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MAJOR ARTICLE

Oral Versus Standard Antimicrobial Treatment for Pyogenic Native Vertebral Osteomyelitis: A Single-Center, Retrospective, Propensity Score-Balanced Analysis

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Background. Interest in shorter antimicrobial regimens and oral treatment for osteoarticular infections is growing. The aim of this study is to assess whether there is an association between the administration of an entirely oral antibiotic therapy (OT) and the clinical outcome of native vertebral osteomyelitis (NVOs).

Methods. We conducted a single-center, retrospective, observational study on consecutive patients with pyogenic NVOs over a 10-year period (2008–2018). We performed multivariate logistic regression analysis to identify risk factors for clinical failure, both in the whole population and in subgroups. The impact of OT versus standard treatment (intravenous induction followed by oral treatment whenever possible) was assessed in patients with a non-multidrug-resistant microorganism (MDRO) etiology, and the impact of a rifampin-containing regimen was assessed in patients affected by NVOs caused by staphylococci or of unknown etiology.

Results. The study population included 249 patients, and 33 (13.3%) experienced clinical failure; the OT group consisted of 54 patients (21.7%). Multivariate regression analysis of the whole population selected Charlson comorbidity index (adjusted odds ratio [aOR], 1.291; 95% confidence interval [CI], 1.114–1.497; $P = .001$) and MDRO etiology (aOR, 3.301; 95% CI, 1.368–7.964; $P = .008$) as independent factors for clinical failure. Among patients affected by a non-MDRO NVO, OT was not associated with an increased risk of clinical failure (aOR, 0.487; 95% CI, .133–1.782; $P = .271$), even after adjustment for the propensity score of receiving OT. In the subgroup of patients with staphylococcal or unknown etiology, NVO rifampin was independently associated with favorable outcome (aOR, 0.315; 95% CI, .105–.949; $P = .040$).

Conclusions. An entirely oral, highly bioavailable treatment, including rifampin, may be as effective as parenteral treatment in selected patients with NVOs.

Keywords. antibiotic therapy; oral therapy; outcome; vertebral osteomyelitis.

Native vertebral osteomyelitis (NVO) is an infection of the vertebrae and intervertebral discs not related to vertebral surgery. The disease's course is often complicated by epidural abscess, spinal instability, and neurologic deficits with an overall mortality rate of 2%–20% and a reported relapse rates of 1%–32% [1, 2]. In the past decades, incidence of NVO has steadily increased; in France, it increased from 2/100 000 inhabitants/year in 2002 to 11.3/100 000 inhabitants in 2019 [3, 4]. This increased incidence may be related to ageing of population, higher prevalence of people with chronic diseases (diabetes, chronic renal, and liver failure), immunosuppression, invasive treatments and procedures (dialysis, medical devices, etc), and more effective diagnostic techniques [3].

Management of NVO is based on prolonged antimicrobial treatment (at least 6 weeks) and orthosis protection; surgery is indicated in case of important epidural abscess, progressive neurologic deficits, vertebral instability, or failure of conservative treatment.

Parenteral antibiotics have been historically considered the gold standard for treatment of NVO; concerns about bone penetration and oral bioavailability of antimicrobial may have had a role in this choice [5]. Indeed, Infectious Diseases Society of America (IDSA) guidelines published in 2015 confirmed parenteral therapy as the standard treatment for NVO, whereas oral antibiotics with excellent bioavailability are indicated as a valuable option for early switch. Nevertheless, they do not define patients who may benefit from a parenteral to oral conversion nor the optimal timing for the switch [6].

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In a recent study, similar efficacy of oral and intravenous antibiotics has been described for the treatment of osteomyelitis [7]. Considering that intravenous therapy is associated with substantial risks, inconvenience, and higher costs than oral therapy, it seems very rational to investigate whether oral antibiotics may be an effective treatment option for NVO.

The aim of this study was to describe epidemiology and outcome of NVO and to assess risk factors for clinical failure. In particular, we evaluated whether the administration of an entirely oral antibiotic therapy was associated with clinical outcome.

METHODS

Study Design and Setting

We conducted a single-center, observational, retrospective cohort study on all consecutive adult patients treated for NVO at our center from November 2008 to June 2018. The study was carried out at the Infectious Diseases Unit of IRCSS (Istituto di Ricovero e Cura a Carattere Scientifico) Azienda Ospedaliero Universitaria di Bologna, a 1420-bed tertiary hospital in Northern Italy, where a stable Infectious Diseases (ID) consultant team is dedicated to the management of bone and joint infections, for inpatients (more than 2000 ID bedside consultation in 2018) and outpatients (660 ambulatory visits in 2018). Patients with NVO are managed in close collaboration with the Unit of Oncologic and Degenerative Spine Surgery of the IRCCS Istituto Ortopedico Rizzoli, a referral orthopedic hospital.

Study Population

All adult patients (age ≥18 years) with a diagnosis of NVO were screened for inclusion in the study. Exclusion criteria were previous vertebral surgery (with or without instrumentation, independently of timing) involving the vertebrae involved in the infection, NVO due to direct extension (pressure ulcer or penetrating traumas), and mycobacterial, fungal, or brucellar etiology. These conditions were excluded because their management is different from that of pyogenic NVO.

Patient Management

During the study period, standard diagnostic procedures for NVO included the following: basal full blood chemistry, blood cultures, QuantiFERON and Widal-Wright test, contrast-enhanced magnetic resonance (MRI), positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (18F-FDG PET/CT), and a vertebral biopsy/abscess drainage, when feasible; in case of contraindication to MRI, the patient underwent a contrast-enhanced CT scan.

