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The utility of echocardiography in paediatric patients with musculoskeletal infections and bacteremia

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Abstract

Purpose The clinical utility of echocardiography in the setting of a positive blood culture in paediatric patients presenting with osteomyelitis (OM) and/or septic arthritis (SA).

Methods Retrospective review between 2013 and 2019: Patients < 18 years with OM, SA or combined infection (OM+SA) were included. Patients were excluded for immunodeficiency, loss of follow-up or penetrating infection. Charts with positive blood cultures were reviewed for echocardiography on that admission. Demographic variables were compared utilizing the Student's *t*-test and Fisher's exact test. A multivariable linear regression model was constructed to examine the association between echocardiography and length of stay, controlling for age, sex, fever, white blood cell (WBC) on admission, antibiotic administration and surgery performed.

Results Of 157 patients with OM, SA or combined infection, 44 had a positive blood culture. In all, 26 had an echocardiogram, and none showed endocarditis. Echocardiography was independently associated with a 6.2-day length of stay increase. WBC count and surgical intervention demonstrated a trend toward significance in length of stay, with each WBC unit increase associated with a 0.53-day increase. Surgical intervention was associated with an average 6.3-day length of stay decrease.

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Conclusion No patient had a positive echocardiogram, and no changes in management were initiated. However, an echocardiogram increased stay by 6.2 days. In addition to costs associated with increased stay, patients were billed between \$1460 and \$1700 per echocardiogram. The utility of echocardiograms in the setting of bacteremia associated with musculoskeletal infections in the paediatric population should be re-examined, and guidelines should be updated to reflect the cost-benefit analysis.

Level of Evidence: III

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Keywords: echocardiography; musculoskeletal infection; bacteremia; infectious disease; osteomyelitis

Introduction

Echocardiography is an invaluable clinical tool, which allows for the assessment of structural abnormalities of heart tissue and valves, flow irregularities, blood clots, masses or vegetation within cardiac tissue. In the paediatric population, it is often used to investigate possible congenital anomalies. It is frequently obtained in patients with positive blood cultures to evaluate for the presence of vegetation within the cardiac tissue or heart valves, indicative of infective endocarditis (IE).¹ The incidence of IE in children with no known heart disease or structural anomalies is rare (0.05 to 0.12 cases per 1000 annual admissions).²⁻⁵ The incidence is higher in children with underlying congenital heart disease, ranging from 0.6-6 cases per 1000 annual admissions.²⁻⁵ However, an estimated 8-10% of pediatric IE cases occur in children without any structural abnormalities.^{5,6} As such, while it remains uncommon, the presence of IE should be queried in certain clinical scenarios even in individual with no known heart disease.

The American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines recommend the use of transesophageal (TEE) or transthoracic (TTE) echocardiography to rule out IE, "when there is a strong clinical suspicion of IE with negative blood cultures or in patients with persistent unexplained bacteremia".⁷ Prior to the publication of these guidelines, Sable et al⁸ con-

cluded that “in the absence of physical findings or persistently positive blood cultures, echocardiography is a low-yield study and is unlikely to aid in the diagnosis of IE in children”. However, neither these authors nor the ACC/AHA provide specific recommendations for the use of echocardiography in the setting of musculoskeletal (MSK) infection.

In the absence of clinical guidelines pertaining specifically to the use of echocardiography in the setting of MSK infections, many physicians default to the general guidelines for presumed IE in the setting of bacteremia.⁹ Consequently, echocardiography is often ordered reflexively in patients with bacteremia and an underlying MSK infection, despite the relatively low incidence of IE in children. This is particularly common in academic centres where care for patients with MSK infections is divided amongst multiple services, including orthopaedics, general paediatrics and paediatric infectious disease, all of which have competing interests and variable understandings of the appropriate use of echocardiography.

The goal of this study was to assess the incidence of and utility for obtaining a reflexive echocardiogram in a paediatric population with positive blood cultures in the setting of MSK infection. We hypothesize that there is no diagnostic benefit of reflexive echocardiography in this patient population and that the guidelines for ordering such a test should be clarified.

Patients and methods

An institutional review board-approved retrospective review was completed. A paediatric population of patients ≤ 18 years old with culture/biopsy-proven diagnoses of osteomyelitis (OM), septic arthritis (SA) or combined infection (OM+SA) that were admitted to a single institution between February 7, 2012 and February 1, 2019 was included. Patients were excluded for immunodeficiency, history of penetrating trauma or loss of follow-up. The records of patients fulfilling inclusion criteria were screened for blood culture results during the hospital admission. The record of patients with positive blood cultures were then further assessed to identify those in whom an echocardiogram had been ordered and completed during the same admission. In patients with documented echocardiography, results were recorded.

