Management of Acute Otitis Media Updates

Fall APP Pharmacology Conference 2023

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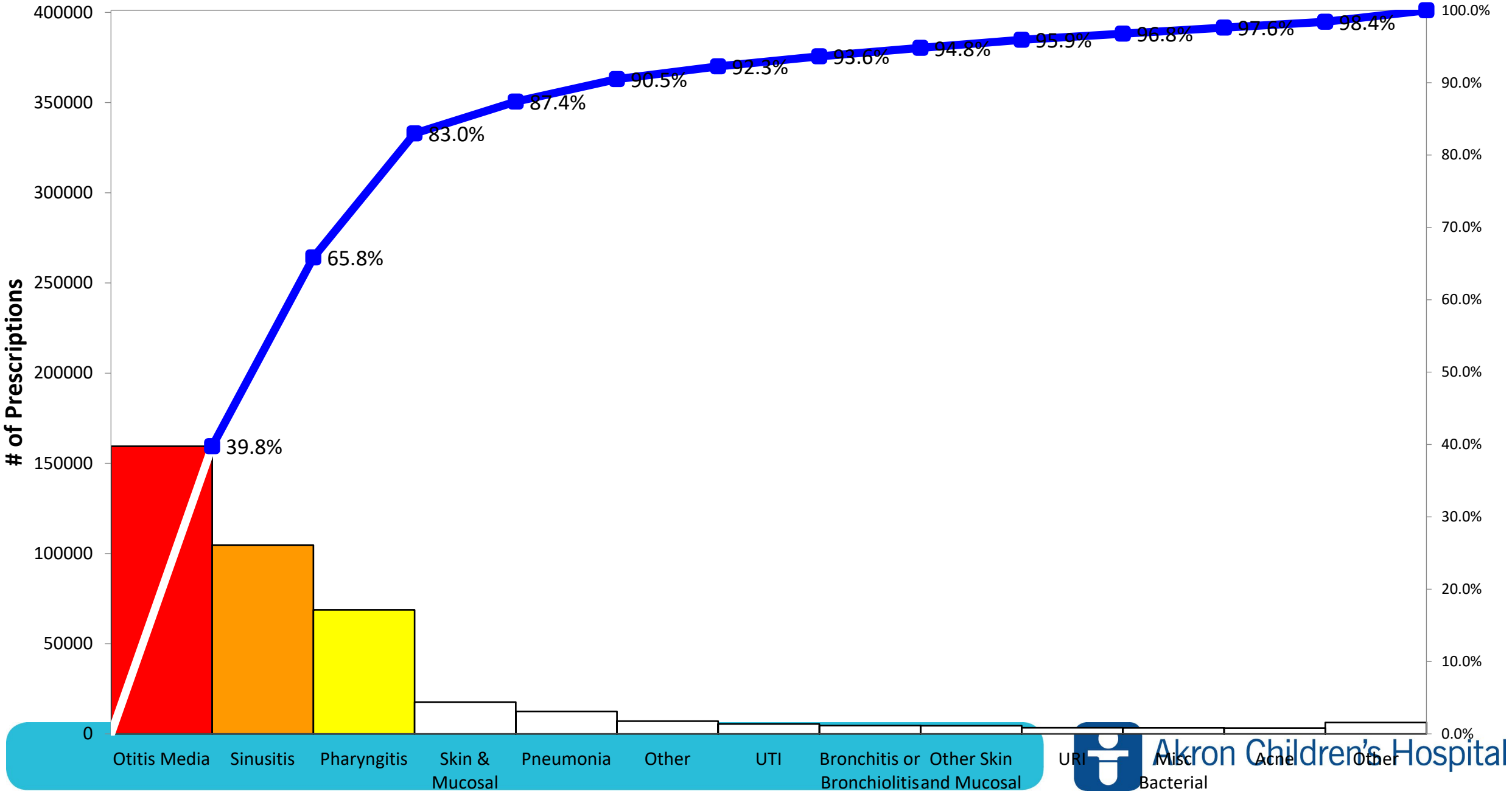
Objectives

- Identify appropriate patients with AOM for watchful waiting
- Understand systems strategies to improve uptake of watchful waiting
- Prescribe appropriate empirical therapy for acute otitis media in children
- Prescribe appropriate second line therapy
- Use a systematic framework for evaluating treatment failure
- Know the indications for Nirsevimab and how it may affect disease in children
- Explain the indications and rationale for the COVID-19 vaccine and 2023-24 booster to patients