During antibiotic therapy, weekly assessment of full blood chemistry including inflammatory markers was recommended. After end of treatment (EOT), we planned a monthly assessment of full blood chemistry including inflammatory markers. Clinical and radiological evaluations were scheduled at EOT and 6 months and 12 months after EOT. The choice and the duration of the antimicrobial regimen were at the discretion of the attending ID physician according to clinical characteristics, response to treatment, and culture results when available.

The orthopedic surgeon visited all patients diagnosed with NVO; surgery was usually reserved to patients presenting with neurologic compromise, large epidural abscess, significant vertebral destruction with instability, and uncontrolled pain.

Study Variables and Definitions

We defined NVO as follows: (1) histologically and microbiologically proven NVO - in presence of imaging and clinical and laboratory findings consistent with NVO associated with typical histopathological finding plus a microorganism cultured from the involved vertebra, intervertebral disc space, paravertebral or epidural abscesses drainage (obtained through percutaneous biopsy or open surgery); (2) probable NVO - in presence of imaging and clinical and laboratory findings consistent with NVO and at least 1 blood culture positive for *Staphylococcus aureus* or imaging and clinical and laboratory findings consistent with NVO associated with typical histopathological findings but negative cultures from involved vertebra, intervertebral disc space, paravertebral, or epidural abscesses (if patients had at least 1 positive blood culture for a pathogen different from *S aureus* or not); (3) presumptive NVO - in presence of imaging and clinical and laboratory findings consistent with NVO, but histology and culture of spinal tissue were not done. Bacteria were defined as multidrug-resistant microorganism (MDRO) in case of nonsusceptibility to at least 1 agent in 3 or more antimicrobial categories; methicillin-resistant *S aureus* (MRSA) is always considered multidrug-resistant [8].

The endpoint variable was clinical cure, defined as sustained absence of fever and normal inflammatory markers plus remission of pain and survival at 12 months after the end of the first treatment course (ie, patients with lack of improvement or disease progression during antimicrobials who had their antibiotic therapy discontinued and repeated the diagnostic work-up were considered treatment failures).

Exposure variables were oral and standard parenteral treatment. The oral treatment (OT) group included patients treated exclusively with an oral antimicrobial regimen, based on highly bioavailable molecules for the full course of therapy (<24 hours of parenteral treatment). Standard treatment (ST) was defined as initial parenteral therapy for >24 hours, followed when feasible by oral shift.

Other study variables included the following: demographics (age and sex), comorbidities according to Charlson comorbidity index [9], risk factors for NVO (including invasive procedure in the previous 6 months, recent spinal trauma, injective drug abuse, vascular catheter, hemodialysis, or major infectious

events in the previous 12 months), sign and symptoms of NVO, vertebral site of infection, etiology, and medical and surgical treatment.

Statistical Analysis

For descriptive analysis, categorical variables were presented as absolute numbers and their frequencies, and continuous variables were presented as mean ± standard deviation or median and interquartile range (IQR) according to their distribution. Differences between patients' groups were tested with χ^2 tests or Fisher's exact test when appropriate for categorical variables, and Student *t* test or Mann-Whitney *U* test for normally and nonnormally distributed continuous variables, respectively. To analyze the independent risk factors for clinical failure in the whole population, variables with a $P \leq .1$ at univariate analysis were entered into a multivariate forward logistic binary regression model.

To specifically assess the impact of OT on clinical cure, a further analysis was done including only those patients not affected by MDRO NVO, defined in accordance with the ESCMID definition [8]. Patients included in the OT and ST groups were compared. A propensity score for receiving OT was done. All the of variables with $P < .10$ at univariate analysis were introduced in a nonparsimonious multivariate logistic regression model, which included the following: proven NVO, Charlson comorbidity index, fever at presentation, cervical site, previous infectious event in the last 12 months, CT-guided biopsy, Staphylococcal etiology (coagulase-negative staphylococci and *S aureus*), and surgical treatment. The validity of the model was assessed by estimating goodness-of-fit to the data with the Hosmer-Lemeshow test ($P = .762$) and the receiver operating characteristic curve analysis (Figure 1) with an area under the curve of 0.757 (95% confidence interval [CI], .686–.824; $P < .001$).

Comparison of patients with and without treatment failure was repeated. A multivariate logistic binary regression analysis was done to assess independent risk factors for failure; OT was introduced into the model as the explanatory variable of interest together with the propensity score of receiving OT.

The association with clinical outcome of rifampin-containing regimens on outcome of patients affected by an NVO due to *Staphylococcus* spp, including methicillin-resistant strains and unknown etiology NVO, was evaluated through a multivariate forward logistic binary regression model including all variables with a $P \leq .1$ at univariate analysis.

We used SPSS for Windows, version 20.0 (IBM SPSS, Inc., Chicago, IL) for statistical analysis. All statistical tests were 2-tailed, and $P < .05$ were considered significant.

Patient Consent Statement

Due to its observational, retrospective design, the study does not include factors necessitating patient consent.

