Amoxicillin Is the Most Cost-Effective Therapy for Acute Otitis Media: The Culmination of 40 Years of Research

In this volume of *The Journal*, Shaikh et al[1] report "bang for the buck" rankings for 5 management options for acute otitis media (AOM). Two aspects should interest readers: (1) "cost-utility analysis," a complex but increasingly used method to judge whether the balance between benefits and adverse events justify the overall socioeconomic and treatment costs, and (2) confirmation of AOM guideline recommendations based on decades of increasingly rigorous science.

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Cost-utility Analysis Is an Important Tool

A "cost-utility analysis" may seem arcane, perhaps tedious, but familiarity with cost utility helps understanding of this study. It differs from the more familiar "cost benefit analysis." A cost-benefit analysis measures costs of interventions that produce similar benefit, for example, the cost of drug A vs drug B to cure definitive AOM. In contrast, a cost-utility analysis is more robust, with capability to analyze shades of gray. It can measure costs of interventions with potentially different levels of benefit and harm in light of added variables, for example, the overall cost of drug A vs drug B to cure probable AOM, but also can consider the speed of cure, quantity and quality of side effects, disruption of family's daily routine, and costs other than for the drug itself.

In this study, data from scientifically sound publications were used to calculate quality-adjusted life-days (QALDs) gained and cost differences as incremental cost-effectiveness ratios (ICERs).

A full understanding of QALDs and ICERs is not essential to understanding this study, just as it is not necessary to fully understand the theory behind diagnostic polymerase chain reaction tests.

The cost-utility analysis is thorough, applied by Shaikh et al owing to going beyond drug efficacy and drug cost to add costs of downstream factors (eg, adverse drug events, effects on family routine, parking costs, time away from work), as well as the likelihood of some incorrect diagnoses of AOM. This analysis may be the most comprehensive evaluation to date of the overall cost effectiveness of current AOM treatment options, although a recent cost-effectiveness analysis was published for the management strategy of watchful waiting.[2]

That said, a 40-year history of multiple aspects of AOM science allows us to better appreciate the results reported by Shaikh et al.

ADR	Adverse drug reaction
AOM	Acute otitis media
ICERs	Incremental cost-effectiveness ratios
Mcat	*Moraxella catarrhalis*
ntHi	Nontypeable *Haemophilus influenzae*
QALDs	Quality-adjusted life-days
Spn	*Streptococcus pneumoniae*

Before AOM Science

Forty years ago, AOM was the bane of primary care practice. AOM science was a disjointed wilderness of partial truths. Clinicians had their own "treatment styles" and cared for a core group of AOM "frequent flyers" (children with 6-8 healthcare visits per year for AOM and its sequelae). Families were frustrated by less than optimal outcomes and the provider's "What can I prescribe this time?" approach.

Options in 1970 were penicillin or erythromycin, with or without sulfisoxazole. The development of oral ampicillin in 1967 was followed by amoxicillin and cefaclor in the mid 1970s. The antibiotic race for the AOM market continued through the 1980s and 1990s, with multiple pharmaceutical companies developing candidate antibiotics and a "wild-west"–like atmosphere surrounding which drug was best. Practitioners were grateful for more options. However, it was less clear which antibiotic was the "drug of choice" for which category of AOM (intermittent vs recurrent vs persistent) and at what patient age. Other contributors to uncertainty were variations in AOM diagnostic criteria, suboptimal otoscope hardware, and spotty practitioner training in otoscopy.

Rigorous Science for AOM

Our current understanding of AOM is due to the efforts of many. Seminal work was performed by many in the academic community. Some of the most important early work was by Virgil Howie[3] and Richard Schwartz,[4] both private practice–based general pediatricians who championed tympanocentesis. Cultures of middle ear samples confirmed the relative importance and antibiotic susceptibilities of the "big three" otopathogens (*Streptococcus pneumoniae* [Spn], nontypeable *Haemophilus influenzae* [ntHi], and *Moraxella catarrhalis* [Mcat]).[5-9]

Dr Howie first reported pathogen-specific spontaneous cure rates: 50%-80% for Mcat, 50% for ntHi, and 20% for Spn.[3] Recognizing background spontaneous cure rates was important in understanding the conflicting results of some trials of relative antibiotic efficacy, especially when tympanocentesis was not performed.

