Original Clinical Article

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The effect of antibiotic timing on culture yield in paediatric osteoarticular infection

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Abstract

Purpose To assess the influence of antibiotic timing on surgical culture yield in paediatric patients with haematogenous osteoarticular infection.

Methods All patients aged 0 to 15 years admitted to a National Children's Hospital with the diagnosis of acute, haematogenous, osteoarticular infection (osteomyelitis and/or septic arthritis) between June 1997 and December 2016 were retrospectively analyzed. Only patients with positive blood cultures undergoing surgery for culture and debridement were included. Patients were allocated into pre-treatment and post-treatment groups, according to whether they received antibiotics before or after surgical cultures were obtained. Outcomes measured included baseline variables, treatment characteristics and surgical culture yield.

Results A total of 131 patients were included; 107 patients in the pre-treatment group and 24 patients in the post-treatment group. There was no significant difference with respect to patient age (p = 0.870), white blood cell count (p = 0.197), ethnicity (p = 0.203) or infection multi-focality (p = 0.883) between the two groups.

The administration of systemic antibiotics prior to obtaining surgical cultures had no clinically significant effect on surgical culture yield (rate of positive surgical cultures, 85% (pre-treatment) *versus* 54.2% (post-treatment); p = 0.002).

Within the pre-treatment group, there was no significant difference in duration of pre-surgical antibiotic treatment between patients who had positive or negative surgical cultures (mean duration, 45.9 hours (positive cultures) *versus* 47.9 hours (negative cultures); p = 0.743).

Conclusion In paediatric patients with acute, haematogenous, osteoarticular infection, antibiotic administration before surgery does not decrease surgical culture yield. Our results suggest that paediatric patients presenting with suspected osteoarticular infection should receive appropriate systemic antibiotics promptly after blood cultures are obtained.

Level of Evidence Level III - retrospective case-control study

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Keywords: paediatric musculoskeletal infection; culture yield; antibiotic timing; osteoarticular infection; osteomyelitis; septic arthritis

Introduction

Acute paediatric hematogenous osteoarticular infection (AHOI) is relatively common. Significant regional variation exists in the epidemiology of AHOI, with especially high reported rates in New Zealand when compared with other first world countries. This was shown in 2015 by Crawford et al[1] with an incidence in New Zealand of 1:4000 and a disproportionate overrepresentation among indigenous New Zealand Maori and Pacific Island people, compared with rates in the United States of 1:5000.[1-3]

Targeted antibiotic therapy and judicious surgical debridement remains the current standard of care for paediatric patients presenting with AHOI, however, the optimal culture strategy is yet to be identified.

Some clinicians prefer withholding antibiotics until local operative cultures can be obtained, with the aim of increasing culture yields, however, others argue that deep osteoarticular collections are relatively avascular and preoperative systemic antibiotics will, therefore, not affect surgical culture yield. It is well established that antibiotics achieve their minimum bactericidal concentrations promptly in synovial fluid following administration,[4,5] with more variable bone penetration reported.[5-7] This poses a theoretical risk of antibiotic administration reducing local culture yields, however, whether this is seen in clinical

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practice, is not yet established. Recent literature suggests pre-treatment with antibiotics does not reduce local culture yields in paediatric populations,[8-13] however, adult literature is conflicting,[14-17] with a recent large study proving the contrary.[17] Unfortunately, many published studies are significantly limited due to the potential of misdiagnoses. Patients with negative blood cultures who subsequently have negative surgical cultures, for example, may represent a diagnosis other than AHOI, significantly confounding any subsequent conclusions. Very few studies have addressed this issue by only including patients with proven hematogenous infections, such as only including patients with positive blood cultures. Furthermore, few studies have included data on the exact duration of pre-surgical antibiotic administration.

The purpose of this study is to determine the influence of antibiotic timing on culture yield, length of hospital admission and number of operative interventions required in paediatric patients with AHOI. The authors' hypothesis is that administration of antibiotics prior to obtaining local tissue or synovial fluid cultures, does not reduce culture yield.

