Published in final edited form as:

Expert Rev Anti Infect Ther. 2023 May ; 21(5): 523–534. doi:10.1080/14787210.2023.2206565.

New insights into the treatment of acute otitis media

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Abstract

Introduction: Acute otitis media (AOM) affects most (80%) children by 5 years of age and is the most common reason children are prescribed antibiotics. The epidemiology of AOM has changed considerably since the widespread use of pneumococcal conjugate vaccines, which has broad-reaching implications for management.

Areas covered: In this narrative review we cover the epidemiology of AOM, best practices for diagnosis and management, new diagnostic technology, effective stewardship interventions, and future directions of the field. Literature review was performed using PubMed and ClinicalTrials.gov.

Expert opinion: Inaccurate diagnoses, unnecessary antibiotic use, and increasing antimicrobial resistance remain major challenges in AOM management. Fortunately, effective tools and interventions to improve diagnostic accuracy, de-implement unnecessary antibiotic use, and individualize care are on the horizon. Successful scaling of these tools and interventions will be critical to improving overall care for children.

Keywords

Acute otitis media; amoxicillin; antibiotic stewardship; pneumococcal vaccines

1. Introduction

Acute otitis media (AOM) is an infection of the middle ear space. It is the most common indication for antibiotics in children, affecting 5 million children and resulting in over 10 million antibiotic prescriptions in the United States (US) each year [1,2]. This review focuses on uncomplicated, non-recurrent, AOM in vaccinated children in the US and other industrialized nations, specifically highlighting the changing epidemiology in the

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post-pneumococcal vaccine era, diagnosis, treatment, complications, and future directions for diagnosis and treatment.

2. Epidemiology of Acute Otitis Media

In the US, 60% of children experience at least one AOM infection before the age of 3 years, and up to 80% experience at least one AOM infection during their lifetime [3]. Globally, the incidence rate of AOM is estimated to be approximately 10.85% [4], although the specific numbers may be difficult to determine due to poor reporting in different regions of the world. Respiratory viruses play an important role in the epidemiology of AOM, whether by causing the AOM themselves, or predisposing the child to bacterial superinfection. Multiple studies evaluating viral pathogens in the nasopharynx and middle ear of children with AOM identified several viruses as the causative agent of AOM [5–8].

2.1 Impact of Pneumococcal Vaccinations on Acute Otitis Media Incidence

Pneumococcal carriage declined with the introduction of pneumococcal conjugate vaccines in the US and Europe [9–11]. Subsequently, the rates of AOM declined substantially. Impact studies with data in children <2 years of age using pneumococcal conjugate vaccine (PCV)13 report 47–51% reduction of all-cause otitis media (primary care, outpatient, ambulatory, emergency department [ED] visits) compared to periods before PCV introduction [12]. One study evaluating children with commercial insurance in the US found that AOM incidence rates declined from 1170.1 episodes in the pre-PCV7 era to 768.8 episodes per 1000 person-year in the post-PCV13 era for children <2 years, from 547.4 to 410.3 episodes per 1000 person-year in children 2–4 years, and from 115.6 to 91.8 episodes per 1000 person-year in children 5–17 years [13]. Similarly, a study from the United Kingdom showed a decline of AOM incidence rate from 40.3% between the pre-PCV7 period and late PCV-13 period from 4451.9 to 2658.5 per 100,000 persons-year [14]. Multiple studies have shown a similar trend, with declines in ambulatory visits due to AOM, mastoiditis, and tympanostomy tube insertion [15–17]. Similar trends since the introduction of PCV10 and PCV13 were seen in Canada [18], Europe [19–24], and South America [25,26].

2.2 Impact of Pneumococcal Vaccinations on Microbiology of Acute Otitis Media

Streptococcus pneumoniae was traditionally the leading cause of AOM [27]. A 2016 systematic review including 38 published reports between 1970 and 2014 evaluating the microbiology of AOM without ear discharge in children globally found that *S. pneumoniae* (28%), *Haemophilus influenzae* (23%), and *Moraxella catarrhalis* (7%) are the most common bacteria associated with AOM. *H. influenzae* was more common in patients with chronic otitis media with effusion (OME), recurrent AOM, and AOM with treatment failure [28]. A 2019 systematic review including 48 studies with 15,871 samples from middle ear fluid in children with AOM found similar distribution (*S. pneumoniae* 30%, *H. influenzae* 23%, and *M. catarrhalis* 5%) [29].