Multiple demographic and clinical variables were recorded. Demographic and clinical variables were compared in a univariate fashion between groups utilizing the Student's *t*-test for continuous variables and the Fisher's exact test for categorical variables. A multivariable linear regression model was constructed to examine the association between the performance of an echocardiogram and hospital length of stay, while controlling for age,

sex, fever on admission, white blood cell (WBC) count on admission, early antibiotics (within 24 hours of admission) and whether or not surgical debridement was performed.

Results

Of 157 patients with a diagnosis of OM, SA or both, 44 patients had at least one positive blood culture during admission. Of those, 30 were diagnosed with OM, 11 SA, and three combined OM+SA. Some had multiple infection sites, but in total, locations were as follows: 11 tibia/fibula, ten femur, five feet, three sacro-iliac joints, three hips, three elbows, two shoulders, two humeri, two knees, two ankles, one clavicle, one wrist and one pelvis. Of the 44 with positive blood cultures, 26 (59%) underwent echocardiography (Group 1) and 18 (41%) did not (Group 2). Groups were comparable demographically, with the mean age of each group being 9.3 years (range 2-18) and 11.3 years (range 7-17), respectively ($p = 0.22$); 73.1% and 72.2% of each group were male, respectively ($p = 1.00$) (Table 1). Echocardiogram was ordered between 0 and 11 days (median 4 days) after admission in Group 1. Two patients underwent two or more echocardiograms due to equivocal results on the first test.

Of the 26 patients who underwent an echocardiogram (Group 1), not one exam resulted in a positive finding of endocarditis or cardiac vegetation. There were six cases in which regurgitation across normal cardiac valves were noted, 50% of which were previously known conditions. In one patient, a possible patent foramen ovale was identified. However, none of these generic findings resulted in alterations in overall clinical management.

There was no difference between patients who underwent echocardiogram (Group 1) and those who did not (Group 2) in terms of vitals or lab values on presentation (Tables 2 and 3). Also, of note, the duration of fever was not significantly different between those who received an echocardiogram (mean 4.3 days, range 2-12) and those who did not (mean 5 days, range 1-7). Additionally, there were no significant differences in blood pathogens in either group. In Group 1, there were 15 cases of methicil-

Table 1 Baseline comparison between bacteremic patients with and without echocardiogram

Variable	Echo performed		p-value for comparison*
	No	Yes	
Total n	18	26	
Mean age, yrs	11.3 (7-17)	9.3 (2-18)	0.22
Male, %	72.2	73.1	1.00
Febrile on presentation, %	44.4	38.5	0.76
Antibiotics within 24 hrs, %	83.3	84.6	0.30
Surgery performed, %	55.6	61.5	0.75

*groups were compared statistically with use of the Student's *t*-test for continuous variables and the Fisher's exact test for categorical variables

lin-susceptible *Staphylococcus aureus* (MSSA), nine cases of methicillin-resistant *Staphylococcus aureus* (MRSA) and two cases of coagulase-negative-staphylococci. In Group 2, there were 14 cases of MSSA, two cases of MRSA and two cases of *Streptococcus pyogenes*. Further, there was no significant difference between groups in terms of time-to-antibiotics upon admission nor response-to-antibiotics, as demonstrated by similar drops in C-reactive protein during admission (Tables 2 and 3).

The performance of an echocardiogram was independently associated with an increase in estimated length of stay by 6.2 days (95% confidence interval 0.2 to 12.3) after controlling for all other variables (Table 4). WBC count on admission and the performance of surgery (irrigation and debridement of the affected site) also demonstrated a trend toward significance in their associations with length of stay. With each one unit increase in WBC,

there was an associated estimated 0.53 day increase in length of stay ($p = 0.093$). Conversely, surgery was associated with a mean 6.3 day decrease in length of stay ($p = 0.056$) (range 5-51 days), although neither trend reached statistical significance.

Discussion

Paediatric patients with OM may be admitted to orthopaedics teams at some institutions, and some surgeons may be less familiar with the management of paediatric bacteremia. Therefore, it is important for orthopaedic surgeons to understand an evidence-based management and work-up for OM and associated bacteremia in paediatric patients. Our series of 44 patients presenting with bacteremia specifically in the setting of an MSK infection demonstrates that acute reflexive echocardiogram in the absence of known cardiac history is without utility – there were no positive echocardiography results and, as a result, no changes in clinical management. The similarities in demographics and presentations between those who underwent echocardiogram and those that did not further demonstrate that echocardiograms may have been ordered without regard to published guidelines and without any clear rationale guiding ordering practices. While these ordering practices may be limited to our centre, previous research has identified similar patterns of over-utilization in other settings.¹⁰

