Candida vertebral osteomyelitis (CVO) 28 cases from a 10-year retrospective study in France

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Abstract
Although increasingly frequent, little is known about the clinical presentation, radiological signs, and outcome of Candida vertebral osteomyelitis (CVO).

We performed a nationwide retrospective study of laboratory-confirmed cases of CVO over a 10-year period in France with a prolonged follow-up. We describe demographic, clinical, biological, and radiological characteristics of patients with CVO, patients’ management, and long-term outcome and determine factors associated with a poor outcome.

In total, 28 patients with laboratory-confirmed CVO were included. A prior systemic Candida infection was evidenced in 13/28 (46%), occurring a median of 6 weeks before CVO was diagnosed. Twenty-six of 28 (93%) had at least 1 underlying condition at risk of invasive fungal disease, and in 19/28 (68%) CVO was health-care related. C albicans was most frequently identified (21/28; 75%) Lumbo-sacral involvement was the most prevalent (20/28 – 71%). Nearly half patients had no fever at presentation, but all had pain. Initial antifungal therapy consisted in fluconazole in 15/28 (53%); surgery was needed in 5 (18%) cases.

One-year mortality was 21% (6/28), directly related to fungal infection in 2 patients. Risk-factors associated with 1-year mortality were age (P=0.02), a high Charlson comorbidity index (P = .001), and a shorter treatment duration (median, 3 months vs 6 months; P = .02).

Among 22 patients who survived, the median follow up duration was 15.5 months (Q1-Q3: 8–93.5); 10 had sequelae, consisting in pain in all and neurological deficit in one. A longer treatment duration was significantly associated with healing without sequelae (P = .04).

CVO concerns patients with serious underlying conditions and risk-factors for invasive candidiasis. Prolonged antifungal treatment appears to improve survival without sequelae.

Abbreviations: BVO = bacterial vertebral osteomyelitis, CRP = C-reactive protein, CT-scan = computerized tomography scanner, CVO = Candida vertebral osteomyelitis, ESCMID = European society of clinical microbiology and infectious diseases, EUCAST = European committee on antimicrobial susceptibility testing, IDSA = Infectious Disease Society of America, IVDU = intravenous drug abuser, MIG = minimal inhibitory concentration; MRI = magnetic resonance imaging, VOF = vertebral osteomyelitis.

Keywords: candida, fluconazole, fungal disease, spondylodiscitis, vertebral osteomyelitis

1. Introduction
Because of the increase in numbers of severely immunocompromised patients, of invasive procedures including central intravascular catheters and use of broad-spectrum antibiotics, the incidence of Candida spp. invasive infections has risen drastically in the last 30 years.[1–3] Management of invasive candidiasis has been thoroughly studied and clear recommendations relying on a high quality of evidence have been published.[4,5] However, bone infections by Candida spp. are rare and remain poorly studied.

Especially, very few data exist concerning Candida vertebral osteomyelitis (CVO), which account for approximately 1% of infectious spondylodiscitis. CVO was previously considered a complication of intravenous drug use,[4,5] but now is mostly a health-care associated infection, such as most invasive Candida infections. With the increase in invasive Candida infections, CVO are increasing, and this trend will likely continue in the future.[6–8]

Both American and European infectious diseases societies have published recommendations for the management of Candida osteomyelitis.[4,5] However, they rely on inconsistent or limited-quality clinical experience based on case reports or series. Most publications date back many years and lack long-term follow-up.[9,10] Additionally, despite some helpful clinical descriptions, practically no radiological description of CVO is available.[11,12] Here, we performed a nationwide retrospective study of laboratory-confirmed cases of CVO having occurred over a 10-year-period in France. Our aim was to describe demographic,
clinical, biological, and radiological characteristics of patients with CVO. We also described patients’ management and long-term outcome and determined factors associated with a poor outcome.

2. Materials and methods

Rheumatologists, infectious diseases, and internal medicine specialists from all main tertiary and secondary healthcare centers in France were contacted. They were asked to report all cases of laboratory-confirmed CVO having occurred in adults between January 1st 2000 and December 31st 2010.