ACH Outpatient Antimicrobial Rx by CDC Dx Category 2012-2018



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AOM – When to Treat

AAP Guidelines

- Immediate Treatment
- Severe AOM
  - Fever >39C
  - Moderate to Severe Pain
  - Pain > 48 hours
- Bilateral AOM in 6 months – 2 years
- All rest use shared decision making on antibiotics vs expectant management

Lieberthal AS, Carroll AE, Chonmaitree T, et al. The Diagnosis and Management of Acute Otitis Media. *Pediatrics*. 2013;131(3):e964-e999. doi:10.1542/peds.2012-3488

Otitis Media is virus-related

- Children aged 1-3 years
  - <1% of otitis media episodes were not preceded by URI symptoms
  - 32% of URI episodes complicated by AOM
  - 70% of the time virus could be recovered
  - Adenovirus uniquely high AOM rate
  - Rhinovirus uniquely low AOM rate
- Effects of antibiotic treatment are limited
- Most cases are probably viral

Chonmaitree T, Revai K, Grady JJ, et al. Viral upper respiratory tract infection and otitis media complication in young children. Clin Infect Dis. 2008;46(6):815-823. doi:10.1086/528685

How are we doing with watchful waiting?

- Retrospective Cohort Study
- Children aged 1-12 in claims database
- Outcome: % of AOM episodes w/ antibiotic dispense w/in 3 days
- Key Findings:
  - **77% were treated w/in 3 days**
  - No change in treatment prevalence over time
  - Strongest predictors of prescribing were provider characteristics
    - Previous prescribing
    - Specialty

Smolinski NE, Antonelli PJ, Winterstein AG. Watchful Waiting for Acute Otitis Media. *Pediatrics*. 2022;150(1):e2021055613. doi:10.1542/peds.2021-055613

How are we doing with watchful waiting?

- Retrospective cohort study
  - Israel
  - Claims data
- Outcome: Antibiotic treatment w/in 2 days of visit
  - ~80% immediate treatment
  - Antibiotic prescribing rates increased after issue of guidelines

Marom T, Shefer G, Tshori S, Mingelgrin S, Pitaro J. Antibiotic prescription policy for acute otitis media: Do we follow the guidelines? *J Antimicrob Chemother*. 2021;76(10):2717-2724. doi:10.1093/jac/dkab250

How much do antibiotics really help?

- Cochrane 2015
  - Systematic Review & Meta-Analysis
  - 13 RCTs
  - 2 months to 13 years
  - Assessed as low-risk of bias

Venekamp RP, Sanders SL, Glasziou PP, Mar CBD, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2015;(6). doi:10.1002/14651858.cd000219.pub4

How much do antibiotics really help?

- Antibiotics VS Placebo[4]
  - Reduced pain at 24 hours? RR:0.89 (0.78-1.01)
  - Reduced pain at 2-3 days? **RR: 0.7** (0.57-0.86) NNTB: 20
  - Reduced pain at 4-7 days? **RR: 0.76** (0.63-0.91) NNTB: 16
  - Reduced pain at 10-12 days? **RR: 0.33** (0.17-0.66) NNTB: 7
  - Abnormal TM 2-4 weeks? **RR: 0.82** (0.74-0.90) NNTB: 11
  - Abnormal TM 3 months? RR: 0.97 (0.76-1.24)
  - TM Perforation? RR: **0.63** (0.24-0.82) NNTB: 33
  - Contralateral otitis? RR: **0.51** (0.05-0.75) NNTB: 11
  - Vomiting, diarrhea, or rash? **RR: 1.38** (1.19 to 1.59) NNTH: 14

Venekamp RP, Sanders SL, Glasziou PP, Mar CBD, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2015;(6). doi:10.1002/14651858.cd000219.pub4

How much do antibiotics really help?

- Other Outcomes
  - Recurrences? No data
  - Serious Complications? Insufficient evidence, but quite rare

Venekamp RP, Sanders SL, Glasziou PP, Mar CBD, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2015;(6). doi:10.1002/14651858.cd000219.pub4

