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Original Article

Clinical characteristics, treatments, and outcomes of hematogenous pyogenic vertebral osteomyelitis, 12-year experience from a tertiary hospital in central Taiwan

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Abstract *Background:* In Taiwan, studies about hematogenous pyogenic vertebral osteomyelitis (HPVO) are limited. We conducted a retrospective study to evaluate the clinical presentations, treatment, and outcomes of patients with the diagnosis of HPVO.
Method: This 12.5-year retrospective study included patients with a diagnosis of HPVO. Medical records of all HPVO patients were thoroughly reviewed and their clinical data were analyzed by the SPSS software.
Result: 414 HPVO cases were included and the mean age was 61.6 ± 13.4 years. The mean duration of symptoms was 29 ± 35.3 days and pain over the affected site was reported by most patients (86.0%). Gram-positive bacteria, especially *Staphylococcus aureus* (162/399 = 40.6%), were the main HPVO pathogens. *Escherichia coli* (42/399 = 10.5%) was the most common gram-negative isolate. Surgery was performed in 68.8% of cases and the mean duration of total antibiotic treatment was 104.7 ± 77.7 days. All-cause mortality and recurrence rates were 6.3% and 18.8%, respectively. In multivariate analysis, polymicrobial infection (OR: 4.154, 95% CI: 1.039–16.604, $p = 0.044$), multiple vertebral body involvement (OR:

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2.202, 95% CI: 1.088—4.457, $p = 0.028$), abscess formation treated with antibiotics alone (OR: 2.912, 95% CI: 1.064—7.966, $p = 0.037$), and the duration of antimicrobial treatment less than 4 weeks (OR: 3.737, 95% CI: 1.195—11.683, $p = 0.023$) were associated with HPVO recurrence. *Conclusion:* In Taiwan, HPVO mainly affected the elderly and *S. aureus* remained the most common HPVO pathogen. In patients with risk factors associated with HPVO recurrence, a longer duration (≥6 weeks) of antimicrobial therapy is suggested.

Introduction

Vertebral osteomyelitis (VO) is an important medical issue and its incidence is increasing in recent years.[1,2] According to its causative agents, VO can be categorized into pyogenic, granulomatous (tuberculous,[3] brucellosis, fungal), and parasitic subtypes. In most cases of pyogenic vertebral osteomyelitis (PVO), the hematogenous spreading of the bacteria from a distant site is the major route in causing infection.[4] Among the culture-proven PVO cases, Gram-positive cocci (GPCs), especially *Staphylococcus aureus*, account for the majority of causative pathogens (26—93%). However, 5—56% of PVO cases are caused by Gram-negative bacilli (GNBs) and 9% by polymicrobial infections.[5,6] Despite relatively few GNB PVO cases, such infection has attracted significant attention recently because of an increasing trend of antimicrobial resistance among these pathogens.[7] Moreover, in the cases where the causative pathogens could not be identified, the so-called culture-negative PVO had been very rarely addressed in the literature.[8] There had been some studies reporting the PVO in Taiwan for the past decades, but only one of them focused on the comparison of the clinical features and the outcomes between GPC-related PVO and GNB-related ones.[9—15] The goals of this study were to evaluate the differences of clinical presentations, treatments, and outcomes among the hematogenous PVO (HPVO) cases caused by GPCs, GNBs, polymicrobial agents, and culture-negative HPVO in Taiwan.

Materials and methods

Study setting and duration

From December 2002 through May 2014, we retrospectively conducted an observational cohort study at China Medical University Hospital (CMUH), a tertiary hospital in central Taiwan, for patients with a discharge diagnosis of vertebral osteomyelitis, discitis, infectious spondylitis, or infectious spondylodiscitis. The electronic medical records of all patients were reviewed and analyzed. The study was approved by the CMUH institutional review board (CMUH104-REC2-173).

Inclusion and exclusion criteria

Patients were excluded if there was a non-hematogenous source of vertebral infection, which included (1) previously placed artificial implants, (2) received laminectomy within 1 year prior to the VO diagnosis, (3) any spine penetrating trauma, or (4) the presence of decubitus ulcer at the same level of VO.[16] Only adult patients (≥18 years) who received antibiotics treatment ≥ 14 days and had completed electronic medical record were included.

