Skeletal Radiology (2023) 52:39–46
https://doi.org/10.1007/s00256-022-04131-4

SCIENTIFIC ARTICLE

Image-guided percutaneous bone biopsy for pediatric osteomyelitis: correlating MRI findings, tissue pathology and culture, and effect on clinical management

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Received: 21 January 2022 / Revised: 18 July 2022 / Accepted: 18 July 2022 / Published online: 26 July 2022

Abstract

Bone biopsy remains the gold standard for diagnosis of osteomyelitis while MRI results in a radiologic diagnosis that generally precedes biopsy. This study's purpose is to examine the diagnostic yield and effect of biopsy results on clinical management in children with suspected osteomyelitis and positive MRI findings. A retrospective review was performed at a tertiary care children's hospital. Search of the EMR and radiology PACS identified patients below 18 years who underwent bone biopsy with interventional radiology for osteomyelitis and had positive MRI findings for osteomyelitis prior to biopsy. Data was collected on patient demographics, MRI findings, biopsy procedural details, tissue culture, histopathology results, and clinical management before and after biopsy. Changes in management were categorized as antibiotic type/quantity, duration, or diagnosis. A total of 82 biopsies in 79 patients with suspicion for osteomyelitis and positive MRIs prior to biopsy were performed over 5 years from 2014 to 2019. All biopsies were successful and sent for tissue culture. 22/82 biopsies (27%) yielded positive cultures. Of those with tissue cultures, 16/22 (72%) resulted in change in clinical management. Of all biopsies, 18/82 (22%) resulted in a change in management (15 antibiotic, 1 duration, 2 diagnosis). The 2 changes in diagnosis included one biopsy done which was positive for cancer and a second which was found to not demonstrate osteomyelitis on histology. In the pediatric population, bone biopsy is a reasonably low morbidity procedure. However, there is a relatively low rate of positive tissue cultures even with MRI findings suspicious for osteomyelitis. Approximately 1 in 5 biopsies resulted in a change in clinical management, mostly in antibiotic selection. Bone biopsy may have a higher clinical impact in pre-specified circumstances.

Keywords Bone biopsy · Osteomyelitis · Magnetic resonance imaging · Pediatrics

Introduction

Osteomyelitis is inflammation of the bone and/or bone marrow, typically by bacterial infection. The most identified bacterial pathogen in pediatric osteomyelitis is *Staphylococcus aureus*, which is responsible for at least 70% of cases in children, while *Kingella kingae*, *Streptococcus pneumoniae*, and *Salmonella* are also cited as frequent causes [1]. In the pediatric population, particularly in skeletally immature children, untreated osteomyelitis has potential for significant morbidity related to physeal and epiphyseal cartilage injury [2]. As such, prompt diagnosis and therapy are of essence.

The diagnosis of osteomyelitis can be made with a combination of clinical features of inflammation, imaging studies, positive identification of a causative organism, and/or response to empiric antimicrobial therapy [3].

While plain radiographs are frequently performed as the initial imaging study in the evaluation of a child with musculoskeletal pain, they are usually normal or inconclusive until the late stages of osteomyelitis [4]. In contrast, magnetic resonance imaging (MRI) has been well established as a tool in the early diagnosis and management of osteomyelitis, with

This research was previously presented as a stand-alone abstract at Society of Pediatric Radiology (SPR) 2020.

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80–100% and 70–100% sensitivity and specificity, respectively [5]. Given this high sensitivity, a negative MRI exam makes the diagnosis of osteomyelitis unlikely [6]. When there are findings suggestive of more extensive disease, such as abscess or bone devascularization (sequestra), MRI not only prompts the indication for operative management but also can guide the surgeon's approach to treatment [3]. In cases where intervention such as surgery or percutaneous biopsy is performed prior to MRI, it has been shown that the resultant imaging findings of the invasive procedure do not affect the diagnostic efficacy of MRI, and thus, MRI remains a powerful tool for downstream diagnostic evaluation when necessitated [7]. Given this knowledge, MRI findings can also help clinicians decide if the pursuit of repeat bone biopsy is warranted as well.

