Clinical Practice Guidelines for the Diagnosis and Management of Acute Otitis Media (AOM) in Children

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

1. Summary
Objective: To 1) indicate methods of diagnosis and testing for acute otitis media (AOM) in children (<15 years); and 2) recommend methods of treatment in accordance with the evidence-based consensus reached by the Subcommittee on Clinical Practice Guidelines for the Diagnosis and Management of AOM in Children (Subcommittee on Clinical Practice Guidelines), in light of the causative bacteria of AOM in Japan and their susceptibility to antimicrobial agents. Methods: We investigated the most recently detected bacteria causing childhood AOM in Japan as well as their antimicrobial susceptibility, developed Clinical Questions(CQ) concerning the diagnosis, testing methods, and treatment of AOM, searched the literature published during 2000–2004, and issued the 2006 Guidelines.1-4) In the 2009 Guidelines we performed the same investigation with the addition of literature that was published during 2005–2008 and that was not included in the 2006 Guidelines. Results: We categorized AOM as mild, moderate, or severe on the basis of otoscopic findings and clinical symptoms, and presented a recommended treatment for each degree of severity. Conclusion: Accurate assessment of otoscopic findings is important for judging the degree of severity and selecting a method of treatment.

2. Authors
The membership of the Subcommittee on Clinical Practice Guidelines for the Diagnosis and Management of Acute Otitis Media (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 of that year on the website of the JSIDO, in the journals of the JOS and the JSPO, on the website of the Japan Council for Quality Healthcare, and in printed form. The 2006 Guidelines underwent evaluation, and work on the production of a revised edition began at the 13th committee meeting on January 7, 2007.

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 on Clinical Practice Guidelines during the production of these Guidelines is provided (attachment).

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 US, 62% of children aged less than one year and 83% of those up to the age of three have suffered from at least one bout of AOM. Faden et al. have reported that it affects 75% of children up to the age of one.

Some authors in Europe and the US 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. Rosenfeld et al. have also reported observation as a management option, and more recent studies have also found no significant difference in clinical outcome if antimicrobial agents are not given immediately but rather are prescribed if there is no improvement in symptoms after 48 or 72 hours. A Cochrane Review that examined randomized controlled trials of antimicrobial agent administration versus placebo also found that antimicrobial agents had little effect on childhood AOM. In addition, a double-blind randomized controlled trial of amoxicillin (AMPC) and a placebo found no significant difference in therapeutic efficacy between the two. Dagan et al. and Toltzis et al., in a review and case-control study, advised that antimicrobial agent use would be reduced because the use of a wide variety of antimicrobial agent increases the survival
of resistant *Streptococcus pneumonia* (*S. pneumonia*) in the nasopharynx, 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 multidrug-resistant bacteria are now being detected more frequently,\textsuperscript{20,21} which means that the recommendation to avoid administration of antimicrobial agents proposed in Europe and the US does not apply. In addition, the criteria and assessment levels used in conventional clinical assessment are not necessarily uniform even within Europe and the US.\textsuperscript{22} 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.\textsuperscript{23}

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.\textsuperscript{24} Therapeutic outcomes of clinical practice that adhered to the guidelines were also generally good.\textsuperscript{25,26} In light of these results, the JOS, JSIDO, and JSPO decided to revise the 2006 Guidelines and issue a new edition in 2009.

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 insufficient evidence of a treatment method’s efficacy does not necessarily mean that treatment is ineffective or should not be carried out. When using such methods of treatment, however, an extra degree of consideration is required with respect to the evaluation of clinical efficacy and communication with the patient. It must be re-emphasized that recommendations in clinical practice guidelines are not legal grounds for dictating the particular types of medical treatment that should be practiced in individual clinical situations.\textsuperscript{27} 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 Guidelines were revised after their
The differences between the 2006 Guidelines and 2009 Guidelines comprise changes in the symptoms and findings used in the severity categories and changes in the criteria for determining the degree of severity. No major changes were made to other items. To enable the 2009 Guidelines to be used as clinical practice guidelines without reference to the 2006 edition, however, they also include material published in the 2006 Guidelines.

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

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 on Clinical Practice Guidelines on recommended treatment methods in light of the causative bacteria and their susceptibility to antimicrobial agents 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, Labour and Welfare’s Pharmaceutical Affairs Bureau Notification No. 1334, Guidance Concerning Clinical Trials of Drugs in Pediatric Populations, released on December 15, 2000,\(^{28}\) 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 defined children using a general criterion of <15 years.

6. Users

The main users of these Guidelines will be otolaryngologists who perform otological procedures including the accurate evaluation of otoscopic 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 tympanostomy tube inserted, who have no craniofacial abnormality, and who 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 on Clinical Practice Guidelines with respect to recurrent otitis media (ROM) (using the definition proposed 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.

*Additional Statement: Proposals for the Treatment 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.29-31)

(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, multidrug-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.32) In terms of causative bacteria, multidrug-resistant pneumococci are reportedly responsible in many cases,33) 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. It has also been conjectured that there is a link between immunity received from the mother via breast milk and the onset of ROM, with the absence of breastfeeding constituting a strong risk factor for ROM. Lifestyle and environmental risk factors include having siblings, attending daycare, and pacifier use.

(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 US 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. Although a Cochrane Review accepts the utility of pneumococcal polysaccharide vaccine, it does not recommend the conjugate vaccine. In a double-blind randomized controlled trial in the Czech Republic, however, 11-valent pneumococcal capsular polysaccharide vaccine conjugated to *H. influenzae*-derived protein D had a significant protective effect against AOM caused by pneumococci or non-typable *H. influenzae*. 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 multidrug-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 *juzentaihoto* has been reported as effective.

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. Myringotomy has not been shown to have any significant effect in reducing the frequency of occurrence of ROM in research on patients in Japan, but insertion of a tympanostomy tube for one year and short-term insertion for one month significantly reduce the frequency of occurrence. As measures to deal with
lifestyle and environmental factors, discontinuation of attendance of group daycare and breastfeeding are desirable.

8. Definition of AOM

In these Clinical Practice Guidelines, AOM is defined as “an acute occurrence of middle ear infection that may be associated with otalgia, fever, or otorrhea.” The following notes are also added.

Notes:

(i) Acute occurrence is defined as a case in which the individual complains of an acute symptom or in which an acute symptom is observed by his/her parent/guardian, and the individual is seen in a clinic within 48 hours.\(^46\) The duration of acute inflammation is commonly defined as not longer than three weeks, though there is no clear evidence serving as the basis for this definition. These Guidelines also adopt these common definitions. It should be noted that acute aggravation of chronic otitis media is excluded from these definitions because its pathological condition differs.

(ii) The Clinical Practice Guidelines for the Diagnosis and Management of AOM reported by the American Academy of Pediatrics (Subcommittee on Management of Acute Otitis Media 2004)\(^47\) 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 middle ear effusion (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

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

9. Bacteria isolated from children with acute otitis media in Japan and antimicrobial activity against them

(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\(^{48}\) showed changes in the frequencies of bacteria isolated from patients of all ages with AOM based on the four previous surveillances conducted in 1994, 1998, 2003, and 2007 (Figure 1 and Table 2). \(S.\ pneumoniae\) tended to increase and was detected in 34.1\% of isolates in the surveillance of 2007. \(Haemophilus\ influenzae\) (\(H.\ influenzae\)) tended to increase during the surveillance of 2003, but slightly decreased to 24.2\% in 2007. \(Staphylococcus\ aureus\) (\(S.\ aureus\)) decreased to 4.4\%. \(Moraxella\ catarrhalis\) (\(M.\ catarrhalis\)) was detected in 7.1\% of isolates in 2003 and in 4.4\% in 2007. Of 45 specimens of pus taken from the middle ear of children aged <15 years with AOM not associated with tympanic membrane perforation, \(H.\ influenzae\) was detected in 22.2\%, \(S.\ pneumoniae\) in 46.7\%, and \(M.\ catarrhalis\) in 4.4\%. Of 23 specimens of pus leaked from the middle ear of which the tympanic membrane was perforated due to spontaneous rupture, \(S.\ aureus\) was found to be increased to 8.7\%. \(H.\ influenzae\) and \(S.\ pneumoniae\) were detected in 47.8\% and 8.7\% of isolates, respectively, in 2007 (Table 3). \(H.\ influenzae\), \(S.\ pneumoniae\), \(M.\ catarrhalis\), and \(Streptococcus\ pyogenes\) are thought to be significant bacteria causing AOM. However, \(S.\ aureus\) appears contaminant from the external ear canal and is unlikely to be a causative bacterium. Reports from the US and Europe also show that \(H.\ influenzae\), \(S.\ pneumoniae\), and \(M.\ catarrhalis\) are the three predominant causative bacteria. Turner et al.\(^{49}\) reported that \(H.\ influenzae\) had been detected in 34\%, \(S.\ pneumoniae\) in 46\%, and \(M.\ catarrhalis\) in 2\% of isolates from 109 infants who experienced 122 episodes of AOM within two months after birth. Commisso et al.\(^{50}\) 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, consisted of AOM (94 patients), acute sinusitis (95 patients), acute tonsillitis (91 patients), peritonsillar abscess (69 patients), chronic otitis media (95 patients), and chronic sinusitis (90 patients). Of 63 \(H.\ influenzae\) strains isolated from these patients, 26 strains (41.3\%) were \(\beta\)-lactamase-non-producing ampicillin-susceptible \(H.\ influenzae\) (BLNAS), 33 strains (52.4\%) were \(\beta\)-lactamase-non-producing ampicillin-resistant \(H.\ influenzae\) (BLNAR), and four strains (6.3\%) were \(\beta\)-lactamase-producing ampicillin-resistant \(H.\ influenzae\) (BLPAR). BLNAR strains, which are significant as multidrug-resistant bacteria, were recovered from 52.4\% of the patients, and showed
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). Multidrug-resistant bacteria—i.e., PISP and PRSP combined—accounted for approximately 50% of the strains, showing a decreasing trend from 60% in 2004.

