Updates in Osteomyelitis Management

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Disclosures

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Objectives

This quick hit session will provide participants with updates on how to manage osteomyelitis in a hospital setting.

1. Review clinical findings suggestive of AHOM
2. Identify the most common pathogens and empiric antibiotic therapy options in pediatric acute hematogenous osteomyelitis (AHOM).
3. Updates regarding controversies surrounding the management of pediatric AHOM.
4. Updates on the existing evidence for managing AHOM.
Recent Publications (Not Reviews)

- New articles for acute hematogenous osteomyelitis since 2015 (PubMed): 17
- Of these, 2 are multi-site!

Background

- AHOM accounts for 1% of pediatric hospitalizations
- Limited evidence results in varied treatment approaches
- Oftentimes a topic of controversy
Why osteomyelitis?

- Uncertainty surrounds:
  - empiric antibiotic selection
  - use of prolonged intravenous versus oral antibiotics
  - optimizing patient follow-up
  - how to manage cases without positive cultures
  - differentiating complicated from uncomplicated AHOM

Outline

- Recognizing the patient suspected with AHOM
- Common pathogens and diagnosis
- Empiric therapy/antibiotic selection
- Oral vs. IV therapy
- Common exclusion criteria/complicated osteo
- PICC lines
- Discharge planning
AHOM Clinical Dx Pearls

- General features:
  - Fever (40-80%); focal pain (NOT infants 56-95%); decreased mobility (50-84%)
  - 2015 review of MSK infections (single site): 68% of pts with septic arthritis had concomitant osteomyelitis
- Preceding symptoms over several days-1week
- Culture-positive more likely to have: trauma; skin findings; higher WBC; shorter sx duration

Supporting Evidence:
Thévenin-Lemoine, et. al., 2016
MRI of acute osteomyelitis in long bones of children: Pathophysiology study.
20 children dx’d with AHO with MRI of long bones
Red-Flag Symptoms

- Fever and gait disturbance
- Focal limb, back, or hip pain not explained by trauma
- Severe, focal back pain (particularly older children)
- Infants with irritability with movement of limb, or persistent history of inconsolability

Guides for evaluation

- WBC is not sensitive (elevated in only 35%)
- ESR/CRP almost always elevated (92% ESR; 98% CRP)
- Plain films insensitive in AHOM
  - 14 days for radiographic changes
- Preferred imaging: MRI
- 2 sets of blood cultures should be obtained in all children prior to initiating antibiotics
Effects of Antibiotic Pre-Treatment

- Zhorne, et. al. 2015
  - 1-year retrospective review of children 2mo-18yo with AHO
  - 67 children who underwent bone biopsy
    - 40 pre-treated with antibiotics
    - No difference in yield for bone bx if antibiotics given (OR 1.37, 95% CI: 0.49-3.86)
      - Longer duration of abx prior to bx associated with lower yield from bx (p=0.04)
    - Bx only microbiological dx in 54% of non-bacteremic children
Case 1

- Previously healthy fully immunized 13 year old male presenting with knee pain
  - Knee pain for 2 days
  - Fever to 102 F at home
  - Minor trauma during sports, nothing specific
  - Knee pain is constant, but worsens with walking

Case 1

- On exam:
  - VS: T 38.1, HR 102, RR 21, BP 117/69
  - Point tenderness over right anterior proximal tibia
  - No palpable knee effusion
  - Mild swelling noted
  - Range of motion of knee normal
Case 1

- Labs:
  - Seg 63
  - Band 0
  - Lymph 22
  - Mono 13
  - ESR 20
  - CRP 11
  - Blood culture pending

Case 1

- Imaging:
  - Xray: “Localized soft tissue swelling adjacent to the metaphysis. Otherwise normal.”
  - MRI result: “Signal abnormality suggestive of osteomyelitis involving the right tibial tuberosity. There is a very small right knee joint effusion and synovitis which is nonspecific and can be reactive”
What Would You Do?

