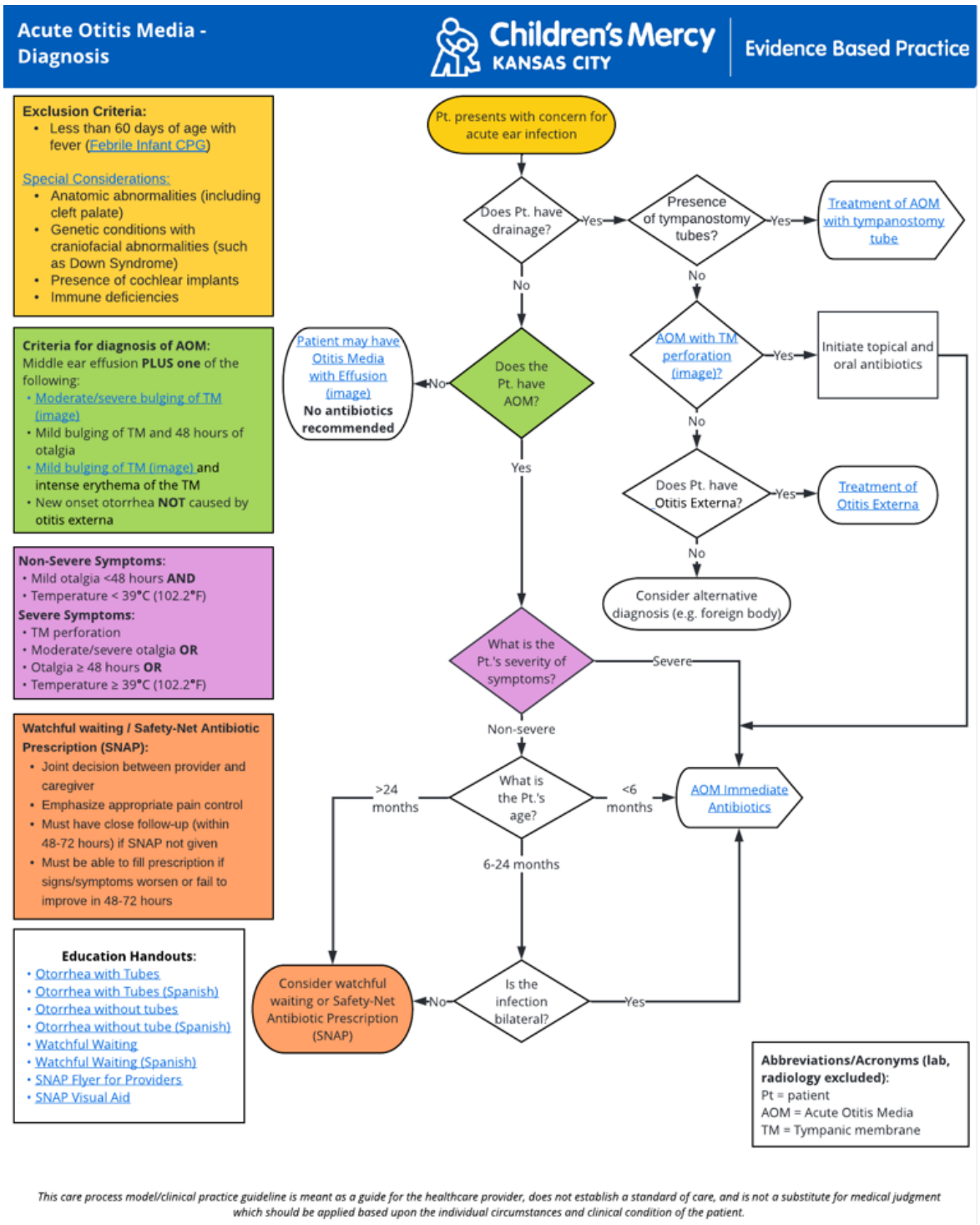
Acute Otitis Media (AOM) Care Process Model



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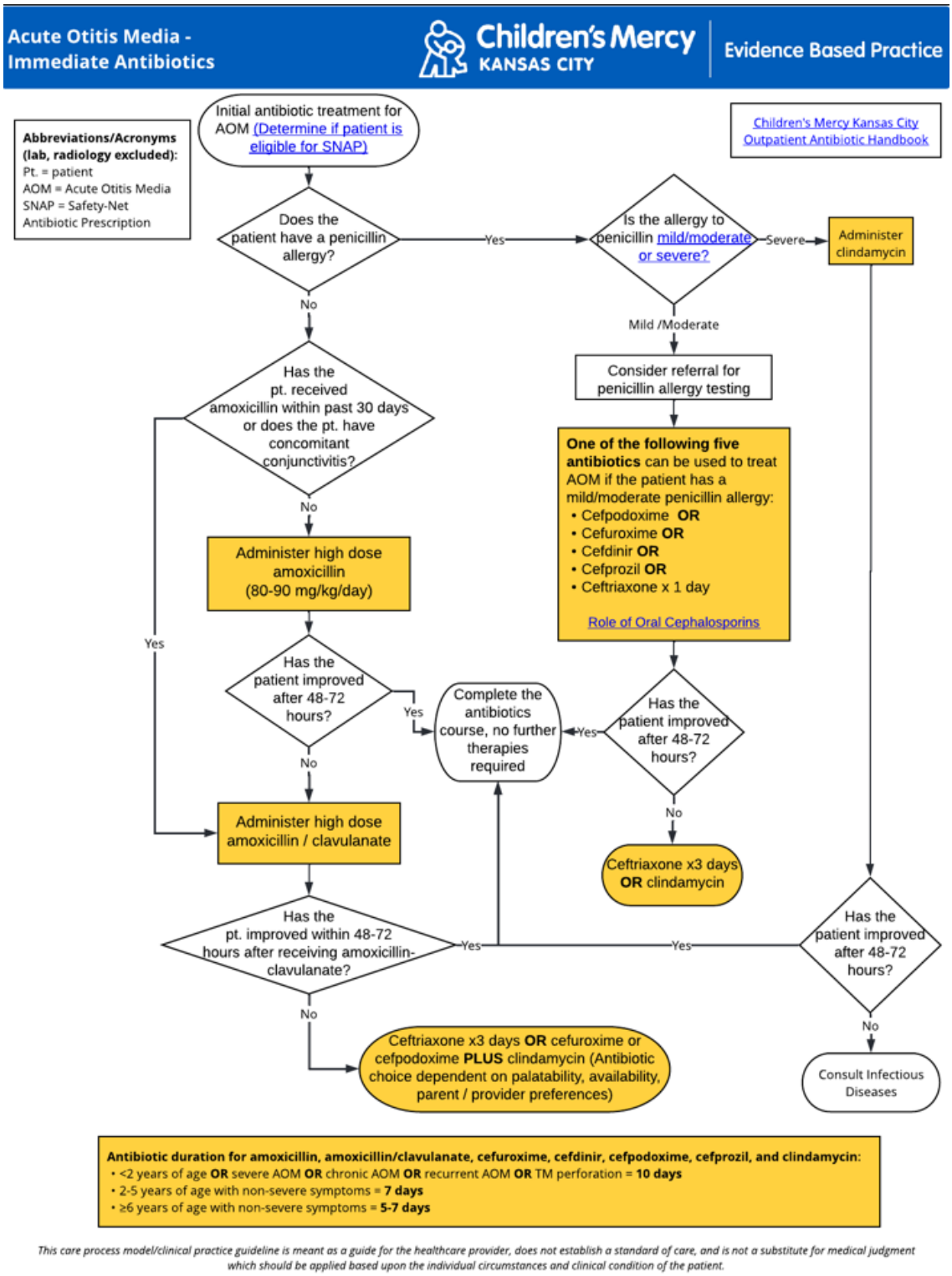

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Acute Otitis Media - Tympanostomy Tube

Children's Mercy KANSAS CITY | Evidence Based Practice

Abbreviations/Acronyms (lab, radiology excluded):
ENT = Ears Nose and Throat
BID = Twice per day

Education Handouts:
- Otorrhea with Tubes
- Otorrhea with Tubes (Spanish)
- Otorrhea without tubes
- Otorrhea without tube (Spanish)

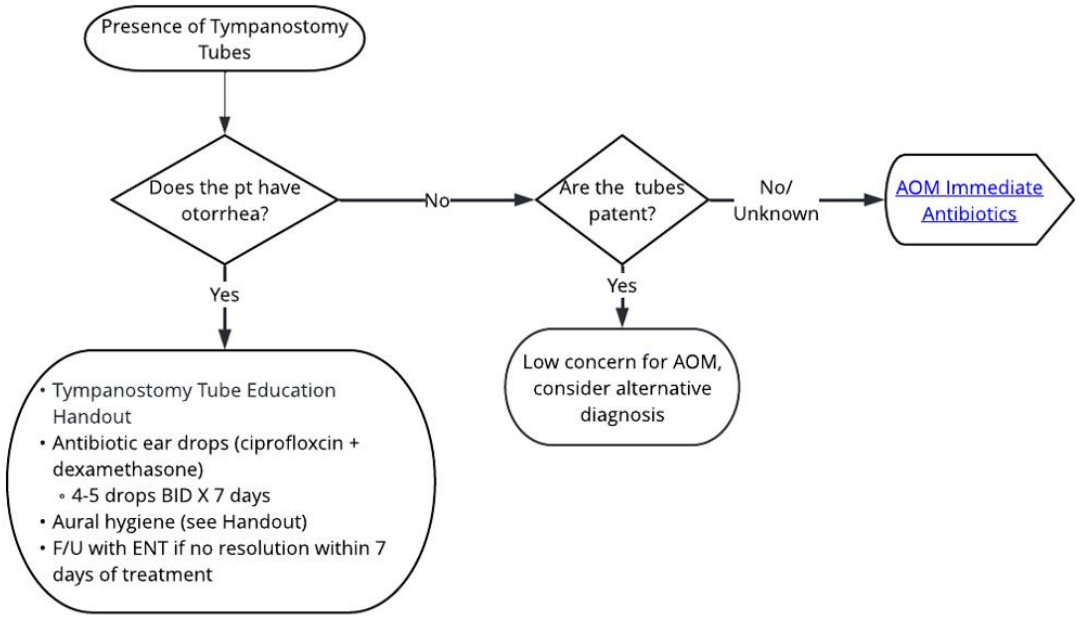

Table of Contents

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Objective To provide care standards for diagnosis and management of acute otitis media throughout the care continuum.

Epidemiology Acute otitis media (AOM) is an infection of the middle ear (Danishyar et al., 2021). It is the second most common pediatric diagnosis in the emergency department. Acute otitis media can occur at any age but is most commonly seen between 6 to 24 months. Roughly 80% of all children will experience otitis media during their lifetime, and between 80-90% of all children will have otitis media with an effusion before school age. There is an increased risk of tympanic membrane perforation with AOM, particularly in children with a history of infections (Pelton & Tahtinen, 2022). Additionally, the most common cause of children with tympanostomy tube otorrhea is AOM (Schmelzle et al., 2008). Fifty-one percent of children with tympanostomies experience $\geq$1 episode of otorrhea (Steele et al., 2017).

Target Users

- Emergency Medicine
- Urgent Care
- Ambulatory Care Clinics
- Pediatric Hospital Medicine
- Pediatric Residents
- Fellows in pediatric subspecialties
- Advance practice providers

Target Population

Inclusion Criteria

- 0 months to 18 years with:
  - Uncomplicated AOM
  - AOM with tympanostomy tubes
  - AOM with acute tympanic membrane perforation

Exclusion Criteria

- <60 days with fever (defer to Febrile Infant Clinical Practice Guideline
- Anatomic abnormalities (including cleft palate)
- Genetic conditions with craniofacial abnormalities (such as Down Syndrome)
- Immune deficiencies
- Presence of cochlear implants

AGREE

The American Academy of Pediatrics national or international guideline(s) provided guidance to the AOM committee (Lieberthal et al., 2011). See Table 1 for AGREE II.

Table 1

AGREE II[b] Summary for the AAP Guideline (Lieberthal et al., 2013)

Domain	Percent Agreement
Scope and purpose	100%
Stakeholder involvement	85%
Rigor of development	93%
Clarity and presentation	93%
Applicability	83%
Editorial independence	83%
Overall guideline assessment	90%
Team's recommendation for guideline use	Yes with modifications

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Note: Four EBP Team members or Scholars completed the AGREE II on this guideline.

AGREE I[Xb] Summary for the NICE Guideline (NICE et al., 2018)

Domain	Percent Agreement
Scope and purpose	100%
Stakeholder involvement	88%
Rigor of development	90%
Clarity and presentation	99%
Applicability	76%
Editorial independence	85%
Overall guideline assessment	90%
Team's recommendation for guideline use	Yes with modifications

Note: Four EBP Team members or Scholars completed the AGREE II on this guideline.

