Clinical Practice Guideline for Diagnosis and Management of Acute Otitis Media (AOM) in Children in Japan

Subcommittee of Clinical Practice Guideline for Diagnosis and Management of Acute Otitis Media in Children
(Japan Otological Society, Japan Society for Pediatric Otorhinolaryngology, Japan Society for Infectious Diseases in Otolaryngology)

January 27, 2015

1. Summary
Objective: To 1) indicate methods of diagnosis and testing for childhood (<15 years) acute otitis media (AOM); and 2) recommend methods of treatment in accordance with the evidence-based consensus reached by the Subcommittee of Clinical Practice Guideline for Diagnosis and Management of AOM in Children (Subcommittee of Clinical Practice Guideline), in light of the causative bacteria and their drug sensitivity of AOM in Japan. Methods: We investigated the most recently detected bacteria causing childhood AOM in Japan as well as antibacterial sensitivity and the worldwide progress of vaccination, produced Clinical Questions concerning the diagnosis, testing methods, and treatment of AOM, searched literature published during 2000–2004, and issued the 2006 Guidelines. In the 2009 and 2013 Guidelines we performed the same investigation with the addition of literature, which were not included in the 2006 Guidelines and published during 2005–2008 and during 2009–2012, respectively. Results: We categorized AOM as mild, moderate, or severe on the basis of tympanic membrane findings and clinical symptoms, and presented recommended treatment for each degree of severity. Conclusion: Accurate assessment of tympanic membrane findings is important for judging the degree of severity and selecting a method of treatment. Some of the new antimicrobial agents and pneumococcal vaccination are recommended as new treatment options.

2. Authors
The membership of the Subcommittee of Clinical Practice Guideline for Diagnosis and Management of AOM in Children is shown in Table 1. This committee is composed of three organizations: the Japan Otological Society (JOS), the Japan Society for Infectious Diseases in Otolaryngology (JSIDO), and the Japan Society for Pediatric Otorhinolaryngology (JSPO). The first committee meeting was held on January 8, 2003, and the 2006 Guidelines were published in March that year on the web site of the JSIDO, in the journals of the JOS and the JSPO, on the web site of the Japan Council for Quality Healthcare, and in printed form (Otol Jpn 2006; Pediatr Otorhinolaryngol Jpn 2006; and Japan Council for Quality Healthcare, Kanehara Shuppan, 2006). The 2006 Guidelines underwent evaluation, and work on the production of a revised edition began at the 13th committee meeting on January 7, 2007. The 2009 Guidelines were published in January, 2009 by Kanehara Shuppan Co., and they first appeared on the website of the Medical Information Network Distribution Service (MINDS) on October 19, 2010. The production of the revised edition (i.e., the 2013 edition) started in May 2010 (Table 1).

Table 1. The Members of the Subcommittee of Clinical Practice Guideline

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References

3. The Japan Council for Quality Healthcare - Minds (http://minds.jcqhc.or.jp/).

3. Financial Backers and Sponsors

Production of these Guidelines was funded by JOS operating expenses. The JOS does not receive support from any specific organizations or companies. A list of organizations and companies that posed non-personal financial conflicts of interest to members of the Subcommittee of Clinical Practice Guideline during the production of these Guidelines is provided (attachment).

Attachment. List of pharmaceutical companies those posed non-personal financial conflicts of interest to members of the Subcommittee of Clinical Practice Guideline (alphabetical)

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4. Introduction

AOM is a typical upper respiratory inflammation commonly affecting children and is mainly treated by otolaryngologists. Its exact frequency of occurrence in Japan is unknown, however. According to reports from Europe and the USA, 62% of children aged less than one year and 83% of those up to the age of three suffer from at least one bout of AOM (Teele et al. 1989). Faden et al (1998) have reported that it affects 75% of children up to the age of one.

Some authors in Europe and the USA do not recommend the use of antimicrobial agents for AOM. In the Netherlands, it has been proposed that antimicrobial agents are unnecessary in at least 90% of cases, and that patients should be observed for 3-4 days without antimicrobial agent administration (van Buchem et al. 1985, Damoiseaux et al. 2000). Rosenfeld et al. have also reported observation as management option (Rosenfeld et al. 2003a, b, c), and more recent studies have also found no significant difference in clinical outcome if antimicrobial agents are not given immediately but are prescribed if there is no improvement in symptoms after 48 or 72 hours (Spiro et al. 2006, Little et al. 2006). A Cochrane Review, which examined randomized controlled trials of antimicrobial agent administration versus placebo also found that antimicrobial agents had little effect on childhood AOM (Glaziou et al. 2004). In addition, a double-blind randomized controlled trial of amoxicillin (AMPC) and a placebo found no significant difference in therapeutic efficacy between the two (Le Saux et al. 2005, McCormick et al. 2005). Dagan et al. (2000, 2001) and Toltzis et al. 2005), in a review and case-control study, advised that antimicrobial agent use would be reduced because the use of a wide variety of drugs increases the survival of resistant Streptococcus pneumonia (S. pneumonia) in the epipharynx, which can cause additional infections in middle-ear (ME) fluid.

In Japan, regular nationwide surveys are performed of the causative bacteria for AOM, acute sinusitis, acute tonsillitis, and peritonsillar abscess. These surveys have reported that antimicrobial agent -resistant bacteria are now being detected more frequently (Suzuki et al. 2000, Nishimura et al. 2004), which means that recommendations for no administration of antimicrobial agents proposed in Europe
and the USA is not applied. In addition, the criteria and assessment levels used in conventional clinical assessment are not necessarily uniform even within Europe and the USA (Chan et al. 2001). Investigation and unified evaluation of the diagnosis and treatment of childhood AOM are therefore required, based on the actual situation in Japan. Based on this perspective, the JOS, the JSIDO, and the JSPO produced 2006 Clinical Practice Guidelines consistent with evidence-based medicine (EBM) with the aim of supporting the diagnosis and treatment of childhood AOM (Nakayama, 2004).

A survey of otolaryngologists and pediatricians in Ishikawa Prefecture showed that 85% of otolaryngologists and 52% of pediatricians were aware of the 2006 edition of the Guidelines, with 56% of those otolaryngologists and 49% of those pediatricians reporting that they used them in practice (Ito et al. 2008). Therapeutic outcomes of clinical practice that adhered to the guidelines were also generally good (Hayashi et al. 2007, Sugawara et al. 2008). In light of these results, JOS, JSIDO, and JSPO decided to revise the 2006 Guidelines and issue a new edition in 2009.

Thereafter, AOM guidelines from Canada (Forgie et al. 2009) and Italy (Marchisio et al. 2010) were published. In Italy’s guidelines, it is noteworthy that, as in Japan’s guidelines, the identification and description of detailed tympanic membrane findings are highlighted, and one of the options for a pediatrician when s/he cannot identify or describe the tympanic membrane findings is to transfer the patient to an otolaryngologist who can examine the tympanic membrane precisely by microscopy and/or endoscopy. That principle seems to agree well with our Guidelines, which propose the management of AOM based on the detailed observations of tympanic membrane findings. In the 2013 AOM Guidelines published by the U.S. as a revision of their 2004 Guidelines, the necessity of detailed observation of the tympanic membrane findings was emphasized (Lieberthal et al. 2013).

In our present 2013 Guidelines, the changes of pathogens and their drug sensitivity and the grading system of AOM including signs and symptoms determining the grade were revised. Descriptions were expanded based on new data obtained by rapid tests for the detection of pneumococcal antigen, vaccinations for Streptococcus pneumoniae, new antibiotics, Japanese herbal medicine, and more. Although no remarkable change has been made to the other parts of the 2009 guidelines, items described in the 2006 and 2009 guidelines were included in the 2013 Guidelines.

These Clinical Practice Guidelines are issued only to assist clinical practice,
and have no binding authority on treatment (Note 1). How they should actually be used for patients in the clinical setting is a matter to be decided in light of the patient’s wishes and values, and based on the medical practitioner’s specialist knowledge and experience. The fact that there is no high level of evidence demonstrating a treatment method’s efficacy does not directly mean that it is ineffective or that it should not be carried out. When using such methods of treatment, however, an extra degree of consideration is required concerning evaluations of its clinical efficacy and communication with the patient. It must be re-emphasized that recommendations in clinical practice guidelines are not legal grounds for the content of medical treatment that should be practiced in individual clinical situations (Hurwitz 1999). These Guidelines will be periodically revised to reflect the opinions of users and patients and as a result of external evaluation, in the same way as the 2006 and 2009 Guidelines were revised after their publication.

Note 1: Guidelines are ranked as follows:
Regulations > directives > recommendations ≥ guidelines  (From A Dictionary of Epidemiology, trans. Japan Epidemiological Association ed. J. Last, (with additions)

References
7. Rosenfeld RM. Kay D. Natural history of untreated otitis media. Laryngoscope 2003(c); 113:1645-57.


5. **Objective and Aim of Production**

These Guidelines were produced to describe diagnostic and testing methods for childhood AOM (below the age of 15* [see note]), and represent the evidence-based consensus of the members of the Subcommittee of Clinical Practice Guideline on recommended treatment methods in light of the causative bacteria and their antimicrobial agents sensitivity in cases of AOM in Japan. The aim is for these Guidelines to be used to assist clinical decision-making in the care of childhood AOM, and for them to prove beneficial in the diagnosis and treatment of patients with AOM.
*Note: In the Ministry of Health, Labor and Welfare’s Pharmaceutical Affairs Bureau Notification No. 1334, *Guidance Concerning Clinical Trials of Drugs in Pediatric Populations*, released on December 15, 2000, the following have been proposed as age categories for the design of clinical trials of drugs on pediatric patients: preterm neonates, full-term neonates (0–27 days), infants (28 days to 23 months), children (2–11 years), and adolescents (12–16 or 12–18 years). In these Guidelines, we have used the general criterion for children of <15 years.

**References**


**6. Users**

The main users of these Guidelines will be otolaryngologists who perform otological procedures including the accurate evaluation of tympanic membrane findings and myringotomy.

**7. Subjects**

The subjects of these Guidelines are AOM patients aged <15 years who were free from AOM or otitis media with effusion (OME) within one month prior to onset, who do not have a ventilation tube inserted, have no cranial or facial deformity, and do not suffer from immunodeficiency. Patients with the following conditions are excluded as subjects: AOM with complications including facial palsy and inner ear disorder, elevated pinna with acute mastoiditis, and AOM with Gradenigo’s syndrome or similar findings. It can be difficult to distinguish between AOM and bullous myringitis, but the latter is not covered by these Guidelines.

The consensus reached by the Subcommittee of Clinical Practice Guideline on recurrent otitis media (ROM) (with a proposed definition explained below) has been included as an additional statement.

Treatment algorithms are included at the end of the Guidelines, in which cases that have not improved after tertiary treatment according to each treatment algorithm are classed as intractable. The care of intractable cases is not covered in
these Guidelines.

**[Addendum]** Proposals for the management of ROM

(a) Definition of ROM

The definition of ROM has yet to be standardized either in Japan or internationally, but in these Guidelines it has been defined as three or more occurrences of AOM within the previous six months, or four or more within the previous 12 months, as generally used in comparatively recent studies (Sher et al. 2005, Ables et al. 2004, Arrieta et al. 2004)

(b) Pathophysiology of and risk factors for ROM

The pathophysiology of ROM can be categorized into two types: recurrent simple AOM, and recurrent AOM occurring as an acute exacerbation in patients suffering from OME.

Proposed risk factors for ROM include young age, resistant causative bacteria, immunity of the affected individual, and lifestyle and environmental factors. Genetic make-up has also been reported as a risk factor in young children aged <2 years (Wiertsema et al. 2006). In terms of causative bacteria, multidrug-resistant pneumococci are reportedly responsible in many cases (van Kempen et al. 2004), with incomplete elimination from the nasopharynx owing to reduced antimicrobial agent efficacy regarded as one cause of recurrence. The involvement of decreased immune response by the host to the causative bacteria is also important (Yamanaka et al. 2008). A link between immunity received from the mother via breast milk and the onset of ROM has also been conjectured, with the absence of breastfeeding constituting a strong risk factor for ROM (Lubianca Neto et al. 2006). Lifestyle and environmental risk factors include having siblings, attending daycare, and pacifier use (Lubianca Neto et al. 2006).

Regarding other risk factors for ROM, the involvement of gastroesophageal reflux (GERD) has been reported based on the results of monitoring. Lelepic et al. (2000) presented results obtained by continual 24-h esophageal pH monitoring of GERD, and other reports provided data concerning the amount of pepsin/pepsinogen protein content of MEE (Taker et al. 2002, Rozmanic et al. 2002). It was reported that two randomized trials found no benefit of antireflux treatment with proton pump inhibitors (Miura et al. 2011).
(c) Treatment of ROM

With the factors described above assumed to constitute risk factors for ROM, bacterial sensitivity tests must always be carried out prior to antimicrobial agent administration to counteract resistant causative bacteria, and an appropriate dose of antimicrobial agents must be selected. Recommended antimicrobial agents are listed in these Guidelines.

Pneumococcal conjugate vaccine is used in Europe and the USA to prevent ROM. In a double-blind randomized controlled trial of a 7-valent pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine in Holland, there was no significant reduction in the frequency of occurrence of ROM (Brouwer et al. 2005). Although a Cochrane Review accepts the utility of pneumococcal polysaccharide vaccine, it does not recommend the conjugate vaccine (Straetemans et al. 2004). In a double-blind randomized controlled trial in the Czech Republic, however, 11-valent pneumococcal capsular polysaccharide vaccine conjugated to protein D had a significant protective effect against AOM caused by pneumococci or influenza viruses (Prymula et al. 2006). In Japan, 7-valent pneumococcal conjugate vaccine was approved for use in 2010. This vaccine covers 60.6% of pneumococcal serotypes isolated from the middle ears of childhood AOM patients in Japan and 87% of antimicrobial agent-resistant bacteria, and is anticipated to provide up to about 17% protection against all forms of AOM.

One form of treatment unique to Japan that has been proposed is the use of Chinese herbal medicines for their protective effect in boosting immunity, and Juzen-taiho-to has been reported as effective (Maruyama et al. 2008, Yoshizaki et al. 2012). Adenoidectomy has not been shown to reduce the frequency of ROM as a surgical treatment in double-blind randomized controlled trials, nor is it regarded as having any preventive effect (Oomen et al. 2005, Hammaren-Malmi et al. 2005, Koivunen et al. 2004). Myringotomy has not been shown to have any significant effect in reducing the frequency of occurrence of ROM in research on patients in Japan (Nomura et al. 2005), but insertion of a ventilation tube for one year and short-term insertion for one month significantly reduce the frequency of occurrence (Uno 2007a, b). As measures to deal with lifestyle and environmental factors, group daycare should be discontinued and breastfeeding is desirable.
Proposals for the management of refractory otitis media (OM) and prolonged OM

Among patients with AOM diagnosed as having a moderate or severe degree of AOM at the first visit, some show no improvement or even worsening in the symptoms or tympanic membrane findings after treatments based on the Guidelines; for example, otorrhea continues or the bulging tympanic membrane recurs after the closure of a myringotomy.

However, the tympanic membrane in some patients with a special condition called semi-hot ear (Sade 1979) shows findings similar to AOM without significant symptoms of AOM. Due to the lack of symptoms of AOM, we clinicians sometimes encounter such cases.

Cases showing no improvement in the signs even after a third-line treatment from the Guidelines should be regarded as refractory OM, and it is necessary to consider the pathophysiology and background of such cases. We herewith propose a definition of refractory OM, and we describe its background and pathophysiology.

1) Definition of refractory OM in the treatment of AOM

The definition of refractory OM has not yet been standardized in Japan or internationally. In the field of infectious disease medicine, a condition tends to be regarded as refractory when it does not improve despite continuous treatment. According to this concept, refractory OM may be defined as incurable OM resistant to treatments based on the Guidelines, including no improvement of tympanic membrane findings and/or the symptoms persist or even become worse.

Refractory OM can thus be defined as a state in which symptoms and/or findings of tympanic membrane persist or become worse despite treatments for infection.

2) Background and pathophysiology of refractory OM

When severe tympanic membrane findings continue despite treatment including a sufficient amount of antibiotics and drainage by myringotomy, it is necessary to recheck aspects of the affected individual’s condition such as immunity, neutrophil dysfunction, vulnerability to infection, GERD (Velepic et al. 2000, Tasker
et al. 2002, Rozmanic et al. 2002, Miura et al. 2012) and causative bacteria, and to reconsider administering more intensive treatments including intravenous antimicrobial agents and the insertion of a tympanostomy tube.

