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Acute Otitis Media: A Review of Pathogens, Increasing Bacterial Resistance and Treatment Considerations

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Acute otitis media (AOM), an inflammation of the middle ear, is one of the most common causes for physician office visits among young children. In 2000, ~ 80% of children presenting with symptoms consistent with AOM were prescribed antibiotics.[1] However, because the vast majority of AOM cases are viral in origin, symptom resolution occurs spontaneously without antibiotic therapy in most children. Thus, appropriate use of antimicrobial therapy is paramount, especially with regard to increasing bacterial resistance. Understanding current resistance trends in acute otitis media will allow clinicians to provide the best care for their patients and ensure judicious prescribing of antimicrobial therapy.

This paper will review acute otitis media, including disease prevalence, common pathogens, bacterial resistance and recent clinical trials. Current treatment guidelines in light of increasing bacterial resistance and the pneumococcal conjugate vaccines' effect on the prevalence of various *S. pneumoniae* serotypes will be discussed.

Pathogensis

Otitis media is most common in infants and young children. Up to 75% of children may have at least one episode in their first year of life.[2] The anatomy of the Eustachian tube contributes to the increased prevalence in children. The angle of the Eustachian tube changes gradually from horizontal to oblique as the child develops. The horizontal angle does not facilitate mucociliary drainage as well, allowing infectious pathogens to infiltrate the middle ear.[3]

Causative Organisms

Viral illnesses will often precede bacterial AOM. Viral upper respiratory infections can cause Eustachian tube dysfunction and swelling of the middle ear mucosa.[4] Inadequate clearance by the mucociliary system then allows for colonization by bacteria normally present in the nasopharynx.[5] Tympanocentesis with subsequent culture is the gold standard for diagnosing and determining optimal treatment of AOM; however, this practice is rarely ever done.[1]

The frequency of common causative pathogens in AOM varies by study. *Streptococcus pneumoniae* is responsible for 20-50% of cases of bacterial AOM.[6,7] Nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis* are responsible for 15-30% and 3-20% of cases, respectively.[6,7] A viral etiology may be present in up to 40-75% of AOM cases with or without concomitant bacterial presence.[1] The high rate of spontaneous resolution is likely reflective of a significant proportion of viral etiologies and effective immune system response to illness.

Older studies suggest that viral AOM and AOM caused by *H. influenzae* are more likely to resolve

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Table 1 | Common pathogens associated with acute otitis media.[1,8,15,16]

Pathogen	Spontaneous resolution	Resistance mechanism	Treatment recommendations	Comments
S. pneumoniae (penicillin-susceptible and intermediate)	~20%	Changes in penicillin binding proteins	High dose amoxicillin (80-90mg/kg/day divided TID)	Amoxicillin concentrates very well in the middle ear. Sufficient doses can overcome intermediately resistant *S. pneumoniae*
Penicillin-Resistant *S. pneumoniae*	~20%	Changes in penicillin binding proteins	Parenteral ceftriaxone; clindamycin	Ceftriaxone more effective for resistant *S. pneumoniae* than other oral antibiotics. If AOM persists, tympanocentesis is recommended. Clindamycin for resistant *S. pneumoniae* unresponsive to initial therapies.
M. catarrhalis	50%	Beta-lactamase production	Amox/clav 90 mg/kg/day of amoxicillin; 6.4 mg/kg/day of clavulanate	May resolve spontaneously
H. influenzae	70-80%	Beta-lactamase production	Amox/clav 90 mg/kg/day of amoxicillin; 6.4 mg/kg/day of clavulanate	Likely to resolve spontaneously

spontaneously and are less likely to develop invasive disease, whereas persistent and recurrent AOM is more frequently caused by resistant strains of *S. pneumoniae* and beta-lactamase-producing *M. catarrhalis*.[1,8] Findings from more recent studies indicate that *H. influenzae* is becoming a more prevalent isolate in refractory and recurrent cases of AOM.[9,10,11,12]

Resistance

As bacterial resistance rates climb among AOM pathogens, health care providers must be aware of the local resistance rates and bacterial mechanisms of resistance in order to provide appropriate treatment. The main mechanisms of drug resistance in AOM pathogens include alteration of the drug binding receptor, decreased amount of drug reaching the receptor, or destruction or inactivation of the drug.[13] Risk factors for resistant pathogens include antibiotic use in the past month, persistent or recurrent AOM, infection during winter/spring months, age <2 years, and daycare attendance.[14] **Table 1** describes the most common bacterial pathogens of AOM, their mechanism of antimicrobial resistance and treatment recommendations.