Definitions

The diagnosis of HPVO was categorized into 3 types. Definite hematogenous vertebral osteomyelitis (D-VO) was diagnosed when a microorganism(s) was isolated from the spine or para-spinal tissues.[8] Probable hematogenous vertebral osteomyelitis (P-VO) was defined as a patient had compatible clinical signs/symptoms and specific radiologic features (either magnetic resonance Imaging [MRI], computed tomography [CT] or bone scan) of vertebral infection accompanied with a positive blood culture which was performed at the time of diagnosis of HPVO; in the case of common skin contaminants, at least 2 sets of positive blood cultures were required.[8,17,18] Culture-negative hematogenous vertebral osteomyelitis (CN-VO) was defined as the patients had compatible clinical signs/symptoms and featured radiologic findings, but no causative agent(s) was isolated.[7]

Comorbidity were classified according to the McCabe classification (category 1: non-fatal diseases, such as diabetes mellitus and intravenous drug users; category 2: ultimately fatal diseases, such as liver cirrhosis, end stage renal disease and malignancy; category 3: rapidly fatal diseases, such as leukemia).[19] Preexisting or synchronous infection was defined as a documented infection at site other than spine within 1 month prior to or at the diagnosis of VO.[15] Onset-to-diagnosis duration was defined as the time elapsed between documented symptom(s) to the diagnosis of HPVO. Multiple vertebral bodies involvement was defined as involvement ≥3 vertebral bodies.[4,16,20] If a surgical procedure was performed within 2 weeks after HPVO diagnosis, it was defined as immediate operation; otherwise, it was defined as delayed operation.

Outcomes of patients were evaluated using following definitions. Recurrence was defined as patients who had any recurrent symptoms and signs (such as fever, pain on the affect site, and abnormal inflammatory markers in the absence of other causes) within 6 months after completion of antibiotic treatment and received a second course of antibiotics.[21] Recovery was defined as survival and disappearance of all signs and symptoms of infection in the

subsequent 6 months since the end of antimicrobial therapy, regardless persistence of clinically significant residual disability, such as motor weakness or paralysis, neurogenic bladder, or pain.[4,8,20,22] Time to recurrence was defined as the duration from the end of the first course of antibiotics therapy to the beginning of the second course of antibiotics therapy. Patients who were followed less than 6 months after completion of antibiotic treatment were regarded as loss to follow-up and were excluded from the analysis of recurrence and recovery.

Statistical analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 22.0; Chicago IL).

Categorical variables were compared using chi-squared or Fisher's exact tests. Continuous variables were compared using Student's t-tests or Mann—Whitney U tests. To identify independent predictors for HPVO recurrence, all significant variables upon univariate analyses were included in a logistic regression model. All statistical tests were two-tailed, and a $p \leq 0.05$ was considered to be statistical significance.

Results

A total of 502 patients with a diagnosis of VO were identified. Fifty-four patients with mycobacterial or fungal infections were excluded. Additional 34 patients were also excluded due to mixed bacterial and mycobacterial infections, mixed bacterial and fungal infections, no identifiable pathogen but clinically suspected mycobacterial infection, age less than 18 years, treatment duration less than 14 days, or P-VO without image study. Finally, 414 HPVO patients were included and categorized into 4 groups (Fig. 1). Group 1 patients (92 cases, 22.2%) were infected by GNBs (GNB-VO); group 2 (224 cases, 54.1%) were those infected by GPCs (GPC-VO); group 3 (31 cases, 7.5%) included patients with polymicrobial infections (Poly-VO); group 4 (67 cases, 16.2%) were culture-negative cases (CN-VO). Table 1 shows the demographics, clinical features, treatment, and outcomes of these patient groups. A comparison between patients with D-VO and P-VO is provided in the Supplementary Table 1 (ST1). The mean age of all HPVO patients was 61.6 ± 13.4 years and 65.5% of the patients were male. Despite male was the predominant gender in each patient group, the percentage of female was significantly higher in the GNB-VO and CN-VO group than those of the GPC-VO and Poly-VO group. Diabetes mellitus was the most common comorbidity (36.7%), followed by liver cirrhosis (12.3%). According to the McCabe classification, a lower proportion of patients in the GPC-VO group had category 1 diseases ($p = 0.012$); however, a higher proportion of patients in the Poly-VO group had category 2 diseases ($p = 0.003$). Urinary tract infection (UTI, 25.1%) was the most common preexisting/synchronous infection in all HPVO cases, and the proportion of such infection was significantly lower in the GPC-VO group (18.8%, $p = 0.015$) than the other 3 groups.

