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Predictors of poor outcome and benefits from antibiotics in children with acute otitis media: pragmatic randomised trial

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Abstract

Objectives To identify which children with acute otitis media are at risk of poor outcome and to assess benefit from antibiotics in these children.

Design Secondary analysis of randomised controlled trial cohort.

Setting Primary care.

Participants 315 children aged 6 months to 10 years.

Intervention Immediate or delayed (taken after 72 hours if necessary) antibiotics.

Main outcome measure Predictors of short term outcome: an episode of distress or night disturbance three days after child saw doctor.

Results Distress by day three was more likely in children with high temperature (adjusted odds ratio 4.5, 95% confidence interval 2.3 to 9.0), vomiting (2.6, 1.3 to 5.0), and cough (2.0, 1.1 to 3.8) on day one. Night disturbance by day three was more likely with high temperature 2.4 (1.2 to 4.8), vomiting (2.1, 1.1 to 4.0), cough (2.3, 1.3 to 4.2), and ear discharge (2.1, 1.2 to 3.9). Among the children with high temperature or vomiting, distress by day three was less likely with immediate antibiotics (32% for immediate *v* 53% for delayed, $\chi^2 = 4.0$; $P = 0.045$, number needed to treat 5) as was night disturbance (26% *v* 59%, $\chi^2 = 9.3$; $P = 0.002$; number needed to treat 3). In children without higher temperature or vomiting, immediate antibiotics made little difference to distress by day three (15% *v* 19%, $\chi^2 = 0.74$; $P = 0.39$) or night disturbance (20% *v* 27%, $\chi^2 = 1.6$; $P = 0.20$). Addition of cough did not significantly improve prediction of benefit.

Conclusion In children with otitis media but without fever and vomiting antibiotic treatment has little benefit and a poor outcome is unlikely.

Introduction

Although otitis media is one of the most common acute respiratory conditions managed in primary care, its treatment is controversial.¹⁻³ Most children will be prescribed antibiotics, but systematic review suggests that there is only marginal benefit.⁴

We determined the predictors of outcome from a randomised trial in primary care and assessed whether

these predictors identify those children who are likely to benefit from immediate antibiotics.

Methods

This study was part of a pragmatic randomised controlled trial of two prescribing strategies for acute otitis media.⁵

Sample

The participants were children aged 6 months to 10 years who were brought to their general practitioner with acute otalgia and otoscopic evidence of acute inflammation (dullness, cloudiness, erythema or bulging, perforation).

Exclusion criteria were otoscopic appearance consistent with crying or fever alone (pink drum); appearance and history more suggestive of otitis media with effusion and chronic suppurative otitis media; serious chronic disease; use of antibiotics for ear infections within the previous two weeks; previous complications (septic complications, hearing impairment); child too unwell to be left to wait and see (very unwell systemically with high fever, floppy, drowsy, not responding to antipyretics).

Intervention

Children were randomised to immediate antibiotics (amoxicillin or erythromycin for those allergic to penicillin) or delayed antibiotics. In the delayed antibiotics group parents were asked to wait for 72 hours after seeing the doctors before considering using the prescription. They were advised to use antibiotics if their child had severe otalgia or fever after 72 hours or if discharge lasted for 10 days or more. We used standardised advice sheets to maximise the support and placebo effect for each strategy and to ensure some consistency between groups, despite the personal prescribing preference of the doctor.⁵⁻⁷

Outcome measurement

The general practitioners recorded days of illness, physical signs, and antibiotic prescription. Parents used daily diaries to record the children's symptoms (earache, unwell, sleep disturbance), perceived severity of pain (from 1 (no pain) to 10 (extreme pain)), number of episodes of distress, number of 5 ml doses

of paracetamol used, and temperature and presence of cough, vomiting, rash, and diarrhoea.

Analysis

We assessed predictors of poor outcome using logistic regression. We then entered variables that were significant in univariate analysis at the 5% level by forward selection, starting with the most significant first, and retained those that remained significant at the 5% level. We then used variables that predicted poor outcome to identify clinical subgroups, estimated the effect of antibiotic in those subgroups, and summarised the effect by the number needed to treat.