Practice Recommendations

The American Academy of Pediatrics (AAP) guideline, The Diagnosis and Management of Acute Otitis Media, served as the parent guideline (Lieberthal et al., 2013) for this care process model (CPM). While the guideline rated high using the AGREE II evaluation tool (Brouwers et al., 2010), the committee recommended modifications due to the age of the guideline. In particular, the guideline includes evidence prior to the use of pneumococcal vaccine which is known to affect the rate and causative organisms of AOM (Eskola et al., 2001).

The National Institute of Health and Care Excellence (NICE) guideline (2018) recommends antibiotics for those <2 years of age with bilateral AOM or for those at any age with otorrhea. For most other children, the guideline focuses on symptomatic care and recommends not providing antibiotics or providing Safety-Net Antibiotic Prescription (SNAP). If an antibiotic is prescribed, amoxicillin with a duration of 5 to 7 days is recommended. Even though NICE (2018) is a more recent guideline, its recommendations are based on the same evidence as the 2013 AAP guideline.

A. Criteria for diagnosis of AOM
   Middle ear effusion PLUS one of the following:
   - Moderate/severe bulging of tympanic membrane (TM)
   - Mild bulging of TM and 48 hours of otalgia
   - Mild bulging of TM and intense erythema of the TM
   - New onset otorrhea NOT caused by otitis externa

B. Criteria for non-severe and severe symptoms:
   - Non-severe: Mild otalgia <48 hours **AND** temperature < 39C (102.2F)
   - Severe: Moderate/severe otalgia **OR** otalgia ≥ 48 hours **OR** temperature ≥ 39C (102.2F)

C. Management of uncomplicated AOM
   - The AAP clinical practice guideline (Lieberthal et al., 2013) recommends using delayed antibiotics for children >6 months of age with mild to moderate unilateral AOM by implementing SNAP.
   - When antibiotics are given, amoxicillin is recommended as first-line therapy for most children with AOM with a duration of:
     - 10 days for patients ≤23 months of age
     - 7 days for patients 2-5 years of age
     - 5-7 days for patients ≥6 years of age with mild to moderate infection

   When amoxicillin has been given in the last 30 days or patient has concomitant conjunctivitis administer high dose amoxicillin/clavulanate (link to evidence)
   - For patients with mild to moderate penicillin allergy, administer cefuroxime, cefdinir, cefpodoxime, cefprozil
   - For patients with severe penicillin allergy, administer clindamycin
   - A few studies have been promising on reducing antibiotic length (El-Shabrawi et al., 2016; Frost et al., 2022), but the committee decided that there is not enough evidence at this time to change our standard recommendation. (link to evidence)

D. Watchful waiting / SNAP

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- Joint decision between provider and caregiver
- Must have close follow-up (within 48-72 hours) if SNAP not given
- Must be able to fill prescription if signs/symptoms worsen or fail to improve in 48-72 hours

E. Management of AOM with acute perforation
- For children with AOM and spontaneous tympanic membrane perforation, oral rather than topical antibiotic therapy is recommended (Pelton & Tahtinen, 2022). AOM with perforation is managed differently than AOM with tympanotomy tube because spontaneous closure of perforation is unpredictable. Topical may provided added benefit but should not be used in place of oral antibiotics (Pelton & Tahtinen, 2022).

F. Management of AOM with tympanostomy tube (link to evidence)
- Antibiotic ear drops (ciprofloxacin + dexamethasone)
- Aural hygiene (see Handout – Appendix A)
- Follow-up with ENT if no resolution within 7 days of treatment

G. Management of otitis media with effusion (OME)
- In most cases, OME resolves without intervention. Antibiotics are not indicated since there is no bacterial infection. In some cases, OME becomes chronic (> 3 months) at which point audiology is recommended. Additional specifics of OME management are outside of the scope of this CPM.

H. Management of otitis externa
- For severe otitis externa (severe ear canal swelling where the TM is not visible), recommendations include: Ear wick placement, ciprofloxacin/dexamethasone BID until wick comes out, strict dry ear precautions and follow-up in 5-7 days for wick removal.
- For less severe otitis externa, where the TM is visible, ciprofloxacin/dexamethasone ear drops without wick placement are recommended. Additional specifics of otitis externa management are outside of the scope of this CPM

Additional Questions Posed by the CPM Committee

1) For pediatric patients with acute otitis media, is short course antibiotics versus longer course antibiotics, equivalent for the outcome of cure rate and adverse events?
2) For pediatric patients with acute otitis media AND tympanostomy tubes, are antibiotic ear drops (topical, drops, otic) versus oral antibiotics better for the outcomes of clinical cure?
3) For pediatric patients with acute otitis media, is low-dose amoxicillin versus high-dose amoxicillin equivalent to or better for the outcomes of clinical cure, failure rate, and adverse events?

Children's Mercy Practice Recommendations and Reasoning

Children's Mercy adopted the majority of the practice recommendations made by the AAP CPG, The Diagnosis and Management of Acute Otitis Media. Additions include:

Management of AOM with tympanostomy tube (link to evidence)
- Antibiotic ear drops (ciprofloxacin + dexamethasone)
- Aural hygiene (see Handout – Appendix A)
- Follow-up with ENT if no resolution within 7 days of treatment

Measures

- Use of watchful waiting and/or SNAP, when appropriate
- Antibiotic duration
- Unplanned return visit within 14 days

Potential Cost Implications

- Reduced financial cost of fewer antibiotics
- Reduced cost of antimicrobial resistance in the community
- Reduced risk of adverse drug events

Potential Organizational Barriers and Facilitators

Potential Barriers
- Provider resistance to change
- Stakeholder (patient's caregiver) resistance to change

Potential Facilitator
- Collaborative engagement across care continuum settings during CPM development

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- High rate of use of CPM

Standardized order set for Ambulatory Clinic, Urgent Care Clinic, Emergency Department, and Hospital Medicine

Preparation

This CPM was prepared by the Evidence Based Practice (EBP) Department in collaboration with content experts at Children's Mercy Kansas City. The development of this CPM supports the Quality, Excellence and Safety Section initiative to promote care standardization that builds a culture of quality and safety that is evidenced by measured outcomes. If a conflict of interest is identified, the conflict will be disclosed next to the committee member's name.

Implementation & Follow-Up

Once approved, the guideline was presented to appropriate care teams and implemented. Care measurements will be assessed and shared with appropriate care teams to determine if changes need to occur. This CPM is scheduled for revision in October 2024.

AOM CPM Committee Members and Representation

- Rana El Feghaly, MD, MSCI | Infectious Diseases | Committee Chair
- Donna Wyly, MSN, RN, APRN, CPNP-AC, PCNP-BC, ONC | Urgent Care | Committee Member
- Holly Austin, MD, FAAP | Urgent Care | Committee Member
- Tanis Stewart, MSN, RN, FNP-BC, CPN | Emergency Medicine| Committee Member
- Thomas Eyen, MD | Ear Nose and Throat (ENT) | Committee Member
- Trisha Williams| Ear Nose and Throat | Committee Member

MIT Committee Members

- George Abraham, MD | Emergency Medicine, Medical Informatics
- Tammy Frank, RPh, CPHIMS | Medical Informatics - Pharmacy
- Tracy Taylor | Medical Informatics – ED, UCC

EBP Committee Members

- Kathleen Berg, MD, FAAP | Hospital Medicine, Evidence Based Practice
- Jarrod Dusin, MS, RD, LD, CPHQ | Evidence Based Practice

Development Funding

The development of this CPM was underwritten by the EBP, Infectious Diseases, Urgent Care, Emergency, and ENT Departments.

Approval Process

This CPM was reviewed and approved by the AOM CPM Committee, Content Expert Departments/Divisions, and the EBP Department. CPMs are reviewed and updated as necessary every 2 years within the EBP Department at CMKC. Content expert committees will be involved with every review and update.

Approval Obtained

Division/Department/Unit	Date Approved
Infectious Diseases	September 2022
Urgent Care	September 2022
Emergency Medicine	October 2022
ENT	September 2022

Version History

Date	Comments
November 2018	Version one
June 2020	Version two
October 2022	Version three

Disclaimer

When evidence is lacking or inconclusive, options in care are provided in the CPM and the power plans that accompany the CPM.

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It is impossible to anticipate all possible situations that may exist and to prepare CPMs for each. Accordingly, these CPMs should guide care with the understanding that departures from them may be required at times.

References

Brouwers, M.C. et al. for the AGREE Next Steps Consortium. (2010) AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *Canadian Medical Association Journal, 182*, E839-842. Retrieved from https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf

Danishyar, A.; Ashurst, J.V. Acute Otitis Media. In StatPearls [Internet]; StatPearls Publishing: Treasure Island, FL, USA, 2021. Available online: https://www.ncbi.nlm.nih.gov/books/NBK470332

Lieberthal, A. S., Carroll, A. E., Chonmaitree, T., Ganiats, T. G., Hoberman, A., Jackson, M. A., ... & Tunkel, D. E. (2013). The diagnosis and management of acute otitis media. *Pediatrics*, *131*(3), e964-e999.

Pelton, S. I., & Tahtinen, P. (n.d.). *Acute otitis media in children: Treatment*. UpToDate. Retrieved July 19, 2022, from https://www.uptodate.com/contents/acute-otitis-media-in-children-treatment#H499264360membrane&topicRef=16516&anchor=H21&source=see_link#:~:text=In%20patients%20with%20AOM%20and,treat%20with%20oral%20antibiotic%20alone.

Schmelzle, J., Birtwhistle, R. V., & Tan, A. K. (2008). Acute otitis media in children with tympanostomy tubes. *Canadian Family Physician*, *54*(8), 1123-1127.

Steele, D. W., Adam, G. P., Di, M., Halladay, C. H., Balk, E. M., & Trikalinos, T. A. (2017). Effectiveness of tympanostomy tubes for otitis media: a meta-analysis. *Pediatrics*, *139*(6).

Appendix A – Education Handouts

Otorrhea with Tubes
Otorrhea with Tubes (Spanish)
Otorrhea without tubes
Otorrhea without tube (Spanish)
Watchful Waiting
Watchful Waiting (Spanish)
SNAP Flyer for Providers
SNAP Visual Aid

Appendix B Antibiotic Length CAT

Specific Care Question

For children >2 years of age with uncomplicated acute otitis media (AOM), are short-course antibiotics (5 days) versus longer-course antibiotics (7-10 days), equivalent for the outcome of cure rate and adverse events?

Recommendations from the AOM CPM Committee

*A **conditional** recommendation is made **against** the use of short-course antibiotics, based on the GRADE Evidence to Decision instrument[a] the Summary of Findings Table[a]. Even though the evidence is promising for the reduction of antibiotic length, the overall certainty in the evidence is very low[a].* Only one *cohort study* (El-Shabrawi et al. 2016) *and a quality improvement study (*Frost et al., 2022) found shorter-course antibiotics to be equivalent or better to longer-course antibiotics for patients with AOM. *When there is a lack of scientific evidence, standard work should be developed, implemented, and monitored.*

Literature Summary

Background Acute Otitis Media is the most common infection in early childhood (Venekamp et al., 2015). Although AOM usually resolves without treatment, it is the most common condition for prescribed antibiotics in the United States (Lieberthal et al., 2013). The American Academy of Pediatrics clinical practice guideline (Lieberthal et al., 2013) recommends using delayed antibiotics for children >6 months of age with mild to moderate unilateral AOM by implementing the safety-net antibiotic prescriptions (SNAP). Amoxicillin is recommended as first-line therapy for most children with AOM with a duration of 10 days for patients ≤23 months of age and 7 days for patients 2-5 years of age with mild to moderate infection (Lieberthal et al., 2013). The National Institute of Health and Care Excellence (NICE) guideline (2018) recommends antibiotics for those <2 years of age with bilateral AOM or for those at any age with otorrhea. For most other children, the guideline focuses on symptomatic care and recommends not providing antibiotics or providing SNAP. If an antibiotic is prescribed, amoxicillin with a duration of 5 to 7 days is recommended. Even though NICE (2018) is a more recent guideline, its recommendations are based on the same evidence as the 2013 AAP guideline. This review aims to explore the current literature on the topic. This review excludes older articles before the pneumococcal vaccine was widely administered due to its effect on the rate and causative organisms of AOM (Eskola et al., 2001). This review will summarize identified literature to answer the specific care question.

Study characteristics. The search for suitable studies was completed on April 13, 2022. T Stewart, MSN, RN, FNP-BC, CPN and D Wyly, MSN, RN, APRN, CPNP-AC, PPCNP-BC, ONC reviewed the 117 titles and/or abstracts found in the search and identified[b] two guidelines and 10 single studies believed to answer the question. After an in-depth review of the guidelines[c] and single studies, two single studies (El-Shabrawi et al., 2016; Frost et al., 2022) answered the question.

Summary by Outcome

Data Summary by Outcome (rationale for evidence certainty rating[a] provided for each outcome)

Cure rate *One cohort* study (El-Shabrawi et al. 2016) measured cure rate, (*N* = 1380). For the outcome of cure rate, the *p*-value indicated the observation of 5 days of antibiotic (cefpodoxime proxetil) was favorable to >5 days of antibiotics (cefpodoxime proxetil), 5 days: 659/779 versus > 5 days: 472/592, *p*-value = .019.