Various serotypes of *S. pneumoniae* have demonstrated resistance to beta-lactam antibiotics, macrolides, fluoroquinolones, tetracyclines and trimethoprim-sulfamethoxazole.[6,13,17] Surveillance studies in the United States from 1998 to 2006 report

Table 2 | Mechanisms of *S. pneumoniae* resistance to various antimicrobial classes.[18]

Drug Class	Mechanism of resistance	Comments
Beta-Lactams	Genetic mutations leading to alterations in 3-4 of the 5 penicillin binding proteins (PBPs)	Renders organisms resistant to penicilliins (amoxicillin) and cephalosporins
Macrolides	Active drug efflux (mefA gene)	Accounts for 66-75% of macrolide resistance in the U.S.
	Alteration of ribosomal binding site (ermB gene)	Confers resistance to macrolides, clindamycin and streptogramins
Fluoroquinolones	Mutations of the quinolone resistance-determining regions (QRDRs) of 2 topoisomerase genes (parC and gyrA); Efflux pumps may also play a role	Renders organisms resistant to fluoroquinolones
Tetracyclines	Efflux mechanisms	
TMP-SMX	Mutations to target binding sites	

Box 1 | Important considerations in suspected AOM.

- Confirmed diagnosis
  - Rapid onset
  - Signs of middle ear effusion
  - Signs/symptoms of middle ear inflammation
- Age
- Illness severity
  - Non-severe: mild otalgia, temperature < 39 °C
  - Severe: moderate-to-severe otalgia; temperature ≥ 39 °C
- Assurance of follow-up
  - Antibiotics may need to be started if symptoms worsen or do not resolve

ceftriaxone resistance rates ranging from 1.2 to 6.9%, with higher rates in the southeastern states.[13] As many as 34% of *S. pneumoniae* isolates from the United States are macrolide-resistant.[13] **Table 2** summarizes the mechanisms by which *S. pneumoniae* has become resistant to these antimicrobial agents.

The genes responsible for resistance to penicillins and other antibiotic classes (e.g. trimethoprim-sulfamethoxazole and macrolides) are frequently linked, resulting in increased development of multidrug resistant pathogens. The definition of multidrug-resistant *S. pneumoniae* is a strain resistant to three or more classes of antimicrobials. Resistance to macrolide antibiotics has escalated in conjunction with beta-lactam resistance; penicillin-resistant *S. pneumoniae* is more likely to be resistant to non-beta-lactam antibiotics than other *S. pneumoniae* strains. This may reflect transfer of non-beta-lactam resistance determinants via transposons.[13] Currently, 15 to 30% of *S. pneumoniae* worldwide are multidrug-resistant.[13,18,19]

Escalating rates of resistance among pathogens commonly associated with AOM complicates the clinician's goal of appropriate empiric prescribing. Rates of *S. pneumoniae* resistance vary by geographical region across the United States; the clinician must be aware of the local resistance pattern in the area in which he or she practices. Resistance of *S. pneumoniae* to penicillin (and amoxicillin) ranges from 30-60% in the United States.[13,20]

The spread of resistant strains of bacteria is facilitated by selective pressure from inappropriate antibiotic use.[13] Some popular supermarkets have initiated a "Free Antibiotics" campaign which may contribute to resistance development via the repetitive use of a select number of antibiotics. Jensen and colleagues found that increased consumption of ciprofloxacin (resulting from generic availability) was significantly correlated with increased ciprofloxacin resistance in urinary *E. coli* isolates.[21]

