案)は，ガイドライン作成委員のコンセンサスが得られた内容を付記として示した。

巻末に，治療アルゴリズムを呈示しているが，おのおのの治療アルゴリズムの3次治療においても軽快しない例は難治例とする。難治例の診療については，本ガイドラインでは対象としていない。

※付記　反復性中耳炎の診療についての提案

1）反復性中耳炎の定義

反復性中耳炎の定義は，国内外で標準化されたものはないが，本ガイドラインでは，比較的最近の論文で汎用されている過去6カ月以内に3回以上，12カ月以内に4回以上の急性中耳炎罹患と定義した(Sher et al. 2005, Ables et al. 2004, Arrieta et al. 2004)。

2）反復性中耳炎の病態とリスクファクター

反復性中耳炎の病態は，単純性の急性中耳炎を繰り返すタイプと，滲出性中耳炎に罹患している患耳が急性増悪として単純性の急性中耳炎を繰り返すタイプに分類される。

反復性中耳炎のリスクファクターとしては，低年齢，起炎菌の耐性化，罹患者の免疫能，生活・環境要因が提唱されている。2歳未満の低年齢は遺伝学的背景からもリスク因子となると報告されている(Wiertsema et al. 2006)。起炎菌では，多剤耐性の肺炎球菌が原因であることが多いという報告(van Kempen et al. 2004)もあり，抗菌薬の効果の低下に伴い，鼻咽腔からの不十分な除菌が反復化の一つの要因と考えられている。宿主の起炎菌に対する低い免疫応答の関与も重要である(Yamanaka et al. 2008)。母乳として母体から得られる免疫能と反復性中耳炎の発症の関連も推測され，母乳哺育の欠如が反復性中耳炎発症の高いリスクとされている(Lubianca Neto et al. 2006)。生活・環境に関する要因としては，兄弟あり，保育園児，おしゃぶりなどがリスクファクターとなっている(Lubianca Neto et al. 2006)。

3）反復性中耳炎の治療

前述した要因が，反復性中耳炎発症のリスクファクターと想定され，起炎菌の耐性化に対しては，抗菌薬投与の前に必ず細菌の感受性検査を行い，適切な投与量の抗菌薬の選択が必要となる。推奨される抗菌薬は本ガイドラインで提示した。

肺炎球菌ワクチン接種が，欧米では反復性中耳炎の予防目的として用いられている。オランダからは，7価蛋白結合型肺炎球菌ワクチンと肺炎球菌多糖体ワクチン接種の二重盲検ランダム化比較試験で，反復性中耳炎の罹患頻度の有意な減少はなかったと報告されている(Brouwer et al. 2005)。また，Cochrane Reviewでは肺炎球菌多糖体ワクチンの有用性は認めるも，蛋白結合型ワクチンは推奨されていない(Straetemans et al. 2004)。一方，チェコからの二重盲検ランダム化比較試験では，インフルエンザ菌D蛋白結合11価莢膜肺炎球菌多糖体ワクチンが，肺炎球菌ならびにインフルエンザ菌による急性中耳炎に有意な予防効果が認められている(Prymula et al. 2006)。わが国では，2009年には7価蛋白結合型肺炎球菌ワクチンが認可される予定である。このワクチンは，本邦の小児急性中耳炎中耳貯留液より分離された肺炎球菌の血清型の62.9%，薬剤耐性菌の78.0%をカバーしており，肺炎球菌に対しては34.4～62.5%，薬剤耐性肺炎球菌に対しては39.8～49.1%の予防効果が期待されている。また，交叉反応性も含めると急性中耳炎全体として，7.6～9.4%の予防効果が期待される。

わが国独自の治療として提唱されているのが，漢方補剤による免疫能の上昇由来による予防効果で，十全大補湯の有効性が報告された(Maruyamaら2008)。

外科的治療として，アデノイド切除術はランダム化比較試験で，反復性中耳炎の頻度を減少させることはなく，予防効果もないとされている（Oomen et al. 2005, Hammaren-Malmi et al. 2005, Koivunen et al. 2004）。一方，鼓膜切開術は本邦の症例対照研究で，反復性中耳炎の発症頻度低下に有意な効果は認められていないが（Nomura et al. 2005），鼓膜換気チューブの1年あるいは1カ月の短期留置で罹患頻度の有意な低下が示されている（宇野 2007a, b）。生活・環境の要因に対処するには，集団保育の中止と，母乳哺育が望ましい。

[文献]