In light of our findings, reflexive echocardiogram in the setting of MSK infections should be reconsidered. In the setting of a known source, such as an MSK infection, there is limited to no role for echocardiogram unless the patient's clinical course is that of a non-responder to proper antibiotic/surgical management. In fact, previous research has demonstrated that a confirmed source of infection is a negative predictive factor for the diagnosis of IE.¹¹ Further, in a series of 155 patients, Liu et al¹¹ reported that individuals without positive predictive factors (i.e. clinical manifestations of IE or prior history of IE) were

Table 2 Vitals on presentation

Variable, mean (sd)	Echo performed		p-value for comparison*
	No	Yes	
Temperature	100.46 (1.44)	99.99 (1.69)	0.32
Systolic blood pressure	113.37 (13.32)	113.22 (18.78)	0.98
Diastolic blood pressure	71.26 (8.23)	68.74 (13.48)	0.44
Heart rate	110.26 (21.97)	121.70 (31.14)	0.15
Respiratory rate	24.35 (7.23)	25.70 (7.94)	0.56

* groups were compared statistically with use of the Student's *t*-test for continuous variables

Table 3 Infectious labs on presentation

Variable, mean (sd)	Echo performed		p-value for comparison*
	No	Yes	
CRP on admission	14.33 (7.44)	12.3 (8.31)	0.40
Days to CRP drop	2.79 (2.35)	2.82 (1.47)	0.92
ESR on admission	51.28 (29.52)	51.22 (25.89)	0.99
WBC on admission	11.93 (6.93)	13.69 (6.87)	0.41
Platelets on admission	276.06 (95.85)	312 (260.06)	0.55

* the *t*-test was used to calculate p values
CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; WBC, white blood cell count

Table 4 Multivariable linear regression model for the outcome of length of stay

Variable	Coefficient	Standard error	95% confidence interval		p-value
			Lower	Upper	
Age, yrs	0.387	0.303	-0.234	1.007	0.212
Male	3.413	3.264	-3.273	10.100	0.305
Febrile on admission	0.636	2.912	-5.330	6.602	0.829
WBC count on admission	0.531	0.305	-0.094	1.155	0.093 [†]
Received antibiotic within 24 hrs	4.757	5.539	-6.590	16.104	0.398
Surgery performed	-6.281	3.149	-12.732	0.170	0.056 [†]
Echo performed	6.241	2.939	0.221	12.261	0.043 [†]

* $p < 0.10$

[†] $p < 0.05$

Coefficients on age and WBC are those associated with a one unit increase in the explanatory variable. Coefficients on the remaining categorical variables are those associated with the presence of the factor (with absence of the factor as the reference)
WBC, white blood cell

found to have a 0% probability of IE diagnosed on TTE. Similarly, those with one or more negative predictive factors, including a known source of infection, had near-zero probability of diagnosing IE on TTE. A recent retrospective review of 300 echocardiograms in 291 children with suspected IE found little evidence to support the use of TTE in patients with no clinical signs of IE based on the Modified Duke's Criteria and 0 to 1 positive blood cultures.⁵ These authors similarly recommended that in the absence of clinical manifestations of IE, an echocardiogram should not be recommended, even in the setting of bacteremia. However, this study did not specifically address the use of TTE in the setting of MSK infections, and the practice of reflexive echocardiography remains widespread in this setting despite this and other reports of poor sensitivity of TTE in diagnosing IE.^{5,12,13}

In the case of non-responders – patients with persistent bacteremia despite standard antibiotic therapy – the work-up may need to be more extensive. Both MSSA and MRSA OM are generally treated with antibiotics for 20 to 30 days, depending on clinical improvement the susceptibility of the causal organism. Clindamycin and first generation cephalosporins are usually used. Intravenous therapy is generally recommended initially, and transition to an oral agent is advised to minimize the risks associated with prolonged intravenous access.^{14,15} If a child fails this therapy, alternative infection sources may be considered, and a TTE may be indicated at that point. A similar standard may be applied to the treatment of septic arthritis and combined infections.

With regard to the association between length of stay and echocardiogram, further investigation is warranted. The retrospective nature of this study precludes us from concluding that echocardiogram directly increases length of stay, as there are significant confounding factors to consider. First, the times between order of echocardiogram and final report were variable. There was a range of a zero to five-day delay between ordering the study and obtaining the final report, possibly delaying discharge in some but not all who had an echocardiogram. Interestingly, in comparing groups, there were no more non-responders in Group 1 than in Group 2, as reflected by a similar drop in C-reactive protein (CRP) in both groups (Table 3), negating the idea that the increased length of stay is reflective of non-responder status. The marked increase in length in stay could also be attributed to variability in the hospital teams and physicians involved in the care of each patient. As the dataset includes subjects spanning a six-year time period, not all patients were treated by the same team(s), and the difference in length of stay likely reflects differences in work pace and/or variable criteria for discharge. However, echocardiogram was evenly ordered throughout the six-year time period without any notable trend toward increased or decreased utilization of echo-

cardiography. As such, there is no evidence to suggest that there were any temporal trends in work-up/discharge speed, nor is there any evidence to suggest trends associated with certain physicians' time-to-discharge as a confounder for increased length of hospital stay. However, our data only included quantitative measures such as labs, vitals and imaging results, and could not account for subjective clinical findings that could have driven both the ordering of an echocardiogram or a prolonged evaluation and stay.

