequelae. Thus, the aims of this study were to identify i) risk factors for development of sequelae after completion of treatment for hematogenous pyogenic VO and ii) the treatment strategy that minimizes the risk of sequelae in high-risk patients.

2. Patients and methods

2.1. Study design and setting

All adult patients diagnosed with hematogenous pyogenic VO between January 2005 and December 2012 at 5 tertiary-care hospitals in the Republic of Korea were enrolled in this observational cohort study. We retrospectively identified all patients discharged with International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) codes for osteomyelitis of the vertebra (M46.2), pyogenic infection of intervertebral disc (M46.3), unspecified discitis (M46.4), other infective spondylopathy (M46.5), other specified inflammatory spondylopathy (M46.8), unspecified inflammatory spondylopathy (M46.9), unspecified spondylopathy (M48.9), and epidural abscess (G06.1 and G06.2). The patients with these ICD-10-CM codes and positive microbiological results were reviewed to determine whether they met the study criteria defined below. The study was conducted using the format recommended by the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (von Elm et al., 2007).

2.2. Inclusion and exclusion criteria

Adult patients (≥16 years of age) who presented with microbiologically proven hematogenous pyogenic VO were included. Hematogenous pyogenic VO was defined using both radiographic evidence of VO and microbiologic demonstration of bacterial pathogens, either from the site of infection itself (e.g., abscess, intervertebral disc, or vertebral bone) or in the blood. Cases with a nonhematogenous source of vertebral infection, which included i) penetrating trauma, ii) previously placed hardware, iii) laminectomy within 1 year prior to diagnosis of VO, or iv) the presence of a stage 3–4 decubitus ulcer at the time of diagnosis were excluded (Livorsi et al., 2008; Park et al., 2016). Cases with culture-negative pyogenic VO or tuberculous, brucellar, and fungal VO were excluded. Other reasons for exclusion were incomplete medical records, refusal of medical treatment, and transfer to another hospital before completing the antibiotic therapy.

2.3. Data collection

This work builds on a previous study of the optimal duration of antibiotic treatment for preventing recurrence of hematogenous pyogenic VO (Park et al., 2016). Medical records were reviewed retrospectively for demographic information, underlying illnesses/conditions, presumed source of infection, diagnostic workup, clinical presentation, laboratory and radiological data, medical and surgical treatments, and clinical outcomes. During the study period, the antibiotic regimen and duration of therapy were usually determined by infectious disease specialists based on the culture results.

2.4. Definitions

Sequelae were defined as an inability to walk without assistance (Modified McCormick Scale Grade III–V), bladder/bowel incontinence, and/or unresolved pain that required analgesic therapy at 12 months after completing the treatment. Recurrence was defined as patients who had recurrent symptoms and signs (such as fever, back pain, and high inflammatory markers in the absence of other causes) after completing antibiotic treatment and who received a second course of parenteral antibiotics (Park et al., 2015). Patients who underwent surgery within 48 h after documentation of neurologic deficit were defined as early surgery cases.

2.5. Surgical and medical therapy

During the study period, surgical therapies were given at the discretion of the treating physicians. The antibiotic regimen and duration of therapy were usually determined by infectious disease specialists based on culture results.

2.6. Statistical analyses

All statistical analyses were performed using SPSS for Windows, version 18.0 (IBM SPSS, Inc., Chicago, IL). Categorical variables were compared using χ^2 or Fisher's exact test, as appropriate. For ordinal data, we used a linear-by-linear association test (Mantel–Haenszel χ^2 test for trend). Continuous variables were compared by Mann–Whitney *U* test. To identify independent risk factors for sequelae, all variables found to be significant in univariate analyses were included in a multivariate logistic regression model. All statistical tests were 2-tailed, and $P \leq 0.05$ was considered to indicate statistical significance.

3. Results

A total of 370 patients microbiologically diagnosed with hematogenous pyogenic VO were identified during the study period. Of these 370 cases, 25 were excluded for the following reasons: transfer to another hospital before completing antibiotic therapy ($n = 15$), refusal of medical treatment ($n = 6$), or incomplete medical records ($n = 4$). Finally, 345 patients met the inclusion criteria and were enrolled in this study.