With the introduction of pneumococcal vaccinations, *S. pneumoniae* became less prevalent in cultures of middle ear fluid from children with AOM. A 2020 systematic review of

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15 publications of 11 trials (60,733 children, range 74 to 37,868 per trial) of 7- to 11-valent PCVs versus control vaccines found that administration of these pneumococcal vaccines during early infancy was associated with large relative risk reductions in pneumococcal AOM [30]. However, implementation of PCV7 resulted in shifts to non-vaccine pneumococcal serotypes isolated from invasive pneumococcal disease and AOM [31]. After introduction of PCV13, the rate of pneumococcal isolation from middle ear fluid declined substantially. This decline coincided with an increase in recovery from middle ear fluid of non-typeable *H. influenzae* and *M. catarrhalis* [3,32]. Non-typeable *H. influenzae* detection frequency surpassed *S. pneumoniae* detection in AOM patients within several countries including the US [33–35], Spain [36], France [37] and Israel [38]. A pooled analysis of results from 10 AOM etiology studies from around the globe found that the majority, 55.5% (95% confidence interval: 47.0%−65.7%) of 1124 AOM episodes, were positive for a bacterial pathogen: 29.1% (24.8%−34.1%) yielded *H. influenzae*, and 23.6% (19.0%−29.2%) *S. pneumoniae*. Proportions of *H influenzae* were higher in PCV-vaccinated children. *S. pneumoniae* cases are more likely to present with severe symptoms [RR: 1.42 (1.01–2.01)] [39]. *H. influenzae* and *M. catarrhalis* cause less severe disease, are less likely to be associated with perforation, and are much more likely to resolve without antibiotics [40]. Whereas pneumococci continue to be isolated from middle ear fluids when the infection is not treated, approximately one-half of infections due to non-typable *H. influenzae* and up to 80% of those due to *M. catarrhalis* clear spontaneously [41].

Resistance patterns also appear to be changing in the post-PCV era. A 2019 meta-analysis of 48 studies found that the pooled proportion of bacterial culture-positive episodes of AOM that could be effectively treated with amoxicillin and amoxicillin-clavulanate were 85% and 95%, respectively. *S. pneumoniae* was found to be 87% (69%−95% CI) susceptible to amoxicillin. Beta-lactamase production was reported to be at 29% for *H. influenzae* and ~100% for *M. catarrhalis* [29]. A recent single-center study in the US demonstrated a steady increase in *S. pneumoniae* resistance to antibiotics over the years when tested from nasopharyngeal colonization and middle ear fluid. *S. pneumoniae* amoxicillin non-susceptibility was 10.5–10.8%, while beta lactamase production was found in 45.5–48.6% of *H. influenzae* isolates [35]. These rates are similar to what a recent study evaluating H. influenzae in middle ear fluid and nasopharyngeal colonization found [42]. Resistance data from developing countries are not readily available. A systematic review evaluation of AOM from developing countries showed a potentially higher resistance to penicillin in the two studies that included resistance [43].

Streptococcus pneumoniae (26.1%), followed by *H. influenzae* (18.8%), *Staphylococcus aureus* (12.3%), and *Streptococcus pyogenes* (11.8%) continue to be the most prevalent bacteria recovered from AOM WITH otorrhea, with no evidence of a clear shift in prevalence of bacteria and resistance over time in the US [27].

2.3. Risk Factors for Acute Otitis Media

Meta-analyses have identified risk factors for recurrent and chronic AOM, particularly allergies and allergic rhinitis. Additional factors identified include family history of AOM, day care attendance, recurrent upper respiratory tract infections, second-hand smoking, low socio-economic status, indoor exposure to mold, laryngopharyngeal reflux, and lack of breastfeeding [44–47].

2.4 Acute Otitis Media in the Era of COVID-19

The importance of viruses as either causative agents or etiologies that predispose to bacterial etiologies of AOM was highlighted during the COVID-19 pandemic when incidence of circulating viruses and subsequently incidence of AOM decreased dramatically while viral transmission mitigation strategies were in place [48–50]. One published case series describes 7 children co-infected with SARS-CoV-2 and AOM [51].

3. Diagnosis of Acute Otitis Media

Children with acute otitis media may present with fevers, otalgia (or tugging at the ear), hearing deficit, otorrhea, or balance disorder [52]. The American Academy of Pediatrics (AAP) AOM guidelines recommend using clinical criteria to diagnose AOM; these include the presence of a middle ear effusion in addition to moderate to severe bulging of the tympanic membrane (TM), new onset otorrhea not due to otitis externa, and mild bulging of the TM with >48 hours onset of ear pain or intense erythema of the TM [53]. Although many European guidelines differ in management approaches, diagnostic recommendations have considerable similarities with three main requirements: evidence of middle ear effusion, TM inflammation, and acute symptoms [54].

A study evaluating 263 children found that bulging of the TM was the finding that best discriminated AOM from OME; 92% of children with AOM had a bulging TM compared with 0% of children with OME. An algorithm that used bulging and opacification of the TM correctly classified 99% of ears in an independent dataset [55].

Pneumatic otoscopy is an important tool to evaluate TM mobility. If the TM does not move perceptibly with applications of gentle positive or negative pressure, middle ear effusion is likely [56]. A study evaluating 11,804 ear-related visits of 2,911 children at ages 0.5–2.5 years found that impaired mobility had the highest sensitivity and specificity (approximately 95% and 85%, respectively) in diagnosing AOM. Bulging had high specificity (<97%) but lower sensitivity (<51%) [57]. Many European guidelines recommend pneumatic otoscopy as a tool to evaluate AOM [54].