Certainty Of The Evidence For Cure Rate. The certainty of the body of evidence was very low. The body of evidence was assessed to have serious risk of bias and serious imprecision. The risk of bias was serious due to the potential selection bias of the cohort study and imprecision was serious due to the low number of participants. As only one study was identified to answer this question consistency could not be assessed.

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Data Summary by Outcome (rationale for evidence certainty rating[a] provided for each outcome)

Treatment Failure and AOM Recurrence *One quality improvement (QI)* study (Frost et al., 2022) measured AOM recurrence and treatment failure rate, (*N* = 1017). The study measured these outcomes after the implementation of measures to decrease antibiotic length to 5 days from 10 days for AOM. After the implementation of these measures, there was no significant change in the negative outcomes of recurrence or treatment failure, *p*-value > 0.05.

Certainty Of The Evidence For Cure Rate. The certainty of the body of evidence was very low. The body of evidence was assessed to have serious risk of bias and serious indirectness, and serious imprecision. The risk of bias was serious due to the potential selection bias of a QI study. Indirectness was serious due to the generalizability of QI studies. As only one study was identified to answer this question, consistency could not be assessed.

Identification of Studies

Search Strategy and Results (see Figure 1)

(**2002**:py OR **2003**:py OR **2004**:py OR **2005**:py OR **2006**:py OR **2007**:py OR **2008**:py OR **2009**:py OR **2010**:py OR **2011**:py OR **2012**:py OR **2013**:py OR **2014**:py OR **2015**:py OR **2016**:py OR **2017**:py OR **2018**:py OR **2019**:py OR **2020**:py OR **2021**:py OR **2022**:py) AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim) AND (**'article'**/it OR **'article in press'**/it) **'amoxicillin'**/exp OR **amoxicillin** OR **'amoxicillin plus clavulanic acid'**/exp OR **'amoxicillin plus clavulanic acid'** OR **'cephalosporin'**/exp OR **cephalosporin** OR **'cefdinir'**/exp OR **cefdinir** OR **'cefpodoxime'**/exp OR **cefpodoxime** OR **'cefaclor'**/exp OR **cefaclor** OR **'cefixime'**/exp OR **cefixime 'time'**/exp OR **time** OR **'time factor'**/exp OR **'time factor'** OR **'treatment duration'**/exp OR **'treatment duration'** OR **'duration'**/exp OR **duration** OR **course** OR **days** OR **short** OR **long**

Records identified through database searching *n* = 111

Additional records identified through other sources *n* = 6

Studies Included in this Review

Citation	Study Type
El-Shabrawi et al. (2016)	Cohort
Frost et al. (2022)	QI

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Dagan et al. (2008)	Patients less than 3 years of age
Di Mario et al. (2016)	No comparison to 5 days of antibiotics
Frost et al. (2020)	No outcome of interest
Frost et al. (2021)	Survey
Hoberman et al. (2016)	Patients less than 2 years of age
Kozyrskyj et al. (2010)	Inappropriate antibiotics and older studies prior to pneumococcal vaccine
Neumark et al. (2007)	5 days versus no antibiotics
Venekamp et al. (2015)	Antibiotics vs placebo

Methods Used for Appraisal and Synthesis

[a]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings (SOF) table(s) for this analysis. Using the GDT, the author of this CAT rates the certainty of the evidence based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. Each factor is subjectively judged against the author's confidence of the estimated treatment effect. Confidence is assessed as not serious, serious or very serious. If the attribute of serious or very serious is assessed, the author will provide an explanation.

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[c]The Appraisal of Guidelines Research and Evaluation II (AGREE II) is an international instrument used to assess the quality and reporting of clinical practice guidelines for this analysis (Brouwers et al. 2010).

[d]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

[e]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

References to Appraisal and Synthesis Methods

[a]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[b]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[c]Brouwers, M.C. et al. for the AGREE Next Steps Consortium. (2010) AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *Canadian Medical Association Journal, 182*, E839-842. Retrieved from https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf

[d]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

[e]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

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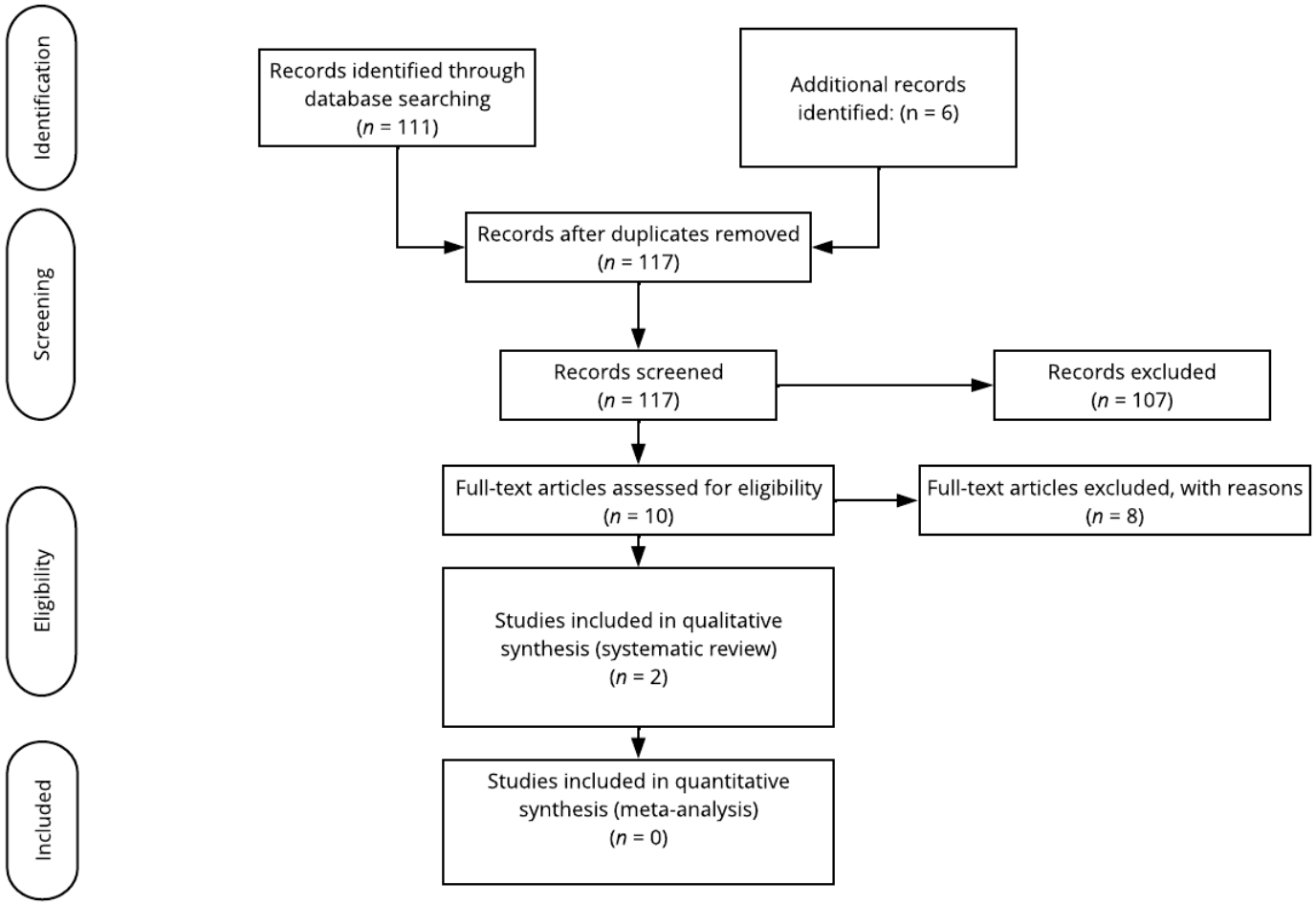
Acronyms Used in this Document

Acronym	Explanation
AGREE II	Appraisal of Guidelines Research and Evaluation II
AOM	Acute Otitis Media
CAT	Critically Appraised Topic
EBP	Evidence Based Practice
NICE	National Institute of Health and Care Excellence
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SNAP	Safety-net antibiotic prescriptions

Statistical Acronyms Used in this Document

Statistical Acronym	Explanation
M or $\bar{X}$	Mean
Mdn	Median
n	Number of cases in a subsample
N	Total number in sample
OR	Odds Ratio
P or p	Probability of success in a binary trial
SD	Standard deviation
SR	Systematic Review

Figure 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[e]



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Characteristics of Intervention Studies

El-Shabrai et al. (2016)

Methods	Cohort
Participants	**Participants:** Children ages 1-13 diagnosed with AOM **Setting:** 26 Egyptian medical centers **Number enrolled into study:** *N* = 1380 • **Group,** cefpodoxime proxetil 8 mg/kg/day**:** *N* = 1380 **Gender, males (as defined by researchers):** • **Group:** *n = 788 (57.2%)* **Race / ethnicity or nationality (as defined by researchers):** • Not reported **Age, mean in years,** • **Group 1:** 3.8 ± 2.5 years **Inclusion Criteria:** • Diagnosis of purulent AOM based on triad of clinical symptoms: otalgia, fever and irritability, tympanic membrane (TM) signs of AOM such as middle ear effusion characterized by bulging, limited or absent mobility of the TM or air-fluid level behind membrane; and evidence of TM inflammation indicated by erythema, perforation of otorrhea in at least one ear. **Exclusion Criteria:** • Patients with hypersensitivity to cephalosporin antibiotics **Covariates Identified:** • Not reported
Interventions	The study was conducted in two visits, a baseline visit at clinical evaluation and treatment initiation, and a follow-up visit (days 7–14) • **Group:** cefpodoxime proxetil 8mg/kg/day for 5-10 days
Outcomes	**Primary outcome(s):** • *Cure rate • *Failure rate **Secondary outcome(s):** • Length of therapy **Safety outcome(s):** • *Adverse events *Outcomes of interest to Children's Mercy CPM development team
Results	**Results:** • The most frequently reported prescription durations ○ Five days in 783 (56.8%) ○ Seven days in 326 (23.7%)

	○ Ten days in 269 (19.5%) • Patients with a 5-day course therapy had a significantly higher cure compared to those receiving 7 to 10 day of antitibics: (p = .019) ○ Five days: 84.6% (659/779) ○ > Five days 79.7% (472/592) • 1371 completed the study (2 did not show and 7 were non-compliant) ○ 1131 patients (82.5%) were cured, cure or improvement rate was 100% in all signs and symptoms except: ▪ spontaneous otorrhea (98%), ▪ purulent discharge (98.5%), ▪ nasal discharge (93.5%) • 15 patients (1.1 %) failed to respond to therapy • Adverse events were reported by 16 patients (1.2%) which included diarrhea (n = 9) and skin rash (n = 7), both mild to moderate in nature and did not require dose reduction or discontinuation. **Limitations:** • Not reported

Frost et al. (2022)

<table>
<tr><th>Methods</th><th>Quality Improvement</th></tr>
<tr><td>Participants</td><td>
Participants: Children ≥ 2 years of age with Acute Otitis Media
Setting: Denver Health System; Family Medicine Clinics
Number enrolled into study: N = 1017
• Pre-intervention, Bundled ASP interventions: n = 388
• Post-intervention, Bundled ASP interventions: n = 115
• Pre-intervention, Electronic Health Record (HER)-only interventions: n = 409
• Post-intervention, EHR-only interventions: n = 105

Gender, males (as defined by researchers):
• Pre-intervention: n = 50.0 (%)
• Post-intervention: n = 44.4 (%)
• Pre-intervention: n = 48.9 (%)
• Post-intervention EHR: n = 45.7 (%)

Race (as defined by researchers):
<table>
<tr><th>(%)</th><th>Preintervention</th><th>Postintervention</th></tr>
<tr><td>Black</td><td>11.3</td><td>8.7</td></tr>
<tr><td>White</td><td>76.3</td><td>79.1</td></tr>
<tr><td>Other</td><td>12.4</td><td>12.2</td></tr>
</table>
Ethnicity:
<table>
<tr><th>(%)</th><th>Preintervention</th><th>Postintervention</th></tr>
<tr><td>Non-Hispanic</td><td>27.8</td><td>27.8</td></tr>
<tr><td>Hispanic</td><td>72.2</td><td>72.2</td></tr>
</table>
Age, mean in years:
• Pre-intervention Bundled: 5.8
• Post-intervention Bundled: 6.0
• Pre-intervention EHR: 5.5
• Post-intervention EHR: 6.2
Inclusion Criteria:
• Children ≥ 2 years of age
• Uncomplicated Acute Otitis Media
Exclusion Criteria:
• Antibiotic use within 30 days prior to visit
• History of tympanostomy or tubes
• Competing bacterial diagnosis
• Patients receiving intramuscular antibiotics
• Patients receiving azithromycin
</td></tr>
<tr><td>Interventions</td><td>Bundled ASP intervention:</td></tr>
</table>