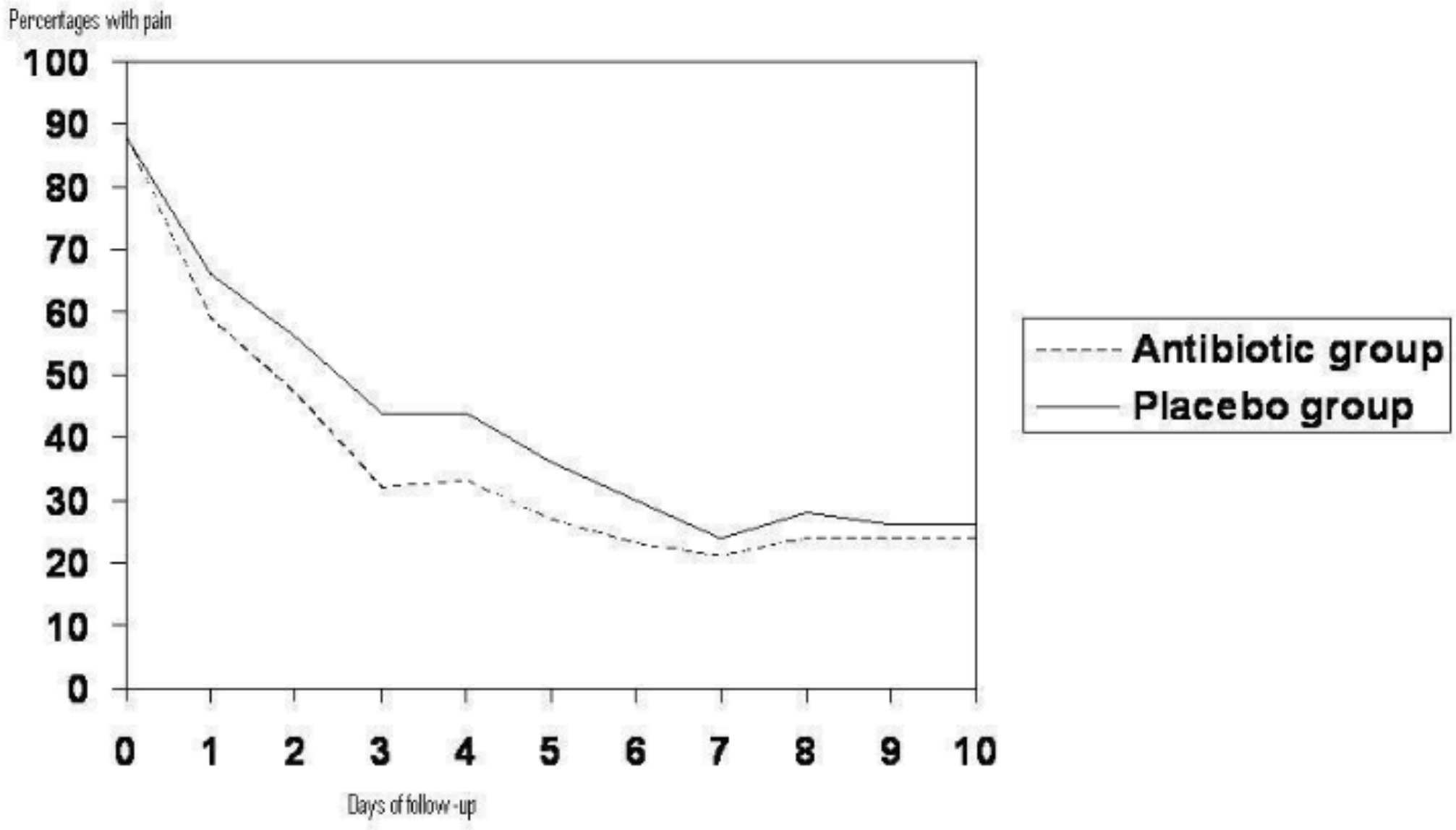
How much to antibiotics really help?

- VS Expectant Observation
  - Pain at 3-7 days? RR: 0.75 (0.5 – 1.12)
  - Pain at 11-14 days? RR: 0.91 (0.75 – 1.10)
  - Vomiting, diarrhea, or rash? **RR: 1.71** (1.24-2.36) **NNTH: 9**

  - Rare complications additional data (Djabali[4])
    - Meta-analysis of 6 studies
    - Mixed placebo and expectant observation comparators
    - Mastoiditis **OR: 0.48** NNTB: 5368

Venekamp RP, Sanders SL, Glasziou PP, Mar CBD, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2015;(6). doi:10.1002/14651858.cd000219.pub4

Figure 6. Percentage with pain based on the subset of six studies included in the IPD meta-analysis (Rovers 2006).



Venekamp RP, Sanders SL, Glasziou PP, Mar CBD, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2015;(6). doi:10.1002/14651858.cd000219.pub4

Antibiotics helped more in these subpopulations?

