RESEARCH ARTICLE

# Comparison of Empiric Antibiotics for Acute Osteomyelitis in Children

Sarah McBride, MD,[a] Cary Thurm, PhD,[b] Ramkiran Gouripeddi, MBBS, MS,[c] Bryan Stone, MD,[c] Phil Jaggard,[b] Samir S. Shah, MD, MSCE,[d] Joel S. Tieder, MD, MPH,[e] Ryan Butcher, MS,[c] Jason Weiser, BA,[d] Matt Hall, PhD,[b] Ron Keren, MD, MPH,[f] Christopher P. Landrigan, MD, MPH[a]

ABSTRACT

**OBJECTIVES:** Broad-spectrum antibiotics are commonly used for the empiric treatment of acute hematogenous osteomyelitis and often target methicillin-resistant *Staphylococcus aureus* (MRSA) with medication-associated risk and unknown treatment benefit. We aimed to compare clinical outcomes among patients with osteomyelitis who did and did not receive initial antibiotics used to target MRSA.

**METHODS:** A retrospective cohort study of 974 hospitalized children 2 to 18 years old using the Pediatric Health Information System database, augmented with clinical data. Rates of hospital readmission, repeat MRI and 72-hour improvement in inflammatory markers were compared between treatment groups.

**RESULTS:** Repeat MRI within 7 and 180 days was more frequent among patients who received initial MRSA coverage versus methicillin-sensitive *S aureus* (MSSA)–only coverage (8.6% vs 4.1% within 7 days [$P = .02$] and 12% vs 5.8% within 180 days [$P < .01$], respectively). Ninety- and 180-day hospital readmission rates were similar between coverage groups (9.0% vs 8.7% [$P = .87$] and 10.9% vs 11.2% [$P = .92$], respectively). Patients with MRSA- and MSSA-only coverage had similar rates of 72-hour improvement in C-reactive protein values, but patients with MRSA coverage had a lower rate of 72-hour white blood cell count normalization compared with patients with MSSA-only coverage (4.2% vs 16.4%; $P = .02$).

**CONCLUSIONS:** In this study of children hospitalized with acute hematogenous osteomyelitis, early antibiotic treatment used to target MRSA was associated with a higher rate of repeat MRI compared with early antibiotic treatment used to target MSSA but not MRSA. Hospital readmission rates were similar for both treatment groups.

www.hospitalpediatrics.org
**DOI:**https://doi.org/10.1542/hpeds.2017-0079


Address correspondence to Sarah McBride, MD, Department of Medicine, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115. E-mail: sarah.mcbride@childrens.harvard.edu

HOSPITAL PEDIATRICS (ISSN Numbers: Print, 2154-1663; Online, 2154-1671).

**FINANCIAL DISCLOSURE:** The authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** Funded by grant R01 HS-019862-01 from the Agency for Healthcare Research and Quality of the US Department of Health and Human Services. The opinions expressed in this document are those of the authors and do not reflect the official position of the Agency for Healthcare Research and Quality or the US Department of Health and Human Services.

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

Dr McBride conceptualized and designed the study and drafted the initial manuscript; Drs Thurm, Gouripeddi, Hall, Butcher, and Jaggard conducted the data analyses and reviewed and revised the manuscript; Drs Stone, Shah, and Tieder provided insight into the study design and critical review of the manuscript; Drs Keren and Landrigan provided study site coordination and oversight and insight into the study's design elements and critical review of the manuscript; and all authors approved the final manuscript as submitted.

[a]*Boston Children's Hospital, Boston, Massachusetts;* [b]*Children's Hospital Association, Overland Park, Kansas;* [c]*University of Utah, Salt Lake City, Utah;* [d]*Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio;* [e]*University of Washington, Seattle, Washington; and* [f]*Children's Hospital of Philadelphia, Philadelphia, Pennsylvania*

Acute hematogenous osteomyelitis (AHO) is a bone infection resulting from the hematogenous spread of bacteria without direct inoculation and is an important cause of hospitalization and morbidity among children.[1] In general, half of all the children hospitalized for AHO do not have a causative pathogen identified.[2,3] For this reason, initial and even ongoing antibiotic treatment is often chosen empirically to counter suspected bacterial pathogens, most commonly *Staphylococcus aureus*.[2,4,5] Subsequent clinical improvement on initial empirical antibiotic therapy is used to inform ongoing antibiotic treatment when microbiology data are not revealing. Because of the lengthy duration of antibiotic therapy that is recommended for osteomyelitis, initial antibiotic choice can play a large role in patient outcomes.