Which empiric therapy would you choose:

– Cefazolin
– Clindamycin
– Vancomycin
– Something else
Common pathogens

- **S. aureus** is by far the most common etiology in all age groups
  - MRSA may comprise 50% or more of AHO due to **S. aureus**
- The next most common are GAS, **S. pneumoniae**, or **K. kingae**
  - Study in France using RT-PCR to detect **K. kingae**, 45% were positive (most common in ages 6mos – 3yrs)
  - US study found **K. kingae** as causative agent in children with acute bacterial osteo 3% of time and acute bacterial arthritis 19% of time
Prevalence of organisms


Causative agents and localization of 131 cases of acute hematogenous osteomyelitis of children
Special Considerations: Epidemiology

- GBS and enteric GNRs in neonates
- Salmonella in children with hemoglobinopathies
- *P. aeruginosa* in children with puncture wounds of the foot
- *H. influenzae* now rare with success of HIB vaccine

- In almost half of children with acute osteomyelitis, a bacterial etiology is never established
  - Bone biopsy can help increase microbiological diagnosis

**EMPIRIC THERAPY/ANTIBIOTIC SELECTION**
Empiric Antibiotic Selection

- Always include treatment for *S. aureus*
  - Some experts recommend that if the rate of CA-MRSA is >10%, antibiotics directed against MRSA should be administered from the onset of treatment
  - Vancomycin recommended when MRSA clindamycin resistance >15%
  - Clindamycin is also effective
  - When local clindamycin resistance rates exceed 10-15%, clindamycin is not recommended for initial empiric treatment
- Vancomycin and clindamycin are effective against most GAS and *S. pneumoniae* but NOT *K. kingae*
- Penicillins and cephalosporins are effective against *K. kingae*

IDSA MRSA Guidelines – Vancomycin versus Clindamycin

“For children with acute hematogenous MRSA osteomyelitis and septic arthritis, IV vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin can be used as empirical therapy if the clindamycin resistance rate is low (eg, <10%).”
Take Home Points:
Empiric Antibiotic Selection

- Clindamycin is a good choice for empiric coverage of S. aureus for AHOM in a stable patient if your local susceptibility patterns allow.

- In a patient with bacteremia or abnormal vital signs, consider vancomycin for empiric coverage of S. aureus*.

- In a patient < 3 years of age with septic arthritis, consider addition of a beta lactam for coverage of K. kingae.

ORAL VS. IV THERAPY
Do oral antibiotics work as well as IV?

- LeSaux, BMC ID, 2002
  - Systematic review of short vs. long course parenteral antibiotic therapy for AHOM
  - Identified 11 eligible prospective studies
    - AHOM defined as:
      - +Staph aureus from bone or periosteum, or
      - clinical signs of osteomyelitis with + blood culture, or
      - clinical signs and compatible radiologic study
    - Exposure: <7 days of IV therapy vs. ≥7 days of IV therapy
    - Outcome: Clinical cure rate at 6 months

Pooled Cure Rate: 98.8% [93.6, 99.8]

No significant difference in the cure rate between the two groups (z-test p value 0.838)
Do oral antibiotics work as well as IV?

- Comorbid conditions whose presence suggests complicated or difficult-to-treat osteomyelitis
  - Congenital and acquired immunodeficiencies
  - Sickle cell disease
  - Trauma
  - Osteomyelitis associated with immobilization or pressure ulcers (e.g., spina bifida, quadriplegia, paraplegia, mechanical ventilation, and postoperative infections)
  - Osteomyelitis of the head, face, and orbits
- Conditions that predispose to inadequate absorption of oral medications
- Prior admissions that might increase the risk of subsequent complicated osteomyelitis
  - Cellulitis
  - Sacroiliitis
  - Arthropathy
  - Myositis
  - Congenital or acquired diseases of bone
  - Placement of orthopedic devices or prosthesis

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Do oral antibiotics work as well as IV?

  - Results: Readmissions
    - 5% in prolonged IV therapy
    - 4% in early transition group
    - 3.4% catheter associated complications

What would you do?

