

Updated Guidelines for the Management of Acute Otitis Media in Children by the Italian Society of Pediatrics

Treatment

Paola Marchisio, MD,* Luisa Galli, MD,† Barbara Bortone, MD,† Martina Ciarcia, MD,† Marco Antonio Motisi, MD,† Andrea Novelli, MD,† Luciano Pinto, MD,‡ Sergio Bottero, MD,§ Lorenzo Pignataro, MD,¶|| Giorgio Piacentini, MD,** Roberto Mattina, MD,†† Renato Cutrera, MD,‡‡ Attilio Varicchio, MD,§§ Gian Luigi Marseglia, MD,¶¶ Alberto Villani, MD,||| Elena Chiappini, PhD,† and the Italian Panel for the Management of Acute Otitis Media in Children

Background: New insights into the diagnosis, treatment and prevention of acute otitis media (AOM) have been gained in recent years. For this reason, the Italian Paediatric Society has updated its 2010 guidelines.

Methods: A literature search was carried out on PubMed. Only pediatric studies published between January 1, 2010 and December 31, 2018 in English or Italian were included. Each included study was assessed according to the GRADE methodology. The quality of the systematic reviews was assessed using AMSTAR 2. The recommendations were formulated by a multidisciplinary panel of experts.

Results: Prompt antibiotic treatment is recommended for children with otorrhea, intracranial complications and/or a history of recurrence and for children under the age of 6 months. For children 6 months to 2 years of age, prompt antibiotic treatment is recommended for all forms of unilateral and bilateral AOM, whether mild or severe. Prompt antibiotic treatment is also recommended for children over 2 years with severe bilateral AOM. A watchful-waiting approach can be applied to children over 2 years with mild or severe unilateral AOM or mild bilateral AOM. High doses of amoxicillin, or amoxicillin-clavulanic acid for patients with a high risk of infection by Beta-lactamase producing strains, remain the first-line antibiotics.

Conclusions: AOM should be managed on a case-by-case basis that takes account of the child's age, the severity of the episode and whether it is unilateral or bilateral. In patients under 2 years, prompt antibiotic treatment is always recommended.

Key Words: therapy, acute otitis media, guidelines

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From the *Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico and Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; †Department of Human Health Sciences, University of Florence, AOU Firenze, Italy; ‡Italian Society of Pediatric Emergency Medicine, Naples, Italy; §Airway Surgery Unit, Department of Pediatric Surgery, Bambino Gesù Children's Hospital, Rome, Italy; ¶Department of Otolaryngology and ||Department of Clinical Sciences and Community Health, Fondazione I.R.C.C.S. Ca' Granda, Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; **Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, Pediatric Clinic, University of Verona, Verona, Italy; ††Department of Biomedical, Surgical, and Odontoiatric Sciences, Università degli Studi di Milano, Milan, Italy; ‡‡Respiratory Unit, Academic Department of Pediatrics, Bambino Gesù Children's Hospital, Rome, Italy; §§Department of Otolaryngology, Ospedale San Gennaro, Naples, Italy; ¶¶Department of Pediatrics, University of Pavia, Pavia, Italy; and ||| Pediatric and Infectious Disease Unit, Bambino Gesù Children's Hospital, IRCCS, Rome, Italy.

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Address for correspondence: Elena Chiappini, PhD, Department of Pediatrics, Anna Meyer Children's University Hospital, Viale Pieraccini, 24, Florence, 50100 Italy. E-mail: elena.chiappini@unifi.it.

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The appropriateness of antibiotic treatment in children with acute otitis media (AOM) is a highly important issue. AOM is one of the most common reasons for the antibiotic prescription in this age group, accounting for up to 25% of all such prescriptions.^{1–3}

In the United States, Sweden, United Kingdom, France, Spain and Italy, the introduction of guidelines has been found to be associated with a reduction of up to 12% in erroneous prescriptions and an increase of up to 58% in the correctness of the type and dosage of the prescribed antibiotic.^{4,5} A recent Italian study showed that the implementation of guidelines in a pediatric A&E department led to a reduction from 53.2% to 32.4% in the use of broad-spectrum antibiotics.⁶

AOM management must also include the relief of pain, the most frequently reported symptom.⁷

MATERIALS AND METHODS

Expert Group (Positions, Processes)

To draw up these guidelines, the Italian Paediatric Society assembled a committee that included experts in general pediatrics, research methodology, pulmonology, allergy, emergency medicine, epidemiology, pharmacology and microbiology. The committee members were suggested by the scientific societies in their respective fields.

The development of the guidelines involved various work groups:

- The guideline development group, which organized and directed the various phases of their development;
- A multidisciplinary panel of experts from various professions, which developed the clinical queries, discussed the efficacy evidence and drew up the recommendations;
- A methodology group, which performed a critical analysis of the literature and extracted and tabulated the relevant data; and
- A writing group, which drafted the summary of the scientific literature and the final text of the guidelines.

The writing and methodology groups and the panel met regularly; the meeting dates and previous versions of the guidelines have been logged. To reach agreement on the topics selected for the guidelines and the strength of the recommendations, Delphi's method was adopted.⁸

Target Readers and Topics

These guidelines provide recommendations on the diagnosis, prevention and treatment of AOM in children over 2 months of age. Subjects with acquired or congenital immunodeficiency, grommet, a chronic underlying disorder (eg, cystic fibrosis), and/or facial malformations are excluded.

The guidelines are mainly intended for pediatricians, ENT specialists, GPs, nurses and pharmacists involved in the management of children with AOM.

Developing the Queries

The queries and outcomes were identified by the methodology group and then shared and discussed with the rest of the panel, using the GRADE system. The panel identified the outcomes and classified them by importance through individual voting on a 9-point scale. Only those outcomes categorized as critical and important were considered in the literature review and in the subsequent development of the recommendations.

Evidence Search and Developing the Recommendations

A literature search was carried out on PubMed. Only studies with a pediatric caseload published in English or Italian between 1 January 2010 and 31 December 2018 were included in the review (Appendix, Supplemental Digital Content 1; <http://links.lww.com/INF/D613>). The key words used in the search strategy for each question were established by the members of a subcommittee. Relevant articles cited in the selected studies were also considered. The references were periodically updated during the course of the guideline drafting process. Abstracts and articles were selected and assessed by members of a subcommittee, with particular attention given to randomized double-blind clinical trials, cohort studies, systematic reviews, and all general overviews. When the literature search uncovered existing guidelines, these underwent methodologic evaluation using the AGREE II tool⁹ and a comparative analysis of their recommendations. A further literature review was carried out before producing the final version.

Each study included in the review has been summarized in the tables (summary of findings) and evaluated for methodology and content according to a preestablished checklist based on the GRADE system.¹⁰ The quality of the systematic review was assessed by AMSTAR 2.¹¹ The results of the analysis were then discussed and approved by a meeting of all those who participated in drawing up the guidelines, using the Consensus Conference method.

The GRADE method involves an explicit multi-step process that must be followed rigorously, in line with the proposed sequence: (1) defining the question for which a recommendation must be formulated; (2) identifying all the outcomes for the clinical question and assessing their relative importance for the adequate evaluation of a given intervention; (3) search for data on negative and positive effects of the various interventions being assessed; (4) summary of evidence for individual outcomes considered “essential” or “important”; (5) assessment of the quality of the evidence for each outcome; (6) assessment of the overall quality of the evidence; (7) risk-benefit profile of the intervention; (8) defining the strength of the recommendation; (9) formulating the recommendation; and (10) implementation and verification of impact.

For the formulation of the recommendations, in agreement with the GRADE methodology, the following standard expressions were used as follows: 1. must be used (“strong positive” recommendation); 2. could be used (“weak positive” recommendation); 3. should not be used (“weak negative” recommendation); and 4. must not be used (“strong negative” recommendation).

Question 1. What Pain Relief Should Be Used?

The therapeutic management of AOM must involve the assessment and treatment of pain. This recommendation was confirmed by the 2013 AAP guidelines,¹² in which it was stressed that

the treatment of pain, especially in the first 24 hours, must be performed regardless of whether it is decided to administer antibiotics or adopt a watchful-waiting approach.

Effective treatment of pain requires its careful assessment using appropriate validated instruments. According to the 2010 Italian Ministerial recommendations,¹³ there are no instruments that are completely valid for all pediatric ages; the instrument that should be used depends on the child’s cognitive, behavioral and relational development. Three pain scores from the many available have been identified.

- 1) For infants and preverbal children under 3 years old and children with motor or cognitive disorders making them unable to subjectively assess their pain: FLACC score.¹⁴
- 2) For children >3 years: Wong-Baker scale.
- 3) For children ≥8 years: Numeric scale.

Systemic treatment with paracetamol 15 mg/kg/dose (up to 4 times daily) or with ibuprofen 10 mg/kg/dose (up to 3 times daily) by mouth is the treatment of choice.^{12,13}

A 1996 double-blind RCT investigating the efficacy of ibuprofen (10 mg 3 times daily for 48 hours) and paracetamol (10 mg 3 times daily for 48 hours) did not observe any significant difference between them in the treatment of otalgia: after 48 hours, 7% of patients treated with ibuprofen, 10% of those treated with paracetamol and 25% of those treated with placebo still reported pain.¹⁵

Two later trials^{16,17} included only a small proportion of children with AOM and focused on fever or fever associated with pain. In one Cochrane review,¹⁸ which analyzed the results of both studies (71 randomized children, 39 included in the analysis), no significant difference in pain reduction between paracetamol and ibuprofen was observed after 24 hours [18% vs. 18% relative risk (RR) 1.08, 95% CI: 0.31–3.73] or between 48 and 72 hours (36% vs. 29% RR 1.35, 95% CI: 0.62–2.91) from diagnosis. However, the strength of the evidence for these results is very low, due to the low sample size.¹⁸

There is no evidence on the efficacy of preparations based on natural extracts, such as the application of olive oil or other substances, as the results of the few available studies are of low quality and in any case refer to children over the age of 5 years.^{19–21}

Local anesthetics containing lidocaine or procaine are often used topically. The 2006 Cochrane Review²² evaluated 356 studies, of which only 4 were included in the final analysis: double-blind RCTs comparing an ototopical preparation with an analgesic effect (excluding antibiotics) versus placebo or comparing 2 ototopical preparations with an analgesic effect (excluding antibiotics) in adults or children presenting at primary care settings with AOM without TM perforation. Pain severity and duration was chosen as the primary outcome, while parent satisfaction, absenteeism from school or work and appearance of adverse reactions were considered as secondary outcomes. There was a pain reduction of 25%, 30 minutes after instillation, in those receiving anesthetic drops in comparison with placebo, a statistically significant difference. Trials comparing naturopathic preparations and anesthetic ear drops produced results in favor of the naturopathic preparations, but the differences were not always statistically significant. The review concluded that there was insufficient evidence to establish whether topical pain relief was effective or not.

