



# What the Cough? Management and Controversies of Common Pediatric Infections

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# Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

# Learning Objectives

- Evaluate appropriate therapy of common pediatric infections.
- Evaluate therapy modifications for common infections in pediatric obesity.
- Given a patient case, recommend appropriate pharmacotherapy adjustments.

# Case #1: L.B.

- HPI: L.B., a 5 year old Caucasian female with no known drug allergies and a recent diagnosis of asthma, presents to the emergency department with a 3 day history of subjective fever, otalgia, lethargy, and cough that worsened overnight per caregiver report.

Vitals upon triage	
Weight (kg)	33
HR (beats/minute)	120
RR (breaths/minute)	25
SpO <sub>2</sub> saturation (%)	92 on room air
Temp (C)	39.5

## L.B. Continued

- Pertinent physical exam findings
  - Awake and oriented
  - Severe, unilateral bulging of the tympanic membrane
  - Mild dehydration
- Vaccine history
  - Caregiver states patient received all vaccines “when she was a baby” but has received “the yearly flu shot” in the past
- Medication history
  - Ibuprofen dose unknown, taken 3 times daily over the last 48 hours
  - Multivitamin 1 tablet by mouth once daily
  - Honey tea (homemade recipe)
  - Cefdinir 14 mg/kg/day by mouth divided twice daily X 3 days

# L.B.'s Emergency Department Course

L.B. is given a diagnosis of acute otitis media. She has brief intermittent desaturations while sleeping that self-resolve.



Peripheral IV access is obtained, and the following additional laboratory tests are sent for evaluation:

- Rapid influenza A/B, respiratory syncytial virus (RVP) molecular detection test
- Complete blood count with differential
- Comprehensive metabolic panel

## Which of the following therapies should be initiated for management of L.B.'s acute otitis media?

- A. Amoxicillin - clavulanate 90 mg/kg/day by mouth divided twice daily
- B. Cefpodoxime 10 mg/kg/day by mouth divided twice daily
- C. Clindamycin 30 mg/kg/day by mouth divided three times daily
- D. Trimethoprim - Sulfamethoxazole 10 mg/kg/day TMP divided BID

# Clinical Controversies

What is the appropriate empiric therapy for severe AOM?

What is the appropriate dosing strategy for empiric treatment in obese patients?

What is the role of cefdinir in AOM management?



# Acute Otitis Media (AOM) Management

- American Academy of Pediatrics (AAP), consensus guidelines 2004, 2013
  - Provides definitions for severity of illness
    - Uncomplicated versus severe versus non – severe
    - Aids in determination of watchful waiting strategy versus immediate treatment
    - Age stratified recommendations for durations of therapy
- Associated predominant pathogens
  - 66% bacteria + virus, 27% bacteria, 4% virus alone
  - *Streptococcus pneumoniae*, non-typeable *Haemophilus influenzae*, *Moraxella catarrhalis*
- Self-resolving?
  - 19% *S. pneumoniae*, 48% *H. influenzae*, 75% *M. catarrhalis*

# AOM Guidelines Continued

- Data on susceptibility patterns has decreased due to ↓ tympanocentesis
  - *S. pneumoniae* (all age groups):
    - 83% susceptible to regular dose amoxicillin (40 mg/kg/day)
    - 87% susceptible to high dose amoxicillin (80 - 90 mg/kg/day)
    - Only pediatric patients: ↑ multidrug-resistant, nonvaccine serotypes
  - *H. influenzae*
    - 58% susceptible to regular dose amoxicillin
    - 82% susceptible to high dose amoxicillin
  - *M. catarrhalis*
    - 100% from upper respiratory tract are  $\beta$ -lactamase positive

# AOM Indications to Treat

Age	Otorrhea + AOM	Unilateral or bilateral severe AOM	Bilateral AOM without otorrhea	Unilateral AOM without otorrhea
6 mo – 2 years	Treat	Treat	Treat	Treat or observe
≥ 2 years	Treat	Treat	Treat or observe	Treat or observe

# AOM Immediate or Delayed Treatment

First Line Treatment	Alternative Treatment (Penicillin Allergy)
Amoxicillin 80 – 90 mg/kg/day divided BID	Cefdinir 14 mg/kg/day QD or BID
OR	Cefuroxime 30 mg/kg/day divided BID
Amoxicillin-clavulanate 90 mg/kg/day divided BID	Cefpodoxime 10 mg/kg/day divided BID
	Ceftriaxone 50mg/kg IM or IV x 1 – 3 days

# AOM Treatment after Initial Antibiotic Failure

First Line Treatment	Alternative Treatment
Amoxicillin-clavulanate 90 mg/kg/day divided BID	Ceftriaxone 50 mg/kg IM or IV x 3 days
OR	Clindamycin 30 – 40 mg/kg/day divided TID +/- 3 <sup>rd</sup> generation cephalosporin
Ceftriaxone 50 mg/kg IM or IV x 3 days	

# Additional $\beta$ – lactam Considerations for AOM

- Immediate amoxicillin 90 mg/kg/day most cost-effective
  - Immediate amoxicillin-clavulanate 90mg/kg/day
  - Immediate cefdinir 14 mg/kg/day
- Empiric amoxicillin-clavulanate 90 mg/kg/day and cefpodoxime 10 mg/kg/day divided BID greatest likelihood of pharmacodynamic exposures

# Clinical Controversies

What is the appropriate empiric therapy for severe AOM?

**Amoxicillin**

What is the appropriate dosing strategy for empiric treatment in obese patients?

What is the role of cefdinir in AOM management?

