SAMPLE PROJECT

The efficacy of antibiotics in ameliorating symptoms of acute otitis media in very young children

1. Background Data (Medical Context for Question)

During my Family Medicine rotation, I found that one of the most common reasons for children to visit their Family Medicine physician was for generalized illness with earache. The children's caretakers (usually their mother) would often request antibiotics – sometimes, even before they stated that they believed their child had an ear infection.

We spent much of our time in clinic trying to help parents understand that their child would get well without antibiotics. Although most of the children we saw with acute otitis media were five- to seven-year-olds, A.W. was a 22-month-old toddler. Ms. W. brought him to clinic because he had been irritable and more 'clingy' than usual over the past few days, had been eating less, and the evening before had started to run a temperature for which he received baby Tylenol. His sister had recently recovered from a head cold, and Ms. W. suspected that A.W. might have contracted his sister's illness.

On physical exam, A.W. was a shy, well-nourished boy who insisted on remaining with his mother and cried throughout the attempt to examine him. With friendly yet firm persistence by the physician and Ms. W.'s cooperation, the physical exam was completed. Though slightly warm to the touch and with reddened cheeks that could have been from crying, A.W. was afebrile. His eyes were without discharge. His pupils were equal and reactive to light, and extra-ocular eye movements were intact. The nostrils were congested with nasal discharge. The right eardrum appeared normal, and the tympanic membrane was opaque with a normal cone of light. The left tympanic membrane was slightly erythematous and bulged outward, with no discharge or other abnormality noted in the ear canal. A.W. strongly resisted exam of both ears. While crying, his erythematous posterior pharynx was seen. Mucous membranes were moist. A.W.'s lungs were difficult to hear due to crying, but there was good air movement. Heart was regular rate and rhythm. Abdomen was soft, non-tender and non-distended. Pulses and strength in the extremities were normal.

A.W. was sent home without antibiotics, with instructions for his mother regarding symptomatic relief and hydration. A.W.'s case caused me to remember the story my parents often tell of the time I had a painful ear infection as a toddler. According to my parents, I was treated with 'some kind of antibiotics.' I began to think about how we had not given antibiotics to A.W. while I had received them when I was nearly the same age so long ago. As a result, I framed the clinical question below.

2. Clinical Question

My question is of the therapy/prevention type. It is as follows:

> What is the efficacy of antibiotics in ameliorating symptoms of acute otitis media in very young children?

3. List the articles identified in the literature search and the one I used.

Please see attached list of articles. The article I used is number 15 on the list. It is entitled:

> Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years. *British Medical Journal*, February 5, 2000, Vol 320 No. 7231, 350-4.

4. Are the results of the study valid?

(Discuss using primary / secondary guides.)

Primary Guides:

Was the assignment of patients to treatment/prevention randomized?

The study was performed in the Netherlands on children aged between six and 24 months who presented to their general practitioner with acute otitis media between 1996 and 1998.

After parental consent was obtained during the first visit, the assignment of patients to treatment was randomized using computerized two-block randomization. Access to the allocation schedule was possible only from the pharmacy of the University Medical Centre in Utrecht. The schedule was protected by computerized code and accessed only if severe complications or side effects occurred in a patient.

The study randomized patients between two arms: treatment with amoxicillin suspension, 40 mg/kg, three times daily for 10 days, or an identical-appearing placebo suspension.

Were all the patients who entered the trial properly accounted for and attributed at its conclusion?

Was follow-up complete?

All patients were properly accounted for and attributed, even though 12 (five percent of the study population) were lost to follow-up over the six weeks of the study. This is presented very clearly in a figure labeled “Trial profile and participant flow” in the paper, and is discussed in the results section as well. Of a total of 240 patients, 117 received amoxicillin and 123 received placebo. Fifteen of the patients (four who were supposed to receive amoxicillin and 11 who were supposed to receive placebo) were allocated as having failed treatment because they took other antibiotics instead. One of the patients receiving placebo was admitted to the hospital due to worsening symptoms. Twelve patients (six each receiving amoxicillin and placebo) were lost to follow-up. The number of patients with the full 42 days’ worth of data for the trial was 107 in the amoxicillin group and 105 in the placebo group.

Were patients analyzed in the groups to which they were randomized?

Yes. The investigators checked the robustness of their conclusion that amoxicillin did not significantly impact the clinical course of acute otitis media. They constructed a ‘best case’ scenario, in which those with incomplete data in the group receiving amoxicillin were assumed to be cured and the incomplete cases in the placebo group were not cured. The analysis did not change the study results.

