Pyogenic Vertebral Osteomyelitis in Adults: Ten-year Experience in Two Italian Hospitals

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Abstract

Background: The incidence of pyogenic vertebral osteomyelitis (PVO) is increasing, but optimal diagnostic strategy and medical management remain controversial. **Methods:** We conducted a retrospective study of PVO in two Italian hospitals, including all the adults admitted from January 2007 to December 2016. PVO was defined probable or definite according to clinical, radiological and microbiological criteria. The main exposures of interest were investigation strategy and antibiotic treatment. The outcome measures were cure rate, mortality during index admission and recurrence rate. **Results:** Most cases were diagnosed with MRI. Biopsy was performed in 47% of patients and was successful only in 49% of them. The microbiological diagnosis (mostly Gram-positive agents) was obtained in 111 patients (62%). Treatment duration did not differ between patients with definite or probable diagnosis (108 and 112 days, respectively). Among the 100 patients (56%) with at least 1-year follow-up, the cure rate, the failure rate and the mortality were 88%, 12% and 3%, respectively. Relapses were uncommon (4%) among patients who completed the follow-up. Among the patients who recovered completely, 47 (59%) had a microbiological diagnosis. Among the 111 patients with a definite diagnosis and 68 with a probable diagnosis, 42% and 49% achieved a full recovery, respectively. **Conclusions:** Despite influencing the antibiotic selection, the etiological diagnosis did not impact the cure rate and/or duration of treatment. Some open questions remain with regard to the optimal starting regimen, the duration of treatment and the time to switch to oral therapy.

Background

Pyogenic vertebral osteomyelitis (PVO) is defined as an infectious process involving the vertebra with the potential for local spread to the adjacent disc, muscular and soft tissues [1]. PVO accounts for approximately 2-5% of all osteomyelitis [2] and, although in some geographical areas tuberculosis and brucellosis play a major role [3], in Western countries the most common pathogens are *Staphylococci*, which hematogenously spread to the vertebra [4].

PVO diagnosis is often delayed due to its rarity, the non-specific clinical features and the high frequency of low backpain in the general population, which requires a high degree of suspicion.

We here report the 10-year experience with PVO in two Italian hospitals and review the open issues as to the medical and surgical management.

Methods

Study setting

We performed a retrospective observational study of PVO in two Infectious Diseases Units: one located in Bergamo (a district hospital of 990 beds, in Northern Italy) and one in Foggia (a University teaching hospital of 800 beds, in Southern Italy), respectively.

Inclusion criteria

All adults (≥ 18 years) with a diagnosis of PVO and followed up at the 2 hospital centers for at least 1 year after the diagnosis.

Definitions

PVO was defined as:

- *Definite*: in the presence of (1) radiological evidence (magnetic resonance imaging (MRI), computed tomography (CT), scintigraphy or positron emission tomography (PET) scans), (2) clinical evidence (one or more of back pain, fever or consistent neurological signs) and (3) microbiological isolation (by biopsy or blood culture)
- *Probable*: if the previous first two criteria were respected, no etiological agent was identified, but resolution was reported following empirical antibiotic treatment.

In case of multiple pathogens, the PVO was defined as *polymicrobial*. Multiple sites involvement was defined as more than 2 vertebral bodies infection, as identified on radiological scans. The *diagnostic delay* was defined as the time elapsed since the onset of symptoms up to the medical diagnosis. Spine invasive procedures included spinal surgery (vertebral stabilization, discectomy, radio frequency ablation, percutaneous vertebroplasty, laminectomy, spinal decompression), lumbar punctures, epidural procedures or infected implanted prosthetic material.

Data collection

We identified all the patients admitted to the two hospitals with a diagnosis of PVO from January 2007 through December 2016. We excluded any case of suspected or proven brucellar or tubercular etiology.

We reviewed the medical records and the database of outpatient visits in both hospitals. We collected the data using a purpose-built paper case report forms and collated data into an electronic database. For each patient, we included the demographic characteristics (age, gender, nationality), the comorbidities, history of intravenous drug abuse, any previous spinal surgery, the presence and the duration of symptoms at admission, the radiographic characteristics, the microbiological findings, the type and duration of antibiotic treatment, the surgical procedures and the follow up.

Outcome measures

The outcome measures were as follows:

- a) *cure rate*: in case of symptom resolutions and radiological improvement following antibiotic treatment, the patient was considered *recovered*.
- b) *mortality* during hospitalization;

c) *recurrence rate*: re-occurrence of sign/symptoms after the completion of therapy and need for restarting therapy.