	• **Pre-intervention:** No monthly individualized provider audit and feedback, education or electronic decision support in EHR • **Post-intervention:** Monthly individualized provider audit and feedback, education or electronic decision support in EHR **EHR-only intervention:** • **Pre-intervention:** No hyperlink to guidelines for common pediatric infections, help text for antibiotic selection/duration of therapy, quick buttons to select appropriate dosing/duration of therapy • **Post-intervention**: Hyperlink to guidelines for common pediatric infections, help text for antibiotic selection/duration of therapy, quick buttons to select appropriate dosing/duration of therapy
Outcomes	**Primary outcome(s):** • Guideline-concordant prescribing rates **Secondary outcome(s):** • Treatment failure* • Recurrence* **Safety outcome(s):** • Not reported *Outcomes of interest to the CMH CPG /CAT development team
Results	**Results:** • Guideline-concordant prescribing rates increased from 10.6% to 85.2% with bundled intervention from 14.4% to 63.8% with EHR-only intervention • *Treatment failure was not significant for the bundled intervention and the EHR intervention, *p*-value = .62 and *p*-value =0.64, respectively • *Recurrence in the bundled intervention and EHR-only intervention were not significant, *p*-value = .18, *p*-value = 1.0, respectively **Limitations:** • Interventions took place in a single healthcare system and may not be generalizable to other organizations • Bundled interventions took place in only pediatric clinics, EHR-only interventions only in family medicine clinics so unable to evaluate effectiveness in each specialty • Unclear whether observed improvement in prescribing due to actual intervention or how each intervention was received from providers • Unable to account for antibiotics prescribed outside of Denver Health System • Effect of COVID-19 pandemic and number of patients presenting with AOM • Unable to evaluate long-term sustainability of program due to short study duration

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Evidence to Decision Assessment

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Acute Otitis Media is the most common infection in early childhood (Venekamp et al., 2015). Although AOM usually resolves without treatment, it is the most common condition for prescribed antibiotics in the United States (Lieberthal et al., 2013).	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	***Cure rate*** *One cohort* study (El-Shabrawi et al. 2016) measured cure rate, (*N* = 1380). For the outcome of cure rate, the *p*-value indicated the observation of 5 days of antibiotic (cefpodoxime proxetil) was favorable to >5 days of antibiotics (cefpodoxime proxetil), 5 days: 659/779 versus > 5 days: 472/592, *p*-value = .019. 85% versus 80% cure rate	The desirable effects of a shorter course are fewer adverse drug reactions, medication side effects, and antimicrobial resistance.

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	***Treatment Failure and AOM Recurrence*** *One quality improvement (QI)* study (Frost et al., 2022) measured AOM recurrence and treatment failure rate, (*N* = 1017). The study measured these outcomes after the implementation of measures to decrease antibiotic length to 5 days from 10 days for AOM. After the implementation of these measures, there was no significant change in the negative outcomes of recurrence or treatment failure, *p*-value > 0.05. No difference in treatment failure	Undesirable effects of shorter-course are treatment failure of AOM Return to care

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Certainty Of The Evidence For Cure Rate.** The certainty of the body of evidence was very low. The body of evidence was assessed to have serious risk of bias and serious imprecision. The risk of bias was serious due to the potential selection bias of the cohort study and imprecision was serious due to the low number of participants. As only one study was identified to answer this question consistency could not be assessed. **Certainty Of The Evidence For Treatment Failure and Recurrence.** The certainty of the body of evidence was very low. The body of evidence was assessed to have serious risk of bias and serious indirectness, and serious imprecision. The risk of bias was serious due to the potential selection bias of a QI study. Indirectness was serious due to the generalizability of QI studies. As only one study was identified to answer this question, consistency could not be assessed.	Minimal evidence exists on outcomes of longer vs shorter therapy. Only one quality improvement study and one cohort study (see above) make this comparison.

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability		Some providers (e.g. Antimicrobial Stewardship) may weigh more heavily on the risk of adverse drug events, side effects, and antimicrobial resistance. Some parents/families of patients may weigh more heavily the risk of treatment failure.

○ Probably no important uncertainty or variability ○ No important uncertainty or variability		

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Minimal evidence exists on outcomes of longer vs shorter therapy. Only one quality improvement study and one cohort study (see above) make this comparison.	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The mean cost of treatment for the amoxicillin group is $189.20 versus $198.68 for the SNAP group. (Gaboury et al., 2010) The indirect costs of AOM, accrued primarily by parental time lost are $1330.58, 95% CI [$1008.75, $1652.43] (Alsarraf et al., 1999).	

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No studies compared 5 versus 10 days of antibiotics.	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Likely lower cost 5 versus 10 days. No included studies.	

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact		Families would have to travel to pharmacies, obtain prescriptions, and follow written prescription instructions regardless of the duration. However, the cost would be greater for the longer antibiotic course.

** These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different, and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time. It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.*

○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		If evidence is stronger, stakeholders would likely be accepting of the intervention of a shorter duration.

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No issues with feasibility in prescribing short versus long course.	

CONCLUSIONS

Recommendation

*A **conditional** recommendation is made **against** the use of short-course antibiotics based on the GRADE Evidence to Decision instrument.*

** These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different, and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time. It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.*

Appendix C Antibiotic Length CAT

Specific Care Question

In pediatric patients with acute otitis media (AOM) AND tympanostomy tubes, are antibiotic ear drops (topical, drops, otic) versus oral antibiotics better for the outcomes of resolution and adverse events?

Recommendations from the AOM CPM Committee

*A **conditional** recommendation is made **for** the use of ear drops over oral antibiotics for patients with tympanostomy tubes, based on the GRADE Evidence to Decision instrument[a] and the Summary of Findings Table[a]. Even though the certainty of the evidence is low to very low[a], antibiotic ear drops were favorable compared to oral antibiotics for the resolution of ear discharge. Also, adverse events were found to be no difference between the two interventions. Standard work should be developed, implemented, and monitored when there is a lack of scientific evidence.*

Literature Summary

Background Acute otitis media is the most common infection in early childhood (Venekamp et al., 2015) and ear discharge (otorrhea) is common in children with tympanostomy tubes. The most common treatment for AOM strategies includes oral antibiotics, antibiotic ear drops, or ear drops containing a combination of antibiotics and corticosteroids (Venekamp et al., 2016). This review will summarize identified literature to answer the specific care question.

Study characteristics. The search for suitable studies was completed on April 25, 2022. T. Williams RN, APRN, CPN, CPNP, and H. Austin MD, FAAP reviewed the 54 titles and/or abstracts found in the search and identified[b] eight single studies believed to answer the question. After an in-depth review of the single studies[d], two answered the question (Steele et al., 2017; Venekamp et al., 2016). Venekamp et al. (2016) is a systematic review/meta-analysis which includes the comparison of ear drops antibiotics versus systemic antibiotics in patients with tympanostomy tubes and ear discharge.
Steele et al. (2017) is a network meta-analysis that indirectly compares ear drop antibiotics versus systemic antibiotics in pediatric patients with tympanostomy tubes and ear discharge.

Summary by Outcome

Data Summary by Outcome (rationale for evidence certainty rating[a] provided for each outcome)

Resolution of ear discharge at one week

The systematic review by Venekamp et al. (2016) found one RCT (Heslop et al., 2010) that measured resolution of ear discharge at one week, (N = 42). For the outcome of resolution, the results indicated the intervention of antibiotic ear drops (with or without corticosteroids) was favorable to the comparator of oral antibiotics, OR = 2.58, 95% CI [1.27, 5.22], p-value = 0.01.

> **Certainty Of The Evidence For Resolution of ear discharge at one week.** The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious inconsistency nor indirectness, however was assessed to have serious risk of bias and serious imprecision. Risk of bias was serious due to lack of blinding in the study which could have affected outcome assessment. Imprecision was serious due the low number of events (n = 23) and subjects (N = 42). As only one study, Heslop et al. (2010), was identified to answer this question, consistency could not be assessed.

Resolution of ear discharge at two to four weeks

The systematic review by Venekamp et al. (2016) found two RCTs (Dohar et al., 2006; Van Dongen et al., 2014) that measured resolution of ear discharge at two to four weeks (N = 232). For the outcome of resolution, the results indicated the intervention of antibiotic ear drops (with corticosteroids) was favorable to the comparator of oral antibiotics, OR = 1.59, 95% CI [1.35, 1.88], p-value < .0001.

Certainty Of The Evidence For Resolution of ear discharge at one week. The certainty of the body of evidence was low. The body of evidence was assessed to not have serious inconsistency nor indirectness, however, was assessed to have serious risk of bias and serious imprecision. Risk of bias was serious due to lack of blinding in the study which could have affected outcome assessment. Imprecision was serious due to the low number of subjects (*N* = 232).

Adverse events

The systematic review by Venekamp et al. (2016) found three RCTs (Dohar et al., 2006; Goldblatt et al., 1998; Van Dongen et al., 2014) that measured adverse events, (*n* = 232). For the outcome of adverse events, the results indicated the intervention of antibiotic ear drops (with and without corticosteroids) was not different to the comparator of oral antibiotics, *OR* = 0.37, 95% CI [0.12, 1.09], *p*-value = .07.

Certainty Of The Evidence For Resolution of ear discharge at one week. The certainty of the body of evidence was low. The body of evidence was assessed to not have serious imprecision nor indirectness, however, was assessed to have serious risk of bias and serious inconsistency. Risk of bias was serious due to the lack of blinding in the study which could have affected the outcome assessment. Imprecision was serious as evidenced by the substantial heterogeneity I^2=88%.

Relative effectiveness

The network meta-analysis by Steele et al. (2017) measured relative effectiveness of different treatments for otorrhea in patients with tympanostomy tubes, (*N* = 7 Studies). For the outcome of relative effectiveness, the results indicated the intervention of antibiotic ear drops (with or without corticosteroids) was favorable to the comparator of oral antibiotics, *OR* = 5.30, 95% CI [1.20, 27].

Certainty Of The Evidence For Resolution of ear discharge at one week. The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious inconsistency, however, was assessed to have serious risk of bias, serious indirectness, and serious imprecision. The risk of bias was serious due to the lack of blinding in the study which could have affected the outcome assessment. Indirectness was serious due to the study being a network meta-analysis and imprecision was serious due to the wide confidence interval.

Identification of Studies

Search Strategy and Results (see Figure 1)

(**2012**:py OR **2013**:py OR **2014**:py OR **2015**:py OR **2016**:py OR **2017**:py OR **2018**:py OR **2019**:py OR **2020**:py OR **2021**:py OR **2022**:py) AND ([adolescent]/lim OR [child]/lim OR [infant]/lim OR [newborn]/lim OR [preschool]/lim OR [school]/lim) AND (**'article'**/it OR **'review'**/it) **'cure'**/exp OR **cure** OR **'treatment outcome'** OR **'outcome'**/exp OR **'outcome'** OR **'patient assessment'**/exp OR **'patient assessment'** OR **'treatment failure'**/exp OR **'treatment failure' 'tympanostomy tube*'** OR **'tympanostomy tube otorrhea'**/exp OR **'tympanostomy tube otorrhea'** OR **'tympanostomy tube'**/exp OR **'tympanostomy'**/exp OR **tympanostomy** OR **'eardrum perforation'**/exp OR **'eardrum perforation'** OR **'tympanic membrane perforation' 'acute otitis media'**/exp OR **'acute otitis media'** OR **'otorrhea'**/exp OR **otorrhea 'amoxicillin'**/exp OR **amoxicillin** OR **'amoxicillin plus clavulanic acid'**/exp OR **'amoxicillin plus clavulanic acid'** OR **'cephalosporin'**/exp OR **cephalosporin** OR **'cefdinir'**/exp OR **cefdinir** OR **'cefpodoxime'**/exp OR **cefpodoxime** OR **'cefaclor'**/exp OR **cefaclor** OR **'cefixime'**/exp OR **cefixime** OR **ceftriaxone** OR **'ciprofloxacin plus dexamethasone'**/exp OR **ciprodex** OR **ciprofloxacin** OR **ofloxacin** OR **'prednisolone sodium**

phosphate plus sulfacetamide'/exp OR **vasocidin** OR **'boric acid' #1'ear drops**'/exp OR **'ear drops'** OR (('**antibiotic agent**'/exp OR **'antibiotic agent'** OR **'antibiotic therapy**'/exp OR **'antibiotic therapy'** OR **'antiinfective agent**'/exp) AND (**oral** OR **enteric** OR **topical** OR **otic** OR **drop***))
Records identified through database searching *n* = 54
Additional records identified through other sources *n* = 0

Studies Included in this Review

Citation	Study Type
Steele et al. (2017)	Systematic Review/Meta-Analysis
Venekamp et al. (2016)	Systematic Review/Meta-Analysis

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Gupta et al. (2014)	Chronic otitis media and study includes adults
Hullegie et al. (2021)	Study protocol
Spektor et al. (2017)	Study of ear drops only
Syed et al. (2013)	Study on postoperative care
Van Dongen et al. (2014)	Included in Venekamp et al. (2016) SR
Van Dongen et al. (2015)	Cost study

Methods Used for Appraisal and Synthesis

[a]The GRADEpro Guideline Development Tool (GDT) Using the GDT, the author of this CAT rates the certainty of the evidence based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. Each factor is subjectively judged against the author's confidence of the estimated treatment effect. Confidence is assessed as not serious, serious, or very serious. If the attribute of serious or very serious is assessed, the author will provide an explanation.

