Diagnosis, Microbial Epidemiology, and Antibiotic Treatment of Acute Otitis Media in Children

A Systematic Review

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Context Acute otitis media (AOM) is the most common condition for which antibiotics are prescribed for US children; however, wide variation exists in diagnosis and treatment.

Objectives To perform a systematic review on AOM diagnosis, treatment, and the association of heptavalent pneumococcal conjugate vaccine (PCV7) use with AOM microbiology.

Data Sources PubMed, Cochrane Databases, and Web of Science, searched to identify articles published from January 1999 through July 2010.

Study Selection Diagnostic studies with a criterion standard, observational studies and randomized controlled trials comparing AOM microbiology with and without PCV7, and randomized controlled trials assessing antibiotic treatment.

Data Extraction Independent article review and study quality assessment by 2 investigators with consensus resolution of discrepancies.

Results Of 8945 citations screened, 135 were included. Meta-analysis was performed for comparisons with 3 or more trials. Few studies examined diagnosis; otoscopic findings of tympanic membrane bulging (positive likelihood ratio, 51 [95% confidence interval {CI}, 36-73]) and redness (positive likelihood ratio, 8.4 [95% CI, 7-11]) were associated with accurate diagnosis. In the few available studies, prevalence of *Streptococcus pneumoniae* decreased (eg, 33%-48% vs 23%-31% of AOM isolates), while that of *Haemophilus influenzae* increased (41%-43% vs 56%-57%) pre- vs post-PCV7. Short-term clinical success was higher for immediate use of ampicillin or amoxicillin vs placebo (73% vs 60%; pooled rate difference, 12% [95% CI, 5%-18%]; number needed to treat, 9 [95% CI, 6-20]), while increasing the rate of rash or diarrhea by 3% to 5%. Two of 4 studies showed greater clinical success for immediate vs delayed antibiotics (95% vs 80%; rate difference, 15% [95% CI, 6%-24%] and 86% vs 70%; rate difference, 16% [95% CI, 6%-26%]). Data are absent on long-term effects on antimicrobial resistance. Meta-analyses in general showed no significant differences in antibiotic comparative effectiveness.

Conclusions Otoscopic findings are critical to accurate AOM diagnosis. AOM microbiology has changed with use of PCV7. Antibiotics are modestly more effective than no treatment but cause adverse effects in 4% to 10% of children. Most antibiotics have comparable clinical success.

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ACUTE OTITIS MEDIA (AOM) IS the most common childhood infection for which antibiotics are prescribed in the United States.[1-3] A study using 2006 Medical Expenditure Panel Survey data demonstrated an average expenditure of $350 per child with AOM, totaling $2.8 billion.[4] Timely and accurate diagnosis and appropriate management of AOM may have significant consequences for ambulatory health care utilization and expenditures.

Multiple systematic reviews on AOM diagnosis and management have been conducted,[5-10] including our 2001 study,[11] which was the basis for the 2004 American Academy of Pediatrics and American Academy of Family Physicians joint practice guidelines.[12] Since then, new trials have been published, the heptavalent pneumococcal conjugate vaccine (PCV7) has become widely used, and clinician practice has changed regarding antibiotic choice for AOM.[13]

See also Patient Page.

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In light of these additional studies and practice changes, we conducted a systematic review to support the new AOM practice guidelines (currently in preparation) from the American Academy of Pediatrics. We report on the evidence for (1) the precision and accuracy of AOM diagnosis, (2) the association of PCV7 use with changes in AOM microbial epidemiology, (3) the decision about whether to treat with antibiotics, and (4) the comparative effectiveness of different antibiotics for uncomplicated AOM in average-risk children and associated antibiotic-related adverse events.

METHODS

Literature Search and Study Selection

We searched PubMed, the Cochrane Controlled Clinical Trials Register Database, the Cochrane Database of Reviews of Effectiveness, and the Web of Science for articles published January 1999 through July 2010 on AOM diagnosis, treatment outcomes, and association of PCV7 use with changes in AOM microbiology using Medical Subject Headings terms (eg, *otitis media*, *vaccines*), key words (eg, *diagnostic*, *microbiology*, *therapy*), and individual antibiotic terms. This search supplemented a previous January 1966 through March 1999 search with additional key words for PCV7 and newer antibiotics.[11] We performed reference mining of relevant systematic reviews.