Results

From January 2007 to December 2016 we identified 179 patients with PVO: 134 (75%) Bergamo and 45 (25%) in Foggia.

As shown in Table 1, 64% patients were males, the mean age at diagnosis was 65 years and 81% had comorbidities, while the risk factors (present in less than 50% of patients) included: current intravenous drug use in 9 patients (5%), recent spine invasive procedures in 27 patients (15%), concomitant or prior sepsis and/or endocarditis in 34 patients (19%), recurrence of prior PVO in 7 patients (4%). The mean diagnostic delay was 57 days (range: 3-370). The most common symptoms at diagnosis were localized spinal pain (94%) and fever (55%), while neurological deficits were reported in 20% of the patients on admission. Almost half of the patients (49%) received an empirical antibiotic treatment before PVO diagnosis.

PVO diagnosis

Most cases (163, 91%) were diagnosed by the MRI, in 27 cases (17%) following a non-diagnostic CT scan. PET was used in case of technical contraindications to MRI and also during radiological follow up in 14 patients (7%). The lumbar site was the most commonly affected spinal region (125 patients, 70%), followed by the thoracic (40 patients, 22%) and cervical (14 patients, 8%) one. In 38 patients (21%) multiple sites were involved. In 36 (20%) patients there was also a soft tissue involvement and in 54 (30%) an epidural or paravertebral abscess was present (Table 1).

Blood cultures were performed in 137 (77%) patients and 74 of them (54%) were positive. Vertebral CT-guided fine needle biopsy were performed in 84 patients (47%), but the microbiological diagnosis was achieved only in 41 (49%).

As shown in Table 2, the etiological diagnosis was obtained in 111 patients (62%) and *Staphylococcus aureus* was the most frequent pathogen (44 patients, 40% of the *definite* cases), followed by *coagulase-negative staphylococci* (CoNS). Methicillin-resistance was identified in 4 patients with *Staphylococcus aureus* isolation (9%) and in other 4 patients with CoNS isolation (18%).

Therapeutic approach

All patients were prescribed antibiotic treatment. The mean time of hospitalization was 26 days (range 3-114). A total of 147 patients (82%) were prescribed rigid orthosis immobilization, for a mean duration of 22 weeks (range 1-69), and only 11 patients (6%) underwent surgical stabilization.

Type of regimen

The most frequently used regimens included two antibiotics. Only one patient with a pansensitive strain of *Enterococcus faecalis* was successfully treated with ampicillin monotherapy. As shown in Table 3, a total of 44 (25%) patients received only **oral treatment**, while 18 patients (10%) only intravenous agents. Among the patients in the first group, the most commonly used regimens were rifampicin *plus* a fluoroquinolone (approximately 50%) and cotrimoxazole *plus* another molecule (32%). Other 8 patients (18%) received an association including a beta-lactam antibiotic. In the 18 (10%) patients treated only with **parental therapy**, 80% of them received beta-lactam antibiotics. Among the 115 (64%) patients treated **with both oral and intravenous drugs**, 12 (10%) started simultaneously with both, while the majority were switched later to oral therapy. Of this group, 25 (22%) received a glycopeptide-based regimen, mostly as empiric treatment.

Duration of antibiotic therapy

In the 100 patients who completed the follow-up, the mean treatment duration was 16 weeks (range 6-68), while intravenous therapy was continued for 5 weeks (range 0.5-19) and oral treatment for 16 weeks (range 6-68). A total of 8 and 23 of the 100 patients who completed the follow-up were treated only with intravenous or oral treatment, respectively. There was no significant difference in treatment duration between patients with *definite* or *probable* diagnosis (108 and 112 days, respectively, in patients who completed follow-up).

Tolerability and adverse events

Only 5 patients (3%) reported allergies to antibiotics (in all cases to β -lactams) before starting treatment. In 6 patients (3%), skin rash was reported during therapy (severe in one case). Treatment was discontinued in 19 cases (11%) following intolerance or toxicity (renal, hepatic or bone marrow). The adjustment of the initial dose was required in 10 patients (6%) due to reduced renal clearance.

Follow-up and clinical outcome

Thirty-two patients (18%), with a similar proportion in both centers, were lost to follow-up. Forty-two patients (24%) had not completed 1-year follow-up, although at their first visits they were clinically improved.

A total of 100 patients (56%) were followed up for at least one year. Eighty (80%) of them had a full recovery, without changing the initial therapy, eight patients recovered after clinical flare-up requiring a therapeutic change, 8 patients had radiologic improvement, but with long-term sequelae, and the last 4 patients relapsed after the conclusion of the initial therapy, but they responded to a new cycle of therapy with different antimicrobials. Five patients (3%) died during hospitalization due to septic complications.

