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REVIEW ARTICLE

Reported Rates of Diarrhea Following Oral Penicillin Therapy in Pediatric Clinical Trials

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OBJECTIVES: Antibiotic-associated diarrhea (AAD) is a well-recognized adverse reaction to oral penicillins. This review analyzed the literature to determine the incidence of AAD following amoxicillin, amoxicillin/clavulanate, and penicillin V oral therapy in pediatric clinical trials.

METHODS: An advanced search was conducted in MEDLINE and Embase databases for articles in any language reporting the incidence of AAD following oral penicillin therapy for any indicated infection in children (0-17 years). The search was limited to clinical trials. Articles were excluded if treatment was related to chronic conditions, involved concomitant antimicrobials, or if the dose or number of patients was not specified.

RESULTS: Four hundred thirty-five articles relating to clinical trials were identified (307 from Embase; 128 from MEDLINE). Thirty-five articles reporting on 42 studies were included for analysis. The indications included acute otitis media, sinusitis, pharyngitis, and pneumonia. Thirty-three trials reported on amoxicillin/clavulanate, 6 on amoxicillin, and 3 on penicillin V. In total, the 42 trials included 7729 children who were treated with an oral penicillin. On average, 17.2% had AAD. Data were pooled for each penicillin. The AAD incidence was 19.8% for amoxicillin/clavulanate, 8.1% for amoxicillin, and 1.2% for penicillin V. The amoxicillin/clavulanate data were analyzed according to formulation: pooled-average. The incidence of ADD was 24.6% for the 4:1 formulation, 12.8% for the 7:1 formulation, 19.0% for the 8:1 formulation, and 20.2% for the 14:1 formulation.

CONCLUSIONS: These results demonstrate substantially increased incidence of AAD following use of amoxicillin/clavulanate, compared to use of amoxicillin and penicillin V, as well as varying AAD rates with different amoxicillin/clavulanate formulations. These findings warrant consideration when prescribing. The underlying mechanisms of AAD in children remain unclear.

INDEX TERMS: amoxicillin, amoxicillin/clavulanate, antibiotic, antibiotic-associated diarrhea, oral penicillins, penicillin V

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INTRODUCTION

Oral penicillins are the most commonly prescribed antibiotics for children worldwide. Specifically, amoxicillin is the recommended first-line therapy for acute otitis media (AOM), the most common childhood infection for which antibiotics are prescribed in the United States.[1] While there have been numerous studies on the effectiveness of different antibiotics for common childhood infections, the risk of adverse effects from antibiotic treatment (with the exception of allergy) has been less well studied.[2] In the short term these effects include diarrhea and vomiting; in the longer term, antibiotic resistance. As a result, there is a need for increased awareness of these effects so that clinicians can routinely communicate these to parents at the time of prescribing and to further define the benefit-to-harm balance in antimicrobial prescribing.

Diarrhea is one of the most significant short-term adverse effects of antibiotic therapy. When it occurs in conjunction with antibiotic use, in the absence of any other cause, it is referred to as antibiotic-associated diarrhea (AAD).[3] In order to ascertain the incidence and risk factors

for AAD in children, this review considers the reported mechanisms of AAD and then reports the diarrhea rates in clinical trials in children prescribed oral penicillins. The results of this review are presented in the form of a diarrhea rate chart for each oral penicillin so that clinicians can advise parents of the expected rate and risk factors for diarrhea with respect to the penicillin prescribed. Finally, we discuss how AAD in children can be effectively managed and prevented.

ANTIBIOTIC-ASSOCIATED DIARRHEA

Pathophysiology of AAD

The spectrum of AAD ranges from mild symptomatic loose stools to life-threatening colitis.[4] Unfortunately, very few studies have been performed on the mechanisms underlying AAD in children. As with adults, the most commonly cited mechanism for AAD is intestinal overgrowth with pathogenic microorganisms, especially *Clostridium difficile,* following alterations to the normal intestinal flora induced by antibiotics. However, in a study from 1996[5] that evaluated AAD and *C difficile* in stool specimens from children before and after a 10-day amoxicillin/clavulanate course for AOM, only 27% of children with amoxicillin/clavulanate–related AAD were positive for *C difficile* toxins on enzyme immunoassay; none of the affected children had *C difficile* toxins on enrollment. Other mechanisms for AAD are therefore hypothesized to include antibiotic-induced disturbance to the functions of the normal intestinal flora and to gut motility. These 3 mechanisms are described below.

Disturbance to Functions of Normal Flora

In adults 2 key disturbances have been described.[4,6] Although it is likely that these also occur in children, further studies will be needed to verify this. First, various antibiotics (including ampicillin) have been reported to reduce the fermentation of carbohydrates by colonic bacterial flora. As a result there is an increase in undigested carbohydrates in the colon, leading to an osmotic diarrhea. Second, owing to the reduced carbohydrate fermentation, there is a deficiency in the short chain fatty acid (SCFA) metabolites from this process, which normally stimulate salt and water reabsorption in the colon. This lack of SCFAs can lead to profuse diarrhea.

Impact on Gut Motility

It is thought likely that the clavulanate component of amoxicillin/clavulanate stimulates peristalsis in children, leading to increased intestinal motility, and that a reduced clavulanate component will reduce diarrhea rates.[7] This is discussed further in the "Drug and Dose" section below.

