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Factors Influencing Culture Positivity in Pyogenic Vertebral Osteomyelitis Patients with Prior Antibiotic Exposure

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We conducted a retrospective cohort study to evaluate factors influencing tissue culture positivity in patients with pyogenic vertebral osteomyelitis exposed to antibiotics before diagnosis. Tissue culture was positive in 48.3% (28/58) of the patients, and the median antibiotic-free period was 1.5 days (range, 0.7 to 5.7 days). In a multivariate analysis, a higher C-reactive protein (CRP) level (adjusted odds ratio [aOR], 1.18; 95% confidence interval, 1.07 to 1.29) and open surgical biopsy (aOR, 6.33; 95% confidence interval, 1.12 to 35.86) were associated with tissue culture positivity.

If pyogenic vertebral osteomyelitis (PVO) is suspected, tissue cultures and/or blood cultures are recommended (1). Prior antibiotic exposure has been reported in some studies to have a negative effect on microbiologic diagnosis (2–5). In view of this, it is recommended that, for clinically stable patients, biopsy be delayed until at least 48 h after the last antibiotic has been administered (6). The aims of this study were to investigate the factors influencing tissue culture positivity in patients with PVO who were exposed to antibiotics prior to biopsy and to establish whether an antibiotic-free period improves culture positivity rates.

We conducted a retrospective cohort study at three university-affiliated teaching hospitals from May 2012 through February 2014. Patients with PVO who had been exposed to antibiotics during the 2 weeks before the acquisition of tissue culture specimens were investigated. Patients who were <18 years old and patients with infectious spondylitis caused by *Mycobacterium tuberculosis* or fungi were excluded. PVO was diagnosed when the causative microorganism was isolated from spinal or paraspinal tissues or if there were compatible clinical signs or symptoms and radiologic evidence of vertebral infection as described previously (7). The antibiotic-free period was defined as the time interval between the administration of the latest antibiotic and acquisition of specimens for tissue culture. If the antibiotic administered was not active on the microorganism eventually isolated, the patient was considered not to have been exposed to antibiotics. Tissue culture specimens were acquired by percutaneous biopsy or open surgical biopsy. The latter was performed during surgical treatment of the PVO. The Mann-Whitney U test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. Multivariate analysis was performed with binary logistic regression to investigate the factors influencing tissue culture positivity. All P values were two tailed, and $P < 0.05$ was considered statistically significant.

During the study period, a total of 58 patients with PVO received antibiotics before the acquisition of tissue culture specimens. Blood cultures were done for 53 patients, and 30.2% (16/53) gave positive results. The tissue culture positivity rate was 48.3% (28/58). Tissue culture specimens of 48 patients were obtained by computed-tomography or fluoroscopy-guided percutaneous needle biopsy, whereas those of the other 10 patients were obtained during surgical debridement. The median number of culture specimens was 2 in the percutaneous biopsy group and 3.5 in the surgical debridement group ($P = 0.66$). Age, sex, the proportion of patients with abscesses, white blood cell (WBC) counts, and the duration of prior antibiotic exposure did not differ between patients with tissue culture-positive and -negative PVO, but CRP levels were significantly higher in the tissue culture-positive patients (17.2 versus 6.5 mg/dl, respectively) (Table 1). The median antibiotic-free period was significantly shorter in the patients with tissue culture-positive PVO (1.1 versus 3.3 days, respectively). The most common causative organism was *Staphylococcus aureus* (14 patients), followed by *Streptococcus* (5 patients), *Escherichia coli* (3 patients), etc. The most common antibiotics given prior to biopsy were third-generation cephalosporins (22 patients), followed by first-generation cephalosporins (18 patients) and fluoroquinolones (11 patients), in both groups. The tissue culture positivity rates were 62.5% (20/32), 30.0% (3/10), and 31.3% (5/16) in patients whose antibiotic-free periods were <48 h, 48 to 120 h, and ≥120 h, respectively ($P = 0.029$) (Table 2). In a multivariate logistic regression analysis, open surgical biopsy (adjusted odds ratio [aOR], 6.33; 95% confidence interval [CI], 1.12 to 35.86) and a higher CRP level (aOR, 1.18, 95% CI, 1.07 to 1.29) were significantly associated with tissue culture positivity (Table 3).