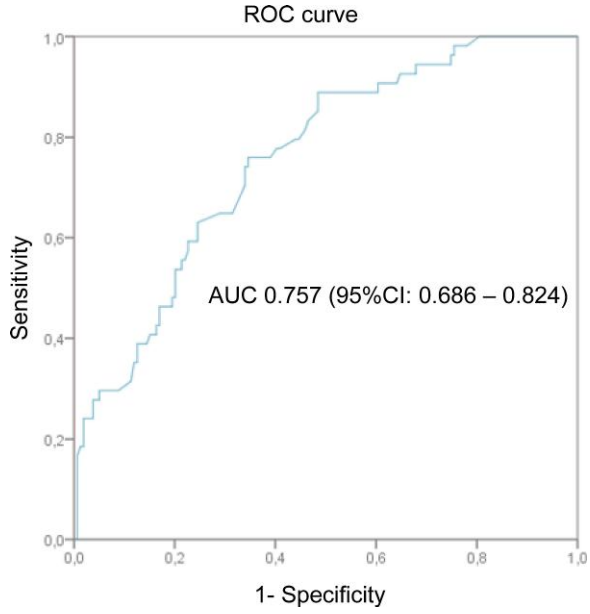

Figure 1. Propensity score of receiving oral treatment (covariates included the following: definite native vertebral osteomyelitis, systemic infection in the previous 12 months, Charlson comorbidity index, fever, cervical spine involved, Staphylococcal etiology, surgical treatment, computed tomography-guided biopsy done). AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic.

RESULTS

During the study period, 272 patients were treated at our center for pyogenic NVO, and 23 of them were excluded: 19 were lost to follow up before 12 months from EOT and 4 had incomplete data. Thus, the study population consisted of 249 patients (Figure 2).

Patient characteristics, demographics, and clinical characteristics of study population are summarized in Table 1. Median age was 69 (IQR, 57–76) years and 81 patients (32.5%) were females; the median Charlson comorbidity index was 5 (IQR, 3–7). The most common risk factor for NVO was the presence of a systemic infection in the past 12 months (35.7%).

Median diagnostic delay from symptoms onset was 44 days (IQR, 23.5–77), and back pain was the most common presenting symptom (96.8%), followed by fever (61.0%). Median C-reactive protein (CRP) at baseline was 5.0 mg/dL (IQR, 3.0–11.0) with reference range ≤0.5 mg/dL. Magnetic resonance imaging, computed tomography, and FDG-PET were available for 210 (84.3%), 111 (44.6%), and 221 (88.8%) patients, respectively. Involvement of lumbar tract was predominant (68.7%), with evidence of epidural abscess in 74 patients (34.3%) and paravertebral abscess in 93 cases (43.1%). Concomitant infectious endocarditis was ascertained in 36 patients (21.8%). According to our definition of NVO, there were 49 proven NVO, 134 probable NVO, and 66 presumptive NVO.

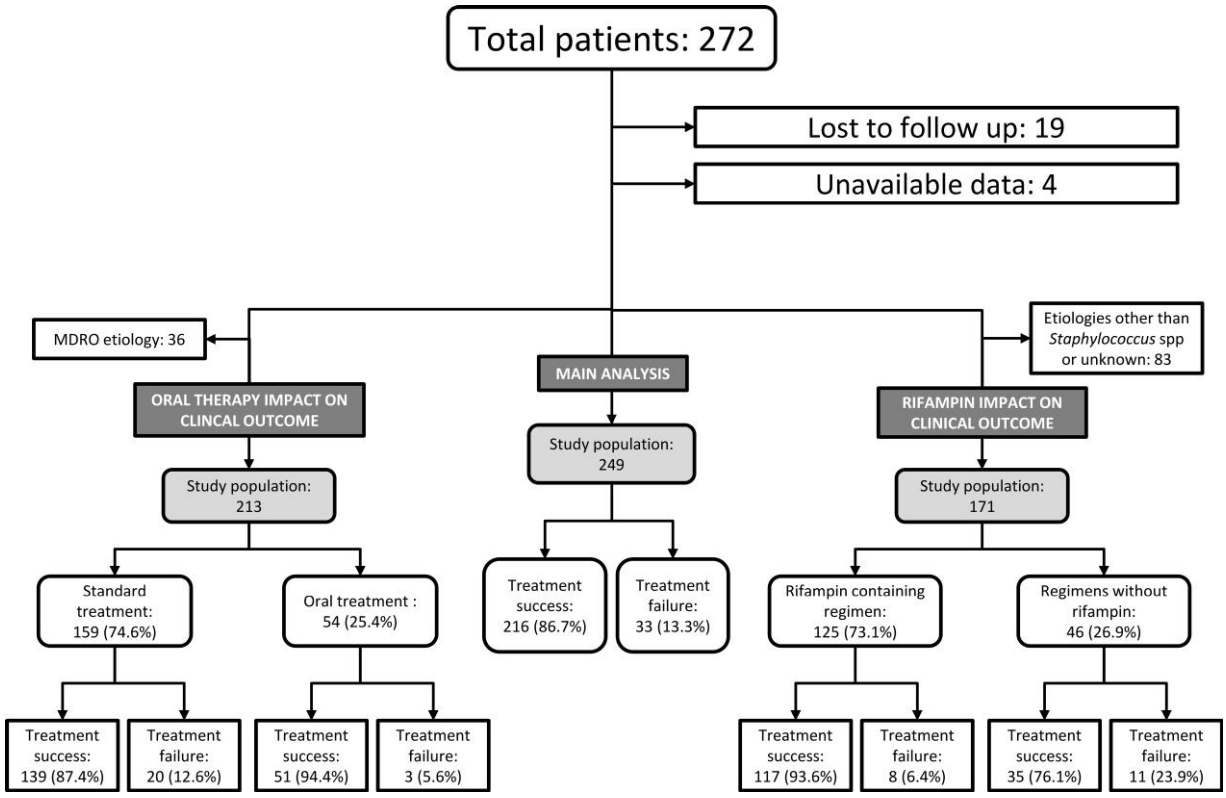

Figure 2. Flow-chart of the study population. MDRO, multidrug-resistant organism.