Overgrowth with Pathogenic Microorganisms

Antibiotics, especially penicillins, cephalosporins, and clindamycin, have been reported[6] to alter intestinal flora and amino acid contents. As a result, microorganisms, including *C difficile, Clostridium perfringens, Salmonella, Staphylococcus aureus,* and *Klebsiella*, which are usually kept in check by a combination of bacterial antagonism and mucosal defenses, become pathogenic.[6] In this regard, it has been reported[8] that up to 70% of infants may be asymptomatically colonized with non-pathogenic, commensal *C difficile* but that this colonization rate decreases with age, reaching adult levels in children older than 2 years. However, recent studies[8,9] have demonstrated that the US rate of pediatric *C difficile*–related hospitalizations increased from 7.24 to 12.80 from 1997 to 2006, with an increase in the severity of infection due to a new hypervirulent strain. Interestingly, an increasing proportion of children with *C difficile* infection (CDI) have community-associated disease, and with many of these infections there has been no history of antibiotic use. Importantly, while CDI symptoms usually develop 4 to 10 days after the initiation of antibiotic therapy, they can also take several weeks to develop after discontinuation of antibiotics.[8]

CLINICAL TRIALS OF ORAL PENICILLINS

Literature Search and Study Selection

Our review focused on AAD in children arising from the use of oral preparations of amoxicillin, amoxicillin/clavulanate, flucloxacillin, and penicillin V (hereafter referred to as the "oral penicillins"). Using the Ovid databases, we conducted an Advanced Search in the EMBASE database (1980–March 28, 2012) and MEDLINE databases (Ovid Medline In-Process and Other Non-Indexed citations and Ovid Medline 1946–March 28, 2012) for any article reporting on rates of AAD arising from the use of any oral penicillin to treat an indicated infection in children (0-17

Table 1. DMID Severity Grading for Diarrhea in Children Older Than 3 Months of Age

Grade 1	Grade 2	Grade 3	Grade 4
Slight change in consistency and/or frequency of stools	Liquid stools	Liquid stools greater than 4 times the amount or number normal for this child	Liquid stools greater than 8 times the amount or number normal for this child (or any diarrhea considered life-threatening by clinician)

DMID, Division of Microbiology and Infectious Diseases

years). There was no restriction on the language of publication or the location of the reported studies. We then limited the articles to those reporting on clinical trials only.

Outcome Measure

The pre-specified outcome for data collection from each article was the rate of AAD arising from the use of an oral penicillin for an indicated infection. Additional data collected included the following: the dose and duration of the oral penicillin therapy, the definitions of diarrhea and diarrhea severity used, the age and size of the study population, the length of posttherapy follow up, and the number of children who discontinued therapy as a result of AAD (these items are collectively referred to as "relevant data" for the purposes of this review). Specifically, it was assumed that the articles used the World Health Organization (WHO) definition of diarrhea—"the passage of 3 or more loose or liquid stools per day, or more frequently than is normal for the individual"[10]—unless otherwise stated, and the Division of Microbiology and Infectious Diseases (DMID) severity grading set out in Table 1.[11]

Data Screening and Collection

The title and abstract of all articles were screened by 2 independent researchers for relevant data or for a reference indicating relevant data were available in the full text. The relevant data for each article were then extracted onto a data collection form. Any article that primarily focused on diarrhea occurring in children with chronic conditions (e.g., cochlear implants in otitis media studies) or that did not offer information about the number of pediatric patients or the dose of oral penicillin given was excluded. Likewise, articles reporting on the concurrent use of any oral penicillin with other antibiotics (e.g., in the treatment of *Helicobacter pylori*) were excluded. On completion of the data collection process the researchers agreed upon a list of articles for inclusion in the primary analysis.

Data Analysis

Primary analysis involved the preliminary pooling of studies and calculation of AAD rates for each of the oral penicillins. To calculate this rate, the total number of children reported in the studies to be affected by diarrhea from each of the oral penicillins was divided by the total number of children receiving that oral penicillin. No corrections were made to the AAD rates reported as an adverse event in the studies. Specifically, patients who withdrew from the studies were not excluded.

RESULTS

The initial database searches identified 1154 articles; this number was reduced to 435 articles (307 from EMBASE and 128 from MEDLINE) after the clinical trial limit was applied. After title and abstract screening, 35 articles reporting on 42 studies were identified for inclusion in the primary analysis, as seen in Figure 1.

The studies reported rates of AAD when using the oral penicillins (excluding flucloxacillin, as this is not used in the United States[12]) to treat AOM, sinusitis, pharyngitis, and pneumonia. Of these, 33 studies reported on amoxicillin/clavulanate, 6 studies reported on amoxicillin, and 3 studies reported on penicillin; none of the articles reporting on flucloxacillin use met the inclusion criteria. Tables 2 through 4 summarize the studies for each oral penicillin, detailing the clinical indication for its use, the number and age of children treated, the dose used, the rate of AAD, the length of posttherapy follow up, and the number of children who discontinued therapy as a result of AAD.