Pain on the affected site was the most common symptom in all patient groups (86.0%, range 83.9—91.0%). However, fever was unexpectedly recorded only in less than half of all patients (48.3%, range 40.4—64.5%). The mean onset-to-diagnosis duration was 29.0 ± 35.3 days and there was no

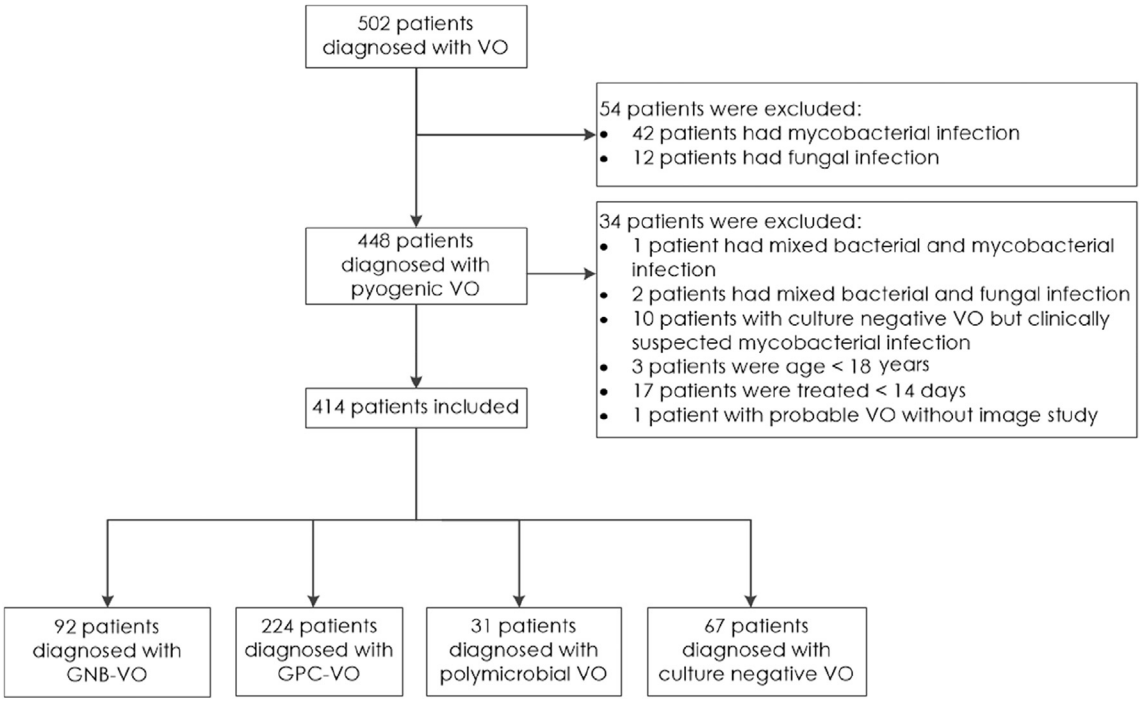

Figure 1. The flowchart of patients included in this study. Abbreviations: GNB = Gram-negative bacilli; GPC = Gram-positive cocci; VO = vertebral osteomyelitis.