- Children < 2 years of age
- Children with bilateral AOM
- Children with ear discharge

Venekamp RP, Sanders SL, Glasziou PP, Mar CBD, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2015;(6). doi:10.1002/14651858.cd000219.pub4

So why don’t we use watchful waiting?

- 83% “reasonable”
- 83% cited parental reluctance
- 30% cited difficulty and cost of follow up

Vernacchio L, Vezina RM, Mitchell AA. Management of Acute Otitis Media by Primary Care Physicians: Trends Since the Release of the 2004 American Academy of Pediatrics/American Academy of Family Physicians Clinical Practice Guideline. *Pediatrics*. 2007;120(2):281-287. doi:10.1542/peds.2006-3601

Evidence to Practice

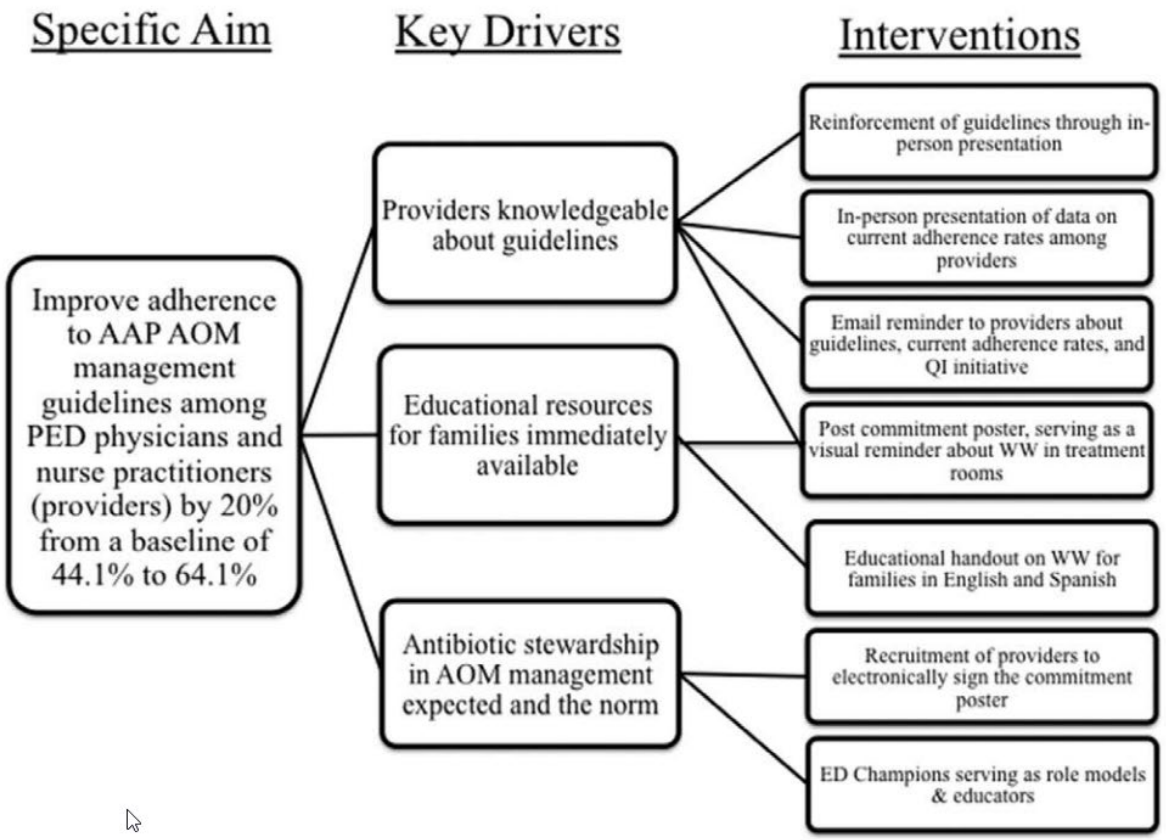


Fig. 2. Key driver diagram. PED, pediatric emergency department.

Sun D, Rivas-Lopez V, Liberman DB. A Multifaceted Quality Improvement Intervention to Improve Watchful Waiting in Acute Otitis Media Management. *Pediatr Qual Saf*. 2019;4(3):e177. doi:10.1097/pq9.0000000000000177

Current Trends in Otitis Media Pathogens

- Overall AOM incidence
  - Declining
  - Timing c/w effect from PCV vaccines
  - Reduction in middle ear colonization with PCV strains
  - Mostly attributable to decline in *S. pneumoniae* infections
- Shift toward increased H. flu burden

Wald ER, DeMuri GP. Antibiotic Recommendations for Acute Otitis Media and Acute Bacterial Sinusitis: Conundrum No More. Pediatr Infect Dis J. 2018;37(12):1255-1257. doi:10.1097/INF.0000000000002009

What bacteria cause AOM?

