POSITION STATEMENT

Management of acute otitis media in children six months of age and older

Posted: Feb 5 2016

Principal author(s)

Nicole Le Saux, Joan L Robinson; Canadian Paediatric Society, Infectious Diseases and Immunization Committee (https://www.cps.ca/en/documents/authors-auteurs/infectious-diseases-and-immunization-committee)

Paediatr Child Health 2016;21(1):39-44

Abstract

Acute otitis media (AOM) continues to be a common infection in young children. Milder disease, usually due to viruses or less virulent bacteria, resolves equally quickly with or without antibiotics. A bulging tympanic membrane, especially if yellow or hemorrhagic, has a high sensitivity for AOM that is likely to be bacterial in origin and is a major diagnostic criterion for AOM. Perforation of the tympanic membrane with purulent discharge similarly indicates a bacterial cause. Immediate antibiotic treatment is recommended for children who are highly febrile (≥39°C), moderately to severely systemically ill or who have very severe otalgia, or have already been significantly ill for 48 h. For all other cases, parents can be provided with a prescription for antibiotics to fill if the child does not improve in 48 h or the child can be reassessed if this occurs. Amoxicillin remains the clear drug of choice. Ten days of therapy is appropriate for children <2 years of age, whereas older children can be treated for five days.

Key Words: *AOM; MEE; OME; PCV13; TM*

The present position statement updates a previous CPS document released in 2009.[1] Based on published evidence, this revision is intended to be a guide for sound clinical decision making. The recommendations are not intended for treating children <6 months of age or for those with craniofacial abnormalities, immunocompromising conditions, tympanostomy tubes or recurrent acute otitis media (AOM).

The pathogenesis of AOM

AOM is extremely common, and 75% of children experience at least one ear infection before starting school.[2] Normally, mucocilliary clearance mechanisms in the eustachian tube (ET) ventilate and drain fluid away from the middle ear. ET dysfunction or obstruction due to a viral infection or other causes of mucosal inflammation can impair this normal mechanism. The lack of middle ear drainage leads to fluid stasis and, if the fluid is colonized with bacterial and/or viral pathogens, can lead to AOM. Children are predisposed to AOM because they acquire viral infections more often than adults, and their ETs are also shorter and more horizontal compared with adults.[3][4]

Risk factors for AOM include young age and frequent contact with other children, which increases exposure to viral illnesses. Other risk factors include orofacial abnormalities (such as cleft palate), household crowding, exposure to cigarette smoke, pacifier use, shorter duration of breastfeeding, prolonged bottle-feeding while lying down and a family

history of otitis media. Children of First Nations or Inuit ethnicity are also at higher risk for AOM.[5][6] A small proportion of children have lower levels of secretory immunoglobulin A or persistent biofilms in the middle ear, which may play a role in increasing the risk for recurrent AOM.[7]-[9]

There is a clinical spectrum of middle ear infections associated with the initiation and progression of infection leading to bacterial AOM. Middle ear fluid from AOM cases often harbour both viruses and bacteria; however, children who experience spontaneous resolution of AOM are likely to have viral infections alone or to have bacterial organisms that are less virulent (eg, *Moraxella catarrhalis* and some strains of *Haemophilus influenzae*) compared with *Streptococcus pneumoniae* and *Streptococcus pyogenes* (group A streptococci [GAS]).[10] In one prospective study, 22% of children between six months and three years of age developed AOM during the first week of an upper respiratory infection, while a further 7% had myringitis without effusion.[11] Thus, the clinical presentation of AOM can vary with the stage of illness (early versus later). Also, children may or may not progress to overt bacterial AOM depending on which viruses or bacteria are present in the nasopharynx.[12]

Bacteria commonly associated with AOM

The most common bacteria causing AOM are *S pneumoniae, H influenzae, M catarrhalis* and (less commonly) GAS. Usually there is a single bacterial pathogen but coinfection can occur. Studies following the routine use of the seven-valent conjugated pneumococcal vaccine (PCV7) demonstrated the increasing importance of nonvaccine type *S pneumoniae* and non-typable *H influenzae*.[13] However, more recent studies performed during the 13-valent pneumococcal vaccine era have shown lower carriage rates for *S pneumoniae* overall.[14] It is not yet known whether the absolute number or only the percentage of cases of AOM due to *H influenzae* and *M catarrhalis* will increase with the widespread use of the 13-valent conjugated pneumococcal vaccine (PCV13).

