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MAJOR ARTICLE

Culture Yield in the Diagnosis of Native Vertebral Osteomyelitis: A Single Tertiary Center Retrospective Case Series With Literature Review

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Background. Vertebral osteomyelitis is a serious condition that requires prompt diagnosis to avoid delays in proper management. There is no well-defined gold standard for diagnosis. We describe the current diagnostic approach at our institution, with a focus on the yield of image-guided vertebral biopsy.

Methods. We performed a single-centre 10-year retrospective case series, including adults with imaging suggestive of vertebral osteomyelitis/discitis, with either positive blood cultures, and/or a vertebral biopsy. We defined positive histopathology as our gold standard for test characteristic evaluation of biopsy cultures.

Results. Out of 694 patients identified, 221 met our inclusion criteria, and 173/221 (78.2%) patients underwent a spinal biopsy. Of those patients with biopsies, 113 (65%) had received antibiotics within 2 weeks preceding their evaluation. Six of 43 (13.9%) bone specimens were positive by culture, while 66/152 (43.4%) of disc specimens were culture positive. Forty-seven of 84 (55.9%) histopathology (bone or disc) specimens were diagnostic for osteomyelitis/discitis. The sensitivity of bone and disk culture were 30.0% and 56.0%, respectively, with specificities of 92.8% and 75.0%, respectively. Twenty-three (13.4%) patients had repeat biopsies, including 10 bone specimens and 14 disc specimens, and 11 (47.8%) specimens had histopathology performed which diagnosed an additional 3/23 patients (13% additional diagnostic yield).

Conclusions. Culture of percutaneous biopsy of disc resulted in the highest diagnostic yield. Histopathology added to the diagnostic yield in culture-negative specimens. Histopathologic evaluation of bone had better yield than bone culture. A repeat biopsy can add to the diagnostic yield.

Keywords. aspiration; biopsy; discitis; spondylodiscitis; vertebral osteomyelitis.

KEY POINTS

When evaluating patients with suspected vertebral osteomyelitis, blood cultures followed by culture of percutaneous biopsy of disc, plus histopathologic examination of clinical specimens, resulted in the highest diagnostic yield. Histopathology improved the diagnostic yield, especially in culture-negative specimens.

Native vertebral osteomyelitis (NVO) is a serious condition, one that if misdiagnosed on initial presentation can lead to delays in proper management. Vertebral osteomyelitis is the most common form of hematogenous osteomyelitis in adults >50 years old and represents 3%–5% of all osteomyelitis cases [1]. Early and accurate diagnosis is difficult to achieve, but critical to reduce overall morbidity. In a recent epidemiologic study of vertebral osteomyelitis in the United States, >200 000 patients were hospitalized between 1998 and 2013 with this disease, with incidence increasing from 2.9/100 000 to 5.4/100 000. Mortality during hospitalization was 2.1%, with a mean length of stay of approximately 9 days, and the total estimated cost of hospitalizations more than tripled during that 15-year period [2].

Given the impact of this disease, it is important to gain a better understanding of the diagnostic approach that is most beneficial to this patient population. In September 2015, the Infectious Diseases Society of America (IDSA) published a clinical practice guideline to aid in the diagnosis and treatment of NVO [1]. With this in mind, the purpose of our study is to evaluate the efficacy of our current methodologies to diagnose NVO. We hypothesized that the acquisition of both bone and disc from the vertebral biopsy, coupled with a microbiologic

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and histopathologic examination, will produce the highest diagnostic yield.

METHODS

Study Design

This is a retrospective, single-center case series of patients diagnosed with native vertebral osteomyelitis at our institution between 1 January 2007 and 31 July 2017. We use the term native vertebral osteomyelitis to include discitis as well as osteomyelitis of the vertebra. We did not have an institutional protocol for this diagnostic evaluation, so we sought to examine our current practices to determine the best approach. Patients were initially identified using the Healthcare Enterprise Repository for Ontologic Narration (HERON) database, by searching for *International Classification of Diseases*, *Ninth Revision* and *Tenth Revision* (*ICD-9* and *ICD-10*) codes for vertebral osteomyelitis, spondylodiscitis, disc infection, and intraspinal abscess (Supplementary Table 1) [3, 4]. This was followed by electronic records review to confirm the diagnosis. This study was approved by our institutional review board.

Inclusion and Exclusion Criteria

Our study included patients 18 years of age or older at the time of NVO diagnosis, with 1 or more of the following criteria: (1) vertebral and/or intervertebral disc biopsy positive for known pathogens including *Staphylococcus aureus*, *Staphylococcus lugdunensis*, *Brucella* species (spp), anaerobes, fungi, or mycobacteria or repeatedly positive for skin flora such as coagulase-negative *Staphylococcus*, *Cutibacterium acnes*, or diphtheroids; (2) abnormal imaging suggestive of spondylodiscitis with positive blood culture for *S aureus*, *S lugdunensis*, *Brucella* spp, gram negatives such as *Escherichia coli*, *Proteus* spp, *Klebsiella* spp, and *Pseudomonas* spp; (3) abnormal imaging suggestive of spondylodiscitis with negative vertebral and/or intervertebral disc biopsy on microbiologic examination, but positive histopathologic examination. See Supplementary Methods for definitions of magnetic resonance imaging (MRI) and computed tomographic (CT) evidence of osteomyelitis.

Exclusion criteria included any patients with sacral osteomyelitis secondary to decubitus ulcers, and those with known spinal instrumentation or trauma at the spinal level of interest within the preceding 6 months. Patients who underwent open vertebral biopsy were also excluded.

We defined positive histopathology as our gold standard for diagnosis when calculating test characteristics of biopsy cultures. Histopathologic criteria for NVO diagnosis include acute or chronic inflammation, multinucleated cells or granulomas present, or tissue necrosis. The interventional radiologist at our institution obtained samples using CT-guided or fluoroscopic techniques for bone and disc aspiration. Biopsy yields a vertebral bone specimen, disc/fibrous tissue specimen, or a combination of both.