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

Variable	GNB-VO, n = 92	GPC-VO, n = 224	Poly-VO, n = 31	CN-VO, n = 67	*p* Value
Age (year), mean ± SD	62.0 ± 12.5	61.2 ± 13.5	62.2 ± 14.1	62.0 ± 14.0	0.931
Gender, female	39 (42.4)	63 (28.1)	9 (29.0)	32 (47.8)	**0.007**
Comorbidity					
Diabetes mellitus	36 (39.1)	76 (33.9)	15 (48.4)	25 (37.3)	0.422
Intravenous drug users	4 (4.3)	27 (12.1)	3 (9.7)	2 (3.0)	**0.043**
Liver cirrhosis	15 (16.3)	28 (12.5)	4 (12.9)	4 (6.0)	0.276
End stage renal disease	0 (0)	23 (10.3)	7 (22.6)	4 (6.0)	**<0.001**
Malignancy	7 (7.6)	21 (9.4)	8 (25.8)	2 (3.0)	**0.003**
Preexisting or synchronous infection					
Pneumonia	14 (15.2)	23 (10.3)	7 (22.6)	5 (7.5)	0.103
Urinary tract	30 (32.6)	42 (18.8)	10 (32.3)	22 (25.1)	**0.015**
Intra-abdomen	11 (12.0)	17 (7.6)	3 (9.7)	1 (1.5)	0.105
Bloodstream	15 (16.3)	39 (17.4)	6 (19.4)	4 (6.0)	0.128
Skin and soft tissue	4 (4.3)	17 (7.6)	1 (3.2)	2 (3.0)	0.389
Symptom					
Fever	44 (47.8)	109 (54.5)	20 (64.5)	27 (40.3)	0.172
Pain on the affect site	80 (87.0)	188 (83.9)	27 (87.1)	61 (91.0)	0.510
Limbs weakness	25 (27.2)	63 (28.1)	10 (32.3)	15 (22.4)	0.735
Limbs numbness	15 (16.3)	46 (20.5)	1 (3.2)	16 (23.9)	0.076
Paralysis	3 (3.3)	12 (5.4)	4 (12.9)	4 (6.0)	0.246
Onset-to-diagnosis duration (day)	26.7 ± 32.3, n = 89	26.9 ± 32.3, n = 220	29.4 ± 27.8, n = 30	38.5 ± 48.2	0.110
Laboratory data at vertebral osteomyelitis diagnosis					
WBC count (/mm^3, mean ± SD)	11,055 ± 5421	12,102 ± 6173	12,904 ± 5736	9, 540 ± 4,031, n = 66	**0.006**
C-reactive protein (mg/dL, mean ± SD)	11.2 ± 9.5, n = 88	13.2 ± 10.4, n = 215	15.1 ± 9.8	7.4 ± 6.2, n = 63	**<0.001**
ESR, mm/h, (mean ± SD)	75.1 ± 31.9, n = 91	82.2 ± 30.5, n = 222	90.0 ± 32.8	73.9 ± 31.2	**0.026**
Radiologic data					
Cervical spine	9 (9.8)	24 (10.7)	4 (12.9)	8 (11.9)	0.954
Thoracic spine	23 (25.0)	53 (23.7)	1 (3.2)	15 (22.4)	0.067
Lumbar spine	66 (71.7)	161 (71.9)	25 (80.6)	48 (71.6)	0.771
Sacral spine	14 (15.2)	37 (16.5)	8 (25.8)	10 (14.9)	0.541
Multiple vertebral bodies involvement	15 (16.3)	52 (23.2)	10 (32.3)	9 (13.4)	0.086
Epidural abscess	35 (38.0)	96 (42.9)	12 (38.7)	20 (29.9)	0.289
Paraspinal abscess	37 (40.2)	82 (36.6)	8 (25.8)	12 (17.9)	**0.012**
Psoas abscess	27 (29.3)	45 (20.1)	8 (25.8)	13 (19.4)	0.285
Treatment					
Immediate operation	45 (48.9)	119 (53.1)	19 (61.3)	31 (46.3)	0.493
Delayed operation	23 (25.0)	34 (15.2)	4 (12.9)	11 (16.4)	0.176
Drainage without operation	7 (7.6)	29 (12.9)	7 (22.6)	3 (4.5)	**0.029**
Total duration of antibiotics therapy (day)	113.1 ± 70.5	102.0 ± 74.6	116.8 ± 99.7	96.6 ± 86.0	0.420
Intravenous antibiotics therapy duration (day)	41.5 ± 21.0, n = 90	34.9 ± 26.8, n = 223	69.2 ± 71.2	29.2 ± 19.2, n = 64	**<0.001**
Oral antibiotics therapy duration (day)	88.2 ± 69.0, n = 77	73.2 ± 71.5, n = 204	84.6 ± 100.9, n = 17	73.5 ± 79.5, n = 63	0.452
Outcome					
All-cause mortality	5 (5.4)	11 (4.9)	9 (29.0)	1 (1.5)	**<0.001**
Recurrence[a]	13 (17.3), n = 75	31 (19.1), n = 162	6 (40.0), n = 15	7 (13.5), n = 52	0.138
Recovery[b]	62 (82.7), n = 75	131 (80.9), n = 162	9 (60.0), n = 15	45 (86.5), n = 52	0.138