3) Definition of prolonged OM in the treatment of AOM
The definition of prolonged OM includes acute onset, abnormal findings of tympanic membrane similar to AOM persisting for more than 3 weeks, and no appearance of signs of acute symptoms such as otalgia and fever. This state is called semi-hot ear (Sade 1979) or the state of subacute phase, as reported in the report of a research conference on recent advances in OME (Senturia et al. 1980).

4) Definitions and classifications of terms associated with AOM
The definitions and classifications of terms associated with AOM at this stage are as follows.

- ROM: The state in which AOM occurs more than three times within the last 6 months, or more than four times within the last 12 months (Sher et al. 2005, Ables et al. 2004, Arrieta et al. 2004, Clinical Practice Guideline for the Diagnosis and Management of AOM in Children 2009 in Japan).
- Refractory OM: The state in which symptoms and/or findings of the tympanic membrane persist or even become worse despite continuing infection treatment.
- Prolonged OM: The state in which abnormal findings of the tympanic membrane similar to AOM persist for more than 3 weeks without the appearance of acute symptoms such as otalgia and fever.

The definitions of relapse and recurrence are as follows.

- Relapse: The tympanic membrane findings become worse and symptoms of AOM reappear after the findings and symptoms improved.
- Recurrence: AOM occurs within 3 weeks after the tympanic membrane findings became normalized.

References
8. Definition of AOM

In this clinical practice guideline, AOM is defined as “an acute occurrence of middle ear infection that may be associated with otalgia, fever, or otorrhea.” The following notes are further added.

Notes:

(i) Acute occurrence is defined as a case in which a person complains of an acute symptom or such is observed by his/her parent/guardian, and the person is seen in a clinic within 48 hours (Harabuchi et al. 2001). The duration of acute inflammation is commonly defined as not longer than three weeks, though no clear evidence serves as the basis for this definition. This guideline also adopts these common definitions (Senturia et al. 1980). It should be noted that acute aggravation of chronic OM is excluded from these definitions because its pathological condition differs.

(ii) The clinical practice guideline for diagnosis and management of AOM reported by the American Academy of Pediatrics (Subcommittee on Management of Acute Otitis Media 2004) provides that a diagnosis of AOM requires the following signs and symptoms:

(1) Recent, usually abrupt, onset of signs and symptoms of middle-ear inflammation and MEE;

(2) The presence of MEE, indicated by any bulging of the tympanic membrane, limited or absent mobility of the tympanic membrane, air-fluid level behind the tympanic membrane, and otorrhea; and

(3) Signs or symptoms of middle-ear inflammation as indicated by either distinct erythema of the tympanic membrane or distinct otalgia.

In the AOM Clinical Practice Guidelines issued by the U.S. in 2004, the following three items were required for the diagnosis of AOM: acute onset
of symptoms, presence of ME effusion, and the presence of signs manifesting the acute inflammation of the ME. As stated in Clinical Question 19-1, the 2013 U.S. AOM Guidelines recommended the following three features for the definition of AOM (Lieberthal et al. 2013).

(1) The presence of moderate to severe bulging of the tympanic membrane or new onset of otorrhea not due to acute otitis externa.

(2) The presence of mild bulging of the tympanic membrane and an acute (within 48 hours) onset of otalgia (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the tympanic membrane.

(3) Excluding patients who do not have MEE (based on pneumatic otoscopy and/or tympanometry).

References

9. Bacteria isolated from children with AOM in Japan and antibacterial activity
(1) Bacteria isolated from children with AOM

The report of the Fourth Nationwide Surveillance of Clinical Isolates from Patients with Otorhinolaryngological Infections in 2007 (conducted from January through June 2007, Suzuki et al. 2008) showed yearly changes in frequencies of
bacteria isolated from patients of all ages with AOM in the four previous surveillances conducted in 1994, 1998, 2003, 2007 and 2012 (Figure 1 and Table 2). *S. pneumoniae* tended to decrease from 34.1% of isolates in the surveillance of 2007 to 29.2% in 2012. *Haemophilus influenzae* (*H. influenzae*) tended to increase during the surveillance of 2003, and remained at approx. 25% until 2012. *Staphylococcus aureus* (*S. aureus*), which decreased to 4.4% in 2007, increased again to 14.4% in 2012. *Moraxella catarrhalis* (*M. catarrhalis*) was detected in 7.1% in 2003 and in 4.4% in 2007, but increased to 11.3% in 2012.

*H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, and *Streptococcus pyogenes* are thought to be significant as bacteria causing AOM. However, *S. aureus* appears to enter mainly from the external ear canal and is unlikely to be a causative bacterium. Reports from the U.S. and Europe also show that *H. influenzae*, *S. pneumoniae*, and *M. catarrhalis* are the three predominant causative bacteria. Turner et al. (2002) reported that *H. influenzae* had been detected in 34%, was *S. pneumoniae* in 46%, and *M. catarrhalis* in 2% of isolates from 109 infants who experienced 122 episodes of AOM within two months after birth. Commissio et al. (2000) also reported from Argentina that *S. pneumoniae* and *H. influenzae* had been detected in the majority of isolates (39.4% and 32.7%, respectively).

The cases reported in the 2007 Nationwide Surveillance of Clinical Isolates from Patients with Otorhinolaryngological Infections including adult patients were AOM (94 patients), acute sinusitis (95 patients), acute tonsillitis (91 patients), peritonsillar abscess (69 patients), chronic OM (95 patients), and chronic sinusitis (90 patients). Of 63 *H. influenzae* strains isolated from these patients, 26 strains (41.3%) were β-lactamase-non-producing ampicillin-susceptible *H. influenzae* (BLNAS), 33 strains (52.4%) were β-lactamase-non-producing ampicillin-resistant *H. influenzae* (BLNAR), and four strains (6.3%) were β-lactamase-producing ampicillin-resistant *H. influenzae* (BLPAR). BLNAR strains, which are significant as drug-resistant bacteria, were recovered from 52.4% of the patients, showing an increasing trend each year. Of the *S. pneumoniae* strains, 42 strains (53.8%) were penicillin-susceptible *S. pneumoniae* (PSSP), 26 strains (33.3%) were penicillin-intermediately resistant *S. pneumoniae* (PISP), and 10 strains (12.8%) were penicillin-resistant *S. pneumoniae* (PRSP). Drug-resistant bacteria, PISP and PRSP combined, accounted for approximately 50%, showing a decreasing trend from 60% in 2004.
According to the results of a nationwide surveillance of bacterial pathogens from patients with the six main diseases encountered in the otorhinolaryngological field conducted by the Surveillance Committee of the Japanese Society of Chemotherapy, the Japanese Association for Infectious Diseases, and the Japanese Society for Clinical Microbiology in 2012 (2012 Nationwide surveillance by 3 organizations, Suzuku et al, 2015 in press), the incidences of pathogens harvested from ears with AOM were nearly the same as those examined in 2007, but the proportion of *H. influenzae* was found to increase in children under the age of 15 (Fig. 1).

A multicenter clinical study was conducted in 701 patients in Japan from February 2005 to February 2008. Among isolates in nasopharyngeal swab specimens of 684 patients, *S. pneumoniae* was detected in 486 patients, *H. influenzae* in 427 patients, and *M. catarrhalis* in 333 patients. Among isolates in MEE of 592 patients, *S. pneumoniae* was detected in 183 patients, *H. influenzae* in 208 patients, and *M. catarrhalis* in 38 patients. Combined, among the 701 patients, *S. pneumoniae* was detected in 490 patients (69.9%), *H. influenzae* in 438 patients (62.4%), and *M. catarrhalis* in 340 patients (48.5%). Of the 183 *S. pneumoniae* strains detected in MEE, 65 strains (35.5%) were PSSP, 68 strains (37.2%) were PISP, and 50 strains (27.3%) were PRSP. Drug-resistant bacteria, PISP and PRSP combined, accounted for a large proportion (approximately 65%) of the isolates (Figure 2). This analysis also showed that, of the 208 *H. influenzae* strains derived from MEE, 62 strains (29.8%) were BLNAS, 144 strains (69.3%) were BLNAR, and two strains (0.9%) were BLPAR. BLNAR strains, which are significant as drug-resistant bacteria, accounted for a large proportion (approximately 70%) of the isolates (Figure 3).

According to the 2012 nationwide surveillance by the three organizations noted above, there was a decrease in the ratio of PRSP in *S. pneumoniae*; in 113 strains of *S. pneumoniae* harvested, 57 strains (50.4%) were PSSP, 42 strains (37.2%) were PISP, and the remaining 14 strains (12.4%) were PRSP (Fig. 4). The same study revealed almost the same ratio or a slight increase in the ratio of BLNAR in *H. influenzae*; among 106 strains of *H. influenzae* harvested from MEE, BLNAS was observed in 36 strains (34.0%), BLNAR in 54 strains (50.9%), and BLPAR in 16 strains (15.1%, Fig. 5).

Uno (2009a, b) collected isolates from the upper pharynx of patients with AOM or acute sinusitis younger than 15 years who visited his clinic from 2003 to 2007.
and analyzed antibacterial activity against 5,720 \textit{S. pneumoniae} strains and 5,297 \textit{H. influenzae} strains. PRSP was detected in 51.2\%, PISP in 40.1\%, and PSSP in 8.7\% in 2003. PRSP was detected in 37.1\%, PISP in 36.8\%, and PSSP in 26.1\% in 2007. The proportion of \textit{S. pneumoniae} strains that are resistant to antibacterial agents tended to decrease (Figure 6). BLNAS strains were detected in 55.1\%, low BLNAR strains in 18.1\%, BLNAR strains in 21.1\% and BLPAR strains in 5.7\% in 2003. BLNAS strains were detected in 76.7\%, low BLNAR strains in 9.6\%, BLNAR strains in 2\% and BLPAR strains in 11.7\% in 2007. The proportion of BLPAR strains of \textit{H. influenzae} tended to increase but that of BLNAR strains tended to decrease (Figure 7).

According to periodical surveillance (including the 2012 nationwide surveillance by three organizations), the ratio of drug-resistant strains in \textit{S. pneumoniae} peaked in 2003, then showed a decrease in 2007, and remained the same in 2012 (Fig. 8). The ratio of \textit{H. influenzae} has shown an increasing tendency since 2003, and demonstrated a rapid increase in 2012 (Fig. 9).

(2) Antibacterial activity of various agents against predominantly detected bacteria

a. Antibacterial activity against \textit{S. pneumoniae}

The antibacterial activity results of oral β-lactam antimicrobial agents against \textit{S. pneumoniae} reported in the 2007 Nationwide Surveillance show that amoxicillin (AMPC) and clavulanate/amoxicillin (CVA/AMPC [1:14] formulation) are superior to ampicillin/sulbactam (ABPC/SBT) by one tube. Cefditoren pivoxil (CDTR-PI) and faropenem (FRPM) are also effective. Macrolide antimicrobial agents are ineffective. New quinolone antimicrobial agents are relatively effective. In particular, sitafloxacin (STFX), tosfloxacin (TFLX), and moxifloxacin (MFLX) are effective, but now only TFLX is approved for use in children in Japan. Telithromycin (TEL) is also effective. However, none of these antimicrobial agents are indicated in children at this point. Among injections, cephems, such as cefpirom (CPR) and ceftriaxone (CTRX), and carbapenems, such as panipenem (PAPM), meropenem (MEPM), and doripenem (DRPM), are very useful. Cefmenoxime (CMX), approved as an eardrop and the only approved nebulizer agent, also has relatively high antibacterial activity (Table 3).

When we compare the results of two surveys done in 2007 and 2012, although the surveys were done by two different facilities, we observed that macrolides
showed deterioration in MIC although there was no remarkable change in β-lactam agents. Tebipenem pivoxil (TBPM-PI) and garenoxacin (GRNX) showed extremely good minimum inhibitory concentrations (MICs, Table 4).

The analysis results of the multicenter clinical study show that S. pneumoniae has relatively high susceptibility to AMPC and CVA/AMPC (1:14 formulation) (Table 5). CDTR-PI and CFPN-PI also have high antibacterial activity. TFLX, a new quinolone antimicrobial agent indicated in children, has high antibacterial activity. Injections, such as CTRX and a carbapenem antimicrobial agent PAPM/BP also exhibit high antibacterial activity.

Yamanaka et al. (2012a) reported that S. pneumonia showed extremely good sensitivity to BPM-PI, and the antimicrobial activities of CDTR-PI and cefcapene pivoxil (CFPN-PI) were also good. The new quinolone agent TFLX, which is indicated for children, had good antimicrobial activities too (Fig. 10).

b. Antibacterial activity against H. influenzae

According to the 2007 Nationwide Surveillance, ABPC is superior to AMPC against H. influenzae by one tube among oral penicillin antimicrobial agents, but a high dose is required based on the MIC. Among cepham antimicrobial agents, CDTR-PI and cefteram-pivoxil (CFTM-PI) have favorable MIC values, but susceptibility of H. influenzae to other antimicrobial agents is low. All new quinolones have very high antibacterial activity, but cannot be used in children at this point. Among injections, CTRX and CMX, cepham antimicrobial agents, and MEPM, a carbapenem antimicrobial agent, are very useful (Table 6).

According to the analysis in the multicenter clinical study, AMPC does not necessarily have high antibacterial activity, with MIC ≥8 μg/mL against more than a half of H. influenzae strains. Approximately 40% of H. influenzae strains are susceptible to CVA/AMPC (1:14 formulation). The antibacterial activity of CDTR-PI is favorable. Approximately 96% of H. influenzae strains are susceptible to azithromycin (AZM). According to Yamanaka, et al, TFLX, a new quinolone antimicrobial agent, has extremely high antibacterial activity. Injections, such as CTRX and MEPM, a carbapenem antimicrobial agent, also have high antibacterial activity (Table 7). Yamanaka et al. (2012b) reported that TFLX, the only quinolone
agent approved for use in children, showed extremely high antimicrobial activity against *H. influenzae* (Fig. 11).

When we compared the results of the 2007 and 2012 surveys, we noted that although the surveys were done by two different facilities, the sensitivities of penicillins and macrolides showed slight improvements in 2012 (Table 8).

c. Antibacterial activity against *M. catarrhalis*

While *M. catarrhalis* is of low pathogenicity, 94% of *M. catarrhalis* strains produce β-lactamase, as shown in the Third Nationwide Surveillance. When they are present with pathogens, they inactivate β-lactam antimicrobial agents. They are therefore significant as so-called indirect causative bacteria. As shown in Table 8, the results of the 2007 Nationwide Surveillance show that there are a total of only 20 strains, and all antimicrobial agents except ABPC, AMPC, PIPC, CPR, and fosfomycin (FOM) can be used against *M. catarrhalis*. All antibacterial agents are effective if they are stable with β-lactamase (Table 9). In the multicenter clinical study, CVA/AMPC (1:14 formulation), CDTR-PI, CFPN-PI, CTRX, and LVFX showed effective antibacterial activity (Table 10).