Subsequently, in a high-quality systematic review in 2012, Wood et al²¹ identified and analyzed 4 randomized trials on the efficacy of ototopical preparations containing benzocaine, procaine, lidocaine, phenazone or plant extracts, concluding that more studies with a more rigorous methodology were needed to definitively demonstrate their inefficacy.

Recommendation 1

The therapeutic management of AOM should prioritize the assessment and treatment of otalgia (strong positive recommendation).

Recommendation 2

The mainstay treatment of otalgia should be the administration of adequate doses of ibuprofen or paracetamol (strong positive recommendation).

Recommendation 3

The topical administration of analgesic drops or the use of analgesic preparations based on natural extracts is not recommended, due to the lack of available high-quality evidence (weak negative recommendation).

Question 2. When and How Should a Watchful-Waiting Strategy Be Used? And When Should Prompt Antibiotic Treatment Be Given?

A watchful-waiting strategy involves the observation of the child’s clinical course over the first 48–72 hours, without beginning any antibiotic treatment.²³ The expected benefits of avoiding immediate administration of antibiotics are reduced cost, reduction in side effects and reduced spread of antibiotic-resistant strains.¹² Watchful waiting should only be considered if the diagnosis of AOM is certain and having taken account of the following 3 clinical parameters: child’s age (below or over 2 years), severity of the episode and whether one or both ears are affected.²⁴ To assess the severity, refer to the diagnosis section.

An overview of the recommendations of the available international guidelines.²⁴ shows that they all include the watchful-waiting option in children >2 years, while there is no general consensus on the approach in children 6 months to 2 years of age.²⁴

The 2013 AAP guidelines, in contrast with the 2003 version, also include the option of a watchful-waiting approach, even in children 6–24 months of age with mild unilateral AOM. This change seems to be supported by recent evidence demonstrating that watchful waiting is safe even in younger children.

A high-quality data meta-analysis by Rovers et al²⁵ posed the objective of identifying subgroups of children who might benefit from prompt antibiotic treatment in terms of reduced pain and fever by 3–7 days after the start of treatment. This meta-analysis aimed to include the individual data of 1643 children between 6 months and 12 years of age included in 4 studies comparing the use of prompt antibiotic therapy versus placebo or no treatment and in 2 studies comparing prompt versus delayed antibiotic treatment. Most benefited from prompt antibiotic treatment: children with bilateral AOM under 2 years of age and children with spontaneous otorrhea (see Table 1).

Sanders et al²⁶ 2009 systematic Cochrane review included 4 more RCTs besides those analyzed by Rovers. These investigated antibiotic treatment versus placebo,²⁷ prompt antibiotic treatment versus watchful waiting^{28,29} and delayed antibiotic prescription.³⁰ From this global analysis of 2928 children, it emerged that antibiotic treatment did not reduce the risk of perforation or recurrence. The sole described case of mastoiditis arose in a child treated with antibiotic. Side effects such as vomiting, diarrhea and rash were more common in children treated with antibiotic than in the control group (RR 1.37, 95% CI: 1.09–1.76). In children undergoing prompt antibiotic treatment, there was a reduction in otalgia between 2 and 7 days (RR 0.72, 95% CI: 1.09–1.76) but not at 24 hours.

This review²⁶ had some limitations. Only studies with cases from a high socioeconomic level were included; children with a

TABLE 1. NNT to Reduce Fever, Pain or Both at 3–7 Days in Subgroups of Children With AOM

Group	AOM	Difference %	95% CI	NNT	
Age (years)	<2				
	<2	Bilateral	-25	20–30	4
	<2	Unilateral	-5	2–8	20
	≥2	Bilateral	-12	7–17	9
≥2	Unilateral	-4	2–6	25	
	Otorrhea	Present	-36	27–45	3
	Absent	-14	11–17	8	
	Bilateral	Present	-20	11–28	5
Absent		-6	0–12	17	

NNT, number needed to treat.
Adapted from Rovers et al.²⁷

high risk of complications or recurrence were excluded; pain was the only parameter considered to measure the duration of the episode, ignoring other signs and symptoms; and the time period used to measure the outcome (2–7 days) is rather broad, with no details of evolution at individual time points.

The latest Cochrane review on the efficacy of antibiotic versus placebo in AOM was published in 2015.³¹ It also included the additional outcomes of pain assessment at 10 and 12 days, tympanometry findings at 2 and 4 weeks and long-term side effects (including parent-reported signs of otitis, antibiotic prescriptions and need for medical intervention within one year of the diagnosis). Analysis of the 13 trials comparing antibiotic treatment against placebo in 3401 children confirmed that there was no significant reduction in pain between the 2 groups at 24 hours (RR 0.89, 95% CI: 0.78–1.1). There was a mild reduction in pain in the antibiotic group between 4 and 7 days (RR 0.76, 95% CI: 0.63–0.91, NNT 16) and between 10 and 12 days (RR 0.33, 95% CI: 0.17–0.66, NNT 7). Antibiotic also reduced the proportion of children with abnormal tympanometry findings between 2 and 4 weeks (RR 0.82, 95% CI: 0.74–0.90, NNT 11) but not at 3 months (RR 0.97, 95% CI: 0.76–1.24), and it did not reduce the risk of AOM recurrence (RR 0.93, 95% CI: 0.7–1.10) versus placebo. Severe complications were rare, with no difference in incidence between the 2 groups. Side effects such as vomiting, rash and diarrhea were significantly more common in children receiving antibiotic treatment versus placebo (RR 1.3, 95% CI: 1.19–1.59, NNT 14).

Analysis of the 4 trials comparing prompt antibiotic treatment versus watchful aiting^{17,28–30} in 959 children did not reveal any significant difference in pain reduction between 3 and 7 days (RR 0.75, 95% CI: 0.50–1.12). There was no significant difference between the groups in tympanometry findings at 4 weeks, in the risk of TM perforation or in the risk of AOM recurrence.²³ It should be noted that a specific sub-analysis for the subgroup of patients under 2 years was taken from Rovers’ 2006 meta-analysis.

The most recent high-quality studies conducted in children under 2–3 years of age were conducted by Hoberman et al³² and Tähtinen et al.³³ Hoberman et al conducted a high-quality double-blind RCT in 291 AOM patients 6–24 months of age, who were randomized to receive prompt treatment with amoxicillin-clavulanic acid (90mg/kg/day) or placebo. The primary outcome was the time to resolution of symptoms, defined as a score of 0 or 1 on the validated AOM-SOS scale, and the global severity of symptoms during the observation period. Among the children who received antibiotic, 35% had initial resolution of symptoms by day 2, 61% by day 4 and 80% by day 7, compared with 28% by day 2, 54% by day 4 and 74% by day 7 among children who received placebo (P = 0.14). The sustained resolution of symptoms (defined as 2 successive scores of 0 or 1 on the AOM-SOS scale) was significantly

greater in children receiving amoxicillin-clavulanic acid versus placebo. The rate of clinical failure (defined as the persistence of signs of acute infection on otoscopic examination) was greater in the placebo group both on day 4 (23% vs. 4%, $P < 0.001$) and on days 10–12 (51% vs. 16%, $P < 0.001$, NNT 2.9). Comparative analysis of children with unilateral and bilateral AOM revealed that clinical failure was more common in bilateral AOM (60% vs. 23%). In conclusion, this study demonstrated that in patients under 2 years, treatment with amoxicillin-clavulanic acid for 10 days tended to reduce the time to resolution of symptoms, the severity of the symptoms and the risk of persistence of signs of AOM on otoscopic examination.³¹

In a very high-quality double-blind RCT, Tähtinen et al³³ investigated 319 patients between 6 and 35 months of age who were randomized to receive prompt treatment with amoxicillin-clavulanic acid 40 mg/kg/day ($n = 161$) or placebo ($n = 158$) for 7 days. The primary outcome was time to treatment failure at the end of treatment. Similar data were also reported in a second trial conducted by the same authors in 2012, who showed that watchful waiting was not associated with a worse outcome in AOM patients 6–35 months of age. However, it was associated with a transient worsening and protraction of signs and symptoms and a greater absenteeism of parents from work.³⁴

A secondary analysis published in 2017³⁵ analyzed the prognostic factors most often associated with treatment failure. This occurred in 18.6% of the 161 children receiving antibiotics versus 44.5% of the 158 children receiving placebo. On treatment day 3, treatment failure was reported in just 13.7% of children receiving amoxicillin-clavulanic acid versus 25.3% of those receiving placebo. There was no statistically significant difference in the use of analgesics/antipyretics between the 2 groups ($P = 0.45$). Adverse effects such as diarrhea and eczema were significantly higher in the antibiotic group (47.8% vs. 26.8%, $P < 0.001$).