[a] n = 304.
[b] n = 304.
Abbreviation: CN = culture-negative; ESR = erythrocyte sedimentation rate; GNB = Gram-negative bacilli; GPC = Gram-positive cocci; SD = standard deviation; VO = vertebral osteomyelitis; WBC = white blood cell.
Data are presented as case number (percentages) or mean ± SD.
Statistical significances are represented in bold.

significant difference between each patient group ($p = 0.831$). Compared to the GPC-VO group, the white blood cell count (WBC, $p = 0.008$) and C-reactive protein value (CRP, $p < 0.001$) were significantly lower in the CN-VO group. Patients with abscess formation in the surrounding tissues of spine had a higher WBC count ($12007.7 \pm 5892.9/mm^3$ vs. $9426.6 \pm 4574.2/mm^3$, $p < 0.001$) and CRP value (12.8 ± 10.1 mg/dL vs. 8.7 ± 8.1 mg/dL, $p = 0.001$) than those without abscess formation. Magnetic resonance imaging, CT, and bone scan were performed in 379 (91.5%), 143 (34.5%) and 133 (32.1%) patients, respectively. Lumbar spine was the most common affected site (72.5%), followed by thoracic spine (22.2%). Overall, 86 patients (20.8%) had multiple vertebral body involvement and the proportion of such involvement in each patient group was not different significantly ($p = 0.086$). Regarding the VO site and the proportion of patients with epidural and psoas muscle abscess formation, there was no significant difference among these 4 patient groups. Compared with the other 3 groups, however, patients in the CN-VO group had significantly lower proportion to develop paraspinal abscess (17.9%, $p = 0.003$).

Table 2 shows the microorganisms isolated from the blood, soft tissues, or bone. Among the GPCs, *Staphylococcus* species (72.0%) was the most common, followed by *Streptococcus* species (21.2%). *S. aureus* was the main member (90.0%) of the *Staphylococcus* species and 30.9% of them were methicillin-resistant. This pathogen was also more commonly isolated from patients with abscess formation in the surrounding tissues of spine (42.7% vs. 24.1%, $p = 0.002$). In GNB, *Escherichia coli* (32.3%) was the most common isolate, followed by *Klebsiella* species (17.7%), *Enterobacter* species (9.2%), and *Salmonella* species (9.2%). The data of antimicrobial susceptibility for various microorganisms were provided in ST 2–3.