In this study, a higher tissue culture positivity rate in patients with PVO who were exposed to antibiotics before the acquisition of tissue culture specimens was associated with a higher CRP level and open surgical biopsy but not with a longer antibiotic-free period. The use of a variety of antibiotics and classes of antibiotics,

Received 3 December 2014 **Returned for modification** 11 January 2015
Accepted 4 February 2015

Accepted manuscript posted online 9 February 2015

Citation Kim C-J, Kang S-J, Yoon D, Lee MJ, Kim M, Song K-H, Jang H-C, Jung S-I, Kim ES, Kim HB, Oh M, Park K-H, Kim NJ. 2015. Factors influencing culture positivity in pyogenic vertebral osteomyelitis patients with prior antibiotic exposure. Antimicrob Agents Chemother 59:2470–2473. doi:10.1128/AAC.04949-14.

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doi:10.1128/AAC.04949-14

TABLE 1 Demographic and clinical characteristics of patients with PVO who received antibiotics before the acquisition of tissue culture specimens

Patient parameter	Total ($n = 58$)	Culture positive ($n = 28$)	Culture negative ($n = 30$)	P value
Age (yr)[a]	66.1 ± 14.3	64.6 ± 13.7	67.4 ± 14.8	0.375
No. (%) of males	24 (41.4)	15 (53.6)	9 (30.0)	0.069
No. (%) with underlying disease/treatment				
Hypertension	16 (27.6)	8 (28.6)	8 (26.7)	0.871
Diabetes mellitus	13 (22.4)	7 (25.0)	6 (20.0)	0.648
Liver cirrhosis	2 (3.4)	1 (3.6)	1 (3.3)	1.000[b]
Spinal procedure in previous yr	14 (24.1)	6 (21.4)	8 (26.7)	0.641
Spinal surgery in previous yr	7 (12.3)	4 (14.3)	3 (10.3)	0.706[b]
No. (%) with:				
Fever[c]	20 (34.5)	10 (35.7)	10 (33.3)	0.849
Spine area pain	56 (96.9)	26 (92.9)	30 (100)	0.229[b]
Motor weakness[d]	10 (17.2)	5 (17.9)	5 (16.7)	1.000[b]
Sepsis[e]	19 (32.8)	12 (42.9)	7 (23.3)	0.113
No. of WBC/mm^3[f]	10,050 (8,215–12,405)	10,480 (8,742–14,350)	9,450 (7,950–11,350)	0.141
CRP level (mg/dl)[f]	11.0 (5.0–18.8)	17.2 (11.0–24.4)	6.5 (1.7–11.3)	<0.001
No. (%) with paravertebral abscesses	13 (22.4)	7 (25.0)	6 (20.0)	0.648
No. (%) with epidural abscesses	28 (48.3)	13 (46.4)	15 (50.0)	0.786
No. (%) with psoas abscesses	19 (32.8)	12 (42.9)	7 (23.3)	0.113
No. (%) with following vertebral area involved:				
C-spine	1 (1.7)	1 (3.6)	0	0.579
T-spine	7 (12.1)	5 (17.9)	2 (6.7)	
TL-spine	4 (6.9)	2 (7.1)	2 (6.7)	
L-spine	32 (55.2)	14 (50.0)	18 (60.0)	
LS-spine	13 (22.4)	6 (21.4)	7 (23.3)	
S-spine	1 (1.7)	0	1 (3.3)	
No. (%) with following no. of vertebral bodies involved:				
1	8 (13.8)	3 (10.7)	5 (16.7)	0.757
2	35 (60.3)	17 (60.7)	18 (60.0)	
3	10 (17.2)	8 (28.6)	2 (6.7)	
≥4	5 (8.6)	0	5 (16.7)	
Duration (days) of prior antibiotic exposure[f]	7.0 (3.0–15.0)	4.5 (2.3–14.3)	7.5 (4.0–15.5)	0.086
Antibiotic-free period (days)[f]	1.5 (0.7–5.7)	1.1 (0.2–3.3)	3.3 (1.2–7.6)	0.007
No. (%) undergoing biopsy by:				
Needle	48 (82.8)	21 (75.0)	27 (90.0)	0.173[b]
Open surgery	10 (17.2)	7 (25.0)	3 (10.0)	