Patients and methods

Methodological considerations

All patients aged 0 to 15 years presenting to Starship Children's Hospital, with a diagnosis of AHOI between 01 June 1997 and 31 December 2016, were identified from electronic hospital records. A retrospective analysis of clinical records was then performed. From this population, only patients with positive blood cultures who underwent surgery for culture and debridement of their osteoarticular infection were included in the study. At our institution all cases of septic arthritis are managed with surgical washout. In patients with osteomyelitis, the indications for surgical intervention include subperiosteal collections or associated abscesses. Patients with chronic osteomyelitis (defined by presence of pathological features, including sequestrum and/or involucrum), previous surgical intervention with insertion of metalware or foreign material, post-traumatic infections, open fractures and those with insufficient data to conduct analyses were all excluded from the study. For patients with repeat presentations for the same infection, only the first acute episode was included. All tissue and aspirate samples collected underwent microscopy, culture, gram stain and direct smear.

Included patients were allocated in to pre-treatment and post-treatment groups, according to whether they received antibiotics before or after surgical cultures were obtained, respectively. The two patient groups were then compared with respect to baseline variables (demographic data, site(s) of infection, serological markers of infection), treatment characteristics (duration of hospital admission, number of surgical interventions, duration of antibiotic administration) and surgical culture yield. Patients were further stratified according to ethnicity, to reflect the established propensity for musculoskeletal infection seen among indigenous New Zealand Maori and Pacific Island people.[1-3]

Statistical analysis

Statistical comparisons were made between the two patient groups in regard to the aforementioned confounding and outcome variables using chi-squared tests, Fisher's exact tests, independent *t*-tests and Mann-Whitney U tests as appropriate. The rates of positive cultures were compared statistically between the two groups using chi-squares or Fisher's exact tests. A multivariate logistical regression model was also used to identify the independent contribution of the putative confounding demographic, clinical features and the timing of antibiotic administration on the presence of positive cultures. A two-sided p-value (< 0.05) was taken to indicate statistical significance.

Results

Between 01 June 1997 and 31 December 2016, 131 patients were identified for the study that satisfied the inclusion and exclusion criteria. Of these patients, 107 received antibiotics prior to the obtainment of local operative tissue or synovial fluid cultures (pre-treatment) and 24 received antibiotics after cultures were obtained (post-treatment).

Baseline variables

There was no statistically significant difference between both groups with respect to age (mean age 7.7 years (0.03 to 14.90) (pre-treatment) *versus* 7.7 years (0.40 to 14.90) (post-treatment); p = 0.870), gender (p = 0.354), or ethnicity (p = 0.203). Demographic data is further depicted in Table 1.

There was no significant difference in rates of multifocal infections on presentation between the pre- and post-treatment groups (p = 0.883).

Table 1 Patient demographic data

Variable*	Pre-treatment (n = 107)	Post-treatment (n = 24)	p-value
Patient age (yrs)	7.7 (0.4 to 14.9)	7.7 (0.03 to 14.9)	0.870
Male gender	73 (*68.2*)	14 (*58.3*)	0.354
Ethnicity			0.203
New Zealand European	38 (*35.5*)	4 (*16.7*)	
Maori	34 (*31.8*)	8 (*33.3*)	
Pacific Islander	3 (*2.8*)	2 (*8.3*)	
Other	32 (*29.9*)	10 (*41.7*)	

*continuous data are presented as mean (range) and categorical data as number of patients (percentage of group of patients)

Regarding serological markers of infection on presentation, the pre-treatment group had higher C-reactive protein (CRP) (mean 189.8 mg/L (SD 106.4) (pre-treatment) *versus* 126.5 mg/L (SD 120.2) (post-treatment); p = 0.008), however, no significant difference existed between both groups in absolute white blood cell count (WBC) (mean 15.0 x 10^9/L (SD 6.7) (pre-treatment) *versus* 12.4 x 10^9/L (SD 4.5) (post-treatment); p = 0.197), age-specific WBC (proportion above age-specific reference range, 58.9% (pre-treatment) *versus* 54.2% (post-treatment); p = 0.490) or erythrocyte sedimentation rate (mean 57.8 mm/hr (SD 30.3) (pre-treatment) *versus* 45.6 mm/hr (SD 22.5) (post-treatment); p = 0.111). Details on infection characteristics are further depicted in Table 2.