We included articles in any language that studied children aged 4 weeks to 18 years. We excluded studies on children with immunodeficiencies and craniofacial anomalies. Systematic reviews, randomized controlled trials (RCTs), controlled clinical trials, and observational studies were included in the initial search; case reports, clinical overviews, editorials, and practice guidelines were excluded.

Observational studies were considered for the PCV7 and diagnostic questions but excluded for the treatment question. For the PCV7 question, only articles that assessed AOM microbiology (using middle ear fluid) both before and after PCV7 implementation were included. For the diagnostic question, we considered studies of children that performed independent comparisons of signs or symptoms with a clear criterion standard; studies using clinicians in training were excluded. For the antibiotic comparative effectiveness question, only studies that examined clinical improvement as an outcome (not just microbiologic findings) were included. The search strategy and inclusion/exclusion criteria are detailed elsewhere.[14]

Data Abstraction

Two investigators (T.R.C., M.A.L.) independently reviewed titles and abstracts for potentially relevant articles. They then independently abstracted data from the full-text articles using structured review forms that included inclusion/exclusion criteria, outcome measures, and study quality. Disagreements were resolved by consensus; the principal investigators (P.G.S., G.S.T.) resolved remaining disagreements. The study biostatistician abstracted data (verified by a clinician investigator) for pooled analyses. One investigator independently abstracted treatment-related adverse event data.

Quality Assessment

We used the Jadad criteria to assess RCT quality,[15] AMSTAR[16] to assess systematic review quality, and QUADAS[17] to assess diagnostic study quality.

Data Synthesis

For diagnostic studies, we report summary data, including sensitivities and specificities, when available. The number of studies was insufficient to allow pooling of data across studies. Furthermore, the criterion standards for the diagnostic studies varied widely.

For studies examining the association between PCV7 use and changes in AOM microbial epidemiology, we report summary data; the studies were too few in number and lacked enough consistency across study design and population for pooled analysis.

For treatment studies, an adequate number of articles was identified for pooled analyses of some comparisons. Comparisons were grouped by individual antibiotics rather than by antibiotic class to maximize the clinical relevance of our findings. The only a priori exception was to group ampicillin with amoxicillin because of similarity. When 3 or more articles examined the same comparison, we used the DerSimonian and Laird random-effects model to pool rate differences across studies.[18] Sensitivity analysis was performed for pooled significant findings.

For pooled estimates, we report the I^2 statistic and P value for the χ^2 test of heterogeneity, which tests the null hypothesis that individual study results are homogeneous.[19,20] I^2 values near 100% represent high degrees of heterogeneity. For assessment of publication bias in our pooled analyses, we report the Egger asymmetry test.

We used Stata version 10.0 to perform the meta-analyses.[21] The study received a waiver of institutional review board review from the RAND Human Subjects Protection Committee.

RESULTS

The literature searches and reference mining yielded 8945 titles. After removal of duplicates and clearly irrelevant titles, 738 went for further review. After 2 rounds of screening, 55 articles were accepted and combined with 80 articles identified from the 2001 systematic review.[11] These included 4 articles (3 research articles plus 1 systematic review) on diagnosis, 6 on PCV7-microbiology, and 125 on antibiotic treatment (FIGURE 1).

AOM Diagnosis

In clinical practice, 3 criteria are used to diagnose AOM: (1) acute symptoms of infection, (2) evidence of middle ear inflammation, and (3) presence of middle ear effusion (MEE).[12] Published research focuses on what constitutes acute symptoms of infection and what physical findings are associated with middle ear inflammation or effusion. A challenge with

interpreting this research is the lack of a consistent gold standard, which varied from otolaryngologist-made diagnosis to tympanocentesis.

We identified 1 systematic review[5] and 3 additional studies[22-24] that addressed the question of diagnostic accuracy and precision in identifying any or all of the 3 criteria. Detailed data on these studies are available in our evidence report[14]; findings suggest that certain otoscopic signs are strongly associated with AOM, while data on the importance of symptoms as a predictor of AOM are less convincing.