Microbiological Findings

Etiologic agent was identified in 179 patients (71.9%). Etiology was identified through blood cultures in 128 patients (51.4%), vertebral biopsy in 37 cases (14.9%), abscess drainage in 8 cases (4.5%), or both blood culture and spinal specimen culture in 6 patients (2.4%).

Microbiological findings for the 179 patients with a microbiological-defined NVO are displayed in Table 1. Overall, 36 patients (20.1% of culture positive NVO) were affected by an NVO due to an MDRO; almost half of them were MRSA (16 patients).

Management

Surgery was performed in 34 patients (13.7%), with a median time from diagnosis of 23 (IQR, 16–71) days. Only 5 patients underwent surgical intervention within 7 days from NVO diagnosis, because of worsening neurological deficits (3 patients) and spinal instability (2 patients). Indication for delayed surgery in the remaining 29 patients were as follows: spinal instability (12 patients), worsening neurological deficits (8 patients), failure of conservative treatment (5 patients), abscess debridement (3 patients), and spinal deformity (1 patient).

Fourteen of the 128 patients with an abscess (11%) underwent percutaneous drainage of abscess and 3 underwent surgical debridement; in the remaining case, abscesses were managed with antibiotics alone.

All patients received an empiric or targeted antimicrobial treatment. The OT group was composed of 54 patients (21.7%), with a median treatment duration of 96.5 days (IQR, 84.5–110.25). The most common antimicrobials used in the OT group were levofloxacin, rifampin, and minocycline, as shown in Supplementary Table 1. The ST group was composed of 195 patients (78.3%), with a total treatment duration median of 96 days (IQR, 81–122).

Overall, 90 patients were treated with a parenteral route of administration for the whole treatment duration, whereas 105 patients initially received a parenteral antimicrobial regimen for a median duration of 22 days (IQR, 14–42) followed by a highly bioavailable oral therapy. Most common antimicrobials used in the ST group belong to glycopeptide and beta lactam + beta lactam inhibitors (BL/BLI), as reported in Supplementary Table 2.

Outcome

Nineteen patients (7.6%) died during the study period: 11 patients died during antimicrobial treatment and 8 died during the follow up. The median time from diagnosis to death was 108 (IQR, 76–156) days. Fourteen patients (5.6%) experienced persistence or relapse of NVO. Overall, 33 patients (13.3%) were considered as having a treatment failure.

Table 1. Univariate Analysis of Risk Factors for Native Vertebral Osteomyelitis Treatment Failure

Variable	Treatment Success ($n=216$) *N* (%)	Treatment Failure ($n=33$) *N* (%)	Total ($N=249$) *N* (%)	*P* Value
Demographics				
Female gender	67 (31.0)	14 (42.4)	81 (32.5)	.231
Age (years, median; IQR)	68 (55.25–76)	74 (65–81.50)	69 (57–76)	.002
Risk Factors				
Surgical procedure	39 (18.1)	5 (15.2)	44 (17.7)	.810
Invasive procedure	40 (18.5)	4 (12.1)	44 (17.7)	.468
Spinal trauma	22 (10.2)	1 (3.0)	23 (9.2)	.329
Injective drug user	10 (4.6)	2 (6.1)	12 (4.8)	.664
Central venous catheter	14 (6.5)	3 (9.1)	17 (6.8)	.479
Hemodialysis	3 (1.4)	6 (18.2)	9 (3.6)	<.001
Systemic bacterial infection	78 (36.1)	11 (33.3)	89 (35.7)	.847
Comorbidities				
Myocardial infarction	25 (11.6)	10 (30.3)	35 (14.1)	.008
Congestive heart failure	43 (19.9)	11 (33.3)	54 (21.7)	.110
Peripheral vascular disease	72 (33.3)	16 (48.5)	88 (35.3)	.117
Cerebrovascular disease	21 (9.7)	8 (24.2)	29 (11.6)	.023
Dementia	6 (2.8)	2 (6.1)	8 (3.2)	.287
COPD	25 (11.6)	6 (18.2)	31 (12.4)	.393
Peptic ulcer disease	8 (3.7)	2 (6.1)	10 (4.0)	.626
Mild liver disease	16 (7.4)	0 (0.0)	16 (6.4)	.140
Connective tissue disease	4 (1.9)	1 (3.0)	5 (2.0)	.512
Rheumatologic disease	21 (9.7)	2 (6.1)	23 (9.2)	.748
Diabetes without organ damage	31 (14.4)	5 (15.2)	36 (14.5)	>.999
Diabetes with organ damage	9 (4.2)	3 (9.1)	12 (4.8)	.202
Hemiplegia	5 (2.3)	0 (0)	5 (2.0)	>.999
Moderate/severe renal disease	28 (13.0)	15 (45.5)	43 (17.3)	<.001
Neoplasm (previous 5 years)	32 (14.8)	4 (12.1)	36 (14.5)	.797
Lymphoma	2 (0.9)	2 (6.1)	4 (1.6)	.086
Leukaemia	1 (0.5)	1 (3.0)	2 (0.8)	.248
Moderate/severe liver disease	15 (6.9)	7 (21.2)	22 (8.8)	.015
Metastatic solid tumor	5 (2.3)	0 (0.0)	5 (2.0)	>.999
AIDS	4 (1.9)	0 (0.0)	4 (1.6)	>.999
CCI (median; IQR)	4 (2–6)	7 (5–9)	5 (3–7)	<.001
Clinical Presentation				
Pain	210 (97.2)	31 (93.9)	241 (96.8)	.287
Fever	133 (61.6)	19 (57.6)	152 (61.0)	.704
Hypostenia	43 (19.9)	5 (15.2)	48 (19.3)	.640
Hypoesthesia	26 (12.0)	3 (9.1)	29 (11.6)	.777
Fecal/urinary incontinence	10 (4.6)	0 (0.0)	10 (4.0)	.367
Vertebral Site				
Number of vertebral segments involved (median, IQR)	1 (1–1)	1 (1–2)	1 (1–1)	.014
Cervical	14 (6.5)	2 (6.1)	16 (6.4)	>.999
Thoracic	72 (33.3)	16 (48.5)	88 (35.3)	.117
Lumbar	152 (70.4)	19 (57.6)	171 (68.7)	.160
Sacral	31 (14.4)	0 (0.0)	31 (12.4)	.019
Abscesses[a]	112 (59.3)	16 (59.3)	128 (59.3)	>.999
Diagnosis				
Diagnostic delay (days, median, IQR)[b]	44 (22.25–75.50)	45 (28.50–105.50)	44 (23.5–77)	.571
Pre-treatment CRP (mg/dL, median, IQR)[c]	5 (2.5–11.0)	6.50 (4.25–11.75)	5.0 (3.0–11.0)	.124
CRP normalization time (days, mean ± SD)[d]	30 (14–60)	28 (15–72)	30 (14–60)	.865
Positive blood culture[e]	112 (85.5)	22 (91.7)	134 (86.5)	.533
CT-guided biopsy	112 (51.9)	15 (45.5)	127 (51.0)	.576
Positive CT-guided biopsy[f]	38 (33.9)	5 (33.3)	43 (34.1)	>.999
Infectious endocarditis[g]	28 (19.6)	8 (36.4)	36 (21.8)	.096