- When would you consider transition to oral antimicrobial therapy?
  - When CRP normalized and patient is afebrile
  - Following 3-4 days of IV therapy
  - At time of discharge
  - When seen in follow up by PCP
  - When ID tells me to
  - My answer is still never
Timing of transition to oral

- **LeSaux, *BMC ID*, 2002**
  - Using cut off of 7 days, found no difference between long and short-term IV antibiotics courses

  - Prospective study of 44 patients with culture positive AHOM studying trends of CRP/ESR/WBC
  - CRP peaked at day 2, normalized by 1 week
  - ESR peaked at day 3-5, normalized by 3 weeks
Timing of transition to oral

- Arnold, Pediatrics, 2012
  - Single center, retrospective review
    - 194 patients with culture positive AHOM and ABA
    - Transitioned to oral therapy with CRP declining to <2-3 and evidence of clinical response
  - Outcome: Complication rates
    - prolonged therapy, re-hospitalization, relapse, long term complications (joint, AVN, limb-length)

- Findings:
  - 21% (40) had complications
    - 87.5% (35) had “prolonged therapy”; associated with a higher CRP at time of diagnosis and lower CRP at end of IV course
    - 1 had microbiologic failure after oral stepdown therapy

<table>
<thead>
<tr>
<th>Time</th>
<th>Uncomplicated</th>
<th>Complicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admit</td>
<td>8.7 (±7.4)</td>
<td>10.5 (±7.2)</td>
</tr>
<tr>
<td>Max</td>
<td>11.7 (±8.8)</td>
<td>15.7 (±8.1)</td>
</tr>
<tr>
<td>Transition to PO</td>
<td>2.1 (±1.9)</td>
<td>1.5 (±1.4)</td>
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**Bacteremia and oral antibiotics**

- Pääkönen, et. al. 2015
  - Review of 265 patients with AHO and/or septic arthritis, 157 with bacteremia
    - 130 bacteremic with *S. aureus* (most MSSA)
  - All patients had IV antibiotics 2-4 days then transitioned to PO
  - No differences in length of therapy, treatment failure for bacteremic vs non-bacteremic children

**All Oral Therapy?**

- Retrospective analysis of 45 children 1-11 yo with AHO without complications
  - CRP >50mg/L; fever>38.5C; septic shock; periosteal abscess at admission; multifocal infection; immunodepression; Sickle Cell Disease
- 26 pts IV→PO; 19 with amox-clav only
Take Home Points: Transition to Oral Antibiotics

- Oral antibiotics are efficacious in treating **acute, uncomplicated** osteomyelitis
- Early transition to oral antibiotics demonstrates success similar to that of long term IV therapy
- Early transition to oral therapy, even in cases of bacteremia, may be equally efficacious in uncomplicated AHO
Case 2

- 7yo female admitted with fever and L groin pain
  - Groin pain for 2 days
  - Fever to 102 F at home
  - Minor trauma during sports, nothing specific
  - Pain is constant, and she cries with attempts at walking
  - PMH: 2 prior episodes of MRSA skin infections
    (both required I&D followed by TMP- SMX)
Case 2

- MRI of hip: “signal abnormality of the left femoral neck consistent with osteomyelitis”
- On admission started IV vancomycin

- Patient remains febrile and irritable
- Initial blood cultures positive for MRSA
- Repeat blood cultures positive for 4 days
- Repeat MRI: “Left proximal femoral neck osteomyelitis; left hip synovitis, effusion; medial compartment myositis and fasciitis”
What would you do?