# Amoxicillin Dosing in Obesity for AOM

- AAP guidelines do not provide a max dose
- Christian-Kopp S, et al
  - Retrospective study of primary care physicians in a three month period
    - Patients  $\leq 20$  kg received higher mean doses (54.2 vs 40.4 mg/kg/day,  $P < 0.00$ )
- 2004 AOM subcommittee members surveyed
  - 9 members responded (64.3%)
    - 6 would prescribe standard adult dose (1500 mg/day)
    - 3 would prescribe recommended 80 – 90 mg/kg/day



# Clinical Controversies

What is the appropriate empiric therapy for severe AOM?

**Amoxicillin**

What is the appropriate dosing strategy for empiric treatment in obese patients? **Dependent on practice**

What is the role of cefdinir in AOM management?

# Cefdinir: Treatment Failure vs. Optimal Dosing?

- Bowlware, et al
  - Pharmacokinetic analysis of cefdinir 14 mg/kg/day vs. 25 mg/kg/day
  - Adverse effects: diarrhea (20%), emesis (17.9%), abdominal pain (15.4%), red stool (10%), rash (25.6%)
  - T>MIC = 30% for intermediate resistant pneumococci
  - 25 mg/kg/day regimen unlikely effective for intermediate & non-susceptible *S. pneumoniae* strains

# Cefdinir: Treatment Failure vs. Optimal Dosing?

- Arguedas, et al
  - Double tympanocentesis study of cefdinir 25 mg/kg/day in AOM with high risk of persistent or recurrent infection
  - Adverse effects: abnormal stools (26%), diarrhea (14%), vomiting (9%)
  - Although overall successful clinical response (83%), markedly decreased effectiveness against nonsusceptible *S. pneumoniae* and moderate response for *H. influenzae*

# Clinical Controversies

What is the appropriate empiric therapy for severe AOM?

**Amoxicillin**

What is the appropriate dosing strategy for empiric treatment in obese patients? **Dependent on practice**

What is the role of cefdinir in AOM management?

**Limited for empiric therapy**

## Case Update: L.B.

Following initial triage, L.B. is admitted to the general pediatrics floor. She has received two doses of amoxicillin – clavulanate (45 mg/kg/dose), and her SpO<sub>2</sub> saturation remains at 89 - 90% on 2L of O<sub>2</sub> via nasal cannula. IV fluids have been initiated with D5-NS at 70 mL/hour to improve hydration status.



24 hours later, L.B. has intermittent desaturations to 80%, increased dyspnea, and increased purulence cough. She is placed on a venti mask for increased aeration; a chest X-ray and sputum culture are obtained.

- Updated test results are:
  - Rapid influenza (+)
  - Sputum culture pending
  - MRSA surveillance nasal swab (-)
  - WBC = 18,000 cells/ $\mu$ L
  - T<sub>max</sub> 39° C

## Case Update: L.B.

After additional evaluation, it is determined that L.B. likely has a diagnosis of pneumonia. The primary team would like to make adjustments to her therapy to reflect her new diagnosis in addition to maintaining adequate coverage of her AOM.



The institutional antibiogram is reviewed with the team to make appropriate modifications in therapy.

	Streptococcus pneumoniae µg/mL
Penicillin (non-meningitis)	0.05
Penicillin (meningitis)	0.12
Clindamycin	0.25
Ceftriaxone	0.5

\* 78 %  $\beta$ -lactamase producing *H. influenzae*

**Based on progression of L.B.'s symptoms, which of the following modifications to her current therapy is most appropriate?**

- A. Initiate oseltamivir 60 mg by mouth given twice daily and change amoxicillin/clavulanate to ceftriaxone 50 mg/kg intravenously every 24 hours.
- B. Discontinue amoxicillin/clavulanate and initiate oseltamivir 150 mg by mouth given twice daily + azithromycin 10 mg/kg intravenously every 24 hours.
- C. Initiate oseltamivir 60 mg intravenously every 24 hours and change amoxicillin/clavulanate to ampicillin/sulbactam 50 mg/kg intravenously every 6 hours .
- D. Initiate peramivir 12 mg/kg intravenously every 24 hours and escalate amoxicillin/clavulanate to cefepime 50 mg/kg intravenously every 12 hours + azithromycin 10 mg/kg intravenously every 24 hours.

# Clinical Controversies

Do we need to cover empirically for most common bacterial etiology of CAP?

Do we need to expand coverage to include a macrolide?

Is there a role for alternative oseltamivir dosing or use of IV peramivir?