Despite the utility of MRI, isolation of a causative organism remains the gold standard for confirming the diagnosis of osteomyelitis in many practices [1]. Peripheral blood cultures infrequently result in positive identification of a causative organism; thus, tissue sampling of the affected bone is often pursued. Bone tissue samples can be obtained as a surgical excisional biopsy, but studies have shown that image-guided percutaneous biopsy, most commonly by a musculoskeletal or interventional radiologist, is an established procedure that is safe and effective in children [8]. Despite the high technical success rate in obtaining a tissue sample, previous studies demonstrated that positive microbiologic cultures are only obtained in 28–34% of general biopsies and could not identify significant factors associated with positive or negative results [9, 10].

Optimization of procedures while minimizing morbidity is crucial, especially in the pediatric population. Iteratively, bone biopsy devices and techniques have been optimized; however, complications such as hemorrhage and persistent pain at biopsy site are notable in the pediatric population. The need for general anesthesia in younger patients introduces additional procedural risk. Given the inherent procedural risks in the pediatric patient population, non-invasive approaches should be prioritized.

The purpose of this study was to evaluate the clinical impact of bone biopsy in pediatric osteomyelitis patients. The study examined treatment changes based on positive MRI findings alone and biopsies performed following positive MRI findings. The study is of clinical importance because bone biopsy has the potential for greater morbidity in the pediatric population.

Materials and methods

Case selection

With institutional review board approval, a retrospective review was performed with waiver of informed consent. A filtered search of the patient archiving and communication system (PACS) for MRI reports on pediatric patients (less than 18 years of age) containing the keywords "osteomyelitis," "osteo," and "infection" identified a total of 4358 MRIs performed with from October 1, 2014, to September 30, 2019. These studies were manually filtered to include only musculoskeletal studies ordered for suspicion of first-time osteomyelitis in the affected bone (not follow-up exams) with study impressions supporting the diagnosis of osteomyelitis. All studies were interpreted by board-certified pediatric radiologists, the majority of whom had additional subspecialty training in pediatric musculoskeletal imaging. After applying all filters, a total of 465 positive MRIs from 458 patients were included in the study. Seventy-nine of those patients underwent a total of 82 bone biopsies in the interventional radiology department. All diagnostic imaging and all biopsies were performed within a single tertiary free-standing pediatric system.

Clinical algorithm and biopsy technique

Requests for biopsy from the interventional radiology department were made in the form of an interventional radiology consultation at the discretion of the referring providers, usually according to local evidence-based guidelines developed for children greater than 2 months of age. If acute osteomyelitis was suspected based on initial clinical evaluation and blood tests for inflammatory markers, blood cultures were drawn, and treatment was initiated with antibiotics. MRI was often ordered at the same time as antibiotic initiation. If MRI results were positive for osteomyelitis and blood cultures had not yielded an organism within 24 h, the guidelines indicated that patients should then undergo biopsy. Surgical biopsy and debridement were performed in cases with subperiosteal abscess or septic arthritis. Otherwise, the referring provider could request that biopsy be performed percutaneously by the interventional radiology department. The workflow (Fig. 1) offered a streamline approach for clinical decision-making.

Prior to biopsy, verbal and written informed consent was obtained. General anesthesia, if indicated, was provided by the anesthesiology department and separately consented for. A target was identified based on the provided MRI, favoring regions with safe access path and greater extent of signal abnormality (Fig. 2A). Most biopsies were performed using a coaxial technique using the Arrow® OnControl® (NC) powered bone lesion biopsy system (Fig. 3A, B), in which an 11-gauge access needle was inserted into the region of interest under fluoroscopic and ultrasound guidance (Fig. 2B, C) (TeleFlex, Morrisville, NC). If needed, a powered driver could be attached to the access needle to facilitate needle placement into the bone via a drilling mechanism. After confirmation