Symptoms. A 2003 review by Rothman et al[5] found that ear pain (sensitivities: 54%, 60%, 100%; specificities: 82% and 92%; positive likelihood ratio [LR], 3.0 [95% confidence interval {CI}, 2.1 to 4.3]; positive LR, 7.3 [95% CI, 4.4 to 12.1]) and ear rubbing (sensitivity: 42%; specificity: 87%; positive LR, 3.3 [95% CI, 2.1 to 5.1]) were modestly associated with AOM diagnosis. The review by Rothman et al included 4 studies examining specific symptoms among 965 total participants.[25-28] In 2 of the studies, participants were recruited from otolaryngology practices and may not be representative of the general population of children with AOM. A more recent single study found that among 469 children aged 6 to 36 months presenting to primary care offices with parent-suspected AOM, AOM diagnosis was not associated with occurrence, duration, or severity of parent-reported symptoms (eg, ear rubbing, ear pain, fever).[24]

Otoscopic Signs. One study[29] examined in the review by Rothman et al assessed the association of otoscopic findings of middle ear inflammation (redness: positive LR, 8.4 [95% CI, 7 to 11]) and effusion (cloudy: positive LR, 34 [95% CI, 28 to 42]; bulging: positive LR, 51 [95% CI, 36 to 73]; immobile: positive LR, 31 [95% CI, 26 to 37]) with AOM (determined by clinical symptoms and the presence of MEE on tympanocentesis).[5]

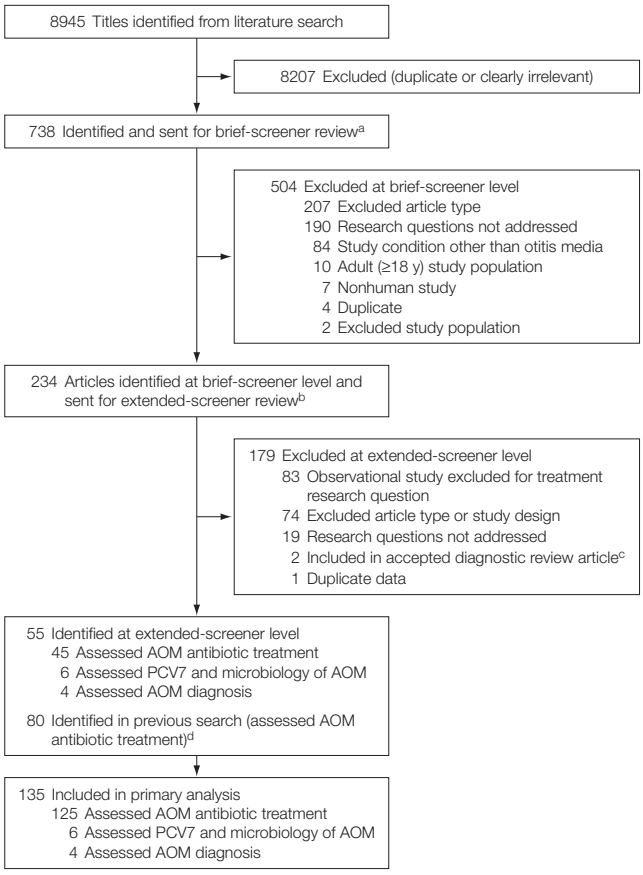
A study published subsequently to the review by Rothman et al examined the accuracy of tympanometric (evaluation of middle ear function by measurement of acoustic impedence) and otoscopic findings compared with tympanocentesis as the criterion standard to determine the presence of MEE. Among children with MEE on tympanocentesis, 97% had type B (abnormal) tympanometry results, and 100% had otoscopic examination findings consistent with AOM. These results may overestimate the accuracy of tympanometry, because the investigators performing otoscopy were not blinded to the tympanometry results, and the criterion standard of tympanocentesis was performed only when otoscopic or tympanometric findings suggested MEE.[22]

In another study subsequent to the review by Rothman et al, 22% of AOM cases diagnosed by a general practitioner were concurrently diagnosed by an otolaryngologist as otitis media with effusion, viral otitis, or a normal tympanic membrane.[23]

PCV7 and AOM Microbial Epidemiology

Six studies examined the association between PCV7 use and changes in AOM microbial epidemiology (TABLE). These studies fit into 2 categories: observational studies of AOM isolates both before and after the 2000 licensure of PCV7 and PCV7 efficacy

Figure 1. Article Selection



AOM indicates acute otitis media; PCV7, heptavalent pneumococcal conjugate vaccine.
[a] The brief screener was a 1-page screener used to screen abstracts to determine if the article contained original research data, met basic inclusion criteria, and addressed research questions.
[b] Extended screeners included more detailed information, including study design, sample size and identity, treatment protocol, types of outcomes reported and by whom, potential influencing factors, and study quality.
[c] Rothman et al.[5]
[d] Takata et al.[11]

RCTs examining AOM-related organisms.

