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Comparison of Amoxicillin/Clavulanate High Dose to Cefdinir in Treatment of Acute Otitis Media

Janet R. Casey, MD¹, Stan Block, MD², Jim Hedrick, MD², Anthony Almudevar, Ph.D⁴, and Michael E. Pichichero, MD^{1,5}

¹Legacy Pediatrics, Rochester NY

²Kentucky Pediatric Research, Bardstown, KT

³University of Rochester School of Medicine, Rochester NY

⁴Department of Biostatistics & Computational Biology, Rochester NY

⁵ Rochester General Research Institute, Rochester NY

Abstract

Objective—To compare the clinical efficacy of amoxicillin/clavulanate high dose (Amox/clav HD) as 10 days therapy to cefdinir as 5 days therapy for acute otitis media (AOM).

Study Design—Diagnosis of AOM was based on specific criteria by validated otoscopists at 2 AOM research centers. The outcome measure was resolution of all symptoms and signs of AOM except persistence of middle ear effusion at test-of-cure (TOC) 12-15 days after antibiotic treatment .

Results—330 children (x = 13.1 months) with AOM were studied. At TOC 256 children were cured, 69 failed and 5 were lost to follow-up. Amox/clav HD-treated children had a better cure rate (86.5%) than cefdinir (71.0%), p=0.001. Clinical outcomes showed that amox/clav HD was correlated with more frequent cure outcomes and that cefdinir was correlated with less frequent cure outcomes as children increased in age between 6 and 24 months.

Conclusion—When children have bona fide AOM an assessment of outcome is judged by validated otoscopists. 10 days amox/Clav HD is significantly more effective than 5 days of cefdinir as therapy for AOM. A trial comparing 10 days of cefdinir may have led to a different conclusion.

Keywords

Acute otitis media; Scoring systems; amoxicillin; cefdinir; antibiotics; clinical trial

Introduction

In 2004, the American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP) recommended amoxicillin/clavulanate high dose (amox/clav HD) and cefdinir as preferred antibiotics for treatment of children with acute otitis media (AOM)¹. The forthcoming 2011 AAP/AAFP guidelines will make the same recommendation. In this paper we describe head-to-head comparison of amox/clav HD vs. cefdinir as 10-day and 5-

day treatments, respectively for AOM in children. Both are approved antibiotics and the studied durations of treatment are approved regimens by the US FDA.

Methods

Study Setting, Population and Design

The study took place at Legacy Pediatrics in Rochester, NY and Kentucky Pediatric Research in Bardstown, KY. Both sites had 2 investigators who are validated expert otoscopists. The socio-demographics of the patient populations of the 2 sites differ. Legacy Pediatrics cares for a predominantly suburban, higher socio-economic status (SES) population. The Bardstown Pediatric Group cares for a predominantly rural, lower SES population. The study was conducted from January 2003-May 2005 with the four validated otoscopists completing the symptom scoring instruments (JC, SB, JH and MP).

Study Design

This was a prospective, randomized, investigator blind trial that included children ages 6 to 24 months with AOM enrolled from two sites. The diagnosis of AOM was based on examination with pneumatic otoscopy that identified a bulging or full tympanic membrane (TM); and purulent middle ear effusion, and reduced TM mobility as documented by both pneumatic otoscopy and an abnormal tympanogram as evidenced by a “B” or “C” curve. Symptoms of otalgia, irritability, anorexia, and fever were assessed at diagnosis and test-of-cure (TOC). The study was conducted from January 2003-May 2005 and 4 of the authors were the clinical investigators who made the diagnosis of AOM on study entry and the determination of clinical outcome at TOC (JC, SB, JH and MP). The study was approved by an investigational review board (Western IRB, Seattle WA) and written informed consent was obtained.

Exclusion criteria—Children with chronic otitis media, chronic middle ear effusion, ventilation tubes, perforated tympanic membranes or otorrhea and patients with “A” curves and “B” curves with obvious dry perforation (high volume) were excluded.