It has been estimated that the routine use of PCV7 in Canada has decreased the incidence of AOM by 13% to 19% because nasopharyngeal colonization with vaccine-type *S pneumoniae* in children has been significantly reduced.[15][16] One recent study showed that AOM cases (and possibly more severe episodes) caused by *S pneumoniae* have decreased since the introduction of PCV13 in 2011, especially in children <2 years of age.[17] Another recent study from Israel reported an 85% decline in AOM due to PCV13 serotypes since the introduction of the universal PCV13 vaccine, and an overall 77% decline in pneumococcal AOM from the period before PCV7 was introduced to the present (post-PCV13) era.[18]

Why accurate diagnosis of AOM is critical

The diagnosis of AOM is the cornerstone of management, yet is often very challenging from a clinical perspective. Using antimicrobials to treat viral AOM or AOM caused by less virulent bacteria (both more likely to resolve spontaneously), or to treat otitis media with effusion (OME) without AOM, leads to unnecessary and potentially harmful side effects, and contributes to colonization with antimicrobial-resistant bacteria. Earlier studies investigating the treatment of AOM did not use stringent criteria for diagnosis and likely included many children who did not have severe AOM, thereby diluting the treatment effect of antibiotics.[19] In some cases, failure to eradicate bacteria in AOM has been shown to increase the risk for relapse.[20] Therefore, determining which children truly have AOM that will resolve faster with antimicrobials is of utmost importance.[21][22]

Symptoms

Symptoms are nonspecific and, by themselves, are insufficient to diagnose AOM. Systemic symptoms, such as difficulty sleeping or decreased playfulness as well as irritability and fever, are common in respiratory viral infections (eg, influenza and respiratory syncytial virus infections) even in the absence of AOM.[23] Symptoms such as ear tugging or ear pain (otalgia), while often helpful in verbal children, may also indicate myringitis due to a viral infection or ET dysfunction with decreased hearing. Otalgia as a symptom should be distinguished from pain in the external canal due to otitis externa (which results in pain on movement of the tragus and inflammation of the ear canal usually without any systemic symptoms). The tempo, severity and duration of illness are also important to elicit because a progressively or severely ill child is more likely to have a bacterial process that may not resolve spontaneously.

Identification and characterization of a middle ear effusion

Using nonspecific symptoms as the sole basis for diagnosing AOM will not only lead to over-diagnosis in many cases but also, potentially, to under-diagnosis in patients who may not have specific symptoms attributable to the middle ear.[24] Using an otoscope with a bright light source (ie, replacing otoscope bulbs yearly) and the largest ear speculum that fits into a child's ear facilitates visualization and the application of validated criteria to diagnose AOM.

The presence of a middle ear effusion (MEE) is a necessary minimal diagnostic criterion for AOM. An effusion is present when there is little or no mobility of the tympanic membrane (TM) when both positive and negative pressure is applied using a pneumatic otoscope. A significant decrease in TM mobility (as visualized with a pneumatic otoscope) has good sensitivity and specificity for MEE; however, appropriate use of pneumatic otoscopy does require practice and, unfortunately, this useful technique is not commonly employed by front-line clinicians. Automated tympanometry is unreliable in infants <7 months of age, and its sensitivity and specificity in other age groups depends on proper use and interpretation. Therefore, information obtained using this tool must be correlated with other findings.[25][26] Other signs of MEE may include loss of bony landmarks or the presence of an air-fluid level. The position and profile of the TM may be neutral, retracted or bulging, depending on the presence of inflammation and chronicity. Normally, the TM is slightly grey in colour; however, it can become red due to crying or infection. Both the TM colour and position are imperative to note and consider, given their central importance in the diagnosis of inflammation of the middle ear.

Diagnostic criteria for AOM

AOM is characterized by acute onset of symptoms (eg, otalgia or suspected otalgia) with middle ear fluid and significant inflammation of the middle ear. As a distinct entity, AOM should be differentiated from OME, which is also characterized by the presence of MEE; however, in contrast to AOM, signs of acute inflammation of the middle ear are absent.

As in all clinical processes, there is a continuum of severity with respect to presentation. A study involving children <1 year of age indicated that AOM developed in 27% of cases with a symptomatic upper respiratory tract infection.[27] In another study involving children who were within one week of the onset of an upper respiratory tract infection, 6% had mild, 59% had moderate and 35% had severe TM inflammation. Of 28 cases with nonsevere AOM managed with watchful waiting, four progressed and three required antimicrobial therapy.[11] A different study involving children with nonsevere AOM reported that two-thirds of cases appeared to resolve their infections without antibiotics, albeit more slowly than those who received antimicrobials.[28] These data support the belief that some children infected with some viral and bacterial pathogens may develop only mild illness and resolve their AOM spontaneously.