Most studies found that *Haemophilus influenzae* became more prevalent as an AOM isolate and that *Streptococcus pneumoniae* became less prevalent although it remained important.[30,31,33] In an observational study of children with persistent AOM or AOM with treatment failure, the proportion of *S pneumoniae* MEE isolates decreased (from 44% in 1998-2000 to 31% in 2001-2003, $P = .02$), while the proportion of *H influenzae* isolates increased (from 43% in 1998-2000 to 57% in

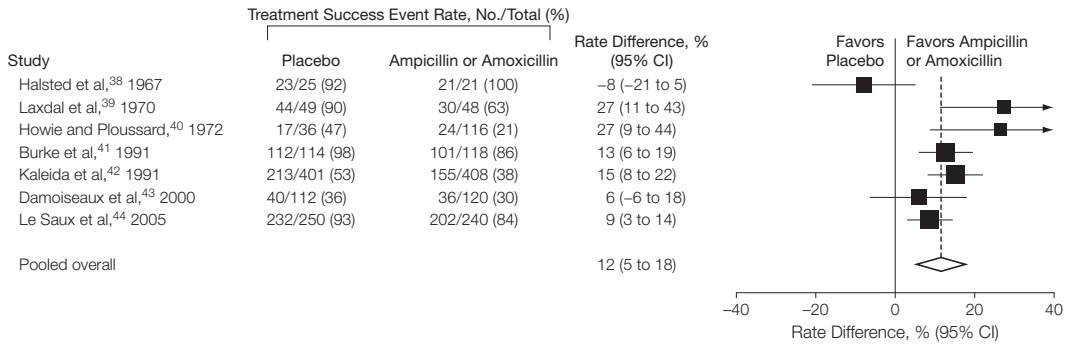
Table. Studies of the Effects of Heptavalent Pneumococcal Conjugate Vaccine on Microbial Epidemiology of Acute Otitis Media

Source	Age	Setting and Inclusive Years	Participants	Postvaccine/Vaccine Group vs Prevaccine/Control Group, %[a]		
				Culture-Positive Specimens, Postvaccine vs Prevaccine		
				Streptococcus pneumoniae	*Haemophilus influenzae*	All Others
Cohort studies						
Casey and Pichichero,[30] 2004	20-22 mo (mean)	Pediatric practice, United States, 1995-2003	551 patients with AOM treatment failure or persistent AOM 1995-1997: n = 103 isolates 1998-2000: n = 114 isolates 2001-2003: n = 89 isolates	31% vs 44% ($P = .02$) 1995-1997: 48% 1998-2000: 44% 2001-2003: 31% Serotypes not examined	57% vs 43% ($P = .01$) 1995-1997: 38% 1998-2000: 43% 2001-2003: 57%	*Moraxella catarrhalis*: 1% vs 4% *Streptococcus pyogenes*: 2% vs 3%
Block et al,[31] 2004	7-24 mo	Pediatric practice, United States, 1992-1998 and 2000-2003	379 patients with severe or refractory AOM 1992-1998: n = 336 isolates 2000-2003: n = 83 isolates For serotype analysis: 1992-1998: n = 132 *S pneumoniae* isolates 2000-2003: n = 22 *S pneumoniae* isolates	31% vs 48% ($P = .007$) PCV7 serotypes: 36% vs 70% ($P = .005$) Non-PCV7 serotypes: 32% vs 22% PCV7-related serotypes: 32% vs 8% ($P = .005$)	56% vs 41% ($P = .01$)	*M catarrhalis*: 11% vs 9% *S pyogenes*: 2% vs 2%
McEllistrem et al,[32] 2005	Not reported	5 hospitals in the United States, 1999-2002	505 isolates (No. of children not specified) 1999: n = 182 isolates 2000: n = 126 isolates 2001: n = 115 isolates 2002: n = 82 isolates	2002 vs 1999: PCV7 serotypes: 52% vs 76% ($P < .01$) Non-PCV7 serotypes: 32% vs 12% ($P < .01$) PCV-related serotypes: 13% vs 10% *P* values are trend over time, 1999-2002	Only *S pneumoniae* examined	Only *S pneumoniae* examined
Brook and Gober,[33] 2009	5 mo-12 y	Outpatient practice, United States, 1993-1998 and 2001-2006	100 patients with AOM with new spontaneous perforation 1992-1998: n = 61 isolates 2001-1006: n = 63 isolates	44% vs 54% Serotypes not reported	24% vs 18%	MSSA: 8% vs 8% MRSA: 10% vs 0% ($P < .05$)
Randomized controlled trials						
Eskola et al,[34] 2001	Infants < 2 mo enrolled (6.5-mo to 25-mo follow-up)	8 clinics in Finland, 1995-1999	1662 (with 2596 episodes of AOM) Vaccine group: n = 1177 AOM episodes with confirmed MEF Control group: n = 1267 AOM episodes with confirmed MEF For serotype analysis: Vaccine group: n = 271 *S pneumoniae* isolates Control group: n = 414 *S pneumoniae* isolates	23% vs 33% ($P < .001$) Serotype analysis: PCV7 serotype: 40% vs 60% ($P < .001$) Non-PCV7 serotype: 46% vs 23% ($P < .001$) PCV7-related serotype: 15% vs 20%	27% vs 23% ($P = .02$)	*M catarrhalis*: 32% vs 30%
Veenhoven et al,[35] 2003	12-84 mo	2 hospitals in the Netherlands, 1998-2002	383 patients with recurrent AOM; 181 with MEF samples Vaccine group: n = 60 AOM episodes with culture-positive MEF Control group: n = 54 AOM episodes with culture-positive MEF For serotype analysis: Vaccine group: n = 13 *S pneumoniae* isolates Control group: n = 19 *S pneumoniae* isolates	22% vs 35% Serotype analysis: PCV7 serotype: 31% vs 42% Non-PCV7 serotype: 70% vs 58% PCV7-related serotype: not reported	35% vs 43%	*Staphylococcus aureus*: 34% vs 17% ($P = .004$) Group A *S aureus*: 10% vs 7%