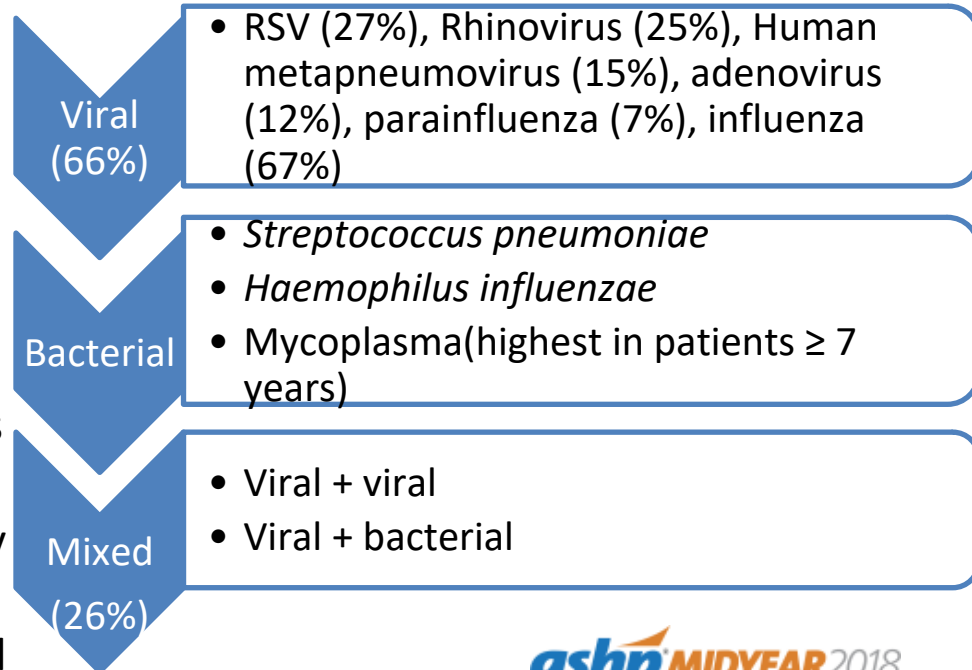


# Community Acquired Pneumonia (CAP) in Hospitalized Children

## Etiology of Pneumonia in the Community Study, EPIC

- Large, multi – site population based study
  - Rates ↑ in children < 2 years (62 cases/10,000 children; 95% CI, 57.6 – 67.1)
  - Defined CAP with radiologic confirmation
  - Robust culture and detection methods utilized
  - Able to characterize pathogen etiology and link to outcomes
  - Predictors of poor outcomes identified

## Pathogen etiology



# Co-Infections in Children Hospitalized with CAP

- Nolan, et al. 2018 (from the EPIC cohort)
  - Demographic and clinical characteristics compared between groups based on pathogen etiology
  - 2,219 children included
    - 26% were co - infected (bacteria + virus or 2 viruses)

Demographics
<ul style="list-style-type: none"><li>• Concomitant diagnosis of asthma</li><li>• Black ethnicity</li></ul>

Level of care
<ul style="list-style-type: none"><li>• ↑ ICU admissions</li><li>• Need for mechanical ventilation</li><li>• Increased lengths of stay</li></ul>

Laboratory findings
<ul style="list-style-type: none"><li>• ↑ frequency of<ul style="list-style-type: none"><li>• leukocytosis</li><li>• Consolidation on CXR</li><li>• Parapneumonic effusions</li></ul></li></ul>

# Clinical Controversies

Do we need to cover empirically for most common bacterial etiology of CAP? **Yes, we should after stratification by risk factors for co-infection**

Do we need to expand coverage to include a macrolide?

Is there a role for alternative oseltamivir dosing or use of IV peramivir?

# Guideline Antibiotic Recommendations for CAP Management in the Inpatient Setting

Fully immunized

- Ampicillin or Penicillin G (IV)
- Oral therapy only considered in patients with moderate illness

Partial immunization, high local level of penicillin resistance, or life-threatening illness

- 3<sup>rd</sup> generation cephalosporin
- Vancomycin provides additional benefit only if high level penicillin resistance (MIC > 0.12) exhibited

School aged children

- Addition of a macrolide recommended

# Beta - Lactam Monotherapy vs. Combination with a Macrolide Antibiotic

## Leyenaar et al. 2014

- Retrospective cohort
- Compared ceftriaxone (CTX) with ceftriaxone + macrolide (CTX +M)
- Children 1 - 17 years included
  - N = 4701 (CTX + M), N= 8892 (CTX)
  - Age based distribution of findings
    - 1 - 4 years = no difference in length of stay; increased cost
    - 5 – 17 years = shorter length of stay [RR 0.95 (95% CI:0.92-0.98)] no difference in cost

## Williams et al. 2017

- Another EPIC cohort study ☺
- Any  $\beta$ -lactam compared with  $\beta$ -lactam + macrolide therapy
- Primary endpoint: length of stay
- Secondary endpoints
  - ICU admissions, length of stay, self reported recovery
- 1418 children included
  - Median age 27 months (IQR 12 – 69 months)

# EPIC Cohort: Key Study Overview and Findings

- Oral or parenteral therapy included
  - $\beta$ -lactam therapy: 2<sup>nd</sup> or 3<sup>rd</sup> generation cephalosporin, penicillin, ampicillin, ampicillin-sulbactam, amoxicillin, and amoxicillin-clavulanate
  - Macrolide therapy: azithromycin and clarithromycin
- Pediatric, board certified radiologist blinded to patient characteristics
- Included PCR testing with nasopharyngeal or oropharyngeal swabs for pathogen determination

$\beta$ -lactam monotherapy (71%) as compared to  $\beta$ -lactam combination therapy (38%)

- Unmatched cohort
  - No difference in lengths of stay
  - Median length of stay, 55 vs. 59 hours
    - Adjusted hazard ratio 0.87; (95% CI, 0.74 - 1.01)
- Propensity matched cohort
  - No significant differences in secondary endpoints

## Another EPIC Cohort study...

- “Mycoplasma pneumoniae among children hospitalized with CAP” (Kutty et al.)
  - Epidemiologic study of patients with CAP
  - Prospective enrollment of patients with radiographic evidence of pneumonia + PCR + *Mycoplasma*
  - Comparison group: radiologically confirmed CAP patients without positive Mycoplasma PCR result
    - n= 182 patients (8% of total population studied)
    - 50%(28) of patients  $\geq 1$  co-pathogen detected
      - 46% of this subset < 5 years of age
      - 2% coinfecting with another bacterial pathogen
      - 96% coinfecting with a viral pathogen

# EPIC Cohort Study: Characteristics associated with *Mycoplasma* detection

- Age
  - 10 - 17 years (aOR, 10.7 [95% CI, 5.4–21.1])
  - 5 - 9 years versus 2 – 4 years (aOR, 6.4 [95% CI, 3.4–12.1])
- Outpatient antibiotics  $\leq$  5 days preadmission
  - OR, 2.3 [95% CI, 1.5–3.5]
- Co - pathogen detection
  - OR, 2.1 [95% CI, 1.3–3.3]
- Clinical characteristics were deemed non specific, however...
  - Less likely to have (as compared to typical bacterial pathogen etiology)
    - consolidation (56% vs 81%;  $P < .01$ )
    - pleural effusion (26% vs 56%;  $P < .01$ )
    - ICU admission (11% vs 36%;  $P < .01$ )
  - More likely to have a shorter hospital length of stay (median, 2 days vs 6 days;  $P < .01$ )