In the more recent secondary analysis, treatment failure was significantly more common in children between 6 and 23 months than in those 23 to 35 months of age (34.4% vs. 20%, $P = 0.04$). The presence of an A or C curve on the initial tympanogram, a marker of the absence of severe TM bulging, was associated with a reduced risk of treatment failure ($P = 0.02$).³⁵ In conclusion, younger children with severe bulging of the TM seemed to benefit most from antibiotic treatment.^{33–35}

The 2 trials, Hoberman et al³² and Tähtinen et al,³³ were further analyzed by Hoberman, who investigated the risk of treatment failure for antibiotic treatment versus placebo after dividing the children into subgroups based on AOM severity and whether one or both ears were affected.³⁵ Children under 35 months with mild unilateral AOM were at greater risk of treatment failure with placebo than with antibiotic treatment (40% vs. 14%, RR 0.34, 95% CI 0.18–0.65).³⁶ (See Table 2.)

Le Saux et al's RCT²⁷ estimated the clinical improvement in children with AOM between 6 months and 5 years of age examined in an emergency department at a children's hospital and randomized

to receive prompt amoxicillin treatment (60 mg/kg/day) or placebo, in any case in combination with ibuprofen, for 5 days. The episodes were defined as of moderate severity, using a 3-point clinical score. Clinical resolution evaluated by telephone follow-up was significantly greater in the treated subjects than in the control group (after 14 days: placebo 84.2% vs. antibiotic 92.8%, difference 8.6%). Children who received placebo had significantly more pain and fever in the first 48 hours, regardless of age.

A recent Cochrane review³⁷ analyzed the impact of watchful waiting in the management of both adult and pediatric patients affected by various types of respiratory infection. It also included a sub-analysis on the management of AOM in pediatric patients, which included 3 RCTs^{30,38,39} involving 830 children. Watchful waiting was associated with a slight protraction and worsening of symptoms (pain, fever, general malaise) versus prompt treatment, but there was no significant difference in complications. However, the results were not analyzed in relation to child's age or severity of the episode.

A cost-utility analysis by Shaikh et al⁴⁰ in 2017 compared 5 treatment strategies (immediate amoxicillin-clavulanic acid, immediate amoxicillin, immediate cefdinir, watchful waiting and delayed prescription for antibiotic for use if symptoms did not improve) for cost-utility by calculating QALD (quality adjusted life days) in 500 patients under 2 years divided into the 5 groups. The results revealed that the most effective treatment regimen was immediate amoxicillin-clavulanic acid, followed in order by immediate amoxicillin, immediate cefdinir, watchful waiting and delayed prescription for antibiotic. A strong point of this study was the type of analysis, which considered not only benefits in terms of healthcare expenditure but also measured the costs of each regimen in relation to its potential benefits (speed of clinical improvement, quality and number of side effects, impact on the family). However, this study did not stratify patients <2 years old by severity of AOM and the presence or absence of otorrhea, therefore no definitive conclusions can be drawn on a possible watchful-waiting strategy in children 6–24 months of age.⁴⁰

In contrast, Sun et al⁴¹ confirmed the superior efficacy of watchful waiting over prompt antibiotic treatment, in terms of cost-effectiveness for healthcare expenditure, in a study of 250 patients <18 years old treated according to the 2013 AAP guidelines. This result was also supported by the results of a previous study.⁴²

The applicability of watchful waiting to children attending emergency departments has been demonstrated in international studies. In addition to studies in the United States,^{5,30} in a retrospective study in Spain, Mintegi Raso demonstrated that observation without immediate antibiotic therapy in selected patients with mild AOM was associated with a 25% reduction in the number of prescriptions of antibiotics.^{5,43}

In 2017 Rothman et al demonstrated, in an analysis of 1493 visits of children with AOM to an emergency department, that 20%

TABLE 2. Treatment Failure in Children With AOM Classified by Ears Affected (Unilateral/Bilateral) and Severity of Otitis at Onset (Hoberman 2013)

Ears Affected and Severity of AOM on Arrival	Children With Treatment Failure/Total Children (%)								
	Pittsburgh Study		Turku Study		Unified Studies		RR, amoxicillin-clavulanic acid vs. placebo (95% CI)	ARR (95% CI)	NNT
	Amoxicillin-clavulanic acid	Placebo	Amoxicillin-clavulanic acid	Placebo	Amoxicillin-clavulanic acid	Placebo			
Unilateral; mild	4/39 (10)	15/42 (36)	6/33 (18)	11/23 (48)	10/72 (14)	26/65 (40)	0.34 (0.18–0.65)	0.27 (0.13–0.41)	4
Unilateral; severe	2/29 (7)	14/28 (50)	9/48 (19)	19/42 (45)	11/77 (14)	33/70 (47)	0.28 (0.10–0.79)	0.34 (0.18–0.50)	3
Bilateral; mild	7/40 (18)	18/35 (51)	6/20 (30)	11/20 (55)	13/60 (22)	2/55 (53)	0.43 (0.25–0.73)	0.31 (0.14–0.48)	4
Bilateral; severe	10/34 (29)	26/38 (68)	7/34 (21)	18/37 (49)	17/68 (25)	44/75 (59)	0.43 (0.27–0.67)	0.34 (0.18–0.48)	3

of cases were treated inappropriately (prompt antibiotic treatment rather than watchful waiting) according to the latest guidelines.^{5,12} Data on the application of watchful waiting in emergency departments in Italy are also available. In a study by Palmaet al,⁴⁴ it emerged that the antibiotic prescription rate since the publication of the Italian national guidelines is almost unchanged in comparison with previous years (81% vs. 82%).⁴³ More recently, Dona et al⁶ demonstrated that the proportion of children managed in emergency departments by watchful waiting can be increased through the use of a guideline implementation program.

Regardless of the child's age, the involvement of parents (information on the risks and benefits of treatment, management of follow-up) is crucial for the success of a watchful-waiting strategy. The child's family situation must enable ready communication with the doctor, and follow-up—including a possible clinical reassessment, given that the otoscopic findings can change significantly over just a few hours—must be possible.^{45,46} It is necessary that, after the initial medical consultation, an adult can carefully follow the child's clinical progress, recognize the clinical signs of severity (above all irritability, loss of appetite and reduced play) and rapidly access a second medical checkup if there is no sure clinical sign of improvement.

Watchful waiting was accepted more readily if the parent felt included in the treatment decision.⁴⁷⁻⁴⁹ Once adherence was obtained, similar levels of parent satisfaction were seen in both a watchful-waiting group and an antibiotic treatment group, especially for children >2 years old.²⁸ A more recent study by Broides et al⁴⁹ confirmed that the parents' adequate understanding of the use of antibiotics, their side effects and the problem of resistance was significantly correlated with the acceptance and success of watchful waiting.

Given all these studies, the therapeutic strategy for AOM underwent lengthy discussion by the panel of experts. Although Rovers' 2006 meta-analysis highlighted the possibility of watchful waiting in children <2 years old with mild unilateral AOM, 2 later high-quality RCTs^{25,32,33} revealed a greater risk of treatment failure in this group with placebo than with antibiotic. Given this evidence, after 2 discussion sessions and votes, the panel concluded that prompt antibiotic treatment is indicated in all children <24 months old, even those with mild unilateral AOM (see Table 3).

For children >24 months old, the panel discussed the results of the Cochrane review,³¹ which demonstrated that watchful waiting can be safe and effective in severe unilateral AOM. However, it was stressed that prompt antibiotic treatment may be preferable in some cases of severe AOM in this group; for this reason, the watchful-waiting strategy was added in this group of patients as a weak positive recommendation.

Recommendation 4

Prompt antibiotic treatment is recommended for all children with otorrhea, intracranial complications and/or a history of recurrence and for children <6 months old with AOM. For children 6 months to 2 years of age, prompt antibiotic treatment

is recommended for all forms of unilateral and bilateral AOM, whether mild or severe. Prompt antibiotic treatment is also recommended for children >2 years old with severe bilateral AOM.

Recommendation 5

A watchful-waiting approach can be applied to children >2 years old with mild or severe unilateral AOM or mild bilateral AOM.

Recommendation 6

Watchful waiting should be assessed on a case-by-case basis and discussed with the parents; it should only be applied where follow-up is possible within 48–72 hours.
(strong positive recommendation)

Question 3. What Drugs Are Recommended for the Antibiotic Treatment of AOM?