Results

Symptom duration was documented in 285 children (90%). There were no differences in clinical characteristics between non-responders and responders.⁵

Predictors of poor outcome

Predictors of earache lasting for more than three days were ear discharge (adjusted odds ratio 2.6, 95% confidence interval 1.4 to 4.7), three or more previous courses of antibiotics compared with none (0.2, 0.1 to 0.5), and moderate compared with extreme satisfaction with the consultation (3.0, 1.3 to 7.1). However for children whose symptoms lasted over 72 hours earache was mostly mild (mean score 2.6), and interviews with parents suggested the outcomes that matter more to them are night time disturbance and episodes of distress.

Distress by day three was predicted by higher temperature (>37.5°C) recorded by parents on day one (4.5, 2.3 to 9.0), parental reporting of vomiting (2.6, 1.3 to 5.0), and cough (2.0, 1.1 to 3.8). Although prescription of antibiotics may confound these associations, this is unlikely as we have shown that randomisation group did not predict distress.⁵ Furthermore when we added randomisation group to the logistic model predicting distress, the estimates of all the predictive variables changed by less than 10% (odds ratios were 4.9 for temperature, 2.3 for vomiting, 2.1 for cough).

Night disturbance by day three was predicted by higher temperature recorded on day one (2.4, 1.2 to 4.8), vomiting (2.1, 1.1 to 4.0), cough (2.3, 1.3 to 4.2), and ear discharge (2.1, 1.2 to 3.9).

Benefit of immediate antibiotics

Children with a high temperature or vomiting were more likely to have poor outcomes by day three (table 1). These children represent the simplest way to target

Table 1 Outcome by day three children with otitis media in according to immediate or delayed treatment with antibiotics. Figures are numbers (percentage) of children

| | Immediate | Delayed | P value | NNTB (95% CI) |
|---|-----------|---------|---------|------------------------|
| Children with high temperature or vomiting* | | | | |
| Distress | 12 (32) | 27 (53) | 0.045 | 5 (2 to 83) |
| Disturbed nights | 10 (26) | 30 (59) | 0.002 | 3 (2 to 8) |
| Children without high temperature or vomiting* | | | | |
| Distress | 14 (15) | 19 (19) | 0.39 | 22 (7 to ∞ to NNTB 17) |
| Disturbed nights | 19 (20) | 20 (27) | 0.20 | 13 (5 to ∞ to NNTB 24) |
| Children with two of three symptoms† on day 1 | | | | |
| Distress | 11 (39) | 22 (55) | 0.20 | 6 (3 to ∞ to NNTB 12) |
| Disturbed nights | 9 (32) | 26 (65) | 0.008 | 3 (2 to 10) |

NNTB=number needed to treat to benefit; NNTB=number needed to treat to harm.

*Temperature as measured on day 1, vomiting on any day.

†High temperature, vomiting, cough.

antibiotics for clinicians and are a small minority. Immediate antibiotics resulted in less distress, fewer disturbed nights, and fewer days of crying. Children without higher temperature or vomiting on day one showed less benefit from immediate antibiotics (table 2). Cough also predicted distress and night disturbance by day three. Thus a simple alternative to targeting those with high temperature or vomiting could be to target children with two of the three symptoms: high temperature, vomiting, and cough. However, addition of cough to the symptom count made little difference to the ability to predict benefit from immediate antibiotics.

Discussion

Using data from a randomised controlled trial we found that children with a raised temperature and vomiting were more likely to be distressed or have disturbed nights three days after seeing the doctor and more likely to benefit from immediate antibiotic prescription.

