Laboratory Abnormalities in Children Undergoing Outpatient Therapy for *Staphylococcus aureus* Acute Hematogenous Osteomyelitis: Should We Worry?

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ABSTRACT

Introduction. Recent PIDS practice guidelines for acute hematogenous osteomyelitis (AHO) advocate for regular laboratory monitoring for adverse drug events. Data are limited however with respect to the frequency or clinical impact of antibiotic-related laboratory abnormalities (ARLA) in pediatric AHO. We reviewed the experience with ARLA in children undergoing treatment for *S. aureus* AHO.
Methods. Cases of *S. aureus* AHO in children were reviewed from 2011-2020. Eligible cases were those 1) discharged to complete therapy at home (IV or oral), 2) with baseline complete blood count (CBC), creatinine and AST/ALT obtained during the hospitalization and 3) at least one CBC, creatinine, and/or AST/ALT measurement in the outpatient setting while receiving AHO therapy. Neutropenia, thrombocytopenia and AST/ALT elevation were defined using the NIH DAIDS pediatric toxicity grading system; acute kidney injury (AKI) was defined using pRIFLE.
Results. 207 subjects met inclusion criteria. Outpatient CBC was obtained in 187 subjects, creatinine in 121 and AST/ALT in 63. Patients with and without ARLA were similar with respect to age and demographics. Neutropenia developed in 12 (6.4%) and thrombocytopenia in 5 (2.7%) at a median of 23 and 18 days of therapy, respectively. Outpatient hematologic abnormalities were more common among subjects with MRSA, history of inpatient ARLA and those receiving certain antibiotics, specifically vancomycin (**Tables 1 and 2**). There was no clear relationship with hematologic abnormalities and vancomycin daily dose. Neutropenia prompted modification of therapy in 1 case. No infections or bleeding events were attributable to ARLA. Three cases of outpatient AKI occurred (2.1% [vancomycin, n=1; cefazolin, n=2]); one subject had therapy discontinued. Outpatient AST/ALT elevation occurred in six (9.5%), none of which were symptomatic. Patients with AST/ALT elevation were disproportionately treated with cefazolin (p=0.006).
Conclusions. ARLAs, particularly neutropenia, are common in patients receiving outpatient therapy for AHO after 2-3 weeks of therapy. However, the majority of ARLA are mild and do not result in symptoms or modification of therapy. Further study is necessary to appreciate how these findings might be applicable to all cause osteomyelitis.

AIMS

1. **To examine the frequency of antibiotic-related laboratory abnormalities (ARLA) in children receiving outpatient therapy for *S. aureus* osteomyelitis.**
2. **To identify risk factors for ARLA in children receiving outpatient therapy for osteomyelitis.**

INTRODUCTION

- Acute hematogenous osteomyelitis (AHO) is a serious infection in children with the majority of cases secondary to *Staphylococcus aureus.*
- Antimicrobial therapy can be associated with adverse events including neutropenia, thrombocytopenia, nephrotoxicity and hepatotoxicity.
- Recent guidelines from the Pediatric Infectious Diseases Society advocate for weekly-biweekly laboratory monitoring for adverse events including bone marrow suppression (β-lactams) and renal dysfunction (vancomycin, JPIDS 2021;10:801-844).
- Data are very limited however with respect to the frequency and clinical significance of antibiotic related laboratory abnormalities (ARLA) occurring in the treatment of osteomyelitis.
- We retrospectively reviewed the frequency of ARLA in children receiving outpatient therapy for *S. aureus* acute hematogenous osteomyelitis (AHO).

