

# Amoxicillin Renal Toxicity

## How Often Does It Occur?

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**Objectives:** To determine the incidence of renal symptoms associated with amoxicillin, a retrospective review of exposures to amoxicillin in children younger than 6 years as reported to the National Poison Data System was done.

**Methods:** All ingestions of amoxicillin without coingestants in humans younger than 6 years reported to the National Poison Data System from 2004 through 2008 were analyzed. Data included age, sex, management site, outcome, symptoms, amount ingested, certainty of amount, chronicity, weight, and therapy. The study was approved by the institutional review board. Descriptive statistics were used to characterize the data.

**Results:** A total of 14,717 cases were identified. Related renal symptoms occurred in 5 patients (0.03%). In 1687 patients (9.6%), the total amount (in milligrams) was documented, and the median amount ingested was 1000 mg. In patients with a known amount (in milligrams) along with the child's weight ( $n = 1356$ ), the median amount was 82.6 mg/kg. In this group, 213 ingested greater than 250 mg/kg (range, 251.4–1531.1 mg/kg; median, 366.5 mg/kg). Treatment sites for this group included the following: treated in the home, 129 (60.6%); treated and released from an health care facility, 63 (29.6%); treated while admitted, 2 (0.9%); refused a referral, 7 (3.3%); lost to follow-up, 9 (4.2%); and managed at other sites, 3 (1.4%). Within this group, 94 patients (44.1%) were followed up to a definitive outcome: 77 (81.9%) had no effect, 15 (16.0%) had minor symptoms, and 2 (2.1%) had moderate symptoms.

**Conclusions:** Although renal toxicity may occur with amoxicillin ingestions, it is rare and does not seem to be dose related.

**Key Words:** amoxicillin, renal, toxicity

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Amoxicillin is a popular semisynthetic antibiotic with broad-spectrum bactericidal activity. In 2010, amoxicillin was the fifth most commonly prescribed generic medication, accounting for 51,083,822 prescriptions.<sup>1</sup> Amoxicillin is considered to be relatively safe, but there are isolated reports of pediatric

patients who developed renal complications.<sup>2–9</sup> To determine the incidence of renal toxicity associated with amoxicillin ingestions, a retrospective review of exposures to amoxicillin in children younger than 6 years that were reported to the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS) over a 5-year period was conducted.

### METHODS

The study was approved by the university institutional review board. All ingestions involving amoxicillin without coingestants in humans younger than 6 years that were reported to the AAPCC NPDS from 2004 through 2008 were reviewed. The case query was based on 433 amoxicillin product-specific 7-digit codes, as identified in Poisindex,<sup>10</sup> which were used by specialists in poison information as part of the electronic medical record documentation process. Data reviewed included age, sex, management site, and outcome. The primary outcome parameters were defined as follows: *no effect*, the patient developed no symptoms as a result of the exposure; *minor effect*, the patient exhibited some symptoms as a result of the exposure but they were minimally bothersome to the patient; *moderate effect*, the patient exhibited symptoms as a result of the exposure, which are more pronounced, more prolonged, or more of a systemic nature than minor symptoms; and *major effect*, the patient exhibited some symptoms as a result of the exposure, which were life-threatening or resulted in significant residual disability or disfigurement.<sup>11</sup> When a definitive outcome was unknown, the outcomes were defined as follows: nontoxic, no effects expected; not followed, minimal effects expected; unable to follow, judged as nontoxic; and unrelated.<sup>11</sup> Collected data also included symptoms, amount ingested, certainty of amount, acuity (defined as *acute*, a single, repeated, or continuous exposure occurring during a period of  $\leq 8$  hours; *acute-on-chronic*, a single exposure that was preceded by a continuous, repeated, or intermittent exposure occurring over a period  $> 8$  hours; and *chronic*, a continuous, repeated, or intermittent exposure to the same substance lasting  $> 8$  hours), weight, and therapy.<sup>11</sup> In those cases where the amount ingested was in grams, the amount was converted to milligrams. These data were characterized using descriptive statistics.