3.1. Patient characteristics

The demographic and baseline characteristics of the 345 patients with hematogenous pyogenic VO are shown in Table 1. The median age of the cohort was 65 years, and 181 (52.5%) of the patients were males. The median time from onset of symptoms to diagnosis was 22 days (interquartile range [IQR], 8–40 days), and back pain was the most common presenting symptom (88.7%). Fifty-eight (16.8%) patients presented with neurologic deficit, and 13 (3.8%) had new-onset neurologic deficit during antibiotic treatment. Overall, 71 (20.6%) patients had neurologic deficit at diagnosis or during treatment.

3.2. Microbiological findings

Of the 345 cases with microbiologically diagnosed VO, 89 (25.8%) were identified by diagnostic biopsy, 167 (48.4%) by blood cultures, and 89 (25.8%) by both. The most frequently isolated organisms were methicillin-susceptible *Staphylococcus aureus* (MSSA) (33.3%), follow by methicillin-resistant *S. aureus* (MRSA) (25.5%), aerobic Gram-negative bacteria (21.7%), and *Streptococcus* species (11.3%). Of 67 *Enterobacteriaceae* isolates, 17 (25.4%) were resistant to ciprofloxacin, and 6 (9.0%) were extended-spectrum β-lactamase (ESBL) producers. Of 39 *Streptococcus* species, viridans group streptococci were the most frequently isolated organisms ($n = 20$), followed by *Streptococcus agalactiae* ($n = 13$), *S. pneumoniae* ($n = 4$), and other streptococci ($n = 2$). Coagulase-negative staphylococci, *Enterococcus* species, anaerobes, and polymicrobial organisms accounted for 2.9%, 2.9%, 1.5%, and 0.3%, respectively.

3.3. Management and outcomes

Surgical debridement and percutaneous aspiration drainage were performed in 153 (44.3%) and 24 (7.0%) patients, respectively. Surgery was performed more frequently in patients with neurological deficit (40/71 [56.3%] *vs.* 113/274 [41.2%]; $P = 0.02$) and in those with epidural abscess (84/132 [63.6%] *vs.* 69/213 [32.4%]; $P < 0.001$). The median

Table 1
Baseline characteristics and outcomes of 345 patients with hematogenous pyogenic vertebral osteomyelitis.

Variable	All patients ($n = 345$)
Age, years, median (IQR)	65 (58–72)
Male sex	181 (52.5)
Transfer from outside hospitals	78 (22.6)
Underlying illness/conditions	
Diabetes mellitus	102 (29.6)
Liver cirrhosis	32 (9.3)
Malignancy	31 (9.0)
Immunosuppression	20 (5.8)
End-stage renal disease	15 (4.3)
Rheumatic disease	12 (3.5)
Presumed source of infection	
Urinary tract	35 (10.1)
Skin and subcutaneous tissues	31 (9.0)
Intra-abdomen	26 (7.5)
Infected vascular access	25 (7.3)
Endocarditis	19 (5.5)
Unknown	209 (60.6)
Clinical data	
Time to diagnosis, median days (IQR)	22 (8–40)
Back pain	306 (88.7)
Body temperature > 38 °C	183 (53.0)
Neurologic deficit[a]	71 (20.6)
Concurrent metastatic infection	43 (12.5)
Laboratory data	
WBC, $\times 10^9$/L, median (IQR)	11.4 (7.9–16.4)
CRP, mg/dL, median (IQR)	13.1 (5.5–22.0)
ESR, mm/h, median (IQR)[b]	76 (55–100)
Positive blood cultures	256/327 (78.3)
Radiologic data	
Involvement of >2 vertebral bodies	117 (33.9)
Involvement of cervical spine	28 (8.1)
Involvement of thoracic spine	82 (23.8)
Involvement of lumbosacral spine	272 (78.8)
Epidural abscess	132 (38.2)
Epidural phlegmon	52 (15.1)
Paravertebral abscess[c]	170 (49.3)
Paravertebral phlegmon[c]	64 (18.5)
Outcomes	
In-hospital mortality	31/345 (9.0)
14-day mortality	4/345 (1.2)
30-day mortality	15/345 (4.3)
12-month mortality	49/345 (14.2)
Recurrence within 12 months	31/314 (9.9)
Sequelae at 12 months posttherapy	79/279 (28.3)

NOTE. Values are numbers (%) of patients, unless otherwise indicated. CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IQR = interquartile range; WBC = white blood cell.

[a] Neurologic deficit was documented at diagnosis ($n = 58$) or during treatment ($n = 13$).

[b] Measured in 274 patients.