1) Sher L, Arguedas A, Husseman M, Pichichero M, Hamed KA, Biswas D, Pierce P, Echols R. Randomized, investigator-blinded, multicenter, comparative study of gatifloxacin versus amoxicillin/clavulanate in recurrent otitis media and acute otitis media treatment failure in children. Pediatr Infect Dis J. 2005 ; 24 (4) : 301-8.
2) Ables AZ, Warren PK. High-dose azithromycin or amoxicillin-clavulanate for recurrent otitis media ? J Fam Pract. 2004 ; 53 : 186-8.
3) Arrieta A, Singh J. Management of recurrent and persistent acute otitis media : new options with familiar antibiotics. Pediatr Infect Dis J. 2004 ; 23 : S115-24.
4) Wiertsema SP, Herpers BL, Veenhoven RH, Salimans MM, Ruven HJ, Sanders EA, Rijkers GT. Functional polymorphisms in the mannan-binding lectin 2 gene : effect on MBL levels and otitis media. J Allergy Clin Immunol. 2006 ; 117 : 1344-50.
5) van Kempen MJ, Vaneechoutte M, Claeys G, Verschraegen GL, Vermeiren J, Dhooge IJ. Antibiotic susceptibility of acute otitis media pathogens in otitis-prone Belgian children. Eur. J Pediatr. 2004 ; 163 : 524-9.
6) Yamanaka N, Hotomi M, Billal DS. Clinical bacteriology and immunology in acute otitis media in children. J Infect Chemother. 2008 ; 14 (3) : 180-7.
7) Lubianca Neto JF, Hemb L,Silva DB. Systematic literature review of modifiable risk factors for recurrent acute otitis media in childhood. J Pediatr (Rio J) . 2006 ; 82 : 87-96.
8) Brouwer CN, Maille, AR, Rovers MM, Veenhoven RH, Grobbee DE, Sanders EA, Schilder AG. Effect of pneumococcal vaccination on quality of life in children with recurrent acute otitis media : a randomized, controlled trial. Pediatrics. 2005 ; 115 : 273-9.
9) Straetemans M, Sanders EAM, Veenhoven RH, Schilder AGM, Damoiseaux RAMJ, Zielhuis GA. Pneumococcal vaccines for preventing otitis media. Cochrane Database of Systematic Reviews. 2004 issue 1.
10) Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, Kaliskova E, Kohl I, Lommel P, Poolman J, Prieels JP, Schuerman L. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both Streptococcus pneumoniae and non-typable Haemophilus influenzae : a randomised double-blind efficacy study. Lancet. 2006 ; 367 : 740-8.
11) Maruyama Y, Hoshida S, Furukawa M, Ito M. Effects of Japanese herval medicine, Juzen-taiho-to, in otitis-prone children -a preliminary study. Acta Otolaryngol 2008 Jun 12 : 1-5 (Epub ahead of print) .
12) Oomen KP, Rovers MM, van den Akker EH, van Staaij BK, Hoes AW, Schilder AG. Effect of adenotonsillectomy on middle ear status in children. Laryngoscope. 2005 ; 115 : 731-4.
13) Hammaren-Malmi S, Saxen H, Tarkkanen J, Mattila PS. Adenoidectomy does not significantly reduce the incidence of otitis media in conjunction with the insertion of tympanostomy tubes in children who are younger than 4 years : a randomized trial. Pediatrics. 2005 ; 116 (1) : 185-9.
14) Koivunen P, Uhari M, Luotonen J, Kristo A, Raski R, Pokka T, Alho OP. Adenoidectomy versus chemoprophylaxis and placebo for recurrent acute otitis media in children aged under 2 years : randomised controlled trial. BMJ (Clinical research ed.) . 2004 ; 328 : 487.
15) Nomura Y, Ishibashi T, Yano J, Ichikawa T, Shinogami M, Monobe H, Hirai R, Kaga K. Effect of myringotomy on prognosis in pediatric acute otitis media. Int J Pediatr Otorhinolaryngol. 2005 ; 69 : 61-4.
16) 宇野芳史：小児難治性反復性中耳炎に対する長期鼓膜換気チューブ留置術の有効性について．Otol Jpn. 2007 (a) ; 17 : 16-25.

17) 宇野芳史：小児難治性反復性中耳炎に対する短期鼓膜換気チューブ留置術の有効性について．Otol Jpn .2007(b)；17：194-202.

8. 急性中耳炎の定義

本診療ガイドラインでは，急性中耳炎を，「急性に発症した中耳の感染症で，耳痛，発熱，耳漏を伴うことがある」と定義した。さらに以下の注釈を加えた。

注　釈

①急性に発症とは，本人の訴えあるいは両親や保護者により急性症状が発見され，その48時間以内に受診した場合と定義する（Harabuchi et al. 2001）。急性炎症の持続期間については，明確なエビデンスは存在しないが，3週を超えないとする定義が一般的であるので本ガイドラインでも採用する。また慢性中耳炎の急性増悪は急性中耳炎とは病態が異なるので除く。

②米国小児科学会が報告した急性中耳炎ガイドライン（Subcommittee on Management of Acute Otitis Media 2004）では，急性中耳炎と診断するには下記のような症状，徴候が求められるとしている。

(1) 中耳の炎症と貯留液による症状，徴候が最近，通常突然に発症

(2) 鼓膜の膨隆，可動性の喪失・制限，貯留液の透見，耳漏により中耳貯留液の存在

(3) 鼓膜の発赤，耳痛がみられて明らかな中耳炎の徴候と症状の存在

9. 本邦における小児急性中耳炎症例からの検出菌と抗菌活性

(1) 小児急性中耳炎からの検出菌について

2007年の第4回耳鼻咽喉科領域感染症臨床分離菌全国サーベイランス（2007年1月～6月に施行）結果報告（鈴木ら 2008）では，過去4回（1994年，1998年，2003年，2007年）施行した全年齢における急性中耳炎からの検出菌頻度年次推移が報告された（**図1**，**表2**）。肺炎球菌の検出頻度は増加傾向にあり，2007年のサーベイランスでは34.1％を占め，インフルエンザ菌は2003年のサーベイランスまでは増加傾向にあったが，2007年はやや減少に転じ24.2％であった。黄色ブドウ球菌は減少し4.4％であった。モラキセラ・カタラーリス菌は2003年は7.1％，2007年は4.4％検出された。15歳未満の小児急性中耳炎の非鼓膜穿孔症例の中耳貯留膿汁45検体からは，インフルエンザ菌22.2％，肺炎球菌が46.7％検出され，モラキセラ・カタラーリスが4.4％検出された。鼓膜が自潰穿孔した中耳流出膿汁23検体からは，黄色ブドウ球菌の検出率が8.7％に増加し，インフルエンザ菌が47.8％，肺炎球菌が8.7％を占めた（**表3**）。急性中耳炎の起炎菌として，インフルエンザ菌，肺炎球菌，モラキセラ・カタラーリス，化膿連鎖球菌は重要であると考えられるが，黄色ブドウ球菌は主として経外耳道的混入菌と考えられ，起炎菌としては考えにくい。インフルエンザ菌，肺炎球菌，モラキセラ・カタラーリスが3大起炎菌であるのは，欧米の報告でも同様で，Turner らは，生後2カ月以内の109例122件の検出菌の内訳を，インフルエンザ菌34％，肺炎球菌46％，モラキセラ・カタラーリス2％と報告している。Commisso ら（2000）のアルゼンチンの報告でも，肺炎球菌が39.4％，インフルエンザ菌が32.7％と大多数を占めている。

2007年の耳鼻咽喉科領域感染症臨床分離菌全国サーベイランスで成人を含めた全症例の内訳は，94例（急性化膿性中耳炎），95例（急性副鼻腔炎），91例（急性扁桃炎），69例（扁桃周囲膿瘍），95例（慢性中耳炎），90例（慢性副鼻腔炎）である。この症例から得られた63株のインフルエンザ菌中，26株