[a] Mean ± standard deviation.
[b] Fisher's exact test.
[c] Body temperature of ≥38.0°C.
[d] Motor power, ≤grade 4 (full range of movement but resisted by examiner) (8).
[e] Two or more of the following: body temperature of >38°C or <36°C, heart rate of >90/min, respiratory rate of >20/min or partial CO_2 pressure of <32 mm Hg, WBC count of >12,000/mm^3 or <4,000/mm^3 or >10% bands.
[f] Median (interquartile range).

even broad-spectrum antibiotics such as fluoroquinolones, had no effect on culture positivity. It is well known that the yield of open surgical biopsy is higher than that of needle biopsy (9–11). Also, a higher CRP level occurs more frequently in patients with culture-positive PVO (3, 12, 13). One might expect that the longer the antibiotic-free period is, the higher the culture positivity rate is because more antibiotic would be removed from tissue and the negative effect of antibiotic exposure would be lessened. However, tissue culture positivity rates were significantly higher in patients whose antibiotic-free period was less than 48 h than in those for whom it was 48 to 120 h or >120 h. This could be because patients with shorter antibiotic-free periods underwent open surgical biopsy more frequently and had higher CRP levels than those with longer antibiotic-free periods, and the attending physicians were reluctant to postpone the acquisition of tissue culture specimens from patients with high CRP levels.

In this study, we found no association between the antibiotic-free period duration and a higher culture positivity rate. We suggest that obtaining culture specimens by the open surgical method instead of postponing their acquisition is desirable for patients who have received antibiotics during the preceding 2 weeks in order to increase culture positivity, especially when a needle bi-

TABLE 2 Characteristics and positivity rates of tissue and/or blood cultures according to antibiotic-free periods in patients with PVO

Parameter	Antibiotic-free period of:			*P* value
	<48 h ($n = 32$)	≥48 to <120 h ($n = 10$)	≥120 h ($n = 16$)	
Mean age (yr) ± SD	63.4 ± 14.3	66.5 ± 15.3	71.1 ± 13.1	0.209
No. (%) of males	16 (50.0)	5 (50.0)	3 (18.8)	0.052
No. (%) with fever	12 (37.5)	4 (40.0)	4 (25.0)	0.433
No. (%) with motor weakness	4 (12.5)	2 (20.0)	4 (25.0)	0.273
No. (%) with sepsis	13 (40.6)	4 (40.0)	2 (12.5)	0.065
No. (%) with lumbar spine involvement	27 (84.4)	9 (90.0)	14 (87.5)	0.730
No. (%) with >3 vertebral bodies involved	9 (28.1)	3 (30.0)	3 (18.8)	0.523
No. (%) with abscesses	22 (68.8)	9 (90.0)	11 (68.8)	0.844
No. of WBC/mm^3[a]	10,480 (9,158–14,375)	10,950 (8,463–13,828)	7,625 (6,718–10,025)	0.023[b]
CRP level (mg/dl)[a]	13.6 (6.8–19.3)	15.0 (3.8–21.0)	5.9 (1.6–11.3)	0.089[b]
Prior antibiotic exposure duration (days)[a]	4.0 (3.0–8.8)	5.0 (2.8–12.8)	17.0 (7.0–33.5)	<0.001[b]
No. (%) with cephalosporin as prior antibiotic	25 (78.1)	4 (40.0)	14 (87.5)	0.768
No. (%) with quinolone as prior antibiotic	5 (15.6)	1 (10.0)	5 (31.2)	0.245
No. (%) with glycopeptide as prior antibiotic	3 (9.4)	1 (10.0)	2 (12.5)	0.747
No. (%) with open surgical biopsy	8 (25.0)	2 (20.0)	0	0.037
No. of tissue cultures positive/total (%)	20/32 (62.5)	3/10 (30.0)	5/16 (31.3)	0.029
No. of blood culture positive/total (%)	12/29 (41.4)	2/10 (20.0)	2/14 (14.3)	0.058