Study limitations

We chose an open trial design and minimally intrusive outcomes (for example, no intrusive measures of compliance or investigation) to assess realistic outcomes after pragmatic prescribing strategies in everyday practice. However, this has the disadvantage of a potential placebo effect. Although the structured advice sheet approach that we used has been shown to reduce the placebo effect,⁶ a component of this effect may contribute to the apparent benefits from antibiotics. Any effect, however, was probably small: parental satisfaction with management did not predict distress and night disturbance, and adjustment for satisfaction or random-

Table 2 Outcome in children with otitis media in week after seeing doctor according to immediate or delayed use of antibiotics. Figures are means (SE)

| | Immediate | Delayed | Difference (95% CI) | P value | |
|---|-------------|-------------|-----------------------|---------|--------------|
| | | | | t test | Mann-Whitney |
| Children with high temperature or vomiting on day 1 | | | | | |
| Days of crying | 1.58 (0.15) | 2.82 (0.24) | 1.24 (0.68 to 1.81) | <0.001 | <0.001 |
| Disturbed nights | 1.95 (0.23) | 2.98 (0.26) | 1.03 (0.35 to 1.72) | 0.004 | 0.005 |
| Episodes of distress* | 0.94 (0.12) | 1.34 (0.22) | 0.40 (-0.10 to 0.90) | 0.11 | 0.71 |
| Children without high temperature or vomiting on day 1 | | | | | |
| Days of crying | 1.53 (0.13) | 1.93 (0.21) | 0.40 (-0.09 to 0.89) | 0.11 | 0.47 |
| Disturbed nights | 1.52 (0.15) | 2.03 (0.21) | 0.51 (0.05 to 1.02) | 0.05 | 0.10 |
| Episodes of distress* | 0.61 (0.08) | 0.55 (0.07) | -0.06 (-0.27 to 0.15) | 0.59 | 0.50 |

*Average per day.

isation group did not confound the estimates nor alter the inferences. Furthermore the estimates from this study (for example, night disturbance, consumption of paracetamol)⁵ were similar to those in the previous largest placebo controlled trial in primary care in a similar study population.⁸ As these data are based on secondary analysis, however, they require cautious interpretation.

Conclusions

Parents are most concerned about symptoms such as distress and night disturbance, both of which were predicted by systemic features (high temperature, vomiting) and cough.

The simplest method to target the minority of children at higher risk of poor outcome is to select those children with systemic features—that is, either high temperature or vomiting. This identifies children who are likely to benefit. Children without systemic features are unlikely to benefit from antibiotics. Whether it is worth treating children with systemic features immediately is debatable as many such children (about half) will still settle within 72 hours. Nevertheless, the results support doctors discussing the likely benefit of antibiotics in systemically unwell children and possibly shortening the delay period from 72 hours to 48 or 24 hours.

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What is already known on this topic

Most children with otitis media will not benefit symptomatically from immediate use of antibiotics

It is unclear which children are more likely to benefit from antibiotics and which features predict poor outcome

What this study adds

Children with high temperature or vomiting were more likely to be distressed or have night disturbance three days after seeing the doctor

Children with high temperature or vomiting were more likely to benefit from antibiotics, although it is still reasonable to wait 24-48 hours as many children will settle anyway

Children without high temperature or vomiting were unlikely to have poor outcome and unlikely to benefit from immediate antibiotics

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Commentary: research directions for treatment for acute otitis media

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Some children are greatly troubled with acute otitis media; others are hardly inconvenienced. This useful subgroup analysis predicts which children benefit most from antibiotics for acute otitis media (mostly those with a temperature $>37.5^{\circ}\text{C}$ or vomiting; about one in five affected children) and the size of the benefit (the number of children we need to treat to shorten the illness is as high as three to six). So we still need to weigh potential benefits against costs, case by case, mixing parental preference and other relevant clinical and psychosocial information into the clinical decision.

General practitioners may worry about withholding antibiotics because of past indoctrination with deductive pathophysiology (“the pain of otitis media is caused by infection in the middle ear, the causative agents are susceptible to the following antibiotics...”). The empirical evidence, however, is that antibiotics

make little difference. They may also worry about the risk of dangerous suppurative complications. Should another study be undertaken to address this? There are so few cases of acute mastoiditis, the most common complication, that such an analysis would require huge numbers. Data from a large observational study of 4860 cases of acute otitis media showed that initially withholding antibiotics from those without severe symptoms led to no extra cases of mastoiditis.¹

Could this study be the end of the story? We don't think so. Firstly, there remain problems with the outcomes measured. We are interested in two vectors of illness in spontaneously remitting illness: the duration of illness (which Little et al measured) and its severity. Severity is harder to measure. Together severity and duration give a measure of “severity days” that more accurately describes the impact of the illness.