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[c]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

[d]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

References to Appraisal and Synthesis Methods

[a]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[b]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[c]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

[d]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

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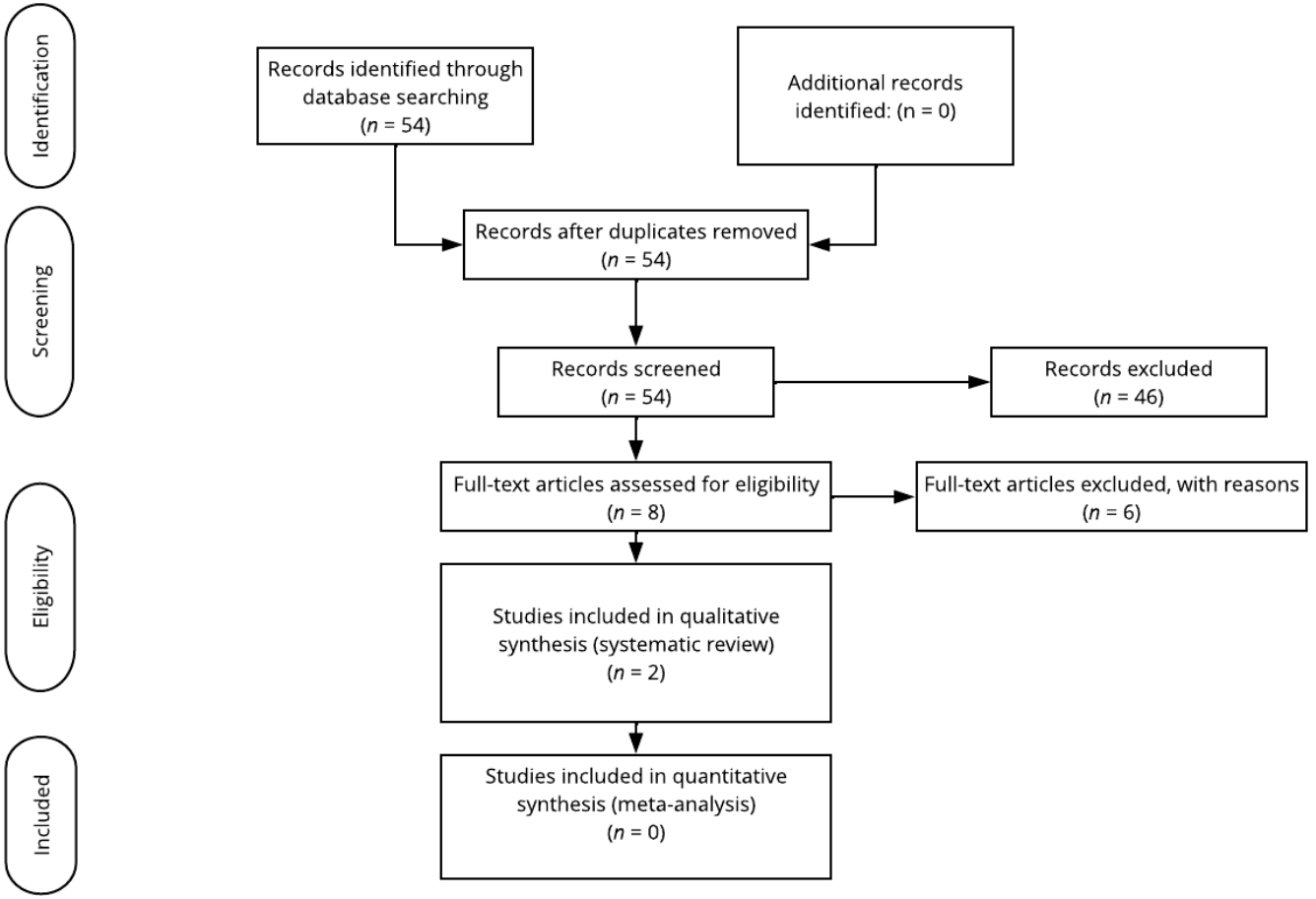
Acronyms Used in this Document

Acronym	Explanation
AGREE II	Appraisal of Guidelines Research and Evaluation II
CAT	Critically Appraised Topic
EBP	Evidence Based Practice
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Statistical Acronyms Used in this Document

Statistical Acronym	Explanation
CI	Confidence Interval
M or $\bar{X}$	Mean
n	Number of cases in a subsample
N	Total number in sample
OR	Odds Ratio
P or p	Probability of success in a binary trial
RCT	Randomized controlled trial
SD	Standard deviation
SR	Systematic Review

Figure 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[d]



** These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different, and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time. It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.*

Characteristics of Intervention Studies

Steele et al., 2017

Design	Quantitative Synthesis (meta-analysis)
Objective	Reviewed evidence for water precautions (ear plugs or swimming avoidance) and effectiveness of topical versus oral antibiotic treatment of otorrhea in children with tympanostomy tube.

Methods	**Criteria for considering studies for this review**
	• **Types of studies:** Randomized controlled trials (RCTs) and nonrandomized comparative studies
	• **Participants:** Children, not specified
	• **Target Condition(s):** Otorrhea in patients with tympanostomy tubes
	
	Search methods for identification of studies
	• **Electronic databases searched:** Medline, the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, Excerpta Medica Database, and the Cumulative Index to Nursing and Allied Health Literature all dates through May 19, 2016.
	• **Search strategy employed:** Not reported
	
	Data collection and analysis
	• **Inclusion criteria:** Comparison of benefits and/or harms of at least two of the following:
	  ○ Symptomatic or asymptomatic children with acute tympanostomy tube otorrhea beyond the immediate postoperative period (30 days after surgery)
	• **Exclusion criteria:**
	  ○ Trials enrolling children with early postoperative otorrhea or chronic suppurative otitis media
	• **Population:** Children, ages not specified
	• **Setting:** Not specified
	• **Study Design:** Systemic review and network meta-analysis
	• **Data collection process:** Not specified
	• **Assessment of Bias:**
	  ○ Cochrane Risk of Bias Tool (RCTs)
	  ○ Newcastle Ottawa Scale (Nonrandomized studies)
	• **Data Synthesis:**
	  ○ **Overall Effect Size**
	  ▪ Odds ratios (ORs) and confidence interval (CI)
	  ▪ Number needed to treat (NNT)

Results	**Study Selection (actual results/data)** **Number of articles identified:** *N* = 13334 **Full-text articles assessed for eligibility:** *n* = 172 ○ **Studies included in qualitative synthesis:** *n* = 7 **Synthesis of quality of evidence**: Moderate

	Synthesis of quantitative evidence ○ **Overall Effect Size:** RCT that studied antibiotic ear drops with corticosteroids versus oral antibiotics on relative effectiveness ▪ Ear drops with corticosteroids versus oral antibiotics: ▪ **OR:** 5.3 ▪ **CI:** 95% CI 1.20 to 27.00 ▪ **NNT:** 3.2 ▪ **Heterogeneity:** Not reported ○ **Overall Effect Size:** RCT that studied antibiotic ear drops without corticosteroids versus oral antibiotics on relative effectiveness ▪ Ear drops without corticosteroids versus oral antibiotics: ▪ **OR:** 3.3 ▪ **CI:** 95% CI 0.74 to 16 ▪ **Heterogeneity:** Not reported
Discussion	**Summary of evidence** • Network meta-analyses suggest that, relative to oral antibiotics, topical antibiotic–glucocorticoid drops were more effective. • Network meta-analyses suggest that, relative to oral antibiotics, topical antibiotics were not more effective **Limitations** • The author used indirect evidence from the network meta-analysis to augment the direct evidence relating to the comparisons of interest for the treatment of otorrhea. The study assumes there is consistency with the effect modifiers across the direct and indirect evidence.

Venekamp et al., 2016

Design	Quantitative Synthesis (meta-analysis)
Objective	Conduct a systemic review and meta-analysis of the interventional and observational studies reporting data on the benefits and harms of current treatment strategies for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion.

Methods	**Criteria for considering studies for this review**
	• **Types of studies:** Randomized controlled trials (RCTs)
	• **Participants:** Patients, less than 18 years, with grommets
	• **Target Condition(s):** Acute ear discharge outside the immediate postoperative period, following grommet insertion
	
	Search methods for identification of studies
	• **Electronic databases searched:** ENT Trials Register, Cochrane Central Register of Controlled Trials, PubMed/MEDLINE, EMBASE, CAB, EBSCO CINAHL, LILACS, KoreaMed, IndMed, PakMediNet, Web of Knowledge, CNKI, ClinicalTrials.gov, ICTRP, ISRCTN, Google Scholar, Google for all dates through June 23, 2016
	• **Search strategy employed:** Mesh terms: (middle ear ventilation or grommet) OR (cerebrospinal fluid otorrhea)
	• **Searching other resources:** Ovid MEDLINE,
	• TRIPdatabase, The Cochrane Library and Google
	
	Data collection and analysis
	• **Inclusion criteria:** Comparison of benefits and/or harms of at least two of the following:
	  ○ Oral corticosteroids
	  ○ Antibiotic ear drops
	  ○ Antibiotic(s)-corticosteroid ear drops
	  ○ Corticosteroid ear drops
	  ○ Cleaning the ear canal using micro suction
	  ○ Saline rinsing of the ear canal
	  ○ Placebo (in the form of ear drops, oral suspension, or tablets, depending on the 'active' intervention that is studied) or no treatment
	• **Exclusion criteria:**
	  ○ Review article
	  ○ Not a randomized trial
	• **Population:** Children, ages 0 to 12 years
	• **Setting:** Secondary or tertiary care setting
	• **Study Design:** Systemic review and meta-analysis
	• **Data collection process:** Two investigators independently review
	• **Assessment of the certainty of the evidence:** GRADE
	• **Data Synthesis:**
	  ○ **Overall Effect Size**

	▪ Mantel-Haenszel (MH) risk ratio (RR) for dichotomous outcomes with 95% confidence interval (CI) ▪ DerSimonian and Laird model for random effects ○ **Heterogeneity** ▪ Chi^2 test ▪ I^2 statistic
Results	**Study Selection** **Number of articles identified:** *N* = 1548 **Full-text articles assessed for eligibility:** *n* = 21 ○ **Studies included in qualitative synthesis:** *n* = 9 **Synthesis of quality of evidence**: Moderate **Synthesis of quantitative evidence** ○ **Overall Effect Size:** RCT that studied antibiotic ear drops with corticosteroids vs oral antibiotics on resolution of ear discharge at two to four weeks ▪ Oral vs ear drop antibiotics: *N* = 213 ▪ **Risk Ratio (RR):** 1.59 ▪ **CI:** 95% CI 1.35 to 1.88, *p* < .0001 ▪ **Heterogeneity:** Not reported ○ **Overall Effect Size:** RCT that studied antibiotic ear drops (with and without corticosteroids) vs oral antibiotics on resolution of ear discharge at one week ▪ Oral vs ear drop antibiotics: *N* = 42 ▪ **Risk Ratio (RR):** 2.58 ▪ **CI:** 95% CI 1.27 to 5.22, *p* = .01 ▪ **Heterogeneity:** Not reported ○ **Overall Effect Size:** RCT studies adverse events likely related to study medications ▪ Adverse events likely related to study medications: *n* = 705 ▪ **Risk Ratio (RR):** 0.37 ▪ **CI:** 95% CI 0.12 to 1.09, *p* – .07 ▪ **Heterogeneity** • Tau^2 = 0.8 • Chi^2 = 16.9 • df = 2 (p = .3) • I^2 = 5.31%
Discussion	**Summary of evidence** ▪ Authors note all studies favor antibiotic ear drops over other interventions. ▪ The difference between treatments was large, in favor of ear drops. ▪ Inconclusive evidence that antibiotic ear drops are more effective than saline rinsing.

	Limitations ▪ Quality of evidence
Funding	**Funding** ▪ Five studies received financial support or were directly funded by pharmaceutical companies. ▪ Pharmaceutical companies provided the study medication in two studies. ▪ One study received governmental funding. ▪ One study was performed without funding.