From a pharmacologic perspective, one of the main objectives of treatment is to achieve antibiotic concentrations in the site of infection that are higher than the minimum inhibitory concentration (MIC) for the pathogen concerned. There is a strict correlation between eradication of the pathogen and clinical evolution. Subjects in whom the pathogen is eradicated in the TM exudate within 3–7 days of the start of treatment improve more quickly and more frequently than children in whom it is not eradicated.^{50,51}

The first study of the use of some beta-lactams and their clinical efficacy [duration at the infection site of concentrations above the MIC (T>MIC) in the period between doses] in the treatment of pediatric AOM dates back over 20 years.⁵² An 80%–85% eradication, and hence good clinical efficacy, can only be obtained when blood concentrations of the antibiotic higher than the MIC for the given pathogen are present for at least 40% of the time between doses (T>MIC ≥40%). In 2 literature reviews, Dagan et al stressed the fundamental role of bacterial resistance, and hence of the ever-higher MICs now seen for both *Streptococcus pneumoniae* and *Haemophilus influenzae*, in predicting the therapeutic result.^{50,53-55}

The 3 most common causes of AOM are *S. pneumoniae*, *H. influenzae* and *Moraxella catarrhalis*. *Streptococcus pyogenes* and *Staphylococcus aureus* usually have a minor role.⁵⁶ An American study reported a change in the microbiology of AOM after the introduction of pneumococcal conjugate vaccine, with a reduction in the proportion of episodes due to *S. pneumoniae* and a relative increase in those attributable to *H. influenzae*.⁵⁷ Furthermore, strains of *H. influenzae* produce beta-lactamase more frequently than in the past.⁵⁸

Some data are available on subjects in Italy with spontaneous otorrhea. A 12-month study conducted in 2016 investigated 177 children between 6 months and 7 years of age with otorrhea caused by spontaneous perforation <12 hours previously. The middle ear effusion was tested with real-time polymerase chain reaction for *S. pneumoniae*, non-typeable (NT) *H. influenzae*, *S. pyogenes*, *M.*

TABLE 3. Summary of Treatment Strategy for Uncomplicated* AOM

AOM Episode Symptom Severity	Bilateral		Unilateral	
	Severe	Mild	Severe	Mild
Age: <6 months	Prompt antibiotic (strong positive recommendation)	Prompt antibiotic (strong positive recommendation)	Prompt antibiotic (strong positive recommendation)	Prompt antibiotic (strong positive recommendation)
Age: 6–24 months	Prompt antibiotic (strong positive recommendation)	Prompt antibiotic (strong positive recommendation)	Prompt antibiotic (strong positive recommendation)	Prompt antibiotic (weak positive recommendation)
Age: >24 months	Prompt antibiotic (strong positive recommendation)	Watchful waiting (strong positive recommendation)	Watchful waiting (weak positive recommendation)	Watchful waiting (strong positive recommendation)

* Absence of otorrhea, intracranial complications, history of recurrences or debilitated general condition.

catarrhalis and *S. aureus*. A single pathogen was identified in 70 samples (39.5%), while 2, 3, and 4 pathogens were identified in 54 (30.5%), 20 (11.3%), and 7 (4.0%) cases, respectively. *H. influenzae* NT was the most common pathogen, identified in 90 children (50.8%), followed by *M. catarrhalis* (62 cases, 35.0%) and *S. pneumoniae* (48 cases, 27.1%). *H. influenzae* NT was the most common in children in co-infections, which were in turn more common in subjects with recurrent AOM. Spontaneous otorrhea thus has a different etiology from uncomplicated otitis, with a high prevalence of *H. influenzae* NT.⁵⁹

First-line Antibiotics

Given the latest epidemiologic data, the international guidelines agree that amoxicillin is the antibiotic of choice for its efficacy, safety, low cost, high palatability and antimicrobial spectrum.^{24,60,61} Furthermore, according to some authors, the use of narrow-spectrum antibiotics such as amoxicillin, while ensuring a similar efficacy to that obtained with broad-spectrum antibiotics (amoxicillin-clavulanic acid, cephalosporins and macrolides), may be associated with a reduced incidence of side effects and a tendentially greater compliance.⁶² In a cohort study, the efficacy of broad-spectrum antibiotics (amoxicillin-clavulanic acid, cephalosporins and macrolides) was compared with that of narrow-spectrum antibiotics (amoxicillin and penicillin) in the treatment of children 6–12 years of age with URTIs. In the retrospective part of the study, there were 19,179 children with a diagnosis of AOM against 30,159 with URTI: treatment with broad-spectrum antibiotics was not associated with a reduced risk of treatment failure (3.4% for broad-spectrum antibiotics versus 3.1%, RR 0.3, 95% CI: 0.4%–0.9%). In the prospective part, there were 1100 children with AOM out of 2473. Treatment with broad-spectrum antibiotics was associated with a greater risk of side effects (3.7% vs. 2.7%, RR 1.1%, 95% CI: 0.4%–1.8%) and the parents/guardians reported a slightly lower level of satisfaction (score 90.2 vs. 91.5) than the parents of children treated with narrow-spectrum antibiotics. These data support the use of narrow-spectrum antibiotics such as amoxicillin as first-line treatment. A limitation of this study was that separate analysis of the subgroup of children with AOM was not performed.⁶²

The addition of clavulanic acid to amoxicillin allows the more effective elimination of bacteria such as *H. influenzae* and *M. catarrhalis*, producers of beta-lactamase, while maintaining excellent activity against penicillin-resistant strains of *S. pneumoniae*.^{58,63} This combination is considered by some authors to be preferable in children who have received antibiotics in the past 30 days, in those with severe symptoms and/or purulent conjunctivitis, in those with a history of recurrent AOM not responsive to amoxicillin, and in those with a high risk of antibiotic resistance (day care attendance, not vaccinated against pneumococcus, living in area with a high prevalence of resistant isolates).^{12,24,59,61,64} In children with AOM and otorrhea from a spontaneous perforation, the use of amoxicillin-clavulanic acid has been suggested by some authors, given the prevalence of beta-lactamase-producing bacteria.⁵⁹

Increasing the dose from 40–50 mg/kg/day to 80–90 mg/kg/day of amoxicillin was associated with an increased amoxicillin concentration in the middle ear,⁶⁵ ensuring efficacy against most strains of *S. pneumoniae*, including those with intermediate resistance (MIC ≥ 2 and < 8 $\mu\text{g/mL}$).⁶⁶ However, highly penicillin-resistant *S. pneumoniae* strains (MIC ≥ 8 $\mu\text{g/mL}$) did not respond to high doses of amoxicillin, although these accounted for $< 2\%$ of all isolated strains.⁶⁷

In any case, the efficacy data are discordant in relation to the optimum dose. A study of 359 children showed that in those with a body weight of > 20 kg, the prescribed amoxicillin dosage per kg was often less than that recommended by the guidelines (mean dosage 74.2 mg/kg < 20 kg vs. 40 mg/kg > 20 Kg), although this was not

correlated with a greater treatment failure or AOM recurrence.⁶⁸ In contrast, in a retrospective study by Chu-Huei et al of 400 children between 2 months and 12 years of age, 89% of prescriptions were low dosage, and this was associated with a worse prognosis in children with bilateral AOM weighing < 20 kg.⁶⁹

The recommendations among different guidelines are also discordant. The 2013 AAP guidelines recommend the use of high dosages (80–90 mg/kg/day), while others propose lower dosages (eg, the Netherlands: 30–40 mg/kg/day).^{12,24,70} This discrepancy can be attributed to the different epidemiologic situations and resistance profiles.⁷¹ In Italy, *S. pneumoniae* resistance to penicillin is 8%, supporting the use of high doses.⁷²

Unlike in the United States, where amoxicillin-clavulanic acid is available as a 14:1 combination, in Italy it is marketed as a 7:1 combination (1 mL = 80 mg amoxicillin + 11.7 mg of clavulanic acid). This concentration of clavulanic acid carries a greater risk of gastrointestinal side effects when used at the recommended dose of 80–90 mg/kg/day of amoxicillin. To avoid the side effects of clavulanic acid, which are much more common on exceeding the recommended dose of 10 mg/kg/day, it is more reasonable to administer the standard dose of the 7:1 amoxicillin-clavulanic acid combination alongside an adequate additional dose of amoxicillin alone, to achieve the desired dosage.⁷³

Second-line Antibiotics

Cefuroxime axetil (30 mg/kg/day in 2 doses) and cefpodoxime proxetil (10 mg/kg/day in 2 doses) have a considerably higher oral bioavailability than the starting compound but are almost never fully absorbed, meaning that antibiotic levels at the site of infection may be insufficient. Moreover, there is a potential risk of disruption of the intestinal microbiota, due to the effects of the active substance on the intestinal flora.¹² Other cephalosporins such as cefaclor seem to have less effect on the intestinal flora and hence a reduced incidence of gastroenteric events.⁷⁴

The therapeutic role of the various oral β -lactam antibiotics in the treatment of AOM is correlated with the duration of the $T > \text{MIC}$ for each pathogen, as reported in Table 2, obtained by using data on the chemosensitivity of the pathogens responsible for community-acquired respiratory infections in Italy.⁷⁵

Cefdinir is a third-generation cephalosporin that is not yet marketed in Italy. It was added to the 2013 AAP as an alternative to amoxicillin-clavulanic acid for the treatment of AOM in patients allergic to penicillin (in the absence of anaphylaxis). However, in children 6–24 months of age, its efficacy is lower than that of the first-line treatment.^{76,60}

All compounds showed good activity against pneumococcus, at least for penicillin-sensitive strains with values between 60% (cefixime) and 100% (amoxicillin-clavulanic acid and cefpodoxime proxetil). For penicillin-intermediate strains, only amoxicillin-clavulanic acid ensured a $T > \text{MIC}$ value of 40% or more. All other compounds were practically inactive.

Both the third-generation cephalosporins (cefixime, cef-tibuten and cefpodoxime proxetil) and amoxicillin-clavulanic acid were active against *M. catarrhalis* and $\beta + H. influenzae$, with $T > \text{MIC}$ varying between 50% and 85%. The 2 second-generation cephalosporins showed good activity against $\beta - H. influenzae$ but were only just adequate against $\beta +$ strains.^{77–79}

Use of intramuscular or intravenous ceftriaxone (50 mg/kg/day) should be restricted to children with persistent vomiting or who are unable to tolerate oral administration.

The cross-reactivity between penicillins and cephalosporins is lower than was once thought. Furthermore, cross-reactivity is greatest with first-generation cephalosporins, but is negligible with the second and third generation. Due to their chemical structure cefuroxime,

cefpodoxime and cefdinir rarely cross-react with penicillin.^{12,80} The American College of Allergy, Asthma and Immunology allows the use of a cephalosporin in patients without a history or recent and/or severe allergy to penicillins when a prick test is unavailable.