Table 1. Continued

Variable	Treatment Success ($n=216$) *N* (%)	Treatment Failure ($n=33$) *N* (%)	Total ($N=249$) *N* (%)	*P* Value
Definitions				
Definite	42 (19.4)	7 (21.2)	49 (19.7)	.812
Probable	119 (55.1)	15 (45.5)	134 (53.8)	.301
Presumptive	55 (25.5)	11 (33.3)	66 (26.5)	.340
Etiology				
Staphylococcus spp	88 (40.7)	13 (39.4)	101 (40.6)	>.999
Staphylococcus aureus	65 (30.1)	9 (27.3)	74 (29.7)	.840
CoNS	23 (10.6)	4 (12.1)	27 (10.8)	.766
Streptococcus spp	23 (10.6)	5 (15.2)	28 (11.2)	.446
Enterococcus spp	9 (4.2)	3 (9.1)	12 (4.8)	.202
Gram positive	122 (56.5)	21 (63.6)	143 (57.4)	.439
Enterobacteriaceae	24 (11.1)	3 (9.1)	27 (10.8)	>.999
Pseudomonas aeruginosa	1 (0.5)	3 (9.1)	4 (1.6)	.008
Gram negative	29 (13.4)	6 (18.2)	35 (14.1)	.464
Anaerobes	2 (0.9)	0 (0.0)	2 (0.8)	>.999
MDRO	26 (12.0)	10 (30.3)	36 (14.5)	.005
MRSA	10 (4.6)	6 (18.2)	16 (6.4)	.003
CoNS Oxa-R	9 (4.2)	3 (9.1)	12 (4.8)	.202
Polymicrobial infection	4 (1.9)	0 (0.0)	4 (1.6	>.999
Unknown etiology	64 (29.6)	6 (18.2)	70 (28.1)	.173
Treatment				
Surgical treatment	27 (12.5)	7 (21.2)	34 (13.7)	.274
Surgery during antimicrobials	23 (85.2)	5 (71.4)	28 (82.2)	.580
Time from diagnosis to surgery (days, median; IQR)	29 (13–74)	25 (13–60)	23 (16–71)	>.999
Previous antimicrobial treatment	93 (43.1)	17 (51.5)	110 (44.2)	.452
Oral treatment	51 (23.6)	3 (9)	54 (21.7)	.07
Length of first treatment course (days, median; IQR)	98 (85.25–118.75)	78 (62–103)	96 (82–116)	.001
Treatment-related adverse event	49 (22.7)	7 (21.2)	56 (22.5)	>.999
Teicoplanin	91 (42.1)	18 (54.5)	109 (43.7)	.192
Piperacillin/tazobactam	75 (34.7)	9 (27.3)	84 (33.7)	.437
Daptomycin	20 (9.3)	5 (15.2)	25 (10.0)	.346
Levofloxacin	134 (62.0)	14 (42.4)	148 (59.4)	.037
Ciprofloxacin	9 (4.2)	2 (6.1)	11 (4.4)	.644
Rifampicin	128 (59.3)	10 (30.3)	138 (55.4)	.002
Minocycline	35 (16.2)	4 (12.1)	39 (15.7)	.797
Trimethoprim-sulphametoxazole	6 (2.8)	0 (0.0)	6 (2.4)	>.999
Linezolid	12 (5.6)	4 (12.1)	16 (6.4)	.241

Abbreviations: AIDS, acquired immune deficiency syndrome; CCI, Charlson comorbidity index; CI, confidence interval; CoNS, coagulase-negative *Staphylococcus*; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computed tomography; IQR, interquartile range; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; NVO, native vertebral osteomyelitis; OR, odds ratio; SD, standard deviation.

[a]Abscess presence available for 216 patients (189 in favorable outcome group and 27 in clinical failure group).

[b]Diagnostic delay measured from first symptoms appearance and date of definitive diagnosis.

[c]Baseline CRP available in 193 patients (165 in favorable outcome group and 28 in clinical failure group).

[d]CRP normalization time available for 138 patients (131 in favorable outcome group and 7 in clinical failure group).