Multiple studies have attempted to correlate the appearance of the TM with the presence of bacterial pathogens.[29]-[31] In a study from Finland,[29] impaired mobility of the TM was the most sensitive and specific (95% and 85%, respectively) predictor of MEE associated with AOM. A bulging TM had a high specificity (>97%) but a lower sensitivity of 51%, while a cloudy TM also had high specificity (93%) with a good sensitivity (74%) for the presence of MEE and clinical symptoms of AOM. Other studies have also indicated that a bulging TM has a higher specificity for the presence of *S pneumoniae* and other bacteria, regardless of the presence of viruses, and is associated with more severe illness.[10][29] In addition to a bulging TM, it was noted that when the TM was yellow, a bacterial pathogen could be cultured 80% of the time.[30] Using a convenience sample of 264 ill children presenting to primary care with typical AOM symptoms, experienced otoscopists wanted to determine and validate which sign was the best predictor of AOM. They concluded that all children with bulging TMs and only 8% of those with non-bulging TMs had AOM, making bulging the most important criteria for the diagnosis.[32] Other features, such as hemorrhagic patches or erythematous TM, had poor interobserver agreement, while erythema, opacity or air fluid levels alone – without a bulging TM – had poor predictive value.[29][32] Therefore, a bulging TM is a very sensitive and specific indicator for acute inflammation consistent with AOM.

Similarly, an acute perforation with purulent discharge (otorrhea) in the setting of AOM strongly supports a bacterial cause. Although *S pneumoniae* is the most common cause of AOM, several studies have isolated *S pyogenes* in a higher percentage of patients who have spontaneous perforations compared with patients whose TMs remain intact.[33]

Importantly, the drainage associated with acute symptoms of AOM and perforation should always be distinguished from otitis externa, chronic ear drainage from a previous perforation (with no middle ear inflammation) or drainage associated with a tympanostomy tube, because management for these conditions would be very different.

Clinical features not consistent with AOM are a TM with normal or slightly reduced mobility, or a non-bulging TM with or without erythema or cloudiness. Air-fluid levels alone, without a bulging TM, are not predictive of AOM.

An excellent video describing otoscopy technique and diagnostic criteria for otitis media is available at www.nejm.org/doi/full/10.1056/NEJMvcm0904397.[34]

Complicated bacterial AOM at presentation

Very rarely, at initial presentation of AOM, infection has already progressed to involve adjacent structures.[35] In some cases, other associated signs or symptoms will predominate. All with spread beyond the middle ear should receive systemic antimicrobial therapy and an evaluation to consider surgical intervention and/or imaging to delineate the extent of the infection.

The most common complication of AOM is acute mastoiditis. Although AOM is usually accompanied by inflammation of the mastoid air cells (including radiographic changes on computerized tomography), clinical symptoms, such as pain or swelling over the mastoid bone (behind the ear), suggest mastoiditis.

Other less common but clinically important syndromes associated with AOM are acute facial (cranial nerve VII) nerve palsy, which is also associated with temporal bone inflammation, or sixth cranial nerve palsy (failure of ipsilateral eye abduction) due to petrous bone inflammation or infection (Gradenigo's syndrome). Additional complications may include labyrinthitis, when infection spreads to the cochlear space, venous sinus thrombosis of the transverse, lateral or sigmoid venous sinuses, and meningitis.

Management of AOM based on accepted criteria

All children with a perforated TM who present with symptoms of AOM should be treated promptly with systemic antimicrobials and examined for associated complications.

To help determine which children without perforated TMs are most likely to benefit from antimicrobial treatment for AOM, two large placebo-controlled studies involving children >6 months of age were conducted in Europe and North America. The criteria for AOM were acute symptoms of fever, ear pain or respiratory symptoms coupled with stringent objective criteria for the middle ear (MEE or TM air-fluid levels, and moderate or marked bulging of the TM, accompanied by marked erythema or hemorrhage, or a yellow TM).[21][22] Using these criteria, there were significantly more failures in the placebo group (35%) compared with the treatment group (19%), strongly suggesting that in children for whom the diagnosis is made using stringent criteria, treatment with antimicrobials is likely to be beneficial. Even then, the number needed to treat to benefit one child with AOM was approximately four. When the results from the two trials for children six months to two years of age with stringent criteria were compared, failure rates with placebo were between 40% and 59% but only 14% to 25% with antimicrobials, further indicating the benefits of antimicrobial therapy in these specific clinical situations.[36]

However, deciding who can be safely treated without empirical antimicrobial therapy must depend somewhat on clinical judgement but should also include objective criteria such as length and severity of illness. Children who have a mild or moderately bulging TM, and who are mildly ill, alert, responding to antipyretics, have a low-grade fever (<39°C) and mild otalgia can be safely managed with an observation or 'watchful waiting' period of 24 h to 48 h. Planned reassessment, access to timely reassessment or "expectant" antimicrobial prescriptions may be acceptable approaches, depending on clinical and social circumstances. Children with AOM (defined by a bulging TM) who are highly febrile (≥39°C) and moderately to severely systemically ill, or children who have severe otalgia or have been significantly ill for 48 h should be treated with antimicrobials (Figure 1).

