

Multiple antibiotic allergy syndrome

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Allergists/immunologists are commonly referred patients with histories of multiple antibiotic allergies and must determine what antibiotics they can safely use. This review covers articles published through September 2003. The history and definition of the multiple antibiotic allergy syndrome are discussed. The clinical and laboratory evidence suggesting that certain individuals make allergic antibody to unrelated antibiotics is explored. A framework for dealing with this potentially vexing problem on a clinical level is developed. Areas that require additional research and development are outlined.

Background

The essential risk factor for experiencing an adverse reaction to an antibiotic is exposure to the antibiotic. True IgE-mediated allergy represents only a small subgroup, approximately 10%, of all adverse antibiotic reactions [1]. Unfortunately, the term *allergy* is often used inappropriately to characterize any adverse reaction, even when an IgE-mediated mechanism is not compatible with the reported symptoms. Physicians appropriately fear antibiotic allergy owing to images from their training. Demonstrations of anaphylaxis, that is, sudden hypotension, bronchospasm, and death, associated with exposure to a normally innocuous antibiotic in a sensitized laboratory animal make a lasting impression. The reality is that most severe adverse antibiotic reactions seen in clinical medicine are not full-blown anaphylaxis. Even most IgE-mediated adverse antibiotic reactions do not result in anaphylaxis.

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The concept of multiple antibiotic allergy dates to the 1960s when cephalosporin use began to become widespread. Some patients who had histories of penicillin allergy were noted to have adverse reactions associated with cephalosporin use [2,3]. The term *multiple antibiotic allergies* first appeared in a title in the clinical literature in 1978 [4].

If the definition of multiple antibiotic allergy is the documentation by a skin test or in vitro specific IgE test of reactivity to two unrelated antibiotics, both of which have been associated with adverse reactions compatible with an IgE-mediated mechanism, the total number of individuals with multiple antibiotic allergy syndrome is small. If the definition is liberalized to include all patients with clinical histories of “adverse” reactions associated with two unrelated antibiotics, approximately 1% of health care–using populations may have the syndrome. Lee and coworkers [5] reported in 2000 on a cohort of 1893 hospitalized patients requiring antibiotic therapy; 85 (4.5%) had a history of two or more antibiotic “allergies.”

A patient survey or clinical history cannot establish IgE-mediated antibiotic allergy without testing [6]. Despite this limitation, an accurate and complete history is the essential element of a useful multiple antibiotic allergy consultation [7]. The history can establish which patients should not be tested for IgE directed against the implicated antibiotic. Patients with a history of toxic epidermal necrolysis, Stevens-Johnson syndrome, hepatitis, nephritis, or hemolytic anemia cannot benefit from being told they do not make IgE to the implicated antibiotic. Because of the life-threatening nature of these reactions and the uncertainty of recurrence rates, they need to continue to avoid the antibiotic.

The more exposures an individual has to different antibiotics, the more likely he or she is to report adverse reactions and “multiple antibiotic allergy.” In a large group of persons exposed to multiple unrelated antibiotics, even if adverse antibiotic reactions are completely random, certain individuals will be identified who have adverse reactions associated with multiple agents. In 1998, Asero [8] presented a retrospective report on 120 individuals with histories of adverse antibiotic reactions. The subjects were given a total of 253 elective oral antibiotic challenges to find an antibiotic they could tolerate. Female sex, a history of multiple antibiotic reactions, and reactions to nonsteroidal anti-inflammatory drugs (NSAIDs) were the main risk factors for reactions to elective oral antibiotic challenges.

A key question that is only starting to be addressed is whether a documented allergic reaction to one antibiotic increases the probability of an allergy to a second unrelated antibiotic. The overall quality of much of the world’s literature on antibiotic-associated adverse events and allergy testing is poor [9]. In a commentary in 2001, Ross [10] noted a myriad of problems, including confusing taxonomy, a lack of prospective data collection, and problems with event ascertainment. This observation is particularly true when multiple antibiotic allergy is considered.

