

Most Antimicrobial Reactions Found to Be Allergic

BY DIANA MAHONEY
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BOSTON — The recent finding that adverse reactions to antimicrobial agents cause more than 142,000 emergency department visits per year in the United States, and that the highest rate occurs in children under 1 year of age should be a wake-up call to health care providers to exercise caution when pulling out the prescription pad.

Dr. Barbara W. Stechenberg gave this warning at the annual meeting of the American Academy of Pediatrics.

The study used nationally representative surveillance data to estimate the rates of adverse events associated with systemic antibiotics and compared the results by antibiotic class, specific drug, and type of adverse event (Clin. Infect. Dis. 2008;47:735-43). Approximately half of the emergency department visits attributable to antimicrobial adverse events were for reactions to penicillins and half were for reactions to multiple other agents, according to researchers Dr. Nadine Shehab and her associates at the Centers for Disease Control and Prevention.

Although infants younger than 1 year accounted for only 6% of the emergency department visits, after controlling for prescription frequency, “the rate of visits [for antimicrobial-related adverse events] was highest in this age group,” said Dr. Stechenberg, director of pediatric infectious diseases at Baystate Medical Center in Springfield, Mass.

The majority of adverse reactions seen in the above study—approximately 80%—were allergic reactions, ranging from

rash to anaphylaxis, and the rest were toxicity related.

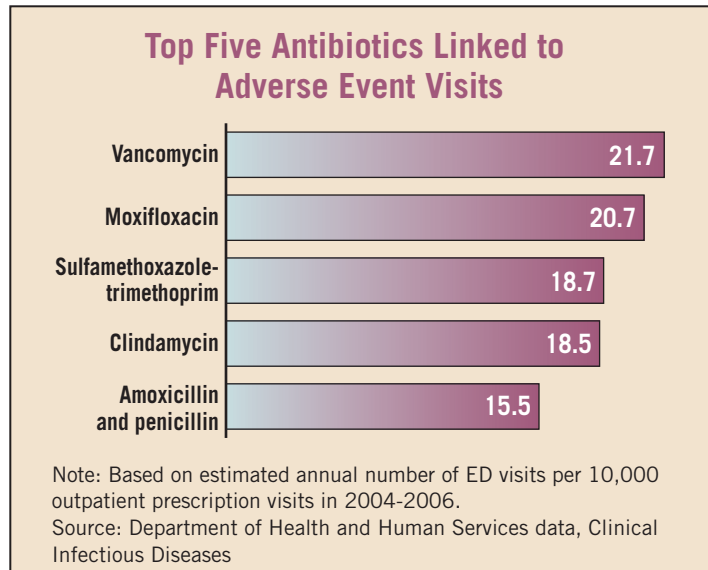
An awareness of the types of adverse reactions that can occur with different antimicrobial agents is critical to management, Dr. Stechenberg stressed. The following are some of the important points to consider with respect to different drug classes and specific drug reactions.

► **Penicillins.** “Penicillins are generally very safe. There is very little dose-related toxicity because of the wide dose range,” said Dr. Stechenberg.

When immediate reactions to β -lactams, especially penicillins, do occur, they are often IgE mediated and typically present as urticaria. The more severe reactions include bronchospasm or hypertension, she said. “Most [IgE-mediated reactions] occur within the first 15-20 minutes, the vast majority in the first hour, but about 5% occur after the first hour, which is important to remember as you think about rechallenging someone with penicillin.”

Among the late reactions to penicillins—which usually occur after 72 hours, often 5-10 days into the course of therapy—are maculopapular rashes and morbilliform rashes, often on the extremities, she said. More severe reactions include hemolytic anemia, neutropenia, and thrombocytopenia.

In terms of management, the timing and character of previous reactions is important. “Reactions late in the course are less likely to be IgE mediated. If the child previously had an idiopathic, nonpruritic late rash, you can consider giving the drug in the future,” said Dr. Stechenberg. In patients with a history of immediate reactions or more severe



late reactions, you wouldn't rechallenge with the same drug.

► **Vancomycin.** Most families think vancomycin hypersensitivity is an allergy. It's really a rate-dependent infusion reaction, said Dr. Stechenberg. It often happens on the first dose, which is different from anaphylaxis, and the rash is more likely to be a diffuse erythema, often on the upper trunk, face, and neck. The package insert states that the drug infusion shouldn't exceed 1 g over an hour. “Sometimes we have to modify that, but if there's a mild reaction, the best thing is to just stop the infusion and wait a short period, then restart at a slower rate,” she said. “If there's a moderate reaction, one might want to treat with diphenhydramine and allow the symptoms to subside, then use a much longer rate.” In patients with severe reactions, “you might have to use an alternate drug.”