Historically, narrow-spectrum B-lactam antibiotics and first-generation cephalosporins have been used as a first-line treatment of pediatric AHO to target methicillin-sensitive *S aureus* (MSSA).[6] However, in response to the prevalence of methicillin-resistant *S aureus* (MRSA), empirical antibiotic choices for *S aureus* coverage have changed in many hospitals.[5,7] Although vancomycin is routinely used for invasive MRSA infections and is recommended as a first-line therapy for pediatric AHO and septic arthritis, the emergence of resistant MRSA strains has been described, and nephrotoxicity is a significant risk associated with its use.[8,9] Sulfamethoxazole-trimethoprim has been shown to be an effective agent against MRSA skin and soft tissue infections, but its use for osteomyelitis is not well defined and is limited by its inactivity against *Streptococcus*.[10] Clindamycin can be used effectively against MSSA and MRSA in osteomyelitis.[11] However, there are variable regional rates of in vitro–inducible macrolide-lincosamide-streptogramin B resistance with clindamycin in both MSSA and MRSA, with inconclusive in vivo effects on treatment efficacy.[12,13] Linezolid is an effective agent against MRSA, but it is often associated with significant side effects when used for longer treatment durations, which are needed for treating osteomyelitis.[14–16] Daptomycin is another newer agent used in the treatment of osteomyelitis, but it is an intravenous medication and has been shown to have limited effectiveness unless coupled with rifampin.[17–19] In addition, prolonged courses of parenteral antibiotics increase the probability of central line–associated complications and adverse drug events, which occur more often with MRSA-covering antibiotics.[20–22]

Studies in which researchers compare the effectiveness of different empirical antibiotic regimens for the early treatment of pediatric osteomyelitis are lacking. To address this gap in knowledge, we used the Pediatric Health Information System database augmented with clinical data (PHIS+)[23–26] to compare empirical antibiotic treatment used to target MSSA versus MRSA among patients hospitalized with AHO. We tested the hypothesis that patients who were treated empirically with antibiotics targeting MSSA but not MRSA may experience a higher rate of treatment failure than patients who were initially treated with an antibiotic that is effective against MRSA.

## METHODS

### Data Source

The PHIS+ database of the Children's Hospitals Association includes administrative data augmented by laboratory,[23] microbiology,[24] and radiographic results.[25] Data from the 6 contributing hospitals were harmonized and standardized by using biomedical terminologies.[26] Microbiology results included cultured organisms and their antibiotic sensitivities. Radiology results included examination title, report text, and impression reported in free-text format. All radiology report text was deidentified in bulk by using De-ID software.[27]

### Assembly of the Study Cohort

Pediatric patients hospitalized with a primary diagnosis of osteomyelitis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM]) from 2007 to 2011 were identified in PHIS+. Patients were included in the cohort if they were aged 2 to 18 years; received a MSSA- or MRSA-covering antibiotic on hospital day 0, 1, or 2; and had inflammatory laboratory results and a microbiology culture ordered in the PHIS+ during the same time frame. Patients were excluded if they had a recent, significant, penetrating trauma; a compound fracture; a recent, invasive orthopedic procedure; prosthesis-associated osteomyelitis; or another major comorbid condition that could prolong the disease course despite appropriate antibiotic coverage. Such comorbidities included chronic orthopedic conditions necessitating bone surgeries and bone hardware, sickle cell disease, malignancy, prematurity, immunodeficiency, chronic systemic steroid use, and other metabolic bone diseases.

### Patient Characteristics

We collected patient demographic information as well as radiographic, microbiologic, and laboratory data obtained in the emergency department or during hospitalization. Values for C-reactive protein (CRP) values and white blood cell (WBC) counts were extracted from the PHIS+. Microbiology culture data with associated antibiotic sensitivity testing were obtained for blood, synovial fluid, soft tissue, and bone cultures. The radiology reports obtained from PHIS+ were manually evaluated and coded as osteomyelitis by a pediatric hospitalist physician (S.M.). A Research Electronic Data Capture data form[27] was used to record information from these radiology reports, including disease site and severity (abscess formation, joint or growth plate involvement, and reference to operative procedures during the index hospitalization) as well as confirmation of the imaging modality.

### Exposures

Children were assigned to 1 of 2 empirical treatment groups for the purpose of this study: those who received of antibiotics during the first 2 days of hospitalization targeting either MRSA or MSSA only. Patients receiving any amount of MRSA coverage during the first 2 days of hospitalization were placed into the MRSA coverage group for the purpose of this study. Patients who did not receive any doses of a MRSA-covering antibiotic but received an MSSA-covering antibiotic during that time were placed into the MSSA-only

coverage group. Therefore, patients in the MRSA coverage group may have received variable amounts of a MRSA-targeting antibiotic during this time period.