Bacteriology of Acute Otitis Media*

Bacterial Species	Prevalence (%) 1999	Prevalence (%) 2017
Streptococcus pneumoniae	40-45	15-25
Haemophilus influenzae	25-30	50-60
Moraxella catarrhalis	12-15	12-15
Streptococcus pyogenes	3-5	3-5
Sterile+	15-20	15-20

S. Pneumo: PCN-I 25%; PCN-R 0%
H. Flu BLAM+L: 30-50%
100% M. Cat BLAM+: 100%

Wald ER, DeMuri GP. Antibiotic Recommendations for Acute Otitis Media and Acute Bacterial Sinusitis: Conundrum No More. Pediatr Infect Dis J. 2018;37(12):1255-1257. doi:10.1097/INF.0000000000002009

Current Treatment Recommendations

Acute Otitis Media

- First Line – High-dose Amoxicillin
  - 90 mg/kg divided BID x 10 days
  - Max dose: 2000 mg/dose
- Risk Factors For Amoxicillin/Clavulanic Acid
  - Receipt of Amoxicillin in previous 30 days
  - Conjunctivitis
  - Treatment failure of amoxicillin

ACH AOM Guideline
Lieberthal AS, Carroll AE, Chonmaitree T, et al. The Diagnosis and Management of Acute Otitis Media. *Pediatrics*. 2013;131(3):e964-e999. doi:10.1542/peds.2012-3488

Acute Otitis Media

- Alternative for (+) risk factors
  - High-dose amox/clav 90 mg/kg divided BID x 10 days
    - Utilize amox/clav ES suspension or amox/clav XR tabs for high-dose therapy
    - Max amox/clav XR dose: 2000 mg/dose
    - Max amox/clav ES susp dose: 1800 mg/dose
- PCN allergy (non-life threatening)
  - Cefdinir 14 mg/kg/day divided BID x 10 days
    - Max dose: 300 mg/dose
    - Consider adding Clindamycin if PCN-resistant *Strep. pneumoniae* concern

ACH AOM Guideline
Lieberthal AS, Carroll AE, Chonmaitree T, et al. The Diagnosis and Management of Acute Otitis Media. *Pediatrics*. 2013;131(3):e964-e999. doi:10.1542/peds.2012-3488

Why?

- Different mechanisms of resistance
  - *Streptococcus pneumoniae* – Altered penicillin binding proteins
  - *Haemophilus influenzae* – Beta-lactamase
  - *Moraxella catarrhalis* – Beta-lactamase
- "High-dose"
  - Intended to overcome altered PBP
- Beta-lactamase stable
  - E.g., suicide inhibitors and cephalosporins
  - Intended to overcome beta-lactamase

Selection of Empirical Antibiotics

Beta-Lactam Antibiotic	S. Pneumo	H. Flu	M. Cat
SD-Amox	75%	50-70%	0%
HD-Amox	100%	50-70%	0%
SD-Amox/Clav	75%	100%	100%
HD-Amox/Clav	100%	100%	100%
Cefdinir	75%	100%	100%

Wald ER, DeMuri GP. Antibiotic Recommendations for Acute Otitis Media and Acute Bacterial Sinusitis: Conundrum No More. Pediatr Infect Dis J. 2018;37(12):1255-1257. doi:10.1097/INF.0000000000002009

An alternative approach?

- SD-Amox/Clav would likely cover a > % of organisms than HD-Amox
- Assumptions:
  - H. Flu BLAM rate is ~50%
  - No difference in rates of self-resolution by pathogen
  - No difference in rates of adverse effects between Amox/Clav and Amox
- Considerations:
  - H. Fly BLAM rate may be lower in some places (closer to 30%)
  - Self-resolution is much more common with H. Flu and M. Cat
  - Adverse effects are likely higher for Amox/Clav vice Amox
  - No evidence that high-dose amox component has higher AE rate
- In Context:
  - Broad empirical therapy generally causes increased antimicrobial resistance
  - High NNT w/ poor adoption of judicial prescribing
  - Highest indication for antimicrobial rx in pediatrics

Wald ER, DeMuri GP. Antibiotic Recommendations for Acute Otitis Media and Acute Bacterial Sinusitis: Conundrum No More. Pediatr Infect Dis J. 2018;37(12):1255-1257. doi:10.1097/INF.0000000000002009

