



## Adverse reaction to Amoxicillin: a case report

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### Abstract

*Penicillin is the drug that most often leads to allergic reactions and anaphylaxis. The incidence of adverse events triggered by penicillins is believed to be between 1% and 10%. Up to one-tenth of these episodes are life-threatening, with the most serious reactions occurring in patients with no history of allergy.*

*The case of a 5 year, 3 month-old female who had a severe allergic reaction to amoxicillin prior to a dental appointment is described. The literature on penicillin hypersensitivity is reviewed and recommendations for management of an allergic reaction in the pediatric dental office are discussed. (Pediatr Dent 22:401-404, 2000)*

**A**dverse drug reactions are the leading cause of medical injury in hospitalized patients in the United States with the number of affected subjects being four times the total number killed in motor vehicle accidents every year.<sup>1</sup>

Antibiotics account for 15-30% of the world's drug expenditure and the penicillins comprise the largest class in this group.<sup>2,3</sup> Therefore it is not surprising that it is the antibiotic that most often triggers allergic and anaphylactic reactions.<sup>3</sup> The incidence of penicillin reactions is believed to be between 1% and 10% although an exact estimate is difficult to be reached because of subjective and non-standardized criteria.<sup>1,3-7</sup> Patients who have taken the antibiotic without problems have a less than 1% risk of an allergic event when rechallenged.<sup>1,3</sup> Up to 10% of adverse reactions to penicillin are life-threatening because of laryngeal edema, bronchospasm, or hypotension, with 2% to 10% of these events being fatal.<sup>8,9</sup> Unfortunately, the most serious reactions occur in patients without any history of allergy.<sup>8</sup>

Physician-diagnosed allergy to beta-lactam antibiotics based on patient examination at the time of the event is more accurate than the patient's history alone. However, it still overestimates the rate of possible true allergy in 66% of the subjects.<sup>10</sup> The term 'penicillin allergy' is often overused in childhood<sup>11</sup> and can describe a number of different reactions to antibiotics.<sup>7</sup> When an adverse event happens, it is necessary to confirm whether it was truly caused by the drug because coincidental reactions are common in pediatrics, e.g., it could have been caused by an illness.<sup>12-16</sup> Several methods are available to diagnose penicillin allergy, such as skin prick tests, skin patches, intradermal skin test, the radioallergosorbent test (RAST), Enzyme-Linked Immunoassay test (ELISA) and oral challenges.<sup>1,3,4,15,17</sup> Withholding antibiotic therapy is the most

effective measure in preventing a problem.<sup>3,8,10</sup> However, when alternative drugs would be either ineffective, associated with unacceptable side effects, or clearly less effective, then the use of penicillin or cephalosporin must be explored using a desensitization protocol, except in patients with Stevens-Johnson Syndrome or other exfoliative diseases.<sup>1,3,4,7,8,18</sup>

The case of a young female who presented a severe allergic reaction to amoxicillin in the reception area of a hospital dental clinic while waiting for her appointment is presented. A literature review on penicillin hypersensitivity and management recommendations are discussed.

### Case report

A 5 year 3 month old Caucasian female was scheduled for an operative appointment in our hospital dental clinic. She was born with hypoplastic left heart syndrome and had undergone multiple surgeries for staged palliation with very good results. Although she had recently complained of increased fatigability and occasional episodes of cyanosis and listlessness of unknown origin, her most recent echocardiogram and physical exam suggested she was in a reasonable cardiovascular condition. She had no known drug allergies and was currently taking Captopril 5 mg bid, Aspirin 81 mg once daily, and Furosemide 10 mg once or twice daily, depending on her general condition. The family history was negative for drug allergies.

She was referred by her cardiologist in January 1998 for evaluation of multiple carious lesions. Due to her medical history and extensive dental needs, she was treated under general anesthesia, receiving ampicillin intravenously for endocarditis prophylaxis according to the American Heart Association recommendations.<sup>19</sup> She returned two weeks later for a follow-up examination and poor oral care was evident again. Oral hygiene instructions and diet counseling were reviewed in detail with the patient and her mother. When she returned for a six-month examination, the hygiene had not improved and several new carious lesions had developed. Operative appointments were made and 1g amoxicillin p.o. one hour before the appointment was prescribed for protection against endocarditis.<sup>19</sup> Her weight was 19 kg.