CVO was considered certain if (i) a positive culture and/or histology of a disk or a vertebral biopsy grew with a *Candida* species, in a presenting patient (ii) clinical symptoms (fever, back pain, neurologic disorder), and (iii) radiologic evidence (vertebral disk or vertebral body or paraspinal abnormality) compatible with vertebral osteomyelitis, according to the recommendations of the European Organization for Research and Treatment of Cancer.[13]

Once CVO cases were identified, a single investigator (CR) collected data in each center with a standardized questionnaire including demographic, clinical, microbiological, treatment, follow-up, and outcome data. Radiological data was reviewed by a single specialized radiologist (DP). Healthcare-associated CVO were defined as either nosocomial or non-nosocomial using *Candida* endocarditis definitions.[14]

Time to diagnosis was defined as the time between the first symptoms (back pain, neurological deficiency, or fever) and the day diagnosis was confirmed. Risks-factors for invasive candidiasis were defined as the use of corticosteroids (>0.3 mg/kg/d of prednisone for at least 3 weeks) or anti tumoral chemotherapy, inherited severe immunodeficiency, recent history of neutropenia, receipt of an allogenic stem cell transplant, treatment with recognized T-cell immunosuppressants, intra-venous drug abuse, parenteral nutrition, presence of a central venous catheter, hemodialysis, recent abdominal surgery, and recent use of broad-spectrum antibiotics.[4,5,13] Sequelae were defined if there was a persistence of pain needing systemic pain killers and/or the persistence of a neurologic deficit after the end of treatment. The primary outcome was death 1 year after diagnosis. Secondary outcomes were sequelae or death at the end of follow-up. All clinicians in charge (hospital specialist and general practitioner if available) were asked for patient’s health status in January 2016.

2.1. Microbiology

All *Candida* strains were studied in the local laboratories. All isolates were identified to the species level by the use of carbon assimilation profiles (ID32C; Biomérieux, Marcy-l’Etoile, France). *In vitro* susceptibility testing was performed according to the recommendations of the European Committee on Antimicrobial Susceptibility Testing (EUCAST). In all the laboratories, fluconazole, voriconazole, fluconazole, and caspofungin were tested as previously described. Breakpoints defined by EUCAST were used for fluconazole and voriconazole.[15–17]

2.2. Statistics

All values are expressed as median (interquartile) or percentages. To determine factors associated with death in the univariate analysis, clinical, microbiological, radiological, and treatment characteristics of patients who died were compared with those of survivors after 1 year of follow-up by using Wilcoxon rank-sum and Fisher tests for continuous and categorical variables, respectively. Among survivors, we compared the same characteristics between patients with and without sequelae. No multivariate analysis was performed because of the small number of patients. In order to avoid bias due to competition between death and treatment efficacy, a Cox-regression model was used to provide an estimation of the effect of treatment duration on mortality. In this model, the main outcome was survival time, that is, follow-up duration. The event of interest was death. Survival times were censored if death did not occur for a patient during follow-up. The estimated regression coefficients are expressed as risk ratios. Data were analyzed using GraphPrism 5 (La Jolla, CA) and SAS 9.2 (SAS Institute, Cary, NC) softwares. A P-value <.05 was considered to be significant.

3. Results

Seventeen hospitals across France reported at least 1 case of CVO. Overall, 28 definite CVO cases occurring in 28 patients were included in this work. Demographic, clinical, and biological characteristics of the patients are shown in Table 1. Individual characteristics of the 28 patients are detailed in Table 2. Only 2 patients (patients no 4 and 15) had no prior risk-factor for invasive candidiasis. Fourteen patients (50%) had experienced a prior invasive candidiasis due to the same *Candida* species, 2 weeks to 4.5 months before the CVO (median, 6 weeks) (Table 2). Patient no 5 did not experience invasive candidiasis but her newborn had experienced a disseminated candidiasis but she had given birth 2 weeks before to a child who presented disseminated candidiasis.

Pain was the most common symptom and was present at diagnosis in all patients, half of which required opioids for pain management. Neurological complications were found in 9 patients (32%) at diagnosis. In all cases, neurological impairment was secondary to epidural or soft tissue abscess rather than spinal instability. Another localization of *Candida* infection was identified in 6 patients (cholecytitis, contiguous infection of an aortic vascular prothetic device, pyelonephritis, pneumonia, sternitis, and uveitis).