[e]Blood cultures done in 155 patients (131 in favorable outcome group and 24 in clinical failure group).

[f]Vertebral biopsy done in 127 patients (112 in favorable outcome group and 15 in clinical failure group).

[g]Echocardiography done in 165 patients (143 in favorable outcome group and 22 in clinical failure group).

In the whole population, multivariate regression analysis selected Charlson comorbidity index (adjusted odds ratio [aOR], 1.291; 95% Conficence Interval [CI], 1.114–1.497; $P=.001$) and MDRO etiology (aOR, 3.301; [95% CI], 1.368–7.964; $P=.008$) as independent factors for clinical failure (Table 2).

In the subgroup of patients with non-MDRO NVO (213 patients), there were 23 failures: 3 (5.6%) in the OT group and 20 (12.6%) in the ST group ($P=.20$) (Table 3 and Supplementary Table 3). Multivariate regression analysis for clinical failure showed that OT was not associated with an increased risk of clinical failure (aOR, 0.487; 95% CI, .133–1.782; $P=.271$). When adjusted for the propensity score of receiving OT instead of ST, the model did not change (Table 4).

Table 2. Multivariable Analysis of Risk Factors for Native Vertebral Osteomyelitis Treatment Failure

Treatment Failure	OR	95% CI	*P* Value
Charlson comorbidity index	1.291	1.114–1.497	.001
MDRO etiology	3.301	1.368–7.964	.008
Number of vertebral levels involved	1.960	0.990–3.877	.053

Abbreviations: CI, confidence interval; MDRO, multidrug-resistant organism; OR, odds ratio.

In the subgroup of patients with staphylococcal NVO or unknown etiology (171 patients), 125 (73.1%) received a rifampin-based antimicrobial regimen. Multivariate regression analysis for clinical failure showed that rifampin was independently associated with favorable outcome (aOR, 0.315; 95% CI, .105–.949; $P = .040$) (Supplementary Table 4).

DISCUSSION

In this study, we describe the epidemiology and outcome of a large cohort of patients with NVO and managed at an ID referral center. The overall failure rate was relatively low (13%), compared to other published cohorts [2, 10, 11]. A higher Charlson comorbidity index and an MDRO etiology were associated with a worse prognosis. The main finding of our study is that a highly bioavailable oral treatment on the first day (including rifampin for staphylococcal NVO and in case of unknown etiology) may be an effective option for the treatment of NVO not caused by MDROs.

Our study population is comparable to previously published cohorts of NVO in terms of demographics, comorbidities, proportion of etiological diagnosis, and proportion of patients with difficult-to-treat microorganisms. However, we observed a low rate of clinical failure (13.3%). In our opinion, this low failure rate may be related (1) to the clinical management shared between skilled ID specialists and dedicated orthopedic surgeons and (2) to the choice of antibiotics with a good penetration into bone tissue. Moreover, in our center, all patients were supported by an active follow up, consisting of periodic blood tests, regular ambulatory visits, and the possibility of a quick contact if needed. Despite spending an extensive amount of time and resources, we believe that active support is the optimal way of improving adherence to therapy and safety of patients receiving prolonged antibiotic treatments [7, 12].

To date, only a few studies have investigated the efficacy and safety of oral therapy in NVO, and they focused on oral shift after initial parenteral treatment. Flury et al [13] published a small retrospective cohort study showing that switching to an oral antibiotic regimen after 2 weeks of intravenous treatment was safe in patients with decreasing CRP and successful drainage of epidural or paravertebral abscesses. In their randomized controlled trial, Bernard et al [11] reported no differences in treatment failure between patients given protracted intravenous treatment (>1 week) and those given intravenous treatment for less than 1 week. However, low incidence of MRSA (5.5%) and spinal abscesses (19.4%) hampered generalization of their result to other population.

The best evidence supporting oral treatment for bone infection is provided by Oral versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) trial, which showed that oral antibiotics were noninferior to intravenous antibiotic therapy for complex orthopedic infections. However, in this trial, only 6.8% of patients had a spinal infection, and all patients received parenteral therapy for up to 7 days before randomization [7]. In our cohort, patients included in the OT group received oral antibiotics for the entire treatment course; we did not find significant differences in terms of efficacy nor adverse events between OT and ST.

Another significant finding of our study is the role of rifampin in the treatment of NVO. Several studies on chronic osteomyelitis and orthopedic implant infections have shown that rifampin in addition to an antibiotic regimen improves cure rates in animal models, in retrospective studies in humans, and in randomized clinical trials [14–17]. Previous studies investigating the impact of antimicrobial therapy on NVO outcome generally reported a favorable but nonstatistically significant effect of rifampin combination [2, 11, 18]. In our cohort, no single combination of antimicrobials demonstrated superiority over the others, whereas rifampin-based regimens were independently associated with better outcome among patients with staphylococcal NVO or due to unknown etiology.

Observed median treatment durations in both ST and OT was longer (more than 12 weeks) than now recommended for NVO. This finding can be explained considering that we included cases of NVO diagnosed between 2008 and 2018, and so many of them were managed before 2015, when Bernard et al [11] published their trial showing that 6 weeks of antibiotic treatment for vertebral osteomyelitis was not inferior to 12 weeks of treatment. Moreover, the large number of patients with abscesses managed nonoperatively could have justified several cases of prolonged antibiotic therapy.

The main strength of our study is that it is a real-life study and included heterogeneous patients with NVO. Indeed, we had high prevalence of vertebral abscesses (paravertebral in 42.9% and epidural abscess in 32.3%) and MDRO pathogens (19% of *S aureus* were MRSA, 50% of coagulase-negative *Staphylococcus* were methicillin-resistant, and 41.2% of *Enterobacteriaceae* were resistant to quinolones), and we included patients with infectious endocarditis and/or concomitant bacteremia, reflecting real-life management of NVO.