Data Collection

We performed an electronic records review on all patients initially identified by our HERON database search to confirm inclusion/exclusion criteria. We abstracted demographic data as well as the presence of comorbidities (Supplementary Table 2), as well as biopsy level, tissue type obtained (bone, disc, or both), and recent antibiotic exposure. Study data were collected and managed using Research Electronic Data Capture (REDCap) hosted at our institution (Supplementary Methods) [5, 6].

Statistical Analysis

Data analysis was performed using SPSS software. Descriptive statistics were used for patient characteristics and biopsy results. Histopathology was the gold standard for culture sensitivity and specificity calculation for bone and disc cultures [7, 8]. Definitions of general yield of biopsies and formulas for sensitivity and specificity calculations are shown in the Supplementary Methods. If multiple biopsy specimens of bone and disc were obtained, their results were combined in the calculation.

In the cohort of patients with spinal biopsies done, a univariate logistic regression analysis was performed to determine variables predicting a positive bone or disc culture, followed by a planned multivariate logistic regression analysis using the same variables to determine predictors of a positive spinal biopsy culture. Determined by logistic regression, a 2-sided P value of $< .05$ was considered statistically significant.

RESULTS

Patient Characteristics/Demographics

Of 694 adult patients who met our *ICD-9* or *ICD-10* search criteria for NVO between 1 January 2007 and 31 July 2017 at our institution, 221 met our inclusion criteria and were retained in the study (Figure 1). There were 138 males (62.4%), and mean patient age was 60.2 years (Supplementary Table 2). Diabetes mellitus (46.6%) and malignancy (15.4%) were the leading comorbidities in our patient cohort. Thirty-three of 221 (14.9%) patients received immunosuppressive medications. See Supplementary Table 2 for additional baseline patient characteristics.

Diagnostic Evaluation

Two hundred twenty patients (99.5%) underwent radiological evaluation. The most common imaging modality was MRI done in 167/220 (75.6%) patients, followed by CT scan in 38/220 (17.2%) (Table 1).

Of the 221 enrolled subjects, 203 (91.8%) had blood cultures and 173 (78.3%) had a spinal biopsy (Figures 1 and 2). Of 203 with blood cultures, 155 (76.3%) had image-guided spinal biopsy. Of 173 patients with biopsies, the lumbar spine was the most common site (67.0%), followed by the thoracic (28.3%) and cervical (4.6%) spine. From the initial biopsy episode, bone

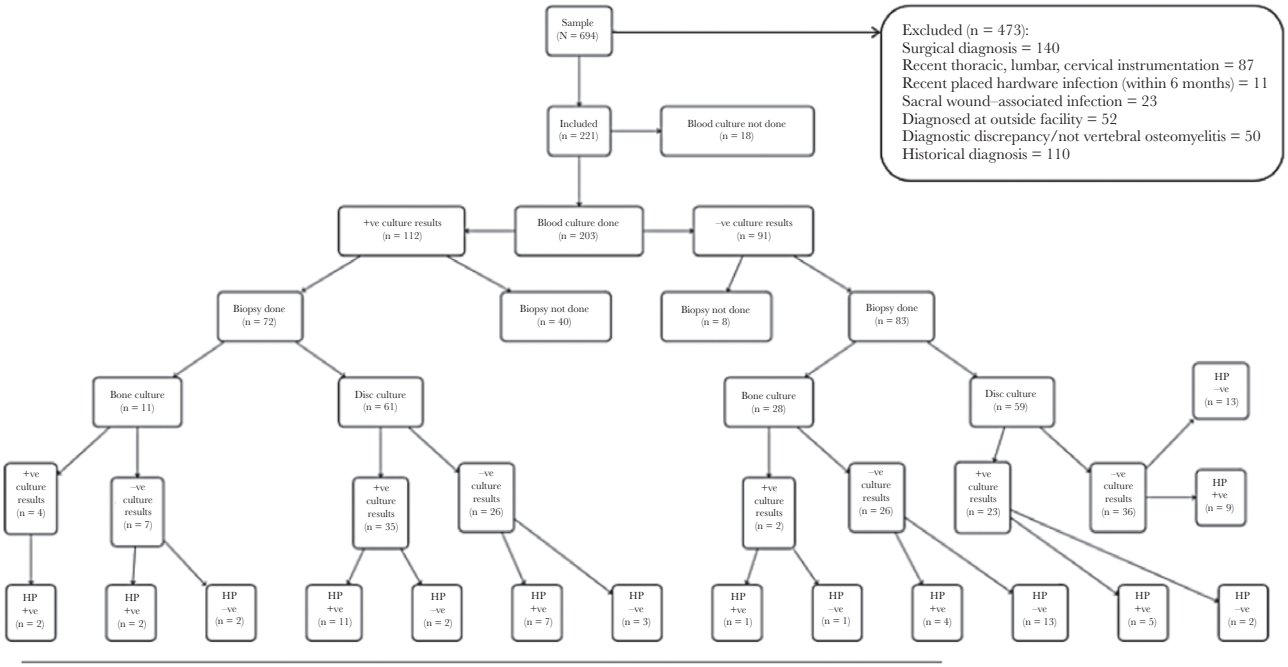

Figure 1. Patient selection and outcomes with blood cultures and biopsy culture with or without histopathology. Abbreviations: -ve, negative; +ve, positive; HP, histopathology.

specimens were collected in 43 (24.9%) patients, disc specimens in 136 (78.6%) patients, both types in 10 (5.8%) patients, and histopathology in 84 (48.5%) patients. A repeat spinal biopsy was obtained in 23/173 (13.3%) patients, with 11 bone specimens and 15 disc specimens obtained, and 11/23 (47.8%) also had histopathology performed.

Among the total number of patients who underwent a biopsy, 113/173 (65%) had received antibiotics within 2 weeks of the evaluation date (Supplementary Table 3). The median duration of antibiotics received prior to vertebral biopsy was 5 days. In those patients who underwent bone biopsy without receiving prior antibiotics, 14.2% (2/14) had positive culture. In those who underwent disc biopsy without prior antibiotics, 45% (18/40) had positive culture.