[c] Includes paravertebral and psoas soft-tissue lesions.

duration of total antibiotic therapy (intravenous and oral) was 68 days (IQR, 46–100 days). The details of the antibiotic treatments are summarized in Supplementary Table 1.

The outcomes of the 345 patients with hematogenous pyogenic VO are shown in Table 1. Thirty-one (9.0%) patients died before completing the antimicrobial treatment. Univariate analysis indicated that liver cirrhosis ($P = 0.001$), end-stage renal disease ($P = 0.04$), high C-reactive protein (CRP) values ($P = 0.04$), positive blood culture results ($P = 0.03$), involvement of multiple vertebra ($P = 0.01$), and epidural abscess ($P = 0.047$) were associated with in-hospital mortality. There was a trend towards higher rates of in-hospital mortality among patients with MRSA infection (13.6% *vs.*7.4%; $P = 0.08$) and concomitant endocarditis (17.6% *vs.* 8.5%; $P = 0.19$), but this did not reach statistical significance. Of the 314 patients who completed treatment, 18 died and 5 were lost to follow-up during the 12 months after completion of treatment, and 12 had incomplete medical records for sequelae at 12 months posttherapy. Finally, 279 patients were evaluable for sequelae at 12 months posttherapy.

3.4. Factors associated with sequelae

Of the 279 patients evaluable for sequelae, 79 (28.3%) had sequelae at 12 months after completing the treatment. Sequelae included persistent pain ($n = 52$ [18.6%]), inability to walk without assistance ($n = 39$ [14.0%]), and/or bowel/bladder dysfunction ($n = 12$ [4.3%]). Univariate analyses indicated that age ≥ 65 years, neurologic deficit at diagnosis or during treatment, CRP level ≥ 10 mg/dL, *S. aureus* infection, involvement of the cervicothoracic spine, epidural/paravertebral abscess, and recurrence within 12 months after treatment completion were risk factors for sequelae (Table 2). Multivariate analysis indicated that neurologic deficit (adjusted odds ratio [aOR], 3.38; 95% confidence interval [CI], 1.77–6.44; $P < 0.001$), recurrence within 12 months (aOR, 2.45; 95% CI, 1.003–5.97; $P = 0.049$), age ≥ 65 years (aOR, 2.05; 95% CI, 1.13–3.70; $P = 0.02$), CRP level ≥ 10 mg/dL (aOR, 2.01; 95% CI, 1.09–3.71; $P = 0.03$), and epidural/paravertebral abscess (aOR, 2.00; 95% CI, 1.07–3.72; $P = 0.03$) were independent risk factors for sequelae (Table 2).

The results of univariate and multivariate analyses of factors associated with sequelae among selected subgroups of patients are shown in Table 3. Among 58 patients with neurologic deficit, sequelae rates differed according to the surgical strategy as follows: 28.6% (early surgery [<48 h]), 55.0% (delayed surgery), and 66.7% (no surgery) ($P = 0.03$; Fig. 1). When only the 58 patients with neurologic deficit were included in the multivariate analysis, early surgery was independently associated with a lower rate of sequelae (aOR, 0.22; 95% CI, 0.06–0.84; $P = 0.03$; Table 3). There was a trend towards a higher sequelae rate in patients with neurologic deficit detected during the course of treatment compared with those with neurologic deficit detected at the time of diagnosis of hematogenous pyogenic VO (71.4% [10/14] *vs.* 47.7% [21/44]; $P = 0.12$). Among 170 patients with epidural/paravertebral abscess, early drainage (<72 h) was associated with a lower rate of sequelae than was delayed or no drainage (20.5% *vs.* 38.9%; $P = 0.03$; Fig. 2). The protective effect of early drainage on sequelae was evident in cases with abscess and a CRP level ≥ 10 mg/dL (19.2% *vs.* 45.2%; $P = 0.02$) but not in cases with abscess and a CRP level < 10 mg/dL (23.1% *vs.* 27.7%; $P > 0.99$; Fig. 3A). This trend was still present when the analysis was restricted to 136 patients without neurologic deficit (Fig. 3B). When the multivariate analysis was restricted to the 170 patients with abscess, early drainage was an independent protective factor for sequelae (aOR 0.35; 95% CI, 0.14–0.88; $P = 0.03$; Table 3). Among 160 patients infected with *S. aureus*, there was no difference in sequelae rates according to methicillin resistance, susceptibility to vancomycin, initial vancomycin trough level, or receipt of rifampin and/or fluoroquinolone (Table 3).