Our comparison of the 2007 and 2012 surveys by two different facilities revealed that the sensitivities of some of the β-lactam agents deteriorated slightly. Those of LVFX and AZM also deteriorated, while TFLX, which can be used for children, showed good antimicrobial activity (Table 11).

d. Antibacterial activity against *S. pyogenes*

*S. pyogenes* is not detected at high frequency, but is a significant causative bacterium with strong pathogenicity (Figure 1). As all antibacterial agents except macrolides and FOM are expected to be effective, safe agents can be selected for use (Table 12).
Table 2. Transition of isolates from acute otitis media (Nationwide survey, Suzuki et al. 2013)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>S.aureus</strong></td>
<td>25.1%</td>
<td>27.7%</td>
<td>17.0%</td>
<td>4.4%</td>
<td>14.4%</td>
</tr>
<tr>
<td><strong>S.epidermidis</strong></td>
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<td>3.3%</td>
<td>6.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>other CNS</strong></td>
<td>9.9%</td>
<td>7.5%</td>
<td>15.4%</td>
<td></td>
<td></td>
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<tr>
<td><strong>CNS</strong></td>
<td>24.6%</td>
<td>15.6%</td>
<td>10.8%</td>
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<td></td>
</tr>
<tr>
<td><strong>S.pneumoniae</strong></td>
<td>15.5%</td>
<td>18.3%</td>
<td>24.1%</td>
<td>34.1%</td>
<td>29.2%</td>
</tr>
<tr>
<td><strong>S.pyogenes</strong></td>
<td>2.9%</td>
<td>3.5%</td>
<td>4.1%</td>
<td>2.2%</td>
<td>2.1%</td>
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<tr>
<td><strong>S.agalactiae</strong></td>
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<td></td>
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<tr>
<td><strong>other Streptococcus spp.</strong></td>
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<td>1.0%</td>
<td>2.5%</td>
<td>4.4%</td>
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<tr>
<td><strong>Enterococcus spp.</strong></td>
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<td>1.0%</td>
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<td><strong>M.(B.) catarrhalis</strong></td>
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<td>2.9%</td>
<td>4.0%</td>
<td>7.1%</td>
<td>4.4%</td>
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<td><strong>H.influenzae</strong></td>
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<td>15.3%</td>
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<td>27.4%</td>
<td>24.2%</td>
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<tr>
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<td></td>
<td>0.2%</td>
<td>0.8%</td>
<td></td>
</tr>
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<td>0.8%</td>
<td>2.0%</td>
<td>1.2%</td>
<td>1.1%</td>
</tr>
<tr>
<td><strong>P.aeruginosa</strong></td>
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<td>2.9%</td>
<td>4.7%</td>
<td>2.1%</td>
<td>1.1%</td>
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<td><strong>other NFGNR</strong></td>
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<td>5.5%</td>
<td>2.5%</td>
<td>2.9%</td>
<td></td>
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<tr>
<td><strong>other G(-) rod</strong></td>
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<td></td>
<td>2.9%</td>
<td></td>
</tr>
<tr>
<td><strong>Candida spp.</strong></td>
<td></td>
<td>1.2%</td>
<td></td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td><strong>others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of strains</th>
<th>Total</th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tr>
<td></td>
<td>386</td>
<td>405</td>
<td>241</td>
<td>91</td>
<td>195</td>
</tr>
</tbody>
</table>

Chronological change of pathogens harvested from acute suppurative otitis media (nationwide surveillance, 1994-2012)

Fig. 1.
Drug sensitivity of *Streptococcus pneumoniae* detected from middle ear effusion (183 cases, Multicenter clinical study 2005-2008)

Classification according to MIC of Penicillin G
- PC susceptible *Streptococcus pneumoniae* (PSSP) \( \leq 0.06 \mu g/mL \)
- PC intermediate-resistant *Streptococcus pneumoniae* (PISP) \( 0.125 \sim 1.0 \mu g/mL \)
- PC resistant *Streptococcus pneumoniae* (PRSP) \( \geq 2 \mu g/mL \)

---

Drug sensitivity of *Haemophilus influenzae* detected from middle ear effusion (183 cases, Multicenter clinical study 2005-2008)

Classification according to MIC of ABPC and to production of \( \beta \)-lactamase
- \( \beta \)-lactamase negative ABPC resistant *Haemophilus influenzae* (BLNAR) \( \geq 2 \mu g/mL \)
- \( \beta \)-lactamase negative ABPC susceptible *Haemophilus influenzae* (BLNAS) \( \leq 1 \mu g/mL \)
- \( \beta \)-lactamase productive ABPC resistant *Haemophilus influenzae* (BLPAR) \( \geq 4 \mu g/mL \)
Drug sensitivity of *Streptococcus pneumoniae*  
(113 cases, National surveillance involving 3 medical societies 2012)

Classification according to MIC of Penicillin G  
- PC susceptible *Streptococcus pneumoniae* (PSSP) \( \leq 0.06 \, \mu g/mL \)  
- PC intermediate-resistant *Streptococcus pneumoniae* (PISP) \( 0.125 - 1.0 \, \mu g/mL \)  
- PC resistant *Streptococcus pneumoniae* (PRSP) \( \geq 2 \, \mu g/mL \)  

Fig. 4.

Drug sensitivity of *Hemophilus influenzae*  
(106 cases, National surveillance involving 3 medical societies 2012)

Classification according to MIC of ABPC and to production of \( \beta \)-lactamase  
- \( \beta \)-lactamase negative ABPC resistant *Hemophilus influenzae* (BLNAR) \( \geq 2 \, \mu g/mL \)  
- \( \beta \)-lactamase negative ABPC susceptible *Hemophilus influenzae* (BLNAS) \( \leq 1 \, \mu g/mL \)  
- \( \beta \)-lactamase productive ABPC resistant *Hemophilus influenzae* (BLPAR) \( \geq 4 \, \mu g/mL \)  

Fig. 5.
Chronological change of drug resistance of *Streptococcus pneumoniae* harvested from nasopharynx (5720 strains, Uno, et al. 2009)

![Graph showing the chronological change of drug resistance of *Streptococcus pneumoniae*.](image)

Fig. 6.

Chronological change of drug resistance of *Haemophilus influenzae* harvested from nasopharynx (5297 strains, Uno, et al. 2009)

![Graph showing the chronological change of drug resistance of *Haemophilus influenzae*.](image)

Fig. 7.
Chronological change of drug resistance of *Streptococcus pneumoniae* (nationwide surveillance, 1994-2012)

![Graph showing percentage resistance over years for Streptococcus pneumoniae](image)

Fig. 8.

Chronological change of drug resistance of *Hemophilus influenzae* (nationwide surveillance, 1994-2012)

![Graph showing percentage resistance over years for Hemophilus influenzae](image)

Fig. 9.
Table 3. Antimicrobial activity of antibiotics against *S. pneumoniae* (Nationwide survey 2007)

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>PISP(42 strains)</th>
<th>PSSP(42 strains)</th>
<th>PRSP(10 strains)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range MIC&lt;sub&gt;50&lt;/sub&gt; MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>Range MIC&lt;sub&gt;50&lt;/sub&gt; MIC&lt;sub&gt;90&lt;/sub&gt;</td>
<td>Range MIC&lt;sub&gt;50&lt;/sub&gt; MIC&lt;sub&gt;90&lt;/sub&gt;</td>
</tr>
<tr>
<td>PCG</td>
<td>≦0.06 ≦0.06 ≦0.06</td>
<td>0.125 - 1 0.5 1</td>
<td>2 2 2</td>
</tr>
<tr>
<td>AMPC</td>
<td>≦0.06 ≦0.06 ≦0.06</td>
<td>0.06 - 2 0.25 1</td>
<td>0.5 - 2 2 2</td>
</tr>
<tr>
<td>PIPC</td>
<td>≦0.06 - 0.25 ≦0.06 0.125</td>
<td>0.06 - 2 1 2</td>
<td>1 - 4 2 4</td>
</tr>
<tr>
<td>SBT/ABPC</td>
<td>≦0.06 - 0.125 ≦0.06 0.06</td>
<td>0.06 - 2 0.5 2</td>
<td>0.5 - 2 1 2</td>
</tr>
<tr>
<td>CVA/AMPC</td>
<td>≦0.06 ≦0.06 ≦0.06</td>
<td>0.06 - 4 0.5 1</td>
<td>0.5 - 4 1 2</td>
</tr>
<tr>
<td>CFTM-PI</td>
<td>0.125 - 0.25 0.125 0.25</td>
<td>0.25 - 4 1 4</td>
<td>2 - 8 4 8</td>
</tr>
<tr>
<td>FMOX</td>
<td>0.25 - 0.5 0.25</td>
<td>0.06 - 2 0.5 1</td>
<td>0.5 - 1 0.5 1</td>
</tr>
<tr>
<td>CMX</td>
<td>≦0.06 - 0.5 0.125 0.25</td>
<td>0.06 - 2 0.5 1</td>
<td>0.5 - 1 0.5 1</td>
</tr>
<tr>
<td>CTRX</td>
<td>≦0.06 - 0.5 0.125 0.25</td>
<td>0.06 - 4 0.5 1</td>
<td>0.5 - 1 0.5 1</td>
</tr>
<tr>
<td>CPR</td>
<td>0.06 - 0.5 0.125 0.25</td>
<td>0.06 - 1 0.5 1</td>
<td>0.125 - 1 0.5 1</td>
</tr>
<tr>
<td>CFPN-PI</td>
<td>0.06 - 0.5 0.25 0.5</td>
<td>0.06 - 4 0.5 1</td>
<td>0.125 - 1 0.25 0.5</td>
</tr>
<tr>
<td>PAPM/BP</td>
<td>≦0.06 ≦0.06 ≦0.06</td>
<td>0.06 - 0.125 ≦0.06 0.125</td>
<td>≦0.06 - 0.125 ≦0.06 0.125</td>
</tr>
<tr>
<td>CDT-PI</td>
<td>≦0.06 - 0.25 0.125 0.25</td>
<td>0.06 - 2 0.25 1</td>
<td>0.25 - 1 0.5 1</td>
</tr>
<tr>
<td>FRPM</td>
<td>≦0.06 ≦0.06 ≦0.06</td>
<td>0.06 - 0.5 ≦0.06 0.25</td>
<td>0.125 - 1 0.25 0.5</td>
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<tr>
<td>DRPM</td>
<td>≦0.06 ≦0.06 ≦0.06</td>
<td>0.06 - 0.25 ≦0.06 0.25</td>
<td>0.125 - 0.5 0.25 0.5</td>
</tr>
<tr>
<td>CAM</td>
<td>≦0.06 - 128 128 128</td>
<td>0.06 - 128 4 128</td>
<td>0.06 - 128 2 128</td>
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<tr>
<td>AZM</td>
<td>≦0.06 - 32 32 32</td>
<td>≦0.06 - 32 32 32</td>
<td>0.125 - 32 8 32</td>
</tr>
<tr>
<td>LVFX</td>
<td>1 - 2 1 2</td>
<td>0.5 - 1 1 1</td>
<td>0.25 - 1 1 1</td>
</tr>
<tr>
<td>TFLX</td>
<td>0.125 - 0.25 0.25 0.25</td>
<td>0.125 - 0.25 0.125 0.25</td>
<td>0.06 - 0.25 0.125 0.25</td>
</tr>
<tr>
<td>STFX</td>
<td>≦0.06 - 0.125 ≦0.06 ≦0.06</td>
<td>≦0.06 ≦0.06 ≦0.06</td>
<td>≦0.06 ≦0.06 ≦0.06</td>
</tr>
<tr>
<td>MFLX</td>
<td>0.125 - 0.25 0.25 0.25</td>
<td>0.125 - 0.25 0.125 0.25</td>
<td>0.06 - 0.25 0.125 0.25</td>
</tr>
<tr>
<td>MEPM</td>
<td>≦0.06 ≦0.06 ≦0.06</td>
<td>0.06 - 0.5 ≦0.06 0.25</td>
<td>0.06 - 0.25 0.125 0.25</td>
</tr>
<tr>
<td>TEL</td>
<td>≦0.06 - 0.5 ≦0.06 0.25</td>
<td>≦0.06 - 0.5 ≦0.06 0.25</td>
<td>≦0.06 - 0.5 ≦0.06 0.125</td>
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</table>

Table 4. Drug sensitivities for *S. pneumoniae* (Comparison between 2007 and 2012 surveillances)

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; 2007 78 strains</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; 2012 113 strains</th>
<th>Antimicrobial agents</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; 2007 78 strains</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; 2012 113 strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCG</td>
<td>2</td>
<td>2</td>
<td>TBPM-PL</td>
<td>-</td>
<td>≦0.06</td>
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<tr>
<td>AMPC</td>
<td>2</td>
<td>2</td>
<td>PAPM/BP</td>
<td>0.125</td>
<td>0.25</td>
</tr>
<tr>
<td>CVA/AMPC</td>
<td>2</td>
<td>2</td>
<td>MEPM</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>SBT/ABPC</td>
<td>4</td>
<td>4</td>
<td>GRNX</td>
<td>0.06</td>
<td>≦0.06</td>
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<tr>
<td>FRPM</td>
<td>0.5</td>
<td>0.5</td>
<td>LVFX</td>
<td>2</td>
<td>2</td>
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<tr>
<td>PIPC</td>
<td>4</td>
<td>2</td>
<td>TFLX</td>
<td>0.25</td>
<td>0.25</td>
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<td>CDT-PL</td>
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<td>0.5</td>
<td>CAM</td>
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<td>AZM</td>
<td>32</td>
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<td>1</td>
<td>1</td>
<td>VCM</td>
<td>-</td>
<td>0.25</td>
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### Table 5. Antimicrobial activity of antibiotics against *S. pneumoniae* (Multicenter clinical study)

<table>
<thead>
<tr>
<th>Antimicrobials</th>
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<th>0.0625</th>
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<th>0.25</th>
<th>0.5</th>
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<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>64</th>
<th>128</th>
<th>256</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
<th>Susceptible (%)</th>
<th>Total</th>
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<td>25</td>
<td>18</td>
<td>28</td>
<td>53</td>
<td>103</td>
<td>7</td>
<td>0.5</td>
<td>2</td>
<td>22.8</td>
<td>329</td>
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<td></td>
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<tr>
<td>Amoxicillin</td>
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<td>21</td>
<td>26</td>
<td>26</td>
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<td>104</td>
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<tr>
<td>CVA/AMPC</td>
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<td>0.5</td>
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<td>1</td>
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<td>200</td>
<td>85</td>
<td>0.5</td>
<td>1</td>
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<td>48</td>
<td>90</td>
<td>64</td>
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<td>2</td>
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<td>0.25</td>
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<tr>
<td>Clarithromycin</td>
<td>24</td>
<td>3</td>
<td>6</td>
<td>34</td>
<td>32</td>
<td>20</td>
<td>20</td>
<td>6</td>
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<td>Azithromycin</td>
<td>4</td>
<td>13</td>
<td>10</td>
<td>2</td>
<td>13</td>
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<td>38</td>
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<td>5.17</td>
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</tbody>
</table>

NA: not available

**Drug resistance of *Streptococcus pneumoniae*  
(Yamanaka et al, Pract Otorhinolaryngol, 2012)**

![Graph showing drug resistance of Streptococcus pneumoniae](image-url)  
(28 strains)
### Table 6. Antimicrobial activity of antibiotics against *H. influenzae* (Nationwide survey 2007)

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>BLNAS (26 strains)</th>
<th>BLNAR (33 strains)</th>
<th>BLPAR (4 strains)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range MIC50 MIC90</td>
<td>Range MIC50 MIC90</td>
<td>Range MIC50 MIC90</td>
</tr>
<tr>
<td>ABPC</td>
<td>0.125 - 0.5 0.25 0.5</td>
<td>1 - 8 2 8</td>
<td>1 - 128 32 128</td>
</tr>
<tr>
<td>AMPC</td>
<td>0.125 - 1 0.5 0.5</td>
<td>2 - 32 8 16</td>
<td>2 - 128 128 128</td>
</tr>
<tr>
<td>PIPC</td>
<td>0.06 - 0.6</td>
<td>0.125 0.25</td>
<td>0.125 - 0.25 0.25</td>
</tr>
<tr>
<td>SBT/ARPC</td>
<td>0.125 - 0.25 0.5 0.5</td>
<td>2 - 32 8 16</td>
<td>0.125 - 32 16 32</td>
</tr>
<tr>
<td>CVA/AMPC</td>
<td>0.125 - 0.125 0.06</td>
<td>0.06 - 1 1 1</td>
<td>0.06 - 0.125 0.125</td>
</tr>
<tr>
<td>CFTM-PI</td>
<td>0.06 - 0.125 0.06</td>
<td>2 - 16 8 16</td>
<td>0.06 - 0.125 0.125</td>
</tr>
<tr>
<td>FMOX</td>
<td>0.25 - 2 0.5 1</td>
<td>0.25 - 8 2 4</td>
<td>0.25 - 0.25 0.25</td>
</tr>
<tr>
<td>CMX</td>
<td>0.06 - 0.125 0.06</td>
<td>0.06 - 0.125 0.125</td>
<td>0.06 - 0.25 0.25</td>
</tr>
<tr>
<td>CTRX</td>
<td>0.06 - 0.125 0.06</td>
<td>0.06 - 0.125 0.125</td>
<td>0.06 - 0.25 0.25</td>
</tr>
<tr>
<td>CFFN-PI</td>
<td>0.06 - 0.25 0.06</td>
<td>0.06 - 8 2 4</td>
<td>0.06 - 0.25 0.25</td>
</tr>
<tr>
<td>PAPM-BP</td>
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<td>0.25 - 8 2 4</td>
<td>0.25 - 0.25 0.25</td>
</tr>
<tr>
<td>CDTR-PI</td>
<td>0.06 - 0.125 0.06</td>
<td>0.06 - 0.125 0.125</td>
<td>0.06 - 0.25 0.25</td>
</tr>
<tr>
<td>FRPM</td>
<td>0.25 - 2 0.5 1</td>
<td>0.5 - 8 4 8</td>
<td>0.25 - 0.25 0.25</td>
</tr>
<tr>
<td>DRPM</td>
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<td>0.125 - 4 0.5 2</td>
<td>0.06 - 0.25 0.25</td>
</tr>
<tr>
<td>CAM</td>
<td>0.125 - 16 8 16</td>
<td>1 - 8 8 8</td>
<td>4 - 16 4 16</td>
</tr>
<tr>
<td>AZM</td>
<td>0.06 - 0.125 0.06</td>
<td>0.25 - 2 0.5 1</td>
<td>0.25 - 0.25 0.25</td>
</tr>
<tr>
<td>MENO</td>
<td>0.125 - 2 0.25 1</td>
<td>0.125 - 0.125 0.25 0.5</td>
<td>0.125 - 0.5 0.25 0.5</td>
</tr>
<tr>
<td>LVFX</td>
<td>0.06 - 0.25 0.06</td>
<td>0.06 - 0.125 0.25 0.5</td>
<td>0.06 - 0.25 0.25 0.5</td>
</tr>
<tr>
<td>TFLX</td>
<td>0.06 - 0.25 0.06</td>
<td>0.06 - 0.125 0.25 0.5</td>
<td>0.06 - 0.25 0.25 0.5</td>
</tr>
<tr>
<td>STFX</td>
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<td>0.06 - 0.125 0.25 0.5</td>
<td>0.06 - 0.25 0.25 0.5</td>
</tr>
<tr>
<td>MFLEX</td>
<td>0.06 - 0.25 0.06</td>
<td>0.06 - 0.125 0.25 0.5</td>
<td>0.06 - 0.25 0.25 0.5</td>
</tr>
<tr>
<td>MEPM</td>
<td>0.06 - 0.25 0.06</td>
<td>0.06 - 0.125 0.25 0.5</td>
<td>0.06 - 0.25 0.25 0.5</td>
</tr>
<tr>
<td>TEL</td>
<td>0.06 - 4 4 4</td>
<td>1 - 4 2 2</td>
<td>1 - 2 2 2</td>
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</table>