Abbreviations: MEF, middle ear fluid; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; PCV7, heptavalent pneumococcal conjugate vaccine.

[a] *P* values are provided for comparisons with $P < .05$.

Figure 2. Treatment Success by Day 14 for Ampicillin/Amoxicillin vs Placebo



Sizes of data markers are proportional to the sample size of each study in the analysis. CI indicates confidence interval.

2001-2003, $P=.01$).[30] Another study found an increase (as a proportion of all *S pneumoniae* isolates) in nonvaccine serotype *S pneumoniae* and a decrease in vaccine serotype *S pneumoniae* (non-PCV7 *S pneumoniae*: from 12% in 1999 to 32% in 2002, $P<.01$).[32] In a vaccine-efficacy RCT, investigators found a greater proportion of *S pneumoniae* isolates in the control group (33%) than in the PCV7 group (23%) ($P<.001$).[34] It is important to note that study findings did not always reach statistical significance, and most studies focused on patients with severe or persistent AOM.

Antibiotics for Uncomplicated AOM

One hundred twenty-five articles compared the effectiveness of antibiotic treatment options in uncomplicated AOM. Older articles that examined antibiotics no longer typically used for AOM are not discussed here but are included in the evidence reports.[14,36]

Benefits of Antibiotic Treatment

Evidence about the benefits of treating with antibiotics comes from 2 types of studies: placebo-controlled studies of immediate use of antibiotics and studies comparing immediate use of antibiotics with a strategy of observation with possible delayed treatment ("wait-and-see" or "prescription-to-hold").

Ampicillin or Amoxicillin vs Placebo

We identified 8 studies that compared ampicillin or amoxicillin with placebo. One did not report clinical success (only pain resolution) and was not included in the pooled analysis.[37]

In pooled analysis of the remaining 7 RCTs, the random-effects pooled rate difference for success by day 14 was estimated at 12% (95% CI, 5% to 18%), with a 73% success rate for ampicillin/amoxicillin and a 60% success rate for placebo. The number needed to treat (NNT) for clinical success was 9 (95% CI, 6 to 20) (eTable 1 [available at http://www.jama.com] and FIGURE 2). The more recent, higher-quality studies reported smaller benefits. The I^2 statistic was 69% ($P=.04$ by χ^2 test of heterogeneity), indicating the presence of unexplained heterogeneity, which could be attributable to differences in the populations studied, research methods used, or both. The Egger test did not suggest publication bias ($P=.77$).