Radiologic data was available for 26 patients, including 13 who had x-rays, 12 who had a CT-scan and 20 who had MRI (Table 3). Microbiological diagnosis was obtained thanks to a needle biopsy in 22 patients; 4 patients required a second needle biopsy. Open biopsy was performed for 5 patients. For the last patient, microbiologic samples were collected during emergency laminctomy. No patient had a positive blood culture for *Candida* spp at the time of CVO diagnosis. The most prevalent species was *C. albicans* (21 patients, 75%) followed by *C. glabrata* (3 patients, 11%).

Nineteen/24 (79%) isolates were susceptible to fluconazole. Three *C. glabrata* presented a decreased susceptibility to fluconazole (MIC=8 mg/mL), 1 *C. albicans* isolate was resistant to fluconazole (MIC=16 mg/mL) in a patient who had previously received fluconazole, and 1 *C. albicans* isolate was resistant to itraconazole (MIC=4 mg/mL) in a patient who had not received azoles before. All others yeasts were susceptible to conventional antifungal drugs used. All yeasts were susceptible to liposomal or deoxycholate amphotericin B and caspofungin.

3.1. Treatment

Seven patients (25%) received a combination antifungal treatment as initial therapy and 21 (75%) received monotherapy.
Initial bitherapy always included flucytosine. Initial treatment was changed during the course of treatment in 24 patients (86%), mostly to switch to an oral treatment (14/28, 50%) or because of side effects (5/28, 18%). Dosages of antifungals were in line with international recommendations.

Five patients (32%) required a surgical management: in 2 cases because of medullar compression (patients 12 and 18), in 3 cases because the medical treatment failed to control the infection (patients 3, 19, and 27).

### 3.2. Outcome

Median follow-up duration was 13 (5–21) months after diagnosis. During the first year, 6/28 (21%) subjects died.

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**Table 1**

Clinical and biological characteristics of 28 patients with *Candida* vertebral osteomyelitis and comparison between survivors and nonsurvivors after 1 year of follow-up.