She had had two operative appointments 3 weeks apart and prior to her last visit, the patient took the antibiotic as usual and within a few minutes presented a foot itch. When she arrived at the dental clinic 30 minutes later, the tongue and lips were swollen, and a body-wide rash and itch were evident. She was immediately taken to the pediatric emergency service,

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where she developed swallowing difficulties. Respiratory distress, chest pain, shortness of breath, and uvular swelling were not detected. She had no viral symptoms, fever, chills, nausea, vomiting, or headache. She had just seen her cardiologist earlier that day who stated she was in good health. On physical examination, her blood pressure was 100/60, pulse 94, respiratory rate 34, blood oxygenation 97%, capillary refill was less than 2 seconds, and her temperature was 99° F. She was alert and interactive. The emergency room physicians concluded that she had had a severe allergic reaction to amoxicillin. An intravenous line was placed and the patient was given 25 mg of diphenhydramine hydrochloride, which had an immediate effect in reducing her lip and tongue swelling, and almost completely resolved her rash after 5 minutes. She was also given 30 mg of methylprednisolone IV. Epinephrine was withheld due to the patient's quick response to the previous drugs. She had no oxygen desaturation or respiratory distress, maintaining the saturation in the 97%-99% range on room air. She was able to tolerate liquids orally at the time of discharge. The physicians advised our service to prescribe clindamycin for future dental appointments. The cardiologist was consulted and made aware of this event.

## Discussion

The term beta-lactam antibiotics refers to penicillins, including amoxicillins, cephalosporins, carbapenems, and monobactams, all of which have a common beta-lactam ring structure.<sup>20</sup> The chemical structure of amoxicillin differs from penicillin in the side-chain where the former contains additional alfa-amino and p-hydroxy groups.<sup>21</sup> Individuals can be allergic to different drugs in the beta-lactam antibiotic group because of the cross-reactivity between members of this drug class.<sup>21,22</sup> In fact, diagnosis of patients with allergic reactions to amoxicillin and good tolerance of other penicillins appears to be increasing.<sup>21</sup> However, reliable incidence and frequency of each reaction with each drug are not always available and most of the information on specific types of allergic reactions comes from data on penicillin but it appears to be similar for the majority of beta-lactam antibiotics.<sup>20</sup>

Allergic reactions are classified as Type I (IgE-mediated), Type II (cytotoxic antibodies, often involving complement), Type III (antigen-antibody immune complex and complement-amplified reaction) and Type IV (cell-mediated hypersensitivity).<sup>7,8,13</sup> However, certain immunopathological reactions do not fit into this classification, such as the maculopapular rashes commonly seen with penicillin therapy.<sup>3,7,22</sup> Although penicillins and other beta-lactam antibiotics, including amoxicillin, are capable of eliciting a broad spectrum of immune response, the acute reactions have been classically related to IgE mechanisms, which are the most important clinically because of its anaphylactic potential.<sup>3,8</sup> They are classified according to their clinical manifestations.<sup>2-4,23,24</sup> As in the case described, *immediate* reactions occur within 30 to 60 minutes of the drug administration and are manifested clinically by diffuse urticaria, rhinitis, wheezing, angioedema, laryngeal edema, hypotension and shock.<sup>3,4,13,14,23-25</sup> *Accelerated* reactions are manifested from 1 to 72 hours after the onset of therapy and may present urticaria, wheezing, angioedema, and occasionally laryngeal edema.<sup>3,4,13,23</sup> Events that lead to fatality occur within one hour of the drug intake in 96% of the cases, with one death per 50,000-100,000 treatment courses.<sup>3,8</sup> *Late or*

*delayed* reactions begin after 72 hours and include urticaria, serum sickness, maculopapular rashes, drug fever, hemolytic anemia, nephritis, thrombocytopenia, leukopenia, exfoliative dermatitis and Stevens-Johnson Syndrome.<sup>3,5,14,23</sup>