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Evidence to Decision Assessment for Tympanostomy Treatment

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Roughly 80% of all children will experience otitis media during their lifetime, and between 80-90% of all children will have otitis media with an effusion before school age. There is an increased risk of tympanic membrane perforation with AOM, particularly in children with a history of infections (Pelton & Tahtinen, 2022). Additionally, the most common cause of children with tympanostomy tube otorrhea is AOM (Schmelzle et al., 2008). **Fifty-one percent of children with tympanostomies experience ≥1 episode of otorrhea (Steele et al., 2017).**	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	***Resolution of ear discharge at one week*** The systematic review by Venekamp et al. (2016) found one RCT (Heslop et al., 2010) that measured resolution of ear discharge at one week, (*N* = 42). For the outcome of resolution, the results indicated the intervention of antibiotic ear drops (with or without corticosteroids) was favorable to the comparator of oral antibiotics, *OR* = 2.58, 95% CI [1.27, 5.22], *p*-value = 0.01. ***Resolution of ear discharge at two to four weeks*** The systematic review by Venekamp et al. (2016) found two RCTs (Dohar et al., 2006; Van Dongen et al., 2014) that measured resolution of ear discharge at two to four weeks (*N* = 232). For the outcome of resolution, the results indicated the intervention of antibiotic ear drops (with corticosteroids) was favorable to the comparator of oral antibiotics, *OR* = 1.59, 95% CI [1.35, 1.88], *p*-value < .0001. ***Relative effectiveness*** The network meta-analysis by Steele et al. (2017) measured relative effectiveness of different treatments for otorrhea in patients with tympanostomy tubes, (*N* = 7 Studies). For the outcome of relative effectiveness, the results indicated the intervention of antibiotic ear drops (with or without corticosteroids) was favorable to the comparator of oral antibiotics, *OR* = 5.30, 95% CI [1.20, 27].	

** These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different, and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time. It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.*

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	***Adverse events*** The systematic review by Venekamp et al. (2016) found three RCTs (Dohar et al., 2006; Goldblatt et al., 1998; Van Dongen et al., 2014) that measured adverse events, (*n* = 232). For the outcome of adverse events, the results indicated the intervention of antibiotic ear drops (with and without corticosteroids) was not different to the comparator of oral antibiotics, *OR* = 0.37, 95% CI [0.12, 1.09], *p*-value = .07.	Treatment failure and recurrence
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Certainty Of The Evidence For Resolution of ear discharge at one week.** The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious inconsistency nor indirectness, however was assessed to have serious risk of bias and serious imprecision. Risk of bias was serious due to lack of blinding in the study which could have affected outcome assessment. Imprecision was serious due the low number of events (*n* = 23) and subjects (*N* = 42). As only one study, Heslop et al. (2010), was identified to answer this question, consistency could not be assessed. **Certainty Of The Evidence For Resolution of ear discharge at one week.** The certainty of the body of evidence was low. The body of evidence was assessed to not have serious inconsistency nor indirectness, however, was assessed to have serious risk of bias and serious imprecision. Risk of bias was serious due to lack of blinding in the study which could have affected outcome assessment. Imprecision was serious due to the low number of subjects (*N* = 232). **Certainty Of The Evidence For Resolution of ear discharge at one week.** The certainty of the body of evidence was low. The body of evidence was assessed to not have serious imprecision nor indirectness, however, was assessed to have serious risk of bias and serious inconsistency. Risk of bias was serious due to the lack of blinding in the study which could have affected the outcome assessment. Imprecision was serious as evidenced by the substantial heterogeneity I2=88%. **Certainty Of The Evidence For Resolution of ear discharge at one week.** The certainty of the body of evidence was very low. The body of	

	evidence was assessed to not have serious inconsistency, however, was assessed to have serious risk of bias, serious indirectness, and serious imprecision. The risk of bias was serious due to the lack of blinding in the study which could have affected the outcome assessment. Indirectness was serious due to the study being a network meta-analysis and imprecision was serious due to the wide confidence interval.	

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		Some providers (e.g. Antimicrobial Stewardship) may weigh more heavily the risk of adverse drug events, side effects, and antimicrobial resistance. Some parents/families of patients may weigh more heavily the risk of treatment failure. Risk aversion

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ Don't know	Evidence is limited but favors the intervention of ear drops	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● Moderate savings ○ Large savings ○ Varies ○ Don't know	At two weeks, the mean total cost per patient is $42.43 for antibiotic-glucocorticoid eardrops, $70.60 for oral antibiotics, and $82.03 for initial observation. At six months, the mean total cost per patient was $368.20, $420.73, and $640.44, respectively. (Dongen et al., 2015)	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies		Recent price drop of ear drops

Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● Favors the intervention ○ Varies ○ No included studies	At two weeks, the mean total cost per patient is $42.43 for antibiotic-glucocorticoid eardrops, $70.60 for oral antibiotics, and $82.03 for initial observation. At six months, the mean total cost per patient was $368.20, $420.73, and $640.44, respectively. (Dongen et al., 2015)	
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○Probably increased ○ Increased ○ Varies ● Don't know		Issues with patients taking antibiotics Cost issues may affect access for some families
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know		

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know		Availability issue cost prohibitive when not covered by insurance

CONCLUSIONS

Recommendation

*A **conditional** recommendation is made **for** the use of ear drops over oral antibiotics for patients with tympanostomy tubes, based on the GRADE Evidence to Decision instrument.*

Appendix E Antibiotic Dosing CAT

Specific Care Question

For pediatric patients with acute otitis media, is low-dose amoxicillin versus high-dose amoxicillin equivalent to or better for the outcomes of clinical cure, failure rate, and adverse events?

Recommendations from the AOM Committee

*A **conditional** recommendation against the intervention of low-dose versus high-dose amoxicillin. Even though the review found no difference between low-dose and high-dose amoxicillin, the overall certainty in the evidence is very low[a]. Only one cohort study (Chu et al., 2014) and one RCT (Bielicki et al., 2021) found lower-dose amoxicillin to be equivalent to high-dose amoxicillin for patients with AOM. When there is a lack of scientific evidence, standard work should be developed, implemented, and monitored.*

Literature Summary

Background. Acute otitis media (AOM) is the most common infection in early childhood (Venekamp et al., 2015). Although AOM usually resolves without treatment, it is the most common condition for which antibiotics are prescribed in the United States (Lieberthal et al., 2013). The American Academy of Pediatrics Clinical Practice Guideline (CPG; Lieberthal et al., 2013) recommends providing safety-net antibiotic prescription (SNAP) to parents of children > 6 months of age with mild to moderate unilateral AOM. A dose of 80-90 mg/kg per day of amoxicillin is recommended as first-line therapy for most children with mild to moderate AOM for a duration of 10 days for patients ≤ 23 months of age and 7 days for patients 2-5 years of age (Lieberthal et al., 2013). Alternatively, in a systematic review (Suzuki et al., 2020) of European CPGs, only 7 of 14 CPGs recommended high dose amoxicillin (80-90mg/kg per day) as an option for first-line treatment.

This review aims to synthesize the current literature on the topic of amoxicillin dosing. This review excludes older articles before the pneumococcal vaccine was widely administered due to its effect on the infection rate and causative organisms of AOM (Eskola et al., 2001). Studies that looked at community acquired pneumonia (CAP) were included in this review as this disease is caused by the same organisms (Eskola et a., 2001). This review will summarize identified literature to answer the specific care question.

Study characteristics. The search for suitable studies was completed on July 11, 2022. R. El Feghaly, MD, MSCI and D. Wyly, MSN, RN, APRN, CPNP-AC, PPCNP-BC, ONC reviewed the 127 titles and/or abstracts found in the search and identified[b] 12 single studies believed to answer the question. After an in-depth review of the single studies, two single studies (Bielicki et al., 2021; Chu et al., 2014) answered the question.

Summary by Outcome

Retreatment by Day 28

One RCT (Bielicki et al., 2021) measured retreatment by day 28, (*N* = 814). For the outcome of re-treatment by day 28, the *OR* indicated that for patients with CAP the intervention of low dose amoxicillin (35-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (70-90 mg/kg/d), *OR* = 1.03, 95% CI [0.68, 1.56] (see Figure 2 & Table 2)

> **Certainty Of The Evidence For Retreatment by Day 28.** The certainty of the body of evidence was low. The body of evidence was assessed to not have serious risk of bias, but serious indirectness, and serious imprecision. Indirectness was serious as the study population investigated was patients with CAP. Imprecision was serious due to the low number of events (*n* = 100). As only one study (Bielicki et al., 2021) was identified to answer this question, consistency could not be assessed.

Adverse Events

One RCT (Bielicki et al., 2021) measured adverse events, (*N* = 814). For the outcome of adverse events, the *OR* indicated that for patients with CAP, the intervention of low dose amoxicillin (35-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (70-90 mg/kg/d), *OR* = 1.14, 95% CI [0.62, 2.11] (see Figure 3 & Table 2).

Certainty Of The Evidence For Adverse Events. The certainty of the body of evidence was low. The body of evidence was assessed to not have serious risk of bias, but serious indirectness, and serious imprecision. Indirectness was serious as the study population investigated was patients with CAP. Imprecision was serious due to the low number of events (*n* = 100). As only one study (Bielicki et al., 2021) was identified to answer this question, consistency could not be assessed.

Successful Control (see Chu et al., 2014, for the definition of this outcome on page 13 of this synopsis)
One cohort study (Chu et al., 2014) measured successful control, (*N* = 165). For the outcome of successful control, the *OR* indicated that for patients with AOM, the intervention of low dose amoxicillin (40-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (80-90 mg/kg/d), *OR* = 0.52, 95% CI [0.14, 1.88] (see Figure 3 & Table 2)

Certainty Of The Evidence For Successful Control. The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious indirectness, but serious risk of bias, and serious imprecision. Risk of bias was serious due to the study being a retrospective cohort that was unable to verify compliance for antibiotics. Imprecision was serious due to the low number of subjects (*N* = 165) and low number of events (*n* = 121). As only one study (Chu et al., 2014) was identified to answer this question, consistency could not be assessed.

Failed Control (see Chu et al., 2014, for the definition of this outcome on page 13 of this synopsis)
One cohort study (Chu et al., 2014) measured failed control, (*N* = 165). For the outcome of failed control, the *OR* indicated that for patients with AOM, the intervention of low dose amoxicillin (40-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (80-90 mg/kg/d), *OR* = 1.93, 95% CI [0.53, 7.03] (see Figure 4 & Table 2).

Certainty Of The Evidence For Failed Control. The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious indirectness, but serious risk of bias, and serious imprecision. Risk of bias was serious due to the study being a retrospective cohort that was unable to verify compliance for antibiotics. Imprecision was serious due to the low number of subjects (*N* = 165) and low number of events (*n* = 44). As only one study (Chu et al., 2014) was identified to answer this question, consistency could not be assessed.

Identification of Studies
Search Strategy and Results (see Figure 1)
(**2010**:py OR **2011**:py OR **2012**:py OR **2013**:py OR **2014**:py OR **2015**:py OR **2016**:py OR **2017**:py OR **2018**:py OR **2019**:py OR **2020**:py OR **2021**:py OR **2022**:py) AND ([child]/lim OR [infant]/lim OR [preschool]/lim OR [school]/lim) AND (**'article'**/it OR **'article in press'**/it) **'acute otitis media'**/exp OR **'acute otitis media' amoxicillin**:ti,ab,kw **'drug dose'** OR **dosing**:ti,ab,kw OR **'low drug dose'** OR **'drug megadose'** OR **'low dose'**:ti,ab OR **'high dose'**:ti,ab OR **dosage**:ti,ab,kw `**amoxicillin'**/exp/dd_do
Records identified through database searching *n* = 132
Additional records identified through other sources *n* = 0

Studies Included in this Review

Citation	Study Type
Chu et al. (2014)	Cohort

Bielicki et al. (2021)	RCT

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Baig et al. (2017)	Outcome of interest not reported
Garrison et al. (2004)	Older studies prior to pneumococcal vaccine
Heinrichs and Frère (2018)	Non-English
Jung et al. (2019)	Outcome of interest not reported
Kondratieva et al. (2019)	Outcome of interest not reported
Lyttle et al. (2019)	Study Protocol
Peters et al. (2016)	Study on Dosing instructions
Pichichero et al. (2013)	No comparison of low versus high dose
Vilas-Boas et al. (2014)	No comparison of low versus high dose
Wu et al. (2021)	Outcome of interest not reported

Methods Used for Appraisal and Synthesis

[a]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings (SOF) table(s) for this analysis. Using the GDT, the author of this CAT rates the certainty of the evidence based on four factors: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. Each factor is subjectively judged against the author's confidence of the estimated treatment effect. Confidence is assessed as not serious, serious, or very serious. If the attribute of serious or very serious is assessed, the author will provide an explanation.

[b]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[c]The Appraisal of Guidelines Research and Evaluation II (AGREE II) is an international instrument used to assess the quality and reporting of clinical practice guidelines for this analysis (Brouwers et al. 2010).