### RESULTS

A total of 14,717 exposures were identified. The patients' ages ranged from 2 days to 5 years. In those cases where the age was expressed in years, the range was 1 to 5 years, with a mean of 2.89 years and a median of 3 years. When the age was documented as days, the range was 2 to 21 days, with a mean of 13.5 days and a median of 15.5 days. The range of age in months was 1 to 23 months, with a median of 13 months and a mean of 12.8 months. There were 8156 males (55.4%) and 6540 females (44.4%), and in 21 patients (0.1%), the sex was unknown. Of all the patients, 13,615 (92.5%) had home management, 815 (5.5%) were treated in a health care facility (HCF), 86 (0.6%)

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Disclosure: The American Association of Poison Control Centers (AAPCC; <http://www.aapcc.org>) maintains the national database of information logged by the country's 61 Poison Control Centers. Case records in this database are from self-reported calls: they reflect only information provided when the public or health care professionals report an actual or potential exposure to a substance (eg, an ingestion, inhalation, or topical exposure, etc), or request information/educational materials. Exposures do not necessarily represent a poisoning or overdose. The AAPCC is not able to completely verify the accuracy of every report made to member centers. Additional exposures may go unreported to Poison Control Centers and data referenced from the AAPCC should not be construed to represent the complete incidence of national exposures to any substance(s).

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were treated at other sites, and 201 (1.4%) were treated at unknown sites. Of the 815 cases treated in an HCF, 784 (96.2%) were treated and released and 31 (3.8%) were admitted. Patient outcomes are tabulated in Table 1.

In the 31 patients who were admitted to an HCF, 17 (57.4%) had no effect or had a minor effect (Table 2). In 1687 patients (9.6%), the amount was identified in milligrams (mg). The median amount ingested was 1000 mg. When the amount was documented along with the child's weight (1356 patients [9.2%]), the median amount ingested was 82.6 mg/kg. Within this group, there were 213 patients with ingestions of 250 mg/kg or greater. The amounts ranged from 251.4 to 1531.1 mg/kg, with a median of 366.5 mg/kg (IQR, 153.9 mg/kg). Most of these patients were managed on site and not in an HCF. Definitive outcomes in this group included no effect or minor effect in 92 patients (43.2%) and a moderate effect in 2 patients (0.9%). The remainder of the 119 patients (55.9%) were coded as unable to follow because either no effect was expected or minor effects were expected or they were judged as potentially toxic—unable to follow.

Acuity included acute (11,041, 75.0%), acute/chronic (3318, 22.5%), chronic (349, 2.4%), and unknown (9, 0.1%).

Renal symptoms included urine color change in 4 patients, hematuria (unknown if related) in 1 patient, urine oxalate crystals in 1 patient, and an increased serum creatinine in 1 patient (Table 3).

## DISCUSSION

There are several published cases of amoxicillin-related adverse renal effects. These include acute interstitial nephritis, acute renal failure, hematuria, and crystalluria.<sup>2-9</sup> These effects have occurred as a result of oral or intravenous administration, an idiosyncratic drug reaction, a single therapeutic dose, chronic therapy, and an overdose. The proposed mechanisms of the renal complications associated with an amoxicillin overdose include the crystallization of the drug within the tubular lumen, renal venules, or interstitium; direct cellular toxicity; vasoconstriction; or an immediate hypersensitivity reaction.<sup>2-9</sup> Renal toxicity has been described in children who ingested amoxicillin either as an acute overdose or after chronic therapeutic use, from 120 to 1136 mg/kg.<sup>4,5,7-9</sup> Four children who ingested a liquid preparation of amoxicillin developed renal symptoms within 3 to 5 hours after exposure.<sup>5,7-9</sup> Symptoms included hematuria and the passage of clots (574 mg/kg), dysuria and hematuria (545 mg/kg), penile pain and hematuria (333–733 mg/kg), and a small white crumbly mass at the urethral meatus (120 mg/kg). A 2.5-year-old ingested 30 to 50 chewable amoxicillin tablets (estimate, 681–1136 mg/kg) and developed gastrointestinal symptoms at 12 hours after exposure, and at 16 hours after exposure, he

**TABLE 2.** Patient Outcome When Admitted to a Health Care Facility

Outcome	n (%)
No effect	12 (38.7)
Minor effect	5 (16.1)
Moderate effect	6 (19.4)
Not followed—unknown effect	7 (22.6)
Unrelated effect	1 (3.2)

became anuric.<sup>5</sup> A 27-month-old girl receiving nightly amoxicillin prophylactic dosing for vesicoureteral reflux presented with weight gain, oliguria, and generalized swelling.<sup>3</sup> After 10 weeks of steroid therapy, she showed no improvement and was diagnosed with amoxicillin-induced acute interstitial nephritis. Her symptoms resolved after discontinuation of the amoxicillin.