| Characteristics | All (n = 28) | Dead (n = 6) | Survivors (n = 22) | P* |
|-----------------|-------------|-------------|-------------------|----|
| Age, years, median, interquartile range | 58 [41–70] | 78 [67–80] | 50 [37–65] | .02 |
| Male, n, % | 23 (82) | 5 (83) | 18 (82) | 1 |
| Community-acquired, n, % | 9 (32) | 0 | 9 (43) | 1 |
| Healthcare-associated, n, % | 19 (68) | 6 (100) | 13 (60) | .13 |
| Host predisposing conditions‡, n, % | 7 (25) | 0 | 7 (32) | .28 |
| Intravenous drug abuse, n, % | 2 (7) | 0 | 2 (9) | 1 |
| Central venous access, CVC, n, % | 14 (50) | 4 (67) | 10 (46) | .38 |
| Parenteral nutrition, n, % | 3 (11) | 0 | 3 (14) | 1 |
| Abdominal surgery within 3 months preceding CVO, n, % | 6 (21) | 2 (33) | 4 (18) | .62 |
| Diabetes mellitus, n, % | 4 (14) | 1 (17) | 3 (14) | 1 |
| Solid cancer or hematological malignancy, n, % | 10 (36) | 5 (83,3) | 4 (18) | 1 |
| Solid-organ transplant recipient, n, % | 2 (7) | 0 | 2 (9) | 1 |
| Neutropenia within 1 month preceding CVO, n, % | 4 (14) | 1 (14) | 3 (14) | 1 |
| Corticosteroid and/or immunosuppressive treatment, n, % | 10 (36) | 5 (83) | 5 (24) | 1 |
| Chronic renal insufficiency, n, % | 4 (14) | 2 (33) | 2 (9) | 1 |
| Broad spectrum antibiotics within 3 months preceding CVO, n, % | 17 (61) | 3 (50) | 14 (64) | 1 |
| Charlson comorbidity index combined to age, median, IQ range | 3 [1–5] | 6 [6–8] | 2.5 [0–4] | .001** |
| Underlying spinal pathology, n, % | 5 (18) | 1 (17) | 4 (18) | 1 |
| Prior colonization with same strain, n, % | 9 (32) | 3 (50) | 6 (27) | .65 |
| Prior treatment for invasive candidiasis with the same strain, n, % | 14 (50) | 4 (63) | 10 (45) | .1 |
| Clinical findings | | | | |
| Fever, n, % | 16 (57) | 2 (29) | 14 (67) | .1 |
| Pain, n, % | 28 (100) | 6 (100) | 22 (100) | 1 |
| Neurologic impairment, n, % | 9 (32) | 3 (50) | 6 (27) | .65 |
| Metastatic involvement, n, % | 6 (21) | 2 (33) | 4 (18) | .62 |
| Biology | | | | |
| C-reactive protein, mg/L, median, IQ range | 82 [55–133] | 73 [46–148] | 82 [61–126] | .73 |
| Neutrophil count, 10³ per mm³, median, IQ range | 5.7 [3.7–6.8] | 6.1 [5–7] | 5.3 [5.2–6] | .79 |
| Diagnosis modality | | | | |
| Blood culture positivity, n | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Open biopsy, n, % | 6 (21) | 2 (33) | 4 (18) | .84 |
| Needle biopsy, n, % | 22 (79) | 5 (83) | 17 (77) | .9 |
| Positive serology, n/performd, % | 11/13 (84) | 3 (50) | 8 (60) | 1 |
| Pathologic findings | | | | |
| Candida species responsible | | | | |
| *C* albicans, n, % | 21 (75) | 5 (83) | 16 (72) | 1 |
| Time to diagnostic, months, median, IQ range | 2.1 [0.9–3] | 3 [2–4] | 1.8 [0.8–2.5] | .06 |
| Treatment | | | | |
| Antifungal therapy | 28 (100) | | | |
| Initial therapy‡ | | | | |
| Fluconazole | 15 (53) | 3 (50) | 10 (45) | 1 |
| Amphotericin B deoxycholate | 5 | 1 (16) | 4 (18) | 1 |
| Liposomal amphotericin B | 6 | 1 (16) | 5 (23) | 1 |
| Caspofungin | 1 | 0 | 1 (5) | 1 |
| Voriconazole | 1 | 0 | 1 (5) | 1 |
| Flucytosine | 7 | 0 | 3 (50) | .4 (18) |
| Antifungal monotherapy | 21 (75) | 4 (67) | 17 (77) | .32 |
| Antifungal biototherapy | 7 (25) | 3 (50) | 4 (18) | 1 |
| Combined medical and surgical therapy | 5 (18) | 1 (12) | 4 (18) | 1 |
| Treatment duration, months, median, IQ range | 6 [3.4–8.3] | 3 [2.6–3.8] | 6 [4.3–9.8] | .02** |

CVC = central venous access; CVO = Candida vertebral osteomyelitis; IQ = interquartile range.

*Comparison between survivors and nonsurvivors.

**P < .05.

† Some patients had more than 1 underlying condition.

‡ Seven patients had an antifungal combination including flucytosine.
Table 2
Individual characteristics of the 28 patients with CVO.