### Table 7. Antimicrobial activity of antibiotics against *H. influenzae* (Multicenter clinical study)

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>MIC (µg/ml)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>0.031 0.0625 0.125 0.25 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>0.031 0.0625 0.125 0.25 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>CVA/AMPC</td>
<td>0.031 0.0625 0.125 0.25 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Cefcapene</td>
<td>0.031 0.0625 0.125 0.25 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Cefditoren</td>
<td>0.031 0.0625 0.125 0.25 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Cefixime</td>
<td>0.031 0.0625 0.125 0.25 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>0.031 0.0625 0.125 0.25 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>0.031 0.0625 0.125 0.25 0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>0.031 0.0625 0.125 0.25 0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

30
Drug resistance of *Hemophilus influenzae*  
(Yamanaka et al, Pract Otorhinolaryngol, 2012)

![Graph showing drug resistance for H. influenzae](image)

Table 8. Drug sensitivities for *H. influenzae* (Comparison between 2007 and 2012 surveillances)

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (2007, 78 strains)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (2012, 113 strains)</th>
<th>Anti-microbial agents</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (2007, 78 strains)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (2012, 113 strains)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPC</td>
<td>128</td>
<td>32</td>
<td>CTRX</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>AMPC</td>
<td>128</td>
<td>32</td>
<td>TBPM-PI</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>CVA/AMPC</td>
<td>16</td>
<td>8</td>
<td>MEPM</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>SBT/ABPC</td>
<td>16</td>
<td>8</td>
<td>GRNX</td>
<td>≤0.06</td>
<td>≤0.06</td>
</tr>
<tr>
<td>FRPM</td>
<td>8</td>
<td>4</td>
<td>LVFX</td>
<td>≤0.06</td>
<td>≤0.06</td>
</tr>
<tr>
<td>PIPC (TAZ)</td>
<td>32</td>
<td>8 (TAZ:0.5)</td>
<td>TFLX</td>
<td>≤0.06</td>
<td>≤0.06</td>
</tr>
<tr>
<td>CDTR-PI</td>
<td>0.5</td>
<td>0.5</td>
<td>CAM</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>CFPN - PI</td>
<td>4</td>
<td>2</td>
<td>AZM</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>CMX</td>
<td>0.5</td>
<td>0.5</td>
<td>MINO</td>
<td>0.5</td>
<td>1</td>
</tr>
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</table>
Table 9. Antimicrobial activity of antibiotics against *M. catarrhalis* (Nationwide survey 2007)

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Total (20 strains)</th>
<th>MIC</th>
<th>MIC</th>
<th>MIC</th>
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</thead>
<tbody>
<tr>
<td>Range</td>
<td>&lt;0.06 - 8</td>
<td>2</td>
<td>8</td>
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</tr>
<tr>
<td>ABPC</td>
<td>≤0.06 - 8</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>AMPC</td>
<td>≤0.06 - 8</td>
<td>2</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>PIPC</td>
<td>≤0.06 - 8</td>
<td>0.25</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>SBT/ABPC</td>
<td>≤0.06 - 0.25</td>
<td>0.125</td>
<td>0.25</td>
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<tr>
<td>CVAAMPC</td>
<td>≤0.06 - 0.25</td>
<td>0.125</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>CFTRM-PI</td>
<td>≤0.06 - 4</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>CMX</td>
<td>≤0.06 - 1</td>
<td>0.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CPR</td>
<td>≤0.06 - 4</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>CFTRN-PI</td>
<td>≤0.06 - 1</td>
<td>0.5</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>FRPM</td>
<td>≤0.06 - 0.5</td>
<td>0.25</td>
<td>0.5</td>
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</tr>
<tr>
<td>CAM</td>
<td>≤0.06 - 0.5</td>
<td>0.125</td>
<td>0.25</td>
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</tr>
<tr>
<td>AZM</td>
<td>≤0.06 - 0.125</td>
<td>≤0.06</td>
<td>≤0.06</td>
<td></td>
</tr>
<tr>
<td>LVFX</td>
<td>≤0.06</td>
<td>≤0.06</td>
<td>≤0.06</td>
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</table>

Table 10. Antimicrobial activity of antibiotics against *M. catarrhalis* (Multicenter clinical study)

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>MIC (µg/ml)</th>
<th>Susceptible(%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>&lt;0.031</td>
<td>0.0625 0.125 0.25 0.5 1 2 4 8 16 32 64 128 256</td>
<td>NA</td>
</tr>
<tr>
<td>CVA/AMPC</td>
<td>4 3 13 73 11 4 1 2</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Cefcapene</td>
<td>8 4 14 51 26 4 3 1</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>Cefditoren</td>
<td>3 2 4 6 29 33 21 8 4 1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>3 3 2 9 39 33 12 5 5</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>Levofoxacin</td>
<td>81 28 1 1</td>
<td>&lt;0.031</td>
<td>0.0625</td>
</tr>
<tr>
<td>Panipenem</td>
<td>15 11 9 11 15 10 11 6 7 4 5 7</td>
<td>0.5</td>
<td>32</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>68 5 23 10 1 1</td>
<td>3</td>
<td>0.0625</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>5 10 35 55 2 1</td>
<td>3</td>
<td>0.5</td>
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</table>

NA: not available
Table 11. Drug sensitivities for *M. catarrhalis* (Comparison between 2007 and 2012 surveillances)

<table>
<thead>
<tr>
<th>Antimicrobial agents</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; 2007</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; 2012</th>
<th>Antimicrobial agents</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; 2007</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPC</td>
<td>8</td>
<td>16</td>
<td>CMX</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>AMPC</td>
<td>8</td>
<td>8</td>
<td>CTRX</td>
<td>-</td>
<td>≦0.06</td>
</tr>
<tr>
<td>CVA/AMPC</td>
<td>0.25</td>
<td>0.5</td>
<td>MEPM</td>
<td>-</td>
<td>≦0.06</td>
</tr>
<tr>
<td>SBT/ABPC</td>
<td>0.25</td>
<td>0.25</td>
<td>LVFX</td>
<td>≦0.06</td>
<td>0.125</td>
</tr>
<tr>
<td>FRPM</td>
<td>0.5</td>
<td>1</td>
<td>TFLX</td>
<td>≦0.06</td>
<td>≦0.06</td>
</tr>
<tr>
<td>PIPC (TAZ)</td>
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<td>(TAZ≤0.06)</td>
<td>GRNX</td>
<td>≦0.03</td>
<td>≦0.06</td>
</tr>
<tr>
<td>CDTR-PL</td>
<td>-</td>
<td>1</td>
<td>CAM</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>CFPN-PL</td>
<td>0.5</td>
<td>1</td>
<td>AZM</td>
<td>≦0.06</td>
<td>0.125</td>
</tr>
<tr>
<td>CFTM-PL</td>
<td>2</td>
<td>2</td>
<td>MINO</td>
<td>-</td>
<td>0.25</td>
</tr>
</tbody>
</table>

Table 12. Antimicrobial activity of antibiotics against *S. pyogenes* (Nationwide survey 2007)

<table>
<thead>
<tr>
<th>Antibiotics</th>
<th>Total (45 strains)</th>
<th>Antibiotics</th>
<th>Total (45 strains)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>Range MIC&lt;sub&gt;50&lt;/sub&gt; MIC&lt;sub&gt;90&lt;/sub&gt;</td>
</tr>
<tr>
<td>ABPC</td>
<td>≦0.06</td>
<td>≦0.06</td>
<td>≦0.06</td>
</tr>
<tr>
<td>AMPC</td>
<td>≦0.06</td>
<td>≦0.06</td>
<td>≦0.06</td>
</tr>
<tr>
<td>CVA/AMPC</td>
<td>≦0.06</td>
<td>≦0.06</td>
<td>≦0.06</td>
</tr>
<tr>
<td>CFTM-PI</td>
<td>≦0.06</td>
<td>≦0.06</td>
<td>≦0.06</td>
</tr>
<tr>
<td>CMX</td>
<td>≦0.06</td>
<td>≦0.06</td>
<td>≦0.06</td>
</tr>
<tr>
<td>CPR</td>
<td>≦0.06</td>
<td>≦0.06</td>
<td>≦0.06</td>
</tr>
<tr>
<td>CFPN-PI</td>
<td>≦0.06</td>
<td>≦0.06</td>
<td>≦0.06</td>
</tr>
<tr>
<td>CDTR-PI</td>
<td>≦0.06</td>
<td>≦0.06</td>
<td>≦0.06</td>
</tr>
<tr>
<td>FRPM</td>
<td>≦0.06</td>
<td>≦0.06</td>
<td>≦0.06</td>
</tr>
<tr>
<td>CAM</td>
<td>≦0.06 - 128</td>
<td>≦0.06</td>
<td>8</td>
</tr>
<tr>
<td>AZM</td>
<td>0.06 - 32</td>
<td>0.125</td>
<td>32</td>
</tr>
<tr>
<td>LVFX</td>
<td>0.25 - 2</td>
<td>0.5</td>
<td>2</td>
</tr>
</tbody>
</table>

References


10. Gathering evidence

During the preparation of these Guidelines, existing evidence (literature) was gathered with respect to the following clinical questions by means of the procedures described below:52)
(a) Diagnosis
(b) Testing methods
(c) Treatment

(i) Databases used

For the 2006 and 2009 Guidelines, PubMed and Japan Centra Revuo Medicina Web version 3 and 4 were used, and for the 2013 Guidelines, PubMed, the Cochrane Library, and Japan Centra Revuo Medicina Web version 5 were used.

(ii) Search period
For the 2006 Guidelines, searches were performed in the databases of literature published during 2000–2004. For the 2009 Guidelines articles published in 2004 but not included in the 2006 Guidelines, were added, and we also added articles which were published after 2005 and searchable on April 10, 2008. For the 2013 Guidelines, articles published after 2008 and searchable on January 26, 2012 were added.

(iii) Criteria for use

Priority was given to articles comprising systematic reviews of randomized controlled trials or describing individual randomized controlled trials, and if these were not available then articles describing observational studies such as cohort studies and case controlled studies were used. If these were insufficient, the scope was widened to include articles describing case series. Articles concerning animal experiments and basic science were excluded.

(iv) Method of use

For the 2006 Guidelines, the keyword 中耳炎 (chuujien, “otitis media”) was used to search the Japan Centra Revuo Medicina Web version 3 database with the “meta-analysis,” “randomized controlled trial,” “controlled clinical trial,” and “comparative research” research design tags checked, but no articles suitable for use in these Clinical Practice Guidelines were found. In PubMed, searches were performed with the following keywords: (1) otitis media, treatment; (2) otitis media, antimicrobial agents; (3) acute otitis media, treatment; and (4) acute otitis media, antimicrobial agents. For meta-analyses and systematic reviews using the Cochrane Collaboration, the search format “English [la] AND otitis media [ti] AND (Cochrane Database Syst Rev [jour] OR meta-analysis [pt]) AND 2000:2004 [dp]” was used. Articles cited in the American Academy of Pediatrics Guidelines (2004) were also analyzed. In addition to the literature searches described above, articles published before 2000, those published during 2003–2005 while the Guidelines were in preparation, and those published in Japanese and international journals that were considered to be required for the preparation of the Guidelines were also identified, resulting in a total of 82 articles for investigation.
For the 2009 and 2013 Guidelines, the search format (otitis media/TH or otitis media/AL) and (PT = NOT conference report and RD = meta-analysis, randomized controlled trial, semi-randomized controlled trial, controlled study, clinical practice guidelines) was used to search Japan Centra Revuo Medicina Web version 4 and 5, yielding hits for 104 articles (2003–2008) and 233 articles (2008–2012), respectively. The abstracts or main texts of these articles were studied, and seven and 50 articles were selected for inclusion, respectively.

In PubMed, searches were performed using the following keywords: Search (English[la] OR Japanese[la]) AND (otitis media) AND (treatment OR antimicrobial agents) AND (randomized controlled trial [pt]) AND 2004:2007 [dp]; and Search (English [la] OR Japanese [la]) AND (otitis media) AND (treatment OR antimicrobial agents) AND (meta-analysis[pt] OR Cochrane Database Syst Rev [ta]) AND 2004:2007 [dp], yielding 118 articles. A further 268 articles published between 2004 and April 2007 and containing “otitis media” in their title, abstract, or keywords were also identified from the Cochrane Reviews, Clinical Trials, Other Reviews, Technology Assessments, and Economic Evaluations included in the Cochrane Library. A total of 386 articles found by the above searches were studied and 60 of 386 articles were added to the 2009 Guidelines, excluding those already used in the 2006 Guidelines. In addition, with the cooperation of the Japan Council for Quality Healthcare Medical Information Network Distribution System EBM Medical Information Department, a search of PubMed for articles published after April 1, 2007 was performed on April 10, 2008 using the search format ((“otitis media” [MeSH] AND “therapy”[Subheading]) OR (“otitis media” [MeSH] AND antimicrobial agents) OR (“acute otitis media” AND “therapy”[Subheading]) OR (“acute otitis media” AND antimicrobial agents)) AND ((“meta-analysis”[pt] OR “randomized controlled trial”[pt]) NOT ”Cochrane database of systematic reviews (Online)”[Jour] AND “humans” [MeSH] AND (English [la] OR Japanese [la]) AND 2007/4/1 [edat]: 2008/3/31 [edat]. This identified 11 articles, of which five were selected for study.

In addition to the literature searches described above, three other articles were added that were considered required for preparation of the Guidelines, resulting in 75 articles being added to those used in the 2006 Guidelines giving a final total of 157 articles used in the Guidelines. In the 2013 Guidelines, a further literature search was conducted using the same method, picking up 650 articles, and finally 208 articles
were added. In the 2013 guidelines, the abstract table was inserted on the homepage of the Japan Otological Society (http://www.otology.gr.jp).

11. Criteria for deciding recommendation grades

The method proposed by the Japan Stroke Society to indicate the level of evidence was used in the preparation of these Guidelines, as shown below.

Level of evidence

Ia  Meta-analysis (with homogeneity) of randomized controlled trials
Ib  At least one randomized controlled trial
IIa At least one well-designed, controlled study but without randomization
IIb At least one well-designed, quasi-experimental study
III At least one well-designed, non-experimental descriptive study
     (e.g., comparative studies, correlation studies, case studies)
IV  Expert committee reports, opinions and/or experience of respected authorities

Recommendation grades were determined based on the evidence obtained by the search policies described above and the anticipated degree of benefit or harm. During this process, reference was made to items according to the proposed grades outlined below. Five levels of recommendation grades were established, based on the U.S. Preventive Services Task Force report (http://www.ahrq.gov/clinic/ajpmsuppl/harris3.htm#tb6fn5). In the 2013 Guidelines, considering the consistency with the previous two editions, the same five levels described below were used as well.