Of those with blood cultures, 112/203 (55.2%) had growth. *Staphylococcus aureus* was isolated in 63/112 (56.2%) of positive blood cultures with methicillin-resistant *S aureus* (MRSA) accounting for 26/63 (41.3%) and methicillin-susceptible *S aureus* (MSSA) for 37/63 (58.7%). Of the remaining 112 positive blood cultures, 8 (7.1%) grew gram-negative organisms, 4 (3.6%) grew *Candida* spp, and *S lugdunensis* accounted for 3 (2.7%) (Table 2). We had 51.5% (34/66) concordance between blood cultures and bone or disc biopsy cultures, with 76.5% (26/34) of those being *Staphylococcus* spp.

Of the 43 patients with bone sent for culture, 1 patient had 2 specimens obtained, and both were culture negative. In the remaining 42 patients, 6 (13.6%) bone specimens resulted in positive cultures (Table 2). The most common organism identified on bone culture was *S aureus* (50%). A total of 152 disc specimens were sent from 136 patients, and 66/152 (43.4%) had positive cultures. Fourteen patients had 2 disc specimens cultured, with growth in both specimens in 3/14, while 4/14 had only 1 disc specimen culture positive. One patient had 3 disc specimens cultured, with 1 positive (Table 2). The most common organisms identified on disc culture were *S aureus* (44.8%) and coagulase-negative *Staphylococcus* (15.5%). Ten patients had both bone and disc cultures obtained, and 1/10 (10.0%) had both cultures positive.

Histopathology was obtained in 84/173 patients. Of those 84, 47 (55.9%) specimens were consistent with vertebral osteomyelitis/discitis: soft tissue acute inflammation/discitis in 25/84 (29.8%), osteomyelitis in 20/84 (23.8%), and soft tissue inflammation with osteomyelitis in 2/84 (2.4%). The remaining 37 specimens were tissues consistent with malignancy (3/84 [3.6%]), normal tissue (25/84 [29.8%]), and other findings (9/84 [10.7%]). Four patients had tissue biopsies obtained for histopathology, but no microbiological investigation was performed.

The strict sensitivity of initial bone culture to establish the diagnosis was 30.0% (3/10), with a specificity of 92.8% (13/14). The strict sensitivity of initial disc culture to establish the diagnosis was 56% (14/25), with a specificity of 75.0% (15/20). The general initial bone culture sensitivity was 27.3% (3/11), with a specificity of 93.7% (15/16), and the general initial disc culture sensitivity was 50.0% (19/38), with a specificity of 77.3% (17/22). General sensitivity of the initial biopsy episode culture was 42.2% (19/45) and specificity was 80.0% (28/35).

Twenty-three patients had repeat biopsies. The most common site for repeat biopsies was the lumbar spine (69.6%) followed by

Table 1. Univariate Analysis for Predictors of Positive Biopsy Culture

Characteristic		Overall[a] (N = 221)	Univariate Analysis[b] Positive Biopsy Culture (n = 69)	Univariate Analysis[b] Negative Biopsy Culture (n = 102)	*P* Value[c]
Age, y, mean (SD)		60.18 (13.4)	57.77 (14.4)	60.25 (12.5)	.23
Sex	Male	138 (62.4)	46 (66.7)	62 (60.8)	.53
	Female	83 (37.6)	23 (33.3)	40 (39.2)	
Comorbidities					
Diabetes mellitus	Yes	103 (46.6)	33 (47.8)	45 (44.1)	.75
	No	118 (53.4)	36 (52.2)	57 (55.9)	
Malignancy	Yes	34 (15.4)	13 (18.8)	16 (15.7)	.74
	No	187 (84.6)	56 (81.2)	86 (84.3)	
HIV[d]	Yes	5 (5.1)	3 (8.8)	2 (4.4)	.65
	No	93 (94.9)	31 (91.2)	43 (95.6)	
Immunosuppressed	Yes	33 (14.9)	12 (17.4)	14 (13.7)	.66
	No	188 (85.1)	57 (82.6)	88 (86.3)	
Alcoholism[d]	Yes	22 (11.5)	7 (10.8)	11 (12.8)	.90
	No	170 (88.5)	58 (89.2)	75 (87.2)	
IV drug use[d]	Yes	19 (11.0)	7 (11.5)	10 (13.0)	.99
	No	154 (89.0)	54 (88.5)	67 (87.0)	
Indwelling vascular catheter	Yes	42 (19.0)	15 (21.7)	19 (18.6)	.76
	No	179 (81.0)	54 (78.3)	83 (81.4)	
Diagnostics					
Blood culture result	Positive	112 (55.2)	39 (60.9)	32 (36.0)	<.01
	Negative	91 (44.8)	25 (39.1)	57 (64.0)	
Organism in blood culture	*Staphylococcus aureus*	63 (56.2)	22 (56.4)	16 (50.0)	.84
	Staphylococcus lugdunensis	3 (2.7)	2 (5.1)	1 (3.1)	
	Other	46 (41.1)	15 (38.5)	15 (46.9)	
Biopsy site[e]	Cervical	8 (3.6)	1 (1.4)	7 (6.9)	.15
	Thoracic	49 (22.2)	17 (24.6)	31 (30.4)	
	Lumbar	116 (52.5)	51 (73.9)	64 (62.7)	
Prior antibiotics (within 2 wk)	Yes	150 (67.9)	49 (71.0)	71 (69.6)	.98
	No	71 (32.1)	20 (29.0)	31 (30.4)	
Imaging modality	MRI	167 (75.6)	57 (82.6)	75 (73.5)	.25
	CT	38 (17.2)	9 (13.0)	17 (16.7)	
	PET scan	3 (1.4)	1 (1.4)	1 (1.0)	
	Nuclear medicine	8 (3.6)	1 (1.4)	5 (4.9)	
	X-ray	4 (1.8)	0 (0.0)	4 (3.9)	

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: CT, computed tomography; HIV, human immunodeficiency virus; IV, intravenous; MRI, magnetic resonance imaging; PET, positron emission tomography; SD, standard deviation.

[a]Overall percentages are calculated out of the overall cohort.

