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Effectiveness of oral cephalexin as completing treatment for bacteremic vertebral osteomyelitis caused by Methicillin-susceptible *Staphylococcus aureus*

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Background

- Levofloxacin plus rifampicin or linezolid are recommended oral antimicrobial agents for methicillin-susceptible Staphylococcus aureus (MSSA)-induced pyogenic vertebral osteomyelitis (PVO) [1].
- However, oral first-generation cephalosporins, which are widely used as first-line agents for non-PVO MSSA infections, should also be considered in PVO to prevent drug resistance and minimize side effects.
- This study was conducted to determine the usefulness of switching to oral cephalexin as antibiotic therapy for MSSA-induced PVO.

Methods

- This single-center, retrospective, descriptive study in Japan enrolled patients aged 18 years or more who were diagnosed with PVO and MSSA-induced bacteremia and used cephalexin for at least 1 day between April 2012 and March 2021 at the National Center for Global Health and Medicine Hospital.
- Treatment efficacy was determined at two timepoints: at the end of intravenous antimicrobial therapy (compared with that at treatment initiation) and at the end of cephalexin therapy (compared with that at the completion of intravenous antimicrobial therapy).
- A 5-point scale (score >4/5 indicates treatment success) was developed based on clinical, laboratory, radiographic findings to determine the treatment response (**Table 1**).
- Relapse, diagnosed by clinical judgment, within 1 year after cephalexin termination was evaluated.

Results

- There were 385 cases of MSSA bacteremia. Of these, 44 had coexisting PVO, and 16/44 cases received oral cephalexin treatment. Owing to polymicrobial infection, 1 of these 16 patients was excluded, and a total of 15 cases were included in the study.
- **Table 2** presents the participant characteristics of these 15 patients: 8 (53%) were female, the median age was 75 [interquartile range (IQR) 67.5-80.5] years, the median weight was 57.0 [IQR 45.5-62.5] kg, the median BMI was 22.1 [IQR 19.8-24.0] kg/m^2. The median Charlson Comorbidity Index score was 2 [IQR 0-4]. None of the patients had a history of spinal surgery or spinal implants.
- The affected vertebrae were at the cervical, lumbar, and sacral level in 3 (20%), 5 (33%), 10 (67%), and 4 (27%) patients, respectively. Spinal abscesses including paravertebral, epidural, or iliopsoas abscesses occurred in 12 patients (80%). Abscesses of other organs occurred in 4 patients (27%). None of the patients had infective endocarditis.
- The median [IQR and range] duration (days) of intravenous antimicrobial therapy, oral antimicrobial therapy, cephalexin administration, and total treatment was 36 [32-61 and 21-86], 40 [26-93 and 11-251], 29 [19-82 and 8-251], and 86 [59-125 and 37-337], respectively (**Table 3**).
- Cephalexin was used for the oral transition from intravenous antibacterial agents in 14 patients (93%), whereas amoxicillin was used in the remaining patient. A patient with taste disorder after 1-month amoxicillin treatment was switched to cephalexin.

Table 1. Evaluation of treatment efficacy for vertebral osteomyelitis using a 5-point scale

Pain	CRP	Comorbid conditions, besides vertebral osteomyelitis, that can increase CRP	Imaging	Judgment	Score
I / U	I / U		I	Definite success	5
〃	〃		-	Probable success	4
〃	〃		U	Probable success	4
〃	〃		W	Inconclusive	3
〃	W	Yes	I	Probable success	4
〃	〃	〃	-	Inconclusive	3
〃	〃	〃	U	Inconclusive	3
〃	〃	〃	W	Probable failure	2
〃	〃	No	I	Probable success	4
〃	〃	〃	-	Inconclusive	3
〃	〃	〃	U	Inconclusive	3
〃	〃	〃	W	Probable failure	2
W	I / U		I	Probable success	4
〃	〃		-	Inconclusive	3
〃	〃		U	Inconclusive	3
〃	〃		W	Probable failure	2
〃	W	Yes	I	Probable success	4
〃	〃	〃	-	Inconclusive	3
〃	〃	〃	U	Inconclusive	3
〃	〃	〃	W	Probable failure	2
〃	〃	No	I	Inconclusive	3
〃	〃	〃	-	Probable failure	2
〃	〃	〃	U	Probable failure	2
〃	〃	〃	W	Definite failure	1

I: improving, U: unchanged, W: worsening, -: unknown

Table 2. Baseline characteristics of participants with bacteremic vertebral osteomyelitis due to methicillin-susceptible *Staphylococcus aureus* (n=15)

Age, years		75 [67.5–80.5]
Female		8 (53%)
BMI*		22.1 [19.8–24.0]
Charlson Comorbidity Index		2 [0–4]
Site of vertebral osteomyelitis**		
	Cervical level	3 (20%)
	Thoracic level	5 (33%)
	Lumbar level	10 (67%)
	Sacral level	4 (27%)
Previous spinal implant placement		0 (0%)
Complications		
	Endocarditis	0 (0%)
	Spinal abscesses†	12 (80%)
	Abscesses at remote sites‡	4 (27%)