| Patient | Age, years | Species | Vertebral level | Underlying condition | Time before diagnosis (months) | Time since prior invasive candidiasis (months) | Associated visceral involvement | Medical treatment | Surgery/indications | Status at 1 year: Alive (months) | Long term follow-up time to last news, months |
|---------|------------|---------|----------------|----------------------|-------------------------------|-----------------------------------------------|---------------------------------|----------------|-------------------|-------------------------------|---------------------------------------------|
| 1       | 37         | C albicans | L4-L5   | IVDA                 | 2.8                           | 0                              | Candidemia, then knee osteoarthrosis (4.3) | dAmB 8d. then FCZ 2m. | No                | Alive, no sequela (2)          | Alive, no relapse (15)                           |
| 2       | 52         | C albicans | L1-L2   | SOT, IE, bs-AB       | 6.4                           | 0                              | Vascular prothetic device                 | dAmB 6d. then FCZ 2m. | No                | Alive, no sequela (6)          | Alive, no relapse (7)                           |
| 3       | 60         | C albicans | L2-L3   | Toxemia, vascular prothetic device, CRI, Pn, malnutrition, CVC | 4.0                           | 0                              | Candidemia, angiocholitis (0.5)          | dAmB 8d. then FCZ 2m. | No                | Alive, no sequela (12)         | Alive, no relapse (15)                           |
| 4       | 47         | C albicans | L1-L2   | Chronic alcoholism   | 2.4                           | 0                              | Candidemia, angiocholitis (0.5)          | dAmB 8d. then FCZ 2m. | No                | Alive, no sequela (6)          | Alive, no relapse (2)                           |
| 5       | 73         | C albicans | L5-S1   | Cancer, IE, bruineppia, bs-AB, CVC | 0.5                           | 0                              | Candidemia, angiocholitis (0.5)          | dAmB 8d. then FCZ 2m. | No                | Alive, no sequela (17)         | Alive, no relapse (17)                           |
| 6       | 65         | C albicans | L5-S1   | Complicated acute pancreatitis, Toxemia, bs-AB, CVC, Pn, DB, vascular prothetic device | 3.3                           | 0                              | Candidemia, angiocholitis (0.5)          | dAmB 8d. then FCZ 2m. | No                | Alive, no sequela (17)         | Alive, no relapse (17)                           |
| 7       | 60         | C albicans | T11-L2  | Cancer, DB, CVC, malnutrition | 3.3                           | 0                              | Candidemia (0.9)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (14)         | Alive, no relapse (15)                           |
| 8       | 60         | C albicans | L4-L5   | VDIA, chronic HIV    | 2.1                           | 0                              | Candidemia (0.9)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (17)         | Alive, no relapse (17)                           |
| 9       | 53         | C albicans | L5-S1   | Cancer, abdominal surgery | 0.5                           | 0                              | Candidemia, angiocholitis (0.5)          | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (11)         | Alive, no relapse (17)                           |
| 10      | 38         | C albicans | T12-L2  | Chronic alcoholism   | 2.5                           | 0                              | Resistant fungal uveitis                     | FCZ 2m.            | No                | Alive, no sequela (5)          | Alive, no relapse (5)                           |
| 11      | 52         | C albicans | L5-S1   | Cancer, abdominal surgery | 3.1                           | 0                              | Candidemia, angiocholitis (0.5)          | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 12      | 37         | C albicans | T6      | VDIA                 | 1.1                           | 0                              | Candidemia, angiocholitis (0.5)          | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 13      | 42         | C albicans | T12-L2  | Chronic alcoholism   | 5.4                           | 0                              | Candidemia, angiocholitis (0.5)          | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 14      | 54         | C albicans | L4-L5   | SOT, IE, bs-AB, DB   | 20.2                          | 0                              | Candidemia, angiocholitis (0.5)          | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 15      | 28         | C albicans | L2-L3   | Pregnant (past deferred) | 2.1                           | 0                              | Candidemia, angiocholitis (0.5)          | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 16      | 76         | C albicans | L4-L5   | CRI, vascular prothetic device, cancer, abdominal surgery, malnutrition, chronic neurologic impairment, CVC, chronic osteoarthrosis | 2.7                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 17      | 35         | C albicans | L2-L3 and L4-L5 | IVDA                 | 0.7                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 18      | 32         | C albicans | L2-L3   | DB, abdominal surgery, bs-AB, Pn, maker | 1.4                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 19      | 63         | C albicans | T6–8 and L3-L5 | Hemotological malignancy, CVC, Pn, bruineppia, bs-AB | 2.3                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 20      | 45         | C albicans | L4-L5   | IVDA                 | 3.9                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 21      | 35         | C albicans | L1-L2   | CVC, chronic HIV, chronic osteoarthrosis, Pn, DB | 1.5                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 22      | 62         | C albicans | T8-T9   | Cancer, IE, bruineppia, CVC, malnutrition, prior Pn, disease | 4.2                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 23      | 62         | C albicans | T10-T12 | Chronic osteoarthrosis, vertebral fracture, chronic renal failure, CVC, bs-AB, Pn, maker | 0.9                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 24      | 69         | C albicans | T10     | Abdominal surgery, splenectomy | 0.5                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 25      | 52         | C albicans | T7-T11  | Vascular prothetic device, CVC, Pn, DB | 1.2                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 26      | 83         | C albicans | T1-T2 and T8-T9 | Neumorphy                          | 1.5                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 27      | 68         | C albicans | L5-S1   | Hemotological malignancy, IE, CVC, CRI, Pn, DB | 0.3                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |
| 28      | 81         | C albicans | T4-T6   | CT, CRI, bs-AB       | 0.5                           | 0                              | Candidemia (0.5)                         | dAmB 2m. then FCZ 2m. | No                | Alive, no sequela (16)         | Alive, no relapse (16)                           |