Our study has several limitations that must be considered when interpreting results. First, it is a single-center study and all patients were managed by the same ID specialistis with great experience in the management of NVO, limiting the possibility to generalize results. Second, some patients have been excluded from the analysis due to loss to follow up or incomplete data,

Table 3. Comparison of Patients' Characteristics Between Oral Treatment and Standard Treatment Groups

Characteristics	Oral Treatment ($n=54$) *N* (%)	Standard Treatment ($n=159$) *N* (%)	Total ($n=213$) *N* (%)	*P* Value
Demographics				
Female gender	17 (31.5)	51 (32.1)	68 (31.9)	.936
Age (years, median; IQR)	68 (55.75–74.25)	68 (56–77)	68 (56–77)	.398
Risk Factors for NVO				
Surgical procedure	6 (11.1)	32 (20.1)	38 (17.8)	.135
Invasive procedure	13 (24.1)	25 (15.7)	38 (17.8)	.166
Spinal trauma	4 (7.4)	16 (10.1)	20 (9.4)	.788
Injective drug user	5 (9.3)	7 (4.4)	12 (5.6)	.181
Central venous catheter	4 (7.4)	10 (6.3)	14 (6.6)	.756
Hemodialysis	2 (3.7)	3 (1.9)	5 (2.3)	.603
Systemic bacterial infection	24 (44.4)	50 (31.4)	74 (34.7)	.083
Comorbidities				
Myocardial infarction	9 (16.7)	22 (13.8)	31 (14.6)	.610
Congestive heart failure	9 (16.7)	37 (23.3)	46 (21.6)	.308
Peripheral vascular disease	17 (31.5)	57 (35.8)	74 (34.7)	.560
Cerebrovascular disease	4 (7.4)	17 (10.7)	21 (9.9)	.604
Dementia	0 (0.0)	7 (4.4)	7 (3.3)	.195
COPD	8 (14.8)	18 (11.3)	26 (12.2)	.498
Peptic ulcer disease	1 (1.9)	8 (5.0)	9 (4.2)	.454
Mild liver disease	3 (5.6)	12 (7.5)	15 (7.0)	.765
Connective tissue disease	1 (1.9)	2 (1.3)	3 (1.4)	>.999
Rheumatologic disease	7 (13.0)	13 (8.2)	20 (9.4)	.297
Diabetes without organ damage	10 (18.5)	20 (12.6)	30 (14.1)	.278
Diabetes with organ damage	1 (1.9)	8 (5.0)	9 (4.2)	.454
Hemiplegia	2 (3.7)	3 (1.9)	5 (2.3)	.603
Moderate/severe renal disease	6 (11.1)	28 (17.6)	34 (16.0)	.260
Neoplasm (prior 5 years)	4 (7.4)	26 (16.4)	30 (14.1)	.117
Lymphoma	0 (0.0)	4 (2.5)	4 (1.9)	.574
Leukaemia	0 (0.0)	1 (0.6)	1 (0.5)	>.999
Moderate/severe liver disease	6 (11.1)	13 (8.2)	19 (8.9)	.513
Metastatic solid tumor	0 (0.0)	4 (2.5)	4 (1.9)	.574
AIDS	1 (1.9)	3 (1.9)	4 (1.9)	>.999
Charlson comorbidity index (median; IQR)	4 (2–6)	5 (2–7)	5 (2–7)	.125
Symptoms				
Pain	53 (98.1)	153 (96.2)	206 (96.7)	.682
Fever	26 (48.1)	100 (62.9)	126 (59.2)	.057
Hypostenia	11 (20.4)	29 (18.2)	40 (18.8)	.729
Hypoestesia	6 (11.1)	18 (11.3)	24 (11.3)	.966
Fecal/urinary incontinence	2 (3.7)	6 (3.8)	8 (3.8)	>.999
Vertebral Site				
Number of vertebral segments involved (median; IQR)	1 (1–1)	1 (1–1)	1 (1–1)	.619
Cervical	7 (13.0)	8 (5.0)	15 (7.0)	.049
Thoracic	16 (29.6)	55 (34.6)	71 (33.3)	.504
Lumbar	34 (63.0)	114 (71.7)	148 (69.5)	.228
Sacral	7 (13.0)	19 (11.9)	26 (12.2)	.844
Abscess[a]	31 (62.0)	76 (55.1)	107 (56.9)	.397
Infectious endocarditis[b]	3 (10.7)	30 (27.5)	33 (24.1)	.083
Diagnosis				
Diagnostic delay (median days, IQR)[c]	50 (24.75–83.75)	42 (24–77)	45 (24.5–78)	.292
Pretreatment C-reactive protein (mg/dL, median, IQR)[d]	4.0 (2.0–9.00)	6.0 (3.0–11–0)	5.0 (2.5–11.0)	.069
C-reactive protein negativization timing (days, median; IQR)[e]	30.0 (14–46.25)	30 (10.0–61.0)	30 (14–58)	.801
Positive blood culture[f]	20 (76.9)	93 (89.4)	113 (86.9)	.091
CT-guided biopsy	36 (66.7)	71 (44.7)	107 (50.2)	.005
Positive CT-guided biopsy[g]	15 (41.7)	17 (23.9)	32 (29.9)	.059
Definition				
Proven	16 (29.6)	18 (11.3)	34 (16.0)	.002

