Category: Therapeutics/ Prevention

Study type: Randomised controlled trial

Author's declarative title: Clinical failure is more common in young children with acute otitis media who receive a short course of antibiotics compared to standard duration

Citation: Hoberman A, Paradise JL, Rockette HE, et al. Shortened Antimicrobial Treatment for Acute Otitis Media in Young Children. *N Engl J Med*. 2016;**375**:2446-56.

Commentary (800 words starting from context and including references)

Context

Acute otitis media (AOM) is a leading cause of doctor consultations and antibiotic prescriptions in young children.[1] Strategies to reduce antibiotic prescribing for AOM and thereby the emerging spread of antimicrobial resistance have focused on watchful waiting and delayed prescription, in particular in children over two years.[2] An alternative strategy to combat antimicrobial resistance is to reduce the duration of antibiotic treatment. So far, the evidence to support this strategy in young children with AOM has been incomplete.[3]

Methods

Hoberman and colleagues recruited 520 children from an academic children's hospital and affiliated paediatric practices and a private paediatric research practice in the US. Children were aged 6-23 months and diagnosed with AOM based on the following criteria: (i) recent onset of parent-reported AOM symptoms (score ≥3 on a 0-14 point scale), (ii) presence of middle ear effusion, and (iii) bulging of the tympanic membrane. Children were randomised to a 10-day course of amoxicillin-clavulanic acid (90/6.4mg/kg body weight) or a 5-day course followed by 5 days of placebo. The main outcome was the proportion of children who had clinical failure, defined as worsening or incomplete resolution of signs (primarily bulging of the tympanic membrane) and symptoms by the end of treatment at day 12-14. Secondary outcomes included symptom burden over days 6-14, the proportion of children whose symptom scores improved by at least 50% from baseline to end of treatment, AOM recurrence during the ongoing respiratory infection season, adverse events, nasopharyngeal colonization with penicillin-nonsusceptible pathogens, healthcare resource use, and parental satisfaction with study treatment. Data were primarily analysed according to the intention-to-treat principle.

Findings

Clinical failure was more common in children who were treated with a 5-day course of amoxicillin-clavulanate than in those treated with a 10-day course: 77/229 (34%) versus 39/238 (16%), respectively (difference 17%, 95% CI 9-25%, number needed to treat [NNT] = 6). Mean symptoms scores on the 0-14 point AOM symptom scale were 1.61 versus 1.34 (p=0.07) over days 6-14 and 1.89 versus 1.20 (p=0.001) at the 12-14 day assessment for the 5- and 10-day course groups, respectively. At day 12-14, children treated with amoxicillin-clavulanate for 5 days were less likely to have symptom scores improved by at least 50% from baseline than those treated for 10 days: 181/227 (80%) versus 211/233 (91%) (p=0.003). There were no significant differences in other secondary outcomes.

Commentary
This well-designed and rigorously conducted non-inferiority trial provides important evidence on the effectiveness of a short- versus a long-course of antibiotics in young children with AOM. The study suggests that in young children with AOM a short (5 days) course is inferior to a standard (10 days) course; the between-group difference in clinical failure, a composite end-point of otoscopic findings and symptoms, did clearly exceed the pre-defined non-inferiority margin.

The question remains, however, whether this difference means that all children aged 6-23 months with AOM should be treated with antibiotics for 10 days. The difference in the outcome that matters most to parents and caregivers, i.e. ear pain, fever, sleeping and feeding problems, was at most small, and the majority of children had substantial improvement of symptoms by the end of treatment.[4] This is consistent with the findings of a previous individual patient data meta-analysis of six trials (1643 patients) of antibiotics for AOM carried out in more economically developed countries, showing that even in children of this particular young age group, most cases of AOM resolve spontaneously.[5] The benefit of antibiotics on symptoms was modest and most straightforward in children with bilateral AOM and in those presenting with acute ear discharge.[5]

The rate of adverse events observed in the current trial is remarkable high, with one in three children reported as suffering from diarrhoea and dermatitis requiring a topical antifungal agent. This is important information for clinicians to share with parents and caregivers of young children when making decisions about antibiotic treatment.

Implications for practice
This high-quality trial improves the knowledge base for the management of childhood AOM. Based upon its findings, recommendations regarding the duration of antibiotic treatment in young children with AOM are unlikely to change. The high rate of resolution of symptoms in both groups and lack of effect of treatment duration on AOM recurrence, suggests that it is reasonable to advise parents to stop giving antibiotics after 5 days if AOM symptoms have resolved.

Commentator details
Roderick P Venekamp
Affiliation: Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht
Correspondence address: University Medical Center Utrecht, Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands
Email: R.P.Venekamp@umcutrecht.nl

and

Name: Anne GM Schilder
Affiliation: evidENT, Ear institute, University College London and Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht
Correspondence address: Royal National Throat Nose and Ear Hospital, 330 Gray's Inn Road, London WC1X 8DA, United Kingdom
Email: A.Schilder@ucl.ac.uk

References

1. Marom T, Tan A, Wilkinson GS, et al. Trends in otitis media-related health care use in the United States, 2001-2011. *JAMA Pediatr.* 2014;**168**:68-75.
2. Lieberthal AS, Carroll AE, Chonmaitree T, et al. The diagnosis and management of acute otitis media. *Pediatrics* 2013;**131**:e964-e999.
3. Kozyrskyj A, Klassen TP, Moffatt M, et al. Short-course antibiotics for acute otitis media. *Cochrane Database Syst Rev* 2010;**9**:CD001095.
4. http://blogs.bmj.com/bmj/2017/02/08/how-to-hide-trial-results-in-plain-sight/
5. Rovers MM, Glasziou P, Appelman CL, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006;**368**:1429-35.

Competing interests

None