表2 中耳検出菌の年次推移（全国サーベイランス，鈴木ら 2008）

	解析年 対象株数			
	1994	1998	2003	2007
S.aureus	25.1%	27.7%	17.0%	4.4%
S.epidermidis		5.7%	3.3%	6.6%
other CNS		9.9%	7.5%	15.4%
CNS	24.6%	15.6%	10.8%	
S.pneumoniae	15.5%	18.3%	24.1%	34.1%
S.pyogenes	2.9%	3.5%	4.1%	2.2%
S.agalactiae		1.0%		
other *Streptococcus* spp.		1.0%	2.5%	4.4%
Enterococcus spp.	1.6%	1.0%		
M. (B.) catarrhalis	2.9%	4.0%	7.1%	4.4%
H. influenzae	15.3%	17.5%	27.4%	24.2%
other *Haemophilus* spp.		0.2%	0.8%	
Enterobacteriaceae	0.8%	2.0%	1.2%	1.1%
P.aeruginosa	2.9%	4.7%	2.1%	1.1%
other NFGNR	5.5%	2.5%	2.9%	
other G (−) rod	2.9%			
Candida spp.		1.2%		1.1%
others				1.1%
検出株 計	386	405	241	91

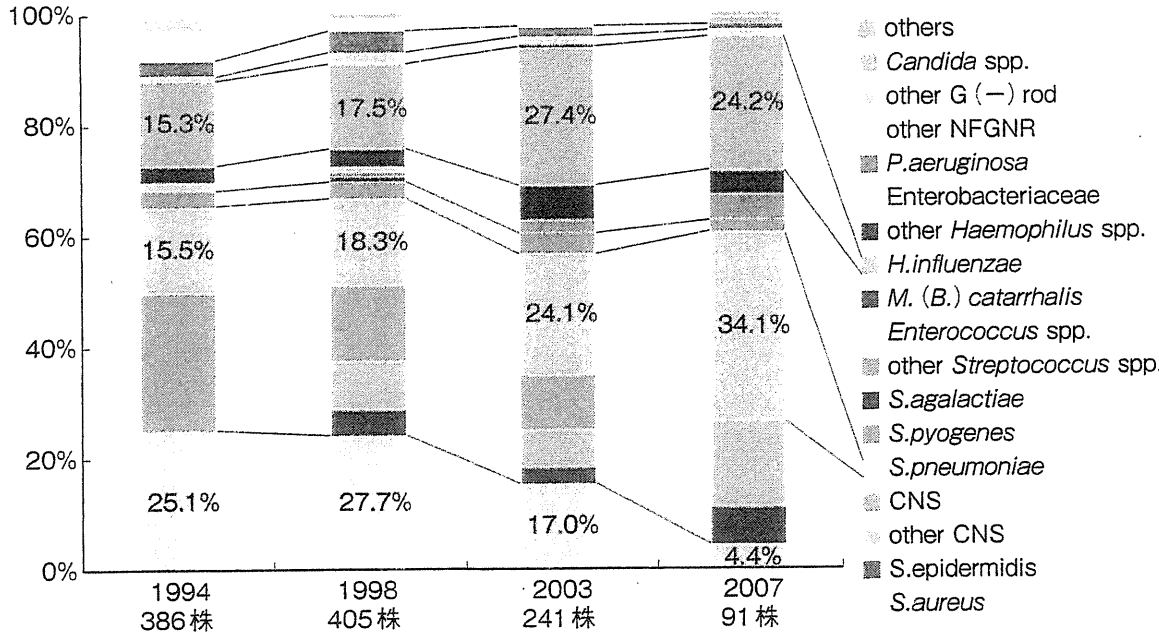


図1 全国サーベイランス年次推移

(41.3%) が β-lactamase non-producing ampicillin susceptible *H. influenzae* (BLNAS)，33株 (52.4%) が β-lactamase non-producing ampicillin resistant *H. influenzae* (BLNAR)，4株 (6.3%) が β-lactamase producing ampicillin resistant *H. influenzae* (BLPAR) であり，薬剤耐性菌として重要な BLNARは

ELSEVIER

Auris Nasus Larynx 39 (2012) 1–8

AURIS NASUS LARYNX
INTERNATIONAL JOURNAL OF ORL & HNS

www.elsevier.com/locate/anl

Clinical practice guidelines for the diagnosis and management of acute otitis media (AOM) in children in Japan

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

Received 11 July 2011; accepted 21 October 2011
Available online 23 December 2011

Abstract

Objective: To (1) indicate methods of diagnosis and testing for acute otitis media (AOM) in children (under 15 years of age); 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 concerning the diagnosis, testing methods, and treatment of AOM, searched the literature published during 2000–2004, and issued the 2006 guidelines. 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, as well as other signs and symptoms, is important for judging the degree of severity and selecting a method of treatment.

Keywords: Acute otitis media (AOM); Antimicrobial agent; Clinical practice guideline; Myringotomy; Multidrug-resistant bacteria; Recurrent otitis media (ROM)

1. Introduction

Acute otitis media (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 [1]. Faden et al. [2] 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 [3,4]. Rosenfeld et al. have also reported observation as a management option [5–7], and more recent

* Corresponding author: Haruo Takahashi
Department of Otolaryngology – Head and Neck Surgery, Nagasaki University Graduate School of Biomedical Sciences, Sakamoto 1-7-1, Nagasaki City, 852-8501, Japan. Tel.: +81 95 819 7349; fax: +81 95 819 7352.
E-mail address: htak0831@nagasaki-u.ac.jp.

0385-8146/$ – see front matter
doi:10.1016/j.anl.2011.09.008

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 h [8,9]. 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 [10]. In addition, a double-blind randomized controlled trial of amoxicillin (AMPC) and a placebo found no significant difference in therapeutic efficacy between the two [11,12]. Dagan et al. [13,14] and Toltzis et al. [15], 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 [16,17], 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 [18]. 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 Japan Otological Society (JOS), the Japan Society for Infectious Diseases in Otolaryngology (JSIDO), and the Japan Society for Pediatric Otorhinolaryngology (JSPO) produced 2006 clinical practice guidelines consistent with evidence-based medicine (EBM) [19] with the aim of supporting the diagnosis and treatment of childhood AOM [20–23], which was revised and published in 2009 [24].

This paper introduces extracts of the important parts of our 2009 edition of clinical practice guideline for diagnosis and management of AOM in children.

2. Users

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

3. 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.

