Antibiotic Rashes in Children

A Survey in a Private Practice Setting

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Objective: To document the frequency and severity of various types of rashes seen with commonly used oral antibiotics in the pediatric outpatient setting.

Design: A retrospective review of 5923 patient records at a pediatric office.

Setting: A private group pediatric practice in northern Virginia with about 12,000 registered active patients.

Patients and Methods: Approximately 50% of the clinic medical records were reviewed. All children (defined as those aged 0-18 years in this study) identified on their medical records as having developed a rash following treatment with 1 or more of the commonly used oral antibiotics were included in the study. For further validation, a questionnaire about parental recollection of description of rash, other associated symptoms, physician verification, and outcome was mailed to families with children designated as being allergic to an antibiotic.

Results: On a prescription basis, significantly more rashes were documented for cefaclor (4.79%) compared with penicillins (2.72%), sulfonamides (3.46%), and other cephalosporins (1.04%). Based on the number of patients for whom each group of antibiotic was prescribed, the documented frequencies of rashes were 12.3%, 7.4%, 8.5%, and 2.6% for cefaclor, penicillins, sulfonamides, and other cephalosporins, respectively. None of the children had rashes severe enough to require hospitalization.

Conclusions: In a review of almost 6000 records in a private pediatric primary care setting, rashes occurred in 7.3% of children who were given the commonly used oral antibiotics. Significantly more rashes were documented with cefaclor use than with use of any of the other oral antibiotics.


ANTIBIOTICS, the most frequently prescribed pediatric outpatient drugs, are the cause of most drug-induced adverse reactions in children.1-3 Although most of these reactions are minor and transient1-4 and include various cutaneous manifestations, fatalities may occur and some of the reactions may necessitate pediatric inpatient care.5 Furthermore, it is possible that these reactions could alter compliance and therapeutic outcomes, resulting in the administration of alternative antibiotics that may be more expensive and more likely to promote the emergence of resistant microbial strains.

There is a paucity of information on the prevalence, distribution, and types of cutaneous eruptions attributable to each of the commonly prescribed antibiotics in the outpatient setting, and the few available studies relate mostly to the adult population. Published studies1,6 specifically documenting the prevalence of these cutaneous adverse drug reactions (ADRs) associated with antibiotics are rare in the pediatric outpatient setting. Where antibiotic-associated rashes have been examined along with various adverse reactions to other drugs, most researchers2,3 have considered the problem small and of minor consequences in their communities.

This study documents the frequency and severity of various types of rashes associated with commonly used oral antibiotics in the pediatric outpatient setting.

RESULTS

A total of 5923 patient medical records were reviewed. Of these, 1927 (32%) patients had no record of an antibiotic being prescribed while they were patients at VPA. An adverse reaction to 1 or more antibiotics was found on 509 (8.6%) of the...
PATIENTS AND METHODS

SETTING

Vienna Pediatric Associates Ltd (VPA) is a private group practice in northern Virginia consisting of 3 board-certified pediatricians. Approximately 12000 children (defined as those aged 0-18 years in this study) were active patients of the practice in 1996. There were nearly 20000 outpatient visits to the office in that year. The most frequent diagnoses necessitating antibiotic therapy were acute otitis media, acute pharyngotonsillitis, and sinusitis.

MATERIALS

From March 1 to July 31, 1996, a trained research assistant (a third-year nursing student) carried out a survey of 50% of active patient records at VPA. The research assistant reviewed all the medical records to document the total number of oral antibiotic prescriptions written, the indications for the antibiotics, and patient demographics. Furthermore, the research assistant noted which patients were labeled as allergic to an antibiotic, the description of any rashes, and the dates of occurrence of the rash.

A written questionnaire with a prestamped envelope and a $2 bill was mailed to each parent of a child designated as having an ADR with an antibiotic. The questionnaire sought to gather information (based on parental recall) about the relation of the rash with administration of a specific antibiotic. It also asked for information about other symptoms that were induced by the antibiotic and about whether the rash had been confirmed as antibiotic related following examination by a physician.

In cases in which the rash occurred before the child became a patient at VPA, attempts were made to obtain copies of relevant records. An abbreviated questionnaire also was mailed to former physicians who attended to the children at the time an antibiotic-related rash occurred.

For this study, antibiotics were divided into 4 groups: (1) penicillins, including amoxicillin and the combination drug amoxicillin and clavulanate potassium; (2) sulfonamides, including the combination drugs trimethoprim and sulfamethoxazole and erythromycin ethylsuccinate and sulfisoxazole acetyl; (3) cefaclor; and (4) cephalosporin antibiotics excluding cefaclor. Only rashes documented with orally administered antibiotics in these categories were included.