In total, 7729 pediatric patients were treated with oral penicillins, and an average of 17.2% had AAD. We then pooled the data reported in the studies for each oral penicillin and recorded the number of patients receiving the oral penicillin and the average rate of AAD. These pooled data are presented graphically in Figure 2. Most strik-

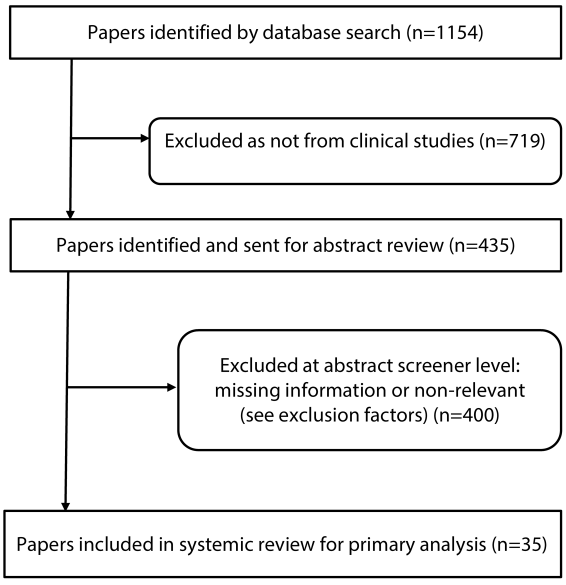

Figure 1. Stages of inclusion/exclusion of the studies.

ingly, there was a much higher incidence of AAD in the amoxicillin/clavulanate group (19.8%), compared to the amoxicillin group (8.1%) and the penicillin V group (1.2%). This trend is in accord with the results of at least 2 other recent pediatric AAD studies.[48,49] The impact that this higher AAD rate has on compliance is demonstrated by the higher rates of discontinuation of therapy as a result of AAD in the amoxicillin/clavulanate group. Specifically, in the 13 amoxicillin/clavulanate studies reporting on discontinuation due to AAD, 53 out of 485 (i.e., 10.9%) of patients with AAD discontinued therapy as a result of AAD.

Limitations and Potential Bias

Only 1 of the articles reviewed[38] indicated the diarrhea definition used in the Study. Hoberman et al[38] stated that "protocol-defined diarrhea … is the occurrence of three or more watery bowel movements in 1 day (1 day of protocol-defined diarrhea), or two watery bowel movements per day for 2 consecutive days (2 days of protocol-defined diarrhea)." Another Study[27] confirmed that "diarrhea was not specifically defined in the protocol and information was collected as presented by parents or caregivers." Otherwise there was reference to the "protocol-defined diarrhea" by Bottenfield et al[34] and to the "Otitis Parent Questionnaire" by Block et al,[21] but no specific definitions. Therefore, for the majority of studies it is not known what definition of diarrhea was used, if any. It was therefore assumed that, in the absence of a distinct definition, any reported diarrhea would meet the WHO definition of diarrhea stated above.[10] However, it is known that the diarrhea was reported by parents and/or elicited by investigators and that the investigators determined whether the diarrhea was related to the oral penicillin (i.e., whether it was AAD or not). Unfortunately, none of the studies report on the timing or duration of AAD, although some studies confirmed that the AAD resolved upon discontinuation of the oral penicillin. In addition, as AAD can occur up to 2 months after the final antibiotic dose, there is the risk of underestimation of AAD where follow up in the studies occurred for a shorter period of time.[50] As shown in Tables 2 through 4, the length of follow up in the studies ranged from 1 to 46 days post–completion of therapy, with less than 50% of the amoxicillin/clavulanate studies having posttherapy follow up of 28 days or more.

In the majority of the studies the investigators categorized diarrhea, along with other adverse effects, as being mild, moderate, or severe, but again, no definitions were stated for this severity grading. It was therefore assumed that the DMID severity grading (Table 1) was used.[11] Overall, 55 cases of AAD were reported as severe or leading to withdrawal from a study, and there were no reports of any deaths or life-threatening colitis.

RISK FACTORS FOR AAD

In order to determine whether there were any particular risk factors for AAD in children, the studies were analyzed for any correlations between AAD rates and the specific oral penicillin used, the dose and duration of the oral penicillin, the clinical indication, and the age of the patients.

Drug and Dose

Penicillin V is a broad-spectrum penicillin similar to the original benzylpenicillin or penicillin G. It was introduced because it was gastric-acid stable and could therefore be given orally (British National Formulary).[51] It is principally indicated in the acute treatment of streptococcal tonsillitis, pharyngitis, and scarlet fever and has the additional benefit of preventing long-term sequelae of these streptococcal infections, such as rheumatic fever and glomerulonephritis.[46] Only 3 of the studies reported on diarrhea rates following the

Table 2. Amoxicillin Studies

Reference	Age (Clinical Indication)	No. of Children (n = 1083)	No. with AAD (Rate of Diarrhea), n (%) [n = 88; total 8.1%]	Dose	Duration, days	No. Who Discontinued Due to AAD	Duration of Follow Up Posttherapy, days
Clegg et al[13]	3-18 yr (streptococcal pharyngitis)	326	16 (4.80)	<40 kg 750 mg/day, >40 kg 1000 mg/day	10	None*	18-25
Arguedas et al[14]	6-30 mo (AOM)	154	27 (17.50)	90 mg/kg/day	10	None*	15-18
Damoiseaux et al[15]	6 mo-2 yr (AOM)	115	20 (17.00)	40 mg/kg/day	10	2*	32
Cohen et al[16]	3-15 yr; mean age 5.9 yr (streptococcal pharyngitis)	161	3 (1.87)	50 mg/kg/day	6	None*	28-31
Foshee and Qvarnberg[17]	6 mo-12 yr (AOM)	143	4 (3.10)	40 mg/kg/day	7	Not specified	10-16
McLinn et al[18]	2 mo-14 yr (AOM)	184	18 (9.80)	50mg/kg/day	10	None*	14-28