Among the 80 patients who recovered completely, 47 (59%) had an etiological isolation, while in the other 33 patients (41%) the diagnosis was *probable*. Alternatively, among the 111 patients with a *definite* diagnosis, only 47 (42%) completed the follow-up with full recovery, while among the 68 patients with a *probable* diagnosis, 33 (49%) recovered completely.

Discussion

We here describe 179 patients with PVO, consecutively diagnosed over 10 years, in two Italian Infectious Diseases centers. In Italy, PVOs are traditionally referred to the Departments of Infectious Diseases, so our data are considered representative and selection bias unlikely.

PVOs have been increasing in Europe over the last 20 years [5], mostly due to the aging population, the longer life expectancy of patients affected by chronic debilitating diseases and immunodeficiency and the iatrogenic infections following the more frequent surgical procedures [6]. In fact, in our study, the mean age at diagnosis was 65 years, 81% of individuals had comorbidities and 15% of patients underwent spine invasive procedures. Sixty-four per cent of our patients were male, but also in literature the male to female ratio is 1.5–2:1[7].

Up to 15% of cases may be asymptomatic [3], causing a mean diagnostic delay of 90 days [8]. In our case the average time to diagnosis was 57 days from symptoms onset. Unremitting back pain and increased inflammatory markers should guide the suspicion of PVO [9]. According to IDSA guidelines, fever is only present in up to 45% of patients with bacterial spondylodiscitis and may be masked in patients taking analgesics with antipyretic effects [10]. At diagnosis, the most common symptom in our patients was localized spinal pain (94%), while fever was described in 55% of cases. Neurological deficits were reported in 35% of cases in previous studies [11], while it was present in 20% of our patients. As in other recent studies, the lumbar tract was the most affected [12] and PVO was commonly confined to one level [11]. According to the literature, when multiple sites are involved, such as in 38 patients (21%) of our study, a longer treatment duration or a surgical approach are not necessarily required [13].

When PVO is suspected, MRI should be the first imaging of choice, as confirmed by our study [14].

The radiologist's role in performing minimally invasive sampling procedures is also highlighted in the literature. We performed a vertebral CT-guided fine needle agobiopsy in 84 patients (47%) with a microbiological diagnosis in less than half the cases, but the usefulness of a second biopsy, if the first one is negative, is a subject of debate [15]. According to the literature, bone biopsy identifies organisms in approximately 40% of the cases, but the yield is reduced if antibiotic therapy had been started [16]. In fact, antibiotics were given before diagnosis to almost half of our patients.

Blood cultures may be successful in identifying the etiological agent. According to several studies [17-18], the rate of positive blood cultures varies from 40 to 89% depending on the prior antibiotic therapy, the relative ease of culturing the pathogen, the concentration of organism in the bloodstream, the local epidemiology and the haematogenous pathogenesis of spondylodiscitis. Despite the best efforts, the pathogen cannot be identified in approximately one third of cases and antibiotics are selected empirically [19]. In our study, the microbiological diagnosis was obtained in 111 patients (62%), without a significant difference in treatment duration and outcome between patients with a *definite* or a *probable* diagnosis. In fact, the cure rate was slightly higher among the 68 patients with a *probable* diagnosis (33/68,49%),

compared to those with a *definite* diagnosis (47/111, 42%), questioning the clinical relevance of etiological identification.

According to the literature, *S. aureus* is the most common agent of hematogenous vertebral osteomyelitis (42-58%) [20] and it is mostly identified in the settings of recent invasive procedures (55% of patients), insulin use (28%) and hemodialysis (20%) [21]. In our case, *S. aureus* was isolated in 40% of patients with a *definite* diagnosis, while risk factors have been identified in less than 50% of them and included a prior surgery or spondylodiscitis, intravenous drug use, sepsis and endocarditis. The prevalence of methicillin-resistant *S. aureus* (MRSA) seems to be increasing, up to 40-57% [22-23], but in our setting MRSA was identified only in 4 patients with *Staphylococcus aureus* isolation (9%).

Tolerability and adverse events

In our study, 13% of patients had mild-to-moderate adverse events leading to therapeutic discontinuation. Only one severe adverse reaction to teicoplanin occurred. A recent meta-analysis on osteomyelitis in adults has shown that oral and intravenous treatments were equally effective, with a similar number of adverse events (16% and 7% of patients had mild and moderate/severe events, respectively) [24]. In a multicenter trial published by Bernard et al. to establish non-inferiority of a 6-week versus a 12-week treatment, the intolerance to antibiotic regimens was reported in 21/351 (6%) patients, without differences between the 2 arms group [25].