The rashes were classified as (1) macular and/or papular drug exanthema; (2) hives, urticaria, welts, and/or angioedema; (3) erythema multiforme; and (4) indistinct other rashes. We classified serum sicknesslike reactions (SSLRs) as definite or probable. Definite SSLRs consisted of a rash with fever, joint pains, and swelling in relation to antibiotic administration for at least 7 days, while probable SSLRs were defined as a rash with fever and joint manifestations documented with antibiotic given for less than 7 days. This classification is arbitrary and is based on the fact that SSLRs typically occur 7 to 10 days following exposure to the offending medication.6-8

If a child developed a rash to more than 1 antibiotic, the antibiotics were enumerated singly. Visual verification by a physician was required for designation as macular and/or papular drug exanthema or an erythema multiforme rash, but parental telephone description of pruritic urticaria and/or angioedema without physician confirmation at an office visit was permitted.

To further validate the data and ensure consistency and accuracy, 2 of us (E.O.I. and B.L.W.) separately scrutinized all the raw data and the returned survey questionnaires. A rash was considered as “indistinct other” if there was lack of documentation of morphologic features on the record or lack of agreement between the 2 researchers regarding its morphologic class.

STATISTICS

Using computer software (Epi Info, Version 6.04a; Centers for Disease Control and Prevention, Atlanta, Ga, and World Health Organization, Geneva, Switzerland), odds ratios were calculated for the observed differences in the age and sex distribution of children with rashes compared with the total number of children in the practice. Confidence intervals were calculated around the frequencies of rashes documented with the prescribed antibiotics, and a 2-sample z test was used to compare differences in these frequencies. P<.05 was considered statistically significant.

5923 medical records. Of these, 37 were discarded because records only documented minor gastrointestinal tract adverse effects or other minor symptoms with no rashes, leaving a total of 472 medical records with rashes recorded for the specific antibiotics. Three patients who developed urticaria to penicillin had similar rashes with erythromycin. No rashes were recorded for any of the newer macrolides (clarithromycin and azithromycin) or tetracyclines, which were rarely prescribed. Of the 472 patients, 254 (53.8%) were boys. Of these boys, 237 (93.3%) and 178 (81.6%) of the 218 girls, were younger than 6 years at the time of the rash. The age of the patients ranged from 5 weeks to 18 years. Overall, there was no statistically significant difference between the boys and girls who reported a rash after receiving an antibiotic. However, there were significantly more rashes documented for boys younger than 3 years and for girls older than 9 years.

ANTIBIOTIC PRESCRIPTION

There were 18867 antibiotic prescriptions for the 3996 patients whose records showed at least 1 antibiotic prescription at the time of occurrence of the rash. The average number of prescriptions per person was similar for the different antibiotics, as shown in Table 2.
Table 1. Age and Sex Distribution of 472 Children With Rashes Following Antibiotic Exposure

<table>
<thead>
<tr>
<th>Age, mo*</th>
<th>Boys†</th>
<th>Girls†</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-35</td>
<td>998 (15.8)</td>
<td>175 (68.9)</td>
<td>1.32 (1.02-1.70)</td>
<td>.04</td>
</tr>
<tr>
<td>36-71</td>
<td>1155 (18.3)</td>
<td>62 (24.4)</td>
<td>1.12 (0.75-1.66)</td>
<td>.64</td>
</tr>
<tr>
<td>72-107</td>
<td>1000 (15.9)</td>
<td>13 (5.1)</td>
<td>0.56 (0.27-1.18)</td>
<td>.14</td>
</tr>
<tr>
<td>≥108</td>
<td>3144 (49.9)</td>
<td>4 (1.6)</td>
<td>0.20 (0.06-0.66)</td>
<td>.004</td>
</tr>
<tr>
<td>Total</td>
<td>6297 (99.9)</td>
<td>254 (100.0)</td>
<td>1.13 (0.93-1.36)</td>
<td>.22</td>
</tr>
</tbody>
</table>

*At the time of the rash. †Data are given as number (percentage) of children.