### Outcome Measures

The primary outcome measures were the rates of treatment failure, which were defined as either readmission to the hospital within 90 or 180 days of index hospital admission or repeat MRI within 7 or 180 days of admission. A secondary outcome measure was the rate of improvement in inflammatory markers within the first 72 hours of hospitalization. Inflammatory laboratory data were grouped into categories of "low," "moderate and/or normal" or "high" on the basis of the statistical distribution (in centiles) for each test's range of values in this study. For CRP values, low was ≤7.9 mg/dL, moderate was 8.0 to 14.9 mg/dL, and high was ≥15.0 mg/dL. For WBC count, low was ≤4.9 cells per $\mu$L, normal was 5 to 14.9 cells per $\mu$L, and high was ≥15 cells per $\mu$L. A change from high to moderate or low for CRP values and a change from high to normal for WBC count within 72 hours was considered an improvement for the purposes of this outcome measure.

### Statistical Analyses

Statistical analysis was conducted by using SAS software (version 9.4; SAS Institute, Inc, Cary, NC). Continuous variables were described as means and SDs. Categorical variables were expressed as proportions and were compared by using $\chi^2$ tests. The level of significance was set at 0.05 because of the size of the population.

### Human Subjects Oversight

This study was approved by the study center's Review Board for Protection of Human Subjects in Research. Informed consent was waived.

## RESULTS

A total of 1265 hospitalized children ages 2 through 18 years were initially identified among the 6 participating PHIS + hospitals with a primary diagnosis of osteomyelitis (Fig 1). Of those, 974 met the inclusion criteria and received empirical antibiotics with activity against *S aureus* (with or without MRSA coverage) during the first 2 days of hospitalization. Demographic and

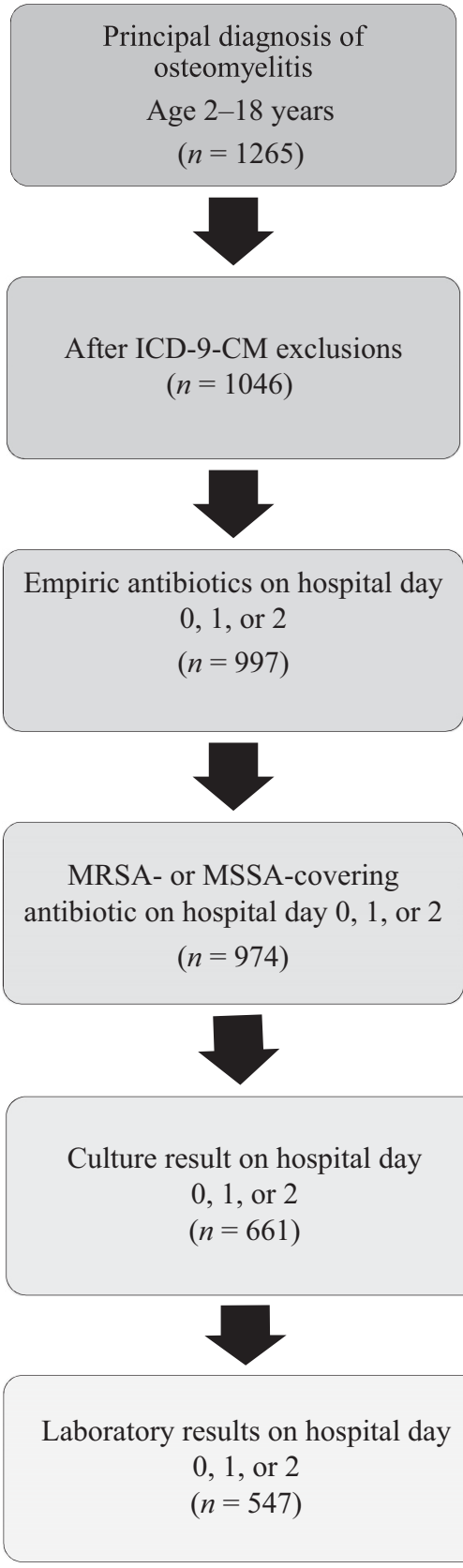


**FIGURE 1** Selection of the cohort.

clinical characteristics of these 974 patients are listed in Table 1.

During the first 2 days of their hospitalization, 732 patients (75%) received some degree of MRSA antibiotic coverage, and 242 (25%) received MSSA-only coverage. The most common antibiotics used during hospitalization are listed in Table 2. The most common MRSA-covering antibiotics were clindamycin, vancomycin, sulfamethoxazole and trimethoprim, and linezolid. The most commonly used MSSA-only antibiotics were cefazolin, nafcillin, oxacillin, and ceftriaxone.