[a] Median (interquartile range).
[b] *P* value calculated by one-way analysis of variance.

opsy does not reveal the causative organism, because the culture positivity rates associated with a surgical biopsy were higher (70%, 7/10) than those associated with a needle biopsy (43.8%, 21/48). Our study had several limitations. First, the number of patients investigated was small and the power of our analysis was limited. Second, the antibiotic-free period was relatively short (median, 1.5 days) and there remains the possibility that a period of a few weeks instead of a few days would improve culture positivity. A

TABLE 3 Multivariate logistic regression analysis of factors associated with tissue culture positivity

Factor	Univariate analysis		Multivariate analysis[a]	
	OR (95% CI)	*P* value	aOR (95% CI)	*P* value
Sex				
Male	1.00			
Female	0.37 (0.13–1.09)	0.072		0.286
Age of ≥65 yr	0.89 (0.31–2.53)	0.825		0.374
Fever	1.11 (0.38–3.28)	0.849		0.533
Motor weakness	1.09 (0.28–4.25)	0.905		0.990
Sepsis	2.46 (0.80–7.63)	0.118		0.405
L-spine involved	0.51 (0.11–2.37)	0.392		0.186
No. of involved vertebral bodies				
1 or 2 levels	1.00			
≥3 levels	1.31 (0.41–4.27)	0.649		0.619
Duration of prior antibiotic exposure	0.97 (0.92–1.02)	0.176		0.783
Prior antibiotic exposure[b]				
Cephalosporin	0.76 (0.23–2.47)	0.649		0.842
Quinolone	0.33 (0.08–1.40)	0.133		0.476
Glycopeptide	1.08 (0.20–5.85)	0.929		0.905
Antibiotic-free period	0.80 (0.66–0.96)	0.015		0.407
Presence of abscess	1.83 (0.56–5.96)	0.314		0.550
Initial CRP level[c]	1.15 (1.06–1.25)	0.001	1.18 (1.07–1.29)	<0.001
Tissue biopsy method				
Needle	1.00			
Open surgery	3.00 (0.69–13.02)	0.142	6.33 (1.12–35.86)	0.037

[a] The aORs were calculated with a stepwise forward selection logistic regression model.
[b] Cephalosporin, glycopeptide, and quinolone were not simultaneously included in the multivariate model.
[c] Because the CRP level and WBC count showed a significant correlation (Pearson correlation coefficient of 0.549, $P < 0.001$), we included only the CRP level in the multivariate analysis model.

prospective observational cohort study investigating the effect of a longer antibiotic-free period on patients who are clinically stable, as defined by the absence of neurologic deficits without progression and with lower CRP levels, would be very helpful.

In conclusion, the tissue culture positivity rate of patients with PVO who were exposed to antibiotics was associated with higher CRP levels and open surgical biopsy; however, it was not improved by an antibiotic-free period of a few days.

ACKNOWLEDGMENTS

This work was supported by a grant from the research fund of the Seoul National University Hospital (0420120420).

We have no conflicts of interest to declare.

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