3.1 Diagnostic Accuracy

Pichichero and Poole evaluated 514 pediatricians and 188 otolaryngologists who viewed nine different videotaped pneumatic otoscopic examinations of TM during a continuing medical education course. The average correct diagnosis by pediatricians was 50% (range 25%−73%) and by otolaryngologists was 73% (range 48%−88%). Pediatricians and otolaryngologists over-diagnosed AOM in an average of 27% (range 7%−53%) and 10% (range 3%−23%) of examinations, respectively [58]. Multiple studies have shown similar low accuracy of AOM diagnosis by direct visualization [59,60], even when evaluating digital images. The accuracy is likely lower in the clinical environment where conditions are not optimal to evaluate the TM. We recently demonstrated that of 205 children enrolled by academically affiliated clinicians in typical community-based practice settings, 31% did not meet the AAP criteria for diagnosis [61].

3.2 Where Are Patients Evaluated?

Despite the rise in patients seeking care at urgent care and retail clinics in the past decade [62], most children with AOM are still seen in the primary care office setting. A study using the 2018 IBM MarketScan Commercial Database of children ages 6 months to 12 years with an (International Classification of Diseases, 10th Revision (ICD-10) diagnosis of AOM found that among over 1 million visits, 88% were in the office setting, 9% in the urgent care setting, and less than 1% each were in the ED and retail health settings [63].

4. Management of Acute Otitis Media

4.1 Observation/Delayed Prescribing

Considering that many AOM infections will self-resolve and weighing the risks of complications related to untreated AOM compared to the risks associated with antibiotic exposure, the AAP and most European guidelines recommend a period of observation prior to initiating antibiotics for a subset of patients whose symptoms are more likely to resolve on their own [2,54]. These patients include those older than 23 months who are immunocompetent, with no chronic ear conditions or otorrhea, and have had otalgia for less than 48 hours, fever < 39°C, and pain that is mild and can be controlled with analgesics. Patients between 6 months and 24 months can be observed prior to starting antibiotics if the infection is in only one ear [53]. Additionally, patients previously treated for AOM within the last 30 days had decreased rates of resolution during a trial of observation [64]. In studies, use of observation or delayed prescribing reduced antibiotic use by 65–88% and resulted in no difference in symptom duration, severe complications, or parent satisfaction [64–68]. When patients received counseling on a period of observation and symptomatic management prior to starting antibiotics, they filled the prescription less often [69]. Consequently, those offered a delayed antibiotic approach reported fewer gastrointestinal side effects [65,69].

Although recommendations to monitor symptoms prior to starting antibiotics in non-severe cases of AOM have been around for almost 2 decades, an IBM MarketScan database reported that 85% of patients diagnosed with AOM in the US and 80% of patients in Europe receive immediate antibiotics [70]. Electronic health record data indicate that more than 95% of children are likely prescribed an immediate antibiotic [71].

4.2 Supportive Care Recommendations

Regardless of whether initial treatment includes immediate antibiotics or a period of observation, families should be counseled on appropriate pain management. Controlling pain reduces anxiety for the patient and caregivers. Additionally, fluid intake improves as pain is controlled. A meta-analysis of ibuprofen and paracetamol demonstrated that either is more effective in pain control than placebo for patients with AOM [72]. Otic analgesic drops have been reported to relieve pain in randomized controlled trials. However, due to the small sample size of these trials, the authors of a Cochrane review concluded that they were unable to draw a conclusion about the efficacy [73–75]. Conversely, antihistamines, decongestants, and steroids have not been found to be effective or results have not been consistent and therefore are not recommended for the management of AOM [76].

4.3 First-line Antibiotic Therapy

When an antibiotic is necessary, the AAP [53] and most European guidelines (82%) [54] recommend amoxicillin for first-line treatment for uncomplicated AOM. Amoxicillin is a preferred agent given its efficacy, tolerability, low cost, and narrow spectrum of activity. However, there has been considerable controversy over the optimal first-line antibiotic treatment for AOM [77]. This controversy has been driven largely by the changing epidemiology of AOM [3] and a robust increase in AOM-associated organisms that are resistant to amoxicillin/penicillin [35]. Unfortunately, no clinical trials have directly compared the efficacy of amoxicillin to placebo or to broader-spectrum antibiotics since the introduction of the pneumococcal conjugate vaccines. Trials in the PCV era that have compared antibiotics to placebo have exclusively used broader-spectrum agents such as amoxicillin-clavulanate [78,79].