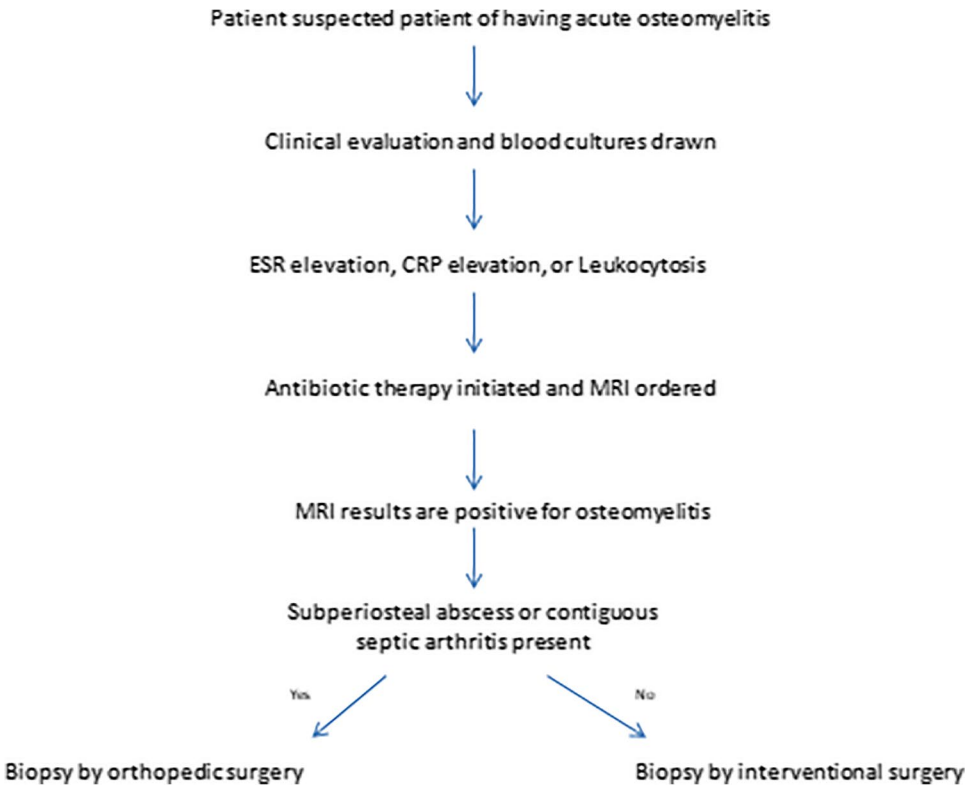

Fig. 1 Flow chart representing the steps involved in clinical decision-making and approach to biopsy

of appropriate access needle placement, the inner stylet of the needle was removed, and a 13-gauge coring needle was inserted through the access needle to obtain tissue samples. Repeat samples could be obtained as needed through the access needle. At least one sample was obtained successfully obtained in each case. Samples, gross photographs provided (Fig. 3C), were submitted fresh for analysis.