A total of 285 patients (68.8%) received surgical intervention. Among these cases, 75.1% of them received immediate operation and the remaining patients received delayed operation. The most common type of surgery in both immediate and delayed operation was discectomy (58.9% and 61.1%), followed by laminectomy (41.5% and 30.6%). The proportion of patients receiving immediate or delayed operation and the types of surgery among these 4 patient groups were not statistically different (Table 1). The proportion of patients receiving drainage without operation was significantly higher in the Poly-VO group (22.6%, $p = 0.029$) than the other 3 groups. The mean duration of intravenous (IV) antibiotic therapy was 38.1 ± 31.8 days, and patients in the Poly-VO group received significantly longer duration of IV antimicrobial therapy (69.2 ± 71.2 days, $p < 0.001$) than the other 3 groups. The oral antibiotic therapy duration and total duration of antibiotic therapy was 77.0 ± 73.9 days and 104.7 ± 77.7 days, respectively. Among these 4 patient groups, there was no difference with regard to the duration of oral antimicrobial therapy and the total duration of antibiotic therapy. The presence or absence of abscess formation did not influence the duration of oral ($p = 0.774$) and IV ($p = 0.641$) antimicrobial therapy.

The outcomes of the HPVO patients are shown in Table 1. Overall mortality rate was 6.3% and a higher rate was observed in the Poly-VO group (29.0%, $p < 0.001$).

Table 2 List of 399 microorganisms isolated from hematogenous pyogenic vertebral osteomyelitis.

Pathogens	Number (percentage)
Gram positive bacteria	250 (62.7)
Staphylococcus species	180 (72.0)
Methicillin-susceptible *S. aureus*	112 (44.8)
Methicillin-resistant *S. aureus*	50 (20.0)
Coagulase-negative staphylococci[a]	18 (7.2)
Streptococcus species	53 (21.2)
Streptococcus agalactiae	16 (6.4)
Streptococcus anginosus	6 (2.4)
Streptococcus bovis	4 (1.6)
Streptococcus constellatus	7 (2.8)
Streptococcus oralis	5 (2.0)
Streptococcus viridans	5 (2.0)
Other streptococcus species[b]	10 (4.0)
Enterococcus species	13 (5.2)
Enterococcus faecalis	9 (3.6)
Other enterococci[c]	4 (1.6)
Other gram positive bacteria[d]	4 (1.6)
Gram negative bacteria	130 (32.6)
Escherichia coli	42 (32.3)
Klebsiella species	23 (17.7)
Salmonella species	12 (9.2)
Enterobacter species	12 (9.2)
Serratia marcescens	9 (6.9)
Pseudomonas species	11 (8.5)
Other Enterobacteriaceae[e]	7 (5.4)
Other gram negative bacteria[f]	14 (10.8)
Anaerobes	19 (4.8)
Gram-positive anaerobes[g]	9 (47.4)
Gram-negative anaerobes[h]	10 (52.6)

[a] Included: 5 *Staphylococcus epidermidis* and 13 not identified coagulase-negative staphylococci.

[b] Included: 2 unidentified group B streptococcus, 1 *Streptococcus dysgalactiae*, 1 *Streptococcus gordonii*, 1 *Streptococcus intermedius*, 1 *Streptococcus mitis*, 1 *Streptococcus parasanguinis*, 1 *Streptococcus pneumoniae*, and 1 *Streptococcus porcinus*.

[c] Included: 3 unidentified *Enterococcus* species and 1 *Enterococcus hirae*.

[d] Included: 2 unidentified gram-positive bacteria, 1 *Erysipelothrix rhusiopathiae* and *1 Aerococcus viridans*.

[e] Included: 1 *Citrobacter koseri*, 1 *Morganella morganii* and 5 *Proteus mirabilis*.

[f] Included: 1 *Acinetobacter baumannii*, 1 *Acinetobacter junii*, 1 *Acinetobacter lwoffii*, 1 *Aeromonas* species, 1 *Bergeyella zoohelcum*, 2 *Burkholderia cepacia*, 1 *Chryseobacterium indologenes*, 1 *Delftia acidovorans*, 1 *Pasteurella pneumotropica*, 1 *Shewanella putrefaciens*, 2 *Stenotrophomonas maltophilia*, 1 *Vibrio fluvialis*.

[g] Included: 2 *Bacillus* species, 3 *Peptostreptococcus micros*, 1 *Peptostreptococcus prevotii*, 2 *Peptostreptococcus magnus*, 1 *Gemella morbillorum*.