The Poisindex poison information system, which is used as the basis for making toxicology treatment decisions by specialists in poison information and by emergency physicians, states that amoxicillin doses that do not exceed 250 mg/kg are unlikely to cause toxicity.<sup>12</sup> This recommendation is based on a single prospective study of 51 cases of amoxicillin ingestion of 250 mg/kg or less in children younger than 6 years, 80% of whom remained completely asymptomatic.<sup>13</sup> In this case series of 14,717 patients, only 5 patients (0.03%) developed renal symptoms. All 5 patients ingested a liquid preparation. Two had amounts that were identified: case 2, 3750 mg or 243.5 mg/kg (estimated); and case 3, 8000 mg or 588 mg/kg (exact). In the other 3 patients, the amounts were either unknown or the dose was expressed in milliliters making it impossible to determine the amount ingested because the concentration of the amoxicillin product was unavailable. Two of these patients were treated and released from a HCF, 2 were admitted, and 1 was lost to follow-up. In the 4 patients where follow-up was performed, all received intravenous fluids only and 3 were asymptomatic within 24 hours. In cases where the amount was identified and there were no renal symptoms ( $n = 1687$ ), the mean amount ingested was 1890 mg and the median amount was 1000 mg. Symptoms exhibited included vomiting, rash, nausea, abdominal pain, and "other." In the 1356 of cases with an available weight and amount, no serious effects were noted. In 213 cases within this group, the amount was 250 mg/kg or greater—the current amount recommended for treatment. Eighty patients (37.5%) were either en route or referred to an HCF for treatment and 63 (78.7%) were treated and released. Two patients were admitted, both to a non-critical care unit, and 133 patients (62.5%) in this group were managed in non-HCFs.

In conclusion, in this case series of 14,717 children who ingested amoxicillin, only 5 developed minor renal symptoms and all recovered within 3 days. There were 213 patients where a milligram-per-kilogram determination was documented and who ingested 250 mg/kg or greater; only 2 exhibited documented renal symptoms, with the majority being asymptomatic within 24 hours. Although renal toxicity may occur with amoxicillin ingestions, it is rare. Poison centers and emergency physicians should conduct a follow-up call at 6 to 8 hours after exposure to evaluate for renal problems (eg, urinary color change, hematuria, difficulty urinating). If these occur, the patient should be referred to an HCF.

## LIMITATIONS

The interpretation of these data is subject to the inherent limitations of all data in the AAPCC NPDS. The AAPCC

**TABLE 1.** Patient Outcomes

Outcome	n (%)
No effect	3023 (20.5)
Minor effect	333 (2.3)
Moderate effect	28 (0.2)
Judged as nontoxic, no effects expected	2185 (14.8)
Not followed, minimal effects expected	8855 (60.2)
Unable to follow, judged as nontoxic	168 (1.2)
Unrelated effects	124 (0.8)
Fatal	1

TABLE 3. Symptomatic Patients

Patient	Amount Ingested	Symptoms	Treatment Site
Case 1 (6-mo-old girl)	5 mL	Urine color change	Refer to a hospital, lost to follow-up
Case 2 (2-y-old girl)	3750 mg	Urine color change	Treated and released from emergency department
	243.5 mg/kg	Hematuria (unknown if related)	Asymptomatic within 24 h
Case 3 (5-y-old girl)	8 g	Urine color change	Admitted
	588 mg/kg	Oxalate crystals	Asymptomatic within 3 d
Case 4 (2-y-old boy)	Unknown	Urine color change	Admitted
			Asymptomatic within 24 h
Case 5 (2-y-old girl)	100 mL	Increased serum creatinine	Treated and released from emergency department
			Asymptomatic within 24 h

(<http://www.aapcc.org>) maintains a national database (NPDS) of information logged by the 57 poison information centers in the United States. Case records in this database are from self-reported calls; they reflect only information provided when the public or health care professionals report an actual or potential exposure to a substance (eg, ingestion, inhalation, dermal exposure). Exposures do not necessarily represent a poisoning or an overdose and are not necessarily confirmed by laboratory analysis. In these exposure reports, some caller information may be incomplete or recorded inaccurately, despite quality control measures taken by individual poison information centers. In 76.2% of the exposures, no follow-up was conducted; therefore, the conclusions reflect only the subset of exposures where a known outcome was determined. No measures were undertaken in this research to verify the accuracy of the individual variables by independently sampling a subset of calls, which, although impractical and impossible because of the nature of the data, would have added to the validity of the exposure reports. Additional exposures may go unreported to poison information centers and the data cited in this article from the AAPCC should not be construed to represent the complete incidence of national exposures to amoxicillin and the true frequency of exposures is likely underestimated. The data presented in this article, the interpretation of the data, and the conclusions do not represent the opinions of the AAPCC.

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