Macrolides and azalides are another class of antibiotics that in theory can be used to treat AOM.^{81–83} In vitro and in vivo studies indicated a concentration-dependent trend for both azithromycin and clarithromycin, and hence the optimal posology for semisynthetic macrolides and for azalides should reach peak concentrations, as the bactericidal action is directly proportional to the value of the peak concentration.⁸⁴ New macrolides such as clarithromycin and azithromycin present a better pharmacokinetic profile than erythromycin, as they have a longer half-life (4–5 hours for clarithromycin and over 40 hours for azithromycin) and are highly lipophilic, thus guaranteeing high tissue concentrations (tissue/blood ratio 1.0–7.0 and 1.0–30, respectively), also in the fluid of the middle ear.^{77,79} These favorable pharmacokinetics mean that only 2 daily administrations of clarithromycin, and just 1 of azithromycin, are needed. Unfortunately, resistance to glucoside macrolides is now high. This is especially true for *Streptococcus*, with reported resistances of 38% for *S. pyogenes* and 26% for *S. pneumoniae* as a whole, meaning these antibiotics cannot be proposed for the treatment of AOM.^{75,85}

In Italy, resistance of *S. pneumoniae* isolates to penicillin was 8%, of which most with an intermediate MIC, while resistance to amoxicillin was even lower (3%).⁷² However, resistance to erythromycin was high (29.4%). *H. influenzae* was resistant to amoxicillin in 17.2% of cases, while 6.3% were resistant to amoxicillin-clavulanic acid. *M. catharralis*, a frequent producer of β-lactamase, showed 89.9% resistance to amoxicillin but only 7.1% of isolates were resistant to amoxicillin-clavulanic acid. Finally, about 10% of *S. pyogenes* isolates were resistant to erythromycin.

A large 2010 meta-analysis compared the efficacy of AOM treatment with macrolides (azithromycin or clarithromycin) against the standard (amoxicillin or amoxicillin-clavulanic acid) in 10 RCTs (N = 2766 children from 6 months to 15 years of age). The primary outcome was clinical failure at 10 and 16 days after diagnosis. The use of macrolides was found to be associated with a greater risk of treatment failure (RR 1.31; 95% CI: 1.07–1.60, P = 0.008, NNT 32), even though the risk of side effects was significantly lower than in children treated with amoxicillin (RR 0.74, 95% CI: 0.60–0.90, P = 0.003).⁸⁶ In contrast, Gerber et al reported more side effects with the use of macrolides.⁶²

In conclusion, the use of macrolides to treat AOM is only indicated when there is a recent and/or severe history of allergy to penicillins. Clarythromycin (15 mg/kg/day) is preferable, due to its pharmacokinetic and pharmacodynamic characteristics. The AOM treatment scheme is summarized in Table 2.

Recommendation 7

For uncomplicated AOM with mild signs and symptoms in children without risk factors for bacterial resistance and with no history of recurrence, amoxicillin at a dose of 80–90 mg/kg/day is recommended (strong positive recommendation) (see Table 4).

Recommendation 8

For AOM in children who have taken antibiotics in the last 30 days, who have severe symptoms and/or purulent conjunctivitis, who have a history of recurrent AOM not responsive to amoxicillin, who have otorrhea from a spontaneous perforation or who present a high risk of bacterial resistance (day care attendance, not vaccinated against pneumococcus, living in area with a high prevalence of resistant isolates), amoxicillin-clavulanic acid 80–90 mg /kg/day (dose of amoxicillin) is recommended (strong positive recommendation).

TABLE 4. Recommended Antibiotic Treatment

Episode Characteristics	Recommended Treatment
Mild symptoms No otorrhea No recurrence No resistance factors *	Amoxicillin (80–90 mg/kg/day in 3 doses)
Severe symptoms or purulent conjunctivitis Otorrhea Recurrence	Amoxicillin–acid clavulanic (80–90† mg/kg/day in 3 doses)

*Risk factors for greater bacterial resistance: day care attendance, not vaccinated against pneumococcus, living in area with a high prevalence of resistant isolates.
† Dose of amoxicillin.

Recommendation 9

Macrolides (clarithromycin 15 mg/kg/day) should only be used in children with a documented history of recent and/or severe allergy to penicillin. Class II or III cephalosporins are recommended in children with not severe allergy to penicillin, since cross reaction between these molecules is rare (strong positive recommendation) (see Table 4).

Question 4. What Is the Ideal Dose Fractioning for Treatment With Amoxicillin?

Given the pharmacodynamic and kinetic properties of β-lactams, the daily dosage should be split into 2–3 doses to ensure that adequate concentrations above the MIC are maintained for a sufficiently long time over a 24-hour period.^{78,79,87} The use of 2 divided doses of amoxicillin or amoxicillin-clavulanic acid has been demonstrated as effective in the treatment of AOM.^{88,89} The most recent meta-analysis, conducted in 2013, analyzed 5 clinical studies (N = 1601 children <12 years old) and confirmed these findings on the efficacy of amoxicillin with or without clavulanate divided into 2 or into 3 doses at the end of the cycle (RR 1.03, 95% CI: 0.99–1.07). The 2 groups were also similar in terms of AOM recurrence (RR 1.21, 95% CI: 0.52–2.81) and percentage of complications (RR 1.04, 95% CI: 0.98–1.10).⁹⁰

The 2013 AAP recommends division into 2 doses. This option could be considered acceptable in subjects at a low risk of hosting resistant *S. pneumoniae*. In other cases, division into 3 high doses ensures that the drug concentrations in the TM exudate are more adequate for the eradication of resistant strains of *S. pneumoniae*.⁵²

The division into 2 doses of amoxicillin or amoxicillin-clavulanic acid is therefore possible in subjects with a low risk of resistant *S. pneumoniae* colonization, while division into 3 doses is recommended in subjects at a high risk of colonization with resistant *S. pneumoniae* strains. However, given the broad diffusion in Italy of penicillin-intermediate strains, the panel recommended the division of amoxicillin into 3 daily doses to maintain the drug concentration above the MIC for a longer time, to ensure the greatest treatment efficacy.

Recommendation 10

The division of amoxicillin or amoxicillin-clavulanic acid into 3 doses is recommended in all cases (weak positive recommendation).

Question 5. What Is the Optimal Duration of the Antibiotic Treatment?

The ideal duration of antibiotic treatment in AOM is still under debate. The traditional 10 days-treatment derives from the duration of treatment of streptococcal pharyngotonsillitis.¹² The 2013 AAP suggests 7 days in children 3 to 5 years of age with mild

or moderate otitis. For children over 6 years with nonsevere otitis, 5 days of oral antibiotic treatment is also considered acceptable. In contrast, in children with severe otitis and children <2 years old, 10 days of antibiotic treatment is still recommended.¹²

The studies comparing 10 days against 1–7 days had numerous methodologic limitations, such as the exclusion of children <2 years old or with recurrent AOM, small cohorts, inadequate diagnostic criteria, use of inappropriate dosages and data analysis without stratification by age. The low-quality 2010 meta-analysis by Gulani et al compared the efficacy of a short antibiotic cycle (<4 days) against a longer cycle (>4 days) in the treatment of AOM, evaluating the results of 35 RCTs in children <12 years old. The trials were grouped by the pharmacokinetic properties of the antibiotics, dividing them into long-acting drugs (azithromycin), short-acting drugs (β -lactams) and parenteral ceftriaxone. The interpretation of the results was, however, invalidated by the fact that macrolides are not the first-line choice for the treatment of AOM. If the observation is limited to results from the subgroup treated with oral β -lactams, the short cycle was associated with a greater risk of failure (RR 2.27; 95% CI: 1.04–4.99).⁸²

In the Cochrane review of 49 studies published in 2010, an overall greater risk of failure (defined as absence of clinical resolution or relapse or recurrence of AOM within 1 month following initiation of therapy) was found in patients treated for <7 days than in those treated with antibiotics for >7 days (21% against 18%, OR 1.34, 95% CI: 1.15–1.55).^{89,91}

A high-quality RCT by Hoberman et al compared the efficacy of amoxicillin-clavulanic acid for 10 days against 5 days in 520 children <2 years of age. Children treated with antibiotic for 5 days had a higher risk of treatment failure than those treated for 10 days (34% vs. 16%, $P = 002$); this difference was even larger in children with bilateral AOM ($P < 0.01$). The percentage of children with a reduction in symptoms was lower in the 5 day group than in the 10 day group (80% vs. 91%; $P = 0.03$). No difference was found between the 2 groups in terms of risk of recurrence, adverse events or nasopharyngeal colonization with penicillin-resistant pathogens. In conclusion, children 6–24 months of age seemed to benefit more from the standard 10-day antibiotic treatment than from shorter regimens.³

In a prospective study of 62 children with AOM 1 to 16 years of age, a reduced treatment duration was associated with an increased risk of nasopharyngeal pneumococcal colonization at the end of the treatment, with a consequent potential risk of recurrence.⁹²

Recommendation 11

The duration of treatment with amoxicillin or amoxicillin-clavulanic acid should be 10 days in children with risk factors for unfavorable evolution (<2 years old and/or with spontaneous otorrhea) (strong positive recommendation).

Recommendation 12

The duration may be reduced to 5 days in children with no risk factors for unfavorable evolution (age >2 years, no otorrhea, unilateral disease and no severe signs or symptoms) (weak positive recommendation).

Question 6. How Should Treatment Failure Be Defined and Managed?