4. Gathering evidence

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.

5. 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.

5.1. 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.
E: 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 (guide to the preparation of clinical practice guidelines, 4th edition) [25] and of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group [26].

- 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.

6. 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 [27] and the Appraisal of Guidelines for Research & Evaluation (AGREE) appraisal instrument for assessing content [28].

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.

7. Diagnosis and examinations

7.1. Clinical question 1: under what conditions is AOM diagnosed?

7.1.1. 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 (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. [29] (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.

7.1.2. Background

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

7.2. Clinical question 2: how is the severity of AOM assessed?

7.2.1. Recommendation

Severity of AOM is classified as mild, moderate and severe according to otoscopic findings and clinical manifestations (level of recommendation grade A).

References used to assess the recommendation level: Hotomi et al. [30,31] (Level IIa), Friedman et al. [32] (Level Ib), Biner et al. [33] (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 [34].
- 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 – ≤9
- Moderate – 10–15
- Severe – ≥16.

7.2.2. 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 [30,31]. Thus, a precise assessment of the tympanic membrane findings and thereby the severity of AOM will lead to a more appropriate choice of treatment [33].

7.3. Clinical question 3: is tympanometry useful to diagnose acute otitis media?

7.3.1. 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. [35] (Level IIa)).

7.3.2. 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.

8. 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, taking prescribed antimicrobial agents and their doses into consideration, also classified as having mild, moderate or severe AOM based on 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 (Figs. 1–3).

8.1. Clinical question 1: is it reasonable not to administer antimicrobial agents for mild AOM?

8.1.1. 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: Damoiseaux et al., 2000 [4] (Level Ib), Glasziou et al., 2000 [36] (Level Ia), Little et al., 2006 [9] (Level IIa).

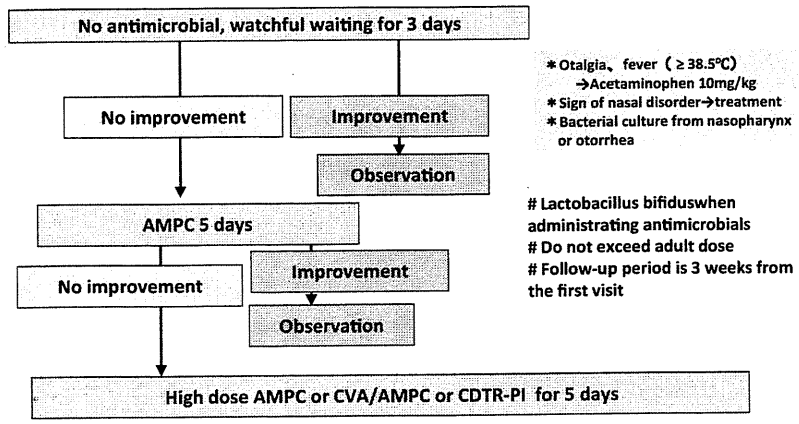


Fig. 1. Treatment algorithm of acute otitis media of mild grade (score 0–9).

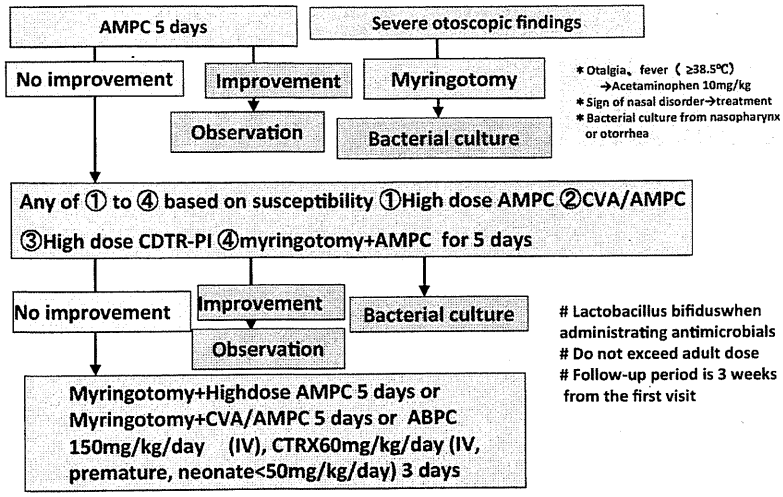


Fig. 2. Treatment algorithm of acute otitis media of moderate grade (score 10–15).

8.1.2. Background

It has been reported that most cases of AOM improve without use of antimicrobial agents [3,4,6,7,36,37]. 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.

8.2. Clinical question 2: which antimicrobial agents should be used for AOM?

8.2.1. 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. [38,39] (Level Ib), Piglansky et al. [40] (Level Ib), Haiman et al. [41] (Level Ib).

8.2.2. Background

Currently in Japan: about 50–60% of *S. pneumoniae* and about 50–70% of *Haemophilus 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 condition of drug sensitivity of bacteria in Japan.

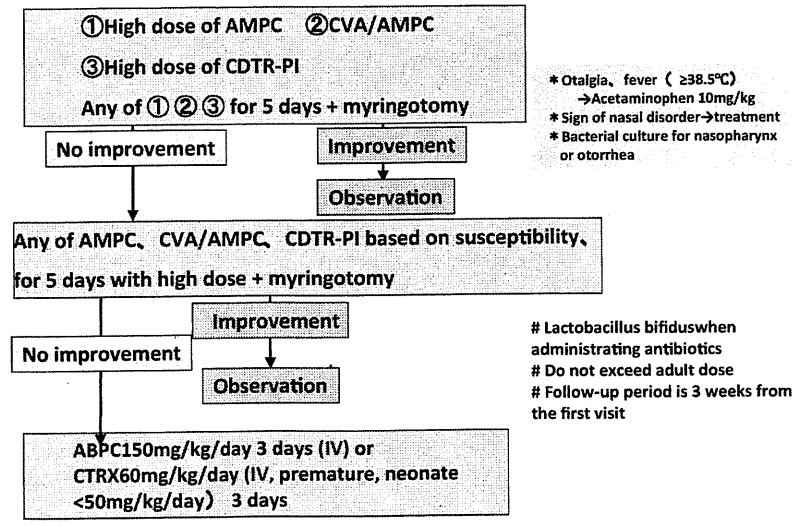


Fig. 3. Treatment algorithm of acute otitis media of severe grade (score ≤16).