[d]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

[e]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

References to Appraisal and Synthesis Methods

[a]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[b]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. Doi:10.1186/s13643-016-0384-4

[c]Brouwers, M.C. et al. for the AGREE Next Steps Consortium. (2010) AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *Canadian Medical Association Journal, 182*, E839-842. Retrieved from https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf

[d]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

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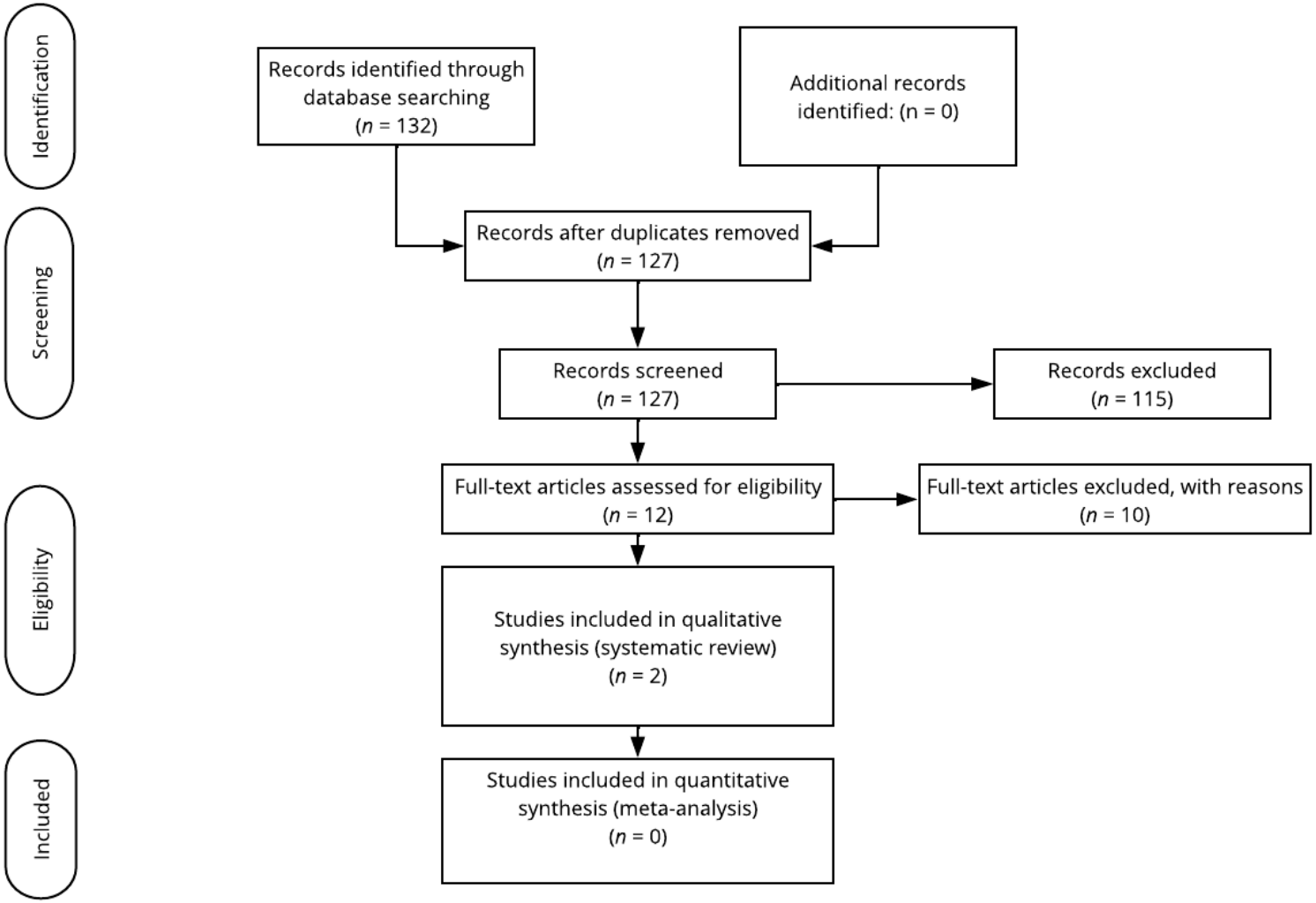
Acronyms Used in this Document

Acronym	Explanation
AGREE II	Appraisal of Guidelines Research and Evaluation II
AOM	Acute Otitis Media
CAP	Community Acquired Pneumonia
CAT	Critically Appraised Topic
CPG	Clinical Practice Guidelines
EBP	Evidence Based Practice
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
OME	Otitis Media with Effusion

Statistical Acronyms Used in this Document

Statistical Acronym	Explanation
CI	Confidence Interval
M or $\bar{X}$	Mean
n	Number of cases in a subsample
N	Total number in sample
OR	Odds Ratio
P or p	Probability of success in a binary trial
RCT	Randomized controlled trial
SD	Standard deviation
SR	Systematic Review

Figure 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[e]



** These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different, and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time. It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.*

Summary of Findings Table(s)
Table 2

Summary of Findings Table[a]

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**High dose**	**Low dose**	**Relative (95% CI)**	**Absolute (95% CI)**	
Re-treatment by day 28											
1	randomized trials	not serious	not serious	serious[d]	serious[e]	none	51/410 (12.4%)	49/404 (12.1%)	**OR 1.03** (0.68 to 1.56)	**3 more per 1,000** (from 35 fewer to 56 more)	⊕⊕◯◯ Low
Serious adverse event											
1	randomized trials	not serious	not serious	serious[d]	serious[f]	none	23/410 (5.6%)	20/404 (5.0%)	**OR 1.14** (0.62 to 2.11)	**7 more per 1,000** (from 18 fewer to 50 more)	⊕⊕◯◯ Low
Successful Control											
1	observational studies	serious[a]	not serious	not serious	serious[b]	none	106/147 (72.1%)	15/18 (83.3%)	**OR 0.52** (0.14 to 1.88)	**111 fewer per 1,000** (from 422 fewer to 71 more)	⊕◯◯◯ Very low
Failed Control											

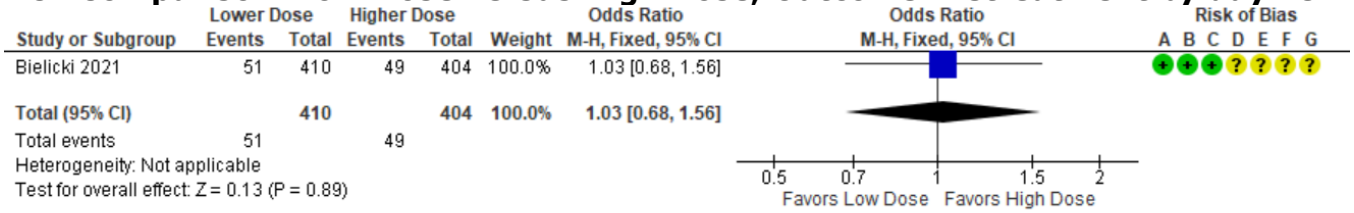
Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High dose	Low dose	Relative (95% CI)	Absolute (95% CI)	
1	observational studies	serious[a]	not serious	not serious	serious[c]	none	41/147 (27.9%)	3/18 (16.7%)	**OR 1.93** (0.53 to 7.03)	**112 more per 1,000** (from 71 fewer to 418 more)	⊕◯◯◯ Very low

Explanations
a. A retrospective cohort that was unable to verify compliance for antibiotics
b. Low number of subjects (*N* = 165) and low number of events (*n* = 121)
c. Low number of subjects (*N* = 165) and low number of events (*n* = 44)
d. Study of patients with Community-Acquired Pneumonia
e. Low number of events (*n* = 100)
f. Low number of events (*n* = 43)

Meta-analysis(es)

Figure *2*

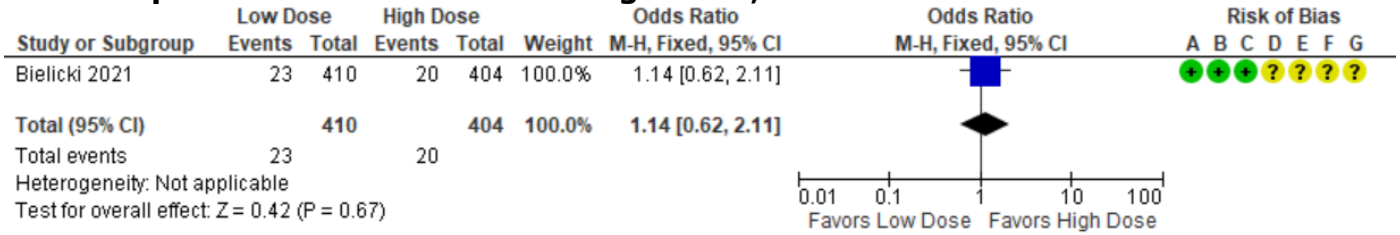
RCT Comparison: Low Dose versus High Dose, Outcome: Retreatment by day 28



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure *3*

RCT Comparison: Low Dose versus High Dose, Outcome: Adverse Events



Risk of bias legend
(A) Random sequence generation (selection bias)
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(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

** These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different, and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time. It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.*

Figure *4*

Cohort Comparison: Low Dose versus High Dose, Outcome: Successful Control

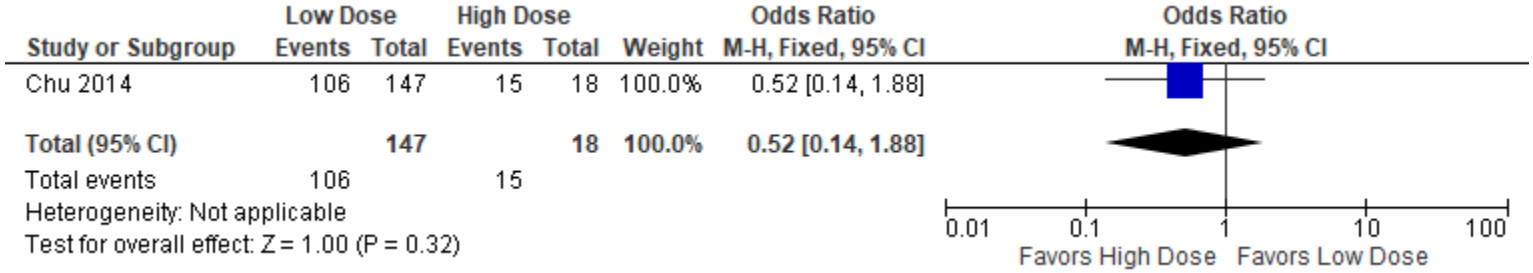
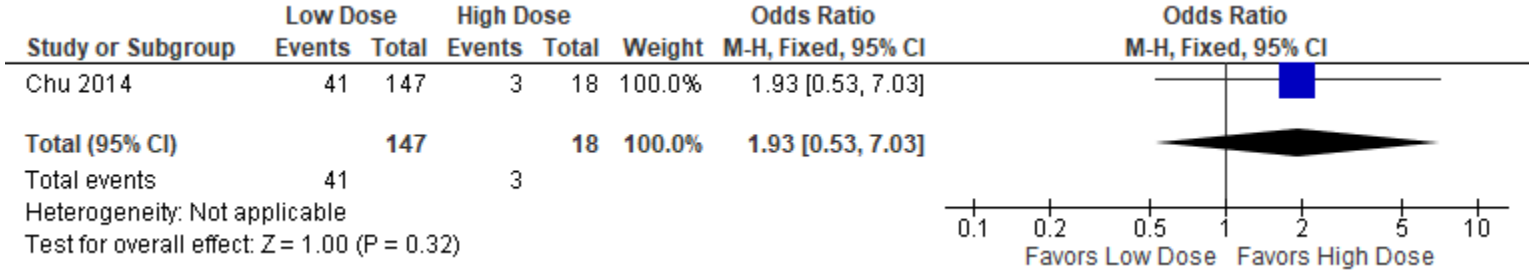


Figure *5*

Cohort Comparison: Low Dose versus High Dose, Outcome: Failed Control



** These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different, and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time. It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.*

Characteristics of Intervention Studies
Bielicki et al. (2021)

Methods	**Randomized Control Trial**
Participants	**Participants:** Children with clinically diagnosed CAP and planned treatment with amoxicillin upon discharge **Setting:** Children discharged from emergency and inpatient wards of 28 hospitals in the UK and 1 in Ireland between February 2017 and April 2019 **Randomized into study:** *N* = 824 • **Group 1, low dose amoxicillin for 3 days:** *n* = 209 • **Group 2, low dose amoxicillin for 7 days:** *n* = 203 • **Group 3, high dose amoxicillin for 3 days:** *n* = 207 • **Group 4, high dose amoxicillin for 7 days:** *n* = 205 **Completed Study:** *N* = 814 • **Group 1:** *n* = 208 • **Group 2:** *n* = 202 • **Group 3:** *n* = 205 • **Group 4:** *n* = 199 **Gender, males (as defined by researchers):** • **Group 1:** *n* = 110 (53%) • **Group 2:** *n* = 100 (50%) • **Group 3:** *n* = 107 (52%) • **Group 4:** *n* = 104 (52%) **Race / ethnicity or nationality (as defined by researchers):**

Race and Ethnicity	Group 1 (*n* = 208)	Group 2 (*n* = 202)	Group 3 (*n* = 205)	Group 1 (*n* = 199)
Asian or British Asian	32 (15%)	23 (11%)	21 (10%)	30 (15%)
Black or British Black	20 (10%)	20 (10%)	20 (10%)	16 (8%)
Multiracial	15 (7%)	17 (8%)	14 (7%)	14 (7%)
White	139 (67%)	136 (67%)	144 (70%)	135 (68%)
Other	2 (1%)	6 (3%)	6 (3%)	4 (2%)