Treatment duration

The optimal duration of parenteral antibiotic therapy and the time to switch to an oral treatment remain unclear. Bernard et al. showed that 6-week treatment for PVO was not inferior to 12-week regimen [25]. However, only 6% of patients in this trial were infected with MRSA and the proportion with concomitant abscess was low (19%). In fact, in a recent large cohort study by Park et al. evaluating the therapeutic outcomes of microbiologically diagnosed PVO, MRSA infection, undrained paravertebral/psoas abscesses, and end stage renal disease were independently associated with recurrence. The authors concluded that a prolonged duration of treatment (more than 8 weeks) should be given to patients with a high risk of recurrence, while, for low-risk patients, a shorter duration (6-8 weeks) may be sufficient [26].

In our data, the etiological diagnosis did not influence the rate of clinical cure and/or duration of treatment, despite influencing the antibiotic selection. In fact, the empirical therapy should include broad-spectrum antibiotics with a proven efficacy on MRSA (such as glycopeptides), but when MSSA is identified, alternatives, such as cefazolin and oxacillin, may be used. In our study, the combination of rifampicin and a fluoroquinolone was used in half of patients treated only with oral antibiotic, with a good *cure rate*. In the trial by Bernard et al [25], the combination of fluoroquinolone and rifampicin was used in 73% of *S. aureus* infected patients. High-dose levofloxacin (500 mg every 12 hours) plus rifampicin 600 mg daily (both orally) has been successfully used also as empirical treatment [27]. The use of rifampicin (as a second agent) is recommended in patients with PVO because of its excellent bone and biofilm penetration [4].

Some studies [28,29] concerning osteoarticular infections postulate that a longer duration of antibiotic therapy implies a greater toxicity even if the duration of treatment they refer to is significantly longer than that reported in our study, both in the case of empiric therapy (242 versus 112 days) [28] and in the case of targeted anti-staphylococcal therapy (26 versus 16 weeks) [29].

Among the therapeutic options not available until recently, dalbavancin may be a promising molecule due to its long half-life, the activity against MRSA, a favorable safety profile and a high bone concentration [30].

The optimal duration of spine **immobilization** was not established. In a recent Italian study [12], the average time of immobilization was approximately 7 months, but our data suggest that a shorter duration (22 weeks) is reasonable for selected cases without medullary involvement, receiving treatment before a definitive spine instability occurs [31].

Response to therapy

In general, the correlation between improvement in MRI findings and clinical recovery is weak [32]. In fact, up to 85% of MRI, taken 4-8 weeks after starting therapy, fails to demonstrate any change [33] and the uptake of contrast on the MRI may persist for several months [34], despite the clinical improvement. A PET study was performed only in 14 of our patients (7%) due to the higher costs and the unavailability in the first years. In these cases, the most reliable criterion to confirm a favorable treatment response was a decrease in maximum standardized uptake values (SUVmax) between the baseline and follow-up studies [35]. Conservative treatment is a safe and effective therapeutic option for patients without neurological deficits, spinal instability and spondylodiscitic complications [11,36]. In our study surgery was required in a minority of cases (6%), when specific complications were present. Rigid orthosis immobilization is necessary to maintain spinal stability until bony ankylosis occurs [37]. The combination of the brace *plus* antibiotic therapy can achieve a high success rate, ranging from 86 to 91% [37-38]. In our study, among patients who completed 1-year follow-up, the *cure rate* was 88%. Following conservative treatment, failure rates range from 12-18% [38-39]. Our *failure rate* was 12%, but we had a high number of patients (79, 44%) who did not complete the 1-year follow up. This is mainly due to the retrospective nature and the time frame (ten years) of our study. There is a wide range of published mortality rates for PVO (4-29%) across a heterogeneous collection of studies [18,40]. In our study, *mortality* was low (3%) and mainly due to septic complications in patients with comorbidities.

Conclusions

Although a rare condition, clinicians should consider PVO in patients with unremitting back pain and increase in inflammatory markers. When PVO is suspected, MRI is the gold standard of imaging and the microbiological diagnosis may be of help in targeting therapy. In the absence of neurological complication, medical treatment may be sufficient. Some open questions remain with regard to the optimal starting regimen, the duration of treatment and the time to switch to oral therapy. A standardized

treatment algorithm based on clinical-radiological classification and including all available medical and surgical therapeutic options could be useful.