In all instances, their caregivers should be informed about and be attentive to any change or worsening of symptoms, and should have ready access to medical care. If symptoms worsen or do not improve within 24 h to 48 h, antimicrobials should be prescribed. Explanations regarding the management plan should be discussed with caregivers so decision-making can be shared. It is vital to provide appropriate advice about analgesics.

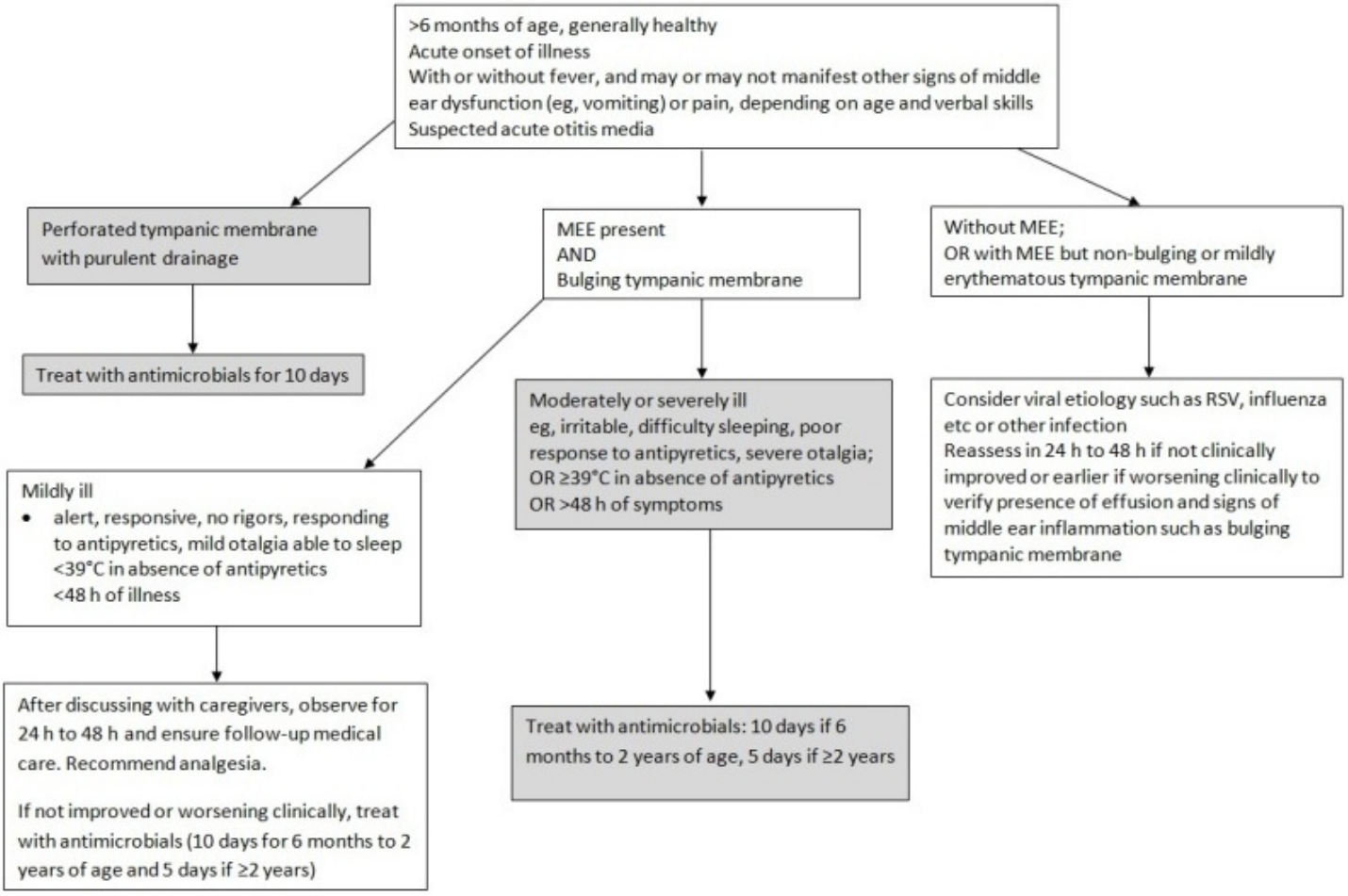

Figure 1) Flow diagram for the management of children with suspected and confirmed acute otitis media. MEE Middle ear effusion; RSV Respiratory syncytial virus

Management in the setting of diagnostic uncertainty

In reality, the clinician often faces a dilemma with children in whom the TM cannot be properly assessed. For many reasons (eg, a less cooperative patient, a small ear canal, an inexperienced observer or inadequate equipment) clinicians may not be able to determine conclusively whether the TM is bulging. In these common situations, the differential diagnosis may still include viral illness affecting the upper respiratory tract with an associated OME, a systemic viral illness or an AOM that could resolve on its own. Using antimicrobials in these situations may not always be the most prudent course of action.