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. Combining these results for the total 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. Multidrug-resistant bacteria—i.e., 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 multidrug-resistant bacteria, accounted for a large proportion (approximately 70%) of the isolates (Figure 3).

Uno collected isolates from the nasopharynx of patients with AOM or acute sinusitis below the age of 15 years who visited his clinic from 2003 to 2007 and analyzed antimicrobial activity against 5,720 *S. pneumoniae* strains and 5,297 *H. influenzae* strains. PRSP was detected in 51.2%, PISP in 40.1%, and PSSP in 8.7% of the isolates in 2003. PRSP was detected in 37.1%, PISP in 36.8%, and PSSP in 26.1% of those in 2007. The proportion of *S. pneumoniae* strains that were resistant to antimicrobial agents tended to decrease (Figure 4). BLNAS strains were detected in 55.1%, low BLNAR strains in 18.1%, BLNAR strains in 21.1% and BLPAR strains in 5.7% of the isolates 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 *H. influenzae* tended to increase but that of BLNAR strains tended to decrease (Figure 5).

The 2006 Guidelines reported that the proportion of resistant bacteria—i.e., PISP and PRSP combined—ranged from 60% to 92% and that of BLNAR strains ranged from 25% to 47% both at the nationwide level and among patients who visited a clinic. However, the subsequent analysis showed that the proportion of resistant *S. pneumoniae* strains decreased and the isolation frequency of resistant *H. influenzae* strains tended to increase. In the Nationwide Surveillance of Clinical Isolates from Patients with Otorhinolaryngological Infections, yearly changes in the proportions of resistant *S. pneumoniae* and *H. influenzae* strains were compared between children below the age of six years and those six years of age and older. The results are shown in Figures 6 and 7. The isolation frequencies of PRSP and PISP were higher in children below the age of six years than in those six years of age and older. The isolation frequency of resistant *S. pneumoniae* strains was highest in the Third Nationwide Surveillance in 2003 and was slightly lower thereafter in both age groups of children (Figure 6). Meanwhile, the isolation frequency of BLNAR strains was higher in children below the age of six years than in those six years of age and older, as with resistant *S. pneumoniae* strains, and tended to increase in both age groups (Figure 7).

Kobayashi et al.51) also tested bacteria in the upper pharynx of children with AOM in 2001 and 2004 and reported that the isolation frequency of resistant *H. influenzae* strains had increased.

(2) Antimicrobial activity of various antimicrobial agents against prevalently detected bacteria

a. Antimicrobial activity against *S. pneumoniae*

The results of the activity of oral β-lactam antimicrobial agents against *S. pneumoniae* reported in the 2007 Nationwide Surveillance showed 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), ceftcapene pivoxil (CFPN-PI), and faropenem (FRPM) are also effective (Table 4). Macrolide antimicrobial agents are ineffective. New quinolone antimicrobial agents, particularly sitafloxacin (STFX), tosfoxacin (TFLX), and moxifloxacin (MFLX), are relatively effective. 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 antimicrobial activity.

The 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-PL and CFPN-PI also have high antimicrobial activity. Levofloxacin (LVFX), a new quinolone antimicrobial agent, has high antimicrobial activity but is not indicated in children. Injections, such as CTRX and PAPM, a carbapenem antimicrobial agent, also exhibit high antimicrobial activity.

b. Antimicrobial 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 (Table 6). Among cephem antimicrobial agents, CDTR-PI and ceferam pivoxil (CFTM-PI) have favorable MIC values, but susceptibility of *H. influenzae* to other antimicrobial agents is low. Although minocycline hydrochloride (MINO) is effective, caution is required when using it in children due to deposition of pigments on the teeth. All new quinolones have very high antimicrobial activity, but cannot be used in children at this point. Among injections, CTRX and CMX, cephem antimicrobial agents, and MEPM, a carbapenem antimicrobial agent, are very useful. According to the analysis in the multicenter clinical study, AMPC does not necessarily have high antibacterial activity, with an MIC $\geq 8 \mu g/mL$ against more than half of all *H. influenzae* strains (Table 7). Approximately 40% of *H. influenzae* strains are susceptible to CVA/AMPC (1:14 formulation). The antimicrobial activity of CDTR-PI is favorable. Approximately 96% of *H. influenzae* strains are susceptible to azithromycin (AZM). LVFX, a new quinolone antimicrobial agent, has high antimicrobial activity but is not indicated in children. Injections, such as CTRX and MEPM, a carbapenem antimicrobial agent, also have high antimicrobial activity.

c. Antimicrobial activity against *M. catarrhalis*

While *M. catarrhalis* has a 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 showed 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 antimicrobial agents are effective if they are stable in the presence of β-lactamase (Table 8).

In the multicenter clinical study, CVA/AMPC (1:14 formulation), CDTR-PI, CFPN-PI, CTRX, and LVFX showed effective antimicrobial activity (Table 9).

d. Antimicrobial 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 antimicrobial agents except macrolides and FOM are expected to be effective, safe agents can be selected for use (Table 10). The abbreviations and descriptions used for the detected bacteria are provided in a separate attachment (Appendix 1).

10. **Gathering evidence**

During the preparation of these Guidelines, existing evidence (literature) was gathered with respect to the following clinical issues by means of the procedures described below:

(a) Diagnosis
(b) Testing methods
(c) Treatment

(i) Databases used

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

(ii) Search period

For the 2006 Guidelines, searches were performed in the databases of the literature published during 2000–2004. And for the 2009 Guidelines, articles published in 2004 but not included in the 2006 Guidelines were added, along with articles published after 2005 and searchable on April 10, 2008.

(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, antibiotics; (3) acute otitis media, treatment; and (4) acute otitis media, antibiotics. 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 Guidelines, the search format (中耳炎/TH or 中耳炎/AL) and (PT=会议録除く and RD=メタアナリシス,ランダム化比較試験,準ランダム化比較試験,比較研究,診療ガイドライン) (otitis media/TH or otitis media/AL) and (PT=NOT conference report and RD=metaanalysis, randomized controlled trial, semi-randomized controlled trial, controlled study, clinical practice guidelines) was used to search Japan Centra Revuo Medicina Web version 4, yielding hits for 104 articles (2003–2008). The abstracts or main texts of these articles were studied, and seven articles were selected for inclusion.

In PubMed, searches were performed using the following keywords: Search
(English[la] OR Japanese[la]) AND (otitis media) AND (treatment OR antibiotics) AND (randomized controlled trial[pt]) AND 2004:2007[dp]; and Search (English[la] OR Japanese[la]) AND (otitis media) AND (treatment OR antibiotics) 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 antibiotics) OR (“acute otitis media” AND “therapy”[Subheading]) OR (“acute otitis media” AND antibiotics)) 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 and giving a final total of 157 articles in the new Guidelines (Abstract Table not attached).

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 US Preventive Services Task Force report (http://www.uspreventiveservicestaskforce.org/uspstf08/methods/proctab4.htm).

A: (strongly recommended: strong evidence is available, benefits substantially outweigh harms)
B: (recommended: fair 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 on Clinical Practice Guidelines 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”52) and of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.53)

- 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 US 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 on Clinical Practice Guidelines. 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 the 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.