Initial radiographic findings used to denote disease burden were not statistically different between the MRSA and MSSA-only coverage groups (Table 1). Nineteen percent of the patients from both coverage groups had an intraosseous or deep soft tissue abscess seen on MRI, ∼14% of each group had evidence of an associated septic joint, and ∼9% of each group had growth plate involvement. The MRSA and MSSA-only groups also had similar rates of surgical intervention referenced (9% and 10%, respectively).

Of the 974 patients, 661 (67%) also had bacterial culture data captured within PHIS+ during the first 2 days of hospitalization. Of the 661, 371 (56%) had *S aureus* grow in their culture, of which 75 (20%) were methicillin resistant. Of the 661, 41 (6%) had a non–*S aureus* organism present. Of the 974 patients, 313 (32%) did not have microbiology results captured in PHIS+. Microbiology results are summarized in Table 3.

Repeated MRIs in this study all revealed radiographic evidence of disease progression when compared with previous MRI studies.

The frequency of repeat MRI within 7 days of admission among patients who received empirical MRSA coverage was 8.6% compared with 4.1% among those patients who received initial MSSA-only coverage ($P = .02$). The rate of repeat MRI within

**TABLE 1** Patient Characteristics

| | $N = 974$ | MRSA Coverage, $n = 732$ | MSSA Coverage, $n = 242$ | $P$ |
|---|---|---|---|---|
| Age, y, mean (SD) | 10 (4) | 10 (4) | 10 (5) | .75 |
| Male sex, *n* (%) | 593 (60.9) | 452 (61.8) | 141 (58.3) | .34 |
| Race, *n* (%) | | | | |
| Non-Hispanic white | 634 (65.1) | 471 (64.4) | 163 (67.4) | — |
| Non-Hispanic African American | 162 (16.6) | 136 (18.6) | 26 (10.7) | — |
| Hispanic | 69 (7.1) | 51 (7) | 18 (7.4) | — |
| Asian American | 13 (1.3) | 6 (0.8) | 7 (2.9) | — |
| Other | 96 (9.9) | 68 (9.2) | 28 (11.6) | <.01 |
| Insurance, *n* (%) | | | | |
| Private | 560 (57.5) | 425 (58.1) | 135 (55.8) | — |
| Government | 318 (32.7) | 244 (33.3) | 74 (30.6) | — |
| Other | 96 (9.9) | 63 (8.6) | 33 (13.6) | .07 |
| Body site of osteomyelitis, *n* (%) | | | | |
| Tibia and/or fibula | 162 (16.6) | 124 (16.9) | 38 (15.7) | .65 |
| Femur | 84 (8.6) | 61 (8.3) | 23 (9.5) | .57 |
| Radius and/or ulna | 17 (1.7) | 14 (1.9) | 3 (1.2) | .49 |
| Humerus | 25 (2.6) | 20 (2.7) | 5 (2.1) | .57 |
| Foot | 96 (9.9) | 76 (10.4) | 20 (8.3) | .34 |
| Hand | 43 (4.4) | 38 (5.2) | 5 (2.1) | .04 |
| Vertebral region | | | | |
| Lumbosacral | 20 (2.1) | 17 (2.3) | 3 (1.2) | .3 |
| Cervical and/or thoracic | 3 (0.3) | 3 (0.4) | 0 (0) | — |
| Pelvic | 93 (9.5) | 69 (9.4) | 24 (9.9) | .82 |
| Not specified | 529 (54.3) | 409 (55.9) | 120 (49.6) | .09 |
| Radiographic findings, *n* (%) | | | | |
| Abscess | 184 (18.9) | 138 (18.9) | 46 (19) | .96 |
| Septic joint | 134 (13.8) | 99 (13.5) | 35 (14.5) | .71 |
| Growth plate involvement | 87 (8.9) | 64 (8.7) | 23 (9.5) | .72 |
| Surgical intervention | 90 (9.2) | 65 (8.9) | 25 (10.3) | .5 |

—, not applicable.

**TABLE 2** Antibiotic Frequency

| | $N = 974$, $n$ (%) |
|---|---|
| MRSA coverage | |
| Clindamycin | 585 (60) |
| Vancomycin | 342 (35.1) |
| Sulfamethoxazole and trimethoprim | 26 (2.7) |
| Linezolid | 21 (2.1) |
| MSSA coverage | |
| Cefazolin | 446 (45.8) |
| Nafcillin and/or oxacillin | 197 (20.2) |
| Ceftriaxone | 103 (10.6) |
| Ciprofloxacin | 50 (5.1) |
| Rifampin | 48 (4.9) |
| Ampicillin | 45 (4.6) |
| Penicillin | 9 (0.9) |
| Ampicillin and sulbactam | 0 (0) |

180 days of admission was 12% among patients with MRSA coverage compared with 5.8% among patients with MSSA-only coverage ($P = .006$; Table 4).