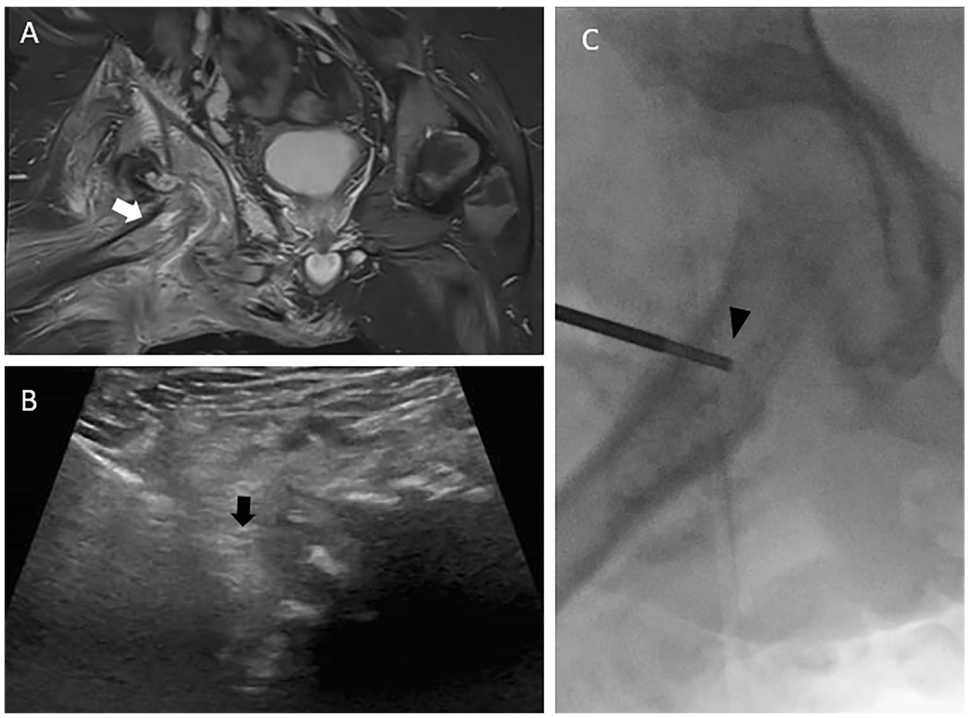

Fig. 2 **A** Coronal MRI T1 post-contrast sequence demonstrating abnormal enhancement and signal changes in the right femur (white arrow) suspicious for osteomyelitis in a child presenting with clinical suspicion of hip infection. **B** Ultrasound image demonstrating needle placement (arrow) within inflammatory changes and cortical irregularity at the proximal femur. **C** Fluoroscopic image demonstrating a 13-gauge core biopsy needle inserted coaxially through an introducer needle at the targeted site

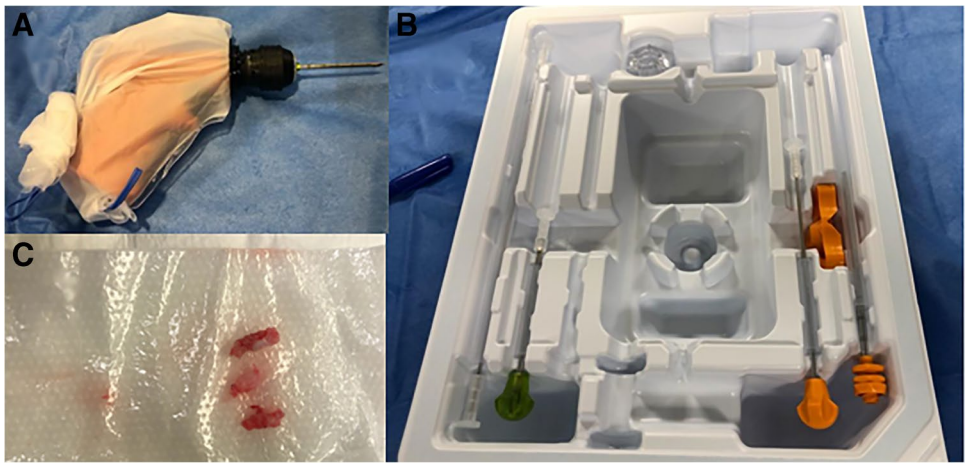

Fig. 3 **A** Photograph of Arrow® OnControl® (NC) powered bone lesion biopsy system. **B** Additional image of biopsy system. **C** Photograph of gross sample

Data collection

For all cases included, the electronic medical record was used to collect information regarding patient age, patient sex, affected bone, whether the patient received antibiotics prior to MRI, and whether there was a change in management after MRI (such as initiation of antibiotics or change in antibiotic dosing regimen). Affected bones were classified as small or large. Small bones included tarsal/carpal bones, mandible, and ribs. Large bones included long bones, pelvic bones, vertebrae, and sacrum.

In cases in which percutaneous bone biopsy was performed, additional data was collected, including pre-biopsy antibiotic therapy (if applicable), microbiologic culture results, histopathology results, and whether there was a change in management after biopsy. Changes in management were identified based on review of provider documentation in the electronic medical record. Changes were categorized as either antibiotic type/dosage, duration of treatment, or change in medical therapy due to alternate diagnosis.

Data analysis

In all cases, analysis was performed to evaluate the effects of patient age and bone size on change in management after MRI, initiation of antibiotics, and post-bone biopsy. In cases involving bone biopsy, evaluation was performed to determine if age, prior positive blood cultures, size of bone, and being on antibiotics prior to biopsy had an association with positive tissue cultures and changes in clinical management. Further analysis was performed to determine if there was a statistically significant difference in rates of change in clinical management between diagnoses made with MRI only and diagnoses made with MRI and biopsy.