SFC = fluconazole, AB = antibiotic therapy, bs-AB = broad-spectrum antibiotic therapy, CAS = caspofungin, CR = chronic renal insuficiency, CS = corticosteroids, d = day, dAmB = amphotericin B deoxycholate, DB = diabetes mellitus, FCZ = fluconazole, HIV = Hepatitis C virus, IS = immunosuppression, ITZ = itraconazole, IVDA = intravenous drug addict, LAmB = liposomal amphotericin B, m = month, PN = parenteral nutrition, SOT = solid organ transplantation, VRZ = voriconazole, w = weeks.
these 6 patients who died during the first year were excluded, median follow-up reached 15.5 months (8–23.5). Concerning the 6 patients who died during the first year, Patient 3 died of recurrent fungal and bacterial infections, patient 9 of fungal and bacterial sepsis, and patient 26 of bacterial sepsis. The 3 remaining death were directly attributable to the underlying cancer from which the patients suffered prior to the CVO (patients 7, 16, and 22). During the rest of the follow-up (>1 year after the CVO), 6 additional patients died (patients 6, 24, and 27 of hematologic or solid tumor malignancy, patient 14 of suicide, patient 28 of chronic respiratory failure, and patient 25 of bacterial endocarditis).

When compared to survivors, patients who died during the first year were significantly older (median age = 78 [67–80] vs 50 years [37–65], P = .02) and had a higher Charlson comorbidity index score (median score = 6 [6–8] vs 2.5 [0–4], P = .001). Although not statistically significant, time to diagnosis tended to be longer in the deceased patients as compared with survivors (3 months [2–4] vs 1.8 months [0.8–2.5]), respectively, P = .06. No difference between both groups was found in terms of clinical, radiological, biological, or microbiological findings or in terms of initial antifungal therapy. However, median treatment duration was significantly higher in surviving patients as compared to deceased patients (6 months [4.3–9.8] vs 3 [2.6–3.8]), respectively, P = .02. The Cox regression model confirmed this result. The estimated hazard ratio for the influence of treatment duration on survival was 0.63 (CI [0.43–0.93], P = .02).

Among the 22 patients who survived at 1 year, sequelae occurred in 10 patients (45%); all them complained of persistent pain at the end of follow-up, one of them also had a neurologic impairment (persistent bilateral leg motor weakness for patient 12). Characteristics of survivors with and without sequelae are summarized in Table 4. Patients without sequelae had been treated for a longer time than patients with sequelae (7.5 [6–11.3] vs 5 [3.1–6] P = .04). No local relapse was reported in any patient.

### 4. Discussion

With 28 patients included over a 10-year period, this work represents the largest report of Candida vertebral osteomyelitis in the literature to date. All patients were included after 2000, allowing the use of modern diagnostic techniques, the availability of potent antifungal therapy, and a high homogeneity in the management of the patients, despite the retrospective and multicentric nature of the study. We used a robust diagnostic definition combining clinical, radiological signs, and a compulsory mycological identification from the involved site.

Several important findings need to be addressed here.