Ninety-day readmission rates for patients receiving empirical MRSA coverage was 9.0% vs 8.7% for those who received MSSA-only coverage ($P = .87$). For patients with MRSA coverage, the 180-day readmission rate was 10.9% compared with 11.2% for patients with MSSA-only coverage ($P = .92$; Table 4).

Forty-three percent of patients with MRSA coverage and 37% of patients with MSSA-only coverage had a CRP value captured in the PHIS+ early during hospitalization. The rates of improvement in CRP values were not significantly different between the coverage groups (6% [11 of 195] for MRSA and 8% [6 of 74] for MSSA only; $P = .57$). Twenty-seven percent of patients with MRSA coverage and 26% of patients with MSSA-only coverage had a WBC count captured during the same time frame. Among the patients with repeated laboratory values to trend during hospital day 0, 1, and 2, patients with MRSA coverage had a lower WBC count normalization rate within 72 hours when compared with those who received MSSA-only coverage (4% [5 of 120] vs 16% [8 of 55] respectively; $P = .02$).

## DISCUSSION

In this study of children with acute osteomyelitis, we found that early empirical antibiotic treatment with MRSA coverage or MSSA-only coverage was associated with overall equivalent hospital readmission rates, but patients with MRSA coverage had a higher rate of repeat MRI compared with patients receiving empirical MSSA-only coverage. The rate of 72-hour improvement in CRP values was not significantly different between the coverage groups. Patients who received MRSA coverage had a lower rate of 72-hour normalization in WBC count compared with patients receiving MSSA-only coverage.

**TABLE 3** Microbiology Results

| Bacterial Culture Result, $N = 661$ | MRSA Coverage, $n = 485$ | MSSA-Only Coverage, $n = 176$ | $\chi^2$ $P$ |
|---|---|---|---|
| | $n$ (%) | $n$ (%) | |
| MSSA | 225 (46) | 71 (40) | — |
| MRSA | 68 (14) | 7 (4) | — |
| Other organism | 30 (6) | 11 (6) | — |
| No growth | 162 (33) | 87 (49) | <.001 |

—, not applicable.

Since the emergence of MRSA as a significant bacterial pathogen for skin and soft tissue infections, variable rates of MRSA have been described across the United States. In this study, we included data from 6 pediatric centers that primarily deliver care to patients in the Northeast, Northwest, and Central regions of the United States. Overall, this study's patient cohort had similar clinical and demographic characteristics to previous regional studies of children with AHO.[7,28,29]

The reliability of this study's data is supported by the multiple levels of data validation performed during the construction of the PHIS+, making the quality of clinical data high. During this process, any inconsistencies between the data source and the PHIS+ were reviewed at a data-mapping level by the PHIS+ information technology teams and the study center research teams. In addition, a significant sample of patient records from this study's cohort underwent electronic medical record chart review for validation and matching at each of the 6 participating hospitals. During each of these stages of data testing, if data quality issues arose, they were rectified, and study sites resubmitted data for bulk review using the same steps described here.

Limitations of the PHIS+ are related to the availability of clinical results for capture by the PHIS+ on the basis of where a test was performed and where the result was reported. For instance, although all 6 study hospitals could submit inpatient clinical data, not all of them could submit outpatient and emergency department data. In addition, test results from referral centers were not available electronically for capture into the PHIS+. These limitations may have affected the ability to capture a complete episode of care for some patients who had testing performed somewhere other than the 6 study centers, specifically regarding microbiology and initial inflammatory laboratory data. There are also inherent limitations to the use of ICD-9-CM codes for identifying patients with a principal diagnosis of interest, which in this case is osteomyelitis.[30] For this reason, it is possible that patients who would have

**TABLE 4** Comparison of Treatment Failure Rates

| | MRSA Coverage, $n = 732$ | MSSA Coverage, $n = 242$ | $P$ |
|---|---|---|---|
| | $n$ (%) | $n$ (%) | |
| Repeat MRI within 7 d | 63 (8.6) | 10 (4.1) | .02 |
| Repeat MRI within 180 d | 88 (12) | 14 (5.8) | .006 |
| Readmission within 90 d | 66 (9.0) | 21 (8.7) | .87 |
| Readmission within 180 d | 80 (10.9) | 27 (11.2) | .92 |

otherwise met clinical criteria for inclusion were not included in this study.