Table 2. Antibiotic Exposure and Frequency of Rashes*

<table>
<thead>
<tr>
<th>Antibiotic Group</th>
<th>No. of Prescriptions</th>
<th>No. of Patients Given This Prescription</th>
<th>Average No. of Prescriptions per Patient</th>
<th>Rashes per Prescription, % (95% Confidence Interval)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>9416</td>
<td>3469</td>
<td>2.7</td>
<td>2.72 (2.39-3.05)</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>5402</td>
<td>2212</td>
<td>2.4</td>
<td>3.46 (2.97-3.95)</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>1357</td>
<td>527</td>
<td>2.6</td>
<td>4.79 (3.66-5.92)</td>
</tr>
<tr>
<td>Other cephalosporins</td>
<td>2692</td>
<td>1058</td>
<td>2.5</td>
<td>1.04 (0.66-1.42)</td>
</tr>
</tbody>
</table>

*Most patients received more than 1 group of antibiotic. †P < .001 (cefaclor vs penicillins), P = .02 (cefaclor vs sulfonamides), and P = .01 (sulfonamides vs penicillins).

Table 2 also shows the frequency of rashes with exposure to the various groups of antibiotics. A statistically higher frequency of rashes is documented for cefaclor than for the other antibiotics. Similarly, a significantly higher frequency of rashes was recorded with sulfonamides than with penicillins. Cephalosporins, other than cefaclor, were associated with the lowest rate of rashes. When the data were analyzed using the number of patients who received the different groups of antibiotics as the denominator, a similar pattern emerged, but with a higher frequency of rashes. Rashes were recorded in 12.3%, 7.4%, 8.5%, and 2.6% of children who received cefaclor, penicillins, sulfonamides, and other cephalosporins, respectively. Overall, rashes were documented in 7.3% of the children who received these antibiotics (the frequency of rashes per patient is not shown in Table 2). The frequency of rashes documented for cefaclor was statistically higher than for all other groups of antibiotics, but significantly more rashes were also recorded for sulfonamides than for penicillins.

The distribution and description of the various types of rashes are shown in Table 3. Rashes described as urticaria, hives, or welts and the macular and/or papular drug exanthemas were the most common types, each accounting for 208 (45.9%) of the 453 describable rashes. Table 4 is a breakdown of the rashes recorded with cephalosporins, other than cefaclor. There were no statistically significant differences within this group except that significantly more rashes were recorded with cefixime than with cefuroxime axetil.

SERUM SICKNESSLIKE REACTIONS

There were 31 cases of SSRLs. Twelve of these were regarded as definite, while 19 were considered probable. The rates of SSRLs documented with the antibiotics are shown in Table 5. Again, compared with others, significantly more SSRLs were recorded with cefaclor than with other antibiotics.

HOSPITALIZATION AND MORTALITY

No cases of Stevens-Johnson syndrome or toxic epidermal necrolysis occurred among any of the children with a rash. There were no deaths, and none of the children with rashes due to antibiotics required hospitalization.

COMMENT

Adverse drug reactions are common and have a significant impact on the health care system. In 1994, approximately 2216000 hospitalized patients in the United States had serious ADRs, and 106000 were fatal, making these reactions the fourth to sixth leading cause of death in this country.

Physicians should have thorough knowledge of the therapeutic and possible adverse effects of prescribed medications, but drug labeling in package inserts may not provide adequate information. Our study has shown that, in a pediatric office, rashes may occur in 7.3% of children following the administration of oral antibiotics but only in less than 3% of exposures to common oral antibiotics when considered per written prescription. However, these rashes are more likely to occur with cefaclor, followed by sulfonamides and penicillins. We also found that in the pediatric outpatient setting, these rashes are most likely to be minor and non-life threatening. However, they may cause discomfort, parental anxiety, frequent visits to the physician, and additional cost. In addition, these reactions indi-
rectly may impair good therapeutic outcomes and contribute to the problem of antibiotic-resistant strains.

Kramer et al,1 in a prospective study documenting ADRs to prescription and nonprescription medications during a period of 1 year in a general pediatric group practice, reported 473 ADRs (11.1%) from 4244 separate courses of drug therapy. The most common ADRs were gastrointestinal tract complaints and rashes associated with antibiotics. Of those 4244 courses of drug prescriptions, oral antibiotics accounted for 64%, and 96% of the prescribed 2714 courses of oral antibiotics were penicillins, sulfonamides, and cephalosporins. The design of that study did not allow determination of the frequency of rashes associated with the different orally administered antibiotics.

Mitchell et al5 reported that 2% of 6546 admissions of children to 4 teaching and 3 community hospitals were due to ADRs, while 2 of the children died of ADRs (the only antibiotic-related death was attributed to theophylline toxicity from a theophylline and erythromycin interaction). In contrast, none of the children in our study died or required hospitalization for antibiotic-associated rashes.