If the child is only mildly ill, does not appear to have severe otalgia, is still feeding reasonably well, has a temperature <39°C for <24 h and reliable caregivers, it is still reasonable to observe, and have child and caregiver return for follow-up the next day. The focus of reassessment is the evolution of the TM or the development of other symptoms or signs. As in the 'watchful waiting' scenario for a confirmed AOM, explanations regarding the management plan should be discussed with caregivers so decision-making can be shared. Again, it is vital to provide appropriate advice about analgesics.

Both choice and dose of antimicrobial are important

While there are less available data regarding the antimicrobial susceptibility of bacteria causing AOM, the penicillin susceptibility rate of *S pneumoniae*, which causes invasive disease, is >90% in most jurisdictions in Canada.[37]-[39] Because *S pneumoniae* is the predominant pathogen in AOM and because it also covers GAS, empirical amoxicillin remains the drug of first choice. *M catarrhalis* and some strains of *H influenzae* are more likely to be amoxicillin-resistant (ie, are more likely to produce beta-lactamases) but they are less common pathogens, and AOM caused by either bacteria is more likely to resolve spontaneously.

Amoxicillin has excellent middle ear penetration (so may still be effective despite in vitro resistance), is inexpensive, well tolerated and has a relatively narrow antimicrobial spectrum. It has a short half-life of approximately 1 h. Given in an adequate oral dose, amoxicillin is more likely than other oral antimicrobials to be effective against penicillin-susceptible – and some penicillin-resistant – *S pneumoniae*, beta-lactamase-negative *H influenzae* and GAS. For clinical cure of AOM, the levels of amoxicillin in the middle ear should be adequate for over 50% of the day. Administering 45 mg/kg/day to 60 mg/kg/day of amoxicillin in three divided doses will achieve adequate middle ear levels, whereas a twice per day dosing regimen requires higher total daily doses of 75 mg/kg/day to 90 mg/kg/day to maintain adequate levels for a comparable percentage of the day (Table 1).[40]

There are certain clinical situations in which other antimicrobials should be considered as first-line. In the setting of AOM with purulent conjunctivitis (otitis-conjunctivitis syndrome), *H influenzae* and *M catarrhalis* are common pathogens and, therefore, treatment with a beta-lactamase inhibitor-amoxicillin combination (eg, amoxicillin-clavulanate) or a second-generation cephalosporin (eg, cefuroxime-axetil) is preferred.[41] Bacterial cultures of purulent conjunctival discharge should be performed when the infection is slow to resolve. It may also be prudent to use amoxicillin-clavulanate if the child has had a recent treatment with amoxicillin – within the previous 30 days – or infection that suggests a relapse of a recent infection or nonresponse to amoxicillin.

If the child has a history of a hypersensitivity reaction to amoxicillin or penicillin, using the second-generation cephalosporins (cefprozil or cefuroxime-axetil) or a third-generation cephalosporin is acceptable, unless the previous reaction was life-threatening (ie, associated with angioedema, bronchospasm or hypotension).[42] Alternatively, using a macrolide/azalide (clarithromycin or azithromycin) or clindamycin is an option; however, these antibiotics generally have inferior bacterial killing capabilities, especially for *S pneumoniae* and *H influenzae*, compared with the beta-lactams (eg, penicillins or cephalosporins). Only rarely are other medications indicated, such as doxycycline in children ≥8 years of age or quinolones; however, such alternatives should only be considered in consultation with an infectious disease physician.

Symptoms should improve within 24 h and resolve within two to three days of starting antimicrobials. If symptoms persist or worsen, the patient should be evaluated again to assess for either complications or persistent AOM. If the AOM persists despite amoxicillin given in recommended doses with good compliance, *H influenzae* and *M catarrhalis* may be causing the AOM. In this setting, treatment should be changed to amoxicillin-clavulanate, reserving intravenous or intramuscular ceftriaxone for cases where oral drugs are not tolerated or amoxicillin-clavulanate failed (Table 1). In this latter uncommon situation, ceftriaxone should be administered for a period of three days because the drug's half-life is longer (approximately 12 h to 24 h), and sampling the middle ear fluid should also be considered.

Middle ear effusions may persist for months, despite clinical and bacteriological resolution. The presence of MEE does not necessitate a change in antimicrobials.

Appropriate duration of antimicrobial therapy for AOM

Five days of antimicrobial treatment with oral amoxicillin has been shown to be at least as effective as 10 days of therapy in most children ≥2 years of age with uncomplicated disease.[43]-[45] Ten days of oral antimicrobial treatment courses are appropriate for children <2 years of age, for children with recurrent AOM or otitis media associated with a perforated TM, and for cases where initial therapy failed.