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**Table 3**

| Radiological findings of 26 patients with CVO for whom radiological data were available. | All | Dead | Survivors | P** |
|------------------------------------------|-----|------|-----------|-----|
| **Standard x-ray, n = 13**               |     |      |           |     |
| Cortical involvement or endplate condensation, n, % | 8/13 (62) | 1/1 | 7/12 (58) |     |
| Disc space narrowing, n, %               | 8/13 (62) | 0/1 | 8/12 (67) |     |
| Erosion of vertebral body, n, %          | 6/13 (46) | 0/1 | 6/12 (50) |     |
| **CT scan, n = 12**                      |     |      |           |     |
| Erosion of vertebral endplate, n, %      | 8/12 (66) | 2/3 (67) | 6/9 (67) | 1.00 |
| Vertebral body’s lysis, n, %             | 11/12 (92) | 3/3 (100) | 8/9 (89) | 1.00 |
| Soft tissue abscess, n, %                | 6/12 (50) | 1/3 (33) | 5/9 (66) | 1.00 |
| Epiduritis, n, %                         | 2/12 (17) | 1/3 (33) | 1/9 (11) | .45  |
| **Magnetic resonance imaging, n = 20**   |     |      |           |     |
| Abnormal signal of vertebral body, n, %  | 14/20 (70) | 2/5 (40) | 12/15 (80) | .13 |
| Loss of intrasdinal key sign, n, %       | 2/20 (10) | 0/5 (0) | 8/15 (55) | .06  |
| Vertebral body edema, n, %               | 18/20 (90) | 5/5 (100) | 13/15 (87) | 1.00 |
| Soft tissue abscess, n, %                | 17/20 (85) | 4/5 (80) | 13/15 (87) | 1.00 |
| Epiduritis, n, %                         | 4/20 (20) | 0/5 (0) | 4/15 (27) | .53  |

**Table 4**

| Differences in clinical characteristics and outcome between 1-year survivors with and without sequelae. | One-year survivors (n = 22) | Patients with sequelae (n = 10) | Patients without sequelae (n = 12) | P** |
|--------------------------------------------------|----------------------------|-------------------------------|-----------------------------------|-----|
| **Characteristics**                               | Age, years, median, interquartile range | Time to diagnosis, months, median, IQ range | Neurologic impairment, n, % | Vertebral level involvement |
|                                                  | 50 [37–65] | 1.8 [0.8–2.5] | 7 (32) | Cervical or thoracic, n, % |
|                                                  | 42 [35–64] | 1.4 [1–2.4] | 3 (33) | 6 (18) |
|                                                  | 52 [46–64] | 2.2 [0.6–2.5] | 4 (12) | 3 (33) |
|                                                  |               |                 |       | 3 (25) |
|                                                  |               |                 |       | 9 (75) |
|                                                  |               |                 |       | 4 (36) |
|                                                  |               |                 |       | 4 (36) |
|                                                  |               |                 |       | 86 |
|                                                  |               |                 |       | 64 |
|                                                  |               |                 |       | .31 |
|                                                  |               |                 |       | .04 |
| **Initial therapy**                              | Monotherapy, n, % | Bitherapy, n, % | Fluconazole, n, % | Treatment duration, months, median, IQ range |
|                                                  | 17 (77) | 5 (23) | 10 (48) | 6 [4.3–9.8] |
|                                                  | 9 (66) | 1 (10) | 7 (70) | 5 [3.1–6] |
|                                                  | 8 (66) | 4 (34) | 3 (25) | 7.5 [6–11.3] |

**Defined as hyperintensity of the intervertebral disk on T2-weighted images with an abnormal configuration.**

**Comparison between survivors with and without sequelae.**
First, although patients with CVO were often immunocompromised and carried multiple risk-factors for invasive candidemia, the clinical, biological, and radiological features of the disease were not fundamentally different from those of patients suffering from bacterial vertebral osteomyelitis (BVO). Indeed, as for BVO, time to diagnosis was particularly long with a median of 2 months since the first symptoms. The paucity of specific clinical signs (most patients complained only of back pain and the absence of general symptoms such as fever or sepsis) is probably to blame for such a delay in diagnosis. This also relates to the low level of inflammatory blood syndrome (CRP and white blood cell levels were only moderately increased). The prolonged time to diagnosis in turn probably explains the importance of the radiological abnormalities found. Indeed, all patients had abnormal CT or MRI scans, with clear signs of vertebral osteomyelitis. Yet, we found no major difference in terms of CT or MRI signs between the CVO cases studied here and the reported imaging findings in BVO. Altogether, because no specific sign of CVO with regard to bacterial VO was found, securing a microbiological diagnosis by performing either a needle biopsy or an open biopsy appears to be mandatory.