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 a 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 format and the Appraisal of Guidelines for Research & Evaluation (AGREE) appraisal instrument for assessing content.

Before publication of the 2006 edition of the Guidelines, opinions were solicited from the 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 the utility of the Guidelines in the clinical setting, and the results were reflected where appropriate.

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 on Clinical Practice Guidelines. Newly published evidence will be systematically assessed and reviewed, 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’ websites 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 a 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 the 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 for the 2006 edition of the Guidelines, the wishes of patients or their parents or guardians were listened to but not actively incorporated. When dealing with individual patients and clinical situations, however, to apply the recommendations in the Guidelines without exception in every case is to mistake the spirit in which they were written, namely, 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 with reference to 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(Figure 8, 9, 10).

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, all generic products are fully included, and updating this information to include brand names would pose too great a burden on the Subcommittee on Clinical Practice Guidelines. 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 and examinations
CQ 19-1: Under what conditions is AOM diagnosed?

Recommendation
AOM is diagnosed when the following tympanic membrane findings are recognized, and thus, detailed inspection of the tympanic membrane is indispensable for its diagnosis (typical otoscopic findings are shown in Figure 11, by Kamide\textsuperscript{56}) (level of recommendation grade: B; Hyperemia, protrusion, diminishment of the light reflex, thickening, bullar formation, cloudiness (turbidity), and perforation of the tympanic membrane, MEE, otorrhea, edema of middle-ear mucosa; references used to assess this recommendation level: Rosenfeld et al., 2001\textsuperscript{57}) (Level IIb)).

[Addendum] Otomicroscopic or otoendoscopic observation of the tympanic membrane is most desirable, but a recent modeling with a pneumatic otoscope is also
acceptable.

Background

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

Comments

As for the findings of the tympanic membrane suitable for the diagnosis of AOM, a range of findings have been observed, including hyperemia, cloudiness (turbidity), protrusion, thickening, bullar formation, perforation, and change of the light reflex of the tympanic membrane, but no uniform standard has been established and applied in the studies reported to date. Among these findings, protrusion of the tympanic membrane is frequently observed and is considered suspicious for the existence of MEE. Tympanic membrane protrusion is, therefore, in combination with color and mobility of the tympanic membrane, the finding considered most suggestive of AOM.\textsuperscript{58-60} Turbidity of the tympanic membrane frequently represents an edema, except when it is due to scar tissue. Although hyperemia of the tympanic membrane by acute inflammation is also frequently observed with AOM, those due to crying or systemic fever should be discriminated, and the differential diagnosis should also include viral otitis media.\textsuperscript{61} It is sometimes the case that hyperemia of the tympanic membrane is not distinct in spite of apparent protrusion of the AOM in infants under the age of one.

Diagnosis of AOM is almost precise when findings of the tympanic membrane related to AOM such as MEE and/or various inflammatory findings are observed by otoscopic examination.\textsuperscript{57} It is a strong sign of MEE when the mobility of the tympanic membrane is observed to be diminished or lost by pneumatic otoscopy. For the appropriate and precise observation of the tympanic membrane, the cerumen should be removed to allow for adequate illumination. As the external ear canal of 0- to 2-year-old children who frequently suffer from AOM is sometimes extremely narrow, a magnifying otoscope with a sufficient amount of light is useful for precise inspection of the tympanic membrane. Although it has been reported that the use of a surgical microscope did not result in a more precise diagnosis of AOM compared to
that achieved using a magnifying otoscope,\textsuperscript{62}) observation of the tympanic membrane by a surgical otomicroscope or an otoendoscope (especially one equipped with a CCD video camera) is desirable for detailed inspection of the tympanic membrane and the chronological recordings and preservation of the data. A prospective clinical trial reported that video endoscopy was a better modality for identifying MEE than pneumatic otoscopy, video endoscopy, tympanometry, or acoustic reflectometry.\textsuperscript{63}) In our country, where optical instruments are highly developed and distributed, tympanic membrane inspection by using a surgical microscope and/or a rigid endoscope equipped with a CCD video camera is recommended.

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

**Recommendation**

Severity of AOM is classified as mild, moderate and severe according to otoscopic findings and clinical manifestations.\textsuperscript{(Level of recommendation grade A)}

References used to assess the recommendation level: Hotomi et al., 2004\textsuperscript{64), 2005\textsuperscript{65)} (Level IIa), Friedman et al., 2006\textsuperscript{66)} (Level Ib), Biner et al., 2007\textsuperscript{67)} (Level Ib)

**Manifestations and findings and their scores used for classification of the severity of AOM (proposal from the Subcommittee on Clinical Practice Guidelines)**

- 3 points are automatically given below the age of 24 months
- Otalgia is scored as 0, 1, or 2.
  - 0: absent; 1: present; 2: present - continuous severe pain.
- Fever (axilla) is scored as 0, 1, or 2.
  - 0: under 37.5 degrees centigrade (°C); 1: higher than 37.5°C but under 38.5°C; 2: higher than 38.5°C.
- Crying and/or bad temper is scored as 0 or 1.
  - 0: absent; 1: present.
- Hyperemia of the tympanic membrane is scored as 0, 2, or 4.
  - 0: absent; 2: present at the manubrium of malleus, or in a part of the eardrum; 4: present in the whole tympanic membrane.
- Protrusion of the tympanic membrane is scored as 0, 4, or 8.
  - 0: absent; 4: present in a part of the tympanic membrane; 8: present in the
whole tympanic membrane (Figure 1256).

- Otorrhea is scored as 0, 4, or 8.
  0: absent; 4: present but the tympanic membrane is visible; 8: present and obstructing visibility of the tympanic membrane.
- Condition of the light reflex of the tympanic membrane is scored as 0 or 4.
  0: normal; 4: diminished or absent due to turbidity.

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

- Mild - $\leq 9$
- Moderate – 10 - 15
- Severe - $\geq 16$

A sample of a score chart used for assessing the severity of AOM in the clinic is shown in Table 11.

**Background**

For AOM, the treatment must be matched appropriately to the disease severity. In patients of younger age, there is often a discrepancy between the general condition and the tympanic membrane findings during the convalescent stage of AOM; that is, the general condition is often much improved even though the tympanic membrane findings are not. Thus, a precise assessment of the tympanic membrane findings and thereby the severity of AOM will lead to a more appropriate choice of treatment.

**Comments**

In these Guidelines, the severity of otoscopic findings and clinical manifestations was scored, and the severity of AOM was assessed by summing those scores. Friedman et al. used similar method; they assessed the severity of AOM by summing the scores of both the total impressions of the child by the guardian and the tympanic membrane findings, and concluded that such an assessment is important for an appropriate choice of treatment. In our previous Guidelines issued in 2006, 3 tympanic membrane findings were chosen to assess the severity of AOM—hyperemia.
(yellowish change), protrusion, and ototrrhea—while turbidity of the tympanic membrane and diminishment of the light reflex were reported to be important for choosing an appropriate treatment for AOM.\textsuperscript{64,65} For these reasons, in the present Guidelines, we reconsidered the factors of tympanic membrane findings used for assessing the severity of AOM by way of the normal group technique (NGT; see the note for details), and decided to pick up “diminishment of the light reflex” in addition to hyperemia, protrusion and ototrrhea. Then, in stratifying these factors, we assigned a score of 0 (normal) or 4 (diminished or absent) to the newly-added factor of “diminishment of the light reflex.” Analysis of the influence of this factor (i.e., addition of the light reflex) on the score of severity of AOM using 721 children revealed that it did not significantly affect the distribution of the severity.

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

In the present Guidelines, as important clinical manifestations for assessing the severity of AOM, we chose three factors—otalgia, fever, and crying/bad temper—which were also chosen for the previous 2006 Guidelines by NGT, and we used the same scoring system as used in those earlier Guidelines.

As for the body temperature, Kaleida et al.\textsuperscript{68} classified mild and severe AOM at 39.0°C (oral cavity) and 39.5°C (anus). Considering that the body temperature is measured at the axilla in our country, the grades of fever were classified into three groups, \(<37.5°C, \leq 37.5 – <38.5°C, and 38.5°C \leq \), based on discussions within the committee using NGT. It was decided that the fever score would be determined based on 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. This topic will be discussed again at the next revision of these Guidelines.

Since younger age appears to be one of the risk factors aggravating and/or prolonging AOM, \(^{64,69-71}\) “under 3 years of age” was adopted as one of the factors determining the severity of AOM in our previous Guidelines in 2006. In this edition, considering the results of several other reports, \(^{69-72}\) we changed this factor to “under 24 months of age.” 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.