Observational studies in the PCV era indicate that amoxicillin likely remains highly effective as first-line treatment for AOM and may result in fewer adverse drug events (ADEs) than broad-spectrum antibiotics [80]. Additionally, narrow-spectrum antibiotics such as amoxicillin are less likely to disrupt the microbiome [81], confer risk of antibiotic-associated *Clostridioides difficile* infections [82], or promote the development of antibiotic-resistant organisms [83]. Gerber et al. reported that among a cohort of prospectively evaluated children with AOM in a single health system, treatment failure rates were low (less than 5%) and were less common for children who received narrow-spectrum versus broad-spectrum antibiotics (3.7% vs 4.6%) [80]. Narrow-spectrum antibiotics also resulted in fewer parent-reported ADEs (25% vs 36%) and higher quality of life than broad spectrum antibiotics [80]. We recently demonstrated that among over a million children in the US with uncomplicated AOM, failure rates were low for all antibiotic agents, and lower for children prescribed amoxicillin (1.7%) compared to those prescribed amoxicillin-clavulanate (11.3%), cefdinir (10.0%), or azithromycin (9.8%) [63]. Additionally, we prospectively demonstrated that treatment failure occurred in less than 5% of children with uncomplicated AOM who were prescribed amoxicillin and followed for 30 days in pragmatic clinical settings. Failure was uncommon for children with all common otopathogens including those that produced beta-lactamase rendering them non-susceptible to amoxicillin (3.7%) [61].

There are two likely explanations for the continued effectiveness of amoxicillin in the face of growing resistance. First, most children diagnosed with AOM will have resolution of symptoms without the use of an antibiotic [84]. This is particularly true for children who are older, have less severe presentation, or who did not have moderate to severe TM bulging at diagnosis. Second, most cases of AOM associated with *M. catarrhalis* (75–85%) and nearly half of cases associated with *H. influenzae* resolve without an antibiotic [41,85,86]. Thus, the organisms most likely to produce beta-lactamase, which might necessitate broader-spectrum coverage, are also the least likely to require an antibiotic. Given the continued efficacy and tolerability of amoxicillin in pragmatic settings, we continue to recommend it as first-line therapy for most children with uncomplicated infections even in the setting of growing resistance among otopathogens. Importantly, macrolides and oral cephalosporins (including azithromycin and cefdinir) either do not achieve adequate concentrations in the middle ear or have poor activity against *S. pneumoniae* [87,88]. Thus, they confer no additional benefit for children but do result in additional harms from their broader spectrum of activity.

4.4 Second-line Therapy

For patients with amoxicillin treatment failure (no improvement or worsening after 2–14 days of antibiotics), recurrence (new infection within 15–30 days of infection), or a history of recurrent infections that have not been previously responsive to amoxicillin, we recommend amoxicillin-clavulanate to provide additional coverage for organisms that produce beta-lactamase. Amoxicillin-clavulanate achieves higher concentrations in the middle ear and provides better coverage against common otopathogens than oral cephalosporins, macrolides, or clindamycin [53,87–89]. For children who have failed treatment with amoxicillin-clavulanate or received initial treatment with a non-penicillin antibiotic, we recommend intramuscular ceftriaxone. Ceftriaxone can be given as a single dose and repeated every 24–48 hours for a maximum of three total doses if the child fails to improve.

4.5 Antibiotic Dosing

The AAP guidelines currently recommend high-dose amoxicillin (80–90 mg/kg/day) in two divided doses as first-line treatment for AOM to overcome penicillin-resistant *S. pneumoniae*, and recent epidemiology studies confirm increasing incidence of penicillin-resistant *S. pneumoniae* in AOM. A classic pharmacokinetics/pharmacodynamics study demonstrated that increasing the dose of amoxicillin from 40–50 mg/kg/day to 80–90 mg/kg/day was associated with increased amoxicillin concentration in the middle ear, ensuring efficacy against most strains of *S. pneumoniae* [90]. There is a paucity of data on the efficacy of low compared to high dose amoxicillin regimens and outcomes have been mixed [75] [76]. A maximum daily dose of amoxicillin has not been established, but most clinicians and pharmacists use a maximum of 4,000 mg/day (2,000 mg/dose) when targeting high-dose amoxicillin regimens based on expert recommendations [73,74]. More research is needed to establish an evidence-based maximum dose based on pharmacokinetics/pharmacodynamics and targeted pathogens.

Given the trend toward an increase in penicillin non-susceptible *S. pneumoniae* isolates, it would be prudent to use high-dose amoxicillin (80–90 mg/kg/day) when the decision is made to use antibiotics to treat AOM. [91,92][93][94]

4.6 Penicillin Allergy

Up to 10% of children have documented penicillin allergy, though the true incidence of immune-mediated reactions is likely less than 1% [95,96]. Clinicians should strongly consider following penicillin delabeling protocols in appropriately selected children to reduce long-term morbidity associated with recurrent use of broader than needed or less optimal antibiotic agents over the lifespan [97]. For patients without a history of a high-risk allergic reaction, we recommend second- and third-generation oral cephalosporins based on regional availability including cefdinir, cefpodoxime, cefuroxime, or intramuscular ceftriaxone For children with a history of high-risk allergic reactions (e.g. anaphylaxis), alternative regimens with clindamycin, clarithromycin, azithromycin, or trimethoprim-sulfamethoxazole can be used. These regimens are less effective than amoxicillin and may not effectively eradicate *H. influenzae* or *S. pneumoniae* [87–89].