[b]Only patients who had a spinal biopsy are included in the univariate analysis. One hundred seventy-three patients had biopsies done, but 2 patients had only histopathology and no cultures performed.

[c]*P* value calculated via logistic regression.

[d]Discrepancy in the total numbers out of the overall cohort due to exclusion of patients with unknown status in each category.

[e]Total percentage does not equal 100% due to the exclusion of patients without a biopsy in the calculation.

thoracic spine (30.4%). Of the 11 bone cultures, 1 (9%) was positive and grew *Candida albicans*, which correlated with blood culture results. Of the 15 disc cultures, 4 (26.7%) had a positive result: 2 *Staphylococcus epidermidis*, 1 *Staphylococcus hominis*, and 1 *Candida glabrata*. Two patients had both bone and disc cultures, but only 1 disc culture was positive. Histopathology was performed on 11/23 (47.8%) repeat biopsy patients. Three of 11 (27.3%) specimens were consistent with vertebral osteomyelitis/discitis. Normal tissue and other findings accounted for 54.5% and 18.2% of the tissue specimens, respectively.

Of the 221 patients in our cohort, 66 had a microbiologic diagnosis by blood culture alone, with a yield of 29.9%. The microbiologic yield of the first biopsy, including bone and disc cultures, was 36.9%. The general yield of the first biopsy (including bone or disc cultures or just histopathology) was 53.7%. The microbiologic yield of the second biopsy was 21.7%, and the general yield (including histopathology) of the second biopsy was 26.1% (6/23). Repeat biopsy resulted in a diagnosis in 3 of 23 (13.0%) patients when the first biopsy was nondiagnostic. In patients with a negative biopsy culture, histopathology added

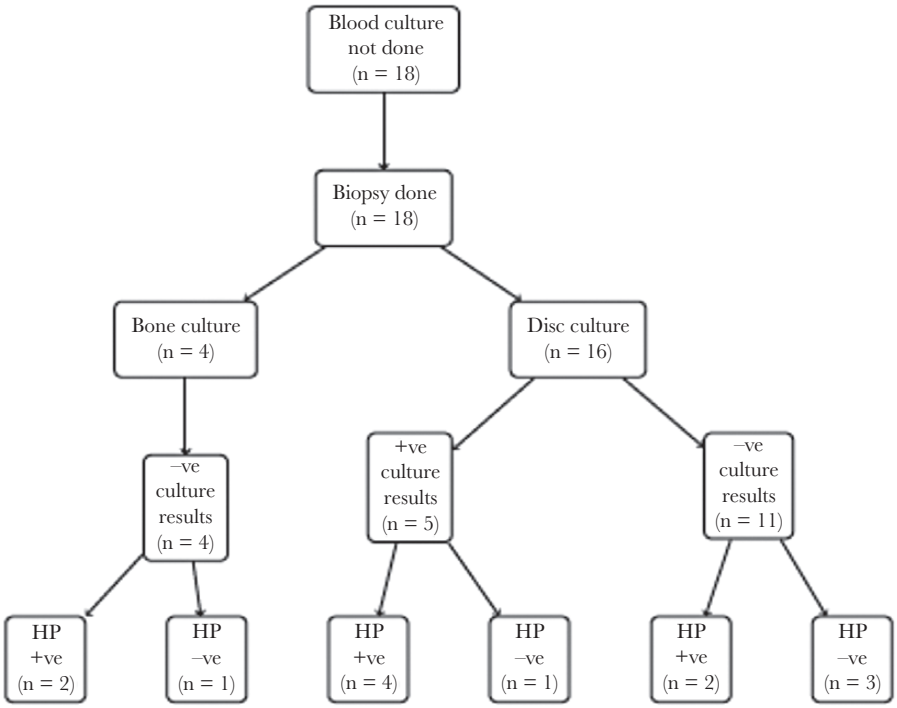

Figure 2. Patient biopsy findings in a subset of patients without blood cultures obtained. Abbreviations: -ve, negative; +ve, positive; HP, histopathology.

Table 2. Blood, Bone, and Disc Culture Results

Blood Culture Organisms	No. of Cultures (n = 112)	Bone Culture Organisms	No. of Cultures (n = 6)	Disc Culture Organisms	No. of Cultures (n = 66)
MSSA	37 (33.0)	MSSA	3 (50.0)	MSSA	14 (21.2)
MRSA	26 (23.2)	*Staphylococcus epidermidis*	2 (33.3)	MRSA	13 (19.7)
Streptococcus agalactiae	7 (6.3)	*Klebsiella pneumoniae*	1 (16.7)	*Staphylococcus epidermidis*	10 (15.2)
Staphylococcus epidermidis	5 (4.5)			*Pseudomonas aeruginosa*	3 (4.5)
Escherichia coli	4 (3.6)			*Staphylococcus lugdunensis*[a]	2 (3.0)
Enterococcus faecalis	3 (2.7)			*Staphylococcus saprophyticus*	2 (3.0)
Staphylococcus lugdunensis	3 (2.7)			*Enterococcus* spp[a]	2 (3.0)
Streptococcus pneumoniae	3 (2.7)			*Streptococcus agalactiae*	2 (3.0)
CoNS	2 (1.8)			CO_2-dependent *Streptococcus*	2 (3.0)
Pseudomonas aeruginosa	2 (1.8)			*Streptococcus anginosis*[a]	2 (3.0)
Candida albicans	2 (1.8)			*Escherichia coli*	2 (3.0)
Candida glabrata	1 (0.9)			*Cutibacterium acnes*	2 (3.0)
Candida parapsilosis	1 (0.9)			*Candida glabrata*	2 (3.0)
Other[b]	16 (14.3)			*Candida albicans*	1 (1.5)
				Staphylococcus haemolyticus[a]	1 (1.5)
				Streptococcus parasanguinis	1 (1.5)
				α-hemolytic *Streptococcus*	1 (1.5)
				Clostridium perfringens	1 (1.5)
				Klebsiella pneumoniae	1 (1.5)
				Enterobacter cloacae	1 (1.5)
				Veillonella spp	1 (1.5)

Abbreviations: CO_2, carbon dioxide; CoNS, coagulase-negative *Staphylococcus*; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

[a]In 4 instances the blood culture organism identified was discordant with the disc culture organism identified (in descending order as shown in the table): 1 with MRSA, 1 with *Klebsiella* spp, 1 with *Streptococcus sanguinis*, and one with *Staphylococcus lugdunensis*.

