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Microbiologically and Clinically Diagnosed Vertebral Osteomyelitis: Impact of Prior Antibiotic Exposure

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We retrospectively reviewed medical records to identify the factors that affect the results of culture in patients with pyogenic vertebral osteomyelitis. In multivariate analysis, the presence of paravertebral abscess was associated with positive results of microbiologic culture. Prior antibiotic exposure, especially of longer duration, was strongly associated with negative results.

Pyogenic vertebral osteomyelitis (PVO) is an infectious disease of the vertebrae or paravertebral structures caused by a variety of bacteria (4, 9). Once a diagnosis of PVO is made, long-term antibiotics are necessary. Because the choice of antibiotic depends on the etiologic microorganism, it is important to identify the pathogen. Most PVO patients have one or more of the following: fever, leukocytosis, and elevation of inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate (1, 2, 5, 8, 11). As a result, empirical antibiotics are frequently used before a specimen is obtained for culture (14). Some factors are related to the results of microbiologic diagnosis of PVO (3), and among them, an effect of prior antibiotic exposure has been reported in some studies (6, 9). Several reports have suggested that prior exposure has a negative effect on microbiologic diagnosis (7, 10, 15), but others suggest that this is not the case (12). All of these studies had limitations, such as small sample size, heterogeneous patient populations that included tuberculous vertebral osteomyelitis and postoperative vertebral osteomyelitis, and failure to consider duration of antibiotic exposure.

To identify the factors associated with positive results of microbiologic diagnosis in patients with PVO and to investigate the effect of prior antibiotic exposure, we retrospectively collected the medical records of patients diagnosed with PVO from September 2003 through December 2009 in two university-affiliated hospitals. The diagnostic criteria of PVO were adapted from previous reports (5, 11, 13). Among the patients who were diagnosed as having PVO, those who underwent neither tissue biopsy procedures nor blood culture were excluded. Also excluded were patients who had undergone spinal surgery or spinal analgesia within 2 years of diagnosis and patients who turned out to have tuberculous vertebral osteomyelitis, as shown by growth of *Mycobacterium tuberculosis*, the presence of granulomatous inflammation in pathology, and/or positive results of PCR for *M. tuberculosis* in biopsy tissue. The included patients were divided into two groups: (i) microbiologically diagnosed PVO (M-PVO), if microbiologic diagnosis was achieved by culture of vertebral tissue and/or blood, and (ii) clinically diagnosed PVO (C-PVO), if culture failed to reveal microorganisms. Antibiotic exposure was defined as patients being exposed to antibiotics prior to obtaining vertebral tissue or blood samples for culture—whichever was first. Duration of antibiotic exposure was defined as the time between initiation of antibiotics and obtaining specimens for culture. If a patient in the M-PVO group underwent microbiologic examination two or more times, duration of antibiotic exposure was defined as the time between initiation of antibiotic and obtaining the specimen that gave the first positive outcome. If a patient in the C-PVO group underwent culture two or more times, duration of antibiotic exposure was defined as the time between initiation of antibiotic and the time the first specimen for culture was obtained.

During the 6-year period, a total of 106 patients with community-acquired PVO were identified, of whom 5 underwent neither tissue nor blood culture. Of the 101 patients who underwent tissue and/or blood culture, 71 (70.3%) were in the M-PVO group and 30 (29.7%) were in the C-PVO group. Baseline characteristics are shown in Table 1.

Overall, 22.8% (23 of 101) of the patients were exposed to antibiotics prior to specimen culture. In the M-PVO group, 12.7% (9 of 71) were exposed prior to obtaining specimens, whereas in the C-PVO group, the proportion was 46.7% (14 of 30) ($P < 0.001$). The median durations of prior antibiotic exposure were 4.0 days (range, 1 to 20 days) among the M-PVO patients and 8.5 days (range, 1 to 40 days) among the C-PVO patients ($P = 0.124$).