Statistical analysis was performed using Statistical Analysis System (SAS) software (version 9.4, Cary, NC). All non-grouped data were assessed for normality. Generalized linear models and general linear mixed methods were used to compare groups of interest. These methods were considered suitable for analysis of correlated data due to repeated measures on subjects. *p*-values of less than 0.05 were considered significant.

Results

Demographics

A total of 465 positive MRI exams from 458 children were evaluated from the study period. A total of 268 were male and 197 were female. Ages ranged from 17 days to 17.8 years, with a mean of 7.9 years and a median of 8 years. The most affected sites were in the lower extremity: the feet (85 patients), tibia (84 patients), pelvis (81 patients), and femur (73 patients). Eighty-five percent of patients either started or continued antibiotics after positive MRI for osteomyelitis.

Effect of positive MRI

The likelihood of management change was significantly higher in patients with positive MRI compared to those undergoing biopsy (65.3% vs 21.9%, OR = 6.60, 95%CI = 3.75, 11.61, $p < 0.0001$) (Table 1)**.** Only 18 cases out of 465 (4%) resulted in a change in management due to biopsy results. Neither rates of biopsy nor rates of change in management after positive MRI were significantly associated with age, sex, or bone size.

Biopsy after positive MRI

Of all positive MRI cases, a total of 82 bone biopsies in 79 patients were performed. All biopsies were successful, sent for tissue culture, and without associated complications.

Table 1 Rates of management change in cases with positive MRI findings, with and without biopsy. $p < 0.01$

Management change	Positive MRI without biopsy ($N = 383$)	Positive MRI and biopsy ($N = 82$)
No	133 (34.7%)	64 (78.1%)
Yes	250 (65.3%)	18 (21.9%)

Twenty-five of 82 biopsies (30%) were negative for osteomyelitis by both histology and culture, but these negative results did not change antibiotic management. Antibiotics were continued as a result of high clinical/imaging suspicion for osteomyelitis. This would support rationale wherein biopsy may not impact management when clinical and imaging suspicion are already high and driving clinical decision-making. Twenty-two of 82 biopsies (27%) yielded positive tissue cultures. Organisms are listed in Table 2. Four of the 22 positive cases (18%) had prior positive blood cultures which were concordant with the positive tissue cultures.

The factors which were significantly associated with positive tissue culture results were older age, positive blood cultures before biopsy, and positive histopathology (Table 3). Bone size, presence of sinus tract or abscess on MRI, and antibiotic therapy prior to biopsy did not have a significant association with positive tissue cultures.

Of all biopsies, 18/82 (22%) resulted in a change in clinical management (15 antibiotic, 1 duration, 2 diagnosis). Of those with positive tissue cultures, 16/22 (72%) resulted in a change in clinical management. In the two cases which had changes in management but negative tissue cultures, one had narrowing of antibiotics based on the negative culture result and the other was initiated on empiric antibiotics based on the histologic diagnosis of osteomyelitis.

Factors which were significantly associated with a change in management after biopsy were age, positive histology, and positive culture (Table 4). Bone size, blood culture results, presence of sinus tract or abscess, and antibiotic therapy prior to biopsy did not have a significant association with a change in management after biopsy.

Discussion

Evidence Based Outcome Center (EBOC) guidelines at the primary institution offered a workflow for osteomyelitis evaluation in suspected patients. Upon suspicion of osteomyelitis, less invasive procedures such as blood culture and MR imaging were indicated and gradually directed practitioners to perform bone biopsy if the initial non-invasive steps were non-conclusive. For the purposes of this study, these guidelines were not used as a framework due to revisions to the guidelines concomitant to data collection. In addition, some patients received biopsies before receiving the recommended precedent work-up. This led to some patients receiving biopsies even after having positive blood cultures.

Another diagnosis to be aware of is chronic non-bacterial osteomyelitis (CNO) which is an auto-inflammatory bone disorder that manifests similarly to infectious osteomyelitis. Diagnostic work-up is similar with radiographs taken that may show sclerotic, mixed, or lytic lesions [12]. A classic radiograph can be done to rule out fracture first and may show sclerotic, lytic, or mixed lesions which can lead to a diagnosis of CNO [12]. MR imaging is the ideal imaging tool to diagnose and monitor CNO. Short Tau Inversion Recovery (STIR) sequence helps localize inflammation while T1 sequences with fat saturation highlight changes in nearby tissue to give an extent of the damage [13]. Biopsy can help diagnose it along with monitoring for changes once medication is started.