Measuring changes on just one axis will considerably underestimate the effect of an intervention on the burden of illness. Future research should collect serial data on severity to estimate changes in "total illness."²

Secondly, for trials of a new intervention the control is usually nothing (placebo). But for trials of antibiotics for acute respiratory infections the established treatment is already antibiotics. These then are trials of "no antibiotics" (the "new" intervention) against "antibiotics." Therefore patients recruited are likely to be the least ill. Re-examining the trials in a Cochrane review³ we could extract this "non-recruitment because the child was too ill" out of the total recruited from only two of the seven trials (52/232 and 27/240). We need a greater understanding of how selection of patients for trials may affect the interpretation and application of results.

We also have surprisingly little information about alternative treatments. With spontaneously remitting

illnesses such as acute otitis media, killing bacteria ("cure") has no advantage over palliating the symptoms.² We know that antihistamines and decongestants contribute modest, if any, benefit.⁴ But which is the best analgesic? Is anything else helpful? Innovative emerging treatments, such as using benign commensals to overwhelm pathological bacteria, may ultimately prove the most effective treatment for acute otitis media⁵ and make the current debate over antibiotic use redundant.

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Prescribing of lipid lowering drugs to South Asian patients: ecological study

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Coronary heart disease is the major cause of morbidity and mortality in the South Asian population in the United Kingdom, and its incidence is higher than in the white population.¹ This excess risk seems to be determined by a combination of metabolic factors leading to the insulin resistance syndrome, psychosocial factors, and established risk factors.² Ten out of 15 coronary risk factors measured were reported to be higher in South Asian patients than in their European counterparts, and several of these factors are believed to reflect relative deprivation. South Asian people are also at risk owing to high triglyceride concentrations and low concentrations of high density lipoprotein cholesterol. Although substantial evidence shows the value of lowering cholesterol in people at risk, studies have shown that many patients are not receiving appropriate treatment.³ We investigated the relation between ethnicity and prescribing of lipid lowering drugs.

Methods and results

We approached all general practices in one health authority to obtain consent to use their prescribing analyses and cost data for 1996-7. Sixty two (63.9%) of 97 practices gave consent. We obtained the following information for each practice from the health authority: proportion of South Asian patients in the nested age bands 35-69, 40-69, 45-69, 50-69, and 55-69, identified by using name based analysis software (Nam Pehchan)⁴; whether single handed or group practice; proportion of general practitioners of South Asian origin; fundholding status (particularly relevant at the time); Jarman index (surrogate measure for practice workload) for the practice's council ward; and Townsend score (measure of deprivation) for the ward. Comparative analyses of these

demographic factors for each practice showed that consenting and non-consenting practices did not differ significantly (table).

We determined the number of defined daily doses of all lipid lowering drugs prescribed per 1000 South Asian patients in each nested age band for each consenting practice. We used multiple regression analysis (backward and forward selection techniques) to explore the relation between the number of defined daily doses prescribed per 1000 patients (aged 35 to 69) and the practice characteristics. Because of non-linearity and heteroscedasticity of the residual errors, we reanalysed the data after logarithmic transformation of the response variable. We identified two practices as extreme cases (as defined by SPSS) and excluded them from the analysis.

The median number of defined daily doses per 1000 patients was 4775 (interquartile range 2592 to 7336). Owing to strong correlation, we analysed Townsend score and Jarman index separately. The table shows the factors ranked in order of importance for predicting volume of prescribing, with Townsend score included. The parsimonious model includes only the percentage of South Asian patients and deprivation of the practice ward. The negative regression coefficients indicate reduction of prescribing levels with increasing numbers of South Asian patients and levels of deprivation. The results were not significantly changed by use of the various nested age bands or by replacement of Townsend score with Jarman index.

Comment

Patients in practices with a greater South Asian population are less likely to be prescribed lipid lowering

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