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Bacteraemia and subsequent vertebral osteomyelitis: a retrospective review of 125 patients

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Summary

Background: Vertebral osteomyelitis (VO) is associated with considerable morbidity and its incidence seems to be increasing. Haematogenous spread is an important aetiological factor.
Aim: The objective was to describe a series of patients with VO and to search for a relationship between preceding bacteraemia and subsequent VO with the same pathogen.
Design and methods: A retrospective study of all treated cases of VO in a tertiary hospital over a 10-year period.
Results: There were 129 cases of VO (involving 125 patients) that received antimicrobial treatment. Eighty-three (66%) were male and the mean age was 59.5 years (range 1 month to 87 years). The vertebral level involved was lumbar in 66 (53%) cases and thoracic in 35 (28%) cases. Seventy-four cases (59%) had a microbiologically confirmed aetiology. The diagnostic yield from procedures was 46 and 36% from blood culture and bone biopsy, respectively. *Staphylococcus aureus* was the most common pathogen [38 of 74 (51%) cases]. Nine of 38 (24%) cases of *Staphylococcus aureus* VO had a preceding bacteraemia with the same pathogen in the previous year.
Conclusions: *Staphylococcus aureus* is an important pathogen causing bacteraemia with the ability to cause metastatic complications including VO. The high proportion of cases developing VO following a documented bacteraemia, sometimes many months previously, reinforce the importance of adequate aggressive treatment for bacteraemia. VO must be considered in all patients presenting with back pain up to a year after bacteraemia. Previous bacteraemias with relevant pathogens can help guide antibiotic treatment at presentation of VO and if biopsy cannot be obtained.

Introduction

Vertebral osteomyelitis (VO), a bacterial infection of the vertebral body and the intervertebral disc, is a relatively rare disease with an incidence of between 1:250 000 and 1:450 000.[1,2] The overall incidence of haematogenous VO has increased steadily in recent years. Predisposing factors include an ageing population, increasing nosocomial bacteraemia secondary to intravascular devices and

other forms of instrumentation and intravenous drug use.[3] Presentation may be acute or chronic, and neurological symptoms may or may not be present. These features may lead to delays in diagnosis and treatment, which may affect prognosis.[4]

The infectious diseases team at our tertiary centre is frequently involved in the diagnosis and management of VO. We observed a number of microbiologically proven cases of VO where similar pathogens were isolated from blood cultures on previous hospital admissions. The majority of published studies on VO in the literature have either described cases or performed detailed analyses of particular aetiological categories or risk factors. To our knowledge, there are only three studies that describe bacteraemia preceding subsequent admission with VO.[5–7]

In the present study of treated cases of VO, we present the pathogens involved and specifically address the relationship between bacteraemia and the subsequent development of VO.

Patients and methods

Study population

The electronic records were reviewed for all patients admitted to Addenbrooke's Hospital, a 1000-bed teaching hospital, from the beginning of January 1997 to the end of December 2006. Addenbrooke's Hospital provides a regional neurosurgical and infectious diseases service. Databases from medical records, radiology and pathology (microbiology and histopathology) were searched. All patients with a discharge diagnosis of 'osteomyelitis of vertebra'; 'infection of intervertebral disc (pyogenic)'; 'discitis, unspecified' and 'osteomyelitis, unspecified' were included. All reported MRI, CT and nuclear medicine studies with the words 'osteomyelitis' or 'discitis' were reviewed. All vertebral biopsy samples received in the microbiology and histopathology laboratories were reviewed. Notes were retrieved in cases where it was unclear from electronic records what antimicrobial treatment patients had received.

Study definitions

The diagnosis of VO was based on a combination of consistent clinical, laboratory and radiological features confirmed by positive cultures from blood, bone or epidural collections or by an appropriate response to antibiotic therapy.

A case represented a single admission during which antimicrobial treatment was administered. Vertebral osteomyelitis was defined as 'definite', 'probable' or 'presumptive' as previously described.[8] 'Definite' was when a pathogen was isolated from the involved vertebra, intervertebral disc space, paravertebral or epidural abscess. 'Probable' when the results of at least one set (aerobic and anaerobic) of blood cultures were positive during a compatible illness. 'Presumptive' when there was radiological evidence during a compatible illness in the absence of any positive cultures.

The characteristics analysed included age, sex, results of investigations including radiological and microbiological tests at the time of diagnosis. We then looked for any positive blood cultures in the year preceding that hospital admission.

Results

Demographic characteristics

During the study period, there were 127 patients with a total of 131 cases of VO. Two patients were excluded, as we were unable to verify, due to missing case notes, whether they received antimicrobial treatment. Of the resulting 125 patients (129 cases) included for analysis, there were 83 male patients (66%) with an age ranging from 1 month to 87 years (mean 59.5 years, median 64 years). The diagnosis was definite in 24 cases (18.6%), probable in 50 cases (38.8%) and presumptive in 55 cases (42.6%) (Figure 1). There was an increasing trend in cases over the 10-year period, although statistical significance was not achieved (chi-squared test 14.86; $P = 0.6712$). Twenty-nine cases (23%) were referrals from other hospitals.

Sites of involvement

The lumbar region was most frequently affected (66; 51%), followed by thoracic (35; 27%), cervical (14; 11%), lumbo-sacral (8; 6%), thoraco-lumbar (5; 4%) and cervical and lumbar (1; 0.7%).

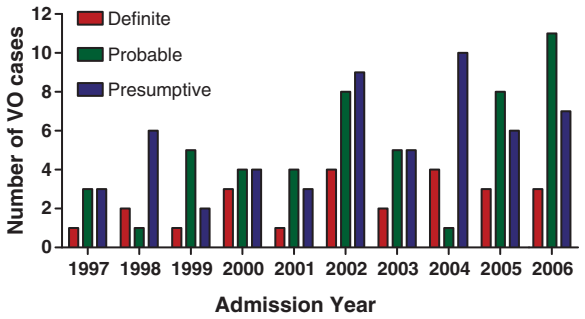

Figure 1. Treated cases of VO in a 10-year period.

Table 1 Causative organisms in the 74 cases of vertebral osteomyelitis

Organism	Definite VO	Probable VO	Total number of cases[a]
MSSA	10	16	26
MRSA	3	9	12
Gram-negative bacilli[b]	3	7	10
CoNS	0	9	9
Streptococci	1	4	5
Enterococcus spp.	1	3	4
Mycobacterium spp.[c]	4	0	4
Miscellaneous[d]	2	0	2
Polymicrobial[e]	0	2	2

MSSA: meticillin-sensitive *Staphylococcus aureus*; MRSA: meticillin-resistant *Staphylococcus aureus*; CoNS: coagulase-negative staphylococci.

[a]Two patients each had separate episodes of VO. In one (probable diagnostic category), the first episode (C1–C2) was caused by MSSA and the second (L1–L2) suspected to be *Mycobacterium tuberculosis*; no positive bacterial culture on biopsy but strongly positive Mantoux test. In the other patient (probable diagnostic category), the first episode (L4–L5) was caused by *Staphylococcus xylosus* and the second (L4–L5) by MRSA.

[b]*Escherichia coli* in five cases, *Proteus mirabilis* in two cases, *Pseudomonas aeruginosa* in two cases and *Serratia marcescens* in one case.

[c]*Mycobacterium tuberculosis* in three cases and *Mycobacterium bovis* in one case.

[d]*Haemophilus parainfluenzae* in one case and *Fusobacterium varium* in one case.

[e]MRSA and *Enterococcus faecium* in one case and *Streptococcus milleri* and coagulase-negative staphylococci in the other.

Microbiological results

A positive microbiological diagnosis occurred in 74 (57.4%) cases of VO. The causative organisms and diagnostic categories are listed in Table 1. Those 'probable' VO cases attributed to coagulase-negative Staphylococci, Streptococcus and Enterococcus species had at least two sets of positive blood cultures and/or positive cultures from line tips making them unlikely to be contaminants in these cases. Culture of biopsy samples (of the spine, intervertebral disc space, epidural or paravertebral abscess) was performed in 66 (51.1%) cases, of which 24 (36.4%) were positive. Blood cultures were performed in all 129 cases. Bacteraemia was documented in 59 (45.7%) cases. Nine cases were positive for both biopsy sample culture and bacteraemia.

In 21 (28.4%) of the 74 VO cases with a microbiological diagnosis, a preceding bacteraemia within the previous year was noted. Ten of these cases were recurrent episodes of bacteraemia due to the same genus and species of organism. In nine of these recurrent bacteraemias, (all *Staphylococcus aureus*), the antibiogram was identical to that of the organism subsequently isolated from bone, abscess or blood at diagnosis of VO (Table 2). Thus, 12.2% of cases (9/74) with microbiologically confirmed VO had a preceding bacteraemia with the same pathogen within the preceding year. In 38 cases of *S. aureus* VO, 9 (23.7%) had a preceding *S. aureus* bacteraemia. Just over 30% of our *S. aureus* isolates were meticillin-resistant. The treatment that these nine cases with *S. aureus* bacteraemia received is summarised in Table 2. In only one of these, nine was the aetiology line-related. Table 3 shows the total number of *S. aureus* bacteraemia episodes for the period 1997–2006. Table 3 also shows the number of bacteraemic episodes and cases of VO due to *S. aureus*. The rate of bacteraemias complicated by VO varied from 0.4 to 3.2% (mean 1.9%).

Discussion

We present a 10-year series of patients with microbiologically proven VO, for whom the incidence of preceding bacteraemia with the same pathogen within a year of admission was determined.

VO remains an infrequent infection, accounting for only 129 of 586 408 admissions over a 10-year period (0.02%). The aetiological diagnosis of VO is frequently difficult, often requiring the performance of tissue biopsies. The spectrum of organisms capable of causing VO is wide, making identification of a causative organism vital to ensure appropriate antimicrobial therapy is given. The percentage of cases with an aetiological diagnosis in our series was 57.4%. As reported by previous studies,[8–16] blood culture was the most useful routine test resulting in the isolation of a pathogen in just under half (46.5%) of the patients from whom it was obtained. Given that a single pathogen causes the vast majority of cases of VO,[17] blood cultures should always be a part of the initial diagnostic evaluation of patients with suspected VO. In our series, 36.4% of cultures obtained through biopsy isolated a pathogen. In only 9 of these 24 cases was the same pathogen isolated in blood cultures taken at around the same time biopsy was performed. Seven of these nine cases were *S. aureus* with the remainder being *Pseudomonas aeruginosa* and group G streptococcus. This argues that bone biopsy is warranted even in the presence of a compatible clinical syndrome, abnormal imaging consistent with VO

Table 2 Cases of VO that had a preceding bacteraemia with same pathogen in the preceding year

Year	Patient	Age	Sex	Vertebral level	Diagnostic category	Pathogen isolated	Antibiogram	Comments	Treatment for previous bacteraemia
1997	1	69	M	T7/8	Probable	MRSA	Identical	Two months earlier had two sets of positive blood cultures with same organism	Vancomycin 1 g IV BD for 3 months
1998	2	81	F	T12/L1	Definite	MRSA	Identical	MRSA isolated from bone biopsy and two sets of blood cultures. Two months earlier two sets of blood cultures were positive for same organism	Vancomycin 1 g IV BD for 2 weeks
2000	3	67	M	T9/10	Definite	MSSA	Identical	MRSA isolated from bone biopsy. Two months earlier one set of blood cultures positive for same organism	Flucloxacillin 2 g IV QDS for 3 days followed by Flucloxacillin 500 mg PO QDS for further 7 days (non-compliant patient)
2002	4	50	M	L1	Probable	MRSA	Identical	MRSA isolated from three sets of blood cultures; bone biopsy (performed while on antibiotics) was negative for culture. Three months earlier one of two blood culture bottles grew MRSA	Vancomycin 1 g IV BD for 14 days
2002	5	52	F	T9/10 and L4/5	Probable	CoNS	Different	Three sets of blood culture positive for CoNS. Progression of spinal infection led to bone biopsy (while on antibiotics) which was negative on culture. A year earlier had three sets of blood cultures positive for CoNS	Teicoplanin 400 mg IV loading dose, followed by Teicoplanin 200 mg IV daily for 21 days (allergy to Vancomycin)
2002	6	64	M	T9/10	Probable	MRSA	Identical	Three months earlier one set of blood cultures was positive for same organism	Vancomycin 1 g IV BD for 6 weeks
2002	7	72	M	T11/12	Definite	MSSA	Identical	MSSA isolated from drained epidural abscess and one set of blood cultures. Two months earlier two sets of blood cultures were positive for same organism	Flucloxacillin 1 g IV QDS and Fusidic acid 500 mg PO TDS for 3 days; and then Flucloxacillin 500 mg PO QDS to complete 4 weeks
2003	8	55	F	T12	Probable	MRSA	Identical	Five months earlier, one set of blood cultures and line tip both grew MRSA	Vancomycin 1 g IV BD for 4 weeks
2004	9	54	F	L4/L5	Definite	MRSA	Identical	Bone biopsy cultured MRSA. Three months earlier two sets of blood cultures isolated same organism	Teicoplanin 400 mg IV loading dose, followed by Teicoplanin 200 mg IV daily for 7 days; no antibiotic treatment for the following 5 days; then Vancomycin 1 g IV BD for 10 days (non-compliant patient)
2005	10	53	F	T8/9	Definite	MSSA	Identical	Six sets of blood cultures and culture of material following laminectomy all grew MSSA. One month earlier four sets of blood cultures were positive for MSSA; 3 days after those blood cultures a further four sets grew MRSA	Vancomycin 1 g IV BD for 10 days; no antibiotic treatment for 7 days; then Vancomycin 1 g IV BD for 11 days

MSSA: Meticillin-sensitive *Staphylococcus aureus*; MRSA: Meticillin-resistant *Staphylococcus aureus*; CoNS: coagulase negative staphylococci.

Table 3 Number of *S. aureus* bacteraemia episodes 1997–2006

Year	Episodes[a]	Number of VO cases due to *S. aureus*	Rate of VO compared to bacteraemic episodes	Hospital admissions	Bacteraemia rate per 1000 admissions
1997	164	4	2.4%	54 755	3.0
1998	212	2	0.9%	54 472	3.9
1999	174	3	1.7%	53 834	3.2
2000	190	4	2.1%	54 036	3.5
2001	213	2	0.9%	53 896	4.0
2002	222	6	2.7%	55 812	4.0
2003	225	4	1.8%	61 827	3.6
2004	230	1	0.4%	64 828	3.5
2005	233	6	2.6%	67 619	3.4
2006	220	7	3.2%	65 329	3.4
Total	2083	39	1.9%[b]	586 408	3.5[c]

VO: vertebral osteomyelitis.
[a]All isolates recovered from an individual patient within 14 days of a positive blood culture were counted as a single episode.
[b]Mean rate of VO cases due to *S. aureus.*
[c]Mean bacteraemia rate for 10-year period.

and positive blood culture. The value of CT-guided biopsy in the diagnosis of septic discitis at our institution has been described previously.[18]

The mainstay of treatment for VO is medical with antimicrobials, though surgery retains an important role in certain cases. Unless the patient is severely unwell, antimicrobials should be delayed pending a microbiological diagnosis. Antimicrobial treatment regimen is guided by culture results from blood or biopsy. Where the index of suspicion for VO is high in the absence of positive cultures empiric treatment is initiated directed against staphylococci, streptococci and Gram negative bacteraemia, the most likely causative organisms. In combination with antimicrobials, surgery has a role in draining epidural or paravertebral masses, in managing difficult cases where disease progresses despite appropriate antimicrobials and whenever the spinal cord is threatened by vertebral collapse or spinal instability.[19] In line with the literature,[20,21] all VO cases in our cohort received a minimum of 6 weeks antimicrobials with parenteral antibiotics for part or all of the treatment duration depending on the clinical response. In addition, about 10% (7/74) of patients with a microbiological diagnosis had a surgical procedure performed with five having epidural abscesses or paravertebral masses drained and two requiring laminectomies.

Staphylococcus aureus is the most common cause of VO (35–75%).[5,8,11,13,14,16–18,20,22–33] In this series it accounted for 51.4% of microbiologically confirmed cases. The high proportion of meticillin-resistant isolates (31.6%) has important implications for empirical treatment in those cases lacking a specific microbiological diagnosis, which should include antimicrobials with activity against meticillin-resistant *S. aureus*. A recent study of 45 patients with VO showed no significant effect on treatment outcomes in patients with and without (24.4%) a microbiological diagnosis.[34] Those patients without a microbiological diagnosis were divided into two groups based on likely aetiology of VO with nosocomially acquired cases (with a high incidence of meticillin-resistance) receiving vancomycin and community acquired cases receiving cefazolin.[34] Both these drugs were chosen for their effectiveness against staphylococci, a common pathogen in VO.

The primary objective of the present series was to determine whether there was a relationship between bacteraemia and subsequently developing VO with the same pathogen. Previous data showed rates ranging from 10 to 33%. Colmenero and colleagues divided the aetiological agent in VO into pyogenic, tuberculous and brucellar.[5] In 22 of 72 (30.6%) cases of pyogenic VO, previous bacteraemia could be reported. Unfortunately, the bacteria involved were not disclosed. Twenty-four patients with brucellar VO had a diagnosis of brucellosis within the previous year with isolation of *Brucella melitensis* in blood culture in eight of them (33.3%). Priest and Peacock retrospectively reviewed the notes of 40 patients with *S. aureus* VO.[6] They found that 10% of patients had a preceding *S. aureus* bacteraemia or vascular catheter infection within the preceding 6 months. Bhavan and colleagues

retrospectively identified 70 patients with haematogeneous VO of whom 19% had a history of bacteraemia (the bacteria involved were not disclosed) in the month prior to admission.[7]

Another approach is to study the rate of relapse (isolation of the same pyogenic organism from blood or discovertebral biopsy) in VO cases. In a cohort of 253, there were 30 relapses (12%) of which 13 were reported to have occurred in patients who received suboptimal antibiotic therapy.[8] In another study designed to compare the risk of relapse of VO according to the duration of antibiotic therapy, the relapse rate was 4% (5 of 120 patients) with all relapses less than six months after the discontinuation of antibiotic therapy.[20] Two of these five patients were true relapses of *S. aureus* VO, whereas the remaining three patients (with pacemaker-related endocarditis) had recurrent coagulase-negative staphylococci bacteraemia without VO. This probably reflects the fact that the pacemakers were not removed after the first infectious episode.

The most important observation in our series is that almost a quarter (23.7%) of patients with *S. aureus* VO had a preceding bacteraemia with an isolate with identical antibiograms in the previous year. Typing (e.g. phage typing or pulsed field gel electrophoresis; PFGE) was not performed to confirm this. The potential late sequelae, including VO, that may occur as a consequence of inadequately treated *S. aureus* bacteraemia has long been emphasized in the literature.[35–42] All nine patients in our series with preceding *S. aureus* bacteraemia received antimicrobial therapy. In some cases the appropriate dosing was given, but in others the dosing and duration of treatment were inappropriate. It seems likely that suboptimal treatment of their original infections may have predisposed some of these patients to the subsequent development of VO. The message is clear—*S. aureus* bacteraemias must be treated aggressively to prevent the occurrence of metastatic complications.

There were several limitations in this study. It is a single-centre study, so results may not be transferable to other hospitals. Typing methods were also not performed on isolates to confirm a relationship. A prospective study evaluating all patients with bacteraemia to see how many of them go on to develop VO would be the most reliable method for studying this problem. However, this would take several years to achieve the necessary number of cases, during which clinical practices may change. Instead, data was acquired retrospectively with the following caveats. This may have led to an over-estimate (not all bacteraemias result in VO) or under-estimate (transient bacteraemias may have been undetected; patients may have been treated for bacteraemia at another hospital; some case notes were missing so patients were not included in analysis) in the number of VO cases. Among the strengths of this study are the detailed review of antimicrobial treatment received in patients with documented bacteraemia who subsequently developed VO and the number of cases with a microbiological diagnosis.

In summary, our series of 74 microbiologically confirmed cases of VO adds to the growing literature. The value of blood culture and bone biopsy in making a positive diagnosis is shown. *Staphylococcus aureus* remains the predominant causative pathogen. In addition, we have observed that just under a quarter of *S. aureus* VO cases had a preceding bacteraemia with the same pathogen, reiterating the need for aggressive treatment of bacteraemia caused by this pathogen.

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