8.3. Clinical question 3: what are appropriate indications for myringotomy?

8.3.1. Recommendation

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

8.3.2. 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.

8.4. Clinical question 4: risk factors deteriorating AOM

8.4.1. 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) (references used to assess the recommendation level: Ovetchkine and Cohen [42] (Level Ia)).

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).

8.4.2. Background

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

9. Recurrent otitis media (ROM)

9.1. 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 [43–45].

9.2. 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 [46]. In terms of causative bacteria, multidrug-resistant pneumococci are reportedly responsible in many cases [47], 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 [48]. 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 [49]. Lifestyle and environmental risk factors include having siblings, attending daycare, and pacifier use [49].

9.3. 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 [50]. Although a Cochrane review accepts the utility of pneumococcal polysaccharide vaccine, it does not recommend the conjugate vaccine [51]. 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. influenza* [52]. 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 [53].

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 [54–56]. Myringotomy has not been shown to have any significant effect in reducing the frequency of occurrence of ROM in research on patients in Japan [57], but insertion of a tympanostomy tube for one year and short-term insertion for one month significantly reduce the frequency of occurrence [58,59]. As measures to deal with lifestyle and environmental factors, discontinuation of attendance of group daycare and breastfeeding are desirable.

References

[1] Teele DW, Klein JO, Rosner B. The Greater Boston Otitis Media Study Group. Epidemiology of otitis media during the first seven years of life in children in Greater Boston: a prospective cohort study. J Infect Dis 1989;160:83–94.

[2] Faden H, Duffy L, Boeve M. Otitis media: back to basics. Pediatr Infect Dis J 1998;17:1105–13.

[3] van Buchem FL, Peeters NIF, van't Hof MA. Acute otitis media: a new treatment strategy. BMJ 1985;290:1033–7.

[4] Damoiseaux R, van Balen FAM, Hoes A, Verheij T, deMelker R. Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years. BMJ 2000;320:350–4.

[5] Rosenfeld RM, Bluestone CD, editors. Evidence-based otitis media. 2nd ed., 2003. p. 199–226.

[6] Rosenfeld RM, Kay D. Natural history of untreated otitis media. In: Rosenfeld RM, Bluestone CD, editors. Evidence-based otitis media. 2nd ed., 2003. p. 180–98.

[7] Rosenfeld RM, Kay D. Natural history of untreated otitis media. Laryngoscope 2003;113:1645–57.

[8] Spiro DM, Tay KY, Arnold DH, Dziura JD, Baker MD, Shapiro ED. Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial. JAMA 2006;296:1235–41.

[9] Little P, Moore M, Warner G, Dunleavy J, Williamson I. Longer term outcomes from a randomized trial of prescribing strategies in otitis media. Br J Gen Pract 2006;56:176–82.

[10] Glasziou PP, Del Mar CB, Sanders SL, Hayem M. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev)2004;(1).

[11] Le Saux N, Gaboury I, Baird M, Klassen TP, MacCormick J, Blanchard C, et al. A randomized, double-blind, placebo-controlled non-inferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age. CMAJ 2005;172:335–41.

[12] McCormick DP, Chonmaitree T, Pittman C, Saeed K, Friedman NR, Uchida T, et al. Nonsevere acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. Pediatrics 2005;115:1455–65.

[13] Dagan R. Treatment of acute otitis media – challenges in the era of antibiotic resistance. Vaccine 2000;19(Suppl. 1):S9–16.

[14] Dagan R, Leibovitz E, Cheletz G, Leiberman A, Porat N. Antibiotic treatment in acute otitis media promotes superinfection with resistant *Streptococcus pneumoniae* carried before initiation of treatment. J Infect Dis 2001;183:880–6.

[15] Toltzis P, Dul M, O'Riordan MA, Toltzis H, Blumer JL. Impact of amoxicillin on pneumococcal colonization compared with other therapies for acute otitis media. Pediatr Infect Dis J 2005;24:24–8.

[16] Suzuki K. The status quo of drug-resistant bacteria in pediatric otolaryngological infectious diseases. Pediatr Otorhinolaryngol Jpn 2000;21:26–31 [in Japanese].

[17] Nishimura T, Suzuki K, Oda M, Kobayashi T, Yajin K, Yamanaka N, et al. The third nationwide survey of clinical isolates from patients with otolaryngological field infections. J Jpn Soc Infect Dis Otolaryngol 2004;22:12–23 [in Japanese].

[18] Chan LS, Takata GS, Shekelle P, Morton SC, Mason W, Marcy SM. Evidence assessment of management of acute otitis media: II. Research gaps and priorities for future research. Pediatrics 2001;108: 248–54.

[19] Nakayama T. Clinical practice guideline consistent with evidence-based medicine manual for development and application. Tokyo: Kanehara Shuppan; 2004 [in Japanese].

[20] Clinical Practice Guideline for Diagnosis and Management of Acute Otitis Media in Children. Otol Jpn 2006;16(Suppl. 1) [in Japanese].

[21] Clinical practice guideline for diagnosis and management of acute otitis media in children. Pediatr Otorhinolaryngol Jpn 2006;27:71–107 [in Japanese].

[22] Japan Council for Quality Healthcare Minds (http://minds.jcqhc.or.jp/).

[23] Clinical Practice Guideline for Diagnosis and Management of Acute Otitis Media in Children. Japan Otological Society, Japan Society for Pediatric Otorhinolaryngology, Japan Society for Infectious Diseases in Otolaryngology, Kanehara Shuppan, Tokyo, 2006 [in Japanese].

[24] Clinical Practice Guideline for Diagnosis and Management of Acute Otitis Media in Children – 2009 edition. Japan Otological Society, Japan Society for Pediatric Otorhinolaryngology, Japan Society for Infectious Diseases in Otolaryngology. Tokyo: Kanehara Shuppan; 2009 [in Japanese].

[25] Fukui T, Tango T. Guide to the preparation of clinical practice guidelines, 4th edition. EBM J 2003;4:284–92 [in Japanese].

[26] Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328(7454):1490.

[27] Shiffman RN, Shekelle P, Overhage JM, Slutsky J, Grimshaw J, Deshpande AM. Standardized reporting of clinical practice guidelines: a proposal from the conference on guideline standardization. Ann Intern Med 2003;139:493–8.