Key findings	
Demographics	Median age = 7 years
Level of care	12% required ICU admission
Distinctive features	26% had pleural effusions
Resistance	4% of isolates (6/169)



# Clinical Controversies

Do we need to cover empirically for most common bacterial etiology of CAP? **Yes, we should after stratification by risk factors for co-infection**

Do we need to expand coverage to include a macrolide? **Maybe not...additional confirmative data needed**

Is there a role for alternative oseltamivir dosing or use of IV peramivir?

# Characteristics of Management of Viral Infections in CAP

- Role of molecular diagnostic testing in antibiotic selection
  - Schulert et al. 2014
    - n = 167; 63%
    - Testing had no impact on antibiotic usage
    - Predominant organism identified via respiratory viral panel, RVP was RSV
- Supportive care is the preferred management strategy for non – influenza virus irrespective of severity of illness
- Initiation of therapy at any point in presentation demonstrates improved outcomes as evidence by lengths of stay and need for supplemental oxygen
  - Goal is to initiate within 24 hours of symptom onset for greatest benefit
  - Can still initiate therapy beyond 72 hours of symptom onset
- Neuraminidase inhibitor (NAI) therapy preferred

# Antivirals for Management of Viruses Associated with CAP

- 1/3 of all hospitalized children with influenza do NOT receive therapy
- Retrospective study assessing neuraminidase inhibitors (NAI)
- N= 784 patients
  - 90% received therapy during pandemic period (H1N1 2009) and 63% in the post pandemic period
  - 6% vs 8% mortality between groups treated and un treated (OR=0.67; 95% CI, 0.34 -1.36)
  - Multivariate analysis showed reduction in mortality for patients in the ICU on mechanical ventilation(OR=0.36; 95% CI, 0.16 -0.83)
  - Earlier time to initiation(< 24) led to greatest mortality benefit
  - 8% of patients were co-infected with bacterial pathogen

# Neuraminidase Inhibitors (NAIs) for Influenza Treatment

## Oseltamivir

- Drug of choice
- Reports of neuropsychiatric events

## Zanamivir

- Inhaled therapy  $\geq 7$  years
- Avoid in patients with asthma

## Peramivir

- Arose secondary to H1N1 (2009)
- IV therapy
- Not FDA approved for hospitalized pediatric patients

- Lack of adequate trial data to suggest best option for severely ill, hospitalized children
- All demonstrate reliable coverage against both influenza A and B
- No seasonal variation in susceptibilities noted... yet 😊

# Neuraminidase Inhibitors for Influenza Treatment

## Oseltamivir

- Safety
  - Systematic review of RCTs
  - 2 stage, random effects meta-analysis
  - Findings
    - Significantly reduced duration of illness in the intention-to-treat (ITT) population (~18 hours)
      - In patient trials excluding asthmatics a larger difference was elucidated
    - Risk of otitis media was decreased in the ITT population (~34%)
- Efficacy
  - Vomiting was significantly different between groups
    - Increased in patients who received oseltamivir versus non receipt
    - RR, 1.63; (95% CI, 1.30 - 2.04)
  - No comment on neuropsychiatric manifestations
- Additional considerations
  - Obese and non – obese patients have similar PK/PD profiles so additional dosing adjustments not warranted
  - Optimal duration of therapy is 5 days
    - Consideration for longer treatment

# Neuraminidase Inhibitors for Influenza Treatment

- “Clinical effectiveness of peramivir in comparison with other neuraminidase inhibitors...”
- Japanese study comparing amantadines and NAIs including peramivir as it relates to time to defervescence
  - n=223 patients with influenza
  - Patients < 18 years
  - Stratified therapy in two unique groups
    - < 10 years of age and 5 -18 years of age
    - Study Rationale(?): increased adverse effects associated with oseltamivir in teenagers and lack of ability to use inhaled zanamivir in patients < 5 years

Influenza A

• 5 - 18 years: median duration of fever was 2 vs. 1 day (p = 0.242)

Influenza B

• 5 - 18 years: median duration of fever was 3 vs. 1 day (p = 0.0097)

# Alternative Dosing of Oseltamivir

- Recommendation states use of 150 mg by mouth twice daily for consideration...
  - Immunocompromised patients
  - Severely ill (no clear definition)
- “Double dose oseltamivir and virologic outcomes in adults and children”
  - Double blind, randomized trial
  - Patients > 1 years of age hospitalized with influenzae
    - 13 hospitals in SE Asia
  - Intervention: oral double dose (150 mg) versus standard dose (75 mg)
  - Primary endpoint: negative viral status via nasal and throat PCR testing at day 5
  - Key findings
    - No difference in clearance
    - No difference in supplemental oxygen requirements
    - Summary: no clinical or virologic advantage in higher dosing

# Clinical Controversies

Do we need to cover empirically for most common bacterial etiology of CAP? **Yes, we should!**

Do we need to expand coverage to include a macrolide? **No, we probably do not... jury still out**

Is there a role for alternative oseltamivir dosing or use of IV peramivir? **High dose oseltamivir provides no additional benefit above traditional dosing, peramivir should be limited to severe cases for whom enteral access is limited**



## Inpatient Day 4: L.B. Status Update

- L.B. has now received 96 hours of appropriately targeted therapy with oseltamivir 60 mg by mouth every 24 hours + Ceftriaxone 50 mg/kg IV every 24 hours and is on room air with SpO<sub>2</sub> saturations of 96%. She has remained afebrile for the last 24 hours and her leukocytosis has also improved.