Age Dependent Durations - <24 months

Patient Population

- 6-11 months
- 12-17 months
- 18-23 months
- Day care exposure (≥10 hrs/week

Intervention

- 10 days high-dose amox/clav
- 5 days high-dose amox/clav + 5 days placebo

Primary Outcome

- % children who had clinical failure

Secondary Outcomes

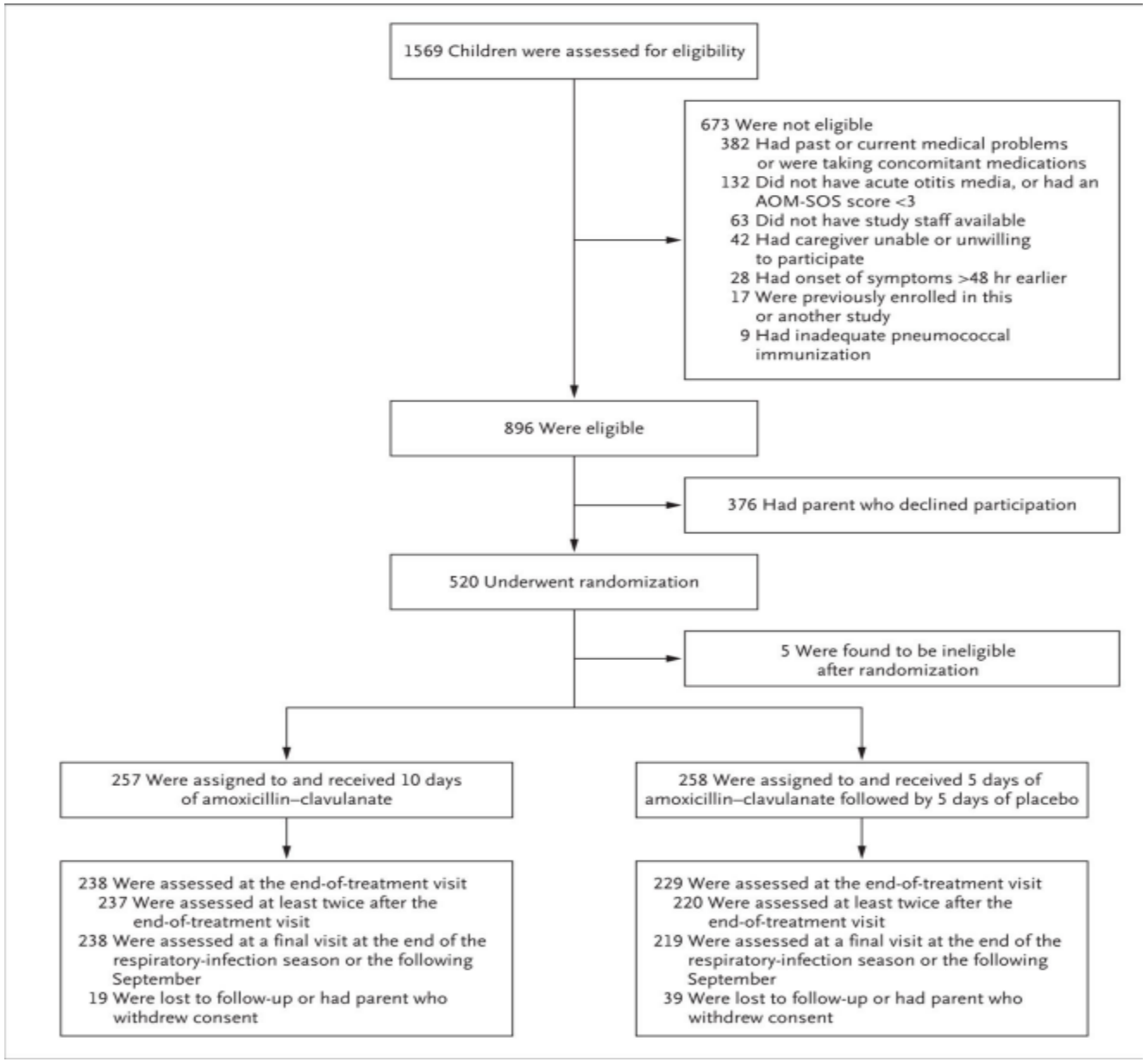
- Symptom burden days 6-14
- Rates of recurrence
- Total days of therapy during resp season