A: (strongly recommended: strong evidence is available, benefits substantially outweigh harms)
B: (recommended: sufficient evidence is available, benefits outweigh harms)
C: (no recommendation made: fair evidence is available, but the balance of benefits and harms is close)
D: (recommended against: harms outweigh benefits)
I: (insufficient evidence to determine the balance of benefits and harms)
The specification of recommendation grades is one of the most important roles expected of clinical practice guidelines, but there is great debate concerning the sort of factors that should be taken into account when determining recommendation grades. The Subcommittee of Clinical Practice Guideline made overall judgments taking into consideration the factors below, with reference to the proposals of Fukui and Tango (Shinryou gaidorain sakusei no tebiki dai 4-pan, “Guide to the Preparation of Clinical Practice Guidelines, 4th edition”) and those of the MINDS Guide to the Preparation of Clinical Practice Guidelines (MINDS Shinryou gaidorain sakusei no tebiki, Igakushoin, 2007).

- Level of evidence
- Quality of evidence
- Consistency of evidence (supported by multiple studies)
- Directness (magnitude of clinical efficacy, external validity, indirect evidence, evaluation by surrogate outcomes)
- Clinical applicability
- Evidence concerning harm or costs

No Level I study reports on AOM in Japan were found. Accordingly, Grade A recommendations were determined based on the existence of at least one piece of level I evidence from Europe or the USA that was judged by the committee to be applicable to Japanese circumstances. The condition for determination of Grade B recommendations was the existence of at least one piece of Level II evidence demonstrating efficacy that was judged by the committee to be applicable to Japanese circumstances.

Opinions on these recommendations were solicited from the directors and executive committee members of the JOS, the JSIDO, and the JSPO before the final decision was made by the Subcommittee of Clinical Practice Guideline. The committee endeavored to maintain objectivity and transparency when deciding on recommendation grades, but it was not possible to guarantee this in every case.

A system will be put in place in future for accepting comments and suggestions from users concerning the content of recommendations and recommendation grades, with a view to the future revision of these Guidelines.
References


12. Procedures for consolidating evidence

To consolidate the evidence, the main findings from each article were identified and an evidence table was prepared. The features of each finding were compared and evaluated. When meta-analyses were found during the literature search, their results were used as reference. No new meta-analyses or decision analyses were conducted in the preparation of these Guidelines.

13. Pre-release review

Before these Guidelines were released for general use, they were reviewed with reference to the Conference on Guideline Standardization (COGS) proposals concerning publication format54 and the Appraisal of Guidelines for Research & Evaluation (AGREE) appraisal instrument for assessing content.55

Before publication of the 2006 edition of the Guidelines, opinions were solicited from JOS, JSIDO, and JSPO, and pediatricians, and corrections were made where necessary. Otolaryngologists, regarded as the general users of the Guidelines, were also surveyed regarding their utility in the clinical setting, and the results were reflected where appropriate. The 2013 Guidelines were assessed before publication by the Subcommittee of the Clinical Practice Guidelines for the Diagnosis and Management of Acute Otitis Media in Children with reference to the appraisal instruments of AGREE II (http://www.agreetrust.org/resource-centre/agree-ii).
References

14. Planned Updates
These Guidelines are scheduled to be updated in around 3–5 years. After their publication, work will begin toward the organization of a new Subcommittee of Clinical Practice Guideline. Newly published evidence will be systematically assessed and reviews carried out, with a Working Group established to contribute resources for the updated Guidelines. Should partial updates to the Guidelines be required, these will be published on the societies’ web sites as appropriate.

15. Recommendations and explanation of reasons
These Guidelines were formulated for otolaryngologists as users, but they are also expected to be used as reference in all situations in which clinical judgments are made concerning the diagnosis and treatment of childhood AOM, by all medical professionals involved in the treatment of this condition, in a wide variety of clinical settings. The specific relationships between recommendations and the literature on which they are based are described in each section of the Guidelines. It must again be emphasized that the recommendation grades indicated by these Guidelines do not constitute an alternative to the judgment of an experienced medical practitioner, but are only provided to assist his or her decision-making.

16. Patients’ wishes
In the process of deciding the recommendations in the 2006 edition of the Guidelines, the wishes of patients or their parents or guardians were listened to but not actively taken into account. When dealing with individual patients and clinical situations, however, to apply the recommendations in the Guidelines without exception
in every case is to mistake what is important, in light of the spirit of the Guidelines as an aid to decision-making in actual clinical situations. It must again be emphasized that decision-making in actual clinical situations must always be carried out by taking into account the evidence and recommendations contained in the Guidelines and elsewhere, the experience and specialist knowledge of the medical practitioner, and the wishes and values of the patient and his or her parents or guardians. Future revisions of the Guidelines will consider efforts to reflect the wishes of patients and their parents and guardians to a greater extent.

17. Algorithms

The generally recommended algorithms according to the degree of severity of AOM are included at the end of the Guidelines.

18. Practical consideration

In principle, in these Guidelines medications are referred to by their generic names rather than brand names. The reasons for this include concerns that it would be unfair to refer only to selected products by name in the Guidelines as well as the strong influence of expert opinion. In addition to which all generic products are fully included, and updating this information to include brand names would pose too great a burden on the Subcommittee of Clinical Practice Guideline. For this reason, we advise the preparation of clinical paths or manuals that take account of the status of medications used and other specific attributes of individual facilities, to enable the smooth acceptance of the recommendations in these Guidelines in actual clinical settings.

19. Diagnosis, examinations

Clinical question 19-1: Under what condition is AOM diagnosed?

Recommendation

AOM is diagnosed when the following eardrum findings are recognized, and thus, detailed inspection of the eardrum is indispensable for its diagnosis (Typical eardrum findings are in Figure 8, by Kamide Y\textsuperscript{56}). (Grade of Recommendation: B) Hyperemia, protrusion, diminishment of the light reflex, thickening, bullar formation, cloudiness (turbidity), perforation, MEE, otorrhea, edema of middle-ear mucosa
Reference used to assess the recommendation level: Rosenfeld et al., 2001\textsuperscript{57} (Level IIb)

[Addendum] Otomicroscopic or otoendoscopic observation of the eardrum is most desirable, but recent model of the pneumatic otoscope is also acceptable.

Background

As AOM is acute inflammation of the middle-ear mucosa, confirmation by inspection of the eardrum findings manifesting middle-ear inflammatory effusion and/or inflammatory change is indispensable for the diagnosis of AOM.

Comments

As for the eardrum findings suitable for the diagnosis of AOM, various descriptions such as hyperemia, cloudiness (turbidity), protrusion, thickening, bullar formation, perforation, and change of the light reflex, have been observed, and there has not been a uniform standard that was used uniformly in the literature issued to date. Among those findings, eardrum protrusion is a finding that is frequently observed and is also suspected of the existence of MEE (Shaikh et al. 2012). Eardrum protrusion is, therefore, in combination with the eardrum color and mobility, the finding that is most suspected of AOM (Karma et al. 1989, Pelton 1998, Pichichero 2000, Shaikh et al. 2012). Eardrum turbidity frequently represents edema of the eardrum except those due to scar tissue. Although hyperemia of the eardrum by acute inflammation is also frequently observed with AOM, those due to crying or systemic fever should be discriminated, and also differential diagnosis includes viral OM (Weiss et al. 1996). It is sometimes the case that eardrum hyperemia is not distinct in spite of apparent protrusion in AOM of infant under the age of one.

AOM is diagnosed based on subjective symptoms (acute onset of symptoms of inflammation in the ME) and objective signs (tympanic membrane findings including hyperemia, bulging, otorrhea, MEE, etc.) (Lee et al. 2012). The 2013 American AOM Guidelines recommended the following three features for the definition of AOM (Lieberthal et al. 2013).

(1) the presence of moderate to severe bulging of the tympanic membrane or new onset of otorrhea not due to acute otitis externa
(2) the presence of mild bulging of the tympanic membrane and acute (within 48 hours) onset of otalgia (holding, tugging, rubbing of the ear in a nonverbal child) or intense erythema of the tympanic membrane
(3) excluding the patients who do not have MEE (based on pneumatic otoscopy and/or tympanometry).

Diagnosis of AOM is almost precise when eardrum findings related to AOM such as MEE and/or various inflammatory findings are observed by otoscopic examination (Rosenfeld et al. 2001). It is a strong evidence of MEE when the eardrum mobility is observed to be diminished or lost by the pneumatic otoscopy. For the appropriate and precise observation of the eardrum, it is necessary to shed lights properly on the eardrum by removing cerumen. As the external ear canal of infants and small children is sometimes extremely narrow, a magnifying otoscope with sufficient amount of light is useful for the precise inspection of the eardrum. Although it was reported that usage of a surgical microscope did not improve the precision of the diagnosis of AOM more than that by a magnifying otoscopy (Hemlin et al. 1998), eardrum observation by a surgical microscope or an endoscope (especially equipped with CCD video camera) is desirable for the detailed inspection of the eardrum and the chronological recordings and preservation of those data. A prospective clinical trial reported that video endoscopy was the best for the identification of the MEE among pneumatic otoscopy, video endoscopy, tympanometry, and acoustic reflectometry (Guo et al. 2002). In our country, where optical instruments are highly developed and distributed, eardrum inspection by using a surgical microscope and/or a rigid endoscope equipped with CCD video camera is recommended.
Representative eardrum findings of AOM

Bullar formation

Thickening

Effusion line

Perforation & mucosal edema

Fig. 12.

References


Clinical question 19-2: How is the severity of AOM assessed?

Recommendation

Severity of AOM is classified as mild, moderate and severe according to eardrum findings and clinical manifestations. (Grade of Recommendation: A)

Reference used to assess the recommendation level: Hotomi et al., 2004, 2005 (Level IIa), Friedman et al., 2006 (Level Ib), Biner et al., 2007 (Level Ib)

Manifestations and findings and their scores used for the classification of the severity of AOM (proposal from the AOM Guideline Committee)

- 3 points are automatically given for the age younger than 24 months
- Otalgia is scored as 0, 1, 2, according to the severity
  0: absent, 1: present, 2: present - continuous severe pain
- Fever is scored as 0, 1, 2, according to the severity
  0: lower than 37.4 degree centigrade (°C), 1: higher than 37.5 but lower than 38.4 °C, 2: higher than 38.5 °C
- Crying and/or bad temper is scored as 0, 1, according to the severity
  0: absent, 1: present
- Hyperemia of the eardrum is scored as 0, 2, 4, according to the severity
0: absent, 2: present – 1st degree at manubrium of malleus, or at a part of eardrum, 4: present at whole eardrum

• Protrusion of the eardrum is scored as 0, 4, 8, according to the severity
  0: absent, 4: present at a part of eardrum, 8: present at whole eardrum

• Otorrhea is scored as 0, 4, 8, according to the severity
  0: absent, 4: present eardrum is visible, 8: present and eardrum is invisible

**Classification of severity of AOM according to the total score**

- Mild - < 5
- Moderate – 6 - 11
- Severe - > 12

A sample of a score chart used for assessing the severity of AOM in the clinic is shown in Table 13.

**Background**

For AOM, appropriate treatments according to its severity are required. In younger age, discrepancy between general condition and the eardrum finding is often seen in the convalescent stage of AOM; where the eardrum findings are not improved even general condition is improved well (Hotomi et al., 2004, 2005). Thus, precise assessment of the eardrum findings and therefore severity of AOM lead to the appropriate choice its treatment (Friedman et al., 2006).

**Comments**

In this guideline, severity of eardrum findings and clinical manifestations was scored, and the severity of AOM was assessed by summing those scores. Friedman et al. (2006) reported a similar study, in which they assessed the severity of AOM by summing the scores of both total impressions of the child by the guardian and eardrum findings, and concluded that such an assessment is important for the appropriate choice of its treatment. Casey et al. (2011) also discussed the grading of the severity of AOM by a scoring system for the diagnosis and evaluation of treatments of AOM, and they did so on the basis of symptoms (otalgia, bad temper, etc.), findings of eardrum, and systemic signs (fever: presence or absence, and degree). In our
previous guideline issued in 2006, 3 factors of the eardrum findings including hyperemia (yellowish change), protrusion, otorrhea were chosen as an assessing tool of the severity of AOM, while eardrum turbidity and diminishment of the light reflex were reported to be important for assessing the cure of AOM (Hotomi et al. 2004, 2005). For these reasons, in the present guideline, we reconsidered the factors of eardrum findings used for assessing the severity of AOM by way of normal group technique (NGT, see the note for detail), and agreed to pick up ‘diminishment of the light reflex’ in addition to hyperemia, protrusion and otorrhea. Then, in stratifying those factors, we assigned the score 0 (normal) and 4 (diminished or absent) on the newly-added factor of ‘diminishment of the light reflex’. Analysis of the influence of the factor (addition of the light reflex) on the score of severity of AOM using 721 children revealed that it did not affect significantly the distribution of the severity.

Until this 2013 issue was edited, the light reflex was reevaluated within the subcommittee to determine whether it is an appropriate and significant factor to assess the severity of AOM, and the conclusion was that it did not contribute sufficiently because of the difficulty of judgment due to the narrow and/or curved ear canal in newborns and infants and due to the lack of an objective or digital index, and also because of possibility of misjudgment due to differences in the observation apparatus or light source, for example.

A multicenter clinical study assessing the factors determining the severity of AOM revealed that the light reflex showed the smallest change in score after treatment, and that the light reflex score did not change even in patients showing successful treatment outcomes. In light of these results, it has been pointed out that the light reflex may not be suitable as a factor determining the severity of AOM, which is directly and closely related to the treatment algorithm (Yamanaka et al. 2012). Thus, in the 2013 Guidelines, the factor ‘light reflex’ was deleted from the factors, and consequently the lineup of factors has become the same as in the 2006 Guidelines.

In the previous issue of our guideline in 2006, we recommended that both eardrum protrusion and otorrhea should not be scored simultaneously, because both cannot exist at the same time, in other words, protrusion must disappear when otorrhea occurs. But in reality, there were not few children showing both of them, and many clinicians were found to score both of them. This is the reason why we recommended to score both of them in the present guideline. Analysis of the influence of this change
on the distribution of the severity of AOM using clinical data of two groups consisting of 1196 and 721 children with AOM revealed that this change did not affect much the distribution of the severity of AOM.

In the present guideline, as important clinical manifestations for assessing the severity of AOM, we chose three factors including otalgia, fever, and crying/bad temper with the same score, which were chosen in the previous guideline in 2006 by NGT, as well.

As for the body temperature, Kaleida et al. (1991) classified mild and severe AOM at 39.0 °C and 39.5 °C. Considering that the body temperature is measured at axilla in our country, the grades of fever were classified into three groups according to <37.4 °C, 37.5 – 38.4 °C, and >38.5 °C from discussion within the committee using NGT. It was defined that the score of the fever was determined by the body temperature measured at the first visit to a clinic. Although it is possible that fever is not necessarily related with the severity of AOM, fever was adopted as one of the factors determining the severity of AOM, because it is one of the basic signs and symptoms for diagnosing acute pediatric febrile diseases including AOM. In their report discussing the scoring of AOM, Casey et al. (2011) noted that the presence or absence of fever and/or the degree of body temperature were considered as two of the factors determining the score.

Since younger age is apparently one of the risk factors aggravating and/or prolonging AOM (Hotomi et al. 2004, Rovers et al. 2004, Ovetchkine et al. 2003, Block et al. 2000), ‘younger than 3 years of age’ was adopted as one of the factors determining the severity of AOM in our previous guideline in 2006. In this edition, considering the results of several other reports (Rovers et al. 2004, 2007, Ovetchkine et al. 2003, Block et al. 2000), we changed it into ‘younger than 24 months’. Analysis of the clinical data of 681 children with AOM revealed that this change caused only a slight shift of the distribution of the severity of AOM.