- The clinical pharmacist would like to step down to oral antibiotic therapy to complete the treatment course and discharge the patient home.

# Pharmacodynamic Considerations for Enteral Therapy

## *Streptococcus pneumoniae*

- Amoxicillin > penicillin
  - Better absorption, longer serum half-life, better taste/tolerability
- No oral cephalosporin has activity at site of infection = to high dose amoxicillin
  - Preferred: cefpodoxime, cefprozil, cefuroxime
- Clindamycin has in vitro activity against 60 – 85%
- Levofloxacin/linezolid provide activity against >95%
- Macrolides not recommended for empiric therapy

## *Haemophilus influenzae*

- Amoxicillin appropriate for mild – moderate infections
- $\beta$ -lactamase producing strains
  - amoxicillin-clavulanate, cefuroxime, cefdinir, cefixime, cefpodoxime, ceftibuten
- Fluoroquinolones not needed unless severe allergy to oral  $\beta$ -lactams

## Case #2: B.K.

- HPI: B. K. is a 10 year old male (55 kg) presenting to the emergency department with right lower leg pain 2 days after enjoying a Justice League themed birthday party at his best friend's home. Over the last 12 hours, he has had trouble bearing weight on his lower limb, so his caregivers brought him in for further evaluation.
- Pertinent social history: Member of the community swim team, plays flag football with a community league. Parents work in healthcare industry.
- The team consults orthopedics and obtains the following laboratory and imaging studies...
  - WBC = 23,000 cells/microliter
  - ESR = 125 mm/hr
  - CRP = 25 mg/dL
  - T = 38.5 C
  - Blood culture pending
  - MRI ordered
- The patient is given a differential diagnosis of osteomyelitis or septic arthritis

# Which of the following empiric regimens is most appropriate for B.K.'s suspected musculoskeletal infection?

- A. Vancomycin 20 mg/kg/dose IV X 1, followed by 20 mg/kg/dose IV every 6 hours
- B. Vancomycin 20 mg/kg/dose IV X 1 , followed by 20 mg/kg/dose IV every 6 hours + Cefazolin 33 mg/kg IV every 8 hours
- C. Clindamycin 40 mg/kg IV divided every 8 hours
- D. Clindamycin 40 mg/kg IV divided every 6 hours + cefazolin 33 mg/kg/dose IV every 8 hours

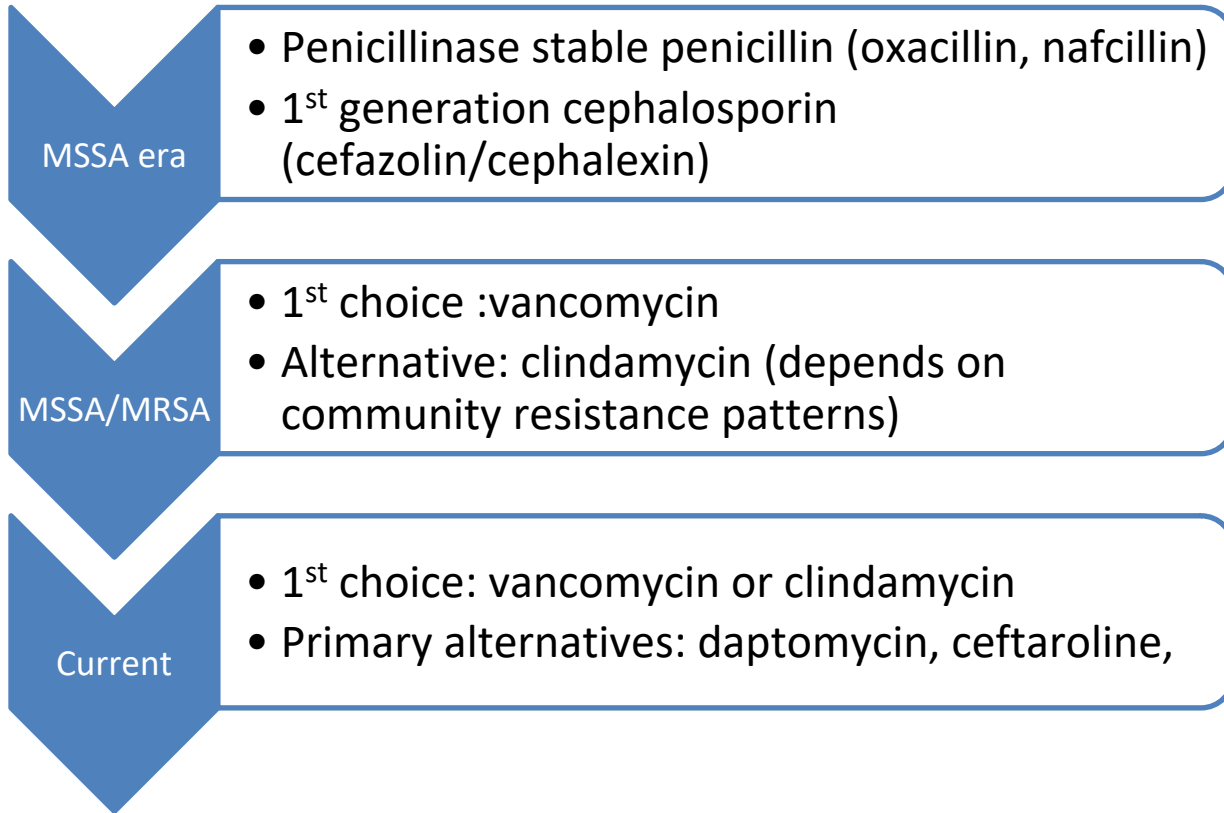
# Clinical Controversies

Is empiric combination therapy warranted in osteomyelitis?