[b]One each of the following: *Aggregatibacter actinomycetemcomitans*, α-hemolytic *Streptococcus*, *Clostridium perfringens*, *Enterococcus* spp, *Enterococcus faecium*, γ-hemolytic *Streptococcus*, group G *Streptococcus*, *Staphylococcus auricularis*, *Staphylococcus cohnii*, *Streptococcus bovis*, *Streptococcus gordonii*, *Streptococcus mitis/oralis*, *Streptococcus parasanguinis*, *Streptococcus sanguinis*, *Klebsiella oxytoca*, *Pantoea agglomerans*.

an estimated 43%–45% yield in establishing the diagnosis of vertebral osteomyelitis/discitis by sensitivity analysis.

Using multivariate logistic regression analysis to identify predictors of a positive biopsy culture, the only significant association we observed was between blood culture and disc culture results (Supplementary Table 4). The adjusted odds ratio (OR) of a positive bone or disc culture with positive blood culture was 3.42 (95% confidence interval [CI], 1.63–7.20; $P = .0012$) (Supplementary Table 4). Receiving prior antibiotics was not statistically associated with decreased biopsy culture yield (OR, 0.49 [95% CI, .20 –1.19]; $P = .11$).

DISCUSSION

We performed a single-center retrospective study to evaluate the diagnostic approach to NVO, with a focus on image-guided biopsy. We elected to exclude patients who underwent open biopsy in order to maintain a standard for comparison among patients in our cohort and to evaluate a less invasive approach to diagnosis.

Obtaining a microbiologic diagnosis is crucial given the need for prolonged antimicrobial therapy with NVO and potential toxicities that can result from broad-spectrum antimicrobial use. The microbiological yield of blood culture alone was 29.9% in establishing the diagnosis of NVO; of those patients with positive blood cultures, 66/112 (58.9%) grew *S aureus* or *S lugdunensis*. In such cases, a vertebral biopsy is not required for diagnosis if imaging is consistent with vertebral osteomyelitis/discitis [1]. However, in our study all 3 of the patients with *S lugdunensis* bacteremia and 24/63 (38.1%) of those with *S aureus* bacteremia underwent spinal biopsy. This provided an opportunity to reform our institutional practice to reduce the morbidity from exposure to unnecessary invasive procedures.

In our study, the most interesting finding was the unexpected higher yield and sensitivity of disc compared to bone biopsies, even when we restricted the comparison to those without prior antibiotic exposure. Authors of the IDSA guideline recommend aspiration of fluid (eg, spinal abscess) and tissue biopsy when evaluating NVO [1]. We aimed to show improvement in diagnostic yield by including bone and disc tissue. Even though we had a limited number of patients with both types of specimens obtained, we had enough patients with either specimens obtained to make a conclusion about the yield. Our initial biopsy culture yield was 36.9% (bone culture yield, 13.6% vs 43.4% for disc culture). Our general initial biopsy yield (including histopathology) was 53.7% (93/173), in range of what has been described in the literature (19%–64%) [8–21]. Given that needle gauge is larger for bone biopsy sampling (11 or 13 gauge), it would be expected to yield more tissue for evaluation, which would theoretically improve the diagnostic yield; however, technical difficulty with obtaining bone biopsies might negatively affect the yield [8]. In our experience, we had fewer bone specimens obtained for culture and histopathology compared to disc. We postulate that ease of biopsy approach as well as biopsy window safety (disc vs transpedicular for bone) play a role in tissue sample obtained. We also noted a higher number of samples obtained for disc-only biopsies (2 or more in 15 cases) compared to bone (1 case with 2 samples) during initial biopsy episodes. Of those cases with more disc tissue obtained for culture, 5/15 (33.3%) had culture positive in only 1 of the 2 or 3 samples obtained. Obtaining multiple samples per biopsy is likely to improve the overall yield to overcome sampling error.

Some studies have evaluated the level of spinal biopsy in relation to diagnostic yield. Kornblum et al reported a lower diagnostic yield in biopsies of the thoracic spine (71%) compared to those from lumbar and sacral levels (90% and 92%, respectively) [22]. In other reports, spinal level had no significant effect on the diagnostic yield [11, 12]. Our results were similar, with the diagnostic yield being independent of level of biopsy (Table 1). In our cohort, the most common pathogen identified in biopsy cultures was *S aureus*, which accounted for 50% of the bone biopsy cultures and 44.8% of the disc biopsy cultures. This is consistent with prior studies reporting growth of *S aureus* in 31%–60% of biopsy specimens [7, 9, 12–16, 23–25].

The timing of antibiotic therapy can play a role in biopsy culture yield, with a heterogeneity of findings in the literature. Some studies demonstrated no significant difference in bacterial growth rates [12, 14, 21], while other studies showed that biopsies obtained without prior antibiotics can achieve microbiologic diagnosis in 50%–90% of cases [9, 15, 17]. In our univariate analysis, the only predictor of a positive biopsy culture was a positive blood culture (60.9% biopsy positive with positive blood culture vs 39.1% biopsy positive with negative blood culture; $P < .01$). However, we still agree with the IDSA guideline and conventional wisdom to delay administration of antibiotics in clinically stable patients prior to obtaining a vertebral biopsy for culture [1].

A systematic review and meta-analysis of the literature regarding biopsy yield for diagnosis of NVO will be useful but also limited by heterogeneity of studies, variety of methodologies, gold standards used, and lack of standardized approach to evaluation.

Two prior studies included both bone and disc culture yield [8, 19], while 4 studies included either only bone biopsies [7, 9, 12, 25] or only disc biopsies [11, 13, 23, 26] in their analysis. Several studies were not specific to which type of tissue was sampled for microbiologic analysis [14–18, 20, 22, 24, 27]. Only a handful of studies evaluated the sensitivity and specificity of the microbiologic and histopathologic yield [7, 8, 23, 26, 27]. In our study population, less than half (48.6%) of the patients had tissue sent for pathology and 56% of specimens tested were diagnostic of NVO. In some cases, the amount of tissue was inadequate and results were inconclusive (10.7%), likely due to sampling error.