[h] Included: 2 *Bacteroides fragilis*, 1 *Bacteroides ovatus*, 1 *Prevotella intermedia*, 1 *Prevotella melanica*, 2 *Fusobacterium nucleatum*, 1 *Veillonella* species, 2 *Prevotella oralis*.

Data are given as case number (percentages).

Eighty-four patients (20.3%) were followed less than 6 months since the end of antibiotic therapy. Among the 330 patients followed for more than 6 months, 57 cases (18.8%) suffered from HPVO recurrence. Although patients in the Poly-VO group had a higher recurrence rate (40.0%) than the other 3 groups, the recurrence rate did not differ significantly between these 4 patient groups ($p = 0.138$). The mean duration of time to recurrence was 68.4 ± 52.3 days. (76.7 ± 49.6 days in GNB-VO group, 69.2 ± 55.3 days in GPC-VO, 53.7 ± 48.3 days in poly-VO group, and 62.1 ± 54.8 days in CN-VO group, $p = 0.831$) Recovery was reported in 247 cases (247/330 = 81.3%). Although recovery rate in the Poly-VO group (60.0%) was lower than the other 3 groups, such difference was also statistically insignificant ($p = 0.138$). The presence or absence of abscess formation did not influence the rates of mortality ($p = 0.952$), or recurrence ($p = 0.906$), and recovery ($p = 0.906$).

Table 3 shows the factors affecting the HPVO recurrence. In univariate analysis, polymicrobial infection ($p = 0.029$), multiple vertebral body involvement ($p = 0.030$), abscess formation treated with antibiotics alone ($p = 0.050$), and the duration of antimicrobial treatment less than 4 weeks ($p = 0.013$) were significantly associated with HPVO recurrence. The male gender had a trend, though not significantly, to be associated with HPVO recurrence (odds ratio [OR]: 1.873, 95% confidence interval [CI]: 0.986–3.560, $p = 0.055$). The recurrence rate did not differ with regard to the performance of operation ($p = 0.198$) and the timing of surgical intervention ($p = 0.742$). In multivariate analysis, we found that polymicrobial infection (OR: 4.154, 95% CI: 1.039–16.604, $p = 0.044$), multiple vertebral body involvement (OR: 2.202, 95% CI: 1.088–4.457, $p = 0.028$), abscess formation treated with antibiotics alone (OR: 2.912, 95% CI: 1.064–7.966, $p = 0.037$), and the duration of antimicrobial treatment less than 4 weeks (OR: 3.737, 95% CI: 1.195–11.683, $p = 0.023$) remained to be the risk factors affecting the recurrence of HPVO.

Discussion

Like the results reported by Mylona et al.,[5] our study showed that GNB-VO and Poly-VO accounted for 22.2% and 7.5% of all PVO cases, respectively. In comparison with the GPC-VO and Poly-VO groups, patients in the GNB-VO group were more likely to be associated with female gender. Such observation might be partially explained by a higher prevalence rate of UTI (39.2%) in our female patients. Similar observation was also reported by Kang et al.[17] Consistent with prior studies,[16,17] pain on the affected site was the most common symptom of HPVO in our study. In the absence of specific signs and symptoms and frequent absence of fever, the diagnosis of PVO may be considerably delayed.[23]

S. aureus remained the most common isolate in GPC-VO; however, only 30.9% of them were methicillin-resistant *S. aureus* (MRSA) and this MRSA proportion was lower than that of other reports.[17,20] Such difference may be explained by the geographic difference in MRSA distribution, the specimen type, and collection methods used.[24] Similar to the results reported by Park et al.,[20] *E. coli* was the most common GNB, followed by *Klebsiella* species. In a cohort study conducted by Kang et al.,[17] the authors found that there was no difference between GPC and GNB patient groups in the laboratory data, the involved site, or abscess formation. Comparable results were also observed in our patients. Similar to the results reported by Kim et al.,[7] patients in the CN-VO group had a lower WBC count ($p = 0.002$), CRP value ($p < 0.001$), and a lower rate to develop paraspinal abscess ($p = 0.003$) than the culture-proven patients.