The label for cefaclor states that the rate of hypersensitivity reactions is 1.5%.10 Specifically, morbilliform rashes, urticaria, and serum sickness are said to occur in 1%, less than 0.5%, and 0.02% to 0.5% of persons, respectively, while Stevens-Johnson syndrome and toxic epidermal necrolysis are rare. None of our 527 patients who received cefaclor developed Stevens-Johnson syndrome or toxic epidermal necrolysis, but 12.3% had various other rashes. Ten (1.90%) developed definite or probable SSLRs to that drug compared with penicillins (0.35%), sulfonamides (0.36%), and other cephalosporins (0.10%). A review11 of the US Food and Drug Administration’s spontaneous adverse drug report database noted that SSLRs constituted 25% of such reports for cefaclor. Other than cefaclor, cephalosporin antibiotics are associated with far fewer rashes than any of the penicillins,12,13 as shown in our study (Table 2).

More than 7% of patients prescribed oral amoxicillin or penicillin in our study developed rashes. In a comprehensive drug surveillance system that monitored

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**Table 3. Antibiotic Exposure and Description of Rashes**

<table>
<thead>
<tr>
<th>Antibiotic Group</th>
<th>Urticaria, Hives, or Welts</th>
<th>Macular and/or Papular Drug Exanthema</th>
<th>Erythema Multiforme</th>
<th>Indistinct Other Rashes</th>
<th>Total No. of Rashes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>85</td>
<td>108</td>
<td>15</td>
<td>48</td>
<td>256</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>80</td>
<td>76</td>
<td>9</td>
<td>22</td>
<td>187</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>28</td>
<td>19</td>
<td>8</td>
<td>10</td>
<td>65</td>
</tr>
<tr>
<td>Other cephalosporins</td>
<td>15</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>28</td>
</tr>
</tbody>
</table>

*Some patients developed rashes to more than 1 group of antibiotic.

**Table 4. Frequency of Rashes and Exposure to Other Cephalosporins**

<table>
<thead>
<tr>
<th>Cephalosporin (Generation)</th>
<th>No. of Prescriptions</th>
<th>No. of Patients for Whom the Cephalosporin Was Prescribed</th>
<th>No. of Patients With a Rash</th>
<th>Rashes per Prescription, % (95% Confidence Interval)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cephalexin (1)</td>
<td>648</td>
<td>255</td>
<td>6</td>
<td>0.93 (0.19 to 1.67)</td>
</tr>
<tr>
<td>Cefadroxil (1)</td>
<td>220</td>
<td>85</td>
<td>3</td>
<td>1.36 (−0.17 to 2.89)</td>
</tr>
<tr>
<td>Cefuroxime (2)</td>
<td>390</td>
<td>154</td>
<td>1</td>
<td>0.25 (−0.25 to 0.75)</td>
</tr>
<tr>
<td>Cefprozil (2)</td>
<td>621</td>
<td>241</td>
<td>7</td>
<td>1.12 (0.29 to 1.95)</td>
</tr>
<tr>
<td>Loracarbef (2)</td>
<td>231</td>
<td>94</td>
<td>1</td>
<td>0.43 (−0.41 to 1.27)</td>
</tr>
<tr>
<td>Cefixime (3)</td>
<td>287</td>
<td>112</td>
<td>6</td>
<td>2.09 (0.43 to 3.75)</td>
</tr>
<tr>
<td>Cefpodoxime proxetil (3)</td>
<td>295</td>
<td>117</td>
<td>4</td>
<td>1.35 (0.30 to 2.67)</td>
</tr>
</tbody>
</table>

*P = .02 (cefuroxime vs cefixime). All other comparisons are not statistically significant.

**Table 5. Oral Antibiotics and Serum Sicknesslike Reactions (SSLRs)**

<table>
<thead>
<tr>
<th>Antibiotic Group</th>
<th>SSLRs*</th>
<th>No. of Patients for Whom the Antibiotic Was Prescribed</th>
<th>SSLRs, % (95% Confidence Interval)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillins</td>
<td>4</td>
<td>3469</td>
<td>0.35 (0.15 to 0.55)</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>3</td>
<td>2212</td>
<td>0.36 (0.11 to 0.61)</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>5</td>
<td>527</td>
<td>1.30 (0.73 to 2.07)</td>
</tr>
<tr>
<td>Other cephalosporins</td>
<td>0</td>
<td>1058</td>
<td>0.10 (−0.09 to 0.29)</td>
</tr>
</tbody>
</table>

*Definite SSLR is defined as antibiotics taken for 7 days or more with rash, fever, and joint pains or swelling; probable SSLR, antibiotics taken for less than 7 days, with rash, fever, and joint pains or swelling.