4.7 Antibiotic Duration

Children should be prescribed the shortest duration of antibiotics necessary to treat their infection [98,99]. Longer durations of antibiotics are associated with increased rates of ADEs [100], *C. difficile* infections, and increased resistance, particularly among *S. pneumoniae* [101]. Most children do not require an antibiotic to treat AOM. The ideal duration in these children is 0 days. When an antibiotic is prescribed, microbiologic studies indicate that organisms are eradicated from the middle ear within a range of 3–6 days [102]. In children with TM perforation or who have received antibiotics for AOM in the prior 30 days, symptom improvement or eradiation of organisms may take longer.

Most European countries (62%) recommend 5–7 days of therapy regardless of patient age [54]. In contrast, guidelines from the AAP recommend 10 days of therapy for children less than 2 years of age and those with severe symptoms or TM rupture [53]. For older children with non-severe infection, a shorter duration is recommended (7 days for ages 2–5 years; 5–7 days for ages 6–12 years). Nevertheless, over 92% of children in the US are prescribed a 10-day duration of antibiotics regardless of age [103–107]. Observational studies and pragmatic clinical trials that include children diagnosed using criteria used in typical clinical practice settings indicate that there is either no benefit or a very modest benefit to using 10 days compared to 5 days of therapy [63,100]. Meta-analyses evaluating long versus short durations estimate that for every 22–28 children treated with 10 days compared to 5 days, only one child would benefit [100]. In studies that do not use stringent diagnostic criteria for enrollment, these findings hold true for children of all ages including those under 2 years of age, though patients under 2 years were largely underrepresented in early clinical trials.

In contrast, a randomized clinical trial of children under 2 years of age diagnosed using stringent criteria demonstrated that a duration of 5 days was inferior to 10 days [108]. Enrolled children had moderate to severe TM bulging and a symptom severity score of 3 or higher. Treatment failure was defined as worsening symptom severity, failure to have complete or near complete resolution of symptoms at the end of treatment, or continued TM bulging at the end of treatment. The number to treat with a long duration compared to a short duration to prevent one case of clinical failure was 6. In a typical practice environment, it is estimated that 16–52% of children treated for AOM may not meet the diagnostic criteria used in this study [58,78,79,109,110]. Thus, the generalizability of these findings to children diagnosed using less stringent criteria is uncertain.

In practice, we have found it challenging for clinicians to remember the nuances of the AAP guidelines and have not experienced higher treatment failure rates for children 2 years and older prescribed 5 compared to 7 or 10 days [111]. Therefore, we recommend a duration of 5 days for most children 2 years of age and older at our institutions. We continue to recommend a 10-day duration of therapy for children under 2 years of age, though it is likely acceptable to use a shorter duration for children with lower severity of symptoms and/or with a definitive follow-up plan to extend the duration in the event they do not have near symptom resolution at the end of treatment. We also recommend a duration of 10 days for children with TM rupture. It is likely that most children prescribed 10 days of antibiotics take them for a shorter duration than prescribed. We found that 205 children ages 6–35 months with AOM who were prescribed 10 days of therapy took antibiotics for a median of 8 days. In contrast, children prescribed 5–7 days were more likely to complete the duration prescribed. For other infections such as pharyngitis, most patients also discontinued therapy at day 8 [102,109]. We also found that some parents are confused by how antibiotic suspensions are dispensed and assume that children should complete the entire bottle of medication rather than take the medication for a defined duration. Thus, clinicians and pharmacists should explicitly explain directions for duration of therapy to families

Importantly, we need to recognize that the optimal duration of therapy is likely different for each child based on their severity of symptoms, associated otopathogens, and immune response. An approach that recommends children take the medication until symptoms are nearly resolved or for a maximum number of days might be beneficial, though to our knowledge has not been studied. Many parents may already be using this approach.

4.8 Tympanic Membrane Rupture

Infection with *S. pneumoniae* is more likely to result in TM rupture than other pathogens and continues to be most common pathogen isolated from children with TM rupture in the PCV era [27,112]. TM rupture can also be associated with *H. influenzae, S. aureus*, and *S. pyogenes*, though it is rarely associated with *M. catarrhalis* [113]. Thus, we recommend amoxicillin as first-line therapy for children with TM rupture. No studies have systematically evaluated the effectiveness of otic versus oral antibiotics for children with TM rupture; only data on children with tympanostomy tubes have been reported. We recommend oral antibiotics for these children because otic antibiotics may not adequately reach the middle ear in the presence of copious drainage and would not reach the middle ear after the perforation heals.