Currently, one can argue that there is no definitive evidence that a multiple antibiotic allergy syndrome exists. In an editorial in 2000, Warrington [11] pro-

posed that several factors must be satisfied to establish its existence. First, gold standard tests need to be used to establish allergy. For antibiotic allergy, this requirement limits the field considerably. The only well-validated tests for antibiotic allergy are for penicillin. Well-characterized *in vivo* and *in vitro* tests exist to identify the presence of clinically significant IgE directed against penicillin metabolites than can haptenate serum proteins. Second, the identification of individuals with the multiple antibiotic allergy syndrome needs to be made prospectively. This goal requires identifying a large group of penicillin history–positive, skin test–positive individuals and determining whether IgE-mediated adverse reactions to other antibiotics are more common than in matched control individuals who are penicillin skin test–negative. Well-validated, widely used tests for clinically significant IgE directed against cephalosporins including minor determinants essentially do not exist [12]. There are few useful tests for clinically significant IgE directed against non–beta-lactam antibiotics [13].

Despite this pessimistic introduction, progress is being made. In 2003, Notman and coworkers [14] reported on progress with skin testing for quinolone allergy. Comprehensive electronic medical records are being developed for health care systems that treat large groups of people. In these systems, a single searchable medical record can potentially capture all antibiotic use and the characteristics of all significant adverse events temporally associated with antibiotic use over long periods. Although such comprehensive data are currently not available for a health care program that widely uses penicillin skin testing in advance of need, this information should be accessible in the near future (E. Macy, MD, personal communication, August 2003).

Antibiotic adverse reaction rates from electronic databases

In 1997, Hunziker and coworkers [15] presented data on 20 years of computerized comprehensive hospital drug monitoring for adverse skin reactions. A total of 34,840 patients had 48,005 consecutive admissions. These patients received 14,355 penicillin courses and had 605 (4.2%) associated maculopapular rashes, 25 (0.2%) associated episodes of urticaria, and 4 (0.03%) associated vasculitic rashes. These patients also received 5789 sulfonamide courses and had 137 (2.4%) associated maculopapular rashes, 5 (0.09%) associated episodes of urticaria, and 5 (0.09%) associated vasculitic rashes. No Stevens-Johnson syndrome, toxic epidermal necrolysis, or anaphylaxis was reported. No attempt was made to identify individuals with reactions to more than one class of antibiotics.

Apter and coworkers in abstract form presented one of the first reports involving adverse events associated with oral penicillin as compiled from a large population electronic database in 2002. They obtained data from a computerized health care record set from Britain containing 8 million records of patients seen in 687 general practitioners' practices [16]. A total of 3.4 million patients received at least one course of a penicillin. Of this group,

18,866 patients (559 per 100,000 patients or 0.56%) experienced an outcome consistent with hypersensitivity. Manifestations of hypersensitivity included anaphylaxis, 4.6 (rate per 100,000 patients exposed to penicillin); angioedema, 19.1; dermatitis, 1.4; toxic epidermal necrolysis, 1.1; erythema multiforme, 36.9; laryngeal spasm, 2.5; urticaria, 422.2; or an allergic reaction attributed to drugs, 80.1. Of the patients initially identified, 10,727 (57%) received a subsequent penicillin course; of that group, 404 (3.8%) had another adverse reaction.

Other factors to consider when investigating multiple antibiotic allergy

The underlying psychologic make up of an individual receiving a drug is a significant factor in the likelihood that he or she will report an adverse drug reaction. This factor complicates the capture of antibiotic use—associated adverse reaction clinical data. In 1996, Meyer and coworkers [17] reported on this phenomenon in placebo reactions. They concluded that the distribution of the incidence of complaints in a nonselected group of healthy volunteers was not random. In 2003, Davies and coworkers [18] reported that patients with psychiatric morbidity were more likely to report non-drug-specific intolerance associated with a particular medication class such as antihypertension medication. The influence of psychiatric comorbidity has not been well studied in individuals with specific histories of multiple antibiotic intolerance to date. In 1991, Patriarca and coworkers [19] reported on a highly selected group of individuals with total drug intolerance. They recommended psychiatric work-ups in these patients. In the future, it will be important to evaluate the influence of psychiatric morbidity on the number of antibiotics patients are exposed to and the rates at which adverse reactions are reported.