From all the results of reviews, we defined the scores for each factors as follows; otalgia: 0, 1, 2, fever: 0, 1, 2, crying and/or bad temper: 0, 1, eardrum hyperemia: 0, 2, 4, eardrum protrusion: 0, 4, 8, otorrhea: 0, 4, 8, and added 3 points for younger than 24 months of age. As the total score, smaller than 5, from 6 to 11, and greater than 12 were defined as mild, moderate, and severe AOM, respectively.
### Table 13. AOM Clinical Score Sheet

<table>
<thead>
<tr>
<th>Patient ID:</th>
<th>Name:</th>
<th>Age: ______ year ______ months</th>
<th>Date: _______</th>
<th>Body weight: ______</th>
<th>Body temperature: ______°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: ______</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>male</td>
<td>female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Scores chart]

<table>
<thead>
<tr>
<th>Age (≤24 mo.)</th>
<th>Otalgia</th>
<th>Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0 (&lt;37.4 °C), 1 (37.5-38.4 °C), 2 (&gt;38.5 °C)</td>
</tr>
<tr>
<td></td>
<td>1 (present)</td>
<td>1 (37.5-38.4 °C)</td>
</tr>
<tr>
<td></td>
<td>2 (continuous &amp; severe)</td>
<td>2 (&gt;38.5 °C)</td>
</tr>
</tbody>
</table>

Grading of eardrum protrusion

- **Moderate (partial)**
- **Severe (total)**

Fig. 13.
Crying bad temper 0 1

Eardrum hyperemia 0 2 (1st degree or partial) 4 (whole eardrum)
Eardrum protrusion 0 4 (partial) 8 (whole eardrum)
Otorrhea 0 4 (visible eardrum) 8 (invisible eardrum)
Light reflex 0 4 (diminished or absent due to turbidity)

Total score

[Assessment]
Mild (0-9) Moderate (10-15) Severe (>15)

[Addendum] normal group technique (NGT)

A method to make a decision on an issue, on which general agreement (consensus) is not obtained due to the lack of positive scientific evidence, or to existence of adverse evidence, is called consensus method. In consensus method, on the basis of individual opinions on an issue, final consensus is attained by intensively discussing and assessing those opinions. As those in the field of medicine or health care, Delphi’s method and Normal group technique (NGT) are often used. Both are characterized by collection and quantification of opinions and its feedback to the participants. In NGT, specialists of the field of the issue get together, directly give opinions, feed them back, and again give opinions with reference to the other’s opinions. A consensus is obtained by repeating those processes. Although this method has a disadvantage that some relationship between the participants may affect the final conclusion, it has a greater advantage that all the participants can directly exchange opinions. In this guideline, by using this method, an agreement was able to be attained on the selection of necessary items of eardrum findings and clinical manifestations for assessing severity of AOM, stratification of each item, scores allotted to the three levels of severity (mild, moderate, severe), as well as the selection of treatment for AOM with each three level of severity. Although the present consensus is not an objective results based on definite scientific evidence, it is expected to be a useful tool for the appropriate judgement in the clinical practice, as it is considered an extract of precious opinions of experienced specialists.
References


11. Block SL, Kratzer J, Nemeth MA, Tack KJ. Five-day cefdinir course vs. ten-day
CQ19-3: Is tympanometry useful to diagnose AOM?

Recommendation

Tympanometry is recommended to identify the presence of MEE after the diagnosis of AOM is confirmed by a precise otoscopic finding. (Grade of Recommendation: B, Saeed et al. 200473; Level IIa)

Background

Tympanometry is a reliable test to identify the presence of MEE in the tympanic cavity. An acoustic reflectometry, recommend to identify the effusion in European countries and the US (Laine et al. 2012), is not recommended in Japan because it has not been available since 1994.

Comments

Tympanometry is a tool to measure the compliance change of middle ear conduction system consisting of the eardrum, ossicles and tympanic cavity by forcing the positive and negative pressures in the sealed external ear canal. The type of tympanogram is roughly divided into three; type A, C, and B. Tympanometry is very reliable to detect the presence of MEE and the negative pressure in the middle ear (Subcommittee on Management of Acute Otitis Media 2004, Saeed et al. 2004, Sakaguchi et al. 1994). Although MEE can be detected using tympanometry, the stage of AOM, i.e. acute stage or resolution stage, cannot be identified (Rosenkranz et al. 2012). Therefore, it is necessary to observe the eardrum precisely using an otomicroscopy or an otoendoscopy. As children with AOM are usually younger than those with OME, we have to take care the following conditions when doing
tympanometry; presence of pain, impact cerumen, crying, insufficiency of an ear probe insertion and lack of a patient’s compliance. In addition, there has been a report that the incidence of antimicrobial agent use did not alter if MEE was detected by tympanometry (Spiro et al. 2004). From these reasons, the reliability of tympanometry for the diagnosis of AOM must be limited.

References

CQ 19-4 Is it necessary to ask patient’s history to diagnose AOM?
Recommendation
It is very important to ask background, past history and family history of a patient to predict the carriage of drug resistant bacteria and intractability of AOM. (Grade of Recommendation: B, Hotomi et al 200464; level IIa, Damiseaux et al. 20068; level IIa)
**Background**

AOM is mostly seen in infants. Young aged children and children in day-care attendance frequently associated with drug resistant bacterial infection and tend to be invasive (Ito et al. 1999, Hotomi et al. 2004). It is also important to know the presence of siblings because bacterial infection also transfers at home (Lubianca Neto et al. 2006).

**Comments**

Drug-resistant bacteria are frequently detected as pathogens of children in day-care attendance (Ito et al. 1999). A home-based child also has a chance to be exposed to drug-resistant bacterial infection if its siblings are taken care in a nursery school. There have been reports from Japan and European countries that AOM in young aged children tends to be severe or intractable (Hotomi et al. 2004, Rovers et al. 2004). The history of recurrent AOM suggests the carriage of drug-resistant bacteria and the presence of immunological weakness in each child. These data can be provided from detailed questionnaire, which is very valuable to predict the severity of AOM and the presence of immunological condition of a child. However, AOM cannot be diagnosed only with the history and/or symptoms (Laine et al. 2012). A sample of a questionnaire for a child with AOM is shown in Table 14.
Table 14. Questionnaire for a child with acute otitis media

Check: appropriate items, and fill out descriptive items, if applicable.

**Family history:**
- Chronic otitis media (yes—paternal grandparents, maternal grandparents, father, mother, siblings, others, none, unknown)
- Chronic sinustitis (yes—paternal grandparents, maternal grandparents, father, mother, siblings, others, none, unknown)
- Allergic rhinitis (yes—paternal grandparents, maternal grandparents, father, mother, siblings, others, none, unknown)
- Bronchial asthma (yes—paternal grandparents, maternal grandparents, father, mother, siblings, others, none, unknown)
- Atopic dermatitis (yes—paternal grandparents, maternal grandparents, father, mother, siblings, others, none, unknown)
- Other diseases (yes—paternal grandparents, maternal grandparents, father, mother, siblings, others, none, unknown)

**Past history:**
- Acute otitis media (yes—first episode, year, months old, times until now, no, unknown)
- Pneumonia (yes—first episode, year, months old, times until now, no, unknown)
- Otitis media with effusion (yes—first episode, year, months old, times until now, no, unknown)
- Rhinosinusitis (yes—first episode, year, months old, times until now, no, unknown)
- Allergic diseases (yes—first episode, year, months old, no, unknown)
  - Bronchial asthma
  - Atopic dermatitis
  - Allergic rhinitis
  - Food allergy
- Drug allergy (yes—name of the drug(s), no, unknown)
- Congenital diseases (yes—name of the disease(s), no, unknown)
- Other diseases (yes—name of the disease(s), at year, months old, no, unknown)
- Hospitalization (yes—name of the disease(s), at year, months old, no, unknown)
- Often get fever? (yes, no, unknown)

**Growth and life history:**
- Birth weight (grams), gestational weeks at birth, days earlier or later than the full term
- Nutrition at neonatal and infantile period—mainly by milk, mainly by breast feed, both mixed
- Day care (yes—from year, months old to year, months old, no, unknown)
- Siblings (brother(s), year old, sister(s), year old)
- Family composition (father, mother, brother(s), sister(s), paternal grandparent(s), maternal grandparent(s))
- Smoking of family member (yes, no)

**Signs and symptoms:**

1. Ear
   - Otalgia (earache) (yes, no, unknown)
   - Only for infants and small children: often touch his or her ear (yes, no, unknown)
   - Only for older children: ear fullness (yes, no, unknown)
   - Palpable tonsils (yes, no, unknown)
   - Otorrhea (ear discharge) (yes, no, unknown)

2. General
   - Flu symptoms (yes, no, unknown)
   - Fever (yes, no, unknown)
   - Cough (yes, no, unknown)
   - Nasal discharge or stuffy (yes, no, unknown)
   - Nausea, vomiting (yes, no, unknown)
   - Diarrhea (yes, no, unknown)
   - Bad tempered or low activity (yes, no, unknown)
References

[Addendum]
It is desirable to determine the presence of sensorineural hearing loss by pure tone audiometry in patients with AOM.
Sensorineural hearing loss is well-known complication of AOM. The association of sensorineural hearing loss suggests the extension and severity of the acute inflammation in the temporal bone.

The recommended method how to obtain a specimen for microbial test is shown in Table 15.

AOM is caused by the invasion of nasopharyngeal pathogens to the middle ear via the Eustachian tube. Therefore, it is valuable to take a specimen of the nasopharynx not orally but nasally. The pathogens detected from otorrhea and the nasopharynx were the same in 90% of *S.pneumoniae* and in 80% of *H.influenzae* (Konno et al. 1999).
Table 15. The method of sampling for microbial test

To detect pathogens of AOM, it is desirable to take specimens not only from middle ear effusion or otorrhea but also from nasopharynx. The main pathogens of AOM such as *Streptococcus pneumoniae* and *Haemophilus influenzae* are very weak under dry condition. A swab should be immediately inoculated into a porter for bacteriological examination.

1) A case without eardrum perforation

After sterilization of the external ear canal with alcohol or popvidone-iodine, the myringotomy is made. The middle ear effusion is taken for a microbial test using Seed-Swab No. 2.

2) A case with eardrum perforation

After removal of otorrhea in the external ear canal followed by the sterilization of the external ear canal with alcohol or popvidone-iodine, the middle ear effusion is taken for a microbial test using Seed-Swab No. 2.

3) Nasopharynx

After removal of nasal discharge followed by the sterilization of a nostril, nasopharyngeal smear is obtained endonasally.

Reference


[Addendum] Clinical usefulness of the Pneumococcal Antigen Rapid Detection Kit (Rapiran-HS®)

The kit has been on the Japan health insurance list since November 2011. The kit is a detection tool for pneumococci in middle ear effusion, ear discharge or nasopharyngeal secretion, and it is not used for other body samples including serum and urine.

The efficiency of the kit was evaluated in a clinical experiment based on microbiological culture results (Hotomi et al. 2012). In middle ear effusion or ear discharge, true positivity was found to be 81.4% (48/59), true negativity was 80.5% (165/205) and the rate of concordance was 80.7% (213/264). In nasopharyngeal secretion, true positivity was 75.2% (121/161), true negativity was 88.8% (95/107) and the rate of concordance was 80.6% (216/268). Moreover, when the results of whole
samples were combined, the true positivity was 76.8% (169/220), true negativity was 83.3% (260/312) and the rate of concordance was 80.6% (429/532). The concordance rates with microbiological culture results in both types of samples were favorable. Based on those results, the kit is considered to be efficient for the diagnosis of pneumococcal infections of the upper respiratory tract including OM and rhinosinusitis.

This kit is effective in the diagnosis of pneumococcus; however, it does not supply information about bacterial resistance or other types of pathogenic bacteria. However, the use of the kit may be efficient when considering the risk factors related to drug resistance in pediatric patients, including children under two years old (Yamanaka 2008), those enrolled in daycare and those administered an antibiotic within the prior month. However, the identification of pathogenic bacteria and the evaluation of drug resistance by bacterial culture methods should have priority. A recent multicenter study on the clinical usefulness of the kit for the management of AOM revealed that the kit was useful for identifying the infecting organism, selecting appropriate antibacterial agents, and giving the information to explain to patients’ guardians about the management of OM (Uchizono et al. 2012, Yamanaka et al. 2014).

The kit will be useful to select appropriate antimicrobial selections in the following cases of AOM.

1. In mild cases showing no improvement after observation, after 3 days’ administration of AMPC, the result of the kit will be useful for the subsequent treatment selection.
2. In moderate cases showing no improvement after the first antimicrobial therapy, the result of the kit will be useful for the subsequent treatment selection.
3. In severe cases at the first visit or cases showing no improvement after the first therapy, the result of the kit will be useful for the subsequent treatment selection.

H. influenzae Antigen Detection: ELISA

For OM or acute sinusitis, the detection of H. influenzae antigen in middle ear effusion or ear discharge and nasopharyngeal cavity or nasal secretion has been covered by the Japan health insurance since November 2012.

The test specifically detects the P6 protein localized in the outer membrane of all serotypes and nontypeable H. influenzae by an enzyme-linked immunosorbent assay (ELISA) and makes the diagnosis of influenzae infection. The remaining fluid
from the pneumococcus rapid detection kit can be used as a test sample, and the result is available within 3 hours (hospital laboratory or private laboratory). For middle ear effusion or ear discharge, the sensitivity was 83.3% (75/90), the specificity was 85.6% (143/164) and the rate of concordance was 84.8% (218/257), and for nasopharyngeal samples, the sensitivity was 71.5% (113/158), the specificity was 92.5% (99/107) and the rate of concordance was 80.0% (212/265) based on the microbiological culture standards.

References

20. Prophylaxis
CQ 20-1: Is PCV-7 effective for preventing AOM in children?

Recommendation
PCV-7 is effective for the prevention of infant AOM. (Grade of Recommendation: A, Benninger 2008 (level I a), Dinleyici 2010 (level I a), Boonacker et al. 2011 (level I a), Gisselsson-Solen et al. 2011 (level I b), and van Gils
et al. 2011(level I b)).

**Background**

Concerning vaccines against pneumococcus in Japan, the 23-valent pneumococcal polysaccharide vaccine Pneumovax® was released in the 1980s. However, this vaccine cannot be used on infants under 2 years of age, and since re-vaccination within five years involves risk, the usefulness and safety of the vaccine are low. On February 24, 2010, a 7-valent pneumococcal conjugate vaccine (PCV-7, Prevenar®), which can be used for infants from 2 months of age was released. In Japan, this vaccine covers 62.9% of serotypes and 78.0% of drug-resistant bacteria of pneumococcus isolated from middle ear fluid of childhood AOM. Preventive effects of 34.4%–62.5% against pneumococcus and 39.8%–49.1% against drug-resistant pneumococcus are expected, respectively.

**Comments**

As of May 2013, pneumococcal vaccines that can be used for children in Japan are the above-mentioned two types. Pneumovax® is 23-valent and the coverage is good at 93.7%; however, this vaccine is primarily intended for the elderly. PCV-7 is a 7-valent (4, 6B, 9V, 14, 18C, 19F, 23F) vaccine and the coverage is 62.9%. A near-lifelong immunity can be achieved by inoculating the individual four times between the age of 2 months and 15 months. PCV-7 has been used as a routine childhood routine vaccination in the U.S. since 2000, mainly for preventing ROM. Although the usability of a pneumococcal polysaccharide vaccine against ROM has been confirmed, conjugate vaccines including PCV-7 are not recommended (Straetemans et al. 2004: Ia). In a double-blind randomized controlled trial of the 7-valent pneumococcal conjugate vaccine and pneumococcal polysaccharide vaccine, there was no significant reduction in the incidence frequency of ROM (Brouwer et al. 2005: I b) and no effects of PneCRM (PCV-7) were indicated against AOM when evaluated by Ply-PCR (Palmu et al. 2009: I b).

However, the usability of the vaccines has been indicated in many Western research studies of cost-effectiveness with a high level of evidence (Jansen et al. 2008: I b; Dinleyici et al. 2010: I a; Gisselsson-Solen et al. 2011: I b; Tyo et al. 2011: III). Inoculation of this vaccine reduces the contained pneumococcus serotype (Boonacker
et al. 2011: Ia; Van Gils et al. 2011: Ib), but on the other hand, it is also reported that it increases serotypes of 19A and 16A and *H. influenzae* that are not included (Benninger 2008: Ia; Sox 2011: Ia). In Japan, the preventive effect of PCV-7 against OM is reported to be 7% to 9%; however, for AOM, when the cost-effectiveness of the vaccination is calculated, the usability is sufficiently high, contributing to an annual reduction of 31.4 billion yen in medical expenditures even after the total cost of vaccination is subtracted (Kamiya et al. 2008: III).

PCV-13 (a 13-valent vaccine) and PHiD-CV (a 10-valent vaccine including *H. influenzae*) have already been adopted in Western countries, and their usability has been demonstrated (Ib). A comparison study of the three types of vaccines is in progress, showing the effectiveness of all three: PCV-13, PHiD-CV, and PCV-7. PCV inoculation is expected to reduce the incidence and symptoms of OM (Shea et al. 2011: Ia; Grijalva et al. 2011: Ia). The cost-effectiveness of all three PCV inoculations was high (Dinleyici et al. 2010: Ia); however, there are reports pointing out the necessity of considering various factors in order to evaluate the true cost-effectiveness (Tyo et al. 2011: III). There are also reports indicating that the economic effect of PCV-13 (Strutton et al. 2012: III) or PHiD-CV (Robberstad et al. 2011: III) is better than those of the other two vaccines. In Japan, PCV-13 was approved in May 2013, and it was approved for production and sales in June of the same year. If PCV-13 and PHiD-CV become available in the near future, the coverage is expected to expand further and the usability is expected to rise. In their guidelines for the treatment for AOM revised in 2013, the U.S. strongly recommended a pneumococcal vaccine for all children (Lieberthal et al. 2013).