Is there a benefit to larger doses of Clindamycin for obese pediatric patients?

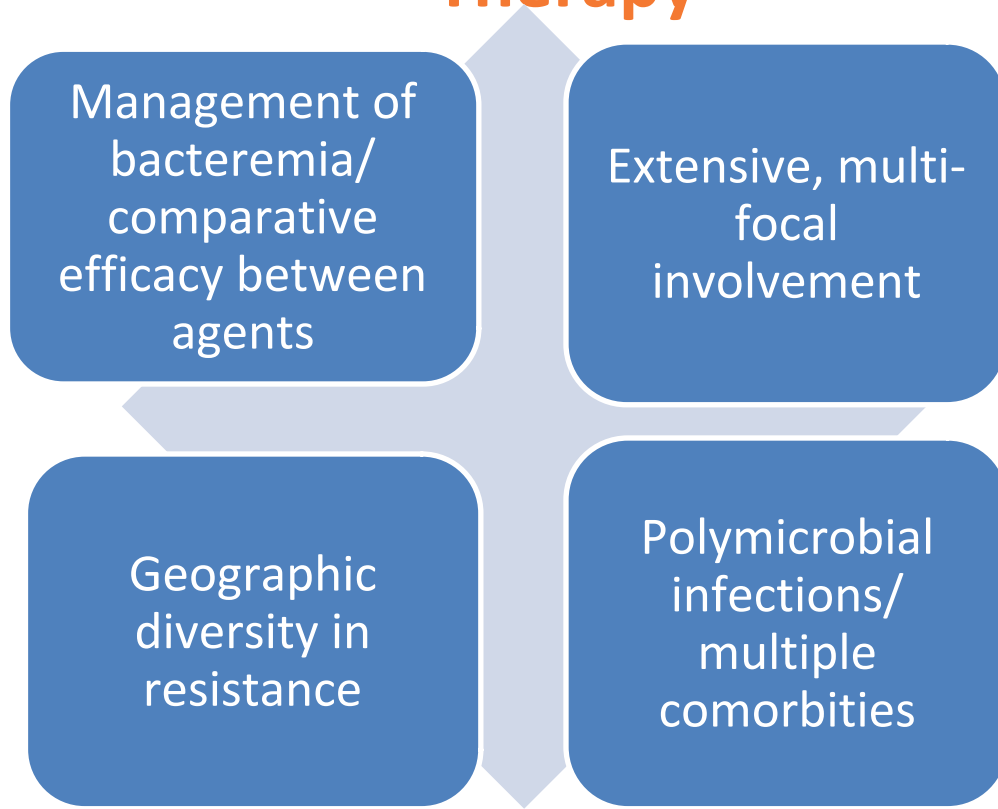
What is the optimal duration of IV therapy before oral stepdown for osteomyelitis?

# Historical Evolution of Empiric Treatment



Coverage	
(+) MSSA, Kingella, H.flu, Strep species	(-) MRSA
(+) MRSA, Strep species	(-) Kingella
MRSA targeted	

# Clinical Considerations for Selection of Combination Therapy



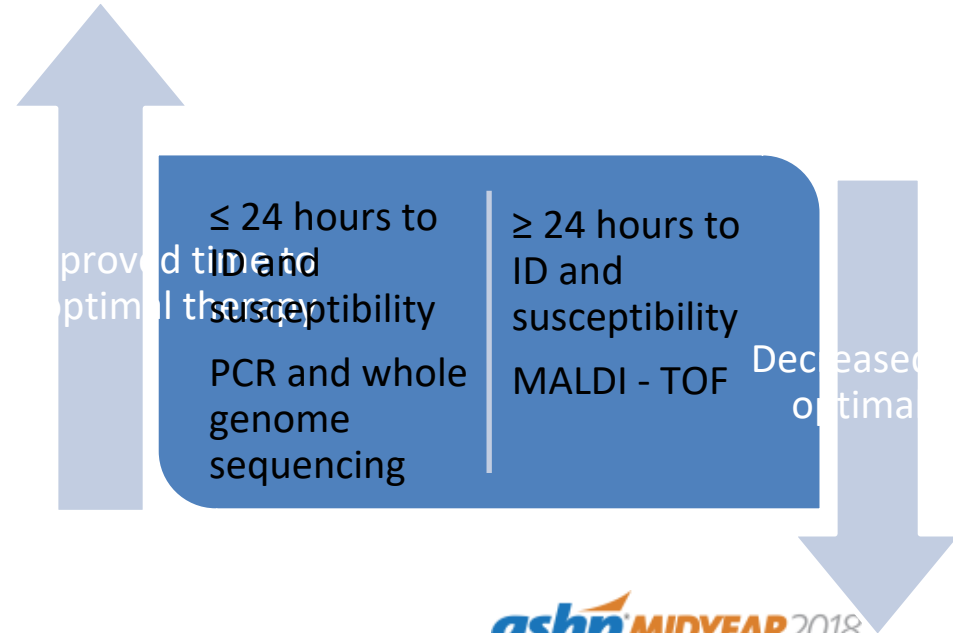
# Combination Therapy Considerations: Antagonism

- Proposed mechanism (s)
  - Inoculum “eagle effect”
  - Impaired target site recognition
  - In vitro data demonstrates concentration dependent impacts
- More likely to occur with MRSA than MSSA
  - Likely secondary to increased activity of clindamycin against MSSA strains than vancomycin
- Antagonism also demonstrated with combinations of vancomycin and linezolid
- 2009: CID and IDSA encouraged discontinuation of combination therapy with vancomycin and other gram positive targeted agents
- **However, mixed studies exist regarding antagonism and clinical implications**



# Combination Therapy Considerations: Efficacy

- Pathogen variability in response
  - MRSA versus MSSA
    - Vancomycin inferiority established against MSSA infections irrespective of site
    - Marginal benefit in adding cefazolin is theoretical and not supported by existing literature
- Microbiologic testing
  - Rapid diagnostics versus traditional culture detection methods



# Clinical Controversies

Is empiric combination therapy warranted in osteomyelitis? **Not routinely recommended however, case based considerations may make this a reasonable option**

Is there a benefit to larger doses of Clindamycin for obese pediatric patients?