A potential limitation to outcome comparisons between the antibiotic exposure groups was the inclusion of patients who received mostly MSSA-only coverage during the first few days of hospitalization in the MRSA coverage group because they had received some degree of MRSA coverage during this time frame. For the purposes of this study, patients were placed into the MSSA-only antibiotic treatment group only if they received no MRSA antibiotic during their first 2 hospital days because it was not possible to determine how much antibiotic providing MRSA coverage was administered in an individual patient and devise a cutoff for empirical treatment categorization. This caused the number of patients in the MRSA coverage group to be disproportionally larger than that of the MSSA-only coverage group. These factors may have impeded the ability to detect additional differences in clinical outcomes between the MRSA and MSSA-only coverage groups.

In the MRSA coverage group, it was also not possible to know when vancomycin dosing had achieved therapeutic drug levels, providing reliable coverage against MRSA. It is possible that some patients who were included in the MRSA coverage group received initial monotherapy with vancomycin without having therapeutic serum drug levels. This could have disadvantaged patients with osteomyelitis caused by MRSA.

In this study, 32% of the patients meeting initial study inclusion criteria did not have microbiology data captured in the PHIS+ during the first 2 days of hospitalization. This may have been because of blood cultures being sent before the index hospitalization at another laboratory other than those at the 6 study sites. Of the 242 patients who initially received only MSSA coverage and had bacterial culture results in the PHIS+, 71 (40%) had MSSA present, and 4% (7 of 176) had MRSA present. None of the 7 patients who had MRSA present and did not receive initial MRSA coverage had repeat MRI or hospital readmission captured in the PHIS+.

Serum CRP is an acute-phase reactant with a relatively short half-life (~19 hours) and can be elevated in infectious, rheumatologic, and oncologic conditions. CRP has been shown to be a useful tool in timing the transition of children with osteoarticular infections from intravenous to oral therapy.[31,32] In addition to clinical examination, response to empirical therapy for osteomyelitis can also be determined by trending inflammatory markers often before any microbiology data are available to guide antibiotic choice. Although there is no universally accepted time frame for expected CRP value improvement in pediatric osteomyelitis as a means of guiding empirical therapy, for the purposes of this study, 72 hours was used. Previous researchers have found a higher initial elevation of CRP values in patients with MRSA osteomyelitis and among patients with an associated septic joint.[31–33] Similarly, the median initial CRP value for patients with MRSA osteomyelitis in this study was 12.3 mg/dL compared with 8.4 mg/dL for MSSA. This could have negatively impacted the rate of CRP normalization among some patients within this cohort who had MRSA osteomyelitis.

Finally, the outcome measures chosen in this study are relatively general measures of treatment failure or success. Not all patients with treatment failure may have been rehospitalized. In addition, although all repeated MRI studies revealed evidence of disease progression or persistence, this may have been because of factors other than initial antibiotic choice, which could not be appreciated by using these study methods. Nevertheless, we were able to capture initial radiographic markers of disease burden, such as an abscess or septic joint, which were not statistically different between the MRSA and MSSA-only coverage groups. Clinical prediction models for determining MRSA infection among children with musculoskeletal infections have been used in an attempt to guide appropriate initial treatment (specifically, judicious antibiotic use) but have been difficult to validate in subsequent studies.[34,35] More descriptive clinical and historical patient data, such as the duration of signs and symptoms at presentation, may assist in assigning disease burden for AHO at the time of hospitalization, guide initial antibiotic treatment, and ultimately aid in predicting responses to treatment.

## CONCLUSIONS

Children who received initial MRSA antibiotic coverage for AHO had higher rates of repeat MRI compared with children receiving initial MSSA-only coverage. Equivalent readmission rates at 90 and 180 days were observed between the 2 treatment groups. Rates of 72-hour improvement in CRP values were equivalent between the groups, but a lower 72-hour normalization rate in WBC count was observed among patients treated empirically with MRSA antibiotics. Further study is needed to guide clinical indications for initial MRSA versus MSSA-only antibiotic coverage as a treatment of AHO in children with unknown MRSA risk.