Among the 279 patients evaluable for sequelae, 30 (9.6%) experienced recurrence within 12 months after completing antibiotic therapy. Patients who experienced recurrence within 12 months were more likely to have sequelae at 12 months posttherapy (51.9% [14/27] *vs.* 25.8% [65/252]; $P = 0.004$). At 12 months after recurrent infection, patients with recurrence had a higher rate of sequelae than did those who did not experience recurrence (44.4% [12/27] *vs.* 25.8% [65/252]; $P = 0.04$). A linear-by-linear association test revealed a significant decreasing trend in 12-month recurrence according to the total duration of intravenous or oral antibiotic therapy: 20.5% (4–6 weeks), 18.4% (6–8 weeks), and 5.2% (≥8 weeks) ($P < 0.001$).

4. Discussion

To our knowledge, this is one of the largest cohort studies of factors associated with the functional outcomes of microbiologically diagnosed pyogenic VO. We found that a substantial proportion of our patients with hematogenous pyogenic VO had sequelae after treatment completion. Sequelae could be prevented by early surgery for neurologic deficit,

Table 2
Univariate and multivariate analyses of risk factors for sequelae among 279 patients with hematogenous pyogenic vertebral osteomyelitis.

Risk factor	No sequelae ($n = 200$)	Sequelae ($n = 79$)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Age ≥ 65 years	102 (51.0)	54 (68.4)	2.08 (1.20–3.59)	0.009	2.05 (1.13–3.70)	0.02
Male sex	108 (54.0)	34 (43.0)	0.64 (0.38–1.09)	0.10		
Underlying illness/conditions						
Diabetes mellitus	57 (28.5)	25 (31.6)	1.16 (0.66–2.04)	0.60		
Malignancy	16 (8.0)	3 (3.8)	0.45 (0.13–1.60)	0.21		
Liver cirrhosis	13 (6.5)	2 (2.5)	0.37 (0.08–1.70)	0.25		
Immunosuppression	12 (6.0)	3 (3.8)	0.62 (0.17–2.25)	0.57		
End-stage renal disease	6 (3.0)	4 (5.1)	1.72 (0.47–6.28)	0.48		
Rheumatic disease	8 (4.0)	2 (2.5)	0.62 (0.13–3.00)	0.73		
Clinical data						
Time to diagnosis, days, median	25 (10–50)	28 (7–41)	1.00 (0.99–1.01)	0.76		
Back pain	180 (90.0)	72 (91.1)	1.14 (0.46–2.82)	0.77		
Body temperature > 38 °C	102 (51.0)	44 (55.7)	1.21 (0.72–2.04)	0.48		
Neurologic deficit	27 (13.5)	31 (39.2)	4.14 (2.26–7.59)	<0.001	3.38 (1.77–6.44)	<0.001
Neurologic deficit at diagnosis	23 (11.5)	21 (26.6)	2.79 (1.44–5.40)	0.002		
New neurologic deficit during the treatment	4 (2.0)	10 (12.7)	7.10 (2.16–23.38)	0.001		
Laboratory data						
WBC, $\times 10^9$/L, median (IQR)	11.3 (7.7–15.4)	11.9 (9.0–16.0)	1.00 (1.00–1.00)	0.07		
CRP, mg/dL, median (IQR)	11.6 (5.5–19.1)	16.1 (6.8–25.4)	1.04 (1.01–1.07)	0.005		
CRP ≥ 10 mg/dL	111 (55.5)	58 (73.4)	2.22 (1.25–3.92)	0.006	2.01 (1.09–3.71)	0.03
ESR, mm/h, median (IQR)[a]	77 (55–103)	78 (55–84)	1.00 (0.99–1.01)	0.41		
Positive blood cultures	139/187 (74.3)	59/74 (79.7)	1.36 (0.71–2.62)	0.36		
Staphylococcus aureus infection	106 (53.0)	54 (68.4)	1.92 (1.11–3.32)	0.02		
Radiologic data						
Involvement of >2 vertebral bodies	63 (31.5)	26 (32.9)	1.07 (0.61–1.86)	0.82		
Involvement of cervicothoracic spine	54 (27.0)	31 (39.2)	1.75 (1.01–3.02)	0.045		
Involvement of lumbosacral spine	162 (81.0)	57 (72.2)	0.61 (0.33–1.11)	0.11		
Epidural/paravertebral abscess	111 (55.5)	59 (74.7)	2.37 (1.33–4.22)	0.003	2.00 (1.07–3.72)	0.03
Epidural abscess	64 (32.0)	36 (45.6)	1.78 (1.04–3.03)	0.03		
Paravertebral abscess	85 (42.5)	46 (58.2)	1.89 (1.11–3.20)	0.02		
Recurrence within 12 months	13 (6.5)	14 (17.7)	3.10 (1.38–6.94)	0.004	2.45 (1.003–5.97)	0.049
Microbiological recurrence	8 (4.0)	12 (15.2)	4.30 (1.68–10.97)	0.001		
Clinical recurrence	5 (2.5)	2 (2.5)	1.01 (0.19–5.33)	>0.99		