What is the optimal duration of IV therapy before oral stepdown for osteomyelitis?

## B.K. Update

- IV access has been obtained. MRI findings significant for osteomyelitis with an effusion identified indicating concomitant septic arthritis.



- Blood cultures result as gram positive cocci in clusters, awaiting final speciation

# Clindamycin Therapy Considerations for Pediatric MSKI

- Retrospective review of pediatric patients over the course of 1 year with community acquired MRSA invasive infections
- Compared outcomes between treatment with clindamycin and vancomycin or beta – lactam therapy
- Key findings
  - Median time to
    - resolution of fever
    - duration of positive blood cultures= no difference comparatively and clinda determined to be effective therapy

MRSA (n=46)  
Median age = 3.5  
years

14  
osteomyelitis

MSSA (n=53)  
Median age = 4.8  
years

14  
osteomyelitis

# Pharmacodynamics of Clindamycin in Obese and Overweight Children

- Clindamycin pharmacokinetic analysis study
  - Data pooled from 3 different trials
    - 420 samples representing 220 children
      - 76 patients included with BMI %  $\geq$  95<sup>th</sup> percentile for age →
  - Additional key findings
    - Post menstrual age and drug clearance correlated
    - Obesity did not provide explanation for interpatient variability

Total body weight was the best measure of size for dosing recommendations

# Clinical Controversies

Is empiric combination therapy warranted in osteomyelitis?

Not routinely recommended however, case based considerations may make this a reasonable option

Is there a benefit to larger doses of Clindamycin for obese pediatric patients? No, standard weight based dosing by total body weight with a max of 2700 mg per day is sufficient

What is the optimal duration of IV therapy before oral stepdown for osteomyelitis?

# Sequential Parenteral to Oral Stepdown Therapy

- Shorter initial IV therapy comparable to longer therapy prior to transition to oral therapy
  - No difference in treatment failures
  - Decrease in catheter-associated complications after discharge
- Role of CRP to predict efficacy of transition to oral therapy
  - Monitor every 24 – 48 hours
  - 50% reduction OR < 2 mg/dL PLUS clinical improvement
- Efficacy of oral therapy with transient bacteremia
  - Cefadroxil

# Clinical Controversies

Is empiric combination therapy warranted in osteomyelitis?

Not routinely recommended however, case based considerations may make this a reasonable option

Is there a benefit to larger doses of Clindamycin for obese pediatric patients? No, standard weight based dosing by total body weight with a max of 2700 mg per day is sufficient

When is it okay to step down from IV therapy for osteomyelitis? Once patient tolerates oral medications, has decline in CRP



## Case #3: A.G.

- A.G. is a 14 month old male who presents to the emergency department with a 2 day history of fever, vomiting, decreased PO intake, and decreased amount of wet diapers.
- Upon triage, his vitals demonstrate the following:

Weight (kg)	12
HR (beats/minute)	180
RR (breaths/minute)	30
SpO <sub>2</sub> saturation (%)	100
Temp (C)	39.1
Blood Pressure (mmHg)	87/50

## A.G. Continued

- Physical exam
  - Sunken eyes, irritability, uncircumcised
  - Caregiver reports "darker than normal" urine
  - Moderate dehydration
- Vaccine history
  - Up to date
- Medication history
  - Pedialyte as tolerated
  - Levetiracetam 40 mg/kg/day divided BID
- Allergies: amoxicillin
  - Reaction: rash

# A.G.'s Emergency Department Course

- Medications
  - Acetaminophen 15mg/kg PO
  - 20 ml/kg NS bolus IV
- Urine obtained via catheterization
- Labs pending: CMP, CBC with differential, urine culture, blood culture

Urinalysis	
Glucose	Negative
Ketones	Moderate
Blood	Negative
Nitrite	Negative
Leukocytes	Positive
WBC (0 – 5/HPF)	37
pH	6.5
Appearance	Slightly Cloudy

# A.G.'s Course Continued

- A.G. remains irritable. His caregiver reports a slight decrease in PO intake but no emesis reported. Decision is made to admit for empiric UTI therapy and rehydration.
- Upon admission to the general pediatrics service, D5-NS at 45 ml/hr is started and a KUB is obtained to rule out constipation.
- Additional information from caregiver reveals past medical history significant for a previous UTI as a neonate; renal and bladder ultrasonography were negative.

# What empiric therapy should be started for A.G.?

- A. Cefixime 8 mg/kg/dose daily
- B. Amoxicillin – clavulanate 40 mg/kg/day divided TID
- C. Ceftriaxone 50 mg/kg/dose daily
- D. Cefepime 50 mg/kg/day divided BID

# Clinical Controversies

Is parenteral therapy necessary?

Is there a role for cefdinir in pediatric UTI treatment?