Secondary Guides

Were patients, health workers, and study personnel 'blind' to treatment/prevention?

Yes. The paper states that the amoxicillin suspension and the placebo suspension looked and tasted the same. The authors also state that "doctors, parents, and investigators remained blinded throughout the study" (p. 351).

Were the groups similar at the start of the trial?

Yes. Table 1 in the paper, titled "Baseline characteristics of 240 children randomised in trial of antibiotic use for treatment of acute otitis media" (p. 352), shows the number of children in each treatment arm that have various characteristics. I have calculated the percentage of each group belonging to each category in the two tables below. The first table shows the categories in which the two groups are most similar.

	Percent of Patients in Group	
	Amoxicillin	Placebo
Male Patients	55%	54%
Breastfed for over six months	18%	18%
Presented between October and March	65%	64%
Symptoms:		
Earache	70%	67%
Fever	68%	65%
Perforated ear drum	15%	17%
Bilateral acute otitis media	64%	62%
Bulging ear drum	22%	24%

Mean age of 13.3 months is identical for both groups.

Differences between the groups of more than three percentage points are in the categories presented below.

	Percent of Patients in Group	
	Amoxicillin	Placebo
Two or more children in family	26%	20%
Smoker in household	39%	32%
Attends day care	24%	15%
Recurrent URTI	32%	27%
Recurrent AOM in family	22%	27%
Recurrent AOM in patient	28%	41%
Allergy	12%	7%
Presented after 3 or more days of illness	49%	44%

Patients were excluded from the trial for the following reasons:

antibiotic treatment in the previous four weeks; proved allergy to amoxicillin; compromised immunity; craniofacial abnormalities; Down's syndrome; or being entered in this study before (p. 350).

Aside from the experimental intervention, were the groups treated equally?

Yes. Except for the difference in receiving actual amoxicillin or a placebo suspension, patients were treated equally. All patients were allowed equal symptomatic treatment, including one drop of decongestant nose spray in each nostril three times daily and use of paracetamol to relieve pain. Patients under one year old received a 120 mg paracetamol suppository, and patients over age one received twice that amount. Parents of all patients kept a diary recording amount of paracetamol used and progression of illness. All patients returned to the general practitioner for follow up on days four and 11, and were visited by the main study investigator at their house six weeks after their initial presentation to the physician.

5. What were the results?

How large was the treatment/prevention effect?
How precise was the estimate of the treatment effect?

The table on the following page includes calculations of the treatment effect in terms of risk and risk reduction, as well as the 95% confidence intervals and P-values reported in the paper for the absolute risk reduction.

Additional outcome measures and accompanying P-values that were reported in the paper are shown below.

Median time to cessation of fever	P-value (log-rank test)
Amoxicillin Group: Two days	0.004
Placebo Group: Three days	
Median time to cessation of pain or crying	P-value (log-rank test)
Amoxicillin Group: Eight days	0.432
Placebo Group: Nine days	
Mean analgesic consumption, first three days	P-value (Mann-Whitney U test)
Amoxicillin Group: 1.7 doses	0.018
Placebo Group: 2.5 doses	
Analgesic consumption, first ten days	P-value (Mann-Whitney U test)
Amoxicillin Group: 2.3 doses	0.004
Placebo Group: 4.1 doses	

Number Needed to Treat

The paper states that seven to eight children need to be treated with amoxicillin in order to improve symptoms at day four in one child. The number needed to treat can be derived in the following manner:

NNT = 1/(Absolute Risk Reduction) = 1/0.13 = 7.69.

I derived the number needed to treat for all categories in the following table.

Size of Treatment Effect						Precision of Treatment Effect	
Outcome	Percent with Outcome	Absolute Reduction	Number Needed to Treat	Relative Reduction	Relative Risk Reduction	P Value	95% CI
Persistent Symptoms at Day Four							
Amoxicillin Group	59%	72%-59%= 13%	1/.13= 7.69	72%/59%= 1.22	1-1.22= -.22 |-.22|x100%=22%	0.03	(1 to 25)
Placebo Group	72%						
No Ear Drum Improvement by Day Four							
Amoxicillin Group	77%	83%-77= 6%	1/.06= 16.66	83%/77%= 1.08	1-1.08= -.08 |-.08|x100%=8%	0.30	(-4 to 16)
Placebo Group	83%						
Treatment Failure at Day 11							
Amoxicillin Group	64%	70%-64= 6%	1/.06= 16.66	70%/64%= 1.09	1-1.09= -.09 |-.09|x100%=9%	0.35	(-6 to 18)
Placebo Group	70%						
Middle Ear Effusion Present at Six Weeks							
Amoxicillin Group	64%	67%-64= 3%	1/.03= 33.33	67%/64%= 1.05	1-1.05= -.05 |-.05|x100%=5%	N/A	(-10 to 16)
Placebo Group	67%						

6. Will the results help me in caring for my patients?

Can the results be applied to my patient care?