► **Clindamycin.** “The biggest issue with this drug is diarrhea. It's often mild and self-limited, which you can treat through. When it persists and is more se-

vere, we worry about *Clostridium difficile*, which can have a wide range of presentations,” Dr. Stechenberg said.

The first line of treatment for *C. difficile* is to stop the drug. “In 20%-25% of patients, this is all you need to do,” Dr. Stechenberg said. If symptoms persist, “try oral metronidazole. We try not to use oral vancomycin because of concerns about vancomycin-resistant enterococcus, but for patients who can't tolerate or fail metronidazole, oral vancomycin is an option,” she said. Another option is linezolid, but it is expensive and has been associated with thrombocytopenia in adults.

► **Trim/sulfa.** This broad-spectrum antibiotic “has been around for a long time, but it has new life in the therapy of methicillin-resistant *Staph aureus*,” said Dr. Stechenberg. It has a reputation as a drug that can cause a rash because a lot of HIV patients who took it developed rashes. In the general population, however, the incidence of rash is fairly low, she said.

► **Azithromycin.** The most common reaction with this drug is gastrointestinal upset. “These are side effects, not allergy. Some people just cannot tolerate macrolides,” Dr. Stechenberg noted. Although rash is uncommon with azithromycin, “when it does occur, it lasts for a long time. One of the nice things about this drug is that treatment is only for 5 days because it stays in the body for a long time, but that means when there's rash, it will persist,” she said.

► **Doxycycline.** Concerns about tooth staining “have led to a magic cutoff age of 8-9 years old for doxycycline, after the eruption of maxillary central incisors,” said Dr. Stechenberg. “In reality, tooth staining results from multiple courses of the drug over long periods.”

Photosensitivity dermatitis also is a concern with doxycycline, but this can be prevented with anticipatory guidance regarding the use of broad-spectrum sunscreen and sun avoidance, she said.

► **Fluoroquinolones.** Small studies have shown that fluoroquinolones are reasonably safe in children, “but they should be reserved for patients who have no other reasonable options,” she said. “Advise patients to report any joint pain so the medication can be stopped before the possibility of tendon rupture.”

► **Acyclovir.** “This is a fairly safe drug to use in children,” said Dr. Stechenberg. However, because it is excreted in the kidney almost unchanged, it can cause renal tubular dysfunction, crystalline nephropathy, and interstitial nephritis. She reported having no disclosures related to her presentation. ■

Birth Control May Impair Natural Defenses Against Herpes

BY HEIDI SPLETE
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WASHINGTON — Using hormonal contraceptives might weaken a woman's natural immunity to the herpesvirus, according to findings from a pilot study of healthy women aged 18-35 years.

Findings from previous epidemiologic studies suggest that women who use hormonal contraception are at increased risk for sexually transmitted infections and herpes simplex virus (HSV) shedding. Yet clinical studies have shown that “cervicovaginal lavage fluid protects against HSV, HIV, and bacteria,” lead author Dr. Gail F. Shust said at the jointly held annual Interscience Conference on Antimicrobial Agents and Chemotherapy

(ICAAC) and the annual meeting of the Infectious Diseases Society of America (IDSA).

Dr. Shust and colleagues from Albert Einstein College of Medicine, New York, measured anti-HSV activity and levels of immunity associated with hormonal contraception use by collecting samples of cervicovaginal lavage (CVL) fluid from 16 women once a week for 3-8 weeks. Nine women had normal ovulatory cycles and served as controls, and seven women used hormonal contraception.

When average values from the repeat CVL samples from each woman were compared, in the follicular phase, women using hormonal contraception showed significantly less anti-HSV activity compared with the controls. In

the luteal phase, the difference did not reach statistical significance.

When individual fluid samples were compared (for a total of 94 samples), the anti-HSV activity in women using hormonal contraception was significantly lower, compared with the controls, in both the follicular and luteal phases.

Correlations between anti-HSV activity and specific mucosal mediators that can inhibit herpes infection were measured through a Spearman's rank correlation coefficient analysis. Based on this measure, anti-HSV activity was positively correlated with levels of human neutrophil peptides (HNPs) 1, 2, and 3 (Spearman's rho = 0.45), lactoferrin ($r_s = 0.52$), lysozyme ($r_s = 0.58$), and IgA ($r_s = 0.44$).

In addition, anti-HSV activity was negatively correlated with interferon-alpha 2 ($r_s = -0.36$). Each of these correlations was statistically significant.

The study was limited by its small size and intrasubject and intersubject variability in anti-HSV activity.

These findings may provide a biologic explanation for the epidemiologic findings of increased risk for acquisition of sexually transmitted infections, and for HSV shedding, in the setting of hormonal contraception, the researchers said. Studies of the factors that modify anti-HSV activity are ongoing, and larger, prospective studies are needed to support the results, they noted.

Dr. Shust reported no financial conflicts of interest. ■