Age, median in years, (IQR)
- **Group 1:** 2.5 (1.7-3.7)
- **Group 2:** 2.6 (1.6-3.9)
- **Group 3:** 2.5 (1.7-3.8)
- **Group 4:** 2.3 (1.4-3.6)

Inclusion Criteria:
- Age 6 months and older
- Weight 6 to 24 kilograms
- Diagnosis of CAP consistent with British Thoracic Society guidelines:
  - Parent- or guardian-reported cough within the previous 96 hours
  - Measured temperature of 38°C or parent- or guardian-reported fever within previous 48 hours
  - Signs of labored or difficult breathing or focal chest sign

	Exclusion Criteria: • Uninterrupted prior β-lactam antibiotic treatment for more than 48 hours or any prior non-β-lactam treatment • Severe underlying chronic disease • Any contraindications to amoxicillin, including allergy • Complicated pneumonia (defined as signs of sepsis or local parenchymal or pleural complications) • Bilateral wheezing without focal chest signs **Power Analysis:** The trial was designed to demonstrate noninferiority of lower dose amoxicillin compared with higher dose amoxicillin, and shorter duration (3 days) compared with longer duration (7 days). The sample size of 800 participants was estimated to achieve 90% power.
Interventions	• **Group 1:** Randomized to receive amoxicillin, 35-50 mg/kg/d for 3 days • **Group 2:** Randomized to receive amoxicillin, 35-50 mg/kg/d for 7 days • **Group 3:** Randomized to receive amoxicillin, 70-90 mg/kg/d for 3 days • **Group 4:** Randomized to receive amoxicillin, 70-90 mg/kg/d for 7 days

Outcomes	**Primary outcome(s):**
	• The primary end point was clinically indicated treatment with systemic antibiotics (other than trial medication) for a respiratory tract infection, including CAP, within 28 days of randomization
	  ○ The noninferiority margin was 8%
	  ○ All primary end points were reviewed by an endpoint review committee, blinded to treatment allocation, to adjudicate whether treatment was clinically indicated and prescribed for respiratory tract infection
	Secondary outcome(s):
	• Severity (graded as not present, slight/little, moderate, bad, severe/very bad) and duration (with the first day the symptom is reported not present defined as resolved) of 9 parent-reported CAP symptoms (fever, cough, phlegm, fast breathing, wheezing, disturbed sleep, eating/drinking less, interference with normal activity, vomiting)
	• Potential amoxicillin-related clinical adverse events (diarrhea, thrush, skin rash)
	• Adherence to trial medication
	• Phenotypic penicillin nonsusceptibility or resistance at 28 days in nasopharyngeal S. pneumoniae isolates
	Safety outcome(s):
	• Serious adverse events

Notes	• Among children with CAP discharged from an ED or hospital ward (within 48 hours), low-dose outpatient oral amoxicillin was noninferior to high dose, and 3-day duration was noninferior to 7 days, with regard to need for further antibiotic retreatment
	• See comparison tables for serious adverse events
	  ○ No participant had more than one serious adverse event, all serious adverse events were hospitalizations (most for respiratory distress), no deaths. The data stratified by randomization groups can be found in Table 10 in Supplement 2.
	  ○ One serious adverse event (hospital admission for intravenous treatment because of vomiting on day 2 in a patient randomized to the higher-dose, shorter-duration group) was classified as related to trial medication.
	• Findings should not be generalized to patients with very severe disease or underlying comorbidities

Risk of bias table

Bias	EBP Scholars' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomization list was produced by the trial statistician based on blocks of 8 and containing an equal number of the 4 possible combinations of dose and duration in random order.
Allocation concealment (selection bias)	Low risk	Trial kits were assigned sequential numbers based on the randomization list and delivered ready to dispense to site pharmacies.
Blinding of participants and personnel (performance bias)	Low risk	Blinding was achieved by independent rebottling, packaging, and labeling of 2 amoxicillin brands. To ensure blinding for the duration comparison, a single amoxicillin brand was used for the first 3 days, followed by a different amoxicillin containing suspension (of the same concentration) or a matching placebo suspension for days 4 to 7.
Blinding of outcome assessment (detection bias)	Unclear risk	Primary endpoint was subjectively adjudicated by an endpoint review committee
Incomplete outcome data (attrition bias)	Low risk	Data analyzed per protocol, however very few subjects were excluded from analysis and would be unlikely to impact results
Selective reporting (reporting bias)	Low risk	Data reported as expected
Other bias	Low risk	No concerns: conflicts of interest reported appropriately and unlikely to impact study results

Chu et al. (2014)

Methods	Retrospective Cohort
Participants	**Participants:** Children with acute otitis media (AOM) **Setting:** Taiwan, General Hospital, January 2005 to December 2008 **Number of medical records with correct diagnosis code:** *N* = 400 **Number who meet inclusion criteria:** *N* = 165 • **Group 1,** Antibiotic with recommended amoxicillin component: *n* = 18 • **Group 2,** Antibiotic with underdosed amoxicillin component *n* = 14 **Gender, males** • 57% (Not specified by group) **Race / ethnicity or nationality (as defined by researchers):** • Not reported **Age, mean +/- SD in years:** • 4.91 +/- 2.52 (Not specified by group) **Inclusion Criteria:** • Children 2 months to 12 years • Diagnosis of AOM ICD-9-CM (diagnosis code 382.00) • Patients treated with amoxicillin-clavulanate **Exclusion Criteria:** • Any anatomic or genetic abnormalities such as craniofacial anomalies or Down syndrome • Immune deficiencies • History of recurrent AOM (three or more previous episodes of AOM within 12 months) • Patients with any history of middle ear of inner ear procedure • Patients with only one visit • Patients with missing records • Patients treated with amoxicillin alone or with another antibiotic **Covariates Identified:** • Illness season • Single vs bilateral disease

Interventions	**Both:** Reassessment performed within 14 days after antibiotic prescription expiry (sic) date
	Amoxicillin doses based on the AOM Clinical Practice Guidelines: Diagnosis and Management of AOM, published in May 2004 (AAP, 2004)
	• **Group 1:** Amoxicillin clavulanate antibiotic dose of amoxicillin 80-90 mg/kg/day, 1500 mg/day max (referred to as "High-dose" in tables)
	• **Group 2:** Amoxicillin clavulanate antibiotic dose < 10% of recommended amoxicillin dose (referred to as "Underdose" in tables)
	  ○ Average dose of amoxicillin component 45.5 mg/kg/day
	  ○ 52.1% of the prescriptions were in the amoxicillin range of 40-50 mg/kg/day

Outcomes	**Primary outcome(s):** • Successful control (defined as a medical record of an eardrum that was either normal or showed otitis media with effusion (OME)) • Failed control, defined as improvement in only one of two affected ears or a change in antibiotics before the end of the treatment period due to failure to control illness rather than side effects
Notes	**Results:** • Control was achieved in 121 patients

	• Patients given the high dose amoxicillin had generally but not statistically significantly better AOM prognosis • Bilateral AOM was borderline significantly correlated with failed control • There was no significant correlation between high dose amoxicillin and better disease control in most groups. • Illness in autumn and winter were strongly associated with a poor prognosis • In this study, the ratio of boys who failed AOM control was not significant, this is different than other studies referenced • The correlation between under dosage and failed control were significant in children below 20 kg with bilateral AOM (*OR* = 1.63; 95% CI [1.02, 2.59], *p* = .04) **Limitations:** • No study of amoxicillin as a standalone medication for AOM • The duration of treatment for both the high dose and the underdose were never specified in this study. The reassessment was performed sometime within 14 days of the prescription but the actual days between diagnosis and reassessment were not specified.

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Appendix

Evidence to Decision Assessment

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Acute Otitis Media is the most common infection in early childhood (Venekamp et al., 2015). Although AOM usually resolves without treatment, it is the most common condition for prescribed antibiotics in the United States (Lieberthal et al., 2013).	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	**Successful Control** (see Chu et al., 2014, for the definition of this outcome on page 13 of this synopsis) One cohort study (Chu et al., 2014) measured successful control (*N* = 165). For the outcome of successful control, the *OR* indicated that for patients with AOM, the intervention of low dose amoxicillin (40-50 mg/kg/d) was not different from the comparator of high dose amoxicillin (80-90 mg/kg/d), *OR* = 0.52, 95% CI [0.14, 1.88].	The desirable effects of a lower dose are fewer adverse drug reactions, medication side effects, and antimicrobial resistance.

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	***Retreatment by Day 28*** One RCT (Bielicki et al., 2021) measured retreatment by day 28, (*N* = 814). For the outcome of re-treatment by day 28, the *OR* indicated that for patients with CAP the intervention of low dose amoxicillin (35-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (70-90 mg/kg/d), *OR* = 1.03, 95% CI [0.68, 1.56]. ***Adverse Events*** One RCT (Bielicki et al., 2021) measured adverse events, (*N* = 814). For the outcome of adverse events, the *OR* indicated that for patients with CAP, the intervention of low dose amoxicillin (35-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (70-90 mg/kg/d), *OR* = 1.14, 95% CI [0.62, 2.11]. **Failed Control** (see Chu et al., 2014, for the definition of this outcome on page 13 of this synopsis) One cohort study (Chu et al., 2014) measured failed control, (*N* = 165). For the outcome of failed control, the *OR* indicated that for patients with AOM, the intervention of low dose amoxicillin (40-50 mg/kg/d) was not different to the comparator of high dose amoxicillin (80-90 mg/kg/d), *OR* = 1.93, 95% CI [0.53, 7.03].	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Certainty Of The Evidence For Retreatment by Day 28.** The certainty of the body of evidence was low. The body of evidence was assessed to not have serious risk of bias, but serious indirectness, and serious imprecision. Indirectness was serious as the study population investigated was patients with CAP. Imprecision was serious due to the low number of events (*n* = 100). As only one study (Bielicki et al., 2021) was identified to answer this question, consistency could not be assessed. **Certainty Of The Evidence For Adverse Events.** The certainty of the body of evidence was low. The body of evidence was assessed to not have serious risk of bias, but serious indirectness, and serious imprecision. Indirectness was serious as the study population investigated was patients with CAP. Imprecision was serious due to the	Minimal evidence exists on outcomes of lower doses versus higher dose. Only one cohort study on patients with AOM and one RCT on patients with CAP were included.

	low number of events (*n* = 100). As only one study (Bielicki et al., 2021) was identified to answer this question, consistency could not be assessed. **Certainty Of The Evidence For Successful Control.** The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious indirectness, but serious risk of bias, and serious imprecision. Risk of bias was serious due to the study being a retrospective cohort that was unable to verify compliance for antibiotics. Imprecision was serious due to the low number of subjects (*N* = 165) and low number of events (*n* = 121). As only one study (Chu et al., 2014) was identified to answer this question, consistency could not be assessed. **Certainty Of The Evidence For Failed Control.** The certainty of the body of evidence was very low. The body of evidence was assessed to not have serious indirectness, but serious risk of bias, and serious imprecision. Risk of bias was serious due to the study being a retrospective cohort that was unable to verify compliance for antibiotics. Imprecision was serious due to the low number of subjects (*N* = 165) and low number of events (*n* = 44). As only one study (Chu et al., 2014) was identified to answer this question, consistency could not be assessed	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		Some providers (e.g. Antimicrobial Stewardship) may weigh more heavily on the risk of adverse drug events, side effects, and antimicrobial resistance. Some parents/families of patients may weigh more heavily the risk of treatment failure.

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Minimal evidence exists on outcomes of lower doses versus higher doses. Only one cohort study on patients with AOM and one RCT on patients with CAP was included.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The mean cost of treatment for the amoxicillin group is $189.20 (Gaboury et al., 2010) The indirect costs of AOM, accrued primarily by parental time lost are $1330.58, 95% CI [$1008.75, $1652.43] (Alsarraf et al., 1999).	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	No studies comparing the required resources of low versus high dose.	

Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● No included studies	Likely lower costs for lower dose. No included studies.	Families would have to travel to pharmacies, obtain prescriptions, and follow written prescription instructions regardless of the dose. However, the cost would be greater for the higher dose.
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ● Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		This would be a large change in practice. Would need stronger evidence.

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	No issues with feasibility in prescribing lower dose	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	**Negligible costs and savings**	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**

** These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different, and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time. It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.*

	JUDGEMENT						
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	**Probably no**	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

CONCLUSIONS

Recommendation
Conditional recommendation against the intervention

** These guidelines do not establish a standard of care to be followed in every case. It is recognized that each case is different, and those individuals involved in providing health care are expected to use their judgment in determining what is in the best interests of the patient based on the circumstances existing at the time. It is impossible to anticipate all possible situations that may exist and to prepare guidelines for each. Accordingly, these guidelines should guide care with the understanding that departures from them may be required at times.*