Staphylococcus aureus constituted 36.6% (26 of 71) of the total isolates, and of these, 19.2% (5 of 26) were methicillin resistant. Viridans group streptococcus was isolated in 13 (18.3%) patients, *Streptococcus agalactiae* in 6 (8.5%) patients, and *Streptococcus pneumoniae* in 3 (4.2%) patients. Gram-negative organisms were isolated in 13 patients, of which 7 were *Escherichia coli* and 3 *Pseudomonas aeruginosa*.

Univariate analysis was carried out by logistic regression for all variables collected. In the univariate analysis, the presence of paravertebral abscess, elevated white blood cell count, proportion of polymorphonuclear leukocytes, and C-reactive protein levels were related to positive outcome, whereas longer duration of previous antibiotic exposure was related to negative outcome. In multivariate analysis, the presence of paravertebral abscess and prior antibiotic exposure of longer duration were independently associated with the outcome of microbiologic diagnosis (Table 2).

In this study, we obtained a similar result to previous studies in

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TABLE 1 Baseline characteristics and clinical findings in M-PVO and C-PVO patients and univariate analysis of factors associated with culture positivity[a]

Parameter	Result for: M-PVO ($n = 71$)	C-PVO ($n = 30$)	*P* value	OR (95% CI)
Age (yr)[b]	57.8 (± 16.1)	63.4 (± 13.9)	0.099	0.98 (0.95–1.01)
No. (%) of patients male	46 (64.8)	18 (60.0)	0.648	1.23 (0.51–2.95)
No. (%) of patients with underlying disease/treatment:				
Hypertension	16 (22.5)	9 (30.0)	0.427	0.68 (0.26–1.77)
Diabetes mellitus	19 (26.8)	11 (36.7)	0.319	0.63 (0.25–1.57)
Liver cirrhosis	9 (12.7)	7 (23.3)	0.233[c]	0.48 (0.16–1.43)
Chronic renal failure	3 (4.2)	1 (3.3)	1.000[c]	1.28 (0.13–12.8)
Previous anticancer chemotherapy	5 (7.0)	0	0.318[c]	N.A.
No. (%) of patients with:				
Pain	65 (91.5)	27 (90.0)	1.000[c]	1.21 (0.28–5.17)
Fever	32 (45.1)	10 (33.3)	0.274	1.64 (0.64–4.00)
Neurological deficit	11 (15.5)	2 (6.7)	0.334[c]	2.57 (0.53–12.4)
Mean time before hospital visit (days)[b]	42.4 ± 90.8	45.4 ± 45.5	0.865	1.00 (0.99–1.01)
No. (%) of patients with previous antibiotic exposure	9 (12.7)	14 (46.7)	<0.001	0.17 (0.06–0.45)
Median (range) duration of previous antibiotic exposure (days)[d]	4.0 (1–20)	8.5 (1–40)	0.124[e]	0.86 (0.77–0.96)
No. (%) of patients with previous antibiotic exposure duration of:				
1–3 days	3 (4.2)	2 (6.7)	0.290	0.39 (0.06–2.52)
4 or more days	6 (8.5)	12 (40.0)	<0.001	0.13 (0.04–0.40)
No. (%) of patients with percutaneous biopsy	39 (54.9)	21 (70.0)	0.159	0.52 (0.21–1.30)
No. (%) of patients with open biopsy	29 (40.8)	10 (33.3)	0.479	1.38 (0.57–3.38)
Specific area affected			0.038	
C-spine	5 (7.0)	0		
T-spine	9 (12.7)	1 (3.3)		
L-spine	44 (62.0)	18 (60.0)		
CT-spine	1 (1.4)	1 (3.3)		
TL-spine	6 (8.5)	1 (3.3)		
LS-spine	6 (8.5)	9 (30.0)		
No. (%) of patients with abscess:				
Psoas	21 (29.6)	5 (16.7)	0.175	2.10 (0.71–6.23)
Paravertebral	36 (50.7)	7 (23.3)	0.011	3.38 (1.29–8.88)
Epidural	34 (47.9)	14 (46.7)	0.911	1.05 (0.45–2.47)
WBC count (1,000/mm^3)	11.849 ± 6.227	8.421 ± 3.171	<0.001	1.19 (1.04–1.35)
PMN (%)	78.2 ± 12.2	70.2 ± 11.3	0. 003	1.06 (1.12–1.10)
CRP (mg/dl)	11.18 ± 9.21	5.75 ± 5.28	<0.001	1.11 (1.03–1.20)
ESR (mm/h)	58.5 ± 29.1	54.9 ± 18.5	0.487	1.01 (0.99–1.02)