[28] Appraisal of Guidelines, Research, and Evaluation in Europe (AGREE) Collaborative Group, Guideline development in Europe, An international comparison, Int J Technol Assess Health Care 2000;16:1039–1049.

[29] Rosenfeld RM, Casselbrant ML, Hannley MT. Implications of the AHRQ evidence report on acute otitis media. Otolaryngol Head Neck Surg 2001;125(5):440–8.

[30] Hotomi M, Yamanaka N, Shimada J, Ikeda Y, Faden H. Factors associated with clinical outcome in acute otitis media. Ann Otol Rhinol Laryngol 2004;113:846–52.

[31] Hotomi M, Yamanaka N, Samukawa T, Suzumot M, Sakai A, Shimada J, et al. Treatment and outcome of severe and non-severe acute otitis media. Eur J Pediatr 2005;164:3–8.

[32] Friedman NR, McCormick DP, Pittman C, Chonmaitree T, Teichgraeber DC, Uchida T, et al. Development of a practical tool for assessing the severity of acute otitis media. Pediatr Infect Dis J 2006;25:101–7.

[33] Biner B, Celtik C, Oner N, Küçükuğurluoğlu Y, Güzel A, Yildirim C, et al. The comparison of single-dose ceftriaxone, five-day azithromycin, and ten-day amoxicillin/clavulanate for the treatment of children with acute otitis media. Turk J Pediatr 2007;49:390–6.

[34] Kamide Y. Classification of tympanic membrane finding son acute otitis media in children and their verification. Oto-Rhino-Laryngol (Tokyo) 2003;46:17–30 [in Japanese].

[35] Saeed K, Coglianese CL, McCormick DP, Chonmaitree T. Otoscopic and tympanometric findings in acute otitis media yielding dry tap at tympanocentesis. Pediatr Infect Dis J 2004;23:1030–4.

[36] Glasziou PP, Del Mar CB, Hayem M, Sanders SL. Update of: Cochrane Database Syst Rev. 2000:CD000219. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev 2000;(4): CD000219.6.

[37] Jacobs J, Springer DA, Crothers D. Homeopathic treatment of acute otitis media in children: a preliminary randomized placebo-controlled trial. Pediatr Infect Dis J 2001;20:177–83.

[38] Ghaffar F, Muniz LS, Katz K, Smith JL, Shouse T, Davis P, et al. Effects of large dosages of amoxicillin/clavulanate or azithromycin on nasopharyngeal carriage of *Streptococcus pneumoniae*, *Haemophilus influenzae*, nonpneumococcal alpha-hemolytic streptococci, and Staphylococcus aureus in children with acute otitis media. Clin Infect Dis 2002;34:1301–9.

[39] Ghaffar F, Muniz LS, Katz K, Reynolds J, Smith JL, Davis P, et al. Effects of amoxicillin/clavulanate or azithromycin on nasopharyngeal carriage of *Streptococcus pneumoniae* and *Haemophilus influenzae* in children with acute otitis media. Clin Infect Dis 2000;31:875–80.

[40] Piglansky L, Leibovitz E, Raiz S, Greenberg D, Press J, Leiberman A, et al. Bacteriologic and clinical efficacy of high dose amoxicillin for therapy of acute otitis media in children. Pediatr Infect Dis J 2003;22:405–13.

[41] Haiman T, Leibovitz E, Piglansky L, Press J, Yagupsky P, Leiberman A, et al. Dynamics of pneumococcal nasopharyngeal carriage in children with nonresponsive acute otitis media treated with two regimens of intramuscular ceftriaxone. Pediatr Infect Dis J 2002;21: 642–7.
[42] Ovetchkine P, Cohen R. Shortened course of antibacterial therapy for acute otitis media. Paediatr Drugs 2003;5:133–40.
[43] Sher L, Arguedas A, Husseman M, Pichichero M, Hamed KA, Biswas D, et al. Randomized, investigator-blinded, multicenter, comparative study of gatifloxacin versus amoxicillin/clavulanate in recurrent otitis media and acute otitis media treatment failure in children. Pediatr Infect Dis J 2005;24:301–8.
[44] Ables AZ, Warren PK. High-dose azithromycin or amoxicillin-clavulanate for recurrent otitis media. J Fam Pract 2004;53:186–8.
[45] Arrieta A, Singh J. Management of recurrent and persistent acute otitis media: new options with familiar antibiotics. Pediatr Infect Dis J 2004;23:S115–24.
[46] Wiertsema SP, Herpers BL, Veenhoven RH, Salimans MM, Ruven HJ, Sanders EA, et al. Functional polymorphisms in the mannan-binding lectin 2 gene: effect on MBL levels and otitis media. J Allergy Clin Immunol 2006;117:1344–50.
[47] van Kempen MJ, Vaneechoutte M, Claeys G, Verschraegen GL, Vermeiren J, Dhooge IJ. Antibiotic susceptibility of acute otitis media pathogens in otitis-prone Belgian children. Eur J Pediatr 2004;163: 524–9.
[48] Yamanaka N, Hotomi M, Billal DS. Clinical bacteriology and immunology in acute otitis media in children. J Infect Chemother 2008;14: 180–7.
[49] Lubianca Neto JF, Hemb L, Silva DB. Systematic literature review of modifiable risk factors for recurrent acute otitis media in childhood. J Pediatr (RioJ) 2006;82:87–96.
[50] Brouwer CN, Maille AR, Rovers MM, Veenhoven RH, Grobbee DE, Sanders EA, et al. Effect of pneumococcal vaccination on quality of life in children with recurrent acute otitis media: a randomized, controlled trial. Pediatrics 2005;115:273–9.
[51] Straetemans M, Sanders EAM, Veenhoven RH, Schilder AGM, Damoiseaux RAMJ, Zielhuis GA. Pneumococcal vaccines for preventing otitis media. Cochrane Database Syst Rev)2004;(1).
[52] Prymula R, Peeters P, Chrobok V, Kriz P, Novakova E, Kaliskova E, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomized double-blind efficacy study. Lancet 2006;367:740–8.
[53] Maruyama Y, Hoshida S, Furukawa M, Ito M. Effects of Japanese herbal medicine, Juzen-taiho-to, in otitis-prone children – a preliminary study. Acta Otolaryngol 2009;129:14–8.
[54] Oomen KP, Rovers MM, van den Akker EH, van Staaij BK, Hoes AW, Schilder AG. Effect of adenotonsillectomy on middle ear status in children. Laryngoscope 2005;115:731–4.
[55] Hammaren-Malmi S, Saxen H, Tarkkanen J, Mattila PS. Adenoidectomy does not significantly reduce the incidence of otitis media in conjunction with the insertion of tympanostomy tubes in children who are younger than 4 years: a randomized trial. Pediatrics 2005;116: 185–9.
[56] Koivunen P, Uhari M, Luotonen J, Kristo A, Raski R, Pokka T, et al. Adenoidectomy versus chemoprophylaxis and placebo for recurrent acute otitis media in children aged under 2 years: randomised controlled trial. BMJ (Clinical research ed) 2004;328:487.
[57] Nomura Y, Ishibashi T, Yano J, Ichikawa T, Shinogami M, Monobe H, et al. Effect of myringotomy on prognosis in pediatric acute otitis media. Int J Pediatr Otorhinolaryngol 2005;69:61–4.
[58] Uno Y. Effects of long-term tympanostomy tubes in children with intractable otitis media. Otol Jpn 2007;17:16–25 [in Japanese].
[59] Uno Y. Effects of short-term tympanostomy tube on intractable recurrent otitis media in children. Otol Jpn 2007;17:194–202 [in Japanese].

