Disclosures

• Current sources of research funding
  • National Institute of Allergy & Infectious Diseases
  • Patient-Centered Outcomes Research Institute
  • National Heart, Lung, & Blood Institute
  • Cincinnati Children’s Research Foundation

• No financial conflicts of interest
Objectives

• Review data supporting the role of early conversion to oral therapy for children with acute hematogenous osteomyelitis

• Discuss a comprehensive for the evidence-based management of acute hematogenous osteomyelitis

AHO = acute hematogenous osteomyelitis
• Age 3 months- 21 years

• Clinical suspicion for acute bone infection
CCHMC Guideline - Excludes

• Non-acute osteomyelitis (symptoms >2 weeks)
• Non-hematogenous osteomyelitis
  • Prior fracture or surgery at site
  • Infections from penetrating trauma
  • Pressure ulcers leading to osteomyelitis
• Atypical patients
  • Immunocompromised
  • Multifocal disease
  • Medically complex patients
CCHMC Guideline

• Local expert consensus
  • Admit to Hospital Medicine
  • Orthopedic consultation
  • Infectious Diseases consultation
CCHMC Guideline- Initial Evaluation

• C-reactive protein
  • Elevated CRP consistent with AHO
  • Normal or minimal elevation suggests other cause
  • ESR not recommended- limited value
    • Correlates with CRP but rises & declines more slowly
  • Procalcitonin not recommended
    • Insufficient data

• Complete blood count
  • Normal in 65% of cases
  • May suggest alternate cause

• Blood culture

• X-ray of affected site
CCHMC Guideline - AHO Diagnosis

• CRP >2 mg/dL
  • High sensitivity (98%)
  • Insufficiently specific to differentiate from other infections

• One or more
  • Characteristic pain
  • Localized signs or symptoms
  • Reduced ROM
  • Reduced weight bearing

• Lack of alternate explanation
CCHMC Guideline

• Cultures
  • Obtain blood culture prior to antibiotics
  • Insufficient data to recommend routine bone aspiration prior to antibiotics
  • If vancomycin initiated, strongly consider source culture

• Defer antibiotics for up to 24h in patients who do not meet formal sepsis criteria if bone or tissue culture will be performed

• Start empiric antibiotics immediately once intended cultures obtained or with positive culture from sterile site (e.g., blood, bone)
CCHMC Guideline- Treatment

• Cefazolin for most patients
CCHMC Guideline- Why Cefazolin?

- Most effective antibiotic vs. MSSA
- CCHMC osteomyelitis
  - >70% MSSA
  - Modest prevalence of clindamycin-resistant MSSA
  - Modest prevalence of clindamycin-resistant MRSA
- Effective vs. *K. kingae*
- Screen for MRSA risk factors
CCHMC Guideline- Treatment

• **Cefazolin** for **most** patients

• **Clindamycin** if **MRSA risk factors**
  • Any prior hospitalization with MRSA infection
  • History of other MRSA infection in past 2 years
  • History of skin abscesses in past 2 years
  • Abscess associated with current infection
  • Immediate family members with MRSA skin abscesses or other infection recently
CCHMC Guideline- Age <4 years

- Review risk factors for *Kingella kingae*
  - Concomitant mucositis, stomatitis, or oral ulcers
  - Mild clinical disease, especially if not responsive to initial clindamycin treatment
- Clindamycin does **not** cover *K. kingae*
  - If clindamycin initiated, consider adding cefazolin or ceftriaxone based on history & risk factors
CCHMC Guideline - Critically Ill

- **Vancomycin & cefazolin** for critical illness

- Definition of critical illness
  - ICU admission
  - Meets formal pediatric sepsis criteria
  - Overall ill appearance
  - Requires large volume fluid resuscitation

- Seriously consider source (i.e. bone) culture when feasible
CCHMC Guideline - Imaging

• MRI
  • Recommended to confirm diagnosis
  • Highly sensitive
  • May guide decisions regarding need for surgery

• Tc99 bone scan is not generally recommended
• Indications for surgical intervention
  • Abscess >1cm identified on clinical exam or imaging
  • Failure to improve after 48h of reasonable medical therapy
• CRP
  • To follow response to therapy
  • Frequency
    • Not more often than every 48 h
    • Less often if patient is improving or received surgery or bone debridement

• Blood culture
  • 1 per day for at least 2 days
  • Daily if bacteremia persists