TABLE 1

Antimicrobial agents for acute otitis media (AOM)

First-line treatment (no penicillin allergy):

- Amoxicillin – 75 mg/kg/day–90 mg/kg/day divided twice per day as capsules or suspension; **OR**
- Amoxicillin – 45 mg/kg/day–60 mg/kg/day divided three times per day as capsules or suspension

First-line treatment if penicillin-allergic (nonlife-threatening reaction):

- Cefuroxime-axetil – 30 mg/kg/day divided twice or three times per day as tablets or suspension
- Ceftriaxone – 50 mg/kg intramuscularly (or intravenously) daily for three days

If initial therapy fails (ie, no symptomatic improvement after two to three days):

- Amoxicillin-clavulanate

In Canada, the preferred suspension is the 7:1 formulation* because it has the most amoxicillin combined with the least amount of clavulanate. Each 5 mL of suspension contains 400 mg of amoxicillin and 57 mg of clavulanate. Therefore, a patient treated with 60 mg/kg/day would receive approximately 8.5 mg/kg/day of clavulanate. This dosage amount does not exceed the 10 mg/kg/day dose of clavulanate linked with higher risk for diarrhea.

- For a child weighing ≤35 kg, 45 mg/kg/day–60 mg/kg/day divided three times a day for 10 days. Specify 400 mg/5 mL suspension of 7:1 formulation.
- For a child weighing >35 kg, 500 mg tablets orally three times a day for 10 days.

If a patient is unable to tolerate oral antimicrobials or if treatment with amoxicillin-clavulanate fails, a course of ceftriaxone – 50 mg/kg/day intramuscularly (or intravenously) once per day for three days – could be considered. Alternatively, referral to an otolaryngologist for tympanocentesis may be considered to determine the etiological agent and guide therapy.

**A 14:1 amoxicillin-clavulanate formulation is not available in Canada*

Recommendations

- To diagnose AOM, there must be acute onset of symptoms such as otalgia (or nonspecific symptoms in nonverbal children), signs of a middle ear effusion associated with inflammation of the middle ear (ie, a TM that is bulging and, usually, very erythematous or hemorrhagic, and yellow or cloudy in colour) or a TM that has ruptured.
- For otherwise healthy children ≥6 months of age who have mild illness with appropriately diagnosed AOM criteria or children who do not fully meet diagnostic criteria, a watchful waiting approach for 48 h is an option if follow-up can be assured. Advice regarding analgesics must be provided. It is recommended to:
    - reassess the child within 24 h to 48 h to document the clinical course; **OR**
    - have the caregiver return if the child does not improve or worsens anytime within 48 h; **OR**
    - provide an antimicrobial prescription to be filled if the child does not improve.

- Children with a bulging TM who are febrile (≥39°C) and moderately to severely systemically ill, or who have severe otalgia, or who have already been significantly ill for 48 h should be treated with antimicrobials.
- If a decision is made to treat with antimicrobials, amoxicillin either divided twice per day at a dose of 75 mg/kg/day to 90 mg/kg/day **or** amoxicillin divided three times per day at a dose of 45 mg/kg/day to 60 mg/kg/day are the first choices for AOM therapy.

A five-day course of an appropriately dosed antimicrobial is recommended for most children ≥2 years of age with uncomplicated AOM, with a 10-day course being reserved for younger children (six to 23 months) and cases with a perforated TM or recurrent AOM.

Acknowledgements

This position statement has been reviewed by the Community Paediatrics Committee of the Canadian Paediatric Society.

CPS INFECTIOUS DISEASES AND IMMUNIZATION COMMITTEE
Members: Natalie A Bridger MD; Shalini Desai MD; Ruth Grimes MD (Board Representative); Charles PS Hui MD (past member); Timothy Mailman MD; Joan L Robinson MD (Chair); Marina Salvadori MD (past member); Otto G Vanderkooi MD
Liaisons: Upton D Allen MBBS, Canadian Pediatric AIDS Research Group; Tobey Audcent MD, Committee to Advise on Tropical Medicine and Travel (CATMAT), Public Health Agency of Canada; Carrie Byington MD, Committee on Infectious Diseases, American Academy of Pediatrics; Rhonda Kropp BScN MPH, Public Health Agency of Canada; Nicole Le Saux MD, Immunization Monitoring Program, ACTive (IMPACT); Dorothy L Moore MD, National Advisory Committee on Immunization (NACI); Patricia Mousmanis MD, College of Family Physicians of Canada
Consultant: Noni E MacDonald MD
Principal authors: Nicole Le Saux MD, Joan L Robinson MD