NOTE. Data are numbers (%) of patients, unless otherwise indicated. aOR = adjusted odds ratio; CI = confidence interval; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; IQR = interquartile range; OR = odds ratio; WBC = white blood cell.
[a] Measured in 227 patients (191 in the no-sequelae group and 36 in the sequelae group).

early drainage of abscess, and antibiotic therapy of appropriate duration to prevent recurrence.

We found that 28.3% of our patients with hematogenous pyogenic VO had sequelae at 12 months after treatment completion. This rate is similar to that reported in a previous systematic review, in which 27.3% (103/377) of VO patients had residual sequelae after completing treatment (Mylona et al., 2009). Despite the considerable rates of residual sequelae after treatment of VO, the patient populations at high risk

Table 3
Univariate and multivariate analyses of factors associated with sequelae among selected subgroups of patients.

Factor	No sequelae	Sequelae	Univariate analysis		Multivariate analysis	
			OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Patients with neurologic deficit	($n = 27$)	($n = 31$)				
CRP ≥ 10 mg/dL	14 (51.9)	25 (80.6)	3.87 (1.20–12.44)	0.02		
Staphylococcus aureus infection	12 (44.4)	26 (83.9)	6.50 (1.92–22.05)	0.002	6.93 (1.91–25.17)	0.003
Early surgery (within <48 h)	12 (44.4)	5 (16.1)	0.24 (0.07–0.82)	0.02	0.22 (0.06–0.84)	0.03
Patients with epidural/paravertebral abscess	($n = 111$)	($n = 59$)				
Age ≥ 65 years	53 (47.7)	39 (66.1)	2.13 (1.11–4.11)	0.02		
Neurologic deficit	20 (18.0)	26 (44.1)	3.58 (1.77–7.26)	<0.001	3.99 (1.86–8.56)	<0.001
Recurrence within 12 months	4 (3.6)	10 (16.9)	5.46 (1.63–18.27)	0.006	3.27 (1.10–9.72)	0.03
Early drainage (within <72 h)	31 (27.9)	8 (13.6)	0.41 (1.73–0.95)	0.03	0.35 (0.14–0.88)	0.03
Patients with *S. aureus* infection	($n = 106$)	($n = 54$)				
MRSA	41/106 (38.7)	22/54 (40.7)	1.09 (0.56–2.13)	0.80		
Vancomycin MIC ≥1.5 mg/L by Etest[a]	14/16 (87.5)	10/12 (83.3)	0.71 (0.09–5.96)	>0.99		
hVISA phenotype[a]	6/16 (37.5)	1/12 (8.3)	0.15 (0.02–1.49)	0.18		
Initial vancomycin trough <10 mg/L	12/26 (46.2)	3/12 (25.0)	0.39 (0.09–1.77)	0.29		
Receipt of rifampin	17/106 (16.0)	6/54 (11.1)	0.65 (0.24–1.77)	0.40		
Receipt of rifampin plus fluoroquinolone	14/106 (13.2)	5/54 (9.3)	0.67 (0.23–1.97)	0.47		
Patients with *Enterobacteriaceae* infection	($n = 43$)	($n = 17$)				
Ciprofloxacin-resistant strain	9 (20.9)	6 (35.3)	2.06 (0.60–7.10)	0.32		
ESBL-producing *Enterobacteriaceae*	3 (7.0)	2 (11.8)	1.78 (0.27–11.71)	0.62		
Receipt of fluoroquinolone	25 (58.1)	9 (52.9)	0.81 (0.26–2.50)	0.71		

NOTE. Data are numbers (%) of patients, unless otherwise indicated. aOR = adjusted odds ratio; CI = confidence interval; CRP = C-reactive protein; ESBL = extended-spectrum β-lactamase; hVISA = heteroresistant vancomycin-intermediate *S. aureus*; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; OR = odds ratio.
[a] Of the 49 cases of bacteremic MRSA vertebral osteomyelitis, 28 blood isolates were available for molecular and microbiological testing.