Sites of infection and radiographic outcomes

A total of 97 patients underwent MRI with all demonstrating radiographic evidence of osteomyelitis. In 79 patients who underwent MRI, subperiosteal collections were identified and were the indication for operative intervention. In a further four patients undergoing MRI, deep submuscular collections were identified and were the indication for operative intervention. In seven patients an ultrasound scan was performed and demonstrated subperiosteal collections, serving as the indication for surgical debridement. In eight patients a bone scan was performed and confirmed the diagnosis of osteomyelitis. Site of infection data is presented in Table 3.

Treatment characteristics

There was no statistically significant difference between both groups in admission durations (mean 29.2 days (SD 24.3) (pre-treatment) *versus* 25.5 days (SD 21.4) (post-treatment); p = 0.332), number of operative interventions (mean 3.2 (SD 2.2) (pre-treatment) *versus* 2.6 (SD 2.0) (post-treatment); p = 0.157) or total duration of antibiotic treatment (mean 51.0 days (SD 18.0) (pre-treatment) *versus* 45.8 days (sd 16.6) (post-treatment); p = 0.196).

Within the pre-treatment group, there was no significant difference in duration of pre-surgical antibiotic administration between patients who had positive or negative surgical cultures (mean duration 45.9 hours (SD 53.8) (positive cultures) *versus* 47.9 hours (SD 56.8) (negative cultures); p = 0.743).

Table 2 Patient infection characteristics

Variable*	Pre-treatment (n = 107)	Post-treatment (n = 24)	p-value
Infection type			0.011
Osteomyelitis (OM)	49 (*45.8*)	4 (*16.7*)	
Septic arthritis (SA)	12 (*11.2*)	7 (*29.2*)	
SA + OM	46 (*43.0*)	13 (*54.2*)	
Multifocal infection	16(*15.0*)	4 (*16.7*)	0.883
CRP (mg/L)	189.8 (21.0 to 461.0)	126.5 (7.3 to 361.0)	0.008
WBC (absolute, 10^9/L)	15.0 (3.2 to 31.9)	12.4 (8.0 to 96.0)	0.197
WBC (age-specific)†	63 (*58.9*)	13 (*54.2*)	0.490
ESR (mm/hr)	57.8 (2 to 129)	45.6 (8 to 96)	0.111
Organism			0.716
MSSA	88 (*82.2*)	21 (*87.5*)	
MRSA	10 (*9.3*)	2 (*8.3*)	
Streptococcus pyogenes	4 (*3.7*)	0	
Streptococcus agalactiae	3 (*2.8*)	0	
Streptococcus pneumonia	2 (*1.9*)	1 (*4.2*)	

*continuous data are presented as mean (range) and categoric data as number of patients (percentage of group of patients)

†number of patients above age-specific reference ranges

CRP, C-reactive protein; WBC, white blood cell count; ESR, erythrocyte sedimentation rate; MSSA, methicillin-sensitive *Staphylococcus aureus*; MRSA, Methicillin-resistant *Staphylococcus aureus*

Table 3 Site of infection data

Osteomyelitis		Septic arthritis	
Site	Number*	Site	Number*
Femur	48	Hip	51
Pelvis	28	Knee	19
Tibia	27	Ankle	10
Radius and/or Ulna	10	Shoulder	5
Humerus	6	Elbow	3
Calcaneus	5	Subtalar	3
Fibula	4	Sacroiliac	1

*data presented as number of isolated events and regional involvement. Bilateral involvement considered as separate events

Surgical culture yield

The administration of systemic antibiotics prior to obtaining surgical cultures had no clinically significant effect on surgical culture yield (rate of positive surgical cultures, 85% (pre-treatment) *versus* 54.2% (post-treatment); p = 0.002) (Fig. 1). There was no statistically significant difference between both groups from time of culture obtainment to culture growth (mean 122.3 hours (SD 74.8) (pre-treatment) *versus* 125.8 hours (SD 44.9) (post-treatment); p = 0.543). Of the 131 patients included, culture method included tissue and synovial fluid sampling in 43 patients, tissue sampling alone in 70 patients and synovial fluid sampling alone in 18 patients. Methicillin-sensitive *Staphylococcus aureus* was the most common organism causing infection, affecting 82.2% of patients in the pre-treatment group and 87.5% of patients in the post-treatment group. No significant differences existed between both groups with respect to rates of specific organisms causing infections (p = 0.490), as detailed in Table 2.