Hoberman A, Paradise JL, Rockette HE, et al. Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children. N Engl J Med. 2016;375(25):2446-2456. doi:10.1056/NEJMoa1606043

Study Follow-Up

- Telephone encounters with parents
  - Completed days 4, 5, or 6
- End of treatment visit
  - Completed days 12, 13, or 14
- In-office assessments q6weeks through the end of respiratory season (October 1 – May 31)
- Parents recorded AOM symptom scores daily during treatment period

Hoberman A, Paradise JL, Rockette HE, et al. Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children. N Engl J Med. 2016;375(25):2446-2456. doi:10.1056/NEJMoa1606043



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Results – Clinical Failure

Characteristic	10 Day Group (n=257)	5 Day Group (n=258)	All Children (n=515)	Odds Ratio (95% CI)	P value
All Children, n (%)	39/238 (16)	77/229 (25)	116/467 (25)	n/a	----
≥ 10 hrs/week exposure to kids				1.7 (1.1-2.7)	0.02
No	13/101 (13)	24/96 (25)	37/197 (19)		
Yes	26/137 (19)	53/133 (40)	79/270 (29)		
# affected ears				2.9 (1.9-4.7)	<0.001
One	10/124 (8)	26/113 (23)	36/237 (15)		
Both	29/114 (25)	51/116 (44)	80/230 (35)		

Hoberman A, Paradise JL, Rockette HE, et al. Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children. N Engl J Med. 2016;375(25):2446-2456. doi:10.1056/NEJMoa1606043

Discussion

- Standard 10 day treatment for AOM in children <24 months had less clinical failure compared to 5 day treatment regimens
- Previous studies also found higher failure rates for short courses of therapy in this age group
  - Cochrane Review in 2010
- Utilized amox/clav as first line therapy

Hoberman A, Paradise JL, Rockette HE, et al. Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children. N Engl J Med. 2016;375(25):2446-2456. doi:10.1056/NEJMoa1606043
Kozyrskyj et al. Cochrane Database Syst Rev 2010;9:CD001095

Age Dependent Durations - >24 months

- 2-5 yrs w/mild to moderate AOM – 7 days
- ≥6 yrs w/mild to moderate AOM – 5-7 days
- Shorter durations for older ages debated across centers/states/countries
  - Older children more likely spontaneously resolve
  - Less likely for treatment failure

The Four “D’s”

- A framework for evaluating treatment failure
- Right Diagnosis
- Right Drug
- Right Dose
- Right Duration

Summary and Key Points

- Rigorous clinical diagnosis is important
- Do watchful waiting in appropriate groups
  - Personal changes
  - Systems changes
- HD Amox is still recommended 1st line therapy
- Remember B-lactamase stability does not help with S. Pneumo
- NNT is high, benefits are modest – minimize harms

An ounce of prevention…

Nirsevimab - Background

- Monoclonal ab targeting a conserved site on the pre-fusion RSV F-protein
  - Hopefully evades antigenic shift/drift
- A portion of the Fc receptor is modified so that the body recycles it
  - Long acting
  - Up to 6 months

Beyfortus™ (nirsevimab-alip) | Now Approved for RSV Prevention. Accessed October 3, 2023. https://www.beyfortus.com/?&utm_source=google&utm_medium=cpc&utm_campaign=Beyfortus+DTC_GGL_BRND_General_AWA_SEA_ALLM_US_EN+KW+-+EN+BR_ALL&utm_term=nirsevimab&gclid=CjwKCAjw9-6oBhBaEiwAHv1OvJve4CZ1GAViOZKRsZiO1Rh6Zik1bOTZHt0eZFIxdiUGzW0R3Yi8BoCiWMQAvD_BwE&gclsrc=aw.ds

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Nirsevimab – Clinical Data

- Population: Infants 29-35 weeks GA; 1st RSV season; n=1453
- Intervention: Nirsevimab (2:1)
- Comparison: Placebo
- Outcome:
  - Primary: Medically attended LRTI: RRR **70.1%** (52.3%, 81.2% 95%CI)
  - Secondary: RSV Hospitalization: RRR **78.4%** (51.9-90.3 95%CI)
  - Outcomes through 150 days post-administration

Beyfortus™ (nirsevimab-alip) | Now Approved for RSV Prevention. Accessed October 3, 2023. https://www.beyfortus.com/?&utm_source=google&utm_medium=cpc&utm_campaign=Beyfortus+DTC_GGL_BRND_General_AWA_SEA_ALLM_US_EN+KW+-+EN+BR_ALL&utm_term=nirsevimab&gclid=CjwKCAjw9-6oBhBaEiwAHv1OvIve4CZ1GAViOZKRsZiO1Rh6Zik1bOTZHt0eZFIxdiUGzW0R3Yi8BoCiWMQAvD_BwE&gclsrc=aw.ds