Based on the results of all the reviews included, we defined the scores for each factor as follows: otalgia: 0, 1, 2; fever: 0, 1, 2; crying and/or bad temper: 0, 1; hyperemia of the tympanic membrane: 0, 2, 4; protrusion of the tympanic membrane: 0, 4, 8; otorrhea: 0, 4, 8; changes of light reflex: 0, 4; and 3 points were added for age of under 24 months. Total scores of less than 9, of 10 to 15, and of greater than 16 were defined as mild, moderate, and severe AOM, respectively.

[Note]: normal group technique (NGT)

The consensus method is used to decide issues on which general agreement (consensus) is not obtained due to a lack of positive scientific evidence or due to the existence of adverse evidence. In the consensus method, final consensus is attained by intensively discussing and assessing individual opinions on an issue. In the fields of medicine or health care, Delphi’s method and the Normal group technique (NGT) are often used. Both are characterized by collection and quantification of opinions and providing feedback to the participants. In NGT, specialists in the field on a particular issue get together, directly give their opinions, receive feedback from the other specialists, and then provide new opinions in response to the feedback. A consensus is obtained by repeating these processes. Although this method has the disadvantage that relationships between the participants may affect the final conclusion, it has a greater advantage that all the participants can directly exchange opinions. In these Guidelines, by using this method, agreement was attained on the selection of necessary items of tympanic membrane findings and clinical manifestations for assessing the severity of AOM, stratification of each item, scores allotted to the three levels of severity (mild, moderate, severe), and the selection of treatment for AOM for of the three levels of severity. Although the present consensus is not an objective result based on definitive
scientific evidence, it is expected to be a useful tool for reaching appropriate judgments in clinical practice, since it effectively distills and refines the opinions of experienced specialists.

CQ19-3: Is tympanometry useful to diagnose acute otitis media?

Recommendation

Tympanometry is recommended to identify the presence of MEE after the diagnosis of AOM is confirmed by a precise otoscopic finding (level of recommendation grade: B; references used to assess the recommendation level: Saeed et al. 200473) (Level IIa)).

Background

Tympanometry is a reliable test to identify the presence of MEE in the tympanic cavity. Acoustic reflectometry, which has been recommended to identify the effusion in European countries and the US, is not recommended in Japan because it has not been available since 1994.

Comments

Tympanometry is a tool to measure the compliance change of the middle ear conduction system consisting of the tympanic membrane, ossicles and tympanic cavity by forcing positive and negative pressures in the sealed external ear canal. Tympanograms can be roughly distributed into three types: types A, C, and B. Tympanometry is a very reliable method for detecting the presence of MEE and the negative pressure in the middle ear.73-75) Although MEE can be detected using tympanometry, the stage of AOM, i.e., the acute stage or resolution stage, cannot be identified. Therefore, it is necessary to observe the tympanic membrane precisely using an otomicroscope or an otoendoscope. As children with AOM are usually younger than those with OME, it is important to be vigilant for the following conditions when performing tympanometry: presence of pain, impact cerumen, crying, insufficiency of an ear probe insertion and lack of a patient’s compliance. In addition, one report has indicated that antimicrobial agents are not always used even when MEE
is detected by tympanometry. For these reasons, the reliability of tympanometry for the diagnosis of AOM might be limited.

CQ 19–4 Is it necessary to acquire the patient’s history when diagnosing AOM?

Recommendation

It is very important to ask patients for their background, past history and family history in order to predict the carriage of multidrug-resistant bacteria and intractability of AOM (level of recommendation grade: B; references used to assess the recommendation level: Hotomi et al. 2004 (level IIa); Damiseaux et al. 2006 8) (level IIa)).

A sample questionnaire is shown in Table 12.

Background

AOM is mostly seen in infants. Younger children and children attending day-care are frequently infected with multidrug-resistant bacteria, and these bacterial strains tend to be invasive. It is also important to determine whether such children have siblings, since bacterial infection is also transferred at home.

Comments

Multidrug-resistant bacteria are frequently detected as pathogens infecting children who attend day-care. A home-based child also has a chance to be exposed to multidrug-resistant bacterial infection if his or her siblings are enrolled in a nursery school. There have been reports from Japan and European countries that AOM in young children tends to be severe or intractable. The history of recurrent AOM suggests the carriage of multidrug-resistant bacteria and the presence of immunological weakness in each child. These data can be provided by a detailed questionnaire, which is very valuable to predict the severity of AOM and the presence of an immunological condition in a child.

Additional remarks

It is desirable to determine the presence of sensorineural hearing loss by pure tone audiometry in patients with AOM. Sensorineural hearing loss is a well-known
complication of AOM. The association of sensorineural hearing loss suggests the extension and severity of acute inflammation in the temporal bone. The recommended method for obtaining a specimen for a microbial test is shown in Table 13. AOM is caused by the invasion of nasopharyngeal pathogens into the middle ear via the eustachian tube. Therefore, it is valuable to take a specimen of the nasopharynx not orally but nasally. In one report, the pathogens detected from otorrhea and the nasopharynx were the same in 90% of *S.pneumonia* and in 80% of *H.influenzae* samples. 79)

20. Treatment

The outcome of the treatment recommended by the present Guidelines is defined by improvement of otoscopic findings such as hyperemia, protrusion, diminishment of the light reflex, thickening, bullar formation, cloudiness (turbidity), and perforation of the tympanic membrane, MEE, otorrhea, and edema of middle-ear mucosa at the time point of 3 weeks after onset. A score of 0 for the tympanic membrane and clinical manifestations except for age factor (under 24 months) is judged as cure of AOM. A patient who has already received antimicrobial agents is also classified as having mild, moderate or severe AOM based on the prescribed antimicrobial agents, tympanic membrane findings, and clinical manifestations at the examination. In addition, the proposed algorithm in these Guidelines should be adopted in consideration of the severity of AOM.

**CQ 20-1 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 mild AOM (level of recommendation grade: A; references used to assess the recommendation level: Glasziou et al. 200080 (level Ia), Little et al. 200613 (level IIa)).

**Background**

It has been reported that most cases of AOM improve without use of antimicrobial agents. 7,8,10,80,81) However, as the incidence of AOM caused by multidrug-resistant bacteria is high in Japan, it is important for us to diagnose mild AOM precisely by the
findings of the tympanic membrane, and to follow a child strictly when we do not use antimicrobial agents.

Comments
The use of antimicrobial agents is closely related with the increase of multidrug-resistant bacteria in the treatment of infectious diseases. It has been reported that most of cases of AOM improve without use of antimicrobial agents.\(^7\) Takata et al.\(^8\) performed a meta-analysis of 74 randomized controlled trials (RCT) and concluded that the cases with simple AOM treated without antimicrobial agents rarely showed complications and the effect of AMPC was minimal in these cases. In a double-blind RCT comparing AMPC and placebo for children with AOM, in which 80% of the cases were classified as moderate AOM, the placebo group did not show poorer recovery compared with the AMPC group.\(^9\) McCormick et al.\(^10\) reported a comparative study between groups with and without administration of AMPC for cases with non-severe AOM, and found that the eradication rate was high but the carriage rate of multidrug-resistant *S. pneumoniae* increased in cases treated by AMPC. They concluded that watchful waiting should be recommended when the following items were resolved: evaluation of the severity of AOM, education for parents, treatment for relief of the symptoms, easy access to the hospital for follow-up, and antimicrobial agent use if necessary.

