QUALITY USE OF MEDICINES: THE CHILD WITH ACUTE OTITIS MEDIA

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Infectious diseases pose quite different challenges to those who seek to apply evidence-based guidelines, as they do to managers of Essential Medicines programmes. The first challenge is that of resistance – unlike the causes of non-infectious conditions, microbes can develop resistance to antimicrobials over time. This may render yesterday's guidelines, based on yesterday's resistance patterns, quite useless today. The second challenge is that of location, the prevalence of causative organisms may vary from site to site (as can resistance), but in addition, factors other than the microbe involved may alter outcomes and hence demand differences in treatment. This review will use acute otitis media (AOM) in children as an example of such a condition, in order to explore these challenges more closely.
(SA Fam Pract 2003;45(9): 42-45)

Current evidence

Otitis media is recognised as a prevalent but largely self-limiting condition in which high levels of antibiotic use may contribute to the ongoing development of resistance. It has therefore been the subject of intensive review, and a variety of guidelines have emerged. In the late 1990s many reviews questioned the need for routine use of antibiotics in AOM.[1,2,3] The questions raised have been comprehensively answered in a Cochrane Review, last updated in August 2002.[4] The Cochrane Review is based largely on work previously published in the BMJ in 1997.[5] Despite a very large body of literature, only 7 trials were included in the Cochrane review, and these involved 2202 children. A number of very important points are made in these reviews: firstly, because AOM is a disease that remits spontaneously, measuring "cure rates" or even "microbiological cure" is not useful. Instead, attention should be paid to the resolution of symptoms (such as pain, fever or deafness) and the incidence of serious complications (such as mastoiditis). The second point is the cautious way in which the issue of location is raised. The 1997 BMJ publication notes the ubiquitous nature of AOM ("by the age of 3 months, 10% of children will have suffered at least one episode"), and its generally mild course ("in Western countries mortality is low"), but then cautions that mortality "may be higher in under-developed countries". Given the high rate of spontaneous remission (2/3 of children receiving placebo were pain free within 24 hours of presentation, and 80% had settled by 2-7 days), it I not surprising that all antibiotics tested had modest impacts on the outcomes measured. An absolute reduction of only 5% was noted at 2-7 days, meaning that 17 children would have to be treated early with antibiotics to prevent one child from experiencing pain by that time. This modest impact in effectiveness was however balanced by a near doubling in the risk of vomiting, diarrhoea or rashes (odds ratio 1.97, 95%CI 1.19-3.25). The authors therefore felt that management should emphasise "advice about adequate analgesia and the limited role of antibiotics", but cautioned that "further research is needed to identify which subgroups will have a prolonged or complicated course".

In direct contrast, a US Centers for Disease Control Working Group recommended in 1999 that amoxicillin be used at double the normal dosage (i.e. at 80-90mg/kg/day) in the empirical treatment of AOM.[6] While certainly necessary in subsets of patients who needed treatment, and in settings of high resistance, this could hardly be generalised to all patients seen in all family practice settings.

Yet another body of evidence has concerned itself with the duration of treatment. A Cochrane Review, last updated in February 2000, showed that 5 days of short-acting antibiotics (e.g. penicillin V, amoxicillin, cefaclor, cefuroxime) were effective in uncomplicated cases.[7] In summary, 17 children would have to be treated with courses of a short-acting antibiotic longer than 7 days to avoid one treatment failure. Short courses of longer-acting antibiotics (e.g. azithromycin and intramuscular ceftriaxone) were also comparable to more than 7 days of other antibiotics. However, another meta-analysis did show a difference in side effect profile, with gastrointestinal effects associated more with some antibiotics (cefixime, amoxicillin-clavulanate) than others (ampicillin, amoxicillin, azithromycin).[8]

These large systematic reviews all seem to point in the same direction. Individual papers sometimes serve more to muddy the waters than provide a way

forward. This was well illustrated by a recent paper that reported on a double-blind assessment of a range of options in an outpatient community clinic setting.[9] In this trial, 171 children, aged 5 to 18 years, were randomised to receive either a naturopathic herbal eardrop (n=42), the same eardrop with oral amoxicillin (n=44), a local anaesthetic eardrop (n=43) or that eardrop with oral amoxicillin (n=42). Pain was assessed at 15 and 30 minutes after each morning dose for 3 days. Despite a regression analysis showing that the herbal preparation used explained only 7.3% of the total pain reduction (in line with the self-limiting nature of the condition), the authors claimed that it "may be very beneficial". Critically, no placebo arm was included. Also, though the authors acknowledged that current evidence supports a 2- to 3-day waiting period before initiating antibiotics, they felt a topical (perhaps herbal) preparation would be indicated where "the physician believes there is an indication for some treatment, especially if the parents are anxious". That is the real question – which patient subset truly needs more active intervention?