* Studies specifically reporting on discontinuation of treatment due to antibiotic-associated diarrhea (AAD).

use of penicillin V (Table 4). Cohen et al[16] reported that only 1 of 160 penicillin V–treated patients (0.63%) was affected by AAD. Pichichero et al[46] reported that 4 out of 202 penicillin V–treated patients (2%) were affected by AAD. The third study by Block et al[47] reported that none of 55 penicillin V–treated patients were affected by AAD. These minimal rates accord with the 3% (2 patients out of 59) combined penicillin V and penicillin G–related AAD rate reported by Turck et al[49] in their epidemiological study of the incidence of oral antibiotic–associated diarrhea in an outpatient pediatric population. Therefore, although only 3 studies have been compared, the low rate of penicillin V–related AAD identified appears to be consistent with the findings of other studies.

Amoxicillin is a semisynthetic broad-spectrum penicillin that was introduced in the United States in 1974.[7] Like all penicillins, its antimicrobial activity is due to its inactivation of bacterial cell wall synthesis via its beta-lactam ring structure. As it was better absorbed and had higher serum concentrations than ampicillin (introduced in the United States in 1962) it soon became, and today remains, the first-line therapy for uncomplicated AOM, sinusitis, and mild to moderate pneumonia in children. In terms of AAD, our results show that use of amoxicillin resulted in a pooled diarrhea rate of 8.1%, with rates ranging from 1.87% to 17.5% (Table 2). This range is consistent with the AAD rates ranging from 3% to 16% found by Coker et al[2] in their review of amoxicillin-related diarrhea rates reported by clinical trials. Finally, our data analysis found no correlation between the dose of amoxicillin and rate, which may well have been due to the small number of amoxicillin studies.

Amoxicillin/clavulanate was introduced in the United States in 1984 to combat the beta-lactamase–producing bacteria that were inactivating amoxicillin (particularly strains of the key causative bacteria of pediatric AOM, sinusitis, and pneumonia: *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*).[7] Amoxicillin/clavulanate is a combination of amoxicillin with clavulanic acid, a beta-lactamase inhibitor. Its original formulation combined amoxicillin/clavulanate in a 4:1 ratio (40/10 mg/kg/day).[7] However, as it was realized that effectiveness against drug-resistant *S pneumoniae* required not only a beta-lactamase inhibitor but also increased concentrations of amoxicillin at the site of infection, the amoxicillin component of amoxicillin/clavulanate was increased to a 7:1

Table 3. Amoxicillin:Clavulanic Acid Studies

Reference	Age (Clinical Indication)	No. of Children (n = 6229)	No. with ADD (Rate of Diarrhea), n (%) [n = 1236; total 19.8%]	Dose (Ratio of Amoxicillin to Clavulanic Acid)*	Duration, days	No. Who Discontinued Due to AAD	Duration of Follow Up Posttherapy, days
Tahtinen et al[19]	6-35 mo (AOM)	161	77 (47.8)	40 mg/5.7 mg/kg/day (7:1)	7	None†	1, but parents can request more
Poachanukoon and Kitcharoensakkul[20]	1-15 yr; mean age co-amox 6.60 yr (acute bacterial rhinosinusitis)	72	13 (18.1)	80-90 mg/kg/day (E:14:1)*	14	None†	46
Block et al[21]	6 mo-6 yr (AOM)	158	44 (28)	90 mg/6.4 mg/kg/day (14:1)	10	8‡	30-32
Lu et al[22]	Not available (LRTI)	110	10 (9.1)	45 mg/kg/day (E:7:1)*	10	Not available	Not available
Sher et al[23]	6 mo-7 yr (AOM)	173	31 (18)	90 mg/6.4 mg/kg/day (14:1)	10	Not specified	21-28
Saez-Llorens et al[24]	6 mo-7 yr (AOM)	121	9 (7.4)	45 mg/6.4 mg/kg/day (7:1)	10	3†	30
Block et al[25]	6 mo-6 yr (AOM)	192	19 (10)	45 mg/6.4 mg/kg/day (7:1)	10	3 due to GI events	15-18
Block et al[26]	6 mo-12 yr (AOM)	173	22 (12.7)	45 mg/kg/day (E:7:1)*	10	3 due to GI events	18-22
Arrieta et al[27]	6 mo-6 yr (AOM)	145	43 (29.9)	90 mg/6.4 mg/kg/day (14:1)	10	1†	18-22
Dunne et al[28]	6 mo-12 yr, mean age 3.5 yr (AOM)	188	27 (14.6)	45 mg/kg/day (E:7:1)*	10	Not specified	14-18
Hedrick et al[29]	6 mo-7 yr (AOM)	153	29 (19)	90 mg/6.4 mg/kg/day (14:1)	10	8‡	4-7
Adler et al[30]	6 mo-12 yr (AOM)	197	25 (12.9)	40 mg/kg/day (E:4:1)*	10	24‡	27-42
Block et al[31]	6 mo-12 yr (AOM)	128	45 (35)	40 mg/10 mg/kg/day (4:1)	10	Not specified	11-27
Pessey et al[32]	6-36 mo (AOM)	255	46 (18)	40 mg/kg/day (E:4:1)*	10	None†	21-28
Pessey et al[32]	6-36 mo (AOM)	209	21 (10)	80 mg/kg/day (E:8:1)*	8	None†	21-28
Cohen et al[33]	Mean age 14.2 ± 6.7 mo (AOM)	228	62 (27.1)	80 mg/10 mg/kg/day (8:1)	10	9†	28-42
Bottenfield et al[34]	3 mo-12 yr (AOM)	201	22 (10.9)	90 mg/6.4 mg/kg/day (14:1)	10	Not specified	12-18