Multivariate analysis

Due to the CRP differences between both groups at baseline, a multivariate analysis was undertaken using a logistical regression model to control for other variables and identify any independent risk factors which predict local tissue or synovial fluid culture yields, admission duration or number of operative interventions required.

Using this method, CRP on presentation (odds ratio (OR) 1.011; 95% confidence interval (CI) 1.004 to 1.018; p = 0.001) and those receiving antibiotics prior to obtainment of local tissue or synovial fluid cultures (OR 0.0043;

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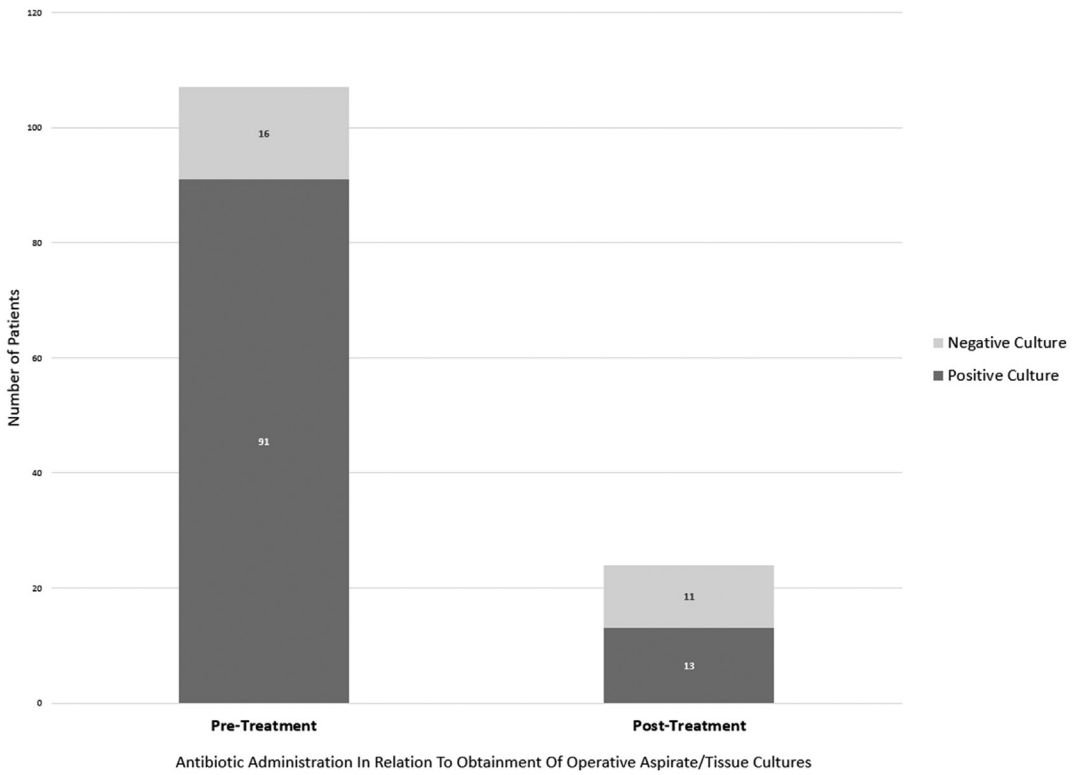

Fig. 1 Relationship between timing of antibiotic administration and surgical culture yield outcomes.

95% CI 3.390 to 1.041; p = 0.043), were identified as significant independent risk factors for development of positive cultures.

CRP (p = 0.001), absolute WBC (p = 0.049) and the coexistence of septic arthritis and osteomyelitis (p < 0.001) were all identified as significant independent predictors of hospital admission duration. CRP (p = < 0.001) and the presence of a multifocal infection (p = 0.042) were both identified as significant independent predictors of number of operative interventions.

Discussion

The results of this study demonstrate that in paediatric patients presenting with AHOI, antibiotic administration prior to obtaining surgical cultures does not reduce surgical culture yield. Among patients receiving antibiotics prior to obtaining surgical cultures, there was no correlation between increasing duration of pre-surgical antibiotic administration and rates of negative cultures. Furthermore, CRP on presentation appears to be the most reliable predictor of culture yield, admission duration and number of operative interventions required for paediatric patients with AHOI.