Second, using the precise definition of healthcare-associated infections developed for *Candida* infective endocarditis, we confirm previous reports showing that CVO is strongly related to healthcare (two-thirds of patients here) or IV drug use (among the 9 patients with community acquired CVO, 7 were IVDU). Therefore, the main difference found between patients with CVO and those with BVO is neither the clinical or radiological presentation but rather the underlying conditions such as the presence of immunodepression or other risk-factors for candidemia.

Third, we found that half of the patients had previously been treated for invasive candidiasis with the same *Candida* species. All subjects had received adequate therapy for their first fungal infection and the time between the first infection and the first symptoms of CVO ranged from 2 to 18 weeks (median 6 weeks). Despite the important time lapse between the initial fungemia and the first symptoms of CVO, it remains possible that the spinal involvement became symptomatic only weeks after the initial fungemia. Yet, whether CVO is the consequence of the initial fungemia or of a relapse after treatment, these findings emphasize the fact that patients with candidemia should be closely monitored and informed in order to detect early signs of osteomyelitis, including CVO, which can occur weeks after the fungemia. This is all the more important that time to diagnosis was longer for patients who died than for survivors, although not significantly, confirming data from invasive fungal infections where time to treatment is regularly found to be a major prognostic factor. 

Fourth, although retrospective and noncontrolled, this cohort study allows us to draw several conclusions concerning CVO treatment, thanks to a relatively homogenous management. All patients received prolonged antifungal therapy and the outcome of survivors was satisfactory with only 1 patient who suffered from long-term neurological sequelae. Therapeutic surgery was required only in 5 cases including 3 for medical treatment failure. It therefore appears that surgical management of CVO should be indicated in the same way as for BVO and that antifungal therapy remains the cornerstone of treatment. Azoles have favorable pharmacokinetics efficacy data as well as a good tolerance profile. Fluconazole or an echinocandin or a lipid formulation of amphotericin B remain the drugs of choice, as recommended by the IDSA and the ESCMID. In previous recommendations, echinocandins were recommended only as alternative, explaining the lower rates of use in our series. Duration of treatment however is less consensual; our findings are in favor of a prolonged treatment, as the median duration of treatment for patients who survived was 6 months. Moreover, our observations suggest that a shorter treatment increases the risk of death. Treatment duration was also significantly longer for patients surviving without sequelae than for survivors with sequelae (7.5 months [6.1–11.3] vs 5 months [3.1–6], respectively, P = .04). Prospective works would be needed to address this. In the meantime, the recommended 6 to 12 months treatment with fluconazole, as suggested by the current guidelines, should be followed. Many questions remain unanswered, in particular the duration of parenteral treatment before a switch to oral fluconazole and the place of antifungal combinations.

As found in previous case series, 1-year mortality was relatively low (21%, with only 2 cases directly related to CVO) compared to that of candidemia which reaches on average 40%, but it remained higher than that observed for BVO (5–13%), mostly because of the underlying diseases of the patients, as described for invasive candidiasis.

The main limitation of this work is its retrospective nature, which is the direct consequence of the rareress of the disease. Obvious limitations such as enrolment biases, patients lost to follow-up and missing data were expected. However, the use of a strict definition of CVO, the careful analysis of the patients’ medical files by a single investigator, the centralized and systematic study of radiologic data, and the prolonged follow-up are major strengths of this work.

In conclusion, CVO is a rare disease, which concerns patients with heavy underlying conditions and combining risk-factors for invasive candidiasis. CVO appears to mimic BVO in terms of clinical, biological, and radiological presentations. A thorough microbiological diagnosis is thus fundamental. Additionally, a prolonged delay between the initial fungemia, clinical signs, and diagnosis is frequently found, emphasizing the importance of closely monitoring patients after fungemia, even when they have been treated as recommended. Little is known about the best management, yet fluconazole seems to be efficient in most cases and a prolonged treatment of several months appears to be essential. Further works are needed to determine the optimal management of this increasingly frequent disease, thanks to a prospective national or international cohort for example.

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