AAD, antibiotic-associated diarrhea; AOM, acute otitis media; E, estimated; GI, gastrointestinal

* The amount of clavulanic acid included in the co-amoxiclav formulation is not detailed; hence, an estimated ratio (E) was used based on the stated amount of amoxicillin and formulations available at the time of the study.

† Studies specifically reporting on discontinuation of treatment due to AAD.

‡ Total number of children who discontinued treatment in a particular study. No breakdown given in the study for discontinuation due to AAD.

Table 3. Amoxicillin:Clavulanic Acid Studies (*cont.*)

Reference	Age (Clinical Indication)	No. of Children (n = 6229)	No. with ADD (Rate of Diarrhea), n (%) [n = 1236; total 19.8%]	Dose (Ratio of Amoxicillin to Clavulanic Acid)*	Duration, days	No. Who Discontinued Due to AAD	Duration of Follow Up Posttherapy, days
Bottenfield et al[34]	3 mo-12 yr (AOM)	207	19 (9.2)	45 mg/6.4 mg/kg/day (7:1)	10	Not specified	12-18
Adam[35]	0-13 yr (AOM)	538	129 (24)	40 mg/kg/day (E:4:1)*	10	Not specified	Not specified
Harris et al[36]	6 mo-5 yr (CAP)	71	26 (36.6)	40 mg/kg/day (E:4:1*)	10	Not specified	28-42
Behre et al[37]	2-12 yr (AOM)	231	15 (6.7)	70 mg/10 mg/kg/day (7:1)	10	13‡	18-32
Behre et al[37]	2-12 yr (AOM)	232	24 (10.3)	60 mg/15 mg/kg/day (4:1)	10	21‡	18-32
Hoberman et al[38]	2 mo-12 yr (AOM)	293	25 (8.7)	45 mg/6.4 mg/kg/day (7:1)	5	7†	27-33
Hoberman et al[38]	2 mo-12 yr (AOM)	287	28 (9.6)	45 mg/6.4 mg/kg/day (7:1)	10	8†	22-28
Hoberman et al[38]	2 mo-12 yr (AOM)	288	77 (26.7)	40 mg/10 mg/kg/day (4:1)	10	22†	22-28
Gooch et al[39]	6 mo-12 yr (AOM)	155	46 (29.7)	40 mg/kg/day (E:4:1)*	10	Not specified	14
Gooch et al[40]	3 mo-12 yr (AOM)	242	73 (30)	40 mg/kg/day (E:4:1)*	10	13‡	14-18
McLinn et al[41]	6 mo-8 yr (AOM)	150	51 (34)	40 mg/kg/day (E:4:1)*	10	12 stopped mostly due to diarrhea	14-28
McLinn et al[42]	3 mo-11 yr (AOM)	98	30 (31)	40 mg/kg/day (E:4:1)*	10	2†	12-16
McCarty et al[43]	6 mo-12 yr (AOM)	177	57 (32)	40 mg/kg/day (E:4:1)*	10	7‡	15-28
Schaad[44]	6 mo-10.2 yr (AOM)	192	32 (16.67)	40 mg/kg/day (E:4:1)*	10	1†	1-10
Foshee and Qvarnberg[17]	6 mo-12 yr (AOM)	142	37 (26.3)	US: 40 mg/kg/day (E:4:1)*	10	Not specified	10-16
Arguedas et al[45]	6 mo-17 yr (AOM)	62	22 (34.9)	40 mg/kg/day (E:4:1)*	10	None†	28-32

AAD, antibiotic-associated diarrhea; AOM, acute otitis media; E, estimated; GI, gastrointestinal

* The amount of clavulanic acid included in the co-amoxiclav formulation is not detailed; hence, an estimated ratio (E) was used based on the stated amount of amoxicillin and formulations available at the time of the study.

† Studies specifically reporting on discontinuation of treatment due to AAD.

‡ Total number of children who discontinued treatment in a particular study. No breakdown given in the study for discontinuation due to AAD.