Little et al.\(^11\) reported on multicenter RCT between two groups, one with immediate use of antimicrobial agents and the other with use of antimicrobial agents only when symptom relief was not obtained for 72 hours, and the results were as follows: there was no significant difference between the two groups if patients showing high fever, restlessness and vomiting were excluded from the analysis. However, immediate use of antimicrobial agents significantly decreased the incidence of restlessness and sleep disturbance in the patients with high fever(\(\geq 37.5^\circ\text{C}\)), restlessness and vomiting. In addition, Little et al.\(^12\) reported the long-term outcome of otalgia and functional scale, i.e., the results at three months and one year after the randomized trial on antimicrobial-agent use in the two groups described above. The results showed that there was no statistically significant difference in the long-term outcome between the two groups. In another report, a policy of wait-and-see for 48 hours without prescription of antimicrobial agents was found to be useful in patients whose
symptoms had not worsened. Rover et al. reported a meta-analysis of RCT, in which the prognosis of the two groups, i.e., a wait-and-see group and an immediate antimicrobial agent use group, was compared with respect to pain and/or fever at 3 and 7 days. They concluded that the symptoms in children with bilateral AOM under 2 years persisted twice longer than those in children with unilateral AOM at the age of 2 years and older. In the RCT between the immediate administration of antimicrobial agents and administration after 72 hours based on the judgment of guardians on otalgia, fever, and other persistent symptoms, the group with immediate use of antimicrobial agents showed significantly lower incidence of otalgia than the other group at 3 months after the trial in cases of recurrent AOM. However, one year after the trial, there was no significant difference in the incidence of otalgia 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 multidrug-resistant bacteria has been increasing. Hotomi et al. classified children with AOM into two categories, mild and severe cases, and children with mild AOM were not given antimicrobial agents. The results showed that it was possible not to use antimicrobial agents for mild AOM as long as 5 days after the onset. Although they showed that the clinical symptoms improved in 94% of the children with both mild and severe AOM irrespective of whether or not antimicrobial agents were administered, otoscopic findings were improved in 55% of the patients with mild AOM and in only 10% of those with 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 be prepared to administer antimicrobial agents at any time if he/she fails to show improvement. In another trial, parents were permitted to administer pre-prescribed antimicrobial agents to their children on an as-needed basis. As a result, only 31% and 34% of children were administered antimicrobial agents. Rover et al. also reported that some children improved without the use of antimicrobial agents, but that it was important to strictly follow these cases for 2–3 days after the onset.
CQ 20-2 Are antimicrobial agents useful for the analgesic treatment of AOM?

**Recommendation**
The efficacy of antimicrobial agents specifically for otalgia is unknown (level of recommendation grade: 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.

**Comment**
Glasziou et al.\(^80\) reported that antimicrobial agents did not significantly improve otalgia compared to the natural course. In contrast, Bascelli et al.\(^87\) 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 an RCT 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 double-blind RCT performed by Bertin et al.,\(^88\) the effect of ibuprofen was significant compared to a placebo, but no significant analgesic effect of acetaminophen was observed.

Note: At the present time in Japan, acetaminophen is selected for analgesic treatment for infants aged 3 years or younger.

**Additional statement**
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 RCT, for which additional study results are anticipated.

CQ 20-3 Which antimicrobial agents should be used for AOM?

Recommendation
Recommended antimicrobial agents depending on bacterial resistance and the severity of AOM are as follows: P.O.: Amoxicillin (AMPC), clavulanate/amoxicillin (CVA/AMPC [1:14] formulation), cefditoren pivoxil (CDTR-PI); and DIV: Ampicillin (ABPC), ceftriaxone (CTRX) (level of recommendation grade: A) (references used to assess the recommendation level: Ghaffar et al. 2002, 2000 (Level Ib), Piglansky et al. 2003 (Level Ib), Haiman et al. 2002 (Level Ib)).

Background
Currently in Japan: about 50-60% of S.pneumoniae and about 50-70% of H. influenzae strains are multidrug-resistant, and it is recommended that the above antimicrobial agents should be chosen corresponding to the severity of AOM based on the susceptibility against pathogens. This does not mean that other antimicrobial agents are not recommendable, but rather that the above antimicrobial agents are recommended in consideration of the current antimicrobial susceptibility in Japan.

Comment
Based on bacteria detected in infants with AOM and the activities of antimicrobial agents against them, oral AMPC, CVA/AMPC, and CDTR-PI and CTRX injection are selected corresponding to the severity. Reports on AMPC treatment in Japan have demonstrated their usefulness.

Regarding studies on AMPC and AMPC/CVA in Western countries, a
prospective observational study reported significant therapeutic results of AMPC. Lund et al. investigated changes in bacterial flora in the oropharynx and nasopharynx in 12 patients treated with AMPC/CVA and 17 patients treated with cefuroxime axetil (CMX-AX) in an RCT, and observed similar effects on *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* in the nasopharynx 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 RCT. Piglansky et al. 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 multidrug-resistant low-risk AOM in a double-blind RCT. Casellas et al. observed no difference in efficacy between AMPC/SBT and AMPC/CVA in a multicenter single-blind RCT. Regarding non-AMPC responders, Block et al. 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. observed no significant difference between twice- and 3 times-per-day administrations of AMPC/CVA in a multicenter RCT. Haiman et al. investigated changes in *S. pneumoniae* in the nasopharynx (before, in the middle of, and after treatment) in an RCT in which ceftriaxone (CTRX) was injected 3 times, and observed a significant reduction of *S. pneumoniae*. Heikkinen et al. also reported that the intramuscular injection of CTRX significantly decreased *H. influenzae* in the nasopharynx. Toltzis et al. 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 an RCT. Wang et al. 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.

The results of a single-blind study of cefaclor (CCL) and AZM\(^{104}\) and efficacy of 5-day administration of CCL (50 mg/kg)\(^{105}\) have been reported, but these are not included in the recommendations due to the current state of pathogens in Japan.

Ioannidis et al.\(^{106}\) performed a meta-analysis of multicenter RCTs, and identified no significant differences in the efficacy or safety of AZM for upper airway infection compared to other antimicrobial agents. Hoberman et al.\(^{107}\) 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.\(^{108}\) noted no significant difference between AZM and AMPC/CVA (45/6.4 mg/day) in a single-blind RCT. Arguedas et al.\(^{109}\) 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 RCT. Regarding the current state of pathogens in Japan, AZM may be selected for *H. influenzae*.

Cohen\(^{110}\) performed a meta-analysis of 5 RCTs, and observed that cefpodoxime (CPDX) was effective. Fulton et al.\(^{111}\) reported that the clinical effect of a 10-day administration of CPDX was significantly more favorable than 5-day administration, but not significantly different at 1-1.5 months after completion of treatment completion in a literature review. These data on CPDX do not meet the challenge of the actual state of pathogens of AOM in Japan, and, accordingly, CPDX is not a treatment option.

The relevant findings on cefdinir (CFDN) are as follows. In a multicenter RCT comparing CFDN administered once at 14 mg/kg, CFDN administered twice at 7 mg/kg, and AMPC/CVA administered 3 times at 40/10 mg/kg, the cure rate was similar in all groups.\(^{112}\) In a case-control study, twice-a-day administration of 7 mg/kg CFDN for 5 days was effective for the eradication of pathogens of less intractable
AOM, including those caused by moderately-resistant *S. pneumoniae* and β-lactamase-producing bacteria. In a multicenter RCT involving the 5-day administration of CFDN at 14 mg/kg/day and 10-day administration of CFPZ (cefprozil) at 33 mg/kg/day, no significant differences were noted in the clinical effect, incidence of diarrhea, or recurrence rate based on the otoscopic findings and clinical symptoms. Adler et al. compared the clinical effect among CFDN administered twice at 7 mg/kg, once at 14 mg/kg, and AMPC/CVA administered twice at 13.3 mg/kg in a multicenter RCT, but observed no difference in the cure rate. Klein et al. reported that CFDN was advantageous with respect to several factors in the meta-analysis, such as the *in-vitro* activity, taste, smell, low dosing-frequency requirement of only 1-2 times/day, and low rate of adverse events, indicating its usefulness for AOM and hemolytic streptococcus-induced pharyngitis in infants. Furthermore, Block et al. reported that the effects of a 10-day administration of CFDN (14 mg/kg) and a high-dose administration of AMPC/CVA (90/6.4 mg/kg) were equivalent. However, CFDN is not recommended based on the current state of pathogens of AOM and antimicrobial agent activities in Japan.

Hedrick et al. observed no significant difference between CFPZ and high-dose AMPC/CVA (45/6.4 kg/day) in an RCT, but CFPZ has not been approved in Japan.

Saes-Llorens et al. and Sher et al. reported that the therapeutic effects of GFLX and AMPC/CVA (90/6.4 mg/kg/day) were equivalent in an RCT, but GFLX has not been approved in Japan.

**CQ20-4. How long should the antimicrobial agents be administered?**

**Recommendation**

In moderate and severe cases, the patient should be treated with 5-day
administration of an antimicrobial agent and the disease status should be evaluated at the third or fourth day of the treatment (level of recommendation grade: A) (references used to assess the recommendation level: Ovetchkine et al. 2003\textsuperscript{70} (level Ia), Kozyrskyj et al. 2000\textsuperscript{119} (level Ia).

**Background**

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

**Discussion and Conclusion**

In a prospective study, Pichichero et al.\textsuperscript{120} evaluated 5-day, 7-day and 10-day periods of antimicrobial therapy for AOM. Although 10-day treatment was found to have a better cure and improvement rate in cases with more than one episode of AOM in the preceding one month, no significant difference in the outcome was observed among the period and the type of the antimicrobial agent, and ages.