References

1. Forgie S, Zhanel G, Robinson J; CPS Infectious Diseases and Immunization Committee. Management of acute otitis media – a summary. Paediatr Child Health 2009;14(7):457-64.
2. Vergison A, Dagan R, Arguedas A, et al. Otitis media and its consequences: Beyond the earache. Lancet Infect Dis 2010;10(3):195-203.
3. Coticchia JM, Chen M, Sachdeva L, Mutchnick S. New paradigms in the pathogenesis of otitis media in children. Front Pediatr 2013;1:52.
4. Marom T, Nokso-Koivisto J, Chonmaitree T. Viral-bacterial interactions in acute otitis media. Curr Allergy Asthma Rep 2012;12(6):551-8.
5. Macintyre EA, Karr CJ, Koehoorn M, et al. Otitis media incidence and risk factors in a population-based birth cohort. Paediatr Child Health 2010;15(7):437-42.
6. Moore HC, Jacoby P, Taylor A, et al. The interaction between respiratory viruses and pathogenic bacteria in the upper respiratory tract of asymptomatic Aboriginal and non-Aboriginal children. Pediatr Infect Dis J 2010;29(6):540-5.
7. Marchisio P, Nazzari E, Torretta S, Esposito S, Principi N. Medical prevention of recurrent acute otitis media: An updated overview. Expert Rev Anti Infect Ther 2014;12(5):611-20.
8. Bakaletz LO. Bacterial biofilms in the upper airway – Evidence for role in pathology and implications for treatment of otitis media. Paediatr Respir Rev 2012;13(3):154-9.
9. Verhoeven D, Pichichero ME. Divergent mucosal and systemic responses in children in response to acute otitis media. Clin Exp Immunol 2014;178(1):94-101.

10. Palmu AA, Herva E, Savolainen H, Karma P, Mäkelä PH, Kilpi TM. Association of clinical signs and symptoms with bacterial findings in acute otitis media. Clin Infect Dis 2004;38(2):234-42.
11. Kalu SU, Ataya RS, McCormick DP, Patel JA, Revai K, Chonmaitree T. Clinical spectrum of acute otitis media complicating upper respiratory tract viral infection. Pediatr Infect Dis J 2011;30(2):95-9.
12. Pettigrew MM, Gent JF, Pyles RB, Miller AL, Nokso-Koivisto J, Chonmaitree T. Viral-bacterial interactions and risk of acute otitis media complicating upper respiratory tract infection. J Clin Microbiol 2011;49(11):3750-5.
13. Casey JR, Adlowitz DG, Pichichero ME. New patterns in the otopathogens causing acute otitis media six to eight years after introduction of pneumococcal conjugate vaccine. Pediatr Infect Dis J 2010;29(4):304-9.
14. Cohen R, Levy C, Bingen E, Koskas M, Nave I, Varon E. Impact of 13-valent pneumococcal conjugate vaccine on pneumococcal nasopharyngeal carriage in children with acute otitis media. Pediatr Infect Dis J 2012;31(3):297-301.
15. Taylor S, Marchisio P, Vergison A, Harriague J, Hausdorff WP, Haggard M. Impact of pneumococcal conjugate vaccination on otitis media: A systematic review. Clin Infect Dis 2012;54(12):1765-73.
16. De Wals PD, Carbon M, Sévin E, Deceuninck G, Ouakki M. Reduced physician claims for otitis media after implementation of pneumococcal conjugate vaccine program in the province of Quebec, Canada. Pediatr Infect Dis J 2009;28(9):e271-5.
17. Tamir S, Roth Y, Dalal I, Goldfarb A, Grotto I, Marom T. Changing trends of acute otitis media bacteriology in Israel in the pneumococcal conjugate vaccine era. Pediatr Infect Dis J 2014;34:1959.
18. Ben-Shimol S, Givon-Lavi N, Leibovitz E, Raiz S, Greenberg D, Dagan R. Near-elimination of otitis media caused by 13-valent pneumococcal conjugate vaccine (PCV) serotypes in southern Israel shortly after sequential introduction of 7-valent/13-valent PCV. Clin Infect Dis 2014;59(12):1724-32.
19. Le Saux N, Gaboury I, Baird M, et al. A randomized, double-blind, placebo-controlled noninferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age. CMAJ 2005;172(3):335-41.
20. Dagan R, Schneider S, Givon-Lavi N, et al. Failure to achieve early bacterial eradication increases clinical failure rate in acute otitis media in young children. Pediatr Infect Dis J 2008;27(3):200-6.
21. Hoberman A, Paradise JL, Rockette HE, et al. Treatment of acute otitis media in children under 2 years of age. N Engl J Med 2011;364(2):105-15.
22. Tähtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A. A placebo-controlled trial of antimicrobial treatment for acute otitis media. N Engl J Med 2011;364(2):116-26.
23. Shaikh N, Hoberman A, Paradise JL, et al. Development and preliminary evaluation of a parent-reported outcome instrument for clinical trials in acute otitis media. Pediatr Infect Dis J 2009;28(1):5-8.
24. Laine MK, Tähtinen PA, Ruuskanen O, Huovinen P, Ruohola A. Symptoms or symptom-based scores cannot predict acute otitis media at otitis-prone age. Pediatrics 2010;125(5):e1154-61.
25. Onusko E. Tympanometry. Am Fam Physician 2004;70(9):1713-20.
26. Takata GS, Chan LS, Morphew T, Mangione-Smith R, Morton SC, Shekelle P. Evidence assessment of the accuracy of methods of diagnosing middle ear effusion in children with otitis media with effusion. Pediatrics 2003;112(6 Pt 1):1379-87.
27. Chonmaitree T, Alvarez-Fernandez P, Jennings K, et al. Symptomatic and asymptomatic respiratory viral infections in the first year of life: Association with acute otitis media development. Clin Infect Dis 2015;60(1):1-9.
28. McCormick DP, Chonmaitree T, Pittman C, et al. Nonsevere acute otitis media: A clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. Pediatrics 2005;115(6):1455-65.
29. Karma PH, Penttilä MA, Sipilä MM, Kataja MJ. Otoscopic diagnosis of middle ear effusion in acute and non-acute otitis media. I. The value of different otoscopic findings. Int J Pediatr Otorhinolaryngol 1989;17(1):37-49.