Table 4. Penicillin V Studies

Reference	Age (Clinical Indication)	No. of Children (n = 417)	No. with AAD (Rate of Diarrhea), n (%) [n = 5; total 1.2%]	Dose	Duration, days	No. Who Discontinued Due to AAD	Duration of Follow Up Posttherapy, days
Cohen et al[16]	3-15 yr (streptococcal pharyngitis)	160	1 (0.63)	45 mg/kg/day	10	None*	28
Pichichero et al[46]	3-18 yr (streptococcal pharyngitis)	202	4 (2)	25 mg/kg/day	10	1 due to GI complaints	14-21
Block et al[47]	4-18 yr (streptococcal pharyngitis)	55	0 (0)	250 mg tid	10	None*	21-42

GI, gastrointestinal

* Studies specifically reporting on discontinuation of treatment due to antibiotic-associated diarrhea (AAD).

ratio (45 mg/6.4 mg/kg/day) and to an 8:1 ratio (80 mg/10 mg/kg/day) and then, in 2001, to a 14:1 ratio (90 mg/6.4 mg/kg/day).[7] As a result of its effectiveness against amoxicillin-resistant strains of bacteria, amoxicillin/clavulanate has become a treatment of choice for children who fail initial therapy with amoxicillin.[7] In terms of AAD, our results show that use of amoxicillin/clavulanate resulted in a pooled diarrhea rate of 19.8%, with rates ranging from 6.7% to 47.8% (Table 3). Again, this is in line with the findings of other reviews: Coker et al[2] reported a 20% amoxicillin/clavulanate diarrhea rate following their systematic review. It is therefore clear that this combined formulation causes considerably more AAD than does amoxicillin alone.

However, there is an interesting trend within these data. When analyzing the formulations used in the amoxicillin/clavulanate studies for the treatment of AOM we found that there was a pooled average diarrhea rate of 24.6% for the 4:1 formulation, a rate of 12.8% for the 7:1 formulation, a rate of 19.0% for the 8:1 formulation, and a rate of 20.2% for the 14:1 formulation. These rates are recorded in Table 5. A proportional reduction of clavulanate from 4:1 (40 mg/10 mg/kg/day) to 7:1 (45 mg/6.4 mg/kg/day) in the amoxicillin/clavulanate formulation appears to correlate to a comparative reduction in amoxicillin/clavulanate–related AAD; however, this is not maintained when the amoxicillin component is doubled from 4:1 (40 mg/10 mg/kg/day) to 8:1 (80 mg/10 mg/kg/day) or from 7:1 (45 mg/6.4 mg/kg/day) to 14:1 (90 mg/6.4 mg/kg/day). This initial trend to reduction was previously identified by Hoberman et al[38] in their study comparing the 4:1 (26.7% AAD rate) and 7:1 (9.6% AAD rate) formulations. One explanation offered by Klein[7] in his review of amoxicillin/clavulanate therapy for pediatric infections is that clavulanate stimulates peristalsis; hence, reducing its concentration will reduce any AAD. However, this fails to explain the apparent increase in diarrhea associated with the 14:1 current formulation. It has also been reported by Harrison[52] that the rates of amoxicillin/clavulanate–related AAD can be reduced by administering amoxicillin/clavulanate with food, as bowel peristalsis is inhibited after eating. It is nevertheless clear that amoxicillin per se causes AAD and that increasing the amoxicillin component of amoxicillin/clavulanate will increase AAD, notwithstanding

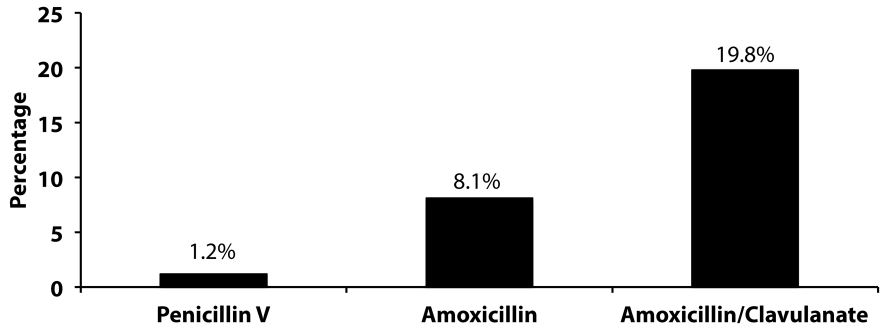

Figure 2. Percent rate of diarrhea by oral penicillin.

a relative reduction of clavulanate, hence the 19.0% and the 20.2% AAD rates identified for the 8:1 and 14:1 formulations, respectively.

Disease

The majority of the studies (34 of the 42) involved the use of amoxicillin/clavulanate (n = 30) or amoxicillin (n = 4) to treat AOM. Five studies involved the use of amoxicillin (n = 2) or penicillin V (n = 3) to treat streptococcal pharyngitis. Two studies used amoxicillin/clavulanate to treat pneumonia, and 1 study used amoxicillin/clavulanate to treat sinusitis. Therefore, in view of the dominance of the use of amoxicillin/clavulanate to treat AOM it was not possible to perform any meaningful analysis related to whether a particular disease condition is associated with a higher incidence of AAD. Furthermore, we are not aware of any study that has analyzed this as a possible risk factor for AAD.