The tendency to react to penicillins is associated with age, immune responsiveness, atopy history, route of administration, dose, previous exposure to penicillin, time elapsed since last reaction and genetic markers. The most important and reliable risk factor is a history of a previous reaction to the drug being considered for treatment or one that is immunochemically similar.<sup>26</sup> Adults between 20 and 49 years of age seem to be at greatest risk, with children presenting a reduced chance because of their less cumulative exposure to antibiotics.<sup>3,8,26,27</sup> About 25% of children with at least one parent who is allergic to an antibiotic may be at risk for development of allergy compared to 2% when neither parent has a drug allergy.<sup>18,22</sup> Topical application is the most likely to elicit sensitization followed by parenteral administration, especially intramuscular injections, whereas the oral route is the safest probably because larger doses are delivered parenterally or intravenously over a shorter period of time.<sup>3,4,8,9,18,26</sup> In general, drugs used continuously for extended periods of time have less chance to trigger an adverse reaction<sup>3,7,18</sup> but multiple intermittent therapy courses increase the risk, as seen in this case.<sup>8,27</sup> The chance of another adverse episode declines as the time interval between the original attack and the drug readministration increases,<sup>4,14,15,28</sup> although this is not universally accepted.<sup>10,29</sup> Immune mechanisms involved in adverse reactions to penicillins may also be related to genetic markers of immune response.<sup>24</sup>

Penicillin is a hapten and, therefore, not immunogenic by itself; it is rather its metabolic products that form the allergenic haptens.<sup>4,7</sup> The penicilloyl group is the major metabolic product and it is thus referred to as the "major determinant," which is also seen in other penicillin analogues such as amoxicillin and ampicillin.<sup>3,4,7,13,20,23</sup> Less than 5% of penicillin is metabolized by other pathways and its products are called "minor determinants" which are associated with the most severe IgE-mediated reactions to penicillin.<sup>3,4,7,13,23</sup> Skin tests constitute the most valuable (96% accuracy at any given time) and convenient method for evaluation of penicillin hypersensitivity but they have no predictive value for non-IgE-mediated reactions.<sup>3,4,7,23,30</sup> There is a trend toward an increase of late response to penicillins nowadays due to the increased consumption of amoxicillin,<sup>2</sup> therefore delayed readings of skin tests can be highly informative.<sup>17,29</sup> The incidence of positive tests in children with a history of penicillin allergy is 10%.<sup>30</sup> In these cases, the patient should not receive penicillins, including semisynthetic ones, and cephalosporins (especially first and second generations) because of their similar metabolites.<sup>3,9,13,20,23</sup> Patients with a history of anaphylaxis should wear medical alert bracelets and carry epinephrine for self-administration such as EpiPen, EpiPen Jr, and Ana-Kit.<sup>31,32</sup>

## Management in the pediatric dental office

In taking steps to prevent a penicillin reaction, the pediatric dentist should always obtain a thorough medical history, including the family history of drug allergy as studies have suggested that children of parents who have demonstrated one or more adverse reactions to drugs have a higher risk to develop an event themselves.<sup>18,22</sup> The risk of a reaction is likely to increase whenever immunodeficiencies are present or the

metabolism or excretion of a drug is impaired due to hepatic or renal insufficiency, with the latter enhancing the risk of toxic, but not allergic, drug reactions.<sup>26</sup> For patients who report an allergy to antibiotics, the dentist should specifically try to determine which substance caused the event and how the patient reacted to it. If a true allergic reaction occurred, one or more of the classic signs or symptoms of allergy should have been evident such as urticaria, swelling, skin rash, chest tightness, dyspnea, shortness of breath, rhinorrhea, and conjunctivitis.<sup>9</sup> A medical consultation is warranted if the history is not clear. When the patient is using the antibiotic for the first time, it should preferably be administered in the dental office and the child should be observed for 30 minutes after the drug administration. The caretakers should be informed about signs and symptoms of an allergic episode and advised to seek immediate care if any reactions occur after leaving the dental office.<sup>9</sup> The dental team must have the ability to quickly recognize a problem and introduce prompt and appropriate management measures.<sup>33</sup>

The scenario seen with this patient is typical.<sup>33</sup> Angioedema or urticarial swelling, a painless soft tissue swelling produced by transudate from surrounding vessels that may trigger itching or burning,<sup>9</sup> developed rapidly around and within the oral cavity a few minutes after the administration of the drug. If only the skin is involved but the reaction is systemic, the following steps should be taken:<sup>32,33</sup>