30. McCormick DP, Lim-Melia E, Saeed K, Baldwin CD, Chonmaitree T. Otitis media: Can clinical findings predict bacterial or viral etiology? Pediatr Infect Dis J 2000;19(3):256-8.
31. Friedman NR, McCormick DP, Pittman C, et al. Development of a practical tool for assessing the severity of acute otitis media. Pediatr Infect Dis J 2006;25(2):101-7.
32. Shaikh N, Hoberman A, Rockette HE, Kurs-Lasky M. Development of an algorithm for the diagnosis of otitis media. Acad Pediatr 12(3):214-8.
33. Leibovitz E, Serebro M, Givon-Lavi N, et al. Epidemiologic and microbiologic characteristics of culture-positive spontaneous otorrhea in children with acute otitis media. Pediatr Infect Dis J 2009;28(5):381-4.
34. Shaikh N, Hoberman A, Kaleida PH, Ploof DL, Paradise JL. Videos in clinical medicine. Diagnosing otitis media – Otoscopy and cerumen removal. N Engl J Med 2010:362(20):e62.
35. Mattos JL, Colman KL, Casselbrant ML, Chi DH. Intratemporal and intracranial complications of acute otitis media in a pediatric population. Int J Pediatr Otorhinolaryngol 2014;78(12):2161-4.
36. Hoberman A, Ruohola A, Shaikh N, Tähtinen PA, Paradise JL. Acute otitis media in children younger than 2 years. JAMA Pediatr 2013;167(12):1171-2.
37. Powis J, McGeer A, Green K, et al. In vitro antimicrobial susceptibilities of Streptococcus pneumoniae clinical isolates obtained in Canada in 2002. Antimicrob Agents Chemother 2004;48(9):3305-11.
38. Leal J, Vanderkooi OG, Church DL, MacDonald J, Tyrrell GJ, Kellner JD. Eradication of invasive pneumococcal disease due to the seven-valent pneumococcal conjugate vaccine serotypes in Calgary, Alberta. Pediatr Infect Dis J 2012;31(9):e169-75.
39. Vanderkooi OG, McConnell A, Church DL, Kellner JD. Antimicrobial susceptibility of invasive and lower respiratory tract isolates of Streptococcus pneumoniae, 1998 to 2007. Can J Infect Dis Med Microbiol 2009;20(4):e139-44.
40. Piglansky L, Leibovitz E, Raiz S, et al. Bacteriologic and clinical efficacy of high dose amoxicillin for therapy of acute otitis media in children. Pediatr Infect Dis J 2003;22(5):405-13.
41. Block SL, Hedrick J, Tyler R, et al. Increasing bacterial resistance in pediatric acute conjunctivitis (1997-1998). Antimicrob Agents Chemother 2000;44(6):1650-4.
42. Lagacé-Wiens P, Rubinstein E. Adverse reactions to ß-lactam antimicrobials. Expert Opin Drug Saf 2012;11(3):381-99.
43. Cohen R, Ovetchkine P, Géhanno P. Current approaches to otitis media. Curr Opin Infect Dis 2001;14(3):337-42.
44. Pichichero ME, Marsocci SM, Murphy ML, Hoeger W, Francis AB, Green JL. A prospective observational study of 5-, 7-, and 10-day antibiotic treatment for acute otitis media. Otolaryngol Head Neck Surg 2001;124(4):381-7.
45. Kozyrskyj A, Klassen TP, Moffatt M, Harvey K. Short-course antibiotics for acute otitis media. Cochrane Database Syst Rev 2010;9:CD001095.

Last updated: **Dec 12 2017**