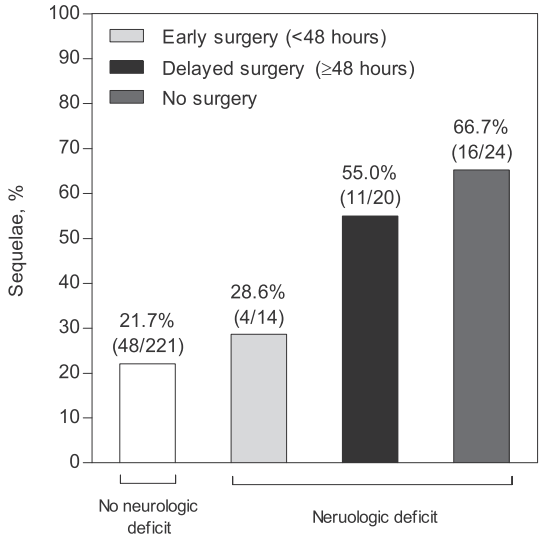

Fig. 1. Sequelae rates of hematogenous pyogenic vertebral osteomyelitis according to neurologic deficit and surgical management for neurologic deficit.

of sequelae and the optimal management strategy are unclear. Many previous studies included a small number of cases, a heterogeneous population, and only vague information on the time points of sequelae assessment. Assessment of sequelae at different time points can lead to unrecognized bias because the functional status following treatment of VO can change over time (Miller et al., 2016). Therefore, we included a number of patients with microbiologically confirmed pyogenic VO who were evaluable for sequelae at the same time point (12 months posttherapy). In this study, we considered pyogenic VO patients with persistent pain to have sequelae. Some may argue that persistent pain should not be considered a sequela because of its subjective nature. However, functional outcomes may be underrecorded if considering neurologic deficit alone, and residual pain and associated disability are common at long-term follow-up even in patients with full neurologic recovery (Miller et al., 2016; O'Daly et al., 2008).

The presence of neurologic deficit and the timing of its surgical correction were independently associated with the functional outcome of patients with pyogenic VO. Although early surgical correction for

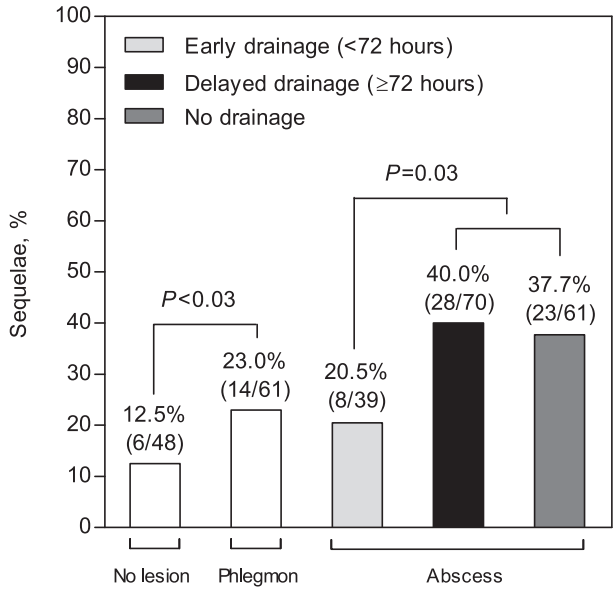

Fig. 2. Sequelae rates of hematogenous pyogenic vertebral osteomyelitis according to characteristics of soft tissue lesions and management for abscess.

neurologic compromise is logically plausible and generally recommended (Berbari et al., 2015; Cottle and Riordan, 2008; Gasbarrini et al., 2005; Gouliouris et al., 2010), supporting evidence is limited. Many previous studies on this subject were observational in nature and did not control for potential confounding factors. The recent study by Lemaignen et al. showed that surgery in pyogenic VO patients with severe neurologic deficit protected against a poor functional outcome, but the association was not significant in a multivariate analysis (hazard ratio, 0.43; $P = 0.06$) (Lemaignen et al., 2017). In this study, multivariate analysis confirmed the protective effect of early surgery on sequelae at 12 months posttherapy. We also showed that, of all documented neurologic deficits, 18.3% occurred during the course of treatment. This rate ranges from 12.0% to 26.0% in previous studies.(Bart et al., 2016; Lemaignen et al., 2017) Notably, the sequelae rate in patients with new neurologic deficit during treatment was higher than that in patients with neurologic deficit at the time of diagnosis of pyogenic VO (71.4% *vs.* 47.7%; $P = 0.12$). We suggest that careful neurological examination be required for hospitalized patients with pyogenic VO, including those with no neurological deficit at the time of diagnosis.