**[Addendum – June 2014]**

In Japan, from November 1st, 2013, PCV-13 [Prevenar13®: a 13-valent pneumococcus conjugate vaccine with a 6-valent serotype (1, 3, 5, 6A, 7F, 19A) newly added to PCV-7] has been used in place of PCV-7 in routine vaccinations. According to the Japanese epidemiological data, the 7-valent serotype accounts for 37% and the newly added 6-valent serotype accounts for 30% of invasive infections by pneumococcus.

As for the use of PCV-13, in clinical trials, the incidence of side effects such as erythema reaction at the injection site was observed to be more than 70% (single
inoculation) and systemic reactions such as fevers (of 37.5°C or more) were observed in more than half of the cases, and therefore, sufficient care should be taken to monitor patients for adverse reactions (Ministry of Health, Labor and Welfare, 9/10/2013).

References


11. Sox C. Acute otitis media: antibiotics are moderately effective and mildly increase the risk of adverse effects; prevalence of different causative bacteria changed after introduction of the heptavalent pneumococcal conjugate vaccine. Evid Based Med 2011; 16:181-2.


21. Treatment

The outcome of the treatment recommended by the present guideline is defined by improvement of otoscopic findings such as “injection, swelling, thickness, blister formation, dullness and perforation of the eardrum, the presence of MEE, otorrhea, and edema of the middle ear mucosa”, at the point of 3 weeks after the onset.
Otoscopic score 0 of each item except for age factor (under 24 months) is judged as cure of AOM.

A patient receiving antimicrobial agents before the onset of AOM is also classified into three stages of AOM such as mild, moderate or severe, and is adapted to the algorithm of the present guideline. However, we should consider an antimicrobial agent which a patient has been given before, and should take otoscopic findings at the examination carefully.

CQ 21-1 Is it reasonable not to administer antimicrobial agents for mild AOM?

Recommendation
Watchful waiting for 3 days without use of antimicrobial agents is recommended for a mild AOM. (Grade of Recommendation: A, Damoiseaux et al. 2000, Glasziou et al. 2000 (level Ia), Little et al. 2006 (level IIa))

Background
It has been reported that most of cases of AOM improve without use of antimicrobial agents (van Buchem et al. 1985, Damoiseaux et al. 2000, Rosenfeld et al. 2003 a, b, Jacobs et al. 2001, Glasziou et al. 2000). However, as the incidence of AOM caused by drug resistant bacteria is popular in Japan, it is important for us to diagnose mild AOM precisely by the finding of the eardrum, and follow a child strictly when we do not use antibiotics.

Comments
The use of antibiotics is closely related with the increase of drug resistant bacteria in the treatment of infectious diseases. It has been reported that most of cases of AOM improve without use of antimicrobial agents (van Buchem et al. 1985, Damoiseaux et al. 2000, Rosenfeld et al. 2003 a, b, Jacobs et al. 2001, Glasziou et al. 2000, Wald et al. 2001). Takata et al. (2001) reported the metaanalysis consisted with 74 comparative studies, and concluded that the cases with simple AOM treated without antimicrobial agents rarely showed complications and the effect of AMPC was minimum for the cases. In the randomized clinical trial (RCT) between AMPC and placebo for children with AOM, in whom 80% of the cases were classified as moderate
AOM, the placebo group did not show poorer recovery compared with the AMPC group (Le Saux et al. 2005). McCormick et al. (2005) reported the comparative study between the groups with and without administration of AMPC for cases with non-severe AOM, the eradication rate was high but the carriage rate of drug resistant S. pneumoniae increased in cases treated by AMPC. They concluded that watchful waiting was recommended when the following items were resolved; evaluation of severity of AOM, education for parents, the treatment for relief of the symptom, easy access to the hospital for follow-up, and antimicrobial agent use if necessary.

Little et al. (2001) reported the multicenter-comparative trial between two groups, one with immediate use of antimicrobial agents and the other with use of antimicrobial agents only when the symptom relief was not obtained for 72 hours, and the results were as follows; there was no significant differences between the two groups if the patients did not show high fever, restlessness and vomiting. However, immediate use of antimicrobial agents significantly decreased the incidence of restlessness and sleep disturbance if the patients showed high fever, restlessness and vomiting. In addition, Little et al. (2006) reported the long-term outcome i.e. three months and one year after the randomized trial regarding antimicrobial agent use in the two groups described above. As the results, there was no statistically different in the long-term outcome between the two groups. In the other report, wait-and-see for 48 hours without prescription of antimicrobial agents is useful if the symptom does not become worse (Spiro et al. 2006).

Rover et al. (2007) reported the meta-analysis of randomized trial, in which the prognosis of the two groups, i.e., wait-and-see group and immediate antimicrobial agent use group, was compared regarding pain and/or fever at 3 and 7 days. They concluded that the symptoms in children younger than 2 years persisted twice longer than those in children at the age of 2 years and older. In the RCT between the immediate use of antimicrobial agents and wait-and-see for 72 hours if a child does not complain otalgia, fever and some other symptoms, the immediate use of antimicrobial agent group showed significantly less otalgia than the wait-and-see group 3 months after the trial particularly in cases of recurrent AOM. However, one year after the trial, there was no difference in the outcome between the two groups (Little et al. 2006). From the results of these reports, it is possible to do watchful waiting for children with good general condition, but it is necessary to evaluate the
clinical signs and symptoms in children with risk factors if they are not administered antimicrobial agents.

In Japan, AOM caused by drug resistant bacteria has been increasing. Hotomi et al. (2005) classified children with AOM into two categories, mild and severe cases, and children with mild AOM were not given antimicrobial agents. As the results, it is possible not to use antimicrobial agents for mild AOM for 5 days. Although they showed that the clinical symptoms improved in 94% of the children with both mild and severe AOM, otoscopic findings improved in 55% of mild AOM and in only 10% of severe AOM at day five. Therefore, when a child is followed without antimicrobial agent use, it is necessary to follow the child watchfully and to prepare the circumstances to give antimicrobial agents to a child anytime if he/she has failed to show improvement. There has been another trial that parents could give a child antimicrobial agents, which had been prescribed beforehand, when needed. As the results, only 31% (Siegel et al. 2003) and 34% (McCormick et al. 2005) of children were administered antimicrobial agents. Rover et al. (2004) also reported that some children improved without the use of antimicrobial agents, but it is important to follow them for 2~3 days strictly.

References
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CQ 21-2 Are antimicrobial agents useful for the analgesic treatment of AOM?

Recommendation
The efficacy of antimicrobial agents specifically for otalgia is unknown.
(Grade of Recommendation: I)

Background
Otalgia is the main clinical symptom of AOM to be treated, but contradictory results concerning the analgesic effect of antimicrobial agents have been reported.

Comments
Glasziou et al.(2004) reported that antimicrobial agents did not significantly improve otalgia compared to the natural course. In contrast, Bascelli et al. (2001) reported that the duration of subjective otalgia was significantly shorter and the consumption of analgesics was significantly reduced in an antimicrobial agents-treated group in a randomized controlled study in which antimicrobial agents were administered immediately after onset and 3 days after onset in cases showing no remission tendency. Therefore, the effect of antimicrobial agents on otalgia is unclear. The effect of analgesics on otalgia has also not been fully investigated. In a multicenter randomized double-blind controlled study performed by Bertin et al. (1996), the effect of ibuprofen was significant compared to a placebo, but no
significant analgesic effect of acetaminophen was observed.

Note: In the current situation in Japan, acetaminophen is selected for analgesic treatment for infants aged 3 years or younger.

[Addendum]

It was reported in 2008 that the local administration of 2% lignocaine into the external acoustic meatus significantly reduced pain to 50% of the pretreatment level at 10 and 30 minutes after ear drop treatment in a double-blind randomized controlled study (Bolt et al. 2008), for which additional study results are anticipated.

References


2. Bascelli LM, Losh DP. How does a "wait and see" approach to prescribing antibiotics for acute otitis media (AOM) compare with immediate antibiotic treatment? J Fam Pract 2001; 50:469.


CQ 21-3 Which antimicrobial agents should be used for AOM?
**Recommendation**

Recommended antimicrobial agents depend on bacterial resistance and the severity of AOM, but the following are often recommended. (Grade of Recommendation: A)

P.O.: Amoxicillin (AMPC), amoxicillin/clavulanate (AMPC/CVA), cefditoren pivoxil (CDTR-PI), and DIV: Ampicillin (ABPC), ceftriaxone (CTRX)

Studies used for the recommendation: Ghaffar et al. 2002, 2000 (Level Ib), Piglansky et al. 2003 (Level Ib), Haiman et al. 2002 (Level Ib)

**Background**

Based on the current situation in Japan, about 50-65% of *S.pneumoniae* and about 50-70% of *H. influenzae* is drug-resistant, therefore, it is recommended to select the above antimicrobial agents corresponding to the severity of AOM based on the sensitivity of pathogens. This does not mean that other antimicrobial agents are not recommendable, but the above antimicrobial agents are recommended in consideration of the current drug sensitivity in Japan.

**Comments**

Based on bacteria detected in infants with AOM in Japan and antimicrobial agent activities on these, AMPC, CVA/AMPC (1:14), CDTR-PI, TFLX and TBPM-PI as peroral agents, and CTRX and ABPC are selected as injection corresponding to the severity. Reports on AMPC treatment in Japan demonstrated their usefulness (Hotomi et al. 2005, Harabuchi et al. 2001). In the U.S. guidelines revised in 2013, AMPC is still recommended as the first-line antimicrobial agent (Lieberthal et al. 2013).

Regarding studies on AMPC and AMPC/CVA in Western countries, a
prospective observational study reported significant therapeutic results of AMPC (Brook et al. 2002). Lund et al. (2001) investigated changes in bacterial flora in the oropharynx and epipharyngeal space in 12 patients treated with AMPC/CVA and 17 patients treated with cefuroxime axetil (CMX-AX) in a randomized controlled study, and observed similar effects on *S. pneumoniae, H. influenzae*, and *M. catarrhalis* in the epipharyngeal space in both groups. The administration of AMPC/CVA at an increased dose (90/6.4 mg/kg/day, 10 days) was effective with regard to the eradication rates of *S. pneumoniae*, PRSP, and *H. influenzae* in a multicenter randomized controlled study (Dagan et al. 2001). Piglansky et al. (2003) also reported that high-dose AMPC (80 mg/kg/day, 10 days) was effective as an early treatment in a prospective observational study. In contrast, high-dose AMPC was neither beneficial nor non-beneficial for antimicrobial agent-resistant low-risk AOM in a double-blind randomized controlled study (Garrison et al. 2004). Casellas et al. (2005) observed no difference in efficacy between AMPC/SBT and AMPC/CVA in a multicenter single-blind randomized controlled study. Regarding non-AMPC responders, Block et al. (2001) reported that many patients in whom the disease was not remitted by AMPC were infected by *S. pneumoniae* in a retrospective observational study. Regarding the dosing frequency, Damrikarnlert et al. (2000) observed no significant difference between twice—and 3 times-per-day administrations of AMPC/CVA in a multicenter randomized controlled study.

Haiman et al. (2002) investigated changes in *S. pneumoniae* in the epipharyngeal space (before, in the middle of, and after treatment) in a randomized controlled study in which ceftriaxone (CTRX) was injected 3 times, and observed a significant reduction of *S. pneumoniae*. Heikkinen et al. (2000) also reported that the intramuscular injection of CTRX significantly decreased *H. influenzae* in the epipharyngeal space. Toltzis et al. (2007) reported that the potentiation of fecal gram-negative bacterial growth by a single intramuscular injection of CTRX was similar to
that by cefprozil (CFPZ), AMPC, and azithromycin (AZM) in a randomized controlled study. Wang et al. (2004) also reported that a single administration of CTRX was as effective as the 10—day administration of AMPC/CVA (40 mg/kg). The intramuscular injection of CTRX is not indicated in Japan, but once-a-day administration to infants was approved on November 13, 2007, and intravenous antimicrobial agent injection at outpatient clinics became available for infants, as in adults.

Ioannidis et al. (2001) performed a meta-analysis of multicenter randomized controlled studies, and identified no significant differences in the efficacy or safety of AZM for upper airway infection compared to other antimicrobial agents. Hoberman et al. (2005) compared high-dose CVA/AMPC (6.4/90 mg/day) and AZM, and observed that CVA/AMPC was more useful than AZM, but Guven et al. (2006) noted no significant difference between AZM and AMPC/CVA (45/6.4 mg/day) in a single-blind randomized controlled study. Arguedas et al. (2005) reported that AZM exhibited an effect equivalent to that of high-dose AMPC (90 mg/kg) and was superior in compliance in a multicenter double-blind randomized controlled study. Regarding the current state of pathogens in Japan, AZM may be selected for *H. influenzae*.

In light of the present status of pathogens of AOM in Japan, cefaclor (CCL), cefpodoxime proxetil (CPDX-PR) cannot be treatment options, and CFPZ and gatifloxacin (GFLX) are also not allowed; they are not approved in Japan.

TFLX is a rare new quinolone agent, the safety of which for children is recognized. TFLX shows excellent antimicrobial activities to gram-positive and -negative bacteria, anaerobic bacteria, several β-lactamase producing bacteriae, and methicillin-resistant *Staphylococcus aureus* (MRSA). TFLX was also clinically demonstrated to have an excellent effect on OM (Suzuki et al. 2010, Yamanaka et al. 2012a), as well as in basic and clinical studies in the field of otorhinolaryngology
TBPM-PI, which is the only peroral carbapenem agent, has a wide range of antimicrobial spectrum and antimicrobial activities that are stronger than those of intravenous carbapenem agents. A randomized controlled trial (RCT) of TBPM-PI on AOM in children showed an effect equivalent to that of a high dose of CDTR-PI (Suzuki et al. 2009). Its good transition to ME tissue was also reported (Baba et al. 2009). A recent multicenter clinical trial revealed its high efficacy on AOM in children, including those with ROM and prolonged OM (Yamanaka et al. 2012b). The present AOM Guideline Subcommittee recommends that TFLX and TBPM-PI should be used only in cases in which the effect of other antimicrobial agents cannot be expected.

References


CQ 21-4 How long is the period for administration of antibacterial agent?

**Recommendation:**

In moderate and severe cases, the patient should be treated with 5-day administration of antibacterial agent and disease status should be evaluated at the third or fourth day of the treatment. (Grade of Recommendation: A)

Studies used for the recommendation: Ovetchkine et al. 2003 (Level Ia), Kozyrskyj et al. 2000 (Level Ia), Bezakova et al. 2009 (Level Ib), Gulani et al. 2010 (Level Ia), Hoberman et al. 2011 (Level Ia), Tahtinen et al. 2011 (Level Ib)

**Background**

Although the period of antibacterial therapy is generally 5-day, 7-day or 10-day, the period is recommended according to the pathogenicity of bacteria and the
efficacy of antibacterial therapy.

Comments

In a prospective study, Pichichero et al. (2001) evaluated 5-day, 7-day and 10-day period of antibacterial therapy for AOM. Although 10-day treatment was found to have better cure and improvement in cases with an episode of AOM in the preceding month or in cases with more than one AOM episodes, no significant difference was observed in the outcome of 5-day, 7-day and 10-day treatment groups between antibacterial types and ages.

On the other hand, a meta-analysis based on 7 randomized controlled trials revealed that longer period of antibacterial therapy was better in the outcome than shorter course in children younger than 2 years of age, attending daycare centers and those with perforated tympanic membrane, while shorter course was recommended in children elder than 2 years even with previous antibacterial treatment or recurrent AOM history (Ovetchkine et al. 2003, Kozyrskyj et al. 2000) compared the clinical efficacy of antibacterial therapies less than seven days and longer course (8 - 19 days) in another meta-analysis of 32 randomized controlled studies. The five-day antibacterial therapy was found to be effective for uncomplicated AOM. Leibovitz et al. (2000) compared 1-day 50mg/kg/day vs. 3-day 50-mg/kg/day of intramuscular CTRX treatment in non-responsive AOM and found 3-day regime to be significantly effective especially for PISP and PRSP. However, intramuscular administration of CTRX is not approved in Japan. Pichicero et al. (2000) found no significant difference
for clinical efficacy between 5 days vs. 10 days treatment of cefuroxime axetil (CXM-AX) and concluded that short course treatment is effective because of better drug compliance. However, CXM-AX is not a treatment alternative in Japan when considering the etiologic bacterial agents. In a multicenter single-blind (doctor blinded) randomized study, Roos et al. (2000) compared 5 days versus 10 days treatment with ceftibuten (CETB) 9mg/kg/day for recurrent AOM and reported that 10 days treatment showed lower recurrence rate in short term follow-up. Another prospective study on duration of antibacterial therapy for cases not previously received antibacterial agents suggested 5 days treatment for AOM in children over 2 years of age (Manarey et al. 2002).