Table 3. Continued

Characteristics	Oral Treatment ($n=54$) *N* (%)	Standard Treatment ($n=159$) *N* (%)	Total ($n=213$) *N* (%)	*P* Value
Probable	28 (51.9)	90 (56.6)	118 (55.4)	.554
Presumptive	10 (18.5)	51 (32.1)	61 (28.6)	.057
Etiology				
Staphylococcus spp	24 (44.4)	49 (30.8)	73 (34.3)	.068
Staphylococcus aureus	15 (27.8)	43 (27.0)	58 (27.2)	.917
CoNS	9 (16.7)	6 (3.8)	15 (7.0)	.001
Streptococcus spp	4 (7.4)	24 (15.1)	28 (13.1)	.170
Enterococcus spp	0 (0.0)	11 (6.9)	11 (5.2)	.069
Gram positive	28 (51.9)	87 (54.7)	115 (54.0)	.715
Enterobacteriaceae	5 (9.3)	14 (8.8)	19 (8.9)	.919
Pseudomonas aeruginosa	2 (3.7)	2 (1.3)	4 (1.9)	.267
Gram negative	7 (13.0)	20 (12.6)	27 (12.7)	.942
Anaerobes	0 (0.0)	2 (1.3)	2 (0.9)	>.999
Polymicrobial infection	0 (0.0)	3 (1.9)	3 (1.4)	.573
Unknown etiology	19 (35.2)	51 (32.1)	70 (32.9)	.674
Treatment				
Surgical treatment	2 (3.7)	21 (13.2)	23 (10.8)	.073
Surgery during antimicrobials	0 (0.0)	6 (3.8)	6 (2.8)	.341
Delayed surgical treatment	2 (3.7)	15 (9.4)	17 (8.0)	.250
Previous antibiotic treatment	27 (50.0)	63 (39.6)	90 (42.3)	.182
Total treatment length (days, median, IQR)	96.50 (84.5–110.25)	97 (81–123)	97 (82–117)	.980
Treatment-related adverse event	11 (20.4)	37 (23.3)	48 (22.5)	.659
Clostridium *difficile* colitis	1 (1.9)	4 (2.5)	5 (2.3)	>.999
Tendinopathy	4 (7.4)	6 (3.8)	10 (4.7)	.274
Gastrointestinal intolerance	1 (1.9)	6 (3.8)	7 (3.3)	.682
Hepatotoxicity	1 (1.9)	2 (1.3)	4 (1.4)	>.999
Hematologic toxicity	2 (3.7)	9 (5.7)	11 (5.2)	.734
Skin rash	2 (3.7)	5 (3.1)	7 (3.3)	>.999
CVC-related complications	0 (0.0)	3 (1.9)	3 (1.4)	.573
Unfavorable outcome	3 (5.6)	20 (12.6)	23 (10.8)	.206

Abbreviations: AIDS, acquired immune deficiency syndrome; CCI, Charlson comorbidity index; CI, confidence interval; CoNS, coagulase-negative *Staphylococcus*; COPD, chronic obstructive pulmonary disease; CT, computed tomography; CVC, central venous catheter; IQR, interquartile range; MDRO, multidrug-resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus*; NVO, native vertebral osteomyelitis; OR, odds ratio; SD, standard deviation.

[a]Abscess presence available for 188 patients (50 in oral treatment [OT] group and 138 in standard treatment [ST] group).

[b]Echocardiography available for 137 patients (28 in OT group and 109 in ST group).

[c]Diagnostic delay measured from first symptoms appearance and date of definitive diagnosis.

[d]Baseline C-reactive protein (CRP) measured in 165 patients (43 in OT group and 122 in ST group).

[e]CRP negativization time available for 119 patients (38 in OT group and 81 in ST group).

[f]Blood culture available for 130 patients (26 in OT group and 104 in ST group).

[g]Vertebral biopsy available for 107 patients (36 in OT group and 71 in ST group).

Table 4. Multivariable Analysis by Logistic Regression of Risk Factors for Treatment Failure in the Subgroup of Patients With a Non-MDRO Etiology

	Multivariate Analysis		Multivariable Propensity Score-Balanced Analysis	
Variable	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Charlson comorbidity index	1.293 (1.109–1.507)	.001	1.251 (1.071–1.461)	.005
Number of vertebral levels	1.968 (0.924–4.194)	.079	2.234 (1.020–4.893)	.045
Oral treatment group	0.487 (0.133–1.782)	.271	0.675 (0.173–2.632)	.571
Propensity score			0.042 (0.001–2.061)	.110

Abbreviations: CI, confidence interval; MDRO, multidrug-resistant organism; OR, odds ratio.

introducing possible biases; however, it is an inherent limitation of retrospective studies. Third, 42.7% of our patients received antibiotics before starting the specific antimicrobial therapy for NVO. This may have introduced some bias in our analysis of OT efficacy; nevertheless, previous antimicrobial treatment rate was equally distributed in OT and ST groups, and it reflects

a common condition of the patient presenting with NVO. In real life, it is very common to diagnose NVO in patients with a relevant diagnostic delay who have been previously treated with antibiotics before NVO diagnosis.

Finally, the choice between OT and ST was made at ID specialist's discretion, without pre-established criteria, which probably introduced multiple bias. We attempted to overcome these confounders with the use of a propensity score, but it is possible that relevant variables may not have been included.

CONCLUSIONS

To conclude, our data suggest that, in patients affected by pyogenic NVO not due to MDRO, an entirely oral highly bioavailable treatment, including rifampin for staphylococcal NVO and in case of unknown etiology, may be as effective as parenteral treatment. Furthermore, prospective studies are needed to investigate this issue and to identify the criteria to select patients suitable for oral therapy.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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