PATIENTS AND METHODS

Subjects. Cases of *S. aureus* AHO from Jan 1 2011-Dec 31 2020 were selected from an ongoing *S. aureus* surveillance study at Texas Children's Hospital (TCH).
Inclusion Criteria.
1). < 18 years of age
2). Discharged from TCH to complete therapy at home with either oral antibiotics or outpatient parenteral antimicrobial therapy (OPAT)
3). Baseline complete blood count, creatinine and AST/ALT collected during the hospitalization
4). At least one CBC, creatinine and/or AST/ALT measurement in the outpatient setting while receiving treatment for AHO
5). The absence of neutropenia, thrombocytopenia, AKI or AST/ALT elevation at time of discharge

PATIENTS AND METHODS

Exclusion Criteria.
1. Age < 28 days.
2. Preexisting renal or hepatic disease or known hematologic diagnosis.

Design. Medical records were reviewed for all subjects through date of last follow-up with a provider in the TCH system.
Definitions. Neutropenia, thrombocytopenia and AST/ALT elevation were graded based on NIAID criteria. Acute kidney injury (AKI) was defined by pRIFLE criteria. ARLA were regarded as neutropenia, thrombocytopenia, AKI and/or AST/ALT elevation while getting outpatient antibiotics for AHO.
Statistical Analysis. Continuous variables were examined with Mann-Whitney U tests; dichotomous variables with χ^2 and Fisher's exact tests.

RESULTS

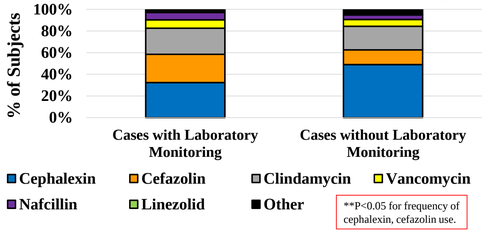
- During the study period, there were 433 cases of *S. aureus* AHO with 207 meeting inclusion criteria (**Table 1, Figure 1).**
- Overall, ARLA developed in 12.6% of patients (**Figure 2**). There was no association of ARLA and patient age or demographics.

Table 1. General Characteristics of Patients

	N=207
Median Age, years*	**8.6 (4.8-11.9)**
Female Gender	**89 (42.9)**
Isolated Osteomyelitis	**134 (64.7)**
Osteomyelitis with Concomitant Septic Arthritis	**73 (35.3)**
MRSA Infection	**64 (30.9)**
ICU Admission	**21 (10.1)**
Duration of Hospitalization, days	**8 (5-11)**
Discharge on Oral Antibiotics	**110 (53.1)**
Inpatient Neutropenia	**7 (3.4)**
Inpatient Thrombocytopenia	**18 (8.6)**
Inpatient AKI	**14 (6.7)**
Inpatient AST/ALT Elevation	**35 (16.9)**
Outpatient CBC Performed	**187 (90.3)**
Outpatient AST/ALT Measured	**63 (30.4)**
Outpatient Creatinine Measured	**121 (58.5)**

*All continuous variables expressed as medians with interquartile ranges (IQR), categorical variables as n (%).

Figure 1. Antibiotics In those With/Without Lab Monitoring**



RESULTS

- Subjects receiving vancomycin and linezolid disproportionately experienced ARLA (**Figure 3**).
- Neutropenia developed in 12 (6.4%) and thrombocytopenia in 5 (2.7%) at a median of 23 and 18 days of therapy, respectively (**Tables 2 and 3).**
- No bleeding or new infections were attributable to ARLA .