On the other hand, a meta-analysis based on 7 RCTs revealed that a longer period of antimicrobial therapy was associated with a better outcome than a shorter course in children under 2 years of age, attending daycare centers and those with perforated tympanic membrane, while a shorter course was recommended in children older than 2 years even with previous antimicrobial treatment or recurrent AOM history (Ovetchkine et al.\textsuperscript{70}). In another meta-analysis of 32 RCTs, Kozyrskyj et al.\textsuperscript{119} compared the clinical efficacy of antimicrobial therapies of less than seven days and those with a longer treatment course (8 – 19 days). The five-day antimicrobial therapy was found to be effective for uncomplicated AOM. Leibovitz et al.\textsuperscript{121} compared the efficacy of 1-day treatment with 50 mg/kg and 3-day treatment with 50 mg/kg/day intramuscular CTRX in non-responsive AOM and found the 3-day regime to be
significantly more effective, especially for PISP and PRSP. However, intramuscular administration of CTRX is not approved in Japan. Pichicero et al.\textsuperscript{122} found no significant difference in clinical efficacy between 5-day and 10-day treatment of cefuroxime axetil (CXM-AX) but concluded that the short-course treatment was more effective because of the 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.\textsuperscript{123} compared 5-day and 10-day treatment with ceftibuten (CETB) 9 mg/kg/day for recurrent AOM and reported that the 10-day treatment achieved a lower recurrence rate in short-term follow-up. Another prospective study on the duration of antimicrobial therapy for patients who had not previously received antimicrobial agents suggested that 5-day treatment for AOM was effective in children over 2 years of age (Manarey et al.\textsuperscript{124}).

CQ20-5. What are appropriate indications for myringotomy?

Recommendation
The indications should be considered depending on the severity of AOM (level of recommendation grade: I).

Background
In AOM, there is fluid accumulation due to inflammatory pathology in the middle ear, and therefore drainage of the 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 for the early cure of the disease.

Discussion and Conclusion
All of the reports showing the clinical efficacy of myringotomy have been
retrospective studies. Myringotomy was performed for cases with infection signs after 48 hours of antimicrobial therapy and all cases showed improvement 48 hours after the procedure.\textsuperscript{125} Hotomi et al.\textsuperscript{126} concluded that myringotomy was necessary depending on the severity of the disease. In a case-control study, Nomura et al.\textsuperscript{43} reported that myringotomy significantly decreased the transition rate of AOM into OME, while it was not effective for prevention of early relapse or recurrence of AOM. An RCT comparing three groups—a group receiving myringotomy only, antimicrobial therapy only, or myringotomy with antimicrobial therapy in severe cases—revealed that there was no clinically significant difference among them.\textsuperscript{7} In another randomized trial of severe cases, Kalaida et al.\textsuperscript{68} compared three regimens, i.e., amoxicillin only, amoxicillin and myringotomy, and placebo and myringotomy (2 years and older), and found that treatment failure in severe patients aged two years and older was higher in the placebo and myringotomy group than in the other group. Based on this trial, it can be inferred that myringotomy only may not be an effective treatment; nevertheless, myringotomy would be effective in combination with antimicrobial therapy.

**CQ20-6. What are appropriate indications for topical otic treatment?**

**Recommendation**

In patients who have undergone tympanostomy tube insertion, antimicrobial eardrops are recommended only for the condition securing full access of antimicrobial solution with high antimicrobial activity into middle ear through the tube (level of recommendation grade: A) (references used to assess the recommendation level: Dohar J et al. 2006\textsuperscript{127} (level 1B)).

**Background**

Topical otic treatment can achieve a high concentration of antimicrobial agent in the
middle ear and may be indicated in selected cases.

**Discussion and Conclusion**

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 a significantly earlier cure and the otic treatment was found to be effective in earlier resolution of otorrhea through tympanostomy tubes. Concerning the type of otic treatment, an RCT comparing CPFX/dexamethasone and ofloxacin (OFLX) revealed CPFX/ dexamethasone to be significantly superior.

**Supplemental note:**

In a double-blind RCT in 2008 evaluating eardrops for pain relief, topical 2% lignocaine was found to reduce significantly pain scores at 10 and 30 minutes by 50% from the baseline.

**CQ20-7. Risk factors deteriorating AOM and medications other than antimicrobial agents**

**Recommendation**

Since younger age and day-care attendance have an important role on deterioration of the disease, attention should be paid during the treatment (level of recommendation grade: A).

In cases of AOM associated with nasal disease, nasal treatments should be considered as complementary to the treatment of AOM (level of recommendation grade: I) (references used to assess the recommendation level: Ovetchkine et al.)
2003\textsuperscript{70} (Level Ia)).

**Background**

It is requisite to treat AOM as an upper respiratory infection in considering the background of AOM being to be serious.

**Discussion and Conclusion**

Flynn et al.\textsuperscript{129} compared anti-inflammatory drug, antihistamine agents and combined treatment of both agents with placebo in a meta-analysis including 13 RCTs, and they did not find any benefit in either the group receiving anti-inflammatory agents or that receiving antihistamine agents. Furthermore, in a recent meta-analysis of Flynn et al.\textsuperscript{130} that included 15 RCTs, a 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. An age of under 2 years is a risk factor for recurrent AOM and persistent MEE after AOM.\textsuperscript{131,132} Hotomi et al.\textsuperscript{64,65} found that severe AOM cases were more common in children with younger age and male gender, while there was no relation between day-care attendance and severity of AOM. However, Ovetchkine et al.\textsuperscript{70} showed that in addition to tympanic membrane perforation and age below 2 years, day-care attendance played a significant role in the severity of AOM.

In a meta-analysis of Glasziou et al. (2000)\textsuperscript{80} consisting of 7 RCTs, antimicrobial agent use was reported to be unnecessary in mild AOM cases, while antimicrobial agent administration was effective in the risk group for mastoiditis.

Pacifier use was reported to be a risk factor for both AOM and respiratory infections in an RCT\textsuperscript{133} and it was also found to be a risk factor for recurrent AOM.\textsuperscript{78}

The role of nasal intervention in the treatment of AOM is not clearly defined. Ito et al.\textsuperscript{134} evaluated the effects of nasal intervention on bacterial flora of the nasopharynx.
in AOM cases by a prospective study. They found that the bacterial population of the nasopharynx showed lower rates of PRSP (57%) and BLNAR (60%) when the nasal intervention was performed. In a prospective study, Irimada et al.\textsuperscript{135} evaluated the change of bacterial population in nasal discharge in a patient group performing nasal wash without antimicrobial agent treatment for two weeks. They reported that the amounts of nasal discharge and postnasal drip decreased and were normalized in 55% and 71% of cases, respectively. Moreover, the bacteria quantity decreased to 80% for \textit{S. pneumoniae} and 60% for \textit{H. influenzae}. Although the level of evidence is not high enough, normalization of bacterial flora in the nasopharynx by nasal intervention as well as better eustachian tube function is very likely to be of benefit in the treatment of AOM.


37. Straetemans M, Sanders EAM, Veenhoven RH, Schilder AGM, Damoiseaux RAMJ,


71. Block SL, Kratzer J, Nemeth MA, Tack KJ. Five-day cefdinir course vs. ten-day


82. Wald ER, Mason EO Jr, Bradley JS, Barson WJ, Kaplan SL, US Pediatric


112. Block SL, McCarty JM, Hedrick JA, Nemeth MA, Keyserling CH, Tack KJ; Cefdinir


134. Ito M, Shirai A, Yoshizaki T, Nishimura T, Miwa T, Furukawa M. The efficacy of

Figure Legends

Figure 1: Nationwide surveillance of clinical isolates from patients with otorhinolaryngological infections

Figure 2: Antimicrobial susceptibility of *Streptococcus pneumoniae* (183 cases) detected in MEE(Multicenter clinical study)
Multidrug-resistant bacteria—i.e., PISP and PRSP combined—accounted for a large proportion (approximately 65%) of the isolates.

Figure 3: Antimicrobial susceptibility of *Haemophilus influenzae* (208 cases) detected in MEE(Multicenter clinical study)
BLNAR strains, which are significant as multidrug-resistant bacteria, accounted for a large proportion (approximately 70%) of the isolates.

Figure 4: Antimicrobial susceptibility of *Streptococcus pneumoniae* (5,720 strains) detected from the nasopharynx of patients with AOM or acute sinusitis(Uno)
The proportion of *S. pneumoniae* strains that were resistant to antimicrobial agents tended to decrease.