- Would you transition this patient to oral therapy prior to discharge?
  - Yes
  - No
  - Uncertain

- Why or why not?
Common Exclusion Criteria

- Patients <1 month and >18 years
- Sub acute or chronic osteomyelitis (sxs >14 days)
- Comorbid conditions (e.g., immunodeficiency, sickle cell disease, trauma, etc…)
- Osteomyelitis of head/face/orbits
- Previous admission for conditions increasing risk for complicated osteomyelitis (e.g., cellulitis, pyogenic arthritis, trauma, fractures, placement of orthopedic devices, etc…)
- Pretreatment with antibiotics
- Culture negative (no positive culture from either blood, bone or joint fluid)
Data Free Zone

- Complicated osteo
- Surgical interventions
- Hardware
- Not a long bone
- Culture negative
- Neonates

Severity Score for AHO

- Athey, et. al. 2016
- Prospective observational cohort of AHO at single center, 2012-2014 (148 children)
- Clinical, radiologic, and lab data used to calculate severity of illness (SOI) score (from within first 4 days)
- Validated by correlating with LOS and APR-DRG and ROM scores
Estimating Severity of Illness

<table>
<thead>
<tr>
<th>CRP initial</th>
<th>CRP 48 hours</th>
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<tbody>
<tr>
<td>&lt;10</td>
<td>&lt;5</td>
</tr>
<tr>
<td>10-15</td>
<td>5-10</td>
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<tr>
<td>&gt;15</td>
<td>&gt;10</td>
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<table>
<thead>
<tr>
<th>Band count</th>
<th>ICU Admission</th>
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<tbody>
<tr>
<td>&lt;1.5</td>
<td>No</td>
</tr>
<tr>
<td>≥1.5</td>
<td>Yes</td>
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Febrile Days on Antibiotics: No = 0; Yes = 1
Disseminated Disease: No = 0; Yes = 1

Chiappini, et al., 2017
Retrospective review of 121 cases AHO 2010-2015
Risk factors for complications:
- Fever
- Upper limb involvement
- WBC >12,000
- CRP >10 mg/L
- S. aureus infection
Case 2 Update

- Patient required 1 trip to the OR for debridement
- Subsequently fever resolved, blood cultures cleared, and CRP trended down
- Clinically, patient significantly improved prior to discharge

Take Home Points: Complicated Osteo

- It’s a headache when patients don’t read the book…
- Involvement of ID specialists to help guide decisions
  - Prolonged IV therapy may be necessary in some cases…
  - But they may be able to transition to oral later in course
- Need for predicting severe cases
  - Role for multi-site studies?
PICC Cautionary Tales

- Catheter-associated complications requiring medical attention occur in ~30% (17-41%) of children with PICC lines at home
  - Rate of complications: 13.9-19.3/1000 PICC days
- Risk factors for complications:
  - osteomyelitis*
  - increased number of daily doses*
  - double-lumen PICCs*
  - increased duration of therapy
  - younger age*
  - lower median household income*

*not consistently found in all studies
PICC Therapy in Osteo

  - 75 patients who received >2 weeks of IV therapy
  - 41% had ≥ 1 CVC-associated complication
    - 17 (23%) had malfunction or displacement
    - 8 (11%) had catheter associated blood stream infection
    - 8 (11%) had fever with negative blood cultures
    - 4 (5%) had local skin infection

Take Home Points: PICC Lines

- Complications are not uncommon.
  - Mechanical complications are most common type of PICC complication.
- It is important to assess the risks and benefits when placing a PICC.
Discharge Planning and Follow Up

- Responsible physician identified prior to discharge
- Close monitoring required
  - Recommends up to a year
- Follow clinical exam and CRP trends
  - If CRP levels rise, concern for complication
- Debate about basing continuation of therapy until normalization of ESR
- X-rays sufficient for detecting sequelae in most circumstances

Take Home Points: Discharge Planning

- Close follow up after discharge is key regardless of antibiotic plan
  - Assure that PCP is comfortable with plan
  - Consider follow up with ID
    - Especially in kids sent home on IV therapy
Summary

- **Know thy enemy.** (local susceptibility patterns)
- Evidence shows us transition to oral is safe and effective in uncomplicated cases.
- There is no consensus on management of complicated osteomyelitis or culture negative cases.
- PICC lines are interventions and not without risk.
- Reliable follow up is key.

References

More References