Biopsy may also be warranted to diagnose Ewing's sarcoma and rule out osteomyelitis. Typically, open biopsy is associated with increased diagnostic accuracy [14]. Radiographic evidence can help make the decision to pursue biopsy due to Codman's triangle, a soft tissue mass, or periosteal reaction.

Table 2 Organism yield from positive tissue cultures

Organism	Cases ($N = 22$)	Cases with matching blood cultures ($N = 4$)
Methicillin-sensitive *Staphylococcus aureus*	11	2
Methicillin-resistant *Staphylococcus aureus*	2	1
Group A *Streptococcus pneumoniae*	2	0
Salmonella	1	0
Klebsiella	1	1
Enterobacter	1	0
Eikenella	1	0
Propionibacterium	1	0
Gram-negative rods, not specified	1	0
Multiple organisms	1	0

Table 3 Factors that affect tissue culture results in patients undergoing biopsy after positive MRI

	Positive cultures ($N=22$)	Negative cultures ($N=60$)	Odds ratio (with 95% confidence)	p
Mean age (years)	9.76 (±5.26)	7.86 (±5.12)	1.11 (1.01–1.21)	0.03
Bone size				
Small	2 (9%)	12 (20%)	2.47 (0.51–12.1)	0.26
Large	20 (91%)	48 (80%)		
Blood cultures before biopsy				
None	1 (5%)	13 (22%)	N/A*	<0.01
Negative	17 (77%)	47 (78%)		
Positive	4 (18%)	0		
Sinus tract/abscess				
No	18 (82%)	52 (87%)	1.47 (0.4–5.57)	0.57
Yes	4 (18%)	8 (13%)		
Histology				
Negative	9 (41%)	40 (67%)	3.26 (1.17–9.07)	0.03
Positive	13 (59%)	20 (23%)		
Antibiotics before biopsy				
No	1 (5%)	8 (13%)	4.11 (0.31–54.6)	0.28
Yes	21 (95%)	52 (87%)		

*Unable to calculate due to absence of cases with both positive blood cultures and negative/absent tissue cultures

Our study illustrates that bone biopsy typically leads to low impact on the final treatment plan for patients with osteomyelitis. Biopsy is typically done after MRI is obtained for further work-up but is often an intrusive step that rarely changes the treatment plan. Our study found that in 465 patient biopsies done, only 18 (4%) resulted in a change

Table 4 Factors that affect change in management in patients undergoing biopsy after positive MRI

	Change in management ($N=18$)	No change ($N=64$)	Odds ratio (with 95% confidence)	p
Mean age (years)	9.94 (±5.25)	7.93 (±5.14)	1.13 (1.03–1.25)	0.01
Bone size				
Small	4 (22%)	11 (17%)	1.38 (0.38–4.99)	0.63
Large	14 (78%)	53 (83%)		
Blood cultures before biopsy				
None	1 (6%)	13 (20%)	0.08 (0.01–1.29)*	0.08
Negative	15 (83%)	49 (77%)	0.31 (0.04–2.39)*	0.26
Positive	2 (11%)	2 (3%)		
Sinus tract/abscess				
No	15 (83%)	55 (84%)	1.25 (0.3–5.18)	0.76
Yes	3 (17%)	9 (14%)		
Histology				
Negative	6 (33%)	43 (67%)	4.44 (1.44–13.7)	<0.01
Positive	12 (67%)	21 (33%)		
Tissue culture				
Negative	2 (11%)	58 (91%)	77.33 (14.2–421)	<0.01
Positive	16 (89%)	6 (9%)		
Antibiotics before biopsy				
No	1 (6%)	8 (13%)	2.35 (0.28–19.4)	43
Yes	17 (94%)	56 (87%)		

*Compared to positive blood cultures

in clinical management. This percentage correlates with existing research on this topic. Hoang et al. did an analysis of 115 patients who presented with signs of osteomyelitis. MRI found that 95 out of 113 (84.1%) were positive for osteomyelitis prior to bone biopsy with 16 (14.2%) being possible osteomyelitis and 2 (1.8%) having no osteomyelitis. Bone biopsy was completed in the patient population and 0% had a change in management and clinical improvement with adjustments based on blood culture and physical exam findings [15]. The findings here further support the concept that the impact of bone biopsy is quite minimal. Said et al. similarly performed an analysis of 60 patients with osteomyelitis who underwent a work-up analogous to the ones performed for this cohort. Positive cultures were obtained in 11 out of 60 biopsies (18%) with modification to the treatment plan occurring in only 3 patients (5%) [16]. This finding agrees with the result we received in our institutional analysis.