Our findings are consistent with several previous studies looking at antibiotic timing and culture yield in paediatric patients.[8-13] Benvenuti et al[12] reported on 113 patients with musculoskeletal infections, with positive culture rates reported at 55% before administration of antibiotics and 89% after administration of antibiotics. Section et al[13] reported on 869 children with musculoskeletal infections and found no association between antibiotic exposure and reduced site-of-infection culture rates. Zhorne et al[10] reported on 67 children with acute hematogenous osteomyelitis undergoing bone biopsies and found no difference in culture rate between patients who received antibiotics prior and those who did not (70% *versus* 63%, respectively). They did, however, report a trend towards longer duration of antibiotic pre-treatment in the group of patients who developed negative cultures. Ratnayake et al[8] reported on 67 patients with osteomyelitis, with culture positivity rates of 84% in patients who were pre-treated with antibiotics and 80% of patients who had no prior antibiotic exposure. These authors concluded that antibiotic treatment should not be delayed for obtainment of operative cultures. Floyed and Steele[9] conducted a retrospective study of 85 patients with osteomyelitis, reporting that pre-treatment with antibiotics was not a discriminating factor in patients who developed negative site-of-infection cultures, with 8% of culture negative patients having been pre-treated, and 10% of culture positive patients having been pre-treated. McNeil et al[11] reported on 250 cases of acute hematogenous osteomyelitis, with no significant difference in rates of culture positivity between patients

who were pre-treated with antibiotics and those who had antibiotics delayed (74.8% *versus* 73.7%, respectively). It is important to note, however, that the aforementioned studies all include patients with positive and negative blood cultures on presentation, raising the possibility that patients with negative blood cultures and site-of-infection cultures may represent a misdiagnosis of infection, and results should, therefore, be interpreted with caution. We see it as a significant strength of our study to have only included patients with positive blood cultures, decreasing the potential impact of misdiagnoses.

Results from previous studies on adult populations have been conflicting,[14–17] with some larger studies reporting reduced surgical culture yields in patients receiving antibiotics prior. Al-Mayahi et al[17] recently reported on 2740 patients with orthopaedic infections, 1167 who received antibiotics prior to operative cultures and 1573 who were not pre-exposed to antibiotics. They reported significantly higher rates of negative culture yields in the group who were pre-treated with antibiotics compared with those who were not (19% *versus* 6%, respectively). This study, and many previous studies looking at adult populations, comprise a significant proportion of prosthetic joint infections and implant-associated infections, resulting in perhaps limited applicability to paediatric populations with AHOI.

The limitations of the present study include its retrospective, non-randomized nature, which introduces an inherent risk of bias. This is importantly seen in the fact that the mean CRP on presentation was not equivalent between the two patient groups at baseline. Multivariate analysis was conducted to account for this variation, however, prospective randomized studies are likely to yield more robust results. Secondly, this study did not include clinical findings, which often influence decision-making with respect to timing of antibiotic administration, and may reveal differences between the two patient groups that were not identified by objective data. Thirdly, while this study was undertaken at a national children's hospital serving a large multicultural population, it lacks the geographic and demographic variability which would make these results generalizable to other regions, especially given the relatively low rates of methicillin-resistant *Staphylococcus aureus* in our population.

Conclusion

In this retrospective study of 131 paediatric patients with acute, hematogenous, osteoarticular infection, we have found that antibiotic administration prior to surgery does not decrease surgical culture yield. To our knowledge, this is the largest comparative study of paediatric patients with proven haematogenous infection published to date. Our results suggest that paediatric patients presenting with suspected osteoarticular infection should receive appropriate systemic antibiotics promptly after blood culture are obtained. Antibiotic delay to facilitate greater surgical culture yield appears to be unwarranted.

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COMPLIANCE WITH ETHICAL STANDARDS

FUNDING STATEMENT

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ETHICAL STATEMENT

Ethical approval: This study was approved by the Central Health and Disability Ethics Committee, New Zealand: No. 16/NTA/205.

Informed consent: Due to the retrospective nature of this study, the need for informed consent was waived by the Committee.

ICMJE CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

M. van der Merwe: Study design, literature review, ethical approval application, data collection, data interpretation, primary author.
K. Rooks: Study design, data collection, data interpretation, co-authorship.
H. Crawford: Study supervisor, study design, manuscript review.
C.M.A. Frampton: Statistical analysis and data interpretation.
M.J. Boyle: Study supervisor, study design, co-authorship and manuscript review.

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