The clinical course of treated AOM is characterized by an improvement within 48–72 hours with a progressive reduction in fever and pain. Follow-up 2–7 days after the end of the treatment can identify treatment failures and recurrences due to the same pathogen that caused the original episode.⁹³ If the initial treatment was amoxicillin, the second-line treatment, if a pathogen is not

isolated by tympanocentesis, should be amoxicillin-clavulanic acid (80–90 mg/kg/day).⁶³ In the event of failure with amoxicillin-clavulanic acid, the next treatment should be oral cephalosporins with high activity against potentially resistant pathogens (cefpodoxime proxetil 10 mg/kg/day in 2 doses or cefuroxime axetil 30 mg/kg/day in 2 doses).⁶³

No recent studies are available on the efficacy of cefaclor in the treatment of AOM, although this drug is only effective against penicillin-sensitive strains. A >50% resistance to cefaclor was reported in a 2018 study on antibiotic sensitivity of *S. pneumoniae* and *H. influenzae* in Greece, the Balkans and Russia.⁹⁴

Ceftriaxone 50 mg/kg/day as a single daily administration (intravenous or intramuscular) for 3 days was found to be effective in AOM episodes considered as treatment failure.⁹³

A review of 4 studies found that gatifloxacin was effective in cases of recurrent or persistent AOM (failure after >3 days with a first-line antibiotic).⁹⁵ Two studies showed that levofloxacin (10 mg/kg twice daily) was not inferior to amoxicillin-clavulanic acid in children 6 months to 5 years of age with recurrent or persistent AOM and did not lead to a rise in side effects.^{96,97} However, gatifloxacin is not registered in Italy, and in any case quinolones are not indicated in pediatric patients. Their use has also been questioned in relation to both resistance and the incidence of side effects.⁹⁸

A future role for fifth-generation cephalosporins (ceftaroline and ceftobiprole) can be hypothesized, although to date there are insufficient studies, and in any case they must be administered intravenously.

The main limitation of these studies is that they included subjects from 2 different categories (recurrent AOM and persistent AOM due to treatment failure) and the results were not stratified. This means their results are not applicable to the treatment of single episodes of AOM.

Recommendation 13

The use of oral cephalosporins with a high activity against potentially resistant pathogens (cefpodoxime proxetil, cefuroxime axetil) or of intramuscular or intravenous ceftriaxone must be restricted to the management of treatment failure (weak positive recommendation).

Recommendation 14

The use of quinolones following AOM treatment failure should be avoided (strong negative recommendation).

Question 7. What Treatments Are Recommended in Combination With Antibiotic Treatment?

Chonmaitree et al⁹⁹ investigated with an RCT whether the use of antihistamines and corticosteroids alongside antibiotic treatment could improve the short- and long-term outcome of AOM. The only statistically significant finding was the greater duration of TM effusion in subjects treated with antihistamines compared with the other treatment groups. The presence of some errors in the study methodology should be taken into consideration (the treatment masking technique is not described, nor is the randomization method). The study population had a high risk of recurrence, therefore these results are not fully applicable to the target population of our guidelines.

A systematic review by Ranakusuma et al¹⁰⁰ evaluated the effects of systemic steroid treatment against placebo in 252 children between 3 months and 6 years of age who had first been treated in a hospital setting with intramuscular ceftriaxone and were then randomized. In the first study analyzed in this review (N = 179), there was an overall improvement in symptoms and resolution of the middle ear inflammation in 94% of the treatment group against 89% of the placebo group (RR 1.06 95% CI:

0.97–1.16) on day 5. In the second study (N = 72), the treatment group presented a reduction in general symptoms without further antibiotic treatment (OR 65.9). The evidence from these studies is low quality, due both to the small sample size and the impossibility of establishing whether the clinical improvement was actually due to the steroid treatment, to the natural course of the disease or to the antibiotic treatment. Therefore, higher quality studies are necessary to establish its efficacy.¹⁰⁰

A systematic review by Ranakusuma et al¹⁰¹ evaluated the efficacy of decongestants (excluding steroids) and antihistamines in children with AOM in terms of resolution of the acute episode, resolution of symptoms, and estimated the occurrence of side effects of the drugs and complications of AOM. The review revealed a slightly lower rate of persistent AOM 2 weeks after diagnosis in subjects taking combined antihistamine and decongestant treatment. A handful of studies investigates the persistence of TM effusion at 4 weeks, was significantly higher in subjects treated with antihistamines. Finally, the side effects of the treatments were considered: there was a 5-fold to 8-fold increased risk of side effects in the decongestant group. However, the review did not consider clinical situations involving nasal and paranasal conditions (allergic rhinitis, turbinate hypertrophy, stenosis of the nasal cavity) that might make antihistamine treatment acceptable. In conclusion, the results of the review did not support the use of decongestants or antihistamines in the treatment of children with AOM.

The use of topical decongestants for AOM has not been investigated in any systematic review. However, it should be remembered that in any case, the use of alpha-adrenergic and imidazole-derivative nasal decongestants has been contraindicated in children in Italy since 2007, due to the risk of local and systemic side effects.

There is still no scientific evidence of the benefit of nasal lavage in relation to middle ear disease, especially in children. However, given the close relationship between the nose, nasopharynx and middle ear, it can be hypothesized, as has already been demonstrated for rhinosinusitis and sinusitis, that the removal of nasal secretions through irrigation of the nasal cavities may help to improve eustachian tube function and may therefore be of use in draining middle ear exudate.

Recommendation 15

The use of treatments other than pain relief in combination with antibiotic treatment is not recommended (strong negative recommendation).

Recommendation 16

The use of systemic and topical decongestants and steroids should be avoided (strong negative recommendation).

Recommendation 17

Removal of nasal secretions through nasal lavage is advisable as a complementary treatment (weak positive recommendation).

Question 8. What Is the Role of Topical Antibiotic or Steroid Ear Treatments in AOM?

Commercially available topical ear treatments mainly consist of a combination of active substances. The most common products include multiple antibiotics, one or more antibiotics and a corticosteroid, an antibiotic and a local anesthetic, or all of the above.¹⁰² Numerous antibiotics are used in ototopical preparations, including: chlortetracycline (to which however there is high pathogenic resistance due to its use in livestock farming), ciprofloxacin (approved by the FDA for ototopical use in 2005), clioquinol, and the “older” antibiotics chloramphenicol, neomycin (which is highly ototoxic), tobramycin and sulfacetamide.

The efficacy of antibiotic ear drops has been evaluated in experimental research and clinical studies that are now somewhat dated and that often involved heterogenic populations, predominantly including subjects with otitis externa alongside subjects with otitis media with or without TM perforation, who were treated with combinations of different antibiotics. A multicenter, observer-blinded RCT¹⁰² demonstrated the superiority of a topical suspension of ciprofloxacin in combination with dexamethasone against oral administration of amoxicillin-clavulanic acid in reducing acute otorrhea in children with tympanostomy tubes. The side effects were also reduced. Although the study methodology was correct, given the specific nature of the clinical indication (otorrhea in AOM with tympanostomy tubes) its results alone are certainly not sufficient to hypothesize changes to the antibiotic treatment of AOM, even if complicated by spontaneous perforation.

Recent studies have investigated the tolerability of topical antibiotic treatment with ciprofloxacin + fluocinolone or ciprofloxacin in children with otorrhea from tympanostomy tubes.^{103,104} Both studies found that topical ear drops containing antibiotics and steroids were more effective than oral treatment in subjects with otorrhea from tympanostomy tubes. Although the data from these studies are of high quality, they cannot be extrapolated to spontaneous perforation with otorrhea. The 2 situations are not comparable, as otorrhea from tympanostomy tubes is not uncommon, is considered an intrinsic risk of the procedure, is self-limiting and, in the vast majority of cases, is caused by co-infection with viruses and bacteria and by the formation of a biofilm.^{105,106}

It should be remembered that in the presence of high concentrations of antibiotic, there is no evidence to exclude cochlear damage, even in the absence of tympanic damage, due to absorption through the inflamed or injured skin of the external auditory meatus, and hence the administration of aminoglycosides is currently not considered ideal. For this reason, in the event of a spontaneous perforation, antibiotics in AOM should only be administered systemically. The use of topical antibiotic ear drops in addition or as an alternative to systemic antibiotic treatment is under investigation, but no evidence is available from controlled clinical trials.³¹

The corticosteroids included in commercially available preparations, which are generally administered as ear drops, are hydrocortisone, beclomethasone, prednisone, dexamethasone and triamcinolone, and are almost always in combination with antibiotics (neomycin, polymyxin). These compounds have a general anti-inflammatory activity and are not ototoxic, but no clinical trials of their efficacy in humans have been conducted with adequate methodology.

Particular attention should be paid to preparations that contain disinfectants such as chlorhexidine, benzalkonium chloride, iodopovidone or alcohol in addition to the aforementioned active substances, as they are all potentially ototoxic. In addition, excipients such as propylene glycol and polyethylene glycol are highly irritant and sensitizing.^{107,108}

Recommendation 18

Ototopical antibiotic treatment, whether or not associated with steroid treatment, is not recommended except in subjects with tympanostomy tubes (strong negative recommendation).