• Not recommended
  • Repeat CBC
  • Any ESR
• Patients should transition to oral therapy as standard practice

• Contraindications to oral therapy
  • Unable to take oral medication
  • Underlying condition affecting drug absorption
  • Isolate resistant to oral antibiotic options

• Concerns about patient adherence are not a contraindication to oral therapy
  • Focus on interventions to promote adherence to oral regimen
• Criteria for transition to oral therapy
  • IV therapy for at least 72h (some exceptions)
  • Significant clinical improvement
    • Improvement in initial symptoms
    • Resolution of fever
  • Resolution of bacteremia
    • Caution if total duration of bacteremia >3 days
  • CRP decreased by 33% from initial value or values downtrending
  • Causative bacteria identified & susceptibilities confirmed OR no organism identified & relevant cultures no growth for >48 h
CCHMC Guideline- Discharge Criteria

• If oral transition criteria met
  • Oral “test” dose given
  • Consider additional observation on oral antibiotics if patient is young or if administration of first dose is challenging
  • Patient has medication “in hand”
  • Consider blister pack for those receiving pills or capsules

• If requires IV therapy, ensure that homecare arranged
• Education completed
• Follow-up scheduled (ID, Ortho, PMD)
CCHMC Guideline - Follow-up Visits

• Oral therapy
  • ID
    • 7-10 days after discharge
    • 4 weeks after discharge +/- 1 week
    • Additional follow-up as indicated
    • More frequent follow-up if issues arise or suspected
  • Orthopedics
    • 2-4 weeks after discharge if immobilization or surgical intervention
    • 4 weeks after discharge with growth plate involvement

• IV therapy
  • ID clinic weekly
  • Orthopedics as above
CCHMC Guideline- Follow-up Labs

- CRP
  - At 1st follow-up visit
  - At 2nd follow-up visit if not normal at initial visit
  - Provide guidance for blood draw prior to appointment

- No other follow-up labs required unless specific indication exists
• 28 days of therapy if
  • CRP normal
  • Clinical symptoms resolved
• Elevated ESR (if checked) is not an indication for prolonging antibiotic therapy
Harms of Prolonged IV Therapy

- Complications
  - Hospital-acquired
  - Catheter placement-associated
  - Catheter-associated
- Medication error
- Financial costs
  - Healthcare system
  - Family
- Emotional toll

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Considerations for Early Switch to Oral Therapy

• Clinical improvement observed
• Oral route not compromised
  • Vomiting, malabsorption, severe diarrhea, or patient refusal of oral medications
• Laboratory or other markers improving (not always necessary if other criteria are met)
• Indication for oral therapy
  • i.e., not meningitis, not endocarditis
• Comparable oral antibiotic option available
Osteomyelitis: Primary Outcome

• Main Exposure
  • Post-discharge antibiotics via PICC or oral route

• Main Outcome
  • Treatment failure
    • ED or hospital revisit resulting in escalation of therapy (e.g., change in antibiotics, switch from PO to IV, abscess drainage, bone debridement)

• Secondary Outcomes
  • Adverse drug reaction (e.g., neutropenia, acute kidney injury, Stevens-Johnson)
  • PICC complication (including fever evaluation)
  • Composite of primary & secondary outcomes
Figure 1. Flowchart of the Study Cohort

8555 Patients 2 mo to younger than 18 y discharged January 1, 2009, through December 31, 2012, with acute osteomyelitis (ICD-9-CM codes 730.01-730.09) or unspecified osteomyelitis (ICD-9-CM codes 730.2-730.29) from 38 PHIS hospitals

6064 Excluded based on PHIS data
758 Subsequent visits
115 Acute or chronic osteomyelitis diagnosis ≤6 mo prior
1054 Chronic condition
1293 Direct admission
99 Transferred out
114 Other specified sites of infection (ICD-9-CM code 730.08)
197 Length of stay <2 d or >14 d
2434 Other excluded ICD-9-CM diagnosis and procedure codes

2491 Underwent medical record review

431 Excluded based on medical record review
3 Subsequent visits
109 Direct admissions
36 Not osteomyelitis
20 No antibiotics at discharge
94 Other excluded diagnoses and procedures
68 At 2 hospitals did not review medical records
101 Other

2060 Final cohort from 36 hospitals

1005 Receive antibiotics via oral route
1055 Receive antibiotics via PICC route
Large and evenly distributed variation in use of PICCs

