Antimicrobials: Use With Care to Avoid Side Effects

The highest rate of ED visits for antimicrobial adverse effects is for children under 1 year of age.

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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 pediatric 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.

"Clearly, adverse reactions to antimicrobials are a huge issue. [These findings] remind us to consider certain underlying principles before we prescribe antibiotics to our patients."

First, ask yourself whether the patient really needs the therapy, "because no therapy is often safer than any therapy," she said.

"Next, name the bug before you choose the drug, so you can use the narrowest spectrum, least toxic drug possible," Dr. Stechenberg advised.

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.

With respect to allergic reactions, said Dr. Stechenberg, "the ones we worry about the most, particularly with penicillins and cephalosporins, are the IgE-mediated reactions which occur fairly early in the course of antibiotic therapy, but a lot of what we see—most of the maculopapular and morbilliform rashes—are non–IgE mediated."

With respect to toxic reactions, "most toxicity that we see is related to giving a dose of antibiotic that is above what the particular host can manage. Sometimes it's the wrong dose or the decimal is in the wrong place, but a lot of times it's related to impaired metabolism: The host child has renal dysfunction or liver dysfunction and is not able to metabolize the drug appropriately."

Other adverse reactions are side effects. "Many patients report stomachaches with erythromycin, for example. Side effects are not IgE mediated or related to toxic levels. They just happen," said Dr. Stechenberg. "This is a reason why taking a thorough history is very important."

Adverse reactions associated with genetic issues occasionally arise. In HIV patients, for example, "we know that people metabolize INH [isoniazid] differently. People who are slow metabolizers may accumulate INH and develop neuropathy," she said.

Finally, underlying diseases also can contribute to antibiotic adverse reactions, Dr. Stechenberg noted.

"Cystic fibrosis patients are more likely to have allergic reactions than other patients, which may be related to the hyperactivity of their immune system. The same is true with HIV patients."

Approximately half of the ED visits attributable to antimicrobial adverse effects were for reactions to penicillins and the other half for reactions to other agents.

An awareness of the types of adverse reactions that can occur with different antimicrobial agents is critical to management of them, 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.

Regarding allergies, "studies have shown that the true incidence of penicillin allergies among patients who report them is only about 10% [as determined by skin testing]. This doesn't mean that they're not going to have a nonimmediate reaction to penicillin, but it does make you feel more comfortable about the risk of anaphylaxis, which is very uncommon," she commented.

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. "For a lot of these, we don't know what the mechanism is. They may be antibody mediated, and certainly these reactions demand our attention.

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, such as Stevens-Johnson syndrome, you wouldn't rechallenge with the same drug, she said.

► **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," she said.

► **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 severe, we worry about *Clostridium difficile*, which can have a wide range of presentations," Dr. Stechenberg said. The diagnosis of *C. difficile* can be made by enzyme immunoassays in most hospital labs, she said, noting, however, that "the fly in the ointment with *C. difficile* is that kids up to 1 year of age will often have asymptomatic *C. difficile*, so they will test positive by toxin assay.

"The occurrence of diarrheal disease [with antibiotic treatment] may be unrelated."

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.

"In kids with HIV, we do see fixed drug eruptions in the same area of the body, and [so] we do talk to families about the possibility of rash."

Trim/sulfa (trimethoprim/sulfamethoxazole) is not recommended for use in infants younger than 2 months because it displaces bilirubin from albumin binding sites, 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. When we're using it as a drug of choice for children younger than 8 years, we're treating for 5-7 days for specific indications."

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.** Pediatricians have been reluctant to use these in children, because they have been linked with cartilage damage in animal and adult studies and because of resