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Health Care Associated Hematogenous Pyogenic Vertebral Osteomyelitis

A Severe and Potentially Preventable Infectious Disease

Carlos Pigrau, MD, Dolors Rodríguez-Pardo, MD, Nuria Fernández-Hidalgo, MD, Laura Moretó, MD, Ferran Pellise, MD, Maria-Nieves Larrosa, MD, Mireia Puig, MD, and Benito Almirante, MD

Abstract: Although hematogenous pyogenic spinal infections have been related to hemodialysis (HD), catheter-related sepsis, and sporadically, to other nosocomial infections or procedures, in most recent studies and reviews the impact of nosocomial infection as a risk factor for vertebral osteomyelitis (VO) is not well established. The aim of our study was to describe the risk factors, infectious source, etiology, clinical features, therapy, and outcome of health care associated VO (HCAVO), and compare them with community-acquired VO (CAVO) cases.

A retrospective cohort study of consecutive patients with hematogenous VO was conducted in our third-level hospital between 1987 and 2011. HCAVO was defined as onset of symptoms after 1 month of hospitalization or within 6 months after hospital discharge, or ambulatory manipulations in the 6 months before the diagnosis.

Over the 25-year study period, among 163 hematogenous pyogenic VO, 41 (25%) were health care associated, a percentage that increased from 15% (9/61) in the 1987–1999 period to 31% (32/102) in the 2000–2011 period ($P < 0.01$). The presumed source of infection was an intravenous catheter in 14 (34%), cutaneous foci in 8 (20%), urinary tract in 7 (17%), gastrointestinal in 3 (7%), other foci in 3 (7%), and unknown in 6 (15%). *Staphylococcus aureus* was the most frequently isolated microorganism (14 cases, 34%), followed by coagulase-negative *Staphylococci* (CoNS) in 6 (15%), and Enterobacteriaceae in 6 (15%) cases.

Compared with CAVO cases, patients with HCAVO were older (mean 66.0 SD 13.0 years vs 60.5 SD 15.5 years), had more underlying conditions (73% vs 50%, $P < 0.05$), neoplasm/immunosuppression (39% vs 7%, $P < 0.005$), chronic renal failure (19% vs 4%, $P < 0.001$), a known source of infection (85% vs 54% $P < 0.05$), *Candida* spp (7% vs 0%, $P < 0.01$) or CoNS infections (15% vs 2%, $P < 0.05$), higher mortality (15% vs 6%, $P = 0.069$), and a higher relapse rate in survivors (9% vs 1%, $P < 0.05$).

Presently, in our setting, one-third of hematogenous pyogenic VO infections are health care associated, and a third of these are potentially preventable catheter-related infections. Compared with CAVO, in health care associated hematogenous VO, mortality and relapse rates are higher; hence, further prevention measures should be assessed.

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Abbreviations: CAVO = community-acquired vertebral osteomyelitis, CoNS = coagulase-negative staphylococci, HCAVO = health care associated vertebral osteomyelitis, HD = hemodialysis, IDRSAB = intravascular device related *Staphylococcus aureus* bloodstream infection, IE = infective endocarditis, IQR = interquartile range, MRSA = methicillin-resistant *S aureus*, MSSA = methicillin-susceptible *S aureus*, SD = standard deviation, UTI = urinary tract infection, VO = vertebral osteomyelitis.

INTRODUCTION

Spontaneous hematogenous pyogenic vertebral osteomyelitis (VO) is an uncommon disease with an estimated incidence of 0.2 to 2.4 cases per 100,000 population/y.[1–20] Previously described risk factors for VO are older age (incidence 6.5–9.8/100,000 population/y), diabetes mellitus, malignancy, immunosuppression, liver disease, end-stage renal failure, liver cirrhosis, intravenous drug use, and previous infection, particularly bloodstream infection.[1–10,21–24] Recently, spinal infections have also been related to hemodialysis (HD),[14,20,25] catheter-related sepsis,[1,2,7,10,16,20,26] and sporadically, other nosocomial infections or procedures.[3,13–16,20,26]

Most recent studies and reviews have not mentioned nosocomial infection as a risk factor for VO. Nonetheless, in a small series of 20 VO cases published 18 years ago, Torda et al[26] found that the infection was of nosocomial acquisition in 60% of patients, and a recent review has suggested that nosocomial infection may have contributed to the increase in spinal infections[3]. In our previous study[10] and 1 by other authors,[14] VO was considered nosocomial-acquired in around 19% of cases. Available data on the impact, source of infection, clinical findings, and outcome of health care associated hematogenous spinal infections, however, are limited.

The aim of this study was to describe the risk factors, infectious source, etiology, clinical features, therapy, and outcome of health care associated hematogenous pyogenic VO (HCAVO), and compare the findings with those of community-acquired VO (CAVO) cases.

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From the Infectious Diseases Department (CP, DR-P, NF-H, LM, BA); Orthopedic Department (FP); Microbiology Department (M-NL), Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona, Barcelona; and REIPI (Spanish Network for Research in Infectious Diseases) (CP, DR-P, NF-H, M-NL, MP, BA), Madrid, Spain.
Correspondence: Carlos Pigrau, Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Passeig Vall d'Hebron 119–129, 08035 Barcelona, Spain (e-mail: cpigrau@vhebron.net).
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PATIENTS AND METHODS

Study Design, Patients, and Settings

In this retrospective review of all consecutive VO cases diagnosed at Vall d'Hebron Hospital, a tertiary referral center for complex vertebral surgery patients, patients with previous spinal instrumentation or surgery, tuberculosis (n = 53), brucellosis (n = 13), or no definitive bacteriological diagnosis (n = 16) were excluded. All consecutive adult patients (≥18 years) diagnosed with VO from January 1987 to December 2011 were enrolled. Patients were identified from our infectious diseases department VO registry, and most of them were followed-up by one of the authors (C.P.).

Data Collection

Demographic, clinical, diagnostic, treatment, and follow-up data were obtained by chart abstraction and entered in a database created specifically for the study. To assess the effectiveness of antibiotic and surgical therapy, only survivor patients followed-up for at least 1.5 years to detect relapses after therapy completion were included.

Definitions

The diagnosis of hematogenous pyogenic VO was established on previously published criteria,[10] which include absence of prior surgery, spinal instrumentation or contiguous VO, and presence of 3 criteria: compatible clinical picture; consistent imaging findings on computed tomography or magnetic resonance imaging, or increased uptake on technetium bone scan; isolation of pyogenic microorganisms in blood culture or samples obtained by open surgery or percutaneous biopsy of bone or adjacent tissues. Coagulase-negative *Staphylococci* (CoNS) and other skin contaminants were considered true pathogens only when isolated from a sterile bone biopsy in at least 2 samples or in 2 or more blood cultures drawn on separate occasions.

VO was considered health care associated according to published criteria with some modifications.[27] First, onset of symptoms >1 month after hospitalization with no evidence of VO at the time of admission; there is not a previously established cutoff period for health care VO-associated designation; all health care cases took at least a month for symptoms to develop, or symptom onset within 6 months after discharge (designated nosocomial VO). Second, ambulatory diagnostic or therapeutic manipulations within 6 months before symptom onset (designated nosohusial VO), including long-term central venous catheter use, autologous or prosthetic arteriovenous fistula for HD, invasive intravascular techniques (cardiac catheterization, pacemaker insertion, other intravascular devices, intravenous chemotherapy, or contrast administration), urological, gynecological, or digestive procedures, and cutaneous manipulations (eg, acupuncture, intramuscular injections).

Catheter-related bloodstream infection is defined elsewhere.[28] As to the presence of infective endocarditis (IE), only patients with definite IE according to the modified Duke criteria were included.

Renal failure was defined as serum creatinine ≥2 mg/dL. Neurological complication was established on the presence of motor deficits or meningitis.

Outcome

Patients were clinically followed-up during hospitalization and in the outpatient clinic. In-hospital mortality was defined as death by any cause during hospitalization. Related mortality was defined as death secondary to sepsis, VO complications, or IE in cases associated with this disease.

Treatment failure was defined based on the following: infection-related death during hospitalization; persistent infection (clinical signs or persistently high acute-phase reactants with no other inflammatory causes and isolation of the same microorganism); or relapse, established on reappearance or worsening of clinical signs and analyses after a period of improvement, and isolation of the same microorganism. To evaluate relapse, only patients followed-up for at least 1.5 years after antibiotic therapy were included.

Statistical Analysis

Normally distributed quantitative variables are expressed as the mean and standard deviation (SD) and those with skewed distribution as median and interquartile range (IQR). Data for discrete variables are expressed as percentages. Continuous variables were compared using the unpaired Student *t* or Mann–Whitney *U* test, and proportions using the χ^2 or Fisher exact test, where appropriate. All statistical tests were 2-tailed, and statistical significance was set at a *P* value of <0.05. Statistical analyses were performed with Microsoft SPSS-PC+, 15.0 (SPSS, Chicago, IL).

Ethical Considerations

Because data collection began in 1987 and no direct patient contact was planned, the requirement for informed consent was waived.

RESULTS

Over the 25-year study period, hematogenous pyogenic VO was diagnosed in 163 patients, and 41 cases (25%) were health care associated. Percentage of HCAVO increased from 15% (9/61) in 1987–1999 to 31% (32/102) in 2000–2011 ($P < 0.01$).

Twenty-six (63%) HCAVO patients were men, with a mean age of 66.3 years (SD 13.0). Mean age was similar in the 2 periods (61.9 years [SD 14.8] vs 62.1 years [SD 15.3], *P* = non significant). Twenty-nine of the 41 cases (71%) were considered nosocomial (in all symptoms of VO started at least 1 month after hospital discharge) and 12 (29%) nosohusial. Demographic data, clinical features, and laboratory results in HCAVO cases are shown in Table 1.

Source of Infection

The infectious source was established in 35 (85%) HCAVO cases (Table 2). The most important was catheter-related infection in 14 (34%), 9 due to central venous catheters and 5 due to peripheral venous catheters. Seven of these patients had a previous documented catheter-related bloodstream infection due to the same microorganism isolated in VO, 4 patients had previous phlebitis, 2 cases of *Candida albicans* infection occurred in patients with previous parenteral nutrition and no other *Candida* foci, and 1 renal transplant patient had well-documented plasmocoagulase-negative VO, with no other source of infection. Microbiological etiologies of catheter-related VO are outlined in Table 2.

Overall, HCAVO was associated with an HD in 5/41 cases (12%), all due to long-term catheter-related infection and none secondary to an arteriovenous fistula.

TABLE 1. Description of the 41 Cases of Health Care Associated Hematogenous Pyogenic VO

	Sex	Age	Previous Hosp., mo	NC/NH	Source of Infection	Microorganism	IE	Neurological Involvement	Vertebral Surgery	Outcome	Follow-up, mo
1	M	66	6	NC	Osteoarticular	MSSA	Yes	No	No	Cured	120
2	F	66	5	NC	Urinary tract	*Streptococcus agalactiae*	Yes	Meningitis	No	Death	—
3	M	77	3	NC	Gastrointestinal	*Enterococcus faecalis*	Yes	No	No	Cured	30
4	F	70	3	NC	Cutaneous	MRSA	No	No	No	Cured	36
5	F	57	2	NC	Catheter (central)	CoNS	No	No	No	Cured	30
6	F	72	2	NC	Catheter (central)	*Candida glabrata*	Yes	No	No	Cured	30
7	M	45	5	NC	Unknown	*Pseudomonas aeruginosa*	No	Deficit	No	Cured	30
8	F	76	2	NC	Catheter (peripheral)	MSSA	No	Meningitis	No	Death	—
9	F	79	3	NC	Catheter (peripheral)	MSSA	Yes	No	Yes	Cured	Relapse (1 mo)
10	M	67	5	NC	Urinary tract	*Escherichia coli*	No	No	No	Cured	30
11	F	71	3	NC	Gynecological	*E faecalis*	No	No	No	Cured	30
12	M	54	5	NC	Unknown	CoNS	No	Deficit	Yes	Cured	30
13	M	76	6	NC	Catheter (central)	*Candida albicans*	No	No	No	Cured	Relapse (6 mo)
14	F	29	3	NC	Cutaneous	MSSA	No	No	No	Cured	36
15	M	81	5	NC	Catheter (central)	*C albicans*	No	No	No	Cured	24
16	F	66	6	NC	Catheter (central)	MRSA	Yes	Deficit	No	Cured	Relapse (2 mo)
17	F	55	4	NC	Catheter (central)	MSSA	No	No	No	Death	c
18	M	60	5	NC	Catheter (peripheral)	CoNS	No	Deficit	No	Cured	6 mo (death)
19	F	67	1	NC	Cutaneous	*Propionibacterium acnes*	No	No	No	Cured	84
20	M	59	2	NC	Unknown	CoNS	No	No	No	Death	—
21	M	48	4	NC	Cutaneous	MSSA	No	Deficit	Yes	Cured	60
22	M	79	1.5	NC	Urinary tract	*E coli*	No	No	No	Cured	36
23	M	86	5	NC	Urinary tract	*Enterobacter cloacae*	No	Deficit	No	Cured	18
24	F	75	1.5	NC	Respiratory	*P aeruginosa*	No	No	No	Cured	7 mo (death)
25	M	57	4	NC	Gastrointestinal	*Streptococcus viridans* group	No	Deficit	No	Cured	72
26	M	73	3	NC	Urinary tract	*E faecalis*	Yes	No	No	Cured	30
27	M	61	4.5	NC	Catheter (peripheral)	CoNS	No	No	No	Cured	4 mo (death)
28	M	71	4	NC	Unknown	*S agalactiae*	No	No	No	Cured	18
29	M	81	1	NC	Catheter (central)	MRSA	Yes	No	No	Cured	18
30	M	59		NH	Gastrointestinal	*Bacteroides fragilis*	No	No	No	Cured	30
31	M	58		NH	Catheter (peripheral)	MSSA	No	No	No	Cured	36
32	M	80		NH	Urinary tract	*E coli*	No	Deficit	No	Death	—
33	M	81		NH	Catheter (central)	MSSA	No	No	No	Death	—
34	F	57		NH	Unknown	MSSA	No	No	No	Cured	36
35	M	81		NH	Catheter (central)	CoNS	No	No	No	Cured	24
36	M	81		NH	Cutaneous	*Streptococcus pyogenes*	No	No	No	Cured	18
37	M	74		NH	Urinary tract	*E coli*	No	Deficit	No	Cured	18
38	F	46		NH	Unknown	*Achromobacter xylosoxidans*	No	No	No	Cured	24
39	M	45		NH	Cutaneous	MSSA	No	Deficit	Yes	Cured	18
40	M	52		NH	Cutaneous	*Klebsiella pneumoniae*	No	Deficit	No	Cured	24
41	F	81		NH	Cutaneous	MSSA	No	No	No	Cured	18

CoNS = coagulase-negative *Staphylococci*, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *S aureus*, NC = nosocomial, NH = nosohusial, Previous hosp. = time since the previous hospitalization, VO = vertebral osteomyelitis.

TABLE 2. Presumed Source of Infection in 41 Health Care Associated Hematogenous Pyogenic VO Cases

Variable	HCAVO Episodes (n = 41)
Confirmed or suspected catheter-related sepsis*	14 (34%)
Other cutaneous foci	8 (20%)
Urinary tract manipulation/infection	7 (17%)
Gastrointestinal manipulation	3 (7%)
Other foci†	3 (7%)
Unknown	6 (15%)

HCAVO = health care associated VO, VO = vertebral osteomyelitis.
* Staphylococcal 11 (methicillin-susceptible *Staphylococcus aureus* 5, methicillin-resistant *S aureus* 2, coagulase-negative *Staphylococci* 4), *Candida* spp 3.
† Gynecological in 1 (hysterectomy with postoperative surgical infection), respiratory in 1, and osteoarticular in 1.

Among the cutaneous foci, 1 had a previous streptococcal cellulitis, 4 infected skin ulcers (2 *Klebsiella* spp, 1 methicillin-susceptible *Staphylococcus aureus* [MSSA], and 1 methicillin-resistant *S aureus* [MRSA]), and 4 skin abscesses (1 developed a gluteus abscess after an intramuscular injection, and 12 weeks later was diagnosed with *S aureus* HCAVO).

Among 7 cases related with previous urological foci, 5 were associated with urinary catheterization, 1 secondary to urological surgery with a complicated postoperative urinary tract infection (UTI), and 1 patient had recurrent UTI after prostatic cancer surgery. Previous bacteriemic UTI was documented in only 1 urinary-related case.

There were 3 digestive-associated cases, 2 related with esophageal manipulation, and 1 with a previous endoscopic retrograde cholangiopancreatography study.

The osteoarticular-related case developed concomitant bacteriemic *S aureus* HCAVO and prosthetic knee joint infection 6 months after the initial prosthetic procedure. The respiratory-related case was a *Pseudomonas aeruginosa* colonized patient who developed *P aeruginosa* VO 1.5 months after tracheal prosthesis manipulation.

Among the 12 nosohusial cases, 3 (25%) were considered catheter-related, all of staphylococcal etiology.

Etiology

Blood cultures were positive in 29/40 (72.5%) patients (Table 3). Bone samples in 22 patients isolated a microorganism in 18 cases (diagnostic yield 82%), all concordant with the blood culture isolate.

S aureus was the most frequently isolated microorganism (14 cases, 34%), followed by CoNS and Enterobacteriaceae (Table 3). There were 2 cases of anaerobic HCAVO. In 1, caused by *Bacteroides* spp, the patient had an esophageal fistula and developed VO after esophageal manipulation, whereas the other patient had well-documented *Propionibacterium acnes* VO (3 positive biopsy samples) 1 month after cardiac catheterization.

Catheter-associated HCAVO cases were due to staphylococci (n = 11) or *Candida* spp (n = 3), and urinary tract related cases were mainly due to gram-negative microorganisms (n = 5/7).

TABLE 3. Microorganisms Causing Health Care Associated Pyogenic VO

Variable	HCAVO, n = 41 (%)
Gram-positives	27 (65.8)
Staphylococci species	20 (48.8)
MSSA	11 (26.8)
MRSA	3 (7.3)
CoNS	6 (14.6)
Streptococcus species	4 (9.8)
Streptococcus viridans	1 (2.4)
Streptococcus pyogenes	1 (2.4)
Streptococcus agalactiae	2 (4.9)
Enterococcus faecalis	3 (7.3)
Gram-negatives (aerobic)	9 (21.9)
Escherichia coli	4 (9.8)
Pseudomonas aeruginosa	2 (4.9)
Klebsiella pneumoniae	1 (2.4)
Enterobacter cloacae	1 (2.4)
Achromobacter xylosoxidans	1 (2.4)
Other	
Candida albicans	2 (4.9)
Candida glabrata	1 (2.4)
Propionibacterium acnes	1 (2.4)
Bacteroides fragilis	1 (2.4)

CoNS = coagulase-negative *Staphylococci*, HCAVO = health care associated VO, IE = infective endocarditis, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *S aureus*, VO = vertebral osteomyelitis.

Comparison Between HCAVO and CAVO

The characteristics of patients with HCAVO and CAVO are presented in Table 4. Patients with HCAVO were older and underlying diseases were more frequent than in the CAVO group, particularly malignancy/immunosuppressive treatment and chronic renal failure, whereas intravenous drug use was associated with CAVO. Of note, malignant disease and immunosuppressor treatment were significantly higher in patients diagnosed after 1999 (23 [22.5%] vs 2 [3.3%], $P = 0.001$). Among these 25 patients, 20 had an active neoplasm and 5 received immunosuppressors for a solid transplant or a systemic disease.

Median diagnostic delay was similar in the 2 groups. The source of infection was established in 85% of HCAVO, whereas in CAVO, the source was unknown in nearly half the cases. Catheter-related infection was the most frequent source in HCAVO, whereas UTI was the most common origin in CAVO patients. As was expected, there were a higher percentage of infections due to CoNS and *Candida* spp in the HCAVO group, mainly associated with well-documented catheter-related infections.

Back pain and fever were the most common symptoms, with back pain being less frequent in HCAVO. Among 5 HCAVO patients who did not present back pain, the clinical presentation was persistent fever in 4 (2 persistent bloodstream infection), and the diagnosis of VO was established after excluding IE and other infectious foci.

Overall, IE was diagnosed in 8/41 (20%) patients, and 8/27 (30%) gram-positive HCAVO; none of the gram-negative HCAVO had IE. Four of the 14 patients (29%) with

TABLE 4. Univariate Comparison Between 41 Patients With Health Care Associated Hematogenous Pyogenic VO (HCAVO) and 122 Patients With CAVO

Variable Demographic Data	HCAVO Group (n = 41)	CAVO Group (n = 122)	OR (95% CI)	*P* Value
Age, median y ± (SD)	66.32 (13.0)	60.54 (15.5)	1.03 (1.002–1.06)	0.033
Male sex	27 (65.9)	81 (66.4)	0.98 (0.46–2.06)	0.95
Underlying conditions	30 (73.2)	61 (50.0)	2.73 (1.25–5.93)	0.01
Diabetes mellitus	13 (31.7)	37 (30.3)	1.07 (0.50–2.29)	0.87
Neoplasm or immunosuppressors	16 (39.0)	9 (7.4)	8.0 (3.19–20.26)	<0.001
Liver cirrhosis	4 (9.8)	25 (20.5)	0.42 (0.14–1.29)	0.12
Chronic renal failure	8 (19.5)	5 (4.1)	5,67 (1.74–18.50)	0.002
Intravenous drug user	0 (0)	10 (8.2)	1.37 (1.24–1.5)	0.06
Source of infection				
Catheter related	14 (34.2)	0 (0)	5.52 (3.92–7.76)	<0.001
Skin and soft tissue	8 (19.5)	25 (20.5)	0.94 (0.39–1.29)	0.89
Urinary tract	7 (17.1)	31 (25.4)	0.60 (0.24–1.50)	0.27
Gastrointestinal	3 (7.3)	5 (4.1)	1.85 (0.42–8.09)	0.41
Other foci	3 (7.3)	5 (4.1)	1.85 (0.42–8.09)	0.41
Unknown	6 (14.6)	56 (45.9)	0.2 (0.08–0.51)	<0.001
Etiology				
MSSA	11 (26.8)	46 (37.7)	0.61 (0.28–1.32)	0.206
MRSA	3 (7.3)	3 (2.5)[‡]	3.13 (0.61–16.17)	0.153
CoNS	6 (14.6)	2 (1.6)	10.29 (1.99–53.24)	0.001
Streptococcus spp[*]	7 (17.1)	37 (30.3)	0.47 (0.19–1.16)	0.098
Enterococcus faecalis	3 (7.3)	5 (4.1)	2.28 (o.68–7.63	0.171
Enterobacteriaceae	6 (14.6)	29 (23.8)	0.55 (0.21–1.44)	0.218
Other gram-negative	3 (7.3)	3 (2.5)	3.1 (0.61–16.17)	0.153
Candida spp	3 (7.3)	0 (0)	4.21 (3.2–5.56)	0.003
Clinical features				
Diagnosis delay in days, median (IQR)	28 (13–56)	28 (8.5–45)	1.00 (0.99–1.01)	0.904
Back pain	36 (87.8)	120 (98.4)	0.12 (0.02–0.64)	0.004
Fever	30 (73.2)	95 (77.9)	0.77 (0.34–1.75)	0.54
Neurological complications	13 (31.7)	30 (24.6)	1.42 (0.65–3.09)	0.37
Neurological deficit	11 (26.8)	26 (21.3)	1.33 (0.6–3.01)	0.47
Meningitis	2 (4.9)	7 (5.7)	0.84 (0.17–4.23)	0.83
IE	8 (19.5)	28 (23)	0.81 (0.34–1.96)	0.65
Vertebral level involved				
Cervical	8 (19.5)	16 (13.1)	1.60 (0.63–4.1)	0.32
Thoracic	13 (31.7)	25 (20.5)	1.80 (0.82–3.97)	0.14
Lumbar	15 (36.6)	75 (61.5)	0.36 (0.17–0.75)	0.006
Multifocal levels	5 (12.2)	6 (4.9)	2.68 (0.77–9.32)	0.11
Laboratory data				
Blood culture (positive)	29/40 (72)	89/119 (75)	0.89 (0.40–1.99)	0.78
ESR (mean, mm/h)	75 (59–73)	94 (76–106)	0.07 (0.96–0.99)	0.03
Leukocytes	9800 (7950–13600)	12000 (9200–17700)	1 (0.99–1.00)	0.451
Therapy				
Treatment duration, median, wk (IQR)	8 (6–10)	8 (6–9)	1 (0.98–1.01)	0.983
Hospitalization, median, d (IQR)	31 (19–50)	33 (22–47)	1.002 (0.99–1.01)	0.762
Vertebral surgery	4 (9.8)	16 (13.1)	0.71 (0.22–2.28)	0.57
Outcome				
Mortality (related)	6 (14.6)	7 (5.7)	2.82 (0.89–8.93)	0.069
Relapse	3/32 (9.4)	1/109 (0.9)	10.45 (1.05–104)	0.015
Treatment failure[†]	9/41 (22)	8/122 (6.6)	3.98 (1.34–11.79)	0.008
Residual neurological deficit[‖]	5/35 (14.3)	11/115 (9.6)	1.58 (0.5–4.9)	0.43
Unfavorable outcome[§]	12/41 (29.3)	19/122 (15.6)	2.24 (0.98–5.15)	0.053

CAVO = community-acquired VO, CI = confidence interval, CoNS = coagulase-negative *Staphylococci*, ESR = Erythrocyte sedimentation rate, HCAVO = health care associated VO, IE = infective endocarditis, IQR = interquartile range, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *S aureus*, OR = odds ratio, VO = vertebral osteomyelitis.

[*] Including *E faecalis*.

[†] Death or relapse.

[‡] 2 Cases with previous community-acquired MRSA recurrent skin abscesses and 1 patient without known risk factors for community or hospital-acquired MRSA.

[§] Unfavorable outcome: death, relapse, or residual neurological deficit.

[‖] Residual neurological deficit is defined as persistence of the deficit after surgery and/or antibiotic therapy.

catheter-related HCAVO had IE. Nevertheless, the percentage of IE was similar in HCAVO and CAVO cases.

Neurological complications were observed in nearly one-third of HCAVO, a percentage slightly higher than in CAVO cases. In HCAVO, 27% of patients had a neurological deficit and 2 had meningitis (5%). Three patients required spinal surgery because of paraplegia. The incidence of neurological complications in *S aureus* HCAVO was similar to non-*S aureus* infections, 4/14 (29%) versus 9/27 (33%).

As to treatment, empirical antibiotics were started only in patients with suspected bloodstream infection, with adjustment according to the susceptibility pattern of isolated bacteria. HCAVO cases were treated for a median of 8 weeks (IQR 6–9 weeks). IE patients received 4 to 8 weeks of intravenous therapy according to the isolated microorganism; 2 patients required further oral therapy due to paravertebral abscesses. Non-IE cases were treated for a median of 8 weeks (IQR 6–10 weeks), within which there were 4 weeks of oral therapy (IQR 2–6 weeks). Five patients, with gram-negative VO, were treated orally alone.

Spinal surgery was performed in 4/41 (10%) cases: in 3 patients because of neurological complications (paraplegia) and in 1 with persistent fever to drain a large paravertebral abscess.

HCAVO patients required lengthy hospitalization (around 1 month), but duration was not longer than in CAVO cases. Six HCAVO patients died during admission (15%). Death was infection-related in all, and 3 patients had *S aureus* sepsis.

Among 35 patients who survived hospitalization and underwent outpatient follow-up, 3 died of their underlying disease in the first 7 months, and the remaining 32 had long-term follow-up (median 30 months, IQR 20–42 months). In this group, 3 (9%) relapsed, and 2 of them ultimately died due to the infection: 1 with *C albicans* HCAVO treated with 8 weeks of fluconazole who relapsed 6 months later and 1 with MSSA VO and concomitant IE treated with cloxacillin for 6 weeks who relapsed 1 month later. The third patient, a catheter-related MRSA HCAVO with IE and a paravertebral abscess, that could not be drained because of surgical contraindications, was treated with vancomycin for 8 weeks and orally with cotrimoxazole/rifampin for 8 weeks, and relapsed 2 months after completing therapy. She was treated with linezolid and relapsed again, and finally cured after 6-month therapy with teicoplanin and rifampin (follow-up 5 years).

Treatment duration and hospital stay were similar in the 2 groups, but HCAVO had a higher percentage of treatment failures and a trend to higher mortality (15% vs 6%, $P = 0.069$) and relapses (9% vs 1%, $P = 0.015$).

DISCUSSION

The results of our study show that nosocomial infection is now a common source of hematogenous pyogenic VO in our setting. One-third of these infections were catheter-related and potentially preventable. Compared with CAVO, health care related hematogenous VO was associated with higher mortality and relapse rates. In our earlier experience (1987–1999), 15% of VO cases were HCAVO, whereas our more recent data (2000–2011) show that nearly one-third of spinal infections are health care associated. The high incidence of HCAVO contrasts with findings from previous studies, with reported rates of 19%.[10,14] Several factors could contribute to this higher incidence: first, our hospital is a referral center for complicated spinal infections, and these are more common in patients with underlying diseases, as was seen in our HCAVO cases; second, the use of diagnostic and therapeutic techniques (outpatient parenteral nutrition and HD) has considerably increased; third, there is a high index of suspicion in our attending physicians, based on a detailed history of previous admissions and health care procedures, particularly those with a risk of bloodstream infection.

Although an increase in the aging of the population and immunosuppression may have had an influence on the higher incidence of VO in recent years, age was similar (61.9 vs 62.1 years) in the 2 study periods in our series, but the incidence of underlying immunosuppressive diseases was higher in the second period. Thus, in our opinion, health care associated infections and malignancy/immunosuppression are now the most important factors that contribute to an increase in the overall incidence of VO in the population.

The most common infectious source was a previous catheter-related infection (one-third of cases), a percentage similar to the 40% (33/83) we found in patients with health care associated IE[27] and lower than the 46% (148/319) of health care associated bloodstream infections.[28] Although our group follows the guidelines for catheter-related bloodstream infections, new VO cases still occur. These data indicate the need to improve the care in all steps provided to patients with intravascular devices and to strictly follow the therapeutic guidelines for catheter-related bloodstream infection, especially regarding septic complications in *S aureus* infection.[29,30]

In other recent studies, VO has also been associated with HD therapy.[14,20,25] In our experience, this was the source of infection in 12% of HCAVO and 3% of all VO cases, similar to the 4% recently reported[14] and <18% reported by Bhavan et al.[20] The percentage of VO in HD patients is not known, although it is estimated that 1.3% of HD patients with bloodstream infection will develop this complication[31] and an incidence of 1 episode every 215 patient-years has been reported.[32] In our patients, no VO cases were associated with arteriovenous fistula infection, in accordance with previous findings of a 3-fold higher incidence in patients dialyzed with tunneled central venous catheters than in those with arteriovenous fistulae.[32] Mortality in this subset of patients is high, at 11% to 46%.[25,32] Thus, it is crucial to reinforce preventive measures and provide prompt diagnosis and treatment.

S aureus was the most commonly isolated microorganism, especially in catheter-related cases. In 2 large series, VO was a complication of *S aureus* bloodstream infection in 1.7% (146/8739 cases)[33] and 3% (22/724 cases)[34] of patients. In our previous study of *S aureus* bloodstream infection, 2/146 (1.2%) hospital-acquired cases had an osteoarticular source of infection and in both patients, it was VO.[35] The risk of VO in patients with intravascular device related *S aureus* bloodstream infection (IDRSAB) is similar, around 2.2% (7/324 cases),[36] although the study did not establish whether VO was a direct consequence of IDRSAB or secondary to concomitant IE. In our study, only 21.4% of catheter-related HCAVO had IE, thus, VO was likely a direct consequence of catheter infection in most cases. The high risk of this complication in patients with nosocomial IDRSAB has practical implications. We believe that radiological imaging should be performed to exclude VO in all patients with a previous IDRSAB and new-onset or increased back pain.

From the clinical viewpoint, it is remarkable that back pain, which is almost always present in VO, was absent in 12% of HCAVO cases in our experience[10] and in 14% in a large review.[2] These patients had persistent fever or bloodstream infection after adequate antibiotic therapy of the underlying

infection, and the diagnosis of VO was ultimately established after excluding other infectious foci (eg, IE and spleen abscess).

The percentage of IE in spontaneous pyogenic HCAVO was high (19%) and similar to CAVO cases. As we reported previously, this high incidence is attributable to our hospital being a referral center for IE and a high index of clinical suspicion.[10] The high rate has practical implications and suggests that conversion to early oral therapy should be avoided until IE has been excluded, at least when it is clinically suspected and in gram-positive infections.[1,3,10]

As our group observed in health care associated IE,[27] HCAVO also affects elderly people with underlying conditions. This comorbid status leads to close contact with the health system and a higher risk of acquiring bloodstream infection, IE, and VO, and it could have an influence on the prognosis of the disease.

In comparison with CAVO, HCAVO cases had higher mortality (15% vs 6%) and surviving patients a higher relapse rate (9% vs 1%) in our study. Although, to a certain extent, these findings may be related to the higher incidence of underlying conditions in HCAVO, difficult to treat microorganisms, such as *Candida* spp and MRSA, and in 1 case, the fact that surgical drainage of a large abscess was unfeasible due to the patient's poor general condition may have influenced the higher mortality rate.

As in all retrospective studies, there is a potential for bias and statistical imprecision. It is possible that in the earlier period, contact with the health care system was overlooked in some patients and they were misclassified as CAVO, although this would have increased the incidence of health care associated cases. Our study has the referral bias of a large tertiary teaching center with an IE and spinal surgery unit, which may have had an impact on the rate of IE cases and neurological complications. Echocardiography was not mandatory in enterobacterial infections, but the uncommon implication of this microorganism in IE leads us to believe that IE rates would not have changed substantially if it had been performed. Extrapolation of the results to other community hospitals should be done with caution. Detection of VO in pluripathological-hospitalized patients requires a high index of suspicion, and some HAVO cases may have been missed in severely ill patients. Nonetheless, our infectious diseases department is highly aware of this disease, and most cases are seen by the same staff member, a fact that would help minimize elements of bias.

In conclusion, in our institution, one-third of current hematogenous pyogenic VO infections are health care associated cases and a third of these are catheter-related infections, and therefore, potentially preventable. HCAVO affects elderly people with underlying conditions and is associated with higher mortality and relapse rates than CAVO. Maximizing aseptic measures before and during any invasive procedure (especially those related to intravascular catheters) could reduce the incidence of this condition.

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