At our institution, based on evidence-based clinical guidelines, percutaneous biopsy is generally only reserved for cases with positive MRI, without evidence of subperiosteal abscess or septic arthritis, and without positive organism yield within 24 h of blood culture. Such a strategy emphasizes the importance of early initiation of antibiotics in the treatment of osteomyelitis over bone biopsy. Given the potential morbidity from delayed treatment, children presenting with probable osteomyelitis (such as those with positive MRI findings) who have not undergone bone biopsy should be managed in the same manner as children with osteomyelitis confirmed by positive blood or bone cultures—with initiation of empiric antimicrobial therapy [11]. While peripheral blood cultures are often drawn before initiation of antimicrobial therapy to maximize the potential for a positive yield, prior initiation of empiric antibiotics has not been shown to significantly affect tissue culture results [12, 13]. Antibiotic therapy was not associated with negative tissue cultures in our evaluation, but our study is not sufficiently powered to address the issue of the therapy's potential impact on biopsy.

Early evaluation with MRI is critical in directing the management of acute osteomyelitis. A positive result may lead to initiation of antibiotics or other change in clinical management. In our study, 65% of cases with positive MRI resulted in a change in clinical management, defined as any change in the antimicrobial treatment regimen (initiation of antibiotic or duration of planned antibiotic therapy). Secondary findings of subperiosteal abscess or joint involvement indicate a need for surgical treatment, while absence of such findings can suggest that antibiotic therapy alone will be sufficient for treatment. In cases which do not require surgical management, percutaneous biopsy is often considered. Although safe and technically effective, percutaneous bone biopsy introduces additional procedural and anesthetic risk to pediatric patients, as well as economic costs. As such, the benefits of biopsy (regarding a potential change in management) should be carefully weighed against the risks. Overall, when considering all cases with suspected osteomyelitis based on positive MRI, only 18 out of 465 (4%) had a change in management following bone biopsy. Rates of positive tissue culture correlated most strongly to a biopsy-related change in management, but tissue cultures were only positive in 27% of cases. The factors which correlated with higher tissue culture yield were prior positive blood cultures, positive histopathology, and older age. In cases with prior positive blood cultures, the same organism was identified in both specimens and there was no significant association with change in management. It is unclear why patients with older age would have a higher likelihood of positive cultures. Other studies have shown that the presence of purulence or a sinus tract may play a role, but this was not seen in our study [12]. In addition to the early initiation of antibiotics, other factors may also result in lower yield of microbiologic cultures, regardless of the tissue source. For example, recent studies suggest that *Kingella kingae* may play a greater role in pediatric osteomyelitis than previously thought. Unfortunately, isolation of *Kingella* requires specific culture techniques or nucleic acid amplification assays that are not routinely performed in the evaluation of pediatric osteomyelitis, and thus, it is not commonly identified as a causative organism [14]. In addition to the factors affecting biopsy yield, the study is limited by the inherent biases of a retrospective analysis. Moreover, positive blood cultures were not an exclusion criteria in this study but we can consider it for future studies. In conclusion, given its high impact on clinical management, MRI appropriately serves as the primary diagnostic modality in osteomyelitis. When positive, bone biopsy results can provide additional clinical impact but should only be used as a troubleshooting tool because of the low yield of organisms and the added procedural risk (especially in the pediatric population). We view the utilization of invasive biopsy as additive to patient care for those patients where treatment has been engaged without significant improvement or in those scenarios wherein MRI/clinical signs and symptoms are indeterminate. We advise against routine performance of bone biopsy and these findings emphasize the utility of following the clinical algorithms and need for appropriate patient selection prior to biopsy.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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