Tympanocentesis-based studies also confirmed what was only suspected from non–culture-based AOM studies. Antibiotic

C.H. receives support from Pfizer as an investigator for a study of pneumococcal seroepidemiology and from Merck for an in vitro susceptibility investigation, and Glaxo SmithKline for vaccine studies.

http://dx.doi.org10.1016/j.jpeds.2017.06.070

susceptibilities were not static. Mcat and then ntHi acquired beta-lactamase genes, rendering amoxicillin less effective.[10-12] Cefaclor and cefprozil, the "tastes great, less killing" duo, also were less effective because of beta-lactamase vulnerabilities.[12,13] Azithromycin supplanted erythromycin, only to be found to have poor activity against ntHi whether beta-lactamase producing or not.[14] Newer cephalosporins (cefuroxime axetil, cefpodoxime proxetil, and cefdinir) improved outcomes for beta-lactamase producing AOM pathogens.[15-17]

But another problem followed—penicillin nonsusceptible Spn,[18] in which pathogens could have intermediate or high-level nonsusceptibility. Spn serotype 19A emerged after pneumococcal conjugate vaccine 7 implementation and was resistant to multiple drugs, including all macrolides, oral cephalosporins, clindamycin, trimethoprim–sulfamethoxazole, and, at times, ceftriaxone.[13,19] Most recently, after universal implementation of pneumococcal conjugate vaccine 13, there has been a decrease in 19A and multidrug-resistant Spn,[20,21] reduced rates of AOM, and particularly of difficult-to-cure AOM.

Presently, AOM studies are scientifically rigorous, and include adverse drug reactions (ADRs) and costs compared with outcomes. Power calculations ensure that sufficient subjects are enrolled to detect a comparator drug's inferiority. This was not the case 20-30 years ago when insufficient subjects camouflaged the weakness of some drug candidates, for example, cephalexin or cefaclor. Efficacy differences as high as 30% were missed in studies not using tympanocentesis, in part owing to the 50% background spontaneous cure rate (ie, the Pollyanna effect).[22] Conflicting 20th-century data led to variable recommendations from experts and confusion of practitioners. In response, the Centers for Disease Control and Prevention convened a group and published a national consensus statement for AOM in 1998.[23]

Guidelines

The 1998 consensus statement was groundbreaking, but antibiotic susceptibilities continued to evolve, as did understanding of factors affecting spontaneous cure rates and age-related and social risk factors. In 2004, the American Academy of Pediatrics and the American Academy of Family physicians, along with other professional clinical organizations, published clinical management guidelines for uncomplicated AOM.[24] These were revised in 2013.[25] Key elements are patient age, clinical severity, diagnostic criteria, and recent antibiotics. The current report's authors based their study at least in part on the guideline.

Guideline-Acceptable Antibiotic Choices

The antibiotic recommendations in the guideline were based on expert opinion and clinical trials. The goal was to minimize drug cost and ADRs while maximizing cure rates based on published susceptibility patterns from 2007 to 2011. Neither azithromycin nor trimethoprim–sulfamethoxazole have been recommended as first line drugs despite their low cost and good ADR profiles because of low in vitro activity against ntHi and SPN and low eradication rates in double-tap tympanocentesis trials.[13,14]

Three currently recommended first-line AOM antibiotics that are well-known to practitioners were chosen for the Shaikh et al analysis. High-dose amoxicillin at 80-90 mg/kg/day divided twice daily provides coverage for the 40%-70% of non–beta-lactamase producing ntHi, and 80%-90% of Spn with in vitro minimum inhibitory concentrations of <4 μg/mL for penicillin. Amoxicillin is inexpensive and has a favorable ADR profile. For penicillin-allergic (nonanaphylaxis type) patients, cefdinir can be considered, and has activity somewhat superior to amoxicillin for ntHi but inferior for Spn. Cefdinir has estimated coverage for approximately 85% of all ntHi, most Mcat, and the 50%-75% of Spn with penicillin minimum inhibitory concentrations of <0.5 μg/mL. The cost of cefdinir is up to 6 times that of amoxicillin, but 15% less than amoxicillin-clavulanate. Cefdinir's ADR profile is good.

High-dose (80-90 mg/kg/day) amoxicillin-clavulanate ES (14:1) is recommended in the guideline for AOM in patients with recent antibiotic exposure, or who have failed empiric amoxicillin or cefdinir. Amoxicillin-clavulanate provides coverage for >98% Mcat, (including beta-lactamase–producing strains), ntHi, and has the same 80%-90% coverage for Spn as high-dose amoxicillin. This broader coverage comes with a higher price in dollars and less acceptable ADR profile.

Guideline Acceptable Nonantibiotic Management Choices

Two nonantibiotic management strategies became mainstream since 2000.[26,27] Nonsevere AOM can be managed by watchful waiting, given 2 caveats. The first is that the family agrees to waiting; the second is that when symptoms do not clear in 48-72 hours, treatment with amoxicillin is reconsidered. Nonsevere AOM also can be managed safely with a rescue amoxicillin prescription. The parent is given a prescription at the initial visit, but counselled not to fill it unless the child's symptoms worsen or are not improved in 48-72 hours.

The Authors' Results

The data or categorized calculations use 2 data categories: projected efficacy and projected costs (**Table**; available at www.jpeds.com).

Why Duration of Therapy for 10 Days and Age Under 2 Years?

The Pittsburgh group previously used rigorous methodology to show that a short course (5 days) is inferior to 10 days of antibiotic therapy in children less than 2 years of age.[28] The authors chose to establish cost effectiveness in the age group for which AOM is most common and difficult to cure.

Projected Efficacy

Relative efficacy measures used were faster resolution of symptoms, lower symptom burden, and resolution of otoscopic evi-