- position the patient comfortably in the upright or erect position
- assess airway, breathing, and circulation, implementing measures as needed. The dental team should minimize the risk of the reaction to progress to involve the respiratory and/or cardiovascular systems. After the clinician determines that those systems are not involved, diphenhydramine hydrochloride 25-50 mg IM or IV (in this case, give slowly) should be administered. Avoid oral administration because the onset is slow.
- observe the patient for 1 hour and only allow him/her to leave the office escorted after the itching has resolved. Prescribe diphenhydramine as follows: - 5 mg/kg/day or 150mg/m<sup>2</sup>/day IM, IV or PO in divided doses every 6-8 hours, not to exceed 300 mg/day for at least 48 hours,<sup>34</sup>  
*OR*
  - 1-2 mg/kg every 6 hours IM, IV or PO, to a maximum of 300 mg/day, for at least 48 hours;<sup>31,35</sup>
  - *OR* 1 mg/kg per dose (up to 50 mg) PO 4 times daily.<sup>32</sup>

The specific recommendations for the prescription of histamine blockers are somewhat arbitrary, with the therapy beginning with low doses titrated upward to relieve symptoms without causing significant adverse effects.<sup>18,36</sup> Maculopapular rashes generally resolve spontaneously within one week of discontinuation of the offending drug.<sup>35</sup> Sedation is the most common side effect of most first generation H1 histamines which helps an itching child sleep. Non-sedating second-generation antihistamines are now available and have the advantage of avoiding the central nervous system depression and anticholinergic effects of the first-generation.<sup>32</sup> However, anaphylactic reactions do occur and histamine blockers are not the first drug of choice in these cases.<sup>22,32</sup>

**Anaphylaxis** is an acute, potentially life-threatening reaction caused by rapid release of mediators from mast cells and

basophils that follows the interaction of allergen with specific cell-bound immunoglobulin.<sup>18</sup> Anaphylaxis to penicillins occurs in 0.04% to 0.2% of treated subjects and the fatalities tend to occur more frequently in atopic individuals and asthmatics with active disease.<sup>22,30</sup> The signs and symptoms of an anaphylactic reaction include soft palate itching, nausea, vomiting, substernal pressure, shortness of breath, hypotension, pruritus, urticaria, laryngeal edema, bronchospasm, and cardiac arrhythmias.<sup>9</sup> Both respiratory and circulatory depression happen early, and is often fatal unless prompt diagnosis and immediate implementation of therapy is done.<sup>9,18,22,32,33</sup>

Management of an anaphylactic reaction should be as follows:<sup>18,22,31-33,36</sup>

- place the patient in an upright or erect position if he/she is conscious and respiratory distress is the primary component of the anaphylactic response. If a significant cardiovascular response is present (e.g., hypotension), place the victim in the supine position with the legs elevated to optimize cerebral perfusion.
- assess airway, breathing and circulation, implementing measures as needed.
- inject epinephrine 1:1000 in a dose of 0.01 ml/kg to a maximum of 0.3 ml subcutaneously or intramuscularly *without* delay. The drug is rapidly metabolized and can be given every 12-15 minutes to maintain adequate blood pressure until recovery occurs (observe the maximum amount).
- call 911.
- administer oxygen at a flow of 5 to 6 l/min.
- administer antihistamine IV or IM as discussed.
- the emergency team takes over the patient.

Corticosteroids are reserved for more severe reactions not relieved by the aforementioned measures.<sup>18,35,36</sup> After being stabilized, the patient will be transported to the nearest medical center for definitive treatment and, depending on the severity of the case, may be admitted for a period of time.<sup>32,33</sup>

## Conclusion

The pediatric dentist often treats patients who need antibiotics for oral infection or endocarditis prophylaxis. A thorough medical history, both of the patient and the family, must be obtained and for those individuals with a positive history a detailed investigation should be done. Unfortunately, the most severe reactions occur in patients with no report of previous adverse events. Furthermore, individuals may have used the antibiotic in the past without any problems and then develop sensitization as in the case described. The dental professional should always err on the side of conservatism, thus the patient should be treated with alternative drugs when possible. Children and adolescents with a history of allergy to penicillins should be prescribed clindamycin or erythromycin.

It is of paramount importance to have an emergency protocol in the pediatric dental office. Regular emergency drills and cardiopulmonary resuscitation training once yearly are essential tools for the rapid implementation of therapy in the event of an adverse reaction. An updated crash cart and monitoring equipment, such as a pulse oximeter, should be readily available.

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