4.9 Otitis-conjunctivitis Syndrome

H. influenzae is the most common pathogen associated with otitis-conjunctivitis syndrome [114]. Because nearly half of *H. influenzae* infections resolve without an antibiotic, it is reasonable to consider initial observation with supportive care for children with non-severe infections. If an antibiotic is prescribed, amoxicillin-clavulanate is preferred for regions with high rates of beta-lactamase production among *H. influenzae* isolates, such as the US [35,115]. Ophthalmic antibiotics should not be prescribed concurrently with oral antibiotics because they offer no additional benefit but confer an 8% risk of ADEs [116].[100][101][102][54][53]f [103][63,100][100] a[108] t[58,78,79,109,110][111][102,109]n

4.10 Risks of Antibiotics

Judicious prescribing requires clinicians to consider the risks and benefits of offering antibiotics. Prior to the dissemination of antibiotics and vaccines, serious bacterial infections from AOM occurred at a much higher rate. However, in resource-rich countries with high vaccination rates, the risk of serious complications from AOM is now very rare [117–119]. Overuse of antibiotics results in increased antibiotic resistance, which is a global health emergency [120]. The Centers for Disease Control and Prevention (CDC)'s *Antibiotic Resistance Threats* released in 2019 reported 2.8 million antibiotic-resistant infections in the US every year resulting in almost 36,000 deaths [83]. In addition to antibiotic resistance, antibiotics are responsible for an estimated 70,000 ED visits annually for ADEs in children, accounting for almost half of all ED visits for ADEs [121,122]. Antibiotic exposure leads to reduced gastrointestinal microbiota diversity and richness [122,123], increasing the risk of *Clostridioides difficile* [124]. Multiple recent studies have associated this disrupted microbiota with chronic conditions such as auto-immune diseases [125–127], obesity [128–130], among others [131].

4.11 Complications

We treat AOM to relieve pain and reduce the risk of complications. However, approximately 60% of patients with AOM experience resolution of pain after 24 hours from symptom onset with or without antibiotics. For patients who continue to experience pain after 2–3 days, those treated with antibiotics are more likely to report pain resolution than those treated with placebo [84].

Complications from AOM can be classified as extracranial and intracranial [118]. While both types of complications are rare in the post-vaccination era, intracranial complications are very rare in resource-rich countries [3,77,132].

Patients treated with placebo had a ruptured TM in 4.8% of cases compared to 1.7% of cases in patients treated with antibiotics [84]. Most TM perforations resolve on their own without long-term sequelae. However, hearing loss increased as the size of the perforation increased. Additionally, patients with perforations located posteriorly on the TM had increased hearing loss [133]. Following the development of pneumococcal vaccination, the prevalence of TM perforations as a complication of AOM has decreased [13]. Prior to antibiotics, mastoiditis occurred in approximately 5–10% of patients with AOM and had a mortality rate of 2/100,000 cases. However, after the advent of antibiotics and the pneumococcal vaccine, the incidence of mastoiditis decreased to 2/100,000 cases with a mortality rate of 1/10,000,000 [119].

5. Prevention

Healthcare providers can counsel families on several interventions that can reduce the incidence of AOM in their child. Vaccinations against bacteria that frequently cause AOMs can decrease the incidence of AOMs in a child. Additionally, the annual influenza vaccine can reduce the frequency of AOM with up to 55% efficacy [53,134]. The antibacterial properties of breastfeeding decrease the risk of AOM for at least 6 months after birth [135]. The positive correlation between tobacco smoke and AOMs is well documented [136–139]. Therefore, counseling families on smoking cessation is an important preventive strategy. Most cases of AOM are due to mucus of the upper airways obstructing the eustachian tube from draining the middle ear fluid. While studies of interventions that promote airway hygiene have not been found to augment treatment of AOM, the use of daily nasal saline rinses in otitis-prone children reduced the incidence of developing AOM [140].

6. Parent Perspectives

When their child has AOM, parents are most concerned about pain control, improved sleep, and avoidance of complications [141–143]. Most parents believe that AOM requires treatment with an antibiotic. Parents may have strong misconceptions about the risks of not treating with an antibiotic or delaying treatment including concerns that children may develop a more severe infection requiring hospitalization or may have permanent damage to the ear, though both are exceedingly rare. Parents also tend to overestimate the benefit of antibiotics in improving symptoms. In contrast, parents tend to underestimate the risks associated with antibiotic use, though most parents we have surveyed are generally concerned about giving children medication unnecessarily, resistance, and ADEs.

Though parents have misconceptions about the need for antibiotics, parental satisfaction is highly associated with pain management and good communication, not an antibiotic prescription [144]. Clinicians prescribe antibiotics more often when they perceive parents want one; however, they are wrong about parental preferences 50% of the time [145,146]. Parents strongly prefer shared decision-making over paternalistic care [147]. They also report similar satisfaction with watchful waiting compared to immediate antibiotic use [64,65,144,147,148] and prefer the shortest duration of antibiotics needed to treat the infection or have no preference for treatment duration [141]. Additionally, once parents receive counseling on the option of monitoring symptoms prior to starting antibiotics, they are more likely to consider this option for future uncomplicated AOM infections [149]. Thus, there is profound disconnect between best practice, clinician prescribing, and parental understanding and preferences.