The route of antibiotic administration can have an important influence on the adverse reaction rate. In 1979, Herman and Jick [20] noted that cutaneous adverse reaction rates were approximately double in patients receiving parenteral versus oral penicillin preparations.

Further complicating the literature on the multiple antibiotic allergy syndrome are conditions that increase drug-associated, allergy-like reactions. One of the most prominent of these conditions is chronic urticaria [21]. NSAID intolerance can predate the onset of clinically apparent chronic urticaria or can be a problem on its own [22]. In 2002, Apter et al commented that individuals with chronic urticaria might be overrepresented in their adverse reaction associated with penicillin use cohort [16]. Individuals with chronic urticaria commonly have flares in the activity of their hives with infections. Often, upper respiratory infections, even viral infections, are treated with antibiotics [23]. Affected individuals then note a “reaction” to the antibiotic and, over the years, can accumulate long lists of drug “allergy.” As many as 20% to 30% of individuals with chronic urticaria may have symptom amplification with NSAID exposure [24].

In 1992, Pozniak and coworkers [25] reported on an association between HIV infection and multiple adverse antibiotic reactions to tuberculosis medications. Johnson and coworkers [26] reviewed the high rates of sulfonamide-associated adverse reactions in HIV-infected individuals in 1990. Burrows and coworkers [27] in 2003 reported on a series of 19 patients with cystic fibrosis who had a mean of 3.3 antibiotic allergies per patient. As many as 30% of patients with cystic fibrosis reported at least one antibiotic allergy. They concluded that desensitization is often required. They also suggested premedication with systemic steroids and antihistamines, although there are no data from a prospective randomized study to support this practice. Earl and Sullivan [28] in 1987 also noted that desensitization could be difficult in patients with cystic fibrosis.

Current clinical literature on multiple antibiotic sensitivity

Despite these problems, a literature exists on the identification and management of patients with apparent multiple antibiotic sensitivities. In 1990, Kamada and coworkers [29] reported on 120 children out of an initial group of more than 300 evaluated for antibiotic allergy who had histories of reactions associated with at least two classes of antibiotics. Two patients (1.7%) had reactions to four or more antibiotic classes, and 22 (18.3%) had reactions to three classes. Almost all of the reactions were rashes, and beta-lactams accounted for most of the reactions. They reviewed the ingredients used in the oral antibiotic formulations and ruled out the possibility that a common additive or preservative was responsible. A subgroup of 115 patients underwent skin or in vitro testing for penicillin allergy, and 31 of the tests (27%) were positive. It was concluded that children with multiple antibiotic sensitivity were likely to be allergic to penicillin, but prospective studies on this topic were needed.

In 1996, Khoury and Warrington [30] reported on 44 penicillin allergy history–positive, skin test–positive individuals and compared them with 44 age- and sex-matched controls with a penicillin allergy history but negative penicillin skin tests and 44 control patients with vasomotor rhinitis and no penicillin allergy history. Their retrospective study was of adequate size to detect a 20% difference in historical adverse reaction rates to non–beta-lactam antibiotics between the three groups, and no significant differences were seen. Contrary to the results of Kamada and coworkers, Khoury and Warrington concluded that the development of penicillin allergy and non–beta-lactam allergy occurs independently.

In 2000, Park and coworkers [31] published a retrospective review of 97 children referred to a tertiary adverse drug reaction clinic for the evaluation of adverse reactions associated with multiple antibiotic classes. The patients represented 11% of the total referrals for adverse antibiotic reactions. They were unable to conclude that multiple antibiotic sensitivity was a distinct clinical syndrome, and suggested that it may be a manifestation of a more fundamental problem in dealing with xenobiotics, or foreign substances, in the set-

ting of infection. They also proposed that, if the syndrome really exists, it is uncommon.

In 2002, Macy and Burchette [32] reported on 83 penicillin allergy history– and skin test–positive individuals and 166 history-positive but penicillin skin test–negative controls matched for age, sex, and length of follow-up. All of the patients used at least one course of oral antibiotics during the follow-up period and were selected out of a total of 1081 patients skin tested between 1994 and 2000. The 249 study subjects were exposed to 1655 courses of oral outpatient antibiotics during routine clinical care over a 34.5-month average follow-up period. For penicillin skin test–positive individuals, the adverse reaction rate was not significantly different with cephalosporin use when compared with non–beta-lactam use ($P = 0.12$). In penicillin skin test–negative individuals, the adverse reaction rate was significantly lower with cephalosporin use when compared with non–beta-lactam use ($P = 0.005$). Overall, the patients with histories of a “penicillin allergy,” whether skin test positive or negative, had adverse reactions associated with antibiotic use 4.4% of the time. It was concluded that penicillin skin testing was only able to predict penicillin-associated adverse antibiotic reactions.