No correlation between hospital osteo volume and use of PICCs
Matching reduces differences

**Table 2. Clinical and Demographic Characteristics of Treatment Groups After Within- and Across-Hospital Matching**

<table>
<thead>
<tr>
<th></th>
<th>Route of Antibiotic Therapy&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td></td>
<td>Unmatched Means</td>
<td>Matched Across Hospital</td>
<td>Matched Within Hospital</td>
<td>Weighted Means&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Matched Across Hospital</td>
<td>Matched Within Hospital</td>
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<td>Oral</td>
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<td>LOS, median, d</td>
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<td>Infection location</td>
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<td>Lower leg, ankle, and/or foot</td>
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<td>46.8</td>
<td>43.5</td>
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<td>Pelvis and thigh</td>
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<td>34.2</td>
<td>33.5</td>
<td>34.8</td>
<td>33.5</td>
<td>34.8</td>
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<td>Upper arm, forearm, and/or hand</td>
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<td>12.0</td>
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<td>Shoulder region</td>
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<td>2.2</td>
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<td>Arthrocentesis</td>
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<td>19.2</td>
<td>14.3</td>
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<td>42.4</td>
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<td>42.4</td>
<td>39.4</td>
<td>42.4</td>
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<td>Soft-tissue incision and drainage</td>
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<td>15.9</td>
<td>16.8</td>
<td>15.9</td>
<td>17.2</td>
<td>15.9</td>
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<td>Arthrotomy</td>
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<td>19.8</td>
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<td>19.8</td>
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<td>21.5</td>
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<td>Causative organism, finding of the culture</td>
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<td>Negative</td>
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<td>35.1</td>
<td>38.7</td>
<td>35.1</td>
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<td>MRSA</td>
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<td>20.4</td>
<td>18.7</td>
<td>18.5</td>
<td>18.7</td>
<td>18.5</td>
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<tr>
<td>MSSA/other</td>
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<td>41.0</td>
<td>46.3</td>
<td>47.6</td>
<td>46.3</td>
<td>47.6</td>
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</tbody>
</table>
### Table 3. Adverse Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Oral Route (n = 1005)</th>
<th>PICC Route (n = 1055)</th>
<th>Across-Hospital Match</th>
<th>Within-Hospital Match</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Raw, No. (%) of Patients</td>
<td></td>
<td>OR (95% CI)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>P Value</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>50 (5.0)</td>
<td>63 (6.0)</td>
<td>1.06 (0.70 to 1.61)</td>
<td>.77</td>
</tr>
<tr>
<td>Adverse drug reaction</td>
<td>22 (2.2)</td>
<td>40 (3.8)</td>
<td>1.83 (1.03 to 3.25)</td>
<td>.04</td>
</tr>
<tr>
<td>PICC complication</td>
<td>NA</td>
<td>158 (15.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All treatment-related</td>
<td>71 (7.1)</td>
<td>234 (22.2)</td>
<td>3.61 (2.64 to 4.93)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>events&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; OR, odds ratio; PICC, peripherally inserted central catheter.

<sup>a</sup> Adjusted results are based on propensity scores and full matching of patients across and within hospitals (or hospital groups).

<sup>b</sup> Estimated using conditional logistic regression, conditioning on the matched sets. An OR of greater than 1.00 means that the PICC route has a higher risk for the adverse outcome.

<sup>c</sup> Estimated using fixed-effects regression stratified by the matched sets. A risk difference of greater than 0 means that the PICC route has a higher risk for the adverse outcome.

<sup>d</sup> Rows do not sum to all treatment-related events because some patients had more than 1 adverse outcome.
Isolation of MRSA as the causative organism did not modify the effect of the treatment route on the outcome of treatment failure.
• Children discharged to complete antibiotic course via oral route did NOT have a higher rate of treatment failure

• MRSA+ infections did not have more treatment failures

• High rate of serious PICC complications
  • 15% required ED revisit or rehospitalization
    • Bloodstream infections
    • Thromboembolism
    • PICC displacement/breakage

Osteomyelitis
Osteomyelitis

- Likely to be strongest evidence available to answer question
  - RCT not feasible

- Results consistent, even with rise in MRSA prevalence (study period 2009-2012)

- Stop using PICC lines to treat acute osteomyelitis in otherwise healthy children who can tolerate oral route

- Oral route equally effective, fewer complications, less expensive and more convenient
Thank You!

Samir.Shah@cchmc.org

@SamirShahMD