資料4

小児反復性中耳炎に対する十全大補湯の有用性に関する

多施設共同ランダム化比較試験

金沢大学 IRB 用　試験計画書

金沢大学附属病院　耳鼻咽喉科・頭頸部外科
准教授　伊藤　真人
作成年月日　2009 年　9 月　11 日（第 8 版）

（2009 年 10 月 14 日、金沢大学附属病院 IRB を通過済）

目　次

1 背景及び試験実施の意義・必要性

近年、市井における耐性細菌（DRSP, BLNAR など）の蔓延と、集団保育の低年齢化により、乳幼児における急性中耳炎の難治例・反復例が増加し、その合併症として薬剤耐性菌による髄膜炎の増加も報告されている。ところがこれらの細菌に有効な抗菌薬は極めて限られており、抗菌薬化学療法の限界がみえている。さらに抗菌薬の多用は耐性菌増加と更なる薬剤耐性化を誘導する。また適正な抗菌薬投与は各時点で発症している細菌感染症に対して有効であっても、以後再発しうる感染症を予防するものではない。難治性・反復性感染症に対し、現行の対感染症治療を補助しその効果を増強する新しい治療法の開発が必要である。

近年，漢方薬に関する基礎・臨床研究が進展しさまざまな有益な効果が証明されてきている。補剤とは病後の状態など体内の生命活動活性の低下した状態を補い、消化吸収能力の改善により食欲増進とともに栄養状態を改善させることにより、身体の恒常性を回復させる一群の漢方薬を指す。

特に代表的補剤である十全大補湯（以下 TJ-48）と補中益気湯については基礎的・臨床的研究が多く報告されており、補剤投与により宿主の免疫賦活作用と生体防御機能が向上[1)-5)]し、感染症の病態において有効に作用することが証明されつつある。ウイルス感染については、ライノウイルス感染抑制効果や[6)]、COPD 患者における感冒罹患回数の減少と体重増加[7)]などが報告されている。細菌感染については MRSA 感染防御に関する基礎的臨床的有効性[8) 9)]、真菌感染についてもカンジダ感染症に対する有用性の報告がなされている[10)]。また乳幼児に対する TJ-48 投与の有効性に関しては肛門周囲膿瘍・痔瘻の病態についての報告[11)12)]があり、この病態に対する標準的治療法の一つとして認められてきている[13)14)]。その他貧血や栄養状態の改善効果を示す報告も認められる[15)16)]。

これまでに申請者らは、乳幼児反復性中耳炎に対し TJ-48 投与を併用することによって、急性中耳炎の罹患頻度が有意に低下することを報告した[17) 18)]。これを受け、小児急性中耳炎診療ガイドライン（2009 年版）[19)]において「反復性中耳炎の治療」の項に、十全大補湯の投与と申請者らの報告が紹介されている。そこで今回，小児反復性中耳炎における TJ-48 の有用性を科学的に検討すべく多施設共同研究計画を立案した。

なお、本研究は厚生労働省科学研究費補助金（H21-臨床研究-一般-007）において施行される。

2. 試験の目的

小児反復性中耳炎症例を対象とし、ツムラ十全大補湯エキス顆粒（医療用）（TJ-48）の中耳炎発症軽減効果、および感染軽減効果、栄養状態改善効果等について prospective に検討する。

3. 試験の評価項目

３－１　主要評価項目（プライマリーエンドポイント）
急性中耳炎罹患回数の減少

３－２　副次的評価項目（セカンダリーエンドポイント）
① 鼻かぜ(coryza)罹患回数
② 全身状態（栄養状態、貧血改善の有無など）
③ 抗菌薬の使用状況
④ 鼓膜チューブ挿入に至った症例数
⑤ 細菌学的検索

４．試験計画・試験デザイン

デザイン名：非盲検ランダム化比較試験

４－１ 対象患者（適格基準）
次の患者選択基準及び除外基準を満たす患者

４－１－１　選択基準

A. Disease Characteristic
十全大補湯の効能効果に示される「病後の体力低下、疲労倦怠、食欲不振、ねあせ、手足の冷え、貧血」のいずれかを満たす症例で、かつ反復性中耳炎の定義である「過去 6 か月以内に 3 回以上、12 か月以内に 4 回以上の急性中耳炎罹患」の経過があり、標準的治療*) での反復抑制が困難な症例
＊：2009 年版小児急性中耳炎治療ガイドライン参照

B. Patient Characteristics
①年齢：6 か月以上 4 歳未満
体重：7 kg以上 20ｋｇ以下
②骨髄機能、肝機能、腎機能など主要臓器機能が保たれている症例
その他、治療の必要な重篤な疾患（心機能、呼吸機能、精神神経機能障害など）のコントロール困難な合併疾患がないこと.
③文書によるインフォームド・コンセントが得られていること.