Using histopathology of biopsies as the gold standard for testing culture characteristics was a strength in our study as there are few other studies that have evaluated the sensitivity and specificity relative to the histopathology of both bone and disc aspirates [7, 8, 23]. Histopathology can play an important role in diagnosis, especially when blood and tissue cultures are negative, but suspicion for vertebral osteomyelitis remains high. Similar to our approach and findings, Chang et al used histopathology as the gold standard for diagnosis in 102 patients, and reported endplate-disc biopsy yield of 19%, disk-only yield of 39%, and soft tissue biopsy yield of 44% (Table 3) [8]. Sehn and Gilula reported 113 cases that underwent microbiological and histopathological evaluation, and when considering either culture or pathology positive, 73/113 (64.6%) were positive, so pathology increased the diagnostic yield from 30.4% to 64.6% [11]. We found the general sensitivity of the initial biopsy episode culture to be 42.2% and specificity to be 80.0%; however, histopathology added an estimated 43%–45% diagnostic yield for NVO when initial biopsy cultures were negative. Table 3 summarizes sample studies in the literature.

If the first biopsy is not diagnostic (eg, grows skin flora), it is recommended to obtain a second biopsy to improve the yield and exclude organisms such as anaerobes, fungi, or mycobacteria, which are more difficult to grow or require special media [1]. Authors of the IDSA guidelines do not explicitly mandate bone and disc tissue sampling on the second biopsy, but suggest that pursuing a repeat image guided biopsy can improve the culture sensitivity [1]. In our study, 23 patients had a repeat biopsy, and the second biopsy had a microbiological yield of 21.7%, adding 13% overall yield to the first biopsy, as 3 of 23 patients had the diagnosis established on the second biopsy when the first biopsy was nondiagnostic. This increase in yield could improve patient care with regard to the ability for targeted antimicrobial therapy, to reduce potential drug reactions, and lower rates of *Clostridioides difficile* infection.

Our number of *Candida* infections was low. Similarly, Chew and Kline reported 9 cases of fungemia, among which 5 of the 9 also grew it on biopsy culture [23]. We were underpowered to make a generalization about the yield of spinal biopsy in *Candida* spondylodiscitis.

Our study is a large retrospective single-center case series with several inherent limitations. There was no uniform protocol in place to guide the diagnostic workup at the time of this study, and it was left to the discretion of the managing physician. There was inconsistent practice regarding the number and type of specimens obtained, as fewer bone cultures were obtained compared to disc cultures, and fewer adequate specimens for histopathology of either type of tissue compared to cultures obtained. This resulted in smaller sample sizes for culture test characteristic calculations. Biopsies may have been obtained from a location without living organisms, reducing the culture yield. We also did not evaluate the particular technique and needle type or size used by our interventional radiologists in their biopsy approach, nor the number of passes made to obtain tissue samples. It is also possible that diagnoses were missed as fungal and mycobacterial cultures were not routinely sent. Aside from blood cultures, we did not include in our analysis other sites of infections reported prior to biopsy. Neither did we evaluate presenting signs and symptoms, nor inflammatory markers such as erythrocyte sedimentation rate or C-reactive protein as predictors of culture yield.

To improve the diagnostic yield, we recommend holding antimicrobials in clinically stable patients with suspected NVO until blood cultures and 1 or 2 spinal biopsies are obtained. Waiting 48 hours after blood cultures are obtained is reasonable before a decision is made about the need for spinal biopsy. Disc tissue, ideally multiple samples, should be obtained via CT or fluoroscopically guided percutaneous aspiration for at least microbiological (aerobic and anaerobic) as well as histopathological analysis with each spinal biopsy, especially if prior antibiotics have been given. With advances in molecular diagnostics, bone or disc biopsy evaluation is recommended on a second biopsy if not performed initially with an extra bone and/or disc specimen kept for potential testing with broad-range bacterial polymerase chain reaction (PCR) [28]. We recommend waiting another 48 hours after the first spinal biopsy to decide on the need for a second biopsy if blood and initial spinal cultures remain negative and before starting empiric antimicrobials in clinically stable patients. Future prospective studies are needed to determine the best diagnostic modality, with incorporation of broad-range PCR coupled with DNA sequencing performed on bone tissue to supplement cultures and further aid in diagnosis in culture-negative cases, especially given the fact that many patients receive antibiotics before cultures can be obtained [29, 30].

In conclusion, blood cultures followed by culture of percutaneous biopsy of disc as well as histopathologic examination resulted in the highest diagnostic yield at our institution. Histopathology added to the diagnostic yield, especially in culture-negative specimens. Histopathology of bone had better yield than bone culture. A repeat biopsy added 13% to the diagnostic yield when the first biopsy was unrevealing, but it is still recommended as establishing a NVO diagnosis with microbiological confirmation is of utmost importance for appropriate antimicrobial use and improving clinical outcomes.

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.

Table 3. Review of Literature Regarding Diagnostic Evaluation of Vertebral Osteomyelitis/Discitis