Current laboratory analyses of multiple antibiotic allergy

Baldo and coworkers have significantly advanced the laboratory study of multiple drug allergy and specifically the analysis of multiple antibiotic allergy as it relates to beta-lactams. In 2002, Baldo and Pham reviewed their own work along with a few contributions from other researchers [12]. They concluded that some patients do have multiple drug allergies. In 2001, Zhao et al [33] reported an analysis of sera from patients with amoxicillin allergy that reacted with amoxicillanyl but not amoxicilloyl determinants. These findings support the concept that small conformational changes can be important in IgE binding. In 2002, Zhao and coworkers [34] presented a study on sera collected from 1797 individuals with suspected beta-lactam allergy. They identified 123 patients (6.8%) with IgE able to bind to benzylpenicillin and cephalothin. An additional 238 patients (13.2%) were negative to benzylpenicillin but positive to cephalothin. Only 15 patients (0.8%) were uniquely benzylpenicillin positive. Unfortunately, the number who were also positive on skin testing to a complete panel of penicillin skin test reagents and the number who had clinically significant adverse reactions associated with cephalothin exposure were not provided. In 2002, Pham and coworkers [35] reported on the existence of IgE directed against substituted amino and ammonium groups in sera from seven highly selected, well-characterized patients with multiple severe, mostly anaphylactoid adverse drug reactions. These patients predominately had histories of reactions to anesthetic agents, but some also had histories of antibiotic reactions and may represent true cases of multiple drug allergy syndrome. These studies show that humans can produce IgE antibodies that bind to small shared determinants on antibiotics and other

drugs. The true clinical significance of these cross-reacting antibodies remains to be determined. The current challenge is to integrate clinical history, skin tests, laboratory tests, and re-challenge results. Isolated laboratory findings have not always turned out to have clinical relevance.

Oral tolerance testing

In 2002, Passalacqua and coworkers [36] reported on a series of outpatient antibiotic challenges in a study of 452 patients, 56% of whom had a history of reacting to two or more drugs. They gave single-dose oral tolerance tests, empirically established at one-tenth of a usual therapeutic dose, to try to determine an unrelated antibiotic they could use. The active challenges were preceded by two placebo challenges. Ninety-eight patients (21.7%) patients, 89 (90.8%) of who were women, reacted to the first placebo, and 34 (7.5%) reacted to the second placebo. A total of 343 one-tenth dose challenges to erythromycin were performed, and had 26 patients (7.5%) had reactions; 258 one-tenth dose challenges to quinolones resulted in 21 (8.1%) reactions, and 38 challenges to amoxicillin resulted in 2 (4.6%) reactions. Follow-up data were available for 407 patients. A total of 355 (87.5%) of the patients used and were able to tolerate one or more of the suggested drugs, 38 (9.3%) did not take any of the suggested drugs, and 14 (3.5%) reacted during a follow-up period of 2 to 4 years to one of the tested and initially tolerated drugs. Once again, a 3.5% adverse reaction rate occurring with antibiotic use was seen in patients with a history of another adverse reaction to an antibiotic.

In 2001, Nettis and coworkers [37] reported on a series of 98 patients with a history of adverse reactions associated with the use of more than one class of antibiotics out of a total cohort of 460 patients. Patients received equal numbers of placebo and test doses starting at one-fifth to one-half of a usual therapeutic dose. Placebo reaction rates were not reported. There were a total of 504 tolerance tests with an overall 2.6% adverse reaction rate. It was concluded that 106 (20.9%) of the patients had multiple drug allergy syndrome. A total of 198 of the subjects (43%) also reported histories of NSAID sensitivity, but this finding was not a significant risk factor for characterization as having multiple drug allergy syndrome. The one significant risk factor was female sex, 83/323 versus 23/137, ($P = 0.038$). Clinical follow-up on how these individuals dealt with future use of the antibiotics they tolerated during testing was not reported.