7. Health Equity Considerations

Health inequity in pediatric antimicrobial prescribing has been described, particularly around racial and ethnic difference [150]. With AOM being the most common condition for which antibiotics are prescribed, health inequity in AOM management is well described. Gerber et al. evaluated rates of antibiotic use for over 1.2 million encounters in 25 pediatric urban, suburban, and rural practices in Philadelphia in 2009 for multiple respiratory infections including AOM. They found that Black children are less likely to receive an antibiotic prescription from the same clinician per acute visit, less likely to receive diagnoses justifying antibiotic use, less likely to receive antibiotic prescriptions, and more likely to receive guideline-concordant narrow-spectrum antibiotics compared to non-Black children [151]. Fleming-Dutra et al. examined otitis media visit rates between 2008 and 2010 for children ≤14 years old using the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey. They found that Black children were less likely to be diagnosed with AOM, or to receive broad-spectrum antibiotics compared to White children [152]. Although with most conditions evaluated, ethnic minorities typically experience lower quality of care, when it comes to antibiotic prescribing, they appear to receive care that is more compliant with current guidelines (i.e. less antibiotics in general, and less broad-spectrum antibiotics). The true driver of this health inequity is still not clear.

8. Conclusion:

AOM is the most common reason children are prescribed antibiotics and most antibiotic use for AOM is unnecessary. The majority children will not benefit from an antibiotic and should be managed with watchful waiting and pain management. When an antibiotic is prescribed clinicians should use the narrowest antibiotic possible (amoxicillin) and prescribe the shortest duration needed to treat the infection. Amoxicillin remains highly effective, despite growing resistance among bacterial otopathogens. Educating parents and engaging parents in shared decision-making are likely key to improving care and reducing unnecessary antibiotic use.

9. Expert Opinion

Current evidence suggests that key aspects of improving care for children with AOM are de-implementation of unnecessary antibiotic prescribing, improving diagnostic accuracy, and shifting to individualized care that can adjust for evolving changes in epidemiology and resistance. Pragmatic interventions that can be effectively scaled to non-academic settings will be critical in moving the field forward.

9.1 Successful Antibiotic Stewardship Initiatives

Multiple quality improvement initiatives have been used in different pediatric settings and were successful in improving first-line antibiotic choice, delayed prescribing, and duration for children with AOM (Table 2). Generally, these initiatives use a combination of education, electronic health record changes, feedback to clinicians on their prescribing compared to their peers, and staff engagement to drive the improvement. In alignment with the CDC recommendations, multi-faceted interventions have proven more effective than single intervention components [153].

9.2 Digital Otoscopy, Artificial Intelligence/Machine Learning

Various otoscopes have been designed to allow patients, their parents, or their clinicians to image the TM and middle ear and send data to clinicians or otolaryngologists for review. The ability of these devices to capture images in digital format has opened the possibility of using artificial intelligence for quick and reliable diagnostic workup [163]. Ngombu et al. reviewed 25 articles evaluating artificial intelligence to diagnose AOM. They found that machine learning (where computers are provided data to learn and make appropriate decisions and predictions, often using image classifiers aids) were the most commonly used techniques and had high accuracy. Less commonly used techniques included natural language processing (where computers are trained to extract textual data) and prototype approaches (e.g. analysis of frequency-modulated waves from the phone’s speaker bouncing off the TM, or a symptom-recording application) [164]. A recent systematic review of 39 articles showed that a digital algorithm achieved an accuracy of 90.7% to differentiate between normal and abnormal otoscopy images. Artificial intelligence algorithms outperformed human assessors, achieving 93.4% accuracy compared to 73.2% accuracy in three studies [60]. Strategies to effectively scale the use of digital otoscopy among providers are needed. Additionally, the role of parent-performed otoscopy in the diagnosis of AOM warrants further evaluation.

9.3 Pathogen-Directed Therapy

Under ideal circumstances, selection of management strategy (initial observation versus antibiotic) and choice of antibiotic agent would be based on the pathogens detected in each individual child rather than generalizing recommendations. Prior studies indicate that outcomes are better for children who receive an antibiotic agent based on the pathogens detected compared to those who receive a standard regimen [165]. While no clinical features can reliably differentiate between pathogens [86] or resistance, rapid diagnostic testing using polymerase chain reaction (PCR) could provide valuable information on which pathogens are present and reliably detect the presence of resistance and virulence genes (e.g. beta-lactamase production by *H. influenzae*). For children with TM perforation or conjunctivitis, direct source testing could be completed. For other children, nasopharyngeal testing could serve as a surrogate to provide important guidance. There is a strong association with the organisms detected in the nasopharynx and middle ear during AOM episodes. While the positive predictive value is variable likely secondary to high carriage of common bacterial otopathogens in the nasopharynx, the absence of an organism in the nasopharynx can reliably exclude the presence of the organism in the middle ear (negative predictive value >79–92% for *H. influenzae, S. pneumoniae, and M. catarrhalis*) [166,167]. We also recently reported that nasopharyngeal PCR has high sensitivity for common otopathogens compared to culture [168]. Testing would allow for real-time changes in management based on regional pathogen epidemiology and resistance patterns.