In sensitivity analyses, we excluded an outlier[38] because its 95% CI favored placebo far more strongly than any other individual study. The pooled analysis with the remaining 6 articles yielded rates of 70% vs 54% (pooled rate difference, 13% [95% CI, 8% to 19%]), with 7 children (95% CI, 5 to 12) needing treatment with ampicillin/amoxicillin to gain a case of clinical success ($I^2=62\%$, $P=.09$; $P=.18$ by Egger test).[39-44] When we pooled the 4 studies with a quality score of 3 or more (of 5), excluding the outlier, the rates were 76% vs 67% (pooled rate difference, 10% [95% CI, 6% to 14%]), and the NNT was 10 (95% CI, 7 to 18), without evidence of heterogeneity ($I^2=0.0\%$, $P=.48$) or publication bias ($P=.26$).[41,43,44]

Other Antibiotics vs Placebo

We identified 5 studies that compared other antibiotics with placebo (eTable 1), but they are not included in pooled analysis because we examined the overall benefit of antibiotics more commonly prescribed for AOM (ie, amoxicillin) over placebo.

Immediate vs Delayed Antibiotics

We identified 4 studies of delayed treatment approaches; 2 reported higher rates of clinical success with immediate compared with delayed use of antibiotics,[45,46] and 2 found no difference.[47,48] One article reported rates of 95% vs 80% (rate difference, 15% [95% CI, 6% to 24%]; NNT, 7 [95% CI, 4 to 17]) favoring amoxicillin over the wait-and-see approach for parent-perceived success at day 12,[49] whereas the other reported rates of 86% vs 70% (rate difference, 16% [95% CI, 6% to 26%]; NNT, 6 [95% CI, 4 to 17]), also favoring amoxicillin over the prescription-to-hold approach for parent-perceived clinical success at day 3.[45] Thirty-four percent[46] and 24%[46] of participants in the delayed antibiotic groups in these studies received delayed antibiotics, respectively.

Short-term Harms of Antibiotic Treatment

The risk of harms from antibiotic treatment for AOM has been less well stud-

ied than the benefits. Four of the 7 placebo-controlled studies reported on harms. One reported the counterintuitive, although not statistically significant, result of more cases of rash and diarrhea in placebo-treated patients than in amoxicillin-treated patients.[44] Pooled analysis of the other 3 trials[39,41,43] yielded rates of 13% vs 8% for diarrhea (pooled rate difference, 5% [95% CI, 0% to 10%]; I^2=23%; P=.30), while 2 individual studies had a rate difference of 4% (4% vs 0%) and 3% (8% vs 5%) for rash[39,41]; these differences did not reach statistical significance. These point estimates are compatible with published estimates of the rate of rash (3%-10%) and diarrhea (5%-10%).[50-53] In the studies by Little et al[45] and Spiro et al,[47] the rate of diarrhea was higher for the antibiotic group than for the prescription-to-hold group (19% vs 9%; rate difference, 10% [95% CI, 2% to 18%] and 23% vs 8%; rate difference, 14% [95% CI, 6% to 22%] for the 2 studies, respectively), with a number needed to harm (NNH) of 10 (95% CI, 6 to 50) and 7 (95% CI, 5 to 17), respectively.[45,47]

McCormick et al[49] reported no difference in the rate of antibiotic-related adverse events, and Neumark et al[48] did not examine adverse events. In RCTs comparing amoxicillin with other antibiotics, the proportion of amoxicillin-treated children reporting rash ranged from 2% to 11% and the proportion reporting diarrhea ranged from 3% to 16%.[54-60]

Long-term Harms of Antibiotic Treatment

None of the studies evaluated the rates of longer-term adverse effects of immediate antibiotic treatment, including antibiotic resistance.

Antibiotic Comparative Effectiveness

eTable 2 describes selected antibiotic comparative effectiveness studies and pooled analyses for comparisons examining 3 or more studies. The Egger test was not suggestive of publication bias for any of the pooled analyses.