４－１－２　除外基準
① 重篤な合併症のある症例（顎顔面奇形・形成不全、人工呼吸器使用中を含む）
② 薬剤アレルギーのため服用が困難と思われる症例
③ その他の免疫療法を併用している症例（免疫グロブリン製剤、ステロイドなどの薬剤使用を含む）
④ その他の漢方薬を服用している症例

⑤ 医学的、心理学的また患者、家族の状況により不適当と考えられる症例
⑥ その他，主治医が本試験を安全に実施するのに不適当と認めた症例

4－2　試験のアウトライン

	試験開始前	試験開始時	試験中	試験終了時
		0週	12週±7日	11～13週
同意取得・登録・割付	○			
中耳炎・上気道炎罹患回数		←―――	○	―――→
細菌学的検討		○	△	○
患者日誌		←―――	○	―――→
採血検査		△		△
有害事象		←―――	―――	―――→

○；検査日、実施日　△；可能な限り実施する

4－3　試験薬の概要

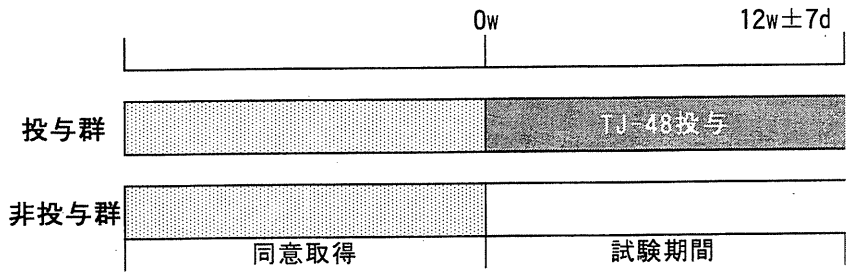
4－3－1　薬剤名（商品名）

ツムラ十全大補湯（TJ-48）エキス顆粒（医療用）

4－3－2　化学名、薬効成分剤型等

薬剤名	ツムラ十全大補湯エキス顆粒（医療用）
規格・含量	本品 7.5ｇ中に十全大補湯乾燥エキス 5.0ｇを含有する。
剤型	顆粒剤
保管条件	薬の品質を保つため、出来るだけ湿気をさけ、直射日光のあたらない涼しい所に保管すること。

4－4　試験方法；非盲検ランダム化比較試験



4－4－1　被験者の登録・割付方法

中央登録。Web 上で登録し、無作為割付をおこなう。

4－4－2　試験薬の投与開始時期

症例登録後、ランダム化比較試験を行う。割付に応じて、投与群には TJ-48 の投与を開始し、非投与群とともに試験を開始する。

４－４－３　試験薬の用法・用量、投与期間

投与群に下記投与量のTJ-48を原則として３ヶ月間、食前または食間に経口的に投与する。

＜投与量＞　0.1～0.25g/kg/日　分２

４－４－４　試験期間

試験開始日から３ヶ月間投与をおこなう。

４－４－５研究観察期間

研究観察期間は以下の期間とする

試験期間：12週間±1週間

４－４－６　併用薬及び併用療法

通常の急性中耳炎等の上気道感染症に対する治療は禁止しない。すなわち試験期間中も小児急性中耳炎診療ガイドライン(日本耳科学会ほか, 2009)[17]に準じた通常の診療行為を施行し、鼓膜切開の施行状況、抗菌薬投与状況などを症例報告書(CRF)に記載する。ただし、免疫グロブリン製剤、ステロイドなどの免疫系に影響を与える薬剤は使用しない。なお、鼓膜チューブ挿入については、試験開始後１ヶ月間は行わないことを原則とし、以後急性中耳炎の反復の制御が困難なために鼓膜チューブ挿入に至った場合はその旨を症例報告書(CRF)に記載する。

５．　重篤な有害事象の対応

重篤な有害事象及び予測できない新たな事象が発現した場合

試験責任医師、分担医師、協力医師は適切な処置を行うとともに病院長・本試験審査委員会・臨床試験事務局に速やかに報告する。

６．試験スケジュール（観察・検査・調査項目・実施期間）

６－１　調査項目

①　症例背景

性別、年齢、身長、体重、急性中耳炎罹患回数、既往歴、アレルギー歴、同意取得日、試験開始日、保育園通園状況、哺乳状況、家族の喫煙状況、鼻副鼻腔疾患・アレルギー疾患の有無、証等

②　その他の併用薬剤、 併用療法の有無

特に免疫グロブリン製剤、ステロイドなどの免疫系に影響を与える薬剤、および、その

他の漢方薬や市販薬、サプリメントの併用状況。

6－2　観察時期ならびに観察項目

6－2－1　観察時期

観察期間は原則として試験開始後 12 週±1 週間とする。
併用薬剤・併用療法は適時症例報告書（CRF）に記載する。
採血検査、細菌培養検査は、可能であれば試験開始前ならびに試験終了日に測定する。
また、担当医師の判断によりこの時期以外にも適宜行うものとする。

6－2－2　観察項目

① 中耳炎罹患回数
② 鼻かぜ(coryza)罹患回数
③ 臨床採血検査
　試験開始時ならびに試験終了時に可能な限り以下の項目を検査する。
　・ 血液検査：赤血球数，血色素量，ヘマトクリット値，白血球数（リンパ球比，好中球比），血小板数，CRP，AST(GOT)，ALT(GPT)，γ-GTP，LDH，T-Bil，クレアチニン，BUN，血清 Na，Cl，K，血清アルブミン値，IgG，IgM，IgA
④ 抗菌薬の使用状況
⑤ 鼓膜チューブ挿入に至った症例数
⑥ 細菌学的検査（鼻咽腔 and/or 耳漏）

6－3　観察スケジュール

	試験開始前	試験開始時	試験中					試験終了時
		0週		4週±7日		8週±7日		12週±7日
同意	○							
症例登録・割付	○							
患者背景	○							
中耳炎罹患回数				○		○		○
鼻かぜ罹患回数				○		○		○
細菌学的検討		○	←		△		→	○
患者日誌		←			○			→
臨床血液検査		△						△
有害事象		←						→

○；実施する　　△；可能な限り実施する

6－4　服薬状況調査

観察時期ごとに試験薬（TJ-48）の服薬状況を調査し、下記の 3 段階に分けて症例報告書（CRF）に記入する。