Compared to the observations made by Park et al.,[20] our patients had a higher HPVO recurrence rate (18.8% vs. 9.9%). According to the results presented by Park and his colleagues, 110 patients in the present study complied with the "high-risk" group of HPVO recurrence. Among these "high-risk" patients, 81.8% of them received greater than 8-week antimicrobial therapy; however, 14.4% of these cases (>8 weeks therapy) still suffered from another HPVO episode and such recurrence rate was still higher than that reported by Park et al. (9.6%). Such discrepancy in the recurrence rate between Park's and our study, either for all patients or patients at "high-risk" of recurrence, might be explained by the different patient population or a shorter duration of intravenous antimicrobial therapy (median duration, 31 days vs. 49 days) in the present study. Additionally, we also found several factors to be associated with HPVO recurrence, such as polymicrobial infection, multiple vertebral body involvement, abscess formation treated with antibiotics alone, and treatment duration less than 4 weeks. In an early study,[4] the authors also disclosed that patients with ≥3 vertebral body involvement had a significantly higher rate of recurrence than those with <3 vertebral body involvement.

Table 3 Factors predict the recurrence of hematogenous pyogenic vertebral osteomyelitis.

Variable	Univariate analysis			Multivariate analysis		
	OR	95%CI	*p* Value	OR	95%CI	*p* Value
Polymicrobial infection	4.286	1.163–15.793	0.029	4.154	1.039–16.604	**0.044**
Male gender	1.873	0.986–3.560	0.055	1.666	0.844–3.288	0.141
Multiple vertebral bodies involvement	2.074	1.075–4.003	0.030	2.202	1.088–4.457	**0.028**
Any abscess formation and treated medical alone	0.379	0.144–0.998	0.050	2.912	1.064–7.966	**0.037**
The duration of antimicrobial treatment less than 4 weeks	3.702	1.317–10.409	0.013	3.737	1.195–11.683	**0.023**

Abbreviation: CI = confidence interval; OR = odds ratio.
Statistical significances in multivariable analysis are represented in bold.

Regarding the duration in treating VO, most guidelines suggested 6—12 weeks as the standard of antimicrobial therapy.[1,23,25,26] In a recent randomized clinical trial conducted by Bernard et al.,[27] they found that 6-week antibiotics therapy was non-inferior to 12-week treatment. Likewise, a recent guideline proposed by the Infectious Diseases Society of America also recommended 6-week antibiotic treatment for HPVO.[28] However, in the presence of abscess(es) in the surrounding tissues of spine (as our cases), multidrug-resistant microorganisms, or the impossibility for using an optimal antibiotic therapy,[23,29] longer duration of antibiotic treatment may be required for patients with HPVO. In the report by Bernard et al., only 19.4% of patients (20.5% in 6-week group and 18.3% in 12-week group) were reported to have abscess formation in the surrounding tissues of spine.[27] Both In the report by Park et al.[20,30] and our study, a considerable proportion of patients (from 48.1% to 49.3%) had para-spinal and/or psoas muscle abscess formation, a possible risk factor for HPVO recurrence, and longer duration of antibiotics therapy ($\geq$8 weeks) was suggested.[20,30]

There were limitations in our study. First, this was a retrospective study and some clinical data were missed or incomplete, including neurological sequelae or physical disability. We excluded those patients (20.3%) who were followed for less than 6 months since the end of antibiotic treatment from the analysis of recurrence and recovery. Such strategy may lead to underestimate the number of patients with recurrence and recovery. Another limitation was that the recurrent cases were not all microbiologically proven; this may overestimate the recurrence rate or underestimate the number of recovery cases. Finally, the inability to address the adherence of medication would influence the results of outcome.

In Taiwan, *S. aureus* remained the most common agent in causing HPVO. Gram-negative microorganisms should be seriously considered as causative agent of HPVO among patients with preexisting or synchronous UTI. Poly-VO had higher mortality rate. In patients with factors associated with HPVO recurrence, we suggested a longer duration (at least $\geq$ 6 weeks) of antimicrobial therapy to prevent HPVO recurrence.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jmii.2017.08.002.