Current practice

Although there is little empiric evidence to back such a claim, it might well be suspected that AOM is frequently treated with antibiotics in the South African family practice setting, increasingly with broad-spectrum antibiotics, and sometimes with courses longer than 5 days. This would, despite the evidence provided above, not be an unusual situation. A review of Spanish outpatient department presenters in 1997 showed that 93% of those diagnosed with AOM received an anti-biotic, with amoxicillin-clavulanate used in 41% of those, amoxicillin in 20%, cefuroxime in 11%, ceflaclor in 6% and azithromycin in 5%.[10] A strong trend towards more broad-spectrum agents was noted in Finland: whereas penicillin V was used in 80.2% in children under 10 years treated in two rural municipalities in 1978-9, this had decreased to 10.5% in 1994-5.[11] A recent survey of New Zealand general practitioners showed that 95% would usually or always use antibiotics, generally amoxicillin or amoxicillin-clavulanate.[12] Interestingly, while 82% recommended a follow-up visit, this varied from 24 hours to 12 weeks after the initial consultation. A national US survey showed that, while annual population-based rates of overall antibiotic prescribing declined significantly from 1989-90 to 1999-2000, from 838 per 1000 children and adolescents aged younger than 15 years to 503 per 1000, the picture was not so simple for respiratory tract infections.[13] Declines were noted in pharyngitis and upper respiratory tract infections, but not in otitis media, bronchitis and sinusitis.

In a perfect world, empiric antibiotic choices would be guided by available local resistance data. For example, a French group tracked resistance patterns of organisms obtained by tympanocentesis (n=1862) or from otorrhoea culture (n=287) from children aged 3 to 36 months presenting with AOM over a 10-year period in the Paris region.[14] The incidence of beta-lactamase producing *Haemophilus influenzae* (the most common pathogen, responsible for 40% of specimens) increased from about 20% in 1987-9 to nearly 70% in 1997. Similarly, 70% of *Streptococcus pneumoniae* (responsible for 31% of isolates overall) showed reduced susceptibility to penicillin in 1997, compared to 7% in 1987. No similar data are available for South African settings. The lack of such data makes it difficult to assess the local applicability of data from comparative studies. A meta-analysis showed, for example, that short-course azithromycin (3-5 days) was as effective as longer courses of other antibiotics (beta-lactams and other macrolides) in treating AOM.[15] It suggested that safety issues (e.g. lower discontinuation rates due to adverse effects), suitability (e.g. convenience of dosing) and cost (e.g. higher acquisition costs for the newer macrolides) could be used to make rational choices, but conceded that in this common infection "no antibiotic may be indicated at all".

Most reviews point to the stark difference in practice between the US (where almost all children with AOM receive antibiotics) and in countries such as the Netherlands (where a small minority – perhaps 13% - receive antibiotics). Two questions seem to remain – is it possible to move practice towards that supported by the evidence, and if so, which patients still need more aggressive management?

Changing practice

A practice experiment in the United Kingdom elicited a mass of responses in 1999. Reacting to the new Cochrane Review, Cates and his partners stopped giving antibiotics to children with AOM "who were not particularly ill".[16] Instead, they emphasised the appro-priate use of paracetamol and issues a prescription for an antibiotic, to be redeemed after a day or two if the parents felt the child was not getting better. They compared their amoxicillin use with another local practice of a similar size. Median numbers of prescriptions for this agent fell from 75 to 47 per month over a 12-month period, a 32% decrease. In contrast, the comparator practice saw only a 12% drop. The practice decided to stay with the new policy, which included the use of a patient information leaflet to accompany the "delayed" or "hold" prescription. A host of letters were exchanged – a hospital-based specialist warned of dire consequences, while family practitioners welcomed a pragmatic approach. A randomised controlled trial of the two approaches was also done, involving 315 children (aged 6 months to 10 years) presenting to general practices in the south west of England. Children were randomised to receive immediate antibiotics or a delayed prescription, to be used after 72 hours if no improvement was noted.[17] Both groups received standardised advice sheets. The results confirmed what the evidence predicted: there were modest gains from immediate treatment at 3 days - 1.1 (95%CI 0.54-1.48) fewer days of illness, 0.72 (95%CI 0.30-1.13)

fewer disturbed nights, 0.52 (95%CI 0.26-0.79) fewer "spoons" of paracetamol administered – but also increased adverse effects (10% more diarrhoea). Of the 150 who received delayed prescriptions, only 36 were redeemed – a potential 76% reduction in usage if applied universally. Perhaps the most important part of the study design though was the test for children considered "too unwell to be left to wait and see" – those with "high fever, floppy, drowsy, not responding to antipyretics". Is that precise enough to identify the subset in need of immediate treatment?