List Of Abbreviations

PVO: pyogenic vertebral osteomyelitis

MRI: magnetic resonance imaging

CT: computed tomography

PET: positron emission tomography

CoNS: *coagulase-negative Staphylococci*

MRSA: methicillin-resistant *Staphylococcus aureus*

MSSA: methicillin-sensitive *Staphylococcus aureus*

Declarations

Ethics approval and consent to participate

Ethical clearance was obtained from Institutional Review Board (IRB) of ASST Papa Giovanni XXIII in Bergamo and University of Foggia. The nature of the study, which was retrospective record review, limits to access study subjects to request their consent to participate into the study. As a result of this, IRB waived the consent from the study participants directly.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

DR and MR conceived of the study, and participated in its design and coordination and helped to draft the manuscript. AC, EB, VR participated in the design of the study. TS coordinated the study in Foggia hospital. All authors read and approved the final manuscript.

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Tables

Table 1 - Baseline characteristics of the study population

Characteristics	Number (%)
Males	114 (64)
Median age, years (range)	65 (33-90)
Comorbidity	145 (81)
Hypertension	63 (43)
Diabetes	34 (23)
Ischemic heart disease	22 (15)
Malignancies	17 (12)
Atrial fibrillation	17 (12)
CKD (clearance < 60 ml/min)	13 (9)
Chronic obstructive pulmonary disease (COPD)	8 (6)
Cirrhosis	5 (3)
Mean diagnostic delay, days (range)	57 (3-370)
Fever	99 (55)
Back pain	169 (94)
Neurological signs	35 (20)
Leucocytes count, median (range) cells/mm ³	8,464 (1,800-30,500)
C-reactive protein, median (range) mg/L	71 (0-356)
Soft tissue involvement	36 (20)
Epidural/paravertebral abscess	54 (30)
PVO localization	40 (22)
Cervical	14 (8)
Thoracic	125 (70)
Lumbar	38 (21)
Multiple	

CRP: C-reactive protein, PVO: Pyogenic Vertebral Osteomyelitis

Due to technical limitations, Table 2 is only available as a download in the supplemental files section.

Table 3 – Type of antibiotic regimen in patients with PVO

Regimen	N. of patients (%)			Outcome
	Total number: 179§	Empiric treatment (n=68)	Microbiologically guided therapy (n=111)	Recovered# (n=88)
Exclusively oral or parental treatment				
Oral only	44 (25)	27 (61)	17 (39)	21 (48)
Rifampicin + Fluoroquinolone	22 (50)	14 (64)	8 (36)	10 (45)
Cotrimoxazole ± others	14 (32)	10 (71)	4 (29)	8 (57)
β-lactam* ± others	8 (18)	3 (38)	5 (62)	3 (38)
Recovered	21 (48)	13 (48)	8 (47)	
Parental only	18 (10)	2 (11)	16 (89)	5 (28)
β-lactam* ± others	14 (78)	2 (14)	12 (86)	4 (29)
Glycopeptide ± others	5 (28)	2 (40)	3 (60)	1 (20)
Recovered	5 (28)	0 (0)	5 (31)	
Parental followed by oral treatment				
Total patients	115 (64)	38 (33)	77 (67)	62 (54)
Parental antibiotic				
β-lactam* ± others	75 (65)	19 (25)	56 (75)	40 (53)
Glycopeptide ± others	25 (22)	15 (60)	10 (40)	13 (52)
Fluoroquinolone ± others	57 (50)	22 (39)	35 (61)	32 (56)
Rifampicin ± others	15 (13)	3 (20)	12 (80)	8 (53)
Oral antibiotic				
β-lactam* ± others	55 (48)	11 (20)	44 (80)	28 (51)
Fluoroquinolone ± others	89 (77)	34 (38)	55 (62)	48 (54)
Rifampicin ± others	30 (26)	13 (43)	17 (57)	19 (63)
Cotrimoxazole ± others	30 (26)	8 (27)	22 (73)	19 (63)
Recovered	62 (54)	21 (55)	41 (53)	

*B-lactam: cefazolin, oxacillin, ampicillin $\pm$ sulbactam, amoxicillin $\pm$ clavulanate, cefalexin, cefixime, cefotaxime, ceftazidime, ceftriaxone, cefepime, piperacillin/tazobactam, ertapenem, meropenem, imipenem.

#Recovered: 80 patients had a full recovery, without changing the initial therapy, while 8 patients recovered after clinical flare-up requiring a therapeutic change.

§: two patients are not included because, after been diagnosed with PVO, they received treatment at another hospital

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplement1.pdf](#)