Antibiotic treatment was amox/clav HD (dose 80 mg/Kg/day amoxicillin divided twice daily) or cefdinir (dose 14 mg/Kg/day divided twice daily). Amox/clav HD was given for 10 days and cefdinir for 5 days. Each AOM research site used an independent computer-generated random number table to allocate subjects. There were 2 assessment visits when symptoms and signs were recorded: one at the time of diagnosis and a second at the TOC visit 12-15 days later. The same otoscopist did both assessments for each child. The determination of compliance was monitored by use of a MEMS Cap dispenser and per protocol analysis required a minimum of 80% compliance with the prescribed dosing regimen.

Clinical outcome

Subjects were classified with a global overall assessment as clinical cure, failure, or indeterminate at TOC as follows:

Clinical cure—Subject had received the prescribed dosing regimen during the first 72 hours of study. Body temperature at the visit was $\leq 38^{\circ}\text{C}$ if temperature was measured rectally or ear/aural $\leq 37.5^{\circ}\text{C}$ if measured orally or $\leq 37.3^{\circ}\text{C}$ if measured axillary. Otoscopic examination of the tympanic membrane was rated as improved by the investigator at the visit, with no evidence of fullness or bulging of the tympanic membrane; presence of middle ear effusion was acceptable. No antibiotic was given for AOM on or before the last day of

the visit window. No surgical procedure was performed for AOM on or before the last day of the visit window. No indeterminate criteria apply.

Clinical failure

Subjects were considered to be a failure at the TOC visit if the subject had received the prescribed dosing regimen during the first 72 hours of study, did not meet any other indeterminate criteria and 1 of the following conditions were met: An antibiotic was prescribed for AOM; or a surgical procedure was performed for AOM on or before the last day of the visit window; or there was evidence of fullness or bulging of the tympanic membrane; or perforation of tympanic membrane; or the subject had unsatisfactory resolution of signs and symptoms of AOM according to the investigator.

Indeterminate

A subject was classified as indeterminate at the TOC visit and censored in the analysis at TOC if: less than 80% of the prescribed treatment was taken; or inadequate data to assess clinical outcome due to lack of follow up.

Statistics

Boxplots were used to summarize location and variability of the sample of measurements. The lower and upper sides of the box represent the 25th and 75th percentile. The centerline represents the median. The extensions to the box indicate the range of the data after removing outliers, while outliers are indicated individually. An outlier is defined to be any value more than 1.5 times the interquartile range (the height of the box) from the median.

Results

Three hundred thirty children were enrolled in the study; their average age was 13.1 months (SD= 4.9 months). One hundred five and 225 children were enrolled at the NY and KY sites, respectively. Three hundred twenty-five children were evaluated at the test-of-cure visit and 5 subjects were lost to follow up.

Table 1 shows the global clinical outcome for the two antibiotic regimens. The clinical cure rates for amox/clav HD, 86.5% and cefdinir, 71.0% were statistically significant, $p=0.001$.

Figure 1 shows an analysis of the variation in dose of amox/clav HD and cefdinir according to the age of the child. There is a significant difference between the two antibiotics ($p<0.002$). The change in efficacy of amox/clav HD between the ages of 6 and 24 months of the children treated did not impact the global cure rate ($p=0.8$). In contrast, there was a change in efficacy of cefdinir between the ages of 6 and 24 months of the children treated did impact the global cure rate ($p=0.01$). In Table 2 the odds ratios of clinical cure is estimated from a logistic regression model. For each increasing month of age, for amox/clav HD the odds for cure remained stable. For cefdinir treatment the odds for cure significantly declined for each month of age ($p=0.01$). Thus if age 6 months is considered an odds of cure to be 100%, then one month later the odds for cure decreases to 93.2% (95% CI = 88.1%, 98.8%) and one month later decreases by another 93.2% compared to the prior month.

Table 3 shows the symptoms and otoscopic signs at the initial and test-of-cure visits at the two study sites. Given the age of the study children, at the initial visit the majority could not complain of ear pain but more than half had a history of irritability. Nearly 100% of subjects had TM erythema, decreased mobility, abnormal effusion color and a full/bulging TM. At the TOC visit, 256 (77%) children were cured and 69 (21%) were classified as treatment

failure. Nearly all signs of AOM were absent at the test-of-cure visit in the cured children with the exception of decreased TM mobility, reflecting persistence of middle ear effusion.