Pneumococcal Conjugate Vaccines

Ninety-one strains (serotypes) of pneumococcal bacteria have been identified. The first heptavalent pneumococcal conjugate vaccine (PCV7, Prevnar®, Wyeth), introduced in 2000, protected against seven of the most common pneumococcal disease-causing serotypes (4, 6B, 9V, 14, 18C, 19F and 23F). In the years following, the rate of invasive pneumococcal disease and consolidative pneumonia decreased substantially. The frequency of vaccine serotype pneumococcal otitis media also dropped; however, the overall benefit is small (about 6% reduction in incidence).[21] The proportion of infectious diseases caused by non-vaccine serotypes has increased substantially in recent years.[23,24] A recent systematic review analyzed studies which looked at the effect of PCV7 on AOM pathogenesis and concluded that AOM pathogenesis has shifted to *S. pneumoniae* serotypes not included in the vaccine.[9] Most antibiotic-resistant *S. pneumoniae* today is serotype 19A, which is covered in the new 13-valent pneumococcal conjugate vaccine (PCV13, Prevnar13®, Pfizer) introduced in the United States in February 2010.[23,24] The new vaccine includes the original seven serotypes in PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F) as well as 1, 3, 5, 6A and 7F. Continued surveillance is required to determine if the new vaccine will reduce rates of otitis media, and not simply cause another shift in the most prevalent pathogenic serotypes.

Treatment Algorithm

The American Academy of Pediatrics (AAP) composed a clinical guideline for the diagnosis and treatment of AOM in 2004. A summary of their recommendations are given in **Box 1** and **Tables 3** and **4**.

Table 3 | Recommended initial management of AOM.

Age	Certain Diagnosis	Uncertain Diagnosis
<6 months	Antibiotics	Antibiotics
6 months to 2 years	Antibiotics	Antibiotics if severe[a]; otherwise, observation[b]
> 2 years	Antibiotics if severe[a]; otherwise, observation[b]	Observation[b]
All ages	Acetaminophen or ibuprofen for pain management	

[a] Severe disease defined as temperature ≥ 39°C or severe otalgia.
[b] Recommended observation period is 48-72 hours.

Observation Period

The emphasis placed on the initial observation period results from placebo-controlled studies which show that most children with AOM do well with or without antimicrobial therapy. Sixty-one percent of children with suspected AOM will have decreased symptoms in 24 hours and symptoms will completely resolve in 75% of children after seven days.[4] Reducing the rate of unnecessary antimicrobial prescribing is preferred for two reasons. First, avoiding antimicrobial therapy in an otherwise healthy child will ensure that the child doesn't suffer undue side effects (such as diarrhea or rash) from the antibiotics. Secondly, exposing bacteria to unnecessary antimicrobial agents can contribute to bacterial resistance.

Treatment Considerations

In order to effectively eradicate bacterial AOM, the pathogen must be susceptible to the antibiotic agent, and the agent must be able to achieve adequate concentrations in the middle ear.[16]

Clinical trials evaluating the efficacy of antibiotics for AOM often contain design flaws, so the high cure rates demonstrated are often unreliable. Unclear criteria for diagnosis of AOM, inclusion of patients with only susceptible organisms and/or mild or moderate disease, exclusion of difficult-to-treat cases, and broad, subjective criteria for "cure" of AOM all contribute to overly positive results. Results are further skewed since AOM has a high rate of spontaneous resolution.[25]

Recently, two well-designed landmark studies aimed to determine whether treatment with antibiotics in younger children (≤ 3 years) with confirmed cases of AOM offered any benefit over placebo.[26,27] Children with confirmed diagnoses based on otoscopic findings who were treated with antibiotics did benefit with respect to symptom duration and clinical failure rate. The discordant findings between these trials and previous studies is, at least in part, attributable to the more strict inclusion/exclusion criteria in the recent trials. As expected, higher rates of diarrhea and rash were seen in the treatment group, and many children in the placebo group also had improvement in symptoms without antibiotics.[26,27]

Antibiotic treatment of AOM is recommended in all children younger than 6 months of age, especially during a first episode. Younger children are at a higher risk of poor outcomes including clinical failure and infection recurrence. Thus, eradication of the pathogen is crucial within the first days of symptom presentation. However, observation is the preferred strategy for older children with milder symptoms, particularly those in which diagnosis is uncertain.[28]

High-dose amoxicillin (90mg/kg/day) remains the

Table 4 | Recommendations for antibiotic selection according to American Academy of Pediatrics Guidelines.[1]