[a] M-PVO, microbiologically diagnosed pyogenic vertebral osteomyelitis; C-PVO, clinically diagnosed pyogenic vertebral osteomyelitis; NA, not applicable; WBC, white blood cell counts; PMN, polymorphonuclear leukocytes; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; OR, odds ratio; CI, confidence interval. C-spine, cervical spine; T-spine, thoracic spine; L-spine, lumbar spine; CT-spine, cervicothoracic spine; TL-spine, thoracolumbar spine; LS-spine, lumbosacral spine.
[b] Values are means ± standard deviations.
[c] Fisher's exact test.
[d] Values are medians with ranges.
[e] Mann-Whitney test.

that antibiotic exposure prior to microbiologic diagnosis was associated with negative outcome of culture (7, 10, 15). We also analyzed the impact of previous antibiotics in a quantitative manner: if there were 4 or more days of antibiotic exposure, the chance of obtaining positive microbiologic cultures was significantly reduced. A recent retrospective cohort study of hematogenous vertebral osteomyelitis patients found that antibiotic exposure before biopsy did not negatively impact pathogen recovery (12). However, in that study, the median duration of antibiotic exposure was 4 days (range, 1 to 37 days), and the quantitative relationship between antibiotic exposure and culture positivity was not examined. Therefore, we may infer that short-term exposure to antibi-

TABLE 2 Multivariate analysis of factors associated with culture positivity in patients with PVO[a]

Factor	Adjusted OR (95% CI)	*P* value
L-spine involved	0.27 (0.04–1.80)	0.177
Paravertebral abscess	5.91 (1.49–23.4)	0.011
Duration of antibiotic exposure		
None[b]	1.00	
1–3 days	0.09 (0.01–1.49)	0.092
4 or more days	0.05 (0.01–0.24)	<0.001
WBC (1,000/mm^3)	1.06 (0.88–1.29)	0.518
PMN (%)	1.02 (0.96–1.09)	0.471
CRP (mg/dl)	1.07 (0.95–1.21)	0.267

[a] PVO, pyogenic vertebral osteomyelitis; WBC, white blood cell counts; PMN, polymorphonuclear leukocytes; CRP, C-reactive protein; OR, odds ratio; CI, confidence interval, L-spine, lumbar spine.
[b] Not exposed to antibiotics.

otics has a weak negative effect on culture outcome and that the effect increases with duration of antibiotic treatment.

Empirical antibiotic therapy in culture-negative PVO may lead to unnecessary broad-spectrum antibiotic treatment, which leads to the emergence of resistant organisms. There may also be an increased risk of therapeutic failure, when we treat patients with PVO empirically.

In the present study, we reviewed over 100 patients with vertebral osteomyelitis and so were able to analyze the predictive factors in a relatively large sample. However, the number of patients enrolled may still have been too small to identify minor factors affecting culture positivity. Because of the retrospective design, we could not compare treatment outcomes in the M-PVO and C-PVO groups.

In conclusion, our study suggests that in patients with pyogenic vertebral osteomyelitis, the presence of paravertebral abscess is associated with positive culture outcome. On the other hand, previous antibiotic exposure is associated with negative culture outcome.

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