Author [Reference]	Year	Country	Mean Patient Age (Range)	Study Sample Size	Microbiologic Yield of Blood, Bone, or Disc Culture	Sensitivity/Specificity of Microbiology or Histopathology	Gold Standard for Sensitivity Calculation
Fouquet et al [26]	1996	France	55.3 y (20–89 y)	120 patients 120 percutaneous biopsies	Disc (patients with symptoms after invasive procedure): 18/53 (34.0%) Disc (patients with septicemia): 17/28 (60.7%) Disc (patients with spontaneous infection): 17/39 (43.5%)	Microbiology: Sensitivity = 63% Specificity = 100% Histopathology: Sensitivity = 72% Specificity = 94%	Combined clinical, laboratory test, microbiological and histopathological criteria
Kornblum et al [22]	1998	USA	60 y (4–91 y)	103 patients 103 CT-guided biopsies	General biopsy[a]: 10/18 (55.5%)	Not mentioned	Not mentioned
Chew & Kline [23]	2001	USA	57.2 y (13–88 y)	92 patients 105 CT-guided disc aspirations	Disc: 39/105 (37.1%)	Microbiology: Sensitivity = 91% Specificity = 100% Histopathology: Sensitivity = 90% Specificity = 75%	Microbiology
Hadjipavlou et al [25]	2003	Greece	(17–81 y)	68 patients 71 biopsies	Bone: 15/24 (62.5%)	Not mentioned	Not mentioned
Rankine et al [15]	2004	United Kingdom	53 y (17 mo—79 y)	20 patients 20 biopsies	Blood: 6/20 (30.0%) General biopsy: 8/20 (40.0%)	Not mentioned	Not mentioned
Michel et al [7]	2006	Switzerland	Not mentioned	41 patients 41 vertebral biopsies	Bone: 11/41 (26.8%)	Microbiology: Sensitivity = 61% Specificity = 100% Histopathology: Sensitivity = 81% Specificity = 100%	Microbiology and histopathology
Hassoun et al [24]	2006	USA	56% >65 y	25 patients 17 biopsies	Blood: 11/25 (44.0%) General biopsy: 11/17 (64.7%)	Not mentioned	Not mentioned
Yang et al [18]	2008	Taiwan	63 y (27–88 y)	52 patients 32 CT-guided biopsies	General biopsy: 15/32 (47.0%)	Not mentioned	Not mentioned
Enoch et al [20]	2008	United Kingdom	60 y (1–81 y)	103 patients 98 CT-guided biopsies	General biopsy: 9/25 (36.0%)	Not mentioned	Not mentioned
De Lucas et al [17]	2009	Spain	58 y (1–88 y)	40 patients 46 CT-guided biopsies	General biopsy: 20/46 (43.0%)	Not mentioned	Not mentioned
Bhavan et al [9]	2010	USA	59.7 y (44–74 y)	70 patients 29 needle biopsies	Blood: 18/70 (26.0%) Bone: 14/29 (48.0%)	Not mentioned	Not mentioned
Nam et al [14]	2011	Korea	61.6 y (12–82 y)	57 patients 30 needle biopsies	General biopsy: 10/30 (33.3%)	Not mentioned	Not mentioned
Sehn & Gilula et al [11]	2012	USA	62 y (1–92 y)	297 patients 323 needle biopsies	Disc: 28/92 (30.4%)	Not mentioned	Not mentioned
Heyer et al [12]	2012	Germany	64.6 y (17–92 y)	159 patients 164 CT-guided biopsies	Bone: 40/127 (31.0%)	Not mentioned	Not mentioned
Garkowski et al [13]	2014	Poland	52 y (21–74 y)	11 patients 1 biopsy	Blood: 5/11 (45.4%) Disc: 1/1 (100.0%)	Not mentioned	Not mentioned
Garg et al [21]	2014	USA	Not mentioned	209 patients 213 biopsies	Biopsy culture: 16/84 (19.0%)	Not mentioned	Not mentioned
Kim et al [19]	2015	Republic of Korea	By biopsy site: Vertebral body: 68 y (56–76 y) Soft tissue: 65 y (53–73 y)	128 patients 136 biopsies	Blood: 52/136 (38.2%) Bone: 29/73 (39.7%) Disc/soft tissue: 40/63 (63.5%)	Not mentioned	Not mentioned

Table 3. Continued

Author [Reference]	Year	Country	Mean Patient Age (Range)	Study Sample Size	Microbiologic Yield of Blood, Bone, or Disc Culture	Sensitivity/Specificity of Microbiology or Histopathology	Gold Standard for Sensitivity Calculation
Chang et al [8]	2015	USA	59 y (15–90 y)	102 patients 111 biopsies	All biopsy: 44/122 (36.0%) Endplate-disc: 5/27 (19.0%) Disc-only: 24/61 (39.0%) Paravertebral soft tissue: 15/34 (44.0%)	All specimens: Sensitivity = 57% Specificity = 89% Endplate-disc: Sensitivity = 38% Specificity = 86% Disc only: Sensitivity = 57% Specificity = 89% Paravertebral soft tissue: Sensitivity = 68% Specificity = 92%	Histopathology
Foreman et al [27]	2017	Germany	70 y (29–94 y)	87 patients 102 biopsies	General biopsy: 29/102 (28.0%)	Microbiology: Sensitivity = 40% (29/73) Specificity = 100% (29/29) Combined microbiology and histopathology: Sensitivity = 60% (44/73) Specificity = 100% (29/29)	Combined clinical, microbiologic, and pathologic criteria
Giordan et al [10]	2019	Italy	64.7 y (16–89 y)	162 patients	Blood: 65/83 (78.3%)	Not mentioned	Not mentioned
Ang et al [16]	2019	Australia	59 y (41–77 y)	36 patients 40 biopsies	Blood: 7/36 (19.4%) General biopsy: 14/40 (35.0%)	Not mentioned	Not mentioned
Current study	2022	USA	60.2 y (27–94 y)	221 patients 173 biopsies	Blood: 112/203 (55.2%) Bone: 6/42 (13.6%) Disc: 66/152 (43.4%)	Initial bone culture[b]: Strict sensitivity = 30.0% (3/10) Strict specificity = 92.8% (13/14) General sensitivity = 27.3% (3/11) General specificity = 93.7% (15/16) Initial disc culture: Strict sensitivity = 56% (14/25) Strict specificity = 75.0% (15/20) General sensitivity = 50.0% (19/38) General specificity = 77.3% (17/22) Initial biopsy episode culture: General sensitivity = 42.2% (19/45) General specificity = 80.0% (28/35)	Histopathology

Abbreviations: CT, computed tomography; USA, United States.

[a]General biopsy = unspecified tissue specimen (bone or disc).

[b]Strict bone or disc culture sensitivity/specificity calculations include only those individual specific tissue types for culture and histopathology, while general bone or disc culture sensitivity/specificity calculations include histopathology of bone and/or disc in the numerator and denominator.