Another important consideration in selecting the optimal treatment strategy for preventing sequelae is management of abscess. In this study, both epidural and paravertebral abscesses were associated with sequelae, and the rate of sequelae was reduced by early abscess drainage. Another potential benefit of early drainage of abscesses is the ability to culture the resulting fluid before exposure to antibiotics for microbiological confirmation (Kim et al., 2012; Rankine et al., 2004). Therefore, early drainage of abscesses may be beneficial in patients with suspected pyogenic VO unless their abscesses cannot or should not be drained (too small or phlegmonous). Although it is widely accepted that patients with clinically significant abscesses associated with spinal cord or nerve root compression require surgical intervention (Berbari et al., 2015; Cottle and Riordan, 2008; Gasbarrini et al., 2005; Gouliouris et al., 2010), little information is available to guide the management of patients with abscesses but no neurologic deficit. Our findings showed that the baseline CRP value was independently associated with the risk of sequelae after completing treatment. Early drainage of abscesses was associated with a lower rate of sequelae in cases with CRP levels ≥10 mg/dL but not in cases with CRP levels <10 mg/dL. This trend was still evident when the analysis was restricted to patients without neurologic deficit. These findings may be explained by the high levels of inflammatory markers observed in pyogenic VO patients with more extensive disease, *S. aureus* infection, and real abscesses (rather than phlegmon) (Euba et al., 2008; Park et al., 2014). Our data suggest that the CRP level may be useful for identifying patients with abscesses at high risk of sequelae and in decisions on early drainage of abscesses in such patients.

In this study, the recurrence of pyogenic VO after completing therapy was significantly related to a higher rate of sequelae (51.9%) at 12 months after initial treatment. It is essential to provide adequate drainage of abscess and duration of antibiotic therapy appropriate for preventing recurrence (Livorsi et al., 2008; McHenry et al., 2002; Park et al., 2016). The current study confirmed that antibiotic treatment of inappropriate duration is associated with a higher risk of recurrence. Most authors recommend minimum treatment duration of 6 weeks for pyogenic VO (Berbari et al., 2015; Bernard et al., 2015; Société de Pathologies Infectieuses de Langue Française (SPILF), 2007; Zimmerli, 2010). A recent multicenter noninferiority trial by Bernard et al. demonstrated that 6 weeks of antibiotic treatment for pyogenic VO was not inferior to 12 weeks of treatment (Bernard et al., 2015). Despite this, some advocate the use of a longer duration of antibiotic therapy in high-risk patients, such as those with MRSA infection and extensive disease (Berbari et al., 2015; Lora-Tamayo and Murillo, 2015). In a previous study of the same patient cohort, we found that an antibiotic therapy of duration ≥8 weeks prevented recurrence in patients with MRSA infection and undrained paravertebral abscess, but antibiotic therapy of 6–8 weeks was sufficient to prevent recurrence in those without these risk factors (Park et al., 2016). Therefore, we suggest that pathogen-