†P < .001 for cefaclor vs penicillins, cefaclor vs sulfonamides, and cefaclor vs other cephalosporins; P = .18 for penicillins vs other cephalosporins; P = .92 for penicillins vs sulfonamides; and P = .17 for sulfonamides vs other cephalosporins.
nearly 4000 consecutive hospital admissions in Boston, Mass, rashes attributable to ampicillin were recorded in 7.7% of 422 patients treated with that antibiotic compared with 2.7% of adult patients with rashes attributable to mixed penicillins. Of the 256 rashes associated with the penicillins in our study, urticaria and erythema multiforme constituted 39.1%. These were thought to be likely allergic. The rest were macular and/or papular drug exanthema and indistinct other rashes that were generally nonpruritic. Such nonpruritic rashes caused by penicillin or amoxicillin are thought not to be IgE mediated and do not mandate abrupt discontinuation of the offending antibiotic. However, they may be the initial presentation of serum sickness or toxic epidermal necrolysis, underscoring the need for close follow-up of patients.

A prospective multicenter study involving 2026 children treated with either amoxicillin or cefaclor in 50 outpatient pediatric offices reported an overall incidence of hypersensitivity-type reactions (maculopapular rash, urticaria, erythema multiforme, or arthritis) of 3.7% with amoxicillin and 5.3% with cefaclor. In that study, however, urticaria occurred 3 times more frequently in the cefaclor-treated children compared with those treated with amoxicillin (2.3% of 1017 children vs 0.7% of 1009 children). In comparison, our study has shown higher rates of rashes in children treated with these antibiotics, with rates of rashes significantly higher with cefaclor than with the penicillins.

The overall frequency of allergic reactions associated with short courses of sulfamethoxazole or sulfisoxazole therapy in hospitalized adults is 3% and is higher with prolonged courses of therapy. Our study showed a rate of 3.6% for urticarialike rashes. We did not investigate the duration of treatment as a risk factor. Infrequently, potentially life-threatening disorders such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and exfoliative dermatitis may occur during or shortly after a course of antibiotics, most notably sulfonamides. These serious adverse reactions almost always require hospitalization and intensive treatment of the affected patient. Our study, like others, did not find any of these serious life-threatening reactions.

Among children older than 9 years in our study, rashes were more common in the girls than the boys. This finding has not been reported previously in children, but Bigby et al. noted a 33% higher rate of cutaneous ADRs among female than male medical inpatients. On the other hand, in children younger than 3 years there were more rashes documented for boys than for girls. The reason and significance of these findings are not clear.

Many of our patients may not have been truly allergic to the antibiotic in question, since only one third of children labeled as allergic either to penicillin or to amoxicillin and 50% of those labeled as allergic to a cephalosporin can be confirmed as having a true IgE-mediated allergy after skin testing or oral challenge. Also, less than 10% of primary care patients with a supposed allergy to penicillin will have a positive radioallergosorbent test result. In patients with a history of true penicillin sensitivity, the risk of a reaction to a cephalosporin is no more than 2%. However, when a drug reaction is suspected, the presence of pruritis, urticaria, angioedema, facial edema, fever, palpable purpura, or blisters necessitates discontinuation of the drug.

There are several limitations that must be considered with the results of this study. The retrospective nature of the study impairs precise ascertainment of all cases of rash recorded for an antibiotic. In addition, the design of the study is apt to produce a rate that is higher than the true rate since the denominator is underestimated. Furthermore, recall bias also could result in an overestimation of adverse effects. Moreover, we have not established that the various antibiotics caused the rashes, and it is likely that some of the rashes were induced by the underlying clinical condition for which the antibiotics were prescribed. In our study, about two thirds of the rashes were physician verified. Even so, Pichichero and Pichichero have observed that physician-diagnosed allergic reactions to β-lactam antibiotics based on patient examination at the time of the reaction, although more accurate than patient history alone, still overestimate the rate of possible true allergy in 66% of patients. Our study also was not designed to determine that the antibiotic was actually taken by the children as prescribed. Furthermore, data on the number of previous exposures to the particular antibiotic and the exact duration of treatment at the time of the rash were not always available. Prospective studies, using skin test, oral challenge, and retest, as suggested by Pichichero and Pichichero, would correct many of these deficiencies but would require significant resources. In addition, skin testing, as an assay for systemic allergy, remains experimental and rudimentary. It has low sensitivity, and there is a great potential for severe adverse consequences. In addition, the sulfonamides, predictive testing for ADRs is reported to be of limited value, skin testing is not useful in assessing risk, and there is no available radioallergosorbent test.

Despite the limitations of our study, we believe that it provides useful information for pediatricians and parents to make more informed choices about antibiotic therapy. In particular, with many excellent and safe alternatives, physicians considering the use of oral cefaclor need to be aware of its relatively high association with rashes.

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REFERENCES