# Urinary Tract Infection Clinical Practice Guideline

- Published by AAP in 1999 and 2011; febrile patients 2 months – 24 months
- Risk factors

Male	Female
<ul style="list-style-type: none"><li>• Nonblack race</li><li>• Temperature <math>\geq 39^{\circ}\text{C}</math></li><li>• Fever &gt; 24 hours</li><li>• Absence of other source of infection</li></ul>	<ul style="list-style-type: none"><li>• White race</li><li>• Age &lt; 12 months</li><li>• Temperature <math>\geq 39^{\circ}\text{C}</math></li><li>• Fever <math>\geq 2</math> days</li><li>• Absence of other source of infection</li></ul>

# Considerations for Therapy

- Common pathogens
  - *E. coli*, *Klebsiella* spp, *P. mirabilis*, *Enterococcus* spp, *Enterobacter* spp
- Urine collection method matters
  - Catheterization or SPA
  - Alternative: Quick-Wee method
- Local antibiogram will influence selection
  - Trimethoprim-sulfamethoxazole, cephalexin
- Duration of therapy: 7 – 14 days

Subcommittee on Urinary Tract Infection, et al. Pediatrics 2011;128(3):595-610.

Bonsu BK, Shuler L, Sawicki L, et al. Acad Emerg Med 2006;13(1):76-81.

Kaufman J, Fitzpatrick P, Tosif S, et al. BMJ 2017;357:i1341.



# Empiric Therapy for UTI

<b>Parenteral</b>	<ul style="list-style-type: none"><li>• Ceftriaxone 75 mg/kg Q24H</li><li>• Cefotaxime 150 mg/kg/day, divided q 6 – 8 hours</li><li>• Ceftazidime 100 – 150 mg/kg/day, divided Q8H</li><li>• Gentamicin 7.5 mg/kg/day, divided Q8H</li><li>• Tobramycin 5 mg/kg/day, divided Q8H</li><li>• Piperacillin 300 mg/kg/day, divided q 6 – 8 hours</li></ul>
<b>Oral</b>	<ul style="list-style-type: none"><li>• Amoxicillin-clavulanate 20 – 40mg/kg/day divided TID</li><li>• Trimethoprim-sulfamethoxazole 6-12 mg/kg/day TMP divided BID</li><li>• Cefixime 8 mg/kg/day daily</li><li>• Cefpodoxime 10 mg/kg/day divided BID</li><li>• Cefprozil 30 mg/kg/day divided BID</li><li>• Cephalexin 50 – 100 mg/kg/day divided QID</li></ul>

# Parenteral versus Oral Therapy

- Chaudhari PP, et al
  - Retrospective analysis of 29,919 children from 36 pediatric hospitals
    - Median age 8.6 (IQR 5.1 – 13.8) months
    - 36% (10,849) patients received parenteral dose prior to discharge
  - Did not reduce revisits leading to admission
- Parenteral or oral therapy is equally efficacious
  - Avoid nitrofurantoin

# Clinical Controversies

Is parenteral therapy necessary? **Not for previously healthy, hemodynamically stable patients able to tolerate PO.**

Is there a role for cefdinir in pediatric UTI treatment?

# A.G.'s Inpatient Course

- A.G. has received 48 hours of ceftriaxone and is tolerating PO well.
- Caregiver reports A.G. has returned to baseline.
- Final urine culture result pending
  - Initial result: 50,000 – 100,000 cfu/ml Gram negative lactose-fermenting rods
- The team is preparing to discharge A.G.

# Which antibiotic would you recommend for transition to oral therapy?

- A. Cefixime 8 mg/kg/day daily
- B. Cefuroxime 30 mg/kg/day divided BID
- C. Cephalexin 75 mg/kg/day divided TID
- D. Ciprofloxacin 20 mg/kg/day divided BID

# Changes in Antimicrobial Resistance in Pediatric UTI

- Single institution over 6 year period (2009 – 2014)
  - Every + aerobic bacterial urine culture for patients <18 years
  - 6515 urinary isolates
  - Majority female (66.8%)
- Decreased resistance rate observed
  - Ceftriaxone 21.1% → 5.9%
  - Cefuroxime 28.5% → 24.1%
- Oral cephalosporin appropriate empiric therapy for uncomplicated UTI

# Cefdinir Use in UTI

- Off label alternative commonly prescribed in outpatient setting
- Single center pediatric ER with 175 patients
  - Majority female (n = 167, 95%)
  - Median age: 6.6 years (range, 1 month – 21 years; IQR, 3.4 – 15.6 years)
  - Confirmed UTI
    - Pyuria (>5 WBC/hpf or + leukocyte esterase urine dipstick) and + bacterial urine culture
  - Cefdinir most common drug prescribed (n = 103, 59%)
    - 7 – 10 days duration of therapy

# Cefdinir Susceptibility in UTI

- Single center ER in a 12 month period: 705 urine samples + bacteria
  - 431 uropathogens from 424 patients
  - Majority female (370, 87.3%)
  - Median age: 4.91 years (IQR 1.68 – 12.97 years)
- Cefdinir: similar antimicrobial activity to ceftriaxone and gentamicin
  - Cefdinir (412/431, 95.6%)
  - Ceftriaxone (421/431, 97.7%)
  - Gentamicin (420/431, 97.5%)
- Cefdinir highly effective and comparable to common antibiotics used for UTI treatment



# Clinical Controversies

Is parenteral therapy necessary? **Not for previously healthy, hemodynamically stable patients able to tolerate PO.**

Is there a role for cefdinir in pediatric UTI treatment? **Yes.**

# KEY TAKEAWAYS

1. Despite significant inter-cephalosporin pharmacodynamic variability, amoxicillin remains the drug of choice utilized for treatment of acute otitis media in children.
2. Coverage of atypical pathogens may not be warranted in every school aged child; additional risk factors should be weighed.
3. Clindamycin can be effectively used as both empiric and targeted therapy for bone and joint infections and should be dosed by total body weight in children with BMI > 95% for age.
4. Oral therapy is potentially as efficacious as parenteral therapy in the treatment of uncomplicated pediatric urinary tract infection.