## REFERENCES


1. Alderson M, Speers D, Emslie K, Nade S. Acute haematogenous osteomyelitis and septic arthritis—a single disease. An hypothesis based upon the presence of transphyseal blood vessels. *J Bone Joint Surg Br*. 1986;68(2):268–274
2. Floyed RL, Steele RW. Culture-negative osteomyelitis. *Pediatr Infect Dis J*. 2003; 22(8):731–736
3. Saavedra-Lozano J, Mejías A, Ahmad N, et al. Changing trends in acute

osteomyelitis in children: impact of methicillin-resistant Staphylococcus aureus infections. *J Pediatr Orthop*. 2008;28(5):569–575

4. Ratnayake K, Davis AJ, Brown L, Young TP. Pediatric acute osteomyelitis in the postvaccine, methicillin-resistant Staphylococcus aureus era. *Am J Emerg Med*. 2015;33(10):1420–1424
5. Arnold SR, Elias D, Buckingham SC, et al. Changing patterns of acute hematogenous osteomyelitis and septic arthritis: emergence of community-associated methicillin-resistant Staphylococcus aureus. *J Pediatr Orthop*. 2006;26(6):703–708
6. Harik NS, Smeltzer MS. Management of acute hematogenous osteomyelitis in children. *Expert Rev Anti Infect Ther*. 2010;8(2):175–181
7. Gafur OA, Copley LA, Hollmig ST, Browne RH, Thornton LA, Crawford SE. The impact of the current epidemiology of pediatric musculoskeletal infection on evaluation and treatment guidelines. *J Pediatr Orthop*. 2008;28(7):777–785
8. Rodvold KA, McConeghy KW. Methicillin-resistant Staphylococcus aureus therapy: past, present, and future. *Clin Infect Dis*. 2014;58(suppl 1):S20–S27
9. Liu C, Bayer A, Cosgrove SE, et al; Infectious Diseases Society of America. Clinical practice guidelines by the Infectious Diseases Society of America for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children [published correction appears in *Clin Infect Dis*. 2011;53(3):319]. *Clin Infect Dis*. 2011;52(3):e18–e55
10. Messina AF, Namtu K, Guild M, Dumois JA, Berman DM. Trimethoprim-sulfamethoxazole therapy for children with acute osteomyelitis. *Pediatr Infect Dis J*. 2011;30(12):1019–1021
11. Martínez-Aguilar G, Hammerman WA, Mason EO Jr, Kaplan SL. Clindamycin treatment of invasive infections caused by community-acquired, methicillin-resistant and methicillin-susceptible Staphylococcus aureus in children. *Pediatr Infect Dis J*. 2003;22(7):593–598
12. Siberry GK, Tekle T, Carroll K, Dick J. Failure of clindamycin treatment of methicillin-resistant Staphylococcus aureus expressing inducible clindamycin resistance in vitro. *Clin Infect Dis*. 2003; 37(9):1257–1260
13. Taylor JJ, Wilson JW, Estes LL. Linezolid and serotonergic drug interactions: a retrospective survey. *Clin Infect Dis*. 2006;43(2):180–187
14. Wu VC, Wang YT, Wang CY, et al. High frequency of linezolid-associated thrombocytopenia and anemia among patients with end-stage renal disease. *Clin Infect Dis*. 2006;42(1):66–72
15. Senneville E, Legout L, Valette M, et al. Effectiveness and tolerability of prolonged linezolid treatment for chronic osteomyelitis: a retrospective study. *Clin Ther*. 2006;28(8):1155–1163
16. Nannini E, Murray BE, Arias CA. Resistance or decreased susceptibility to glycopeptides, daptomycin, and linezolid in methicillin-resistant Staphylococcus aureus. *Curr Opin Pharmacol*. 2010;10(5):516–521
17. Lefebvre M, Jacqueline C, Amador G, et al. Efficacy of daptomycin combined with rifampicin for the treatment of experimental methicillin-resistant Staphylococcus aureus (MRSA) acute osteomyelitis. *Int J Antimicrob Agents*. 2010;36(6):542–544
18. Garrigós C, Murillo O, Euba G, et al. Efficacy of usual and high doses of daptomycin in combination with rifampin versus alternative therapies in experimental foreign-body infection by methicillin-resistant Staphylococcus aureus. *Antimicrob Agents Chemother*. 2010;54(12):5251–5256
19. LaPlante KL, Leonard SN, Andes DR, Craig WA, Rybak MJ. Activities of clindamycin, daptomycin, doxycycline, linezolid, trimethoprim-sulfamethoxazole, and vancomycin against community-associated methicillin-resistant Staphylococcus aureus with inducible clindamycin resistance in murine thigh infection and in vitro pharmacodynamic models. *Antimicrob Agents Chemother*. 2008;52(6):2156–2162
20. Faden D, Faden HS. The high rate of adverse drug events in children receiving prolonged outpatient parenteral antibiotic therapy for osteomyelitis. *Pediatr Infect Dis J*. 2009; 28(6):539–541
21. Maraqa NF, Gomez MM, Rathore MH. Outpatient parenteral antimicrobial therapy in osteoarticular infections in children. *J Pediatr Orthop*. 2002;22(4): 506–510
22. Narus SP, Srivastava R, Gouripeddi R, et al. Federating clinical data from six pediatric hospitals: process and initial results from the PHIS+ consortium. *AMIA Annu Symp Proc*. 2011;2011: 994–1003
23. Gouripeddi R, Warner PB, Mo P, et al. Federating clinical data from six pediatric hospitals: process and initial results for microbiology from the PHIS+ consortium. *AMIA Annu Symp Proc*. 2012; 2012:281–290
24. Gouripeddi RMS, Shah SS, Tieder J, et al. Federating clinical data from six pediatric hospitals: process and initial results for radiology report data from the PHIS+ consortium. In: Proceedings from the AMIA Annual Symposium; November 16–20, 2013; Washington, DC
25. Gouripeddi R, Butcher R, Warner PB, et al. Use of standardized terminologies in federating clinical data from six pediatric hospitals for comparative effectiveness research: lessons learned from the PHIS+ consortium. In: Electronic Data Methods Forum Annual Symposium; June 1–22, 2013; Baltimore, MD
26. De-ID [computer program]. Richboro, PA: De-ID Corp LLC. 2004. Available at: www.de-idata.com. Accessed January 30, 2013
27. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform*. 2009;42(2): 377–381
28. Keren R, Shah SS, Srivastava R, et al; Pediatric Research in Inpatient Settings