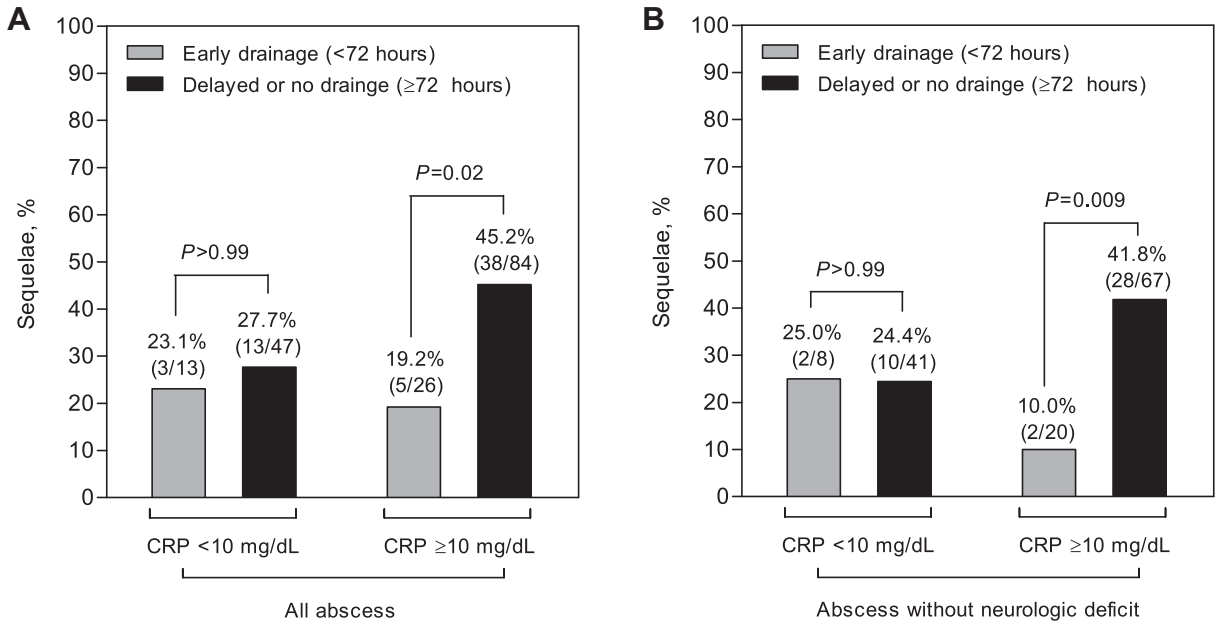

Fig. 3. Sequelae rates of hematogenous pyogenic vertebral osteomyelitis according to timing of abscess drainage and C-reactive protein value among all patients with abscesses (A) and among the subgroup patients with abscesses and no neurologic deficit.

directed antibiotic therapy of at least 6 weeks' duration should be provided to prevent recurrence and its associated sequelae, and longer treatment duration (≥8 weeks) should be considered for patients at high risk of recurrence.

A substantial proportion of our patients were infected with antibiotic-resistant pathogens such MRSA and fluoroquinolone-resistant *Enterobacteriaceae*. We found no correlation between such resistant pathogens and sequelae. In a previous study of hematogenous *S. aureus* VO, MRSA was responsible for as high as 57% of cases, but 17% of patients had residual disability and MRSA was not predictive of residual disability (Livorsi et al., 2008). Some authors suggest fluoroquinolone–rifampin as acceptable alternatives for staphylococcal VO (Berbari et al., 2015; Bernard et al., 2015) because glycopeptides are less active against staphylococci than are antistaphylcoccal β-lactams (Tice et al., 2003). However, our analysis showed no association between use of fluoroquinolone–rifampin and sequelae. Among our patients with infected with *Enterobacteriaceae*, infections due to ciprofloxacin-resistant bacteria tend to higher rate of sequelae, but this did not reach statistical significance. It should be noted that 44.3% of our patients underwent surgery, and so our findings may be due to a greater impact of surgical strategy on residual sequelae than effective antibiotic treatment for antibiotic-resistant infections. Further studies should be performed to clarify the impact of antibiotic resistance and inadequate antibiotic treatment on patients' functional outcome.

Our study had several limitations. First, as with all retrospective studies, some patients were lost to follow-up, and exclusion of these patients may have introduced unrecognized bias. Second, the observational nature of our study and the heterogeneity in treatment regimens preclude any conclusion regarding the association of treatment regimens with patients' functional outcomes. It was unlikely that all patients received adequate antibiotic treatment according to the current guidelines (Berbari et al., 2015; Société de Pathologies Infectieuses de Langue Française (SPILF), 2007). Third, in this study, a large proportion of abscesses (86.4%) were drained surgically, and in such cases, the effect of early percutaneous drainage on functional outcome could not be confirmed. Finally, the proportions of patients with abscesses (61%) and those infected with drug-resistant organisms such as MRSA (22.6%) were high; therefore, caution should be used in extrapolating our results to a different epidemiologic context.

In summary, a large proportion of patients with hematogenous pyogenic VO had risk factors for sequelae after completing treatment. Our data suggest that early identification and close follow-up of patients at risk of sequelae would facilitate provision of optimal care. The optimal management for patients with hematogenous pyogenic VO in terms of preventing sequelae includes early surgery for neurologic deficit, early drainage of abscesses, and antibiotic therapy of appropriate duration.

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Potential conflicts of interest

All authors declare no conflicts of interest and have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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