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Nirsevimab – Clinical Data

- Population: All Infants
  - France, Germany, UK
  - August 2022-Feb 2023
  - N=8058
- Intervention: Nirsevimab
- Comparison: No Injection
- Outcomes:
  - Primary: RSV Hospitalization: RRR **83%** (68%-92% 95%CI)

Evidence to Recommendations Framework : Nirsevimab Updates. Accessed October 3, 2023. https://stacks.cdc.gov/view/cdc/131586

Nirsevimab: AEs

- No difference in Grade II-IV AE compared to placeboa
- Grade I AE > in Nirsevimab arms
- Consistent across studies
- AE with occurrence > placebo
  - Rash ~1%
  - Injection site reaction ~0.3%

Beyfortus™ (nirsevimab-alip) | Now Approved for RSV Prevention. Accessed October 3, 2023. https://www.beyfortus.com/?&utm_source=google&utm_medium=cpc&utm_campaign=Beyfortus+DTC_GGL_BRND_General_AWA_SEA_ALLM_US_EN+KW+-+EN+BR_ALL&utm_term=nirsevimab&gclid=CjwKCAjw9-6oBhBaEiwAHv1QvJve4CZ1GAViQZKRsZiQ1Rh6Zik1bQTZHt0eZFIxdiUGzW0R3Yi8BoCiWMQAvD_BwE&gclsrc=aw.ds

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Current ACIP Nirsevimab Recommendations

- Populations in whom recommended:
  - All infants < 8 months
  - Infants 8-19 months at increased risk of RSV hospitalization
    - CLD of prematurity
    - Severe Immune compromise
    - Certain CF
    - American Indian or Alaskan Native
- Timing
  - Born October – March w/in 1 week of birth
    - Ideally prior to nursery D/C
    - For NICU at/immediately prior to D/C
  - Born outside RSV season – at onset of season (~October)

Jones JM. Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023. MMWR Morb Mortal Wkly Rep. 2023;72. doi:10.15585/mmwr.mm7234a4

COVID-19 Current Pediatric Hospitalization Trends

- 54% of children hospitalized with no underlying medical conditions
- Underlying medication conditions more common > 5 years of age
- Post pandemic:
  - Hosp rates: Similar to influenza for < 5 years of age
  - Lower than influenza for older children
- ICU admission rates slightly exceed influenza
- Being unvaccinated or not recently vaccinated clearly high-risk

COVID-19–Associated Hospitalizations among Infants, Children and Adults — COVID-NET, January–August 2023. Accessed October 3, 2023. https://stacks.cdc.gov/view/cdc/132883

COVID-19 Vaccine Updates

- Current circulating virus are subsets of XBB1.55
  - Omicron sub-variant
  - Very few mutations in spike protein
  - XBB1.55 (2023 vaccine) sera neutralizes all major variants well
- New variant BA 2.86 with more mutations
  - Not circulating at a high level
  - Preliminary XBB.155 vaccine and disease sera shows good neutralization
- Conclusion: XBB1.55 vaccines are expected to be effective against currently circulating variants

Safety and Immunogenicity of Moderna COVID-19 Vaccine (2023-2024 Formula) : Monovalent XBB.1.5 Variant Vaccine. Accessed October 3, 2023. https://stacks.cdc.gov/view/cdc/132894
Current landscape of SARS-CoV-2 lineages. Accessed October 3, 2023. https://stacks.cdc.gov/view/cdc/132882

COVID-19 Current Vaccine Recommendations

What You Need to Know

- CDC recommends the 2023–2024 updated COVID-19 vaccines.
- Everyone aged 5 years and older should get **1 dose of the updated Pfizer-BioNTech or Moderna COVID-19 vaccine** to protect against serious illness from COVID-19.
- People who are moderately or severely immunocompromised may get additional doses of updated COVID-19 vaccine.
- Children aged 6 months–4 years need multiple doses of COVID-19 vaccines to be up to date, including at least 1 dose of updated COVID-19 vaccine.
- COVID-19 vaccine recommendations will be updated as needed.

CDC. COVID-19 Vaccination. Centers for Disease Control and Prevention. Published September 15, 2023. Accessed October 3, 2023. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/stay-up-to-date.html

Questions?