Discussion

Amox/clav HD and cefdinir are recommended first and/or second line antibiotic choices for AOM in children according to the recommendations of the AAP/AAFP guideline for AOM management. Although there have been prior studies of amox/clav and cefdinir as treatment of AOM^{2,3} this is the first study, to our knowledge, where amox/clav HD for 10 days has been compared to cefdinir for 5 days, both approved regimens for AOM in children. The superior outcome for 10 days amox/clav HD over 5 days of cefdinir could be predicted by in vitro testing of the drugs against the dominant otopathogens of AOM⁴. Although tympanocentesis was not performed in this trial, the pathogen mix and antibiotic susceptibility of those pathogens has been extensively characterized over long time periods at both centers, including in the contemporaneous time of the current study⁵⁻⁷. The better efficacy of amox/clav HD we observed must be taken in context that these children were in a clinical trial where compliance is very high. In comparison, in every day clinical practice the higher gastrointestinal upset and diarrhea from amox/clav HD and the marginal taste of amox/clav HD are factors to be considered in prescribing for children^{1,8}.

This study has strengths and limitations. The study design was prospective, randomized, and investigator blinded. The 4 participating clinicians in this study are highly skilled, validated otoscopists and therefore the clinical diagnosis made at study entry and at TOC would likely have a high correlation (>90% for all 4 investigators, data not shown) with tympanocentesis results. Entry into AOM clinical trials based on a clinical diagnosis and outcome assessment has the potential to result in the “Polyanna phenomena”⁹. Indeed such a study design has the potential to disguise true differences in antibiotic comparative trials when sample sizes are small. However in this study the sample size proved adequate to show a statistically significant difference between the two drugs. We contend that this may have occurred because of the skill of the otoscopists in diagnosis at study entry and at TOC. Furthermore, a recent multicenter, open label, double tympanocentesis study of AOM among 447 children at risk for persistent and recurrent AOM higher doses of cefdinir (25 mg/Kg/day once daily for 10 days) was described by Arguedas et al.¹⁰ They found that at higher doses for a longer time interval the bacteriologic eradication rate, based on repeat tympanocentesis was achieved in 91%, 67% and 43% for *S. pneumoniae* that were penicillin susceptible, intermediate and resistant, respectively.

In conclusion, our results suggest that 10-day treatment amox/clav HD is a more effective antibiotic regimen compared to 5 days of cefdinir for AOM in young children. The findings also suggest that the efficacy of cefdinir decreases as a child ages between 6 and 24 months. We recognize that in clinical practice (unlike in a controlled clinical trial) that efficacy of an antibiotic also depends on compliance and that the compliance features of cefdinir are superior to those of amox/clav HD and that this difference is another important factor in antibiotic selection¹. A trial comparing 10 days of cefdinir may have led to a different conclusion.

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Logistic Model

Figure 1. Predicted cure rates for logistic regression model (with separate age slopes for each drug). Sample estimates of cure rate grouped into 4 age bins are superimposed.

Table 1

Global Assessment of Clinical Cure Rate by Amox/Clav HD versus Cefdinir

	Amox/Clav HD	Cefdinir
cure	141	115
failure	22	47
cure rate	86.5%	71.0%

Chi-square = 10.8, df = 1, p-value = 0.001

Table 2

Odds ratios estimated from logistic regression model, given per increasing month of age, for amox/clav HD and cefdinir treatment groups.

	Odds ratio for cure / month of age	95% CI	P value
Amox/clav HD	0.992	(0.932, 1.056)	> .05
Cefdinir	0.932	(0.881, 0.986)	=.01

Table 3

Percentage of patients with the Symptoms and Otoloscopic signs at the initial diagnosis visit and at the test-of-cure visit at the two study sites.

Symptom & Otoloscopic Signs	Initial Visit		Test-of-cure Visit	
	NY site n=105	KY site n=225	NY site n=102	KY site n=223
	Percent of patients	Percent of patients	Percent of patients	Percent of patients
Fever	37%	23%	5%	8%
Ear pain	42%	47%	5%	11%
Irritability	53%	63%	12%	18%
Temperature	9%	11%	4%	1%
TM Erythema	80%	96%	6%	22%
Reduced TM Mobility	98%	100%	48%	38%
Abnormal Effusion Color	97%	99%	16%	24%
TM Full/Bulging	99%	96%	9%	21%
Otorrhea	2%	5%	0%	2%
Perforation	0%	1%	0%	0%

TM = tympanic membrane