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REFERENCES

- Rovers MM, Glasziou P, Appelman CL, et al. Predictors of pain and/or fever at 3 to 7 days for children with acute otitis media not treated initially with antibiotics: a meta-analysis of individual patient data. *Pediatrics*. 2007;119:579–585.
- Oyewumi M, Brandt MG, Carrillo B, et al. objective evaluation of otoscopy skills among family and community medicine, pediatric, and otolaryngology residents. *J Surg Educ*. 2016;73:129–135.
- Hoberman A, Paradise JL, Rockette HE, et al. Shortened antimicrobial treatment for acute otitis media in young children. *N Engl J Med*. 2016;375:2446–2456.
- Deniz Y, van Uum RT, de Hoog MLA, et al. Impact of acute otitis media clinical practice guidelines on antibiotic and analgesic prescriptions: a systematic review. *Arch Dis Child*. 2018;103:597–602.
- Rothman S, Pitaro J, Hackett A, et al. Treatment of acute otitis media in the pediatric emergency department. *Pediatr Infect Dis J*. 2018;37:520–525.
- Dona D, Baraldi M, Brigadoi G, et al. The impact of clinical pathways on antibiotic prescribing for acute otitis media and pharyngitis in the emergency department. *Pediatr Infect Dis J*. 2018;37:901–907.
- Laine MK, Tähtinen PA, Ruuskanen O, et al. Symptoms or symptom-based scores cannot predict acute otitis media at otitis-prone age. *Pediatrics*. 2010;125:e1154–e1161.
- Jones J, Hunter D. Consensus Methods For Medical And Health Services Research. *BMJ*. 1995;376–380.
- Brouwers MC, Kho ME, Browman GP, et al. AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ*. 2014;182:E839–42.
- Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines: 1. Introduction GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383e94
- Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008.
- Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics*. 2013;131:e964–e999.
- Benini B, Manfredini G, Messeri C. *Il dolore nel bambino: Strumenti pratici di valutazione e terapia*. Ministero della salute; 2010.
- Merkel SI, Voepel-Lewis T, Shayevitz, JR. et al. The FLACC: A behavioral scale for scoring postoperative pain in young children. *Pediatr Nurs*. 1997;23:293–297.
- Bertin L, Pons G, d'Athis P. A double-blind, multicentre controlled trial of ibuprofen versus acetaminophen and placebo for symptoms of acute otitis media in children. *Fundam Clin Pharmacol*. 1996;10:387–392.
- Hay AD, Redmond NM, Costelloe C, et al. Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial. *Health Technol Assess*. 2009;13:iii–iv, ix.
- Little P, Moore M, Kelly J, et al.; PIPS Investigators. Ibuprofen, paracetamol, and steam for patients with respiratory tract infections in primary care: pragmatic randomised factorial trial. *BMJ*. 2013;347:f6041.
- Sjoukes A, Venekamp RP, van de Pol AC, et al. Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. *Cochrane Database Syst Rev*. 2016;12:CD011534.
- Hoberman A, Paradise JL, Reynolds EA, et al. Efficacy of Auralgan for treating ear pain in children with acute otitis media. *Arch Pediatr Adolesc Med*. 1997b;151:675–678.
- Sarrell EM, Cohen HA, Kahan E. Naturopathic treatment for ear pain in children. *Pediatrics*. 2003;111(5 pt 1):e574–e579.
- Wood DN, Nakas N, Gregory CW. Clinical trials assessing ototopical agents in the treatment of pain associated with acute otitis media in children. *Int J Pediatr Otorhinolaryngol*. 2012;76:1229–1235.
- Foxlee R, Johansson A, Wejfkalk J, et al. Topical analgesia for acute otitis media (Review). *Cochrane Database Syst Rev*. 2006;CD00565.
- Venekamp RP, Sanders SL, Glasziou PP, et al. Antibiotics for acute otitis media in children *Cochrane Database Syst Rev*. 2015;CD000219
- Ovnat Tamir S, Shemesh S, Oron Y, et al. Acute otitis media guidelines in selected developed and developing countries: uniformity and diversity. *Arch Dis Child*. 2017;102:450–457.
- Rovers MM, Glasziou P, Appelman CL, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet*. 2006;368:1429–1435.
- Sanders S, Glasziou PP, DelMar C, et al. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2009;1.
- Le Saux N, Gaboury I, Baird M, et al. A randomized, double-blind, placebo-controlled noninferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age. *CMAJ*. 2005;172:335–341.
- Neumark T, Mölstad S, Rosén C, et al. Evaluation of phenoxymethylpenicillin treatment of acute otitis media in children aged 2–16. *Scand J Prim Health Care*. 2007;25:166–171.
- McCormick DP, Chonmaitree T, Pittman C, et al. Nonsevere acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. *Pediatrics*. 2005;115:1455–1465.
- Spiro DM, Tay KY, Arnold DH, et al. Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial *JAMA*. 2006;296:1235–1241.
- Venekamp RP, Prasad V, Hay AD. Are topical antibiotics an alternative to oral antibiotics for children with acute otitis media and ear discharge? *BMJ*. 2016;352:i308.
- Hoberman A, Paradise JL, Rockette HE, et al. Treatment of acute otitis media in children under 2 years of age. *N Engl J Med*. 2011;364:105–115.
- Tähtinen PA, Laine MK, Huovinen P, et al. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med*. 2011;364:116–126.
- Tähtinen PA, Laine MK, Ruuskanen O, et al. Delayed versus immediate antimicrobial treatment for acute otitis media. *Pediatr Nurs*. 2012;31:1227–32.
- Tähtinen PA, Laine MK, Ruohola A. Prognostic Factors for Treatment Failure in Acute Otitis Media. *Pediatrics*. 2017; 40:pii: e20170072
- Hoberman A, Ruohola A, Shaikh N, et al. Acute otitis media in children younger than 2 years. *JAMA Pediatr*. 2013;167:1171–2.
- Spurling GK, Del Mar CB, Dooley L, et al. Delayed antibiotic prescriptions for respiratory infections. *Cochrane Database Syst Rev*. 2017;9:CD004417.
- Chao JH, Kunkov S, Reyes LB, et al. Comparison of two approaches to observation therapy for acute otitis media in the emergency department. *Pediatrics*. 2008;121:e1352–6.
- Little P, Gould C, Williamson I et al. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ*. 2001;322:336–42.
- Shaikh N, Dando EE, Dunleavy ML, et al. A cost-utility analysis of 5 strategies for the management of acute otitis media in children. *J Pediatr*. 2017;189:54–60.e3.
- Sun D, McCarthy T, Liberman DB. Cost-effectiveness of watchful waiting in acute otitis media. *Pediatrics*. 2017;139:pii: e20163086.
- Gaboury I, Coyle K, Coyle D, et al. Treatment cost effectiveness in acute otitis media: a watch-and-wait approach versus amoxicillin. *Paediatr Child Health*. 2010;15:e14–e18.
- Mintegi Raso S, Benito Fernandez J, Hernandez Fabian A, et al. Antibiotic treatment vs watchful waiting in non severe acute otitis media: a retrospective study from an emergency department. *Ital J Pediatr* 2007;33:17–21.
- Palma S, Rosafio C, Del Giovane C, et al. The impact of the Italian guidelines on antibiotic prescription practices for acute otitis media in a paediatric emergency setting. *Ital J Pediatr*. 2015;41:37.
- Isaacson G. The natural history of a treated episode of acute otitis media. *Pediatrics*. 1996;98:968–971.
- MacGeorge EL, Smith RA, Caldes EP, et al. toward reduction in antibiotic use for pediatric otitis media: predicting parental compliance with “watchful waiting” advice. *J Health Commun*. 2017;22:867–875.
- Pshetizky Y, Naimer S, Shvartzman P. Acute otitis media—a brief explanation to parents and antibiotic use. *Fam Pract*. 2003;20:417–419.
- Finkelstein JA, Stille CJ, Rifas-Shiman SL, et al. Watchful waiting for acute otitis media: are parents and physicians ready? *Pediatrics*. 2005;115:1466–1473.
- Broides A, Bereza O, Lavi-Givon N, et al. Parental acceptability of the watchful waiting approach in pediatric acute otitis media. *World J Clin Pediatr*. 2016;5:198–205.
- Dagan R, Leibovitz E. Bacterial eradication in the treatment of otitis media. *Lancet Infect Dis*. 2002;2:593–604.