Age

Another major potential risk factor is age. Turck et al[49] studied AAD from penicillins G and V, penicillins A and M, amoxicillin/clavulanate, cephalosporins, macrolides, trimethoprim/sulfamethoxazole, and erythromycin/sulfafurazole and confirmed that the incidence of AAD is significantly greater in children who are <2 years of age compared to in those who are over 2 years of age. Specifically, they reported AAD rates of 18% for children aged 1 month to 2 years, 4% for those aged 2 to 7 years, and 2% for those older than 7 years. Although the AAD age incidence was not reported for each type of penicillin, it was reported that the relative risk of AAD for a child receiving amoxicillin/clavulanate was 2.43 and that if the child was aged less that 2 years that relative risk increased to 3.5. It was not possible in our review to break down the AAD rates by age, as AAD rates were reported for too wide an age range in the studies.

Duration

The duration of antibiotic therapy is another possible risk factor. Some studies[17,38] have demonstrated that a longer duration of amoxicillin/clavulanate is associated with an increased rate of AAD. Because very few of the studies had an oral penicillin duration of less than 10 days, we were unable to confirm this in our review.

MANAGEMENT AND PREVENTION OF AAD

Management

In view of the incidence of AAD with the oral penicillins and the increased incidence of community-associated CDI, parents should be advised of the relevant AAD incidence rate for the oral penicillin prescribed and advised to come back if their child develops moderate or severe diarrhea or becomes dehydrated. The management of AAD will depend on its severity. If it is not severe (i.e., if there are no features of antibiotic-associated colitis, characterized by abdominal cramps, fever, leukocytosis, fecal leukocytes, hypoalbuminemia), then discontinuation of the antibiotic or switching to an antibiotic with reduced risk of AAD should lead to its resolution in the majority of cases. In addition, electrolytes and fluids should be replaced. If the AAD is severe, then in addition to the measures for non-severe diarrhea, hospitalization will be necessary (with isolation measures to prevent spread), and a stool sample should be sent for *C difficile* toxin analysis. If the sample is positive for the toxins, then the CDI should be treated with oral metronidazole or vancomycin.

Prevention

The most effective way of preventing AAD is to reduce the inappropriate use of antibiotics. As this review has demonstrated, there is a significant risk of AAD following the use of amoxicillin

Table 5. Range and Averages of Antibiotic-Associated Diarrhea (AAD) Rates for Common Formulations of Amoxicillin/Clavulanate

Amoxicillin/Clavulanate Formulation Ratio	Dose	Average Duration, days	Rate of Diarrhea (range and average rates), %
4:1	40 mg/10 mg/kg/day (14 studies)* 60 mg/1 5mg/kg/day (1 study)	10	10.3-36.6 24.60
7:1	40 mg/5.7 mg/kg/day (1 study) 45 mg/6.4 mg/kg/day (8 studies)† 70 mg/10 mg/kg/day (1 study)	9.2	6.7-47.8 12.80
8:1	80 mg/10 mg/kg/day (2 studies)	9	10.0-27.1 19
14:1	90 mg/6.4 mg/kg/day (5 studies)‡		10.9-29.9 20.20

* Includes 10 studies with estimated (E) dose of 40 mg/kg/day of amoxicillin, so a 10-mg dose of clavulanate is assumed—see Table 3 for details of estimated doses.
† Includes 3 studies with estimated (E) dose of 45 mg/kg/day of amoxicillin, so a 6.4-mg dose of clavulanate is assumed—see Table 3 for details of estimated doses.
‡ Includes 1 study with estimated (E) dose of 80-90 mg/kg/day of amoxicillin, so a 6.4-mg dose of clavulanate is assumed—see Table 3 for details of estimated doses.

and amoxicillin/clavulanate in AOM. It was expected that the introduction in the 2004 AOM clinical practice guideline of the American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP) of an observation period for mild cases of AOM in a select group of children before deciding if antibiotics are needed would reduce antibiotic use.[1] However, the most recent 2013 AOM clinical practice guideline of the AAP and AAFP[53] reported that while multiple studies had shown the success of an observation period, there had been no difference in the antibiotic prescribing rates since the 2004 guideline, and this was attributed to lack of clinician awareness. In addition, the most recent 2011 studies of Hoberman et al[54] and Tahtinen et al[19] underscored the importance of correctly diagnosing AOM cases requiring antibiotics after finding that young children with a certain diagnosis of AOM recover more quickly after initial treatment with amoxicillin/clavulanate versus observation (as identified by Klein[55] in his editorial for these 2 studies). In order to address these issues the 2013 AOM clinical practice guideline set out recommendations for diagnosing and managing AOM in children aged 6 months and above. For diagnosis, the key recommendations include the following: 1) AOM should be diagnosed in children who have (a) moderate to severe bulging of the tympanic membrane or ear drainage not caused by otitis externa or (b) mild bulging of the tympanic membrane and less than 48 hours of new ear pain or intense redness of the tympanic membrane; and 2) AOM should not be diagnosed in children who do not have middle ear fluid. For management the 2013 guideline confirmed that clinicians should prescribe antibiotics for children 6 months and older with severe unilateral AOM and for children with non-severe bilateral AOM. However for non-severe unilateral AOM in children aged 6 months to 12 years the clinician can offer either antibiotics initially or observation. Under this option antibiotics (amoxicillin or amoxicillin/clavulanate) may be withheld initially and the child must be closely observed. If symptoms worsen within 72 hours, then antibiotic therapy should be started. The decision of whether to start antibiotics or observe will depend on the clinician's certainty about the diagnosis, the child's age, any comorbid conditions, the severity of the AOM, and the likelihood that the parents will follow up if the child's symptoms worsen or do not improve in 48 to 72 hours. Certainty of diagnosis, older age, absence of comorbid conditions, mild AOM, and reliable parents will make patients candidates for observation. It is expected that this observation period will reduce antibiotic use.