Children at risk

It has been suggested that patients under 2 years of age should not receive delayed treatment. This was tested in 53 general practices in the Netherlands.[18] A total of 240 children aged 6 to 24 months were randomised to receive 40mg/kg/day amoxicillin in 3 divided doses for 10 days or a placebo suspension. Each also received 1 drop of oxymetazoline nose drops three times a day, as this was standard practice, and the use of paracetamol (by suppository) was allowed and recorded. Persistent symptoms were rated at day 4, and were less common in the amoxicillin group (risk difference 13%, 95%CI 1-25). The mean duration of fever was 2 days in the placebo group, but only 1 day in the group receiving antibiotics. Although no difference in the duration of pain and crying was noted, those in the placebo group received more doses of parace-tamol (4.1 vs. 2.3 doses, p=0.004). Tympanometry readings were similar at 6 weeks. The authors concluded that "this modest effect does not justify prescription of antibiotics at the first visit, provided close surveillance can be guaranteed". Patients with impaired immunity, cranio-facial abnormalities and Down's Syndrome were excluded. While those with penicillin allergy were also excluded, this was clearly not because of an increased risk of complications from delayed treatment. In contrast, US opinion still holds that those under 2 should be treated more aggressively.[19,20]

A more useful description of the subset at risk was provided by Little *et al*, who re-analysed the data from their RCT in 315 patients, and identified that those with fever (>37.5°C) and vomiting were more likely to have persistent symptoms at three days if not given antibiotics.

A common theme in most reviews is that the choice of whether to treat with antibiotics or not should be guided by the background risk of complications, and in particular mastoiditis. As was noted before, the Cochrane Review limited the application of its recommendations to the Western (developed) world, where mortality is low.[4] This is based on the assumption that antimicrobial use in the developing world is still a problem of underuse, of limited access, rather than of misuse and resistance, and also on the assumption that rates of complications are higher. Historical data in developed settings seem to favour this interpretation – based on such views, a review by Canadian authors stated "withholding antibiotic therapy in the treatment of AOM would more than likely impose greater morbidity and mortality on an already disadvantaged population".[21] A review in 1995 noted the paucity of data from developing country settings, but did provide some data from Uganda.[22] In this setting, community level surveys showed that mastoiditis occurred in 0.17 to 0.74% of children and youth. However, it was diagnosed in 18% of hospital ear, nose and throat clinic presenters, often with dire consequences. Corroborative data of a relationship between treatment intensity and the incidence of mastoiditis has also been found in developed countries – the incidence in countries with higher treatment rates (such as the US and Australia) is about 1.2 to 2.0 per 100 000 patients years, half that seen in countries with low treatment rates, such as the Netherlands (3.8/ 100 000 patient years), Norway (3.5) and Denmark (4.2).[23] Proving that withholding treatment will result in greater risk of mastoiditis in such settings – where the complication is rare – will be almost impossible. For example, an early observational study of this approach in 4860 patients noted no cases of mastoiditis.[24]

A local reaction?

It is possible to surmise that family practitioners reading this article might place themselves in one of two groups. They may consider that their setting is closer to that in the developed countries where many of the studies quoted were conducted – access to care and follow-up is easy and unhindered by economic considerations, patient and carer literacy is high and communication is easy by telephone. Complication rates are low and easily managed – in developed country settings rare cases of mastoiditis clear rapidly on courses of simple antibiotics like amoxicillin. Alternatively, they may be concerned about the possibility that follow-up may not occur, that delayed prescriptions may not be filled because of repeated transport costs and time spent waiting for medicines, and that complications may present late, if at all. In the first instance, advice such as that provided by the Scottish Intercollegiate Guidelines Network can be followed: "children diagnosed with AOM should not routinely be prescribed antibiotics as the initial treatment".[25] In the second, given the lack of data on causative organisms and resistance patterns, either the national Standard Treatment Guidelines can be used, or a choice guided by considerations of efficacy (equal), safety (somewhat different), suitability (mostly based on dosing schedules) and cost (extremely variable, with generics available for most of the older agents) made for that particular setting. Shorter, rather than longer, treatment courses are probably best – not least because these also match parents' actual dosing practice.[26]

This review has not considered another important way to avoid unnecessary antibiotic use – differentiating between AOM and otitis media with effusion (OME), which requires no

antibiotic therapy. The SIGN guideline mentioned above also states "children with AOM should not be prescribed decongestants, antihistamines or oils". The evidence for this statement deserves another review altogether, as do the questions of when, if ever, to use prophylactic antibiotics, surgical interventions and/or tympanocentesis, and pneumococcal vaccines. What it has hopefully identified though is that, despite concerns about the applicability of evidence derived elsewhere, rational antimicrobial use can be pursued aggressively. Those wishing to promote such practice can use a variety of proven methodologies, including academic detailing, feedback from nurses, pharmacists or physicians, local adaptation of available guidelines, small-group interactive sessions and computer-assisted care.[27]❐

Acknowledgment:

The assistance of Janet van Maasdyk in sourcing the literature for this paper is gratefully acknowledged.

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