51. Dagan R, Schneider S, Givon-Lavi N et al. Failure to achieve early bacterial eradication increases clinical failure rate in acute otitis media in young children. *Pediatr Infect Dis J*. 2008;27:200–6.
52. Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26:1–10; quiz 11.
53. Dagan R, Givon-Lavi N, Zamir O, et al. Reduction of nasopharyngeal carriage of *Streptococcus pneumoniae* after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers. *J Infect Dis*. 2002;185:927–936.
54. Sommerfleck P, González Macchi ME, Pellegrini S, et al. Acute otitis media in infants younger than three months not vaccinated against *Streptococcus pneumoniae*. *Int J Pediatr Otorhinolaryngol*. 2013;77:976–980.
55. Ngo CC, Massa HM, Thornton RB, et al. Predominant bacteria detected from the middle ear fluid of children experiencing otitis media: a systematic review. *PLoS One*. 2016;11:e0150949.
56. Van Dyke MK, Pirçon JY, Cohen R, et al. Etiology of acute otitis media in children less than 5 years of age: a pooled analysis of 10 similarly designed observational studies. *Pediatr Infect Dis J*. 2017;36:274–281.
57. Pichichero ME. Helping children with hearing loss from otitis media with effusion. *Lancet*. 2018;392:533–534.
58. Mittal R, Parrish JM, Soni M, et al. Microbial otitis media: recent advancements in treatment, current challenges and opportunities. *J Med Microbiol*. 2018;67:1417–1425.
59. Marchisio P, Esposito S, Picca M, et al; Milan AOM Study Group. Prospective evaluation of the aetiology of acute otitis media with spontaneous tympanic membrane perforation. *Clin Microbiol Infect*. 2017;23:486.e1–486.e6.
60. Suaya JA, Gessner BD, Fung S, et al. Acute otitis media, antimicrobial prescriptions, and medical expenses among children in the United States during 2011–2016. *Vaccine*. 2018;36:7479–7486.
61. Rybak A, Levy C, Bonacorsi S, et al. Antibiotic resistance of potential otopathogens isolated from nasopharyngeal flora of children with acute otitis media before, during and after pneumococcal conjugate vaccines implementation. *Pediatr Infect Dis J*. 2018;37:e72–e78.
62. Gerber JS, Ross RK, Bryan M, et al. Association of broad- vs narrow-spectrum antibiotics with treatment failure, adverse events, and quality of life in children with acute respiratory tract infections. *JAMA*. 2017;318:2325–2336.
63. Pichichero ME. Otitis media. *Pediatr Clin North Am*. 2013;60:391–407.
64. Harrison CJ. Amoxicillin is the most cost-effective therapy for acute otitis media: the culmination of 40 years of research. *J Pediatr*. 2017;189:5–8.e1.
65. Seikel K, Shelton S, McCracken GH Jr. Middle ear fluid concentrations of amoxicillin after large dosages in children with acute otitis media. *Pediatr Infect Dis J*. 1997;16:710–711.
66. Weinstein MP, Klugman KP, Jones RN. Rationale for revised penicillin susceptibility breakpoints versus *Streptococcus pneumoniae*: coping with antimicrobial susceptibility in an era of resistance. *Clin Infect Dis*. 2009;48:1596–1600.
67. Lee GM, Kleinman K, Pelton S, et al. Immunization, antibiotic use, and pneumococcal colonization over a 15-year period. *Pediatrics* 2017;140:pii: e20170001.
68. Christian-Kopp S, Sinha M, Rosenberg DI, et al. Antibiotic dosing for acute otitis media in children: a weighty issue. *Pediatr Emerg Care*. 2010;26:19–25.
69. Chu CH, Wang MC, Lin LY, et al. High-dose amoxicillin with clavulanate for the treatment of acute otitis media in children. *ScientificWorldJournal*. 2013;2013:965096.
70. Damoiseaux R, Van Balen F, Leenheer W, et al. Huisarts Wet NHG-standaard otitis media acuta (Tweede herziening). *Huisarts Wet* 2006;49:615–621.
71. Segal N, Givon-Lavi N, Leibovitz E, et al. Acute otitis media caused by *Streptococcus pyogenes* in children. *Clin Infect Dis*. 2005;41:35–41.
72. Gagliotti C, Buttazzi R, Moro ML, et al. Use of antibiotici e resistenze antimicrobiche in età pediatrica. *Rapporto Emilia-Romagna* 2016.
73. Di Mauro G, Doria M, Chiappini E. L'utilizzo giudizioso della terapia antibiotica nel trattamento delle patologie infettive in età evolutiva; Consensus Conference della Pediatria delle Cure Primarie. 2016. available at HYPERLINK "<http://www.panoramasanita.it/wp%20content/uploads/2016/10/Consensus20Antibioticoterapia.pdf>" "<http://www.panoramasanita.it/wp-content/uploads/2016/10/Consensus20Antibioticoterapia.pdf>
74. Derry JE. Evaluation of cefaclor. *Am J Hosp Pharm*. 1981;38:54–8.
75. Stefani S, Mezzatesta ML, Fadda G et al.. Antibacterial activity of cefditoren against major community-acquired respiratory pathogens recently isolated in Italy. *J Chemother*. 2008;20:561–9.
76. Casey JR, Block SL, Hedrick J, et al. Comparison of amoxicillin/clavulanic acid high dose with cefdinir in the treatment of acute otitis media. *Drugs*. 2012;72:1991–1997.
77. Harrison CJ, Chartrand SA, Rodriguez W et al. HYPERLINK "<https://www.ncbi.nlm.nih.gov/pubmed/9271047>" Middle ear effusion concentrations of cefixime during acute otitis media with effusion and otitis media with effusion. *Pediatr Infect Dis J*. 1997;16:816–7.
78. Novelli A, Fallani S, Cassetta MI, et al. Pharmacokinetics and pharmacodynamics of oral cephalosporins as critical factors in choice of antibiotics. *Int J Antimicrob Agents*. 2000;16:501–505.
79. Mazzei T, Novelli A, Mini E, et al. Penicilline, cefalosporine ed altre β -lattamine. In: *Trattato di Farmacologia*. A cura di F. Rossi, C. Riccardi, V. Cuomo, 2005.
80. Pichichero ME, Casey JR. Emergence of a multiresistant serotype 19A pneumococcal strain not included in the 7-valent conjugate vaccine as an otopathogen in children. *JAMA*. 2007;298:1772–1778.
81. Ramakrishnan K, Sparks RA, Berryhill WE. HYPERLINK "<https://www.ncbi.nlm.nih.gov/pubmed/18092706>" Diagnosis and treatment of otitis media. *Am Fam Physician*. 2007. 1;76:1650–8
82. Gulani A, Sachdev HP, Qazi SA. Efficacy of short course (<4 days) of antibiotics for treatment of acute otitis media in children: a systematic review of randomized controlled trials. *Indian Pediatr*. 2010;47:74–87.
83. Lakoš AK, Pangerčić A, Gašparić M, et al. Safety and effectiveness of azithromycin in the treatment of respiratory infections in children. *Curr Med Res Opin*. 2012;28:155–162.
84. Novelli A, Fallani S, Cassetta MI, et al. In vivo pharmacodynamic evaluation of clarithromycin in comparison to erythromycin. *J Chemother*. 2002;14:584–590.
85. Cunha BA. Therapeutic implications of antibacterial resistance in community-acquired respiratory tract infections in children. *Infection*. 2004;32:98–108.
86. Courter JD, Baker WL, Nowak KS, et al. Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis. *Ann Pharmacother*. 2010;44:471–478.
87. Chiappini E, Mazzantini R, Bruzzese E, et al; Italian Society of Preventive and Social Pediatrics. Rational use of antibiotics for the management of children's respiratory tract infections in the ambulatory setting: an evidence-based consensus by the Italian society of preventive and social pediatrics. *Paediatr Respir Rev*. 2014;15:231–236.
88. Principi N, Marchisio P, Bigalli L, et al. Amoxicillin twice daily in the treatment of acute otitis media in infants and children. *Eur J Pediatr*. 1986;145:522–525.
89. Hoberman A, Paradise JL, Burch DJ, et al. Equivalent efficacy and reduced occurrence of diarrhea from a new formulation of amoxicillin/clavulanate potassium (Augmentin) for treatment of acute otitis media in children. *Pediatr Infect Dis J*. 1997a;16:463–470.
90. Thanaviratnanich S, Laopaiboon M, Vatanasapt P. Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. *Cochrane Database Syst Rev*. 2013;CD004975.
91. Kozyrskyj A, Klassen TP, Moffatt M, et al. Short-course antibiotics for acute otitis media. *Cochrane Database Syst Rev*. 2010;CD001095.
92. Korona-Głowniak I, Zychowski P, Siwiec R, et al. Resistant *Streptococcus pneumoniae* strains in children with acute otitis media- high risk of persistent colonization after treatment. *BMC Infect Dis*. 2018;18:478.
93. Leibovitz E, Piglansky L, Raiz S, et al. Bacteriologic and clinical efficacy of one day vs. three day intramuscular ceftriaxone for treatment of nonresponsive acute otitis media in children. *Pediatr Infect Dis J*. 2000;19:1040–1045.
94. Torumkuney D, Mayanskiy N, Edelstein M, et al. Results from the Survey of Antibiotic Resistance (SOAR) 2014–16 in Russia, Bulgaria, Romania, Serbia and Croatia, Greece, Czech Republic, Ukraine and the Slovak Republic. *J Antimicrob Chemother*. 2018;73(suppl_5):v14–v21.
95. Pichichero ME, Arguedas A, Dagan R, et al. Safety and efficacy of gatifloxacin therapy for children with recurrent acute otitis media (AOM) and/or AOM treatment failure. *Clin Infect Dis*. 2005;41:470–8.
96. Arguedas A, Soley C, Kamicker BJ, et al. Single-dose extended-release azithromycin versus a 10-day regimen of amoxicillin/clavulanate for the treatment of children with acute otitis media. *Int J Infect Dis*. 2011;15:e240–e248.
97. Noel GJ, Blumer JL, Pichichero ME, et al. A randomized comparative study of levofloxacin versus amoxicillin/clavulanate for treatment of infants and young children with recurrent or persistent acute otitis media. *Pediatr Infect Dis J*. 2008;27:483–489.

98. Nota AIFA- Informativa Importante su medicinali contenenti fluorochinoloni, available at <http://www.agenziafarmaco.gov.it/content/nota-informativa-importante-su-medicinali-contenenti-fluorochinoloni-08042019>
99. Chonmaitree T, Saeed K, Uchida T, et al. A randomized, placebo-controlled trial of the effect of antihistamine or corticosteroid treatment in acute otitis media. *J Pediatr*. 2003;143:377–85.
100. Ranakusuma RW, Safitri ED, Thorning SC, et al. Systemic corticosteroids for acute otitis media in children. *Cochrane Database Syst Rev*. 2015;CD000219.
101. Ranakusuma RW, McCullough AR, Safitri ED, et al. Oral prednisolone for acute otitis media in children: protocol of a pilot randomised, open-label, controlled study (OPAL study). *Pilot Feasibility Stud*. 2018;4:146.
102. Dohar J, Giles W, Roland P et al. Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhea through tympanostomy tubes. *Pediatrics*. 2006;118:e561–9.
103. Spektor Z, Pumarola F, Ismail K, et al. Efficacy and safety of ciprofloxacin plus fluocinolone in otitis media with tympanostomy tubes in pediatric patients: a randomized clinical trial. *JAMA Otolaryngol Head Neck Surg*. 2017;143:341–349.
104. Steele DW, Adam GP, Di M, et al. Prevention and treatment of tympanostomy tube otorrhea: a meta-analysis. *Pediatrics*. 2017;139:pii: e20170667.
105. Ruohola A, Meurman O, Nikkari S, et al. Microbiology of acute otitis media in children with tympanostomy tubes: prevalences of bacteria and viruses. *Clin Infect Dis*. 2006;43:1417–1422.
106. van Dongen TMA, Damoiseaux RAMJ, Schilder AGM. Tympanostomy tube otorrhea in children: prevention and treatment. *Curr Opin Otolaryngol Head Neck Surg*. 2018;26:437–440.
107. Vernon J, Brummett R, Walsh T. The ototoxic potential of propylene glycol in guinea pigs. *Arch Otolaryngol*. 1978;104:726–729.
108. Morizono T, Paparella M, Juhn S. Ototoxicity of propylene glycol in experimental animals. *Am J Otolaryng*. 1980; 393–399.