Temp ≥ 39°C or severe oltalgia	Recommended Agent	Alternative (PCN allergy)
Initial antibiotic treatment		
No	Amoxicillin, 80–90 mg/kg/day	Non-type I: cefdinir, cefuroxime, cefpodoxime Type I: azithromycin, clarithromycin
Yes	Amoxicillin/clavulanate, 90 mg/kg/day of amoxicillin; 6.4 mg/kg/day of clavulanate	Ceftriaxone, 1 or 3 days
Non-improvement of symptoms following initial observation period		
No	Amoxicillin, 80–90 mg/kg/day	Non-type I: cefdinir, cefuroxime, cefpodoxime Type I: azithromycin, clarithromycin
Yes	Amoxicillin/clavulanate, 90 mg/kg/day of amoxicillin; 6.4 mg/kg/day of clavulanate	Ceftriaxone, 1 or 3 days
Non-improvement of symptoms following initial antibiotics		
No	Amoxicillin/clavulanate, 90 mg/kg/day of amoxicillin; 6.4mg/kg/day of clavulanate	Non-type I: ceftriaxone, 3 days Type I: clindamycin
Yes	Ceftriaxone, 3 days	Tympanocentesis, clindamycin

recommended empiric therapy for AOM, even with the rising rate of *S. pneumoniae* resistance. A recent systematic review found no evidence of the superiority of any other antibiotic over amoxicillin.[9] Because it concentrates well in the middle ear,[29] amoxicillin maintains efficacy in intermediately resistant *S. pneumoniae* and some highly resistant infections by exceeding the minimum inhibitory concentration levels required. If the patient has a penicillin allergy, alternative therapy with a cephalosporin (cefdinir, cefpodoxime, cefuroxime) or a macrolide (azithromycin, clarithromycin) is recommended.[1]

The addition of a beta-lactamase inhibitor (e.g. clavulanate) to amoxicillin provides no additional benefit over amoxicillin alone for the treatment of resistant *S. pneumoniae*. However, the prevalence of beta-lactamase producing *H. influenzae* and *M. catarrhalis* strains isolated from patients with AOM is increasing and these strains may not respond to empiric therapy with amoxicillin alone. AAP guidelines recommend the addition of a beta-lactamase inhibitor following initial treatment failure of amoxicillin alone. Empiric beta-lactam/beta-lactamase inhibitor combination antibiotics are appropriate only if the clinician suspects *H. influenzae* or *M. catarrhalis.* If the local rate of *S. pneumoniae* resistance is high, alternative therapy with intramuscular ceftriaxone following amoxicillin failure may be preferred since it is more effective against highly resistant *S. pneumoniae* than the alternative oral antimicrobials.[1] Intramuscular ceftriaxone is the only agent other than amoxicillin that can achieve middle ear fluid concentrations above the MIC for more than 40% of the dosing interval.[30] If AOM persists after 3 days of parenteral ceftriaxone therapy, tympanocentesis should be done to identify the pathogen and determine further treatment.[1] Clindamycin may be considered if tympanocentesis cannot be performed.

Summary

Viral etiologies of AOM are common. Bacterial cases can spontaneously resolve without the need for antibiotics. The most common bacterial pathogens in AOM are *S. pneumoniae, M. cattarhalis* and *H. influenzae*.

A short period of observation (48-72 hours) while withholding antimicrobial therapy is often appropriate for non-severe illness, particularly in older children. This observation period can reduce the rate of unnecessary antibiotic prescribing. When antimicrobial therapy is indicated, empiric therapy should be based on the most likely pathogen. As *S. pneumoniae* is responsible for the greatest percentage of bacterial AOM, empiric therapy with amoxicillin alone is appropriate in most cases.

Judicious antibiotic prescribing requires that clinicians be familiar with local bacterial resistance patterns. Though the rate of resistant *S. pneumoniae* is rising, high-dose amoxicillin has the capacity to eradicate intermediately-resistant as well as some resistant *S. pneumoniae* strains. Parenteral ceftriaxone may be preferred for resistant *S. pneumoniae* that does not respond to high-dose amoxicillin. AOM caused by *M. catarrhalis* and *H. influenzae* may resolve spontaneously without antibiotics. However, when antimicrobial therapy is indicated, a beta lactamase inhibitor must be added to high-dose amoxicillin as many strains are now beta-lactamase producers.

Eighty out of 100 children with uncomplicated AOM are apt to have symptom resolution in three days without treatment. If all of these patients were treated with antibiotics, an additional 12 may improve within that time period. However, 5-10 would also get diarrhea and 3-10 would develop a rash.[9] The clinician must weigh the potential benefit of immediate treatment with the risk of adverse drug reactions and antimicrobial resistance facilitated by selective pressure from inappropriate antibiotic use.

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