9.4 The Future of AOM

We speculate that the AOM landscape will look profoundly different within the next 5 years. The changing epidemiology of AOM and rapidly increasing rates of antimicrobial resistance will force the evolution of new diagnostics (including digital otoscopes and rapid diagnostic tests for pathogens) and pragmatic interventions to improve care. As we saw during the COVID-19 pandemic, the emergence of new respiratory viruses will force us to reevaluate the role of viruses in AOM pathogenesis and how we appropriate management infections. Our greatest challenges are likely to be scaling effective tools in pragmatic settings and meeting epidemiologic changes proactively rather than responsively.

Funding

H Frost received salary support from the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number K23HD099925. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Declaration of interest

R El Feghaly has received a research grant from Merck. H Frost serves as a Senior Scientific Advisor for QuidelOrtho and holds a patent for Diagnosing and Treating Otitis Media #63/335,801. QuidoOrtho had no role in the design, content, or interpretation of the review. S Katz serves as a consultant for Optum and has a research grant from Pfizer, neither of which had any role in the design, content, or interpretation of the review. A Nedved serves as a project leader on an antibiotic stewardship project sponsored by the American Academy of Pediatrics and funded by Pfizer. A Nedved has a research grant from Merck. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or material discussed in the manuscript.

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Article highlights:

- The epidemiology of acute otitis media (AOM) has changed with the introduction of pneumococcal vaccines. *Haemophilus influenzae* and *Moraxella catarrhalis* are now more common; both organisms cause less severe disease compared to *Streptococcus pneumoniae* and are more likely to resolve spontaneously without antibiotics.
- Diagnosis of AOM relies on visualization of the tympanic membrane. New technology tools and artificial intelligence allow for higher accuracy and may be the future of AOM diagnostics.
- Delayed antibiotic prescriptions or watchful waiting are appropriate for many patients with AOM symptoms and can help avoid antibiotic exposure in a substantial number of children. However, most patients evaluated for AOM continue to receive immediate antibiotic prescriptions.
- Amoxicillin continues to be the first-line antibiotic for children with AOM and no recent antibiotic exposure or concomitant conjunctivitis.
- Multiple quality improvement efforts have been successful in increasing watchful waiting and reducing duration of antibiotics for AOM. These efforts typically include a combination of education, electronic health record changes, engagement strategies, and feedback to clinicians on their prescribing practices compared to those of their peers.

Table 1:

Complications of Acute Otitis Media[118]

Extracranial	**Intracranial**
Hearing loss	Meningitis
Vertigo	Epidural abscess
Tympanic membrane perforation	Brain abscess
Cholesteatoma	Subdural empyema
Mastoiditis	Cavernous sinus thrombosis
Labyrinthitis	Carotid artery thrombosis
Facial nerve palsy	

Table 2:

Successful Antibiotic Stewardship Initiatives

Study	Pediatric Setting	Interventions	Improvements
Norlin et al. [154]	Primary Care Practices (Regional Collaborative)	-Online learning sessions -Independent PDSA cycles by clinics	-First-line antibiotics: 63.5% to 80.4% -Delayed prescribing: 4.5% to 16.9% - AOM education: 20.4% to 85.6%
Nedved et al. [155]	Urgent Care Clinics (National Collaborative)	-MITIGATE Antimicrobial Stewardship Toolkit -Independent PDSA cycles by clinics	-Appropriate antibiotics (first-line and duration): 43% to 63.4%
Wolf et al. [156]	Primary Care Clinics (Single-Center)	-EHR changes with emphasis on notes, discharge instructions, and order alerts -Education	-Delayed prescribing: 21% to 78% -Adherence to AAP guidelines 78% to 92%
Sun et al. [157]	Emergency Departments (Single-Center)	-Education -Sharing data via email -Posters, handouts -Commitment letter	-Watchful waiting: 2.8% to 11.1%
Frost et al. [158]	Primary Care Clinics (Regional Collaborative)	-Education -Subject matter expert support -Online community collaborative -Continuing education credit	-Delayed prescribing: 2% to 21%
Daggett et al. [159]	Emergency Departments (Single-Center)	-Education -Recognizing high-performers -Algorithm -EHR changes	-Delayed prescribing for all AOM cases: 0.5% to 7.5–7.9% (27.5% qualify)
Uhl et al. [99]	Urgent Care Clinics (Single-Center)	-Education Posters -Blog, podcast -Family education -Involve RNs and Pharm -EHR changes – templates	-Duration: 7% to 67%
Frost et al. [111,160]	Primary Care Clinics and School-based Health Centers (regional)	-Audit and Feedback -Education -EHR changes	-Duration: 10.6% to 85.2%
Kaleida et al. [161]	Residency program (National)	-Online curriculum	-Correct diagnosis: 55% to 67%
Mousseau et al. [162]	Medical Students (Single-Center)	-e-learning module vs small-group lecture	-Diagnostic Accuracy: 76.4–76.5%

Abbreviation key: AOM: acute otitis media; EHR: electronic health record; MITIGATE: A Multifaceted Intervention to Improve Prescribing for Acute Respiratory Infection for Adults and Children in Emergency Department and Urgent Care Settings; PDSA: Plan-Do-Study-Act; RN: registered nurse