Figure 2. Frequency of Subjects with ARLA

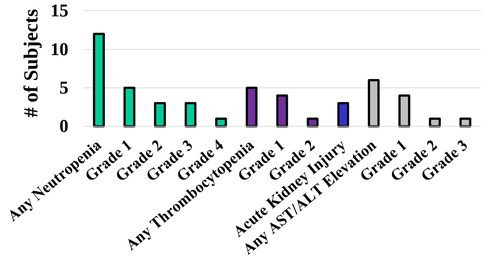


Figure 3. Frequency of ARLA by Discharge Antibiotic

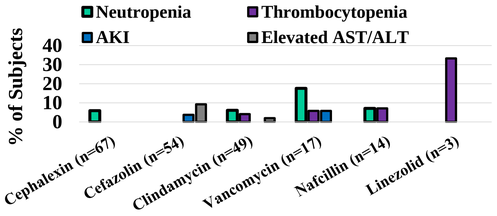


Table 2. Risk Factors Associated with Outpatient Neutropenia

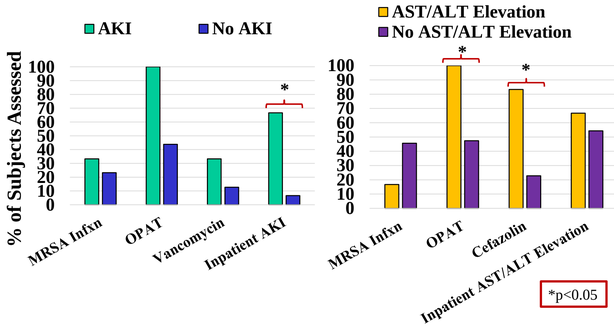
	Outpatient Neutropenia, n=12	No Outpatient Neutropenia, n=175	P value
Age, years	**7.5 (2.1-9.1)**	**8.8 (5-12.2)**	**0.11**
MRSA Infection	**7 (58.3)**	**50 (28.6)**	**0.04**
Inpatient Neutropenia	**2 (16.7)**	**2 (1.1)**	**0.02**
OPAT	**3 (25)**	**35 (20)**	**0.71**
Discharge ABX			**0.01**
Vancomycin	**3(25)**	**9 (5.1)**	
Clindamycin	**3 (25)**	**41 (23.4)**	
Nafcillin	**1 (8.3)**	**12 (6.8)**	
Cefazolin	**0**	**48 (27.4)**	
Cephalexin	**4 (33.3)**	**60 (34.3)**	
Linezolid	**0**	**3 (1.7)**	
Other	**1 (8.3)**	**2 (1.1)**	

RESULTS

Table 3. Factors Associated with Outpatient Thrombocytopenia

	Outpatient Thrombocytopenia, n=5	No Outpatient Thrombocytopenia, n=182	P value
Age, years	**4.7 (1.9-12.5)**	**8.7 (5.3-11.9)**	**0.5**
MRSA Infection	**4 (80)**	**53 (29.1)**	**0.03**
Inpatient Thrombocytopenia	**2 (40)**	**16 (8.7)**	**0.07**
OPAT	**4 (80)**	**34 (18.7)**	**0.006**
Discharge ABX			**0.02**
Vancomycin	**1 (20)**	**11 (6)**	
Clindamycin	**2 (40)**	**42 (23.1)**	
Nafcillin	**1 (20)**	**12 (6.6)**	
Cefazolin	**0**	**48 (26.3)**	
Cephalexin	**0**	**64 (35.2)**	
Linezolid	**1 (20)**	**2 (1.1)**	
Other	**0**	**3 (1.6)**	

Figure 4. Risk Factors for Outpatient AKI or AST/ALT Elevation



- AKI developed in 2.1% of patients at a median of 18 days; all were receiving either vancomycin or cefazolin.
- AST/ALT elevation occurred in 9.5% and was disproportionate in patients receiving cefazolin (**Figure 4**). AST/ALT elevation occurred at a median of 16.5 days of therapy. No cases were associated with abdominal pain or vomiting.
- ARLA prompted modification of therapy in two subjects (0.9%) total (one case each of neutropenia and AKI). In both cases therapy was changed to an alternative agent.

CONCLUSIONS

- Among children receiving outpatient therapy for *S. aureus* AHO, antibiotic related laboratory abnormalities develop in 12.6% with neutropenia being most common.
- ARLA may be more common with select antibiotics, those receiving OPAT and those with a history of ARLA as inpatients.
- The clinical impact of ARLA is low as the majority of ARLA are mild and do not result in symptoms or modification of therapy.
- Further study is needed to determine how these findings apply to all musculoskeletal infections and how laboratory monitoring can be optimized.