Notes

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References

1. Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis **2015**; 61:e26–46.
2. Issa K, Diebo BG, Faloon M, et al. The epidemiology of vertebral osteomyelitis in the United States from 1998 to 2013. Clin Spine Surg **2018**; 31:E102–8.
3. Waitman LR, Warren JJ, Manos EL, Connolly DW. Expressing observations from electronic medical record flowsheets in an i2b2 based clinical data repository to support research and quality improvement. AMIA Annu Symp Proc **2011**; 2011:1454–63.
4. Murphy SN, Weber G, Mendis M, et al. Serving the enterprise and beyond with informatics for integrating biology and the bedside (i2b2). J Am Med Inform Assoc **2010**; 17:124–30.
5. Harris PA, Taylor R, Thielke R, et al. Research Electronic Data Capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform **2009**; 42:377–81.
6. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software partners. J Biomed Inform **2019**; 95:103208.
7. Michel SCA, Pfirrmann CWA, Boos N, Hodler J. CT-guided core biopsy of subchondral bone and intervertebral space in suspected spondylodiskitis. Am J Roentgenol **2006**; 186:977–80.
8. Chang CY, Simeone JF, Nelson SB, et al. Is biopsying the paravertebral soft tissue as effective as biopsying the disc or vertebral endplate? 10-year retrospective review of CT-guided biopsy of discitis-osteomyelitis. Am J Roentgenol **2015**; 205:123–29.
9. Bhavan KP, Marschall J, Olsen MA, et al. The epidemiology of hematogenous vertebral osteomyelitis: a cohort study in a tertiary care hospital. BMC Infect Dis **2010**; 10:158.
10. Giordan E, Marton E, Scotton G, Canova G. Outcomes and risk factors for spontaneous spondylodiscitis: case series and meta-analysis of the literature. J Clin Neurosci **2019**; 68:179–87.
11. Sehn JK, Gilula LA. Percutaneous needle biopsy in diagnosis and identification of causative organisms in cases of suspected vertebral osteomyelitis. Eur J Radiol **2012**; 81:940–46.
12. Heyer CM, Brus LJ, Peters SA, Lemburg SP. Efficacy of CT-guided biopsies of the spine in patients with spondylitis—an analysis of 164 procedures. Eur J Radiol **2012**; 81:e244–9.
13. Garkowski A, Zajkowska A, Czupryna P, et al. Infectious spondylodiscitis—a case series analysis. Adv Med Sci **2014**; 59:57–60.
14. Nam KH, Song GS, Han IH, et al. Diagnostic value of biopsy techniques in lumbar vertebral spondylodiscitis: percutaneous needle biopsy and open biopsy. Korean J Spine **2011**; 8:267–71.
15. Rankine JJ, Barron DA, Robinson P, et al. Therapeutic impact of percutaneous spinal biopsy in spinal infection. Postgrad Med J **2004**; 80:607–9.
16. Ang MT, Wong GR, Wong DR, et al. Diagnostic yield of computed tomography–guided biopsy and aspiration for vertebral osteomyelitis. J Med Imaging Radiat Oncol **2019**; 63:589–95.
17. De Lucas E, M, González Mandly A, et al. CT-guided fine needle aspiration in vertebral osteomyelitis: true usefulness of a common practice. Clin Rheumatol **2009**; 28:315–20.
18. Yang SC, Fu TS, Chen LH, et al. Identifying pathogens of spondylodiscitis: percutaneous endoscopy or CT-guided biopsy. Clin Orthop Relat Res **2008**; 466:3086–92.
19. Kim CJ, Kang SJ, Choe PG, et al. Which tissues are best for microbiological diagnosis in patients with pyogenic vertebral osteomyelitis undergoing needle biopsy? Clin Microbiol Infect **2015**; 21:931–35.
20. Enoch DA, Cargill JS, Laing R, et al. Value of CT-guided biopsy in the diagnosis of septic discitis. J Clin Pathol **2008**; 61:750–53.
21. Garg V, Kosmas C, Young P, et al. Computed tomography guided percutaneous biopsy for vertebral osteomyelitis: a department's experience. Neurosurg Focus **2014**; 37:E10.
22. Kornblum MB, Wesolowski DP, Fischgrund JS, Herkowitz HN. Computed tomography-guided biopsy of the spine: a review of 103 patients. Spine **1998**; 23:81–5.
23. Chew FS, Kline MJ. Diagnostic yield of CT-guided percutaneous aspiration procedures in suspected spontaneous infectious discitis. Radiology **2001**; 218:211–14.
24. Hassoun A, Taur Y, Singer C. Evaluation of thin needle aspiration biopsy in the diagnosis and management of vertebral osteomyelitis (VO). Int J Infect Dis **2006**; 10:486–7.
25. Hadijpavlou AG, Kontakis GM, Gaitanis JN, et al. Effectiveness and pitfalls of percutaneous transpedicle biopsy of the spine. Clin Orthop Relat Res **2003**; 411:54–60.
26. Fouquet B, Goupille P, Gobert F, et al. Infectious discitis diagnostic contribution of laboratory tests and percutaneous discovertebral biopsy. Rev Rhum **1996**; 63:24–9.
27. Foreman SC, Schwaiger BJ, Gempt J, et al. MR and CT imaging to optimize CT-guided biopsies in suspected vertebral osteomyelitis/discitis. World Neurosurg **2017**; 99:726–34.
28. Mayo Medical Laboratories. Broad range bacterial PCR and sequencing. **2021**. https://www.mayocliniclabs.com/test-catalog/Overview/65058/. Accessed 10 May 2021.
29. Fuursted K, Arpi M, Lindblad BE, Pedersen LN. Broad-range PCR as supplement to culture for detection of bacterial pathogens in patients with a clinically diagnosed spinal infection. Scand J Infect Dis **2008**; 40:772–7.
30. Fenollar F, Pierre-Yves L, Raoult D. Usefulness of broad-range PCR for the diagnosis of osteoarticular infections. Curr Opin Rheumatol **2008**; 20:463–70.