Data are median [IQR] or number (%) unless otherwise specified.
* One case was excluded due to missing data.
** Duplicate selections were allowed.
† includes paravertebral, epidural, and psoas abscesses
‡ Each case with a subcutaneous abscess of inguinal region (surgical site), piriformis abscess, posterior neck and erector spinae abscess, and anterior mediastinal abscess, respectively

Table 3. Duration of antibiotic and surgical treatment in bacteremic vertebral osteomyelitis due to methicillin-susceptible *Staphylococcus aureus* (n=15)

Intravenous treatment duration, days	36 [32–61]
Oral treatment duration*, days	40 [26–93]
Cephalexin administration duration*, days	29 [19–82]
Discontinuation of cephalexin before treatment completion	3 (20%)**
Total treatment duration*, days	86 [59–125]
Surgical treatment	5 (33%)

Data are median [IQR] or number (%) unless otherwise specified.

* One case was excluded due to chronic suppression

** One discontinuation due to hepatotoxicity and eosinophilia, one due to concomitant urinary tract infection, and one death due to aspiration pneumonia

Table 4. Efficacy of cephalexin therapy in bacteremic vertebral osteomyelitis due to methicillin-susceptible *Staphylococcus aureus*

Efficacy score at the end of intravenous antibiotic therapy (N=15)	
5	9 (60%)
4	6 (40%)
3	0 (0%)
2	0 (0%)
1	0 (0%)
Efficacy score at the end of cephalexin therapy* (N=15)	
5	1 (7%)
4	12 (80%)
3	2 (13%)
2	0 (0%)
1	0 (0%)
Relapse within 1 year (N=4)	
	0 (0%)

Data are number (%) unless otherwise specified.
* In one case with chronic suppression, efficacy was determined at the median timepoint of the total duration of treatment in the cases, after excluding the one with chronic suppression.

Results (continued)

- Cephalexin was not used in combination with other antimicrobial agents in any of the cases.
- Cephalexin was discontinued before completion of PVO treatment in 3 patients (20%): one patient was switched to clindamycin due to mild elevation of liver enzyme and eosinophilia; one was switched to intravenous cefepime due to a urinary tract infection; and one patient was on cephalexin treatment and died of aspiration pneumonia.
- The median length of hospital stay was 64 [IQR 45-81, range 27-101] days.
- Five patients (33%) underwent surgery: abscess drainage was done in 3 patients, laminectomy in 1 patient, and posterior decompression with fusion in 1 patient.
- At the end of intravenous antimicrobial therapy, the treatment response score was 5 in 9 patients (60%) and 4 in 6 patients (40%), with a treatment success rate of 100% (**Table 4**).
- At the end of cephalexin treatment, the treatment response score was 5 in 1 patient (7%), 4 in 12 patients (80%), and 3 in 2 patients (13%), with a treatment success rate of 87%.
- One of the two patients with a score of 3 for the cephalexin course had cephalexin therapy terminated due to urinary tract infection. The other patient had a CRP level of 0.06 and 0.2 mg/dL at the end of intravenous antimicrobial therapy and cephalexin treatment, respectively, which was considered as worsening.
- During the treatment period of PVO, one death occurred and this was in a patient who had been successfully treated with cephalexin, but died of aspiration pneumonia.
- Four patients were followed up for 1 year after completion of the cephalexin course, and none of the patients relapsed within 1 year (**Table 4**). The median follow-up period after completion of the cephalexin course for all patients was 119 days [IQR 48.5-350], and none of the patients relapsed during the follow-up period.
- A death that occurred during the follow-up period was attributed to liver cirrhosis.

Discussion

- In this single-center, retrospective descriptive study, we demonstrated an 87% treatment success on switching to cephalexin after treatment with intravenous antibacterial agents in adult patients with PVO complicated by MSSA bacteremia. Two patients who did not qualify as treatment success had an efficacy score of 3: with CRP elevation due to concurrent urinary tract infection and a small CRP pre-value in one patient each, and these were not judged as treatment failures for PVO. Thus, cephalexin may be a promising oral antibacterial option for use after intravenous therapy for PVO with MSSA bacteremia. The results of this study may be applicable to patients with MSSA-induced PVO without bacteremia, as the disease severity is expected to be less than that with bacteremia.
- Eighty percent of the patients in this study had a spinal abscess, and this was a higher rate than in a previous study on MSSA-induced PVO [2], which could be explained by the fact that only patients with PVO with bacteremia were included in the present study.
- The median total duration of treatment was 86 days, which was longer than the recommended duration in the guideline. This can be explained for two reasons. First, many of the cases in this study were complicated by abscesses. Second, this study includes cases treated before 2015, when a study [3] was published showing that 6 weeks of treatment was beneficial.
- This study did not include patients with infective endocarditis or implant infection; therefore, these results may not necessarily be applicable to these patients.

Conclusions

- In patients with bacteremic MSSA-induced vertebral osteomyelitis, completing antibiotic treatment with cephalexin is a reasonable option, even in cases with spinal abscess, if at least 3 weeks of effective intravenous antimicrobial therapy is provided.

Reference

[1] Berbari EF, et al. Clin Infect Dis 2015; 61: e26-46, [2] Park KH, et al. J Infect 2014; 69: 42-50, [3] Bernard L, et al. Lancet 2015; 385: 875-82