Yes, the results can be applied to patients such as the little boy in section one. A.W. meets all of the inclusion criteria. He falls in the correct age range, has presented to his primary care doctor after symptoms for several days, and has a similar clinical appearance of acute otitis media as patients in the study. A.W. does not violate any of the exclusion criteria. He has not been given antibiotics in the last month, and does not have an allergy to antibiotics, a craniofacial abnormality, or Down's syndrome.

I agree with the study investigators' conclusion that antibiotics do not significantly impact recovery from acute otitis media in very young children. Treatment with amoxicillin was statistically significantly different from treatment with placebo in only the following three of the eight outcome measures studied: median duration of fever, mean analgesic consumption during the first ten days, and alleviation of symptoms by day four. Even in these categories, amoxicillin's clinical effect was small. It decreased the median duration of fever by only one day, and symptoms were still present by day four in only 13% fewer patients. Although it reduced analgesic consumption by nearly half over ten days, the reduction of doses in absolute numbers (from four to two doses over ten days) is too small to be clinically important. Since the outcomes of the other five measures were not statistically significant, it is likely that any benefit seen from the use of amoxicillin in these categories is due purely to chance.

Were all clinically important outcomes considered?

Yes. The outcomes reported above measured potential benefits of amoxicillin. However, study investigators also measured new-onset diarrhea, a possible harmful side effect of amoxicillin. Although new-onset diarrhea occurred more frequently in the group receiving amoxicillin, the differences between the amoxicillin and placebo groups were not statistically significant. Study results are shown in the table on the following page.

Finally, investigators looked at the amount of medication actually taken in each group, a possible source of bias in the study. They found no significant difference in compliance between the groups. The study reports that eighty percent of children in both groups received the full amount prescribed. An additional 15 percent received 95% of the amount prescribed.

Size of Treatment Effect						Precision of Treatment Effect	
Outcome	Percent with Outcome	Absolute Reduction	Number Needed to Treat	Relative Reduction	Relative Risk Reduction	P Value	95% CI
Diarrhea at Day Four							
Amoxicillin Group	17%	17%-10%= 7%	1/.07= 14.29	17%/10%= 1.70	1-1.70= -.70 |-.70|x100%=70%[1]	N/A	-16 to 2
Placebo Group	10%						
Diarrhea at Day Ten							
Amoxicillin Group	12%	12%-8%= 4%	1/.04= 25	12%/8%= 1.50	1-1.50= -.50 |-.50|x100%=50%[1]	N/A	-12 to 4
Placebo Group	8%						

[1] Note that, since diarrhea is a negative outcome, the relative risk reductions in these cases should be interpreted as 70% and 50% decreased chances of getting diarrhea if patients take placebo rather than amoxicillin. However, since the 95% confidence interval includes zero in both cases, neither number can be considered a statistically significant effect.

Are the likely treatment benefits worth the potential harms and costs?

I calculated the cost of treatment based on the fact that seven to eight children need to be treated to alleviate symptoms at day four in one child, and that the cost of a 150 ml bottle of amoxicillin (250 mg/5 ml) is $7.99 according to epocrates.com. Assuming that the average two-year-old weighs about 26 lbs and that the course of treatment is 10 days, a two-year-old would require:

26 lbs. = 11.8 kg

40 mg/kg = 11.8 kg x 40 mg = 472 mg per dose

472 mg / (250mg / 5ml)= 9.44 ml per dose (about 1.89 teaspoons)

9.44 ml / 150 ml = 15.9 doses per bottle

3 doses per day x 10 days = 30 doses

Each child would need two bottles, or $7.99 x 2 = $15.98 worth of medicine. If seven children must be treated for every one that experiences beneficial effects, then ($15.98 x 7) = $111.86 would have to be spent to alleviate symptoms in a single child. When possible side effects such as diarrhea or allergic reactions to the medication are also considered, it does not seem either cost-effective or worthwhile to use amoxicillin to treat very young children who present to their general practitioner with acute otitis media. As the study investigators state, the number needed to treat "is not sufficiently important clinically to prescribe antibiotics for every affected child within this age group (p 353)."