Once antibiotic therapy has begun, recent studies have looked at whether concurrent use of probiotic formulas has reduced the incidence of AAD. A recent 2011 Cochrane review[56] of the

Table 6. Recommendations to Minimize the Known Risk Factors for Antibiotic-Associated Diarrhea (AAD)

If antibiotic therapy is required and there is a choice of equally efficacious oral penicillin, the oral penicillin with the lowest side-effect profile should be selected (i.e., amoxicillin as first line for AOM wherever possible and amoxicillin/clavulanate as second line).
If amoxicillin/clavulanate is to be prescribed and there is no evidence that any other formulation is more efficacious, clinicians should consider whether formulations other than the 7:1 (45 mg/6.4 mg/kg/day) dosing formulation are really indicated in view of their higher AAD rates.
The oral penicillin should have twice daily or less dosing to ensure that doses are not missed during the day when the child is at school or in daycare and "catch-up" dosing does not then extend the prescribed duration (as advocated by Pichichero[57] in his 2000 study).
Clinicians should advise parents about the risks of AAD when prescribing the oral penicillins (Figure 2) and provide information as to its management and prevention—this is particularly important in view of the recent reports of increases in pediatric community-associated CDI.

AOM, acute otitis media; CDI, Clostridium difficile infection

use of probiotics for the prevention of pediatric antibiotic–associated diarrhea concluded that high-dose *Lactobacillus rhamnosus* and *Saccharomyces boulardii* of 5 to 40 billion colony-forming units/day may prevent the onset of AAD with no serious side effects in otherwise healthy children. However, it qualified this conclusion by suggesting that this benefit of high-dose probiotics be confirmed in a large randomized controlled trial. It also advised that probiotic use be avoided in children at risk of adverse events until further research has been carried out, as moderate to serious adverse events had been reported in severely debilitated or immunocompromised children with underlying risk factors, including central venous catheter use and disorders associated with bacterial/fungal translocation.

Finally, especially in view of reported increases in community-associated CDI, infection control measures to prevent the spread of possible CDI-related AAD will need to be emphasized when prescribing oral penicillins. Specifically, in the event of AAD, parents must be advised to ensure rigorous hand washing with soap by all family members and household cleaning with strong disinfectants to rid the environment of any *C difficile* spores.

CONCLUSIONS

This review confirms that AAD is associated with oral penicillin use in children and demonstrates that the AAD risk is significantly increased with amoxicillin/clavulanate (19.8%) compared to amoxicillin (8.1%) and penicillin V (1.2%). Moreover, the risk of AAD with amoxicillin/clavulanate varies with different formulations, from 24.6% with the 4:1 formulation to 12.8% with the 7:1 formulation, 19.0% with the 8:1 formulation, and 20.2% with the 14:1 formulation. This is particularly relevant as the 14:1 formulation is currently the most widely used amoxicillin/clavulanate formulation. An additional concerning finding is that while the majority of AAD cases in the studies were mild or moderate, there has been a recent increase in reported cases of community associated CDI-related AAD in children. Unfortunately, none of the studies evaluated the risk of AAD as a primary outcome, and there have been few studies investigating the pathophysiology and risk factors for AAD in children. As a result, clinicians have tended to underestimate the importance of AAD and often fail to advise parents of the AAD risk of oral penicillin therapy. Compliance is affected and families are left with no guidance on how to manage AAD in addition to the child's primary diagnosis. Implications of this review for clinicians prescribing oral penicillins for children are to minimize the known risk factors for AAD (Table 6).

The ongoing predominance of the oral penicillins in the treatment of common infectious diseases in children requires that further research focuses on the development of prescribing practice to prevent AAD. Generally, appropriate medical training and diagnostic tools should be developed to enable clinicians to ensure that antibiotics are only prescribed if very stringent diagnostic criteria are met. The importance of this in the context of AOM was underscored by Hoberman et al[54] in their 2011 study. More specifically, we recommend that further research

focuses on 1) AAD rates and risk factors as the primary or secondary outcome measure of large randomized controlled trials. These trials should compare AAD rates with different doses and durations of each of the oral penicillins in different pediatric age groups for each of the common infections. The protocols for these trials should include standardized definitions for diarrhea and diarrhea severity as well as a procedure for daily diarrhea reporting; 2) The mechanisms of AAD in children; 3) Parental views regarding the impact of AAD and how it would influence any treatment decision; and 4) The benefits of probiotics for the prevention of AAD. These need to be evaluated in clinical trials before they are routinely prescribed alongside the oral penicillins.

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Abbreviations AAD, antibiotic-associated diarrhea; AAFP, American Academy of Family Physicians; AAP, American Academy of Pediatrics; AOM, acute otitis media; CDI, *Clostridium difficile* infection; DMID, Division of Microbiology and Infectious Diseases; SCFA, short chain fatty acid; WHO, World Health Organization

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