The success rate differences were statistically nonsignificant in the pooled analyses comparing ampicillin/amoxicillin vs ceftriaxone (4 trials, I^2=50.7%), ampicillin/amoxicillin vs cefixime (4 trials, I^2=22.9%), ampicillin/amoxicillin vs cefaclor (4 trials, I^2=13.0%), amoxicillin-clavulanate vs ceftriaxone (5 trials, I^2=22.9%), cefaclor vs azithromycin (3 trials, I^2=0%), and amoxicillin-clavulanate vs 5 days of azithromycin (5 trials, I^2=62.2%) and vs 3 or fewer days of azithromycin (7 trials, I^2=84.1%).

Statistically significant differences between treatment regimens were found in a few individual studies. Amoxicillin-clavulanate was superior to cefaclor (97% vs 84%; rate difference, 13% [95% CI, 5% to 21%])[61]; 10 days of amoxicillin-clavulanate was superior to 5 days of azithromycin (86% vs 70%; rate difference, 16% [95% CI, 2% to 30%])[62]; 5 days of amoxicillin-clavulanate was not as effective as 7 to 10 days (77% vs 88%; rate difference, –11% [95% CI, –20% to –3%] in the study by Cohen et al[63] and 71% vs 87%; rate difference, –16% [95% CI, –24% to –8%] in the study by Hoberman et al[64]); and 5 days of ceftibuten was not as effective as 10 days of ceftibuten (78% vs 98%; rate difference, –20% [95% CI, –28% to –12%]).[65]

Antibiotic-Related Adverse Events

In the pooled comparisons, use of ampicillin/amoxicillin resulted in a lower rate of diarrhea than cefixime (14% vs 21%; rate difference, –8% [95% CI, –13% to –4%]; NNH, 12 [95% CI, 8 to 25]; I^2=0%), and use of amoxicillin-clavulanate resulted in a higher rate of diarrhea than 1 dose of ceftriaxone (20% vs 9%; rate difference, 11% [95% CI, 7% to 16%]; NNH, 9 [95% CI, 6 to 15]; I^2=10.8%) and higher rates of any adverse event compared with 5 days of azithromycin (26% vs 9%; rate difference, 16% [95% CI, 7% to 25%]; NNH, 6 [95% CI, 4 to 14]; I^2=81.9%).

COMMENT

We identified several important findings for AOM diagnosis, microbiology, and antibiotic management.

Acute otitis media is a clinical diagnosis with 3 components: acute signs of infection, evidence of middle ear inflammation, and effusion.[12] Evidence suggests that certain otoscopic findings (ie, a red and immobile or bulging tympanic membrane) predict AOM, but the accuracy or precision of a clinical diagnosis has not been determined. A major limitation to the evidence regarding diagnosis is the lack of a gold standard. The diagnostic tools studied (eg, otoscopy) are often part of the only available gold standard—a clinical diagnosis. Perhaps the most important way to improve diagnosis is to increase clinicians' ability to recognize and rely on key otoscopic findings.

Since the introduction of PCV7, there have been significant shifts in AOM microbiology, with *S pneumoniae* becoming less prevalent and *H influenzae* becoming more prevalent. A recent study of a single pediatric practice found evidence suggesting that this balance may be shifting again because of an increase in the proportion of AOM with nonvaccine *S pneumoniae* serotypes.[66] These data and the introduction of PCV13 support the need for ongoing surveillance of AOM isolates.

Immediate ampicillin/amoxicillin treatment has a modest benefit compared with placebo or delayed antibiotics but also may be associated with more diarrhea and rash. Of 100 average-risk children with AOM, approximately 80 would likely get better within about 3 days without antibiotics.[67] If all were treated with immediate ampicillin/amoxicillin, an additional 12 would likely improve, but 3 to 10 children would develop rash and 5 to 10 would develop diarrhea. Clinicians need to weigh these risks (including possible long-term effects on antibiotic resistance) and benefits before prescribing immediate antibiotics for uncomplicated AOM.

Most antibiotics used to treat uncomplicated AOM in children at normal risk have similar rates of clinical success; we found no evidence of the

superiority of any other antibiotic over amoxicillin.