It does not appear that “tolerance testing,” at least as it is described herein, is of significant utility because of the lack of follow-up data that give clinical context to the findings. In 2002, Knowles and coworkers [38] outlined what they considered essential components of individualized drug challenges for use in ruling out drug-induced reactions. They stressed the importance of patient consent and cooperation, effective blinding of placebo and active drug, and the establishment of predetermined endpoints measured at predetermined intervals.

Box 1. Essential elements of an effective multiple antibiotic allergy consultation

Collect the following data for each antibiotic associated with an adverse reaction:

- Type of infection last used for
- Prior exposures without reaction
- Prior exposures with reaction
- Dose with last reaction
- Route of administration with last reaction
- Number of doses taken before onset of last reaction
- Number of doses taken after onset of last reaction
- Type of adverse reaction
- Duration of adverse reaction symptoms
- Treatment given for adverse reaction symptoms
- Permanent sequelae
- Diagnostic tests obtained

Collect the following data for each antibiotic tolerated:

- Type of infection last used for
- Dose with last exposure
- Route of administration with last exposure
- Prior exposures without reaction

Other important historical factors

- List all other drugs associated with adverse reactions and dates of last exposure
- Document the existence, if any, of the following risk factors:
 - chronic urticaria, dermographism, NSAID intolerance, liver disease, renal dysfunction, immune deficiency, HIV, cystic fibrosis

Elements of an effective treatment plan

- Antibiotic OK to use if clinically indicated
- Antibiotic should be avoided
- Antibiotic can be used with pretreatment (provide pretreatment plan)
- Antibiotic can be used if a test dose tolerated (provide test dose plan)
- Antibiotic can only be used with prior desensitization (provide desensitization plan)

Management of patients with histories of multiple antibiotic allergies

Oral antibiotics are overused in the United States [23]. In the large prepaid health care system in which I practice in San Diego County, 330,000 courses of oral antibiotics were dispensed to 500,000 members in 2002 (E. Macy, MD, personal communication, August 2003). One of the more effective strategies for the clinical management of patients with a history of multiple antibiotic allergies has been additional education directed at the interaction between the patient and the primary care provider. Providing educational materials to patients that help reduce the expectation that colds should be treated with antibiotics can reduce antibiotic demand. Courses of outpatient oral antibiotics used per member per year in our health plan have fallen from 84 per 100 in 1995 to 66 per 100 in 2002 (E. Macy, MD, personal communication, August 2003). Serous otitis media and clinically diagnosed acute sinusitis are just two of the conditions that are historically overtreated with antibiotics [39,40]. Multiple adverse reactions to antibiotics are often arguably an iatrogenic condition.

The clinical management of individuals with a history of multiple adverse antibiotic reactions has been well outlined by Gruchalla [7]. She stresses the importance of obtaining a thorough history, using penicillin skin testing where appropriate, and developing a patient-specific management plan. One of the key elements is to collect what is often a complex and poorly documented history and to present it in a useful fashion. **Box 1** outlines the essential elements of a successful multiple drug allergy consultation. Data need to be collected and summarized in the medical record for antibiotics associated with adverse reactions and for those that are tolerated. Significant comorbidities, such as NSAID intolerance, chronic urticaria, dermatographism, and immune deficiency, including HIV infection and cystic fibrosis, need to be documented. The management plan needs to state when use, avoidance, substitution, desensitization, graded challenges, or premedication are appropriate. Obtaining serial serum tryptase measurements during acute reactions that appear to be anaphylactoid can be useful [41]

Summary

Most patients with histories of multiple antibiotic allergies do not make IgE directed against unrelated antibiotics. Although a subgroup of individuals may make such IgE, characterization of these individuals will require prospective research. Current management of patients with multiple antibiotic allergies starts with a careful documentation of the clinical history. Penicillin skin testing is used when appropriate. A patient-specific management plan needs to state clearly what antibiotics should be preferentially used, what antibiotics should be avoided, and which antibiotics could be used with appropriate premedication, oral tolerance testing, or desensitization.

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