Furthermore, it should be acknowledged that while there were no significant differences in vitals amongst groups, differences in certain vitals measurements such as heart rate and blood pressure are not directly comparable given the broad age range included in this study. Therefore, these may not be reliable measures for signs of infection severity or response to treatment. However, the lack of a difference is noteworthy, as it does not offer any potential basis for variable echocardiography ordering practices. Additionally, other hospital and patient factors such as insurance status, bed availability or tendencies to delay weekend or holiday discharges to the next working day could have affected length of stay; however, these variables should, theoretically, affect all patients equally. Last, compared with studies with larger cohorts, a relatively small sample size may amplify minor differences between groups. Nonetheless, while the increased length of stay is likely multifactorial, it certainly is inclusive of delays directly associated with the performance and interpretation of the echocardiogram itself.

In addition to a lack of clinical findings, the financial burden of these tests is not insignificant. While coverage discrepancies among insurance providers exist, our institution's billing department charged patients between \$1460 and \$1700 per echocardiogram. Moreover, some patients had more than one echocardiogram during their admission. Further, the cost of one night's stay at our institution can be greater than \$12 000 per night, based upon level of care provided. Given the association between echocardiography and increased length of stay, there may be an additional \$74 400 in incurred costs associated with one echocardiogram. While this dollar amount is specific to our institution, the burden on any medical system is not insignificant.

While our results are quite striking, our study has several limitations that must be noted. First, the retrospective nature of this study imparts limitations in delineating causative conclusions that by administering an echocardiogram for a patient, his/her length of stay in the hospital is increased by more than six days. Resultantly, only associative conclusions can be drawn, and these conclusions must be considered with caution. Further, despite the fact that this is the largest study specifically evaluating echocardiogram in this setting, our sample size was relatively small. In-

ing the power of this study would provide opportunity to strengthen the results and recommendations of this study. Additionally, the locality and institution could be considered limitations as the study population was composed of patients who presented to an academic centre where many physicians-in-training participate in care. These trainees are often less experienced with narrowing differential diagnoses and may order more testing than a community paediatrician. The setting is particularly noteworthy as a recent study reported hospital location was a stronger predictor of ordering an echocardiogram than IE clinical risk factors in the work up of *Staphylococcus aureus* bacteremia.^{11,12} Last, our location may be a limitation to the transferability of our conclusions due to practice variability and the commonality of bacteremia as well as infection patterns depending on location. However, despite these limitations, this study remains salient as it is, to our knowledge, the first report to investigate the utility of echocardiography specifically in the setting of MSK infections, a relatively common diagnosis in the pediatric population.

While echocardiography remains relevant for patients with 'persistent, unexplained bacteremia,' as per the current ACC/AHA guidelines, echocardiogram should not be considered in the setting of bacteremia with a known MSK infection unless: 1) the patient has a known cardiac history; 2) the patient is demonstrating clinical signs of IE; and/or 3) the patient has not responded clinically or serologically (50% decrease in CRP within 48 hours) to appropriate antibiotic coverage and surgical management. An update to the ACC/AHA guidelines addressing this specific population reflecting our findings will decrease unnecessary testing, length of stay and overall healthcare spending.

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COMPLIANCE WITH ETHICAL STANDARDS

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OA LICENCE TEXT

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ETHICAL STATEMENT

Ethical approval: No human or animal testing was undertaken in this work. This work was completed in compliance with the Helsinki declaration. This work was granted IRB approval from our institution: IRB# 19-000256.

Informed consent: Was not required.

ICMJE CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

AT: Drafted the initial manuscript, Reviewed and revised the manuscript, Approved the final manuscript as submitted.

DB: Carried out the initial analyses, Reviewed and approved the final manuscript as submitted.

VH: Carried out the initial analyses, Reviewed and approved the final manuscript as submitted.

AdeStM: Critically reviewed and revised the manuscript, Approved the final manuscript as submitted.

PK: Critically reviewed and revised the manuscript, Approved the final manuscript as submitted.

MS: Critically reviewed and revised the manuscript, Approved the final manuscript as submitted.

RMT: Conceptualized the study, Coordinated and supervised data collection, Reviewed and revised the manuscript, Approved the final manuscript as submitted.

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