Network. Comparative effectiveness of intravenous vs oral antibiotics for postdischarge treatment of acute osteomyelitis in children. *JAMA Pediatr*. 2015;169(2):120–128

29. Zaoutis T, Localio AR, Leckerman K, Saddlemire S, Bertoch D, Keren R. Prolonged intravenous therapy versus early transition to oral antimicrobial therapy for acute osteomyelitis in children. *Pediatrics*. 2009;123(2):636–642
30. O'Malley KJ, Cook KF, Price MD, Wildes KR, Hurdle JF, Ashton CM. Measuring diagnoses: ICD code accuracy. *Health Serv Res*. 2005;40(5, pt 2):1620–1639
31. Arnold JC, Cannavino CR, Ross MK, et al. Acute bacterial osteoarticular infections: eight-year analysis of C-reactive protein for oral step-down therapy. *Pediatrics*. 2012;130(4). Available at: www.pediatrics.org/cgi/content/full/130/4/e821
32. Unkila-Kallio L, Kallio MJT, Peltola H. The usefulness of C-reactive protein levels in the identification of concurrent septic arthritis in children who have acute hematogenous osteomyelitis. A comparison with the usefulness of the erythrocyte sedimentation rate and the white blood-cell count. *J Bone Joint Surg Am*. 1994;76(6):848–853
33. Ju KL, Zurakowski D, Kocher MS. Differentiating between methicillin-resistant and methicillin-sensitive Staphylococcus aureus osteomyelitis in children: an evidence-based clinical prediction algorithm. *J Bone Joint Surg Am*. 2011;93(18):1693–1701
34. Wade Shrader M, Nowlin M, Segal LS. Independent analysis of a clinical predictive algorithm to identify methicillin-resistant Staphylococcus aureus osteomyelitis in children. *J Pediatr Orthop*. 2013;33(7):759–762
35. An TJ, Benvenuti MA, Mignemi ME, et al. Similar clinical severity and outcomes for methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* pediatric musculoskeletal infections. *Open Forum Infect Dis*. 2017;4(1):ofx013

# Comparison of Empiric Antibiotics for Acute Osteomyelitis in Children

Sarah McBride, Cary Thurm, Ramkiran Gouripeddi, Bryan Stone, Phil Jaggard, Samir S. Shah, Joel S. Tieder, Ryan Butcher, Jason Weiser, Matt Hall, Ron Keren and Christopher P. Landrigan

*Hospital Pediatrics* 2018;8;280
DOI: 10.1542/hpeds.2017-0079 originally published online April 6, 2018;

**Comparison of Empiric Antibiotics for Acute Osteomyelitis in Children**

Sarah McBride, Cary Thurm, Ramkiran Gouripeddi, Bryan Stone, Phil Jaggard, Samir S. Shah, Joel S. Tieder, Ryan Butcher, Jason Weiser, Matt Hall, Ron Keren and Christopher P. Landrigan

*Hospital Pediatrics* 2018;8;280
DOI: 10.1542/hpeds.2017-0079 originally published online April 6, 2018;