In most cases of uncomplicated AOM when amoxicillin is appropriate (eg, excluding children with penicillin allergy and those who previously did not improve after a course of amoxicillin), there is no evidence for first-line use of higher-cost antibiotics (eg, cefdinir, cefixime). For a 20-kg child with AOM, a 7-day course of cefdinir costs approximately $96, compared with $34 for an equivalent course of amoxicillin (pricing information available at http://www.drugstore.com). In an analysis of data from the National Ambulatory Medical Care Survey, among visits for AOM (visits for a new problem without additional diagnoses requiring antibiotic therapy), amoxicillin was prescribed in 49%, amoxicillin-clavulanate in 16%, cefdinir in 14%, and other cephalosporins in 6%.[13] If just half of the 14% of the estimated 8 million children who visit a physician for AOM annually[4] were to receive amoxicillin instead of cefdinir (assuming the other half were appropriately prescribed cefdinir because of a non–type-1 penicillin allergy), the estimated annual savings would exceed $34 million. This estimate does not account for potential additional savings from adopting a less aggressive approach to antibiotic prescribing that might avoid a certain number of prescriptions altogether.

This review has several limitations that must be considered. First, article screening and data abstraction were not blinded, which may potentially introduce bias. However, there is evidence that blinding does not alter the results of meta-analyses.[68] Second, we may not have identified some relevant evidence. For example, we did not search EMBASE or seek unpublished data. We used statistical tools to detect publication bias but found no evidence of it in our pooled analyses. Additionally, our findings on diagnosis and microbiology are greatly limited by the small number of studies; thus, caution should be used in interpreting our findings for these topics. To account for variation in study quality, we performed sensitivity analyses that pooled only high-quality studies. Third, the studies varied widely in their definitions of clinical success and in AOM diagnostic criteria. Some studies that did not use all 3 AOM diagnostic criteria may have included participants without AOM but with otitis media with effusion or no middle-ear abnormality at all.[69,70] Lastly, our pooled analyses included studies completed before and after the licensing of PCV7. It is not clear how the changing microbiology of AOM may have influenced study findings; the heterogeneity of AOM over the past 20 years might favor an analysis that does not include pooling data from studies before and after 2000.[69]

One remaining question is what new evidence about antibiotic comparative effectiveness is needed. It is not enough to show statistical significance or lack thereof; the clinical importance of any difference must also be considered. This requires knowing the minimal clinically important difference (MCID) for treatment of AOM. Although there currently is no agreed-on value for the MCID, assuming an MCID of 5% (representing a "small" effect size, according to Cohen's classification[71]) means that when existing evidence falls entirely within or outside of this MCID, equivalence or significance can be concluded; when it does not, it can be concluded that more information is needed. Using this definition, we can conclude equivalence for 2 of the 8 pooled analyses in eTable 2 and that effects are inconclusive for the remaining 6. The MCID has important implications for our conclusions; for example, in contrast to a previous systematic review,[7] we are unable to make definitive conclusions regarding the equivalency of short- vs long-term regimens analyzed by antibiotic when considering an MCID of 5%, except for 7 to 10 days of cefaclor vs 3 days of azithromycin.

To account for both statistical and clinical significance, sample sizes for AOM comparative effectiveness studies need to be large. Because approximately 80% of AOM cases resolve spontaneously,[67] most RCTs will be able to test superiority of different antibiotics with only the remaining 20%. If the success rate is 88% for the treatment group and 80% for the control group, a sample size of 1150 per group would provide a 95% CI of the difference of 5% to 11%, which is outside the ±5% MCID; this sample size is much larger than that of any published AOM comparative effectiveness study.

CONCLUSIONS

We found evidence to guide the diagnosis and management of AOM in children; however, further research is needed that (1) examines clinicians' diagnostic accuracy and precision using the 3 AOM diagnostic criteria; (2) continues surveillance of AOM microbiology, especially in view of the newly approved PCV13; and (3) produces more high-quality studies on AOM management that include clear diagnostic criteria, a better-defined menu of clinical success measures that are universally applied, and more investigation into the comparative antibiotic-related adverse event rates that assesses whether any antibiotic regimen is superior to amoxicillin.

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Study concept and design: Coker, Chan, Shekelle, Takata.
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Online-Only Material: eTables 1 and 2 are available at http://www.jama.com.
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The educator is like a good gardener, whose function is to make available healthy, fertile soil in which a young plant can grow strong roots; through these it will extract the nutrients it requires. The young plant will develop in accordance with its own laws of being, which are far more subtle than any human can fathom, and will develop best when it has the greatest possible freedom to choose exactly the nutrients it needs.

—E. F. Schumacher (1911-1977)