An RCT comparing the effect by questionnaire of 3-day AMPC (40 mg/kg) and a placebo revealed no significant difference in the incidence of recurrence (Bezakova et al. 2009). A systematic review analyzing 35 RCTs comparing the effects of short-term (<4 days) and long-term (>5 days) administrations of peroral antimicrobial agents on AOM in children revealed that the risk of treatment failure increased in the short-term group when short-acting antimicrobial agents were used (Gulani et al. 2010). These results suggested that at least more than 4 days’ administration of antimicrobial agents is recommended whenever necessary.

In another RCT comparing the efficacy of 7-day CVA/AMPC and placebo on AOM in children, a significant difference between the two groups was shown in the incidence of treatment failure from the third treatment day (Tahtinen et al. 2011). Hoberman et al. (2011) also conducted an RCT comparing the effects of 10-day
CVA/AMPC and placebo on AOM in children, and they reported a significant difference in the incidence of the clinical failure from the 4th or 5th administration days. These results may indicate that the clinical efficacy of antimicrobial agents appears on the third administration day at the earliest, and thus, the assessment of efficacy on the third administration day is recommended.

In the U.S. AOM Guidelines revised in 2013, a 10-day administration of antimicrobial agents is recommended for infants under the age of 2 or severe cases, a 7-day administration is recommended for moderate or mild grades in children 2 to 5 years of age, and for moderate or mild grades in children older than 6 years, the Guidelines state that 5–7 days’ administration is sufficient. Also, the U.S. Guidelines recommend the assessment of the effect of the agent on the 2nd or 3rd day of administration in cases of initial use (Lieberthal et al. 2013).

References

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CQ 21-5 What are appropriate indications for myringotomy?

Recommendation

The indication should be considered depending on severity of AOM. (Grade of Recommendation: I)

Background

In AOM, there is fluid accumulation due to inflammatory pathology in middle ear, therefore drainage of inflammatory fluid by myringotomy would be efficient for early cure of the disease. However, currently there are only a limited number of studies about the clinical efficacy of myringotomy on early cure of the disease.

Comments

All of the reports showing the clinical efficacy of myringotomy have been of the retrospective study. Myringotomy was performed for cases with infection signs after 48 hours of antibacterial therapy and all cases showed improvement 48 hours after the procedure (Babin et al. 2003). Hotomi et al. (2002) concluded that myringotomy was necessary depending on severity of the disease. In a case-control study, Nomura et al. (2005) reported that myringotomy significantly decreased the deterioration rate of AOM into OME, while it was not effective for prevention of early relapse or recurrence of AOM. A randomized controlled trial comparing the three groups including myringotomy only, antibacterial therapy only, and myringotomy with
antibacterial therapy in severe cases revealed that there was no clinically significant difference among them, even myringotomy added to antibacterial therapy (van Buchem et al. 1985). In another randomized trial of severe cases, Kalaaida et al. (1991) compared three regimens including amoxicillin only, amoxicillin and myringotomy, and placebo and myringotomy (2 years and older) and found that the treatment failure was higher in placebo and myringotomy group compared with others in severe cases. Based on this trial, it can be inferred that myringotomy only may not be of an effective treatment; nevertheless myringotomy would be effective in combination with antibacterial therapy.

The position statement released in 2009 by the Canadian Paediatric Society recommended a referral to an otolaryngologist for tympanocentesis when a patient with β-lactam allergy does not improve after first-line treatment of antimicrobials and when a patient does not improve after a second-line treatment with antimicrobials (Forgie et al. 2009).

One of the concerns is that most previous studies concerning the effect of myringotomy were based on data obtained under the circumstances of no significant antimicrobial-resistant bacteria. It seems that patients with refractory OM caused by PRSP and/or BLNAR were not included in these studies. Yamanaka and Hotomi (2006) compared the otoscopic findings of the tympanic membrane in patients with severe AOM between those who received antimicrobial treatment with myringotomy and those who received antimicrobial treatment, and they found that the otoscopic findings 2 weeks after the treatment were improved significantly in the myringotomy group compared to the only-antimicrobial treatment group.

Uno (2008) evaluated the effect of myringotomy in patients with AOM, and he concluded that in severe cases, as defined by the severity evaluation, the disease was ameliorated significantly earlier after myringotomy than without it in patients with an ear pain score of 2 and fever score of 1 or 2 on a clinical symptom evaluation, a flare score of 2 and a bulge score of 4 or 8 on otoscopic evaluation, and an otorrhea score of 0. He also found that early in the 10-day follow-up, the overall improvement rate was significantly higher after myringotomy than in the non-myringotomy cases, but the difference was not significant in the final outcome. The recurrence rate in severe cases was also significantly lower in the myringotomy group than in the non-myringotomy group.
References


CQ 21-6 What are appropriate indications for topical otic treatment?
Recommendation

In cases who underwent ventilation tube insertion, antibacterial eardrops is recommended only for the condition securing full access of antibacterial solution with high antimicrobial activity into middle ear through the tube. (Grade of Recommendation: A)

Studies used for the recommendation: Dohar J et al. 2006 (level Ib), Schmelzle et al. 2008 (level Ia)

Background

Topical otic treatment can achieve high concentration of antibacterial agent in middle ear and have an indication in selected cases.

Comments

In a prospective study, 4 drops of topical ciprofloxacin (CPFX 0.3%) / dexamethasone (0.1%) twice daily for 7 days and oral suspension of AMPC/CVA (600mg/42.9mg) every 12 hours for 10 days was compared in AOM cases with otorrhea through tympanostomy tubes, otic drops obtained significant earlier cure and the otic treatment was found to be effective in earlier cessation of otorrhea through tympanostomy tubes (Dohar et al. 2006). Concerning the type of otic treatment, a randomized clinical trial comparing CPFX/dexamethasone and ofloxacin (OFLX) revealed CPFX/ dexamethasone to be significantly superior (Roland et al. 2004).
Schmelzle et al. (2008) reviewed the evidence regarding the antibiotic treatment of AOM in children with tympanostomy tubes, and they discussed antibiotic resistance and ototoxicity, using articles providing level I evidence (randomized controlled trials) for treatment. They reported that the current evidence suggests that a topical fluoroquinolone, with or without a corticosteroid, results in a faster resolution of otorrhea, and that this is the treatment of choice for AOM with tympanostomy tubes.

[Addendum]
In a double-blind, randomized trial in 2008 evaluating eardrops for pain relief, topical 2% lignocaine was found to reduce significantly pain scores at 10, 20 and 30 minutes by 50% from the baseline (Bolt et al. 2008).

References


3) Schmelzle J, Birtwhistle RV, Tan AKW. Acute otitis media in children with
tympanostomy tubes. Can Fam Physician 2008; 54:1123-7


CQ 21-7 Risk factors deteriorating AOM and medications other than antibacterial agents

Recommendation

Since younger age and daycare attendance have an important role on deterioration of the disease, the attention should be paid during the treatment. (Grade of Recommendation: A)

In cases of AOM complicated with nasal disease, nasal treatments should be considered as complementary to the treatment of AOM (Recommendation level I).

The report used for the recommendation: Ovetchkine et al. 2003 (Level Ia), Montanari 2010 (level IIa)

Comments

Flynn et al. (2002) compared anti-inflammatory drug, antihistamine agents and combined treatment of both agents with placebo in a meta-analysis including 13 randomized controlled trials and they did not find any benefit both in anti-inflammatory and antihistamine agents receiving groups. Furthermore, in a more
recent meta-analysis of Flynn et al. (2007) including 15 randomized controlled trials, combination of decongestants and antihistamine agents was evaluated and no benefit was found in the improvement of AOM. Therefore, decongestants are not recommended and standard administration of antihistamine agents is also not recommended. Young age under 2 years is a risk factor for recurrent AOM and persistent MEE after AOM (Kobayashi et al. 2006, Damoiseaux et al. 2006). Hotomi et al. (2004, 2005) found that severe AOM cases were more common in children with younger age and male gender while there was no relation between daycare attendance and severity of AOM. However, Ovetchkine et al. (2003) showed that in addition to tympanic membrane perforation and young age below 2 years, daycare attendance showed significant role on the severity of AOM.

In meta-analysis of Glasziou et al (2000) consisting of 7 randomized controlled trials, antimicrobial agent use was reported to be unnecessary in mild AOM cases, while antimicrobial agent administration was effective in risk group for mastoiditis.

Pacifier use was reported to be a risk factor for both AOM and respiratory infections (Niemela et al. 2000), and it was also found as a risk factor for recurrent AOM (Lubianca Neto et al. 2006).

The role of nasal intervention in treatment of AOM is not clearly defined. Ito et al. (2002) evaluated effects of nasal intervention on bacterial flora of nasopharynx in AOM cases by a prospective study. They found that bacterial population of nasopharynx contained lower detection rates of PRSP (57%) and BLNAR (60%) when the nasal intervention was performed. In a prospective study,
Irimada et al. (1999) evaluated the change of bacterial population in nasal discharge in a patient group performing nasal wash without antimicrobial agent treatment. They reported that amount of nasal discharge and postnasal drips decreased and were normalized in 55% and 71% of cases, respectively. Moreover, bacteria quantity decreased or disappeared to 80% of *S. pneumoniae* and 60% of *H. influenzae*. Although the evidence level is not high enough, normalization of bacterial flora in nasopharyngeal cavity by nasal intervention is very likely to bring a benefit of *S. pneumoniae* and 60% of *H. influenzae*. Although the evidence level is not high enough, the normalization of bacterial flora in the nasopharyngeal cavity by nasal intervention is very likely to provide a benefit for the treatment of AOM by improving the eustachian tube function. Only the Japan guidelines had recommended nasal intervention for the management of AOM. However, recently, the removal of nasal discharge was also recommended by the Italian AOM guidelines (Marchisio et al. 2010). Nowadays, it has been accepted worldwide that nasal intervention is important for the management of AOM. In a prospective study, the use of a nasal aspirator and physiological saline solution (the Narhinel method) was shown to be more effective compared to the use of physiological saline alone in the prevention of acute rhinosinusitis and AOM in children (Montanari 2010).

**References**

2. Montanari G. Observation study on the performance of the Narhinel method (nasal aspirator and physiological saline solution) versus physiological saline
solution in the prevention of recurrences of viral rhinitis and associated complications of the upper respiratory tract infections (URTI), with a special focus on acute rhinosinusitis and acute otitis of the middle ear. Minerva pediatrica 2010; 62:9-16,17-21.


CQ 21-8 Is a revitalizing stimulant in Japanese herbal medicine effective for ROM?

**Recommendation**

As a revitalizing stimulant in Japanese herbal medicine, *Juzen-taiho-to* has the ability to stimulate an immune response and improves the nutritional status, and thus we recommend it for the treatment of ROM in children (Grade of Recommendation: B, references used to assess the recommendation level: Maruyama et al. 2008 [level IIb], Yoshizaki et al. 2012 [level IIa]).

**Background**

The prevalence of ROM is quite high in children under 2 years, who show an immature immune system against microorganisms. It has been reported that a revitalizing stimulant in Japanese herbal medicine, *Juzen-taiho-to*, showed significant efficacy for the improvement of ROM in children.

**Comments**

In Japanese herbal medicine, revitalizing stimulants are administered for patients with poor physical strength to improve their weakness and homeostasis. There are two revitalizing stimulants in Japanese herbal medicine: *Juzen-taiho-to* and *Hochu-ekki-to*. There have been many clinical and basic reports concerning the effects of *Juzen-taiho-to* on the immune-defense system. Clinically, they are: inhibitory effects on rhinovirus infection, weight gain and decrease of the episodes of common cold in patients with COPD (chronic obstructive pulmonary disease), and inhibitory effects on MRSA and Candida infections. In addition, *Juzen-taiho-to* showed efficacy for pediatric patients with perianal abscess, and its administration has become a gold
standard for the treatment of perianal abscess. The effects of Juzen-taiho-to include the improvement of the immune-defense system and nutritional status by the stimulation of phagocytotic activity, modulation of cytokine production, and stimulation of NK cell activity.

Maruyama et al. (2009) reported that otitis-prone children who received Juzen-taiho-to for 3 months showed a reduction in the number of the episodes of AOM, improved febrile duration, shortened duration of the antibiotic administration, and fewer visits to an emergency room. They concluded that the efficacy rate of Juzen-taiho-to was 95.2% in otitis-prone-children. In a randomized study, the episodes of AOM and acute rhinitis associated with the common cold and the use of antimicrobial agents were significantly reduced in otitis-prone children treated with Juzen-taiho-to compared with those without it (Yoshizaki et al. 2012). In particular, those authors concluded that Juzen-taiho-to was significantly more effective for otitis-prone children with the following characteristics:

1) severe cases with frequent episodes of AOM
2) under 2 years of age
3) day-nursery attendance
4) children exposed to tobacco smoking

Of note, in the Japanese insurance health program, Juzen-taiho-to is not supported for OM, but it is supported for conditions such as general fatigue after surgery, tired feeling, loss of appetite, night sweats, cold feeling of extremities, and anemia.

References


CQ 21-9 Treatment algorithms for AOM in children

The following figures show algorithms for treating AOM, which were made
by combining the results of our review of evidence and the opinions of expert-members of the Guideline subcommittee, and the algorithms are recommended for uncomplicated cases of AOM. In clinical practice, therapeutic strategies should be chosen based on the situation of each individual patient. Cases showing no improvement in the signs even after the third-line treatment in these Guidelines should be regarded as having refractory OM, and they are not considered the subjects of these Guidelines.
Treatment Algorithm for Moderate AOM (Score 6-11)

- Otalgia, fever (≥ 38.5°C) → Acetaminophen 10mg/kg
- Sign of nasal disorder → treatment
- Bacterial culture from nasopharynx or otitis media
- Use of Lactobacillus bifidus or Mylarisan when administering antimicrobials
- * Consider change of antimicrobials using rapid detection kit for S. pneumoniae
- Pay attention to secondary hypocalcemia when administering antimicrobials containing piperacillin
- ** *Maximum 7 days by national health insurance program
- Do not exceed the following dose
  - AMPC: 500mg/time, 1500mg/day
  - CDTR-PI: 200mg/time, 600mg/day
  - TBPM-PI: 300mg/time, 600mg/day
  - TFLX: 180mg/time, 360mg/day
- Follow-up period is 3 weeks from the first visit
Treatment Algorithm for Severe AOM (Score >12)

Myringotomy + any of 1~3 for 3 days *
1. High dose AMPC
2. CVA/AMPC (1:14)
3. High dose CDTR-PI

No improvement

Any of 1~4 based on the susceptibility, for 3 days *
1. Myringotomy + CVA/AMPC (1:14)
2. Myringotomy + High dose CDTR-PI
3. TBPM-PI * *
4. TFLX

No improvement

1 or 2 for 5 days *
1. Myringotomy + TBPM-PI * *
2. Myringotomy + TFLX or DIV 1 or 2 for 3 days
3. ABPC 150mg/kg/day
4. CTRX 60mg /kg/day
(premature and neonate <50mg/kg/day)

The same drug for 2 more days

Observation

• Otalgia, fever (≥ 38.5°C) → Acetaminophen 10mg/kg
• Sign of nasal disorder → treatment
• Bacterial culture from nasopharynx or otorrhea
• Use of Lactobacillus bifidus or Miyarisun when administrating antimicrobials
• * Consider change of antimicrobials using rapid detection kit for S. pneumoniae
• Pay attention to secondary hypocalcemia when administrating antimicrobials containing pivoxil
• ** Maximum 7 days by national health insurance program
• Do not exceed the following dose
  AMPC: 500mg/time, 1500mg/day
  CDTR-PI: 200mg/time, 600mg/day
  TBPM-PI: 300mg/time, 600mg/day
  TFLX: 180mg/time, 360mg/day
• Follow-up period is 3 weeks from the first visit