Figure 5: Antimicrobial susceptibility of *Haemophilus influenzae* (5,297 strains) detected from the nasopharynx of patients with AOM or acute sinusitis(Uno)
The proportion of BLPAR strains of *H. influenzae* tended to increase but that of BLNAR strains tended to decrease.

Figure 6: Antimicrobial susceptibility of *S. pneumoniae* between children below the age of six years and those six years of age and older(Nationwide Surveillance of Clinical Isolates from Patients with Otorhinolaryngological Infections)
The isolation frequencies of PRSP and PISP were higher in children below the age of six years than in those six years of age and older.
Figure 7: Antimicrobial susceptibility *H. influenzae* between children below the age of six years and those six years of age and older (Nationwide Surveillance of Clinical Isolates from Patients with Otorhinolaryngological Infections)

The isolation frequency of BLNAR strains was higher in children below the age of six years than in those six years of age and older and tended to increase in both age groups.

Figure 8: Recommended treatment algorithm (Mild AOM)

Figure 9: Recommended treatment algorithm (Moderate AOM)

Figure 10: Recommended treatment algorithm (Severe AOM)

Figure 11: Typical otoscopic findings of AOM
A: bullar formation of the tympanic membrane, B: thickening of the tympanic membrane, C: presence of the middle ear effusion, D: perforation of the tympanic membrane

Figure 12: Protrusion of the tympanic membrane
Upper low: protrusion present in a part of the tympanic membrane is scored as 4. Lower low: protrusion present in whole tympanic membrane is scored as 8.
Table 1. The Membership of the Subcommittee of Clinical Practice Guideline

Ken Kitamura (Chairman): Dept. of Otolaryngology, Tokyo Medical and Dental University
Toshimistu Kobayashi: Dept. of Otolaryngology Head and Neck Surgery, Tohoku University
Haruo Takahashi: Dept. of Otolaryngology Head and Neck Surgery, Nagasaki University
Yoshifumi Uno: UNO ENT Clinic
Yousuke Kamide: Kamide ENT Clinic
Fumiyo Kudo: Dept. of Dietetics, Chiba Prefectural University of Health Sciences
Mitsuko Suetsuke: Momo ENT Clinic
Takeo Nakayama: Dept of Health Informatics, Kyoto University School of Public Health
Yukiko Iino: Dept. of Otolaryngology, Jichi Medical University Saitama Medical Center
Nobuko Kawashiro: Dept. of Otolaryngology, National Center for Child Health and Development
Hidenobu Taiji: Dept. of Otolaryngology, National Center for Child Health and Development
Noboru Yamanaka: Dept. of Otolaryngology Head and Neck Surgery, Wakayama Medical University
Kenji Suzuki: Dept. of Otolaryngology, Banbuntane Hotokukai Hospital, Fujita Health University
Atsunobu Tsunoda (Secretary): Dept. of Otolaryngology, Tokyo Medical and Dental University
Attachment

List of Organizations and Companies that posed non-personal financial conflicts of interest to members of the Subcommittee

Astellas Pharma Inc.
AstraZeneca K.K.
Eisai Co. Ltd.
Otsuka Pharmaceutical Co. Ltd.
Ono Pharmaceutical Co. Ltd.
Lumenis Co. Ltd.
Kissei Pharmaceutical Co. Ltd.
Kyorin Pharmaceutical Co. Ltd.
Kyowa Hakko Kirin Co. Ltd.
GlaxoSmithKline K.K.
Kowa Shinyaku Co. Ltd.
Sanofi-aventis K.K.
Shionogi & Co. Ltd.
Senju Pharmaceutical Co. Ltd.
Daiichi Sankyo Co. Ltd
Taisho Toyama Pharmaceutical Co. Ltd.
Dainippon Sumitomo Pharma Co. Ltd.
Taiho Pharmaceutical Co. Ltd.
Takeda Pharmaceutical Co. Ltd.
Mitsubishi Tanabe Pharma
Chugai Pharmaceutical Co. Ltd.
Nikken Chemical Laboratory Co. Ltd.
Nippon Shinyaku Co. Ltd.
Nippon Boehringer Ingelheim Co. Ltd.
Bayer Pharmaceutical Co. Ltd.
Pfizer Co. Ltd.
Meiji Seika Pharma Co.Ltd.
Nationwide surveillance of clinical isolates from patients with otorhinolaryngological infections
Table 2. Transition of isolates from acute otitis media ( Nationwide survey, Suzuki et al. 2008\textsuperscript{48} )

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<tr>
<th></th>
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<th></th>
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<tr>
<td>S. aureus</td>
<td>25.1%</td>
<td>27.7%</td>
<td>17.0%</td>
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<tr>
<td>S. epidermidis</td>
<td>5.7%</td>
<td>3.3%</td>
<td>6.6%</td>
<td></td>
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<tr>
<td>other CNS</td>
<td>9.9%</td>
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<td>4.0%</td>
<td>7.1%</td>
<td>4.4%</td>
</tr>
<tr>
<td>H. influenzae</td>
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<td>17.5%</td>
<td>27.4%</td>
<td>24.2%</td>
</tr>
<tr>
<td>other Haemophilus spp.</td>
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<td>0.2%</td>
<td>0.8%</td>
<td></td>
</tr>
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<td>Enterobacteriaceae</td>
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<td>1.2%</td>
<td>1.1%</td>
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<td>4.7%</td>
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<td>1.1%</td>
</tr>
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<td>other NFGNR</td>
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<td>2.5%</td>
<td>2.9%</td>
<td></td>
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<tr>
<td>other G(-) rod</td>
<td>2.9%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Candida spp.</td>
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<td>1.2%</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>others</td>
<td></td>
<td></td>
<td></td>
<td>1.1%</td>
</tr>
<tr>
<td>No. of strains Total</td>
<td>386</td>
<td>405</td>
<td>241</td>
<td>91</td>
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</table>
Table 3. The fourth nationwide survey (Suzuki et al. 2008\textsuperscript{48})

<table>
<thead>
<tr>
<th>Organism</th>
<th>Middle ear exudation</th>
<th>Middle ear effusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. pneumoniae</em></td>
<td>2</td>
<td>21</td>
</tr>
<tr>
<td><em>H. influenzae</em></td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td><em>M. (B.) catarrhalis</em></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td><em>S. aureus</em></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><em>S. epidermidis</em></td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other CNS</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td><em>S. pyogenes</em></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Other <em>Streptococcus spp.</em></td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td><em>Corynebacterium spp.</em></td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Detected strains Total</td>
<td>23</td>
<td>45</td>
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</table>
Antimicrobial susceptibility of *Streptococcus pneumoniae* (183 cases) detected in MEE (Multicenter clinical study)
Antimicrobial susceptibility of *Haemophilus influenzae* (208 cases) detected in MEE (Multicenter clinical study)
Antimicrobial susceptibility of *Streptococcus pneumoniae*
Antimicrobial susceptibility of *Haemophilus influenzae*  

Fig. 5
Antimicrobial susceptibility of *S. pneumoniae*

**Under 6 years old**
- 1994: 47.8% PRSP, 33.3% PISP, 20% PSSP
- 1998: 39.7% PRSP, 26.5% PISP, 20% PSSP
- 2003: 57.4% PRSP, 22.2% PISP, 18% PSSP
- 2007: 52.0% PRSP, 28.0% PISP, 18% PSSP

**6 years and over**
- 1994: 31.3% PRSP, 60.4% PISP, 8.4% PSSP
- 1998: 23.5% PRSP, 60.4% PISP, 8.4% PSSP
- 2003: 30.4% PRSP, 60.0% PISP, 8.4% PSSP
- 2007: 24.5% PRSP, 66.0% PISP, 8.4% PSSP

Fig. 6
Antimicrobial susceptibility of *H. influenzae*

**Fig. 7**

<table>
<thead>
<tr>
<th>Year</th>
<th>Under 6 years old</th>
<th>6 years old and over</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1998</td>
<td>2003</td>
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<tr>
<td></td>
<td>2007</td>
<td>2003</td>
</tr>
<tr>
<td></td>
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<tr>
<td>No.</td>
<td>Strains</td>
<td>Strains</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>178</td>
<td>110</td>
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<tr>
<td></td>
<td>17</td>
<td>17</td>
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</tbody>
</table>

- **BLPAR** $\geq 1.0 \mu g/ml$
- **BLNAR** $\geq 1.0 \mu g/ml$
- **BLNAS** $\leq 0.5 \mu g/ml$
Table 4. Antimicrobial activity of various agents against *Streptococcus pneumoniae* (Nationwide survey)

<table>
<thead>
<tr>
<th>Antimicrobials</th>
<th>PSSP (42 strains)</th>
<th>PISP (26 strains)</th>
<th>PRSP (10 strains)</th>
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<tbody>
<tr>
<td></td>
<td>Range</td>
<td>MIC&lt;sub&gt;50&lt;/sub&gt;</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
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<tr>
<td>PCG</td>
<td>≤ 0.06</td>
<td>≤ 0.06</td>
<td>≤ 0.06</td>
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<tr>
<td>AMPC</td>
<td>≤ 0.06</td>
<td>≤ 0.06</td>
<td>≤ 0.06</td>
</tr>
<tr>
<td>PIPC</td>
<td>≤ 0.06 - 0.25</td>
<td>≤ 0.06</td>
<td>0.125</td>
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<td>SBT/ABPC</td>
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<td>CVA/AMPC</td>
<td>≤ 0.06</td>
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<td>CFTM-PI</td>
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<td>FMOX</td>
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<td>CMX</td>
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<tr>
<td>CFPN-PI</td>
<td>≤ 0.06 - 0.5</td>
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<td>PAPM/BP</td>
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<tr>
<td>FRPM</td>
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Table 5. Antimicrobial activity of various agents against Streptococcus pneumoniae (Multicenter clinical study)

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<th>256</th>
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<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></td>
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Table 3. Antimicrobial activity of various agents against *Moraxella catarrhalis* (Nationwide survey)

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Table 9: Antimicrobial activity of various agents against *Moraxella catarrhalis* (Multicenter clinical study)

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Table 10. Antimicrobial activity of various agents against *Streptococcus pyogenes* ( Nationwide survey )

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Appendix 1

The abbreviations and descriptions used for the detected bacteria are as follows.

*Streptococcus pneumoniae* is classified according to the minimum inhibitory concentration (MIC) of Penicillin G.

- Penicillin susceptible *Streptococcus pneumoniae* (PSSP) \( \leq 0.06 \mu g/mL \)
- Penicillin intermediate-resistant *Streptococcus pneumoniae* (PISP) 0.125~1.0 \( \mu g/mL \)
- Penicillin resistant *Streptococcus pneumoniae* (PRSP) \( \geq 2 \mu g/mL \)

*Haemophilus influenzae* is classified according to the minimum inhibitory concentration (MIC) of Ampicillin (ABPC)

- susceptible bacterium \( \leq 1 \mu g/mL \)
- resistant bacterium \( \geq 2 \mu g/mL \)

and is further classified according to the production of \( \beta \)-lactamase

- \( \beta \)-lactamase negative ampicillin resistant *Haemophilus influenzae* (BLNAR)
- \( \beta \)-lactamase negative ampicillin susceptible *Haemophilus influenzae* (BLNAS)
- \( \beta \)-lactamase productive ampicillin resistant *Haemophilus influenzae* (BLPAR)
Treatment Algorithm

Mild (Score 0~9)

No antimicrobial, watchful waiting for 3 days

- No improvement
  - AMPC 5 days
    - No improvement
      - Observation
  - Improvement
    - Observation

- Improvement
  - Observation

High dose AMPC or CVA/AMPC or CDTR-PI for 5 days

- Otalgia, fever (≥ 38.5°C) → Acetaminophen 10mg/kg
- Sign of nasal disorder → treatment
- Bacterial culture from nasopharynx or otorhea

- Lactobacillus bifidus when administrating antimicrobials
  # Do not exceed adult dose
  # Follow-up period is 3 weeks from the first visit

Fig. 8
Moderate (Score 10～15)

- **AMPC 5 days**
  - **No improvement**
  - **Improvement**
  - **Myringotony**
  - **Observation**
  - **Bacterial culture**

- **Severe otoscopic findings**
  - Any of ① to ④ based on the susceptibility:
    - ① High dose AMPC
    - ② CVA/AMPC
    - ③ High dose CDTR-PI
    - ④ Myringotomy+AMPC for 5 days

  - **No improvement**
  - **Improvement**
  - **Bacterial culture**
  - **Observation**

  - Myringotomy+High dose AMPC 5 days or Myringotomy+CVA/AMPC 5 days or ABPC 150mg/kg/day, CTRX 60mg/kg/day (premature, neonate < 50mg/kg/day) 3 days

  - ① Otalgia, fever (≥38.5℃) → Acetaminophen 10mg/kg
  - ② Sign of nasal disorder → treatment
  - ③ Bacterial culture from nasopharynx or otitis media

  - # Lactobacillus bifidus when administrating antimicrobials
  - # Do not exceed adult dose
  - # Follow-up period is 3 weeks from the first visit

Fig. 9
Severe (Score 16 \leq )

① High dose of AMPC  ② CVA/AMPC  ③ High dose of CDTR-PI

Any of ①②③ for 5 days + myringotomy

No improvement  Improvement  Observation

Any of AMPC, CVA/AMPC, CDTR-PI based on susceptibility, for 5 days with high dose + myringotomy

No improvement  Improvement  Observation

ABPC 150mg/kg/day 3 days or CTRX 60mg/kg/day (premature, neonate < 50mg/kg/day) 3 days

Fig. 10

Otalgia, fever ( \geq 38.5 \degree C ) → Acetaminophen 10mg/kg
Sign of nasal disorder → treatment
Bacterial culture for nasopharynx or otorrhea

Lactobacillus bifidus when administrating antibiotics
Do not exceed adult dose
Follow-up period is 3 weeks from the first visit
Typical otoscopic findings of AOM

A: bullar formation

B: thickening

C: presence of middle ear effusion

D: perforation
Protrusion of the tympanic membrane

Score 4: protrusion present in a part of the tympanic membrane

Score 8: protrusion present in the whole tympanic membrane
### Table 11. AOM Clinical Score Sheet (2009)

**Patient ID:**
**Name:**
**Age:** _______ year _______ months

Date: ____________

Body weight: ________

Body temperature: ______°C

Sex: **male** **female**

Other features:

[Scores chart]

<table>
<thead>
<tr>
<th></th>
<th>Score 0</th>
<th>Score 1</th>
<th>Score 2</th>
<th>Score 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&lt;24 mo.)</td>
<td>0</td>
<td>1 (present)</td>
<td>2 (continuous &amp; severe)</td>
<td></td>
</tr>
<tr>
<td>Otalgia</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>0 (Temp&lt;37.5 °C)</td>
<td>1 (37.5 ≤ Temp &lt; 38.5 °C)</td>
<td>2 (38.5 °C ≤ Temp)</td>
<td></td>
</tr>
<tr>
<td>Crying/Bad temper</td>
<td>0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Hyperemia of the tympanic membrane

<table>
<thead>
<tr>
<th></th>
<th>Score 0</th>
<th>Score 2 (at the manubrium or partial)</th>
<th>Score 4 (whole tympanic membrane)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protrusion of the tympanic membrane</td>
<td>0</td>
<td>4 (partial)</td>
<td>8 (whole tympanic membrane)</td>
</tr>
<tr>
<td>Otorrhea</td>
<td>0</td>
<td>4 (visible tympanic membrane)</td>
<td>8 (invisible tympanic membrane)</td>
</tr>
<tr>
<td>Light reflex</td>
<td>0</td>
<td>4 (diminished or absent due to turbidity)</td>
<td></td>
</tr>
</tbody>
</table>

**Total score**

[Assessment]

Mild (0-9) Moderate (10-15) Severe (≥16)
Table 12. 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 sinusitis (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: Bronchial asthma (yes—first episode year months old, no, unknown)
- Atopic dermatitis (yes—first episode year months old, no, unknown)
- Allergic rhinitis (yes—first episode year months old, no, unknown)
- Food allergy (yes—first episode year months old, no, unknown)
- 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 living together (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) Hearing loss (yes, no, unknown)
   - Pulsatile tinnitus (yes, no, unknown) Disequilibrium (dizziness) (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 stuffing (yes, no, unknown)
   - Nausea, vomiting (yes, no, unknown) Diarrhea (yes, no, unknown)
   - Bad temper or low activity (yes, no, unknown)
Table 13. 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 *Heamophilus influenzae* are very weak under dry condition. A swab should be immediately inoculated into a porter for bacteriological examination.

1) A case without perforation of the tympanic membrane
   After sterilization of the external ear canal with alcohol or popvidone-iodine, the myringotomy is performed. The middle ear effusion is taken for a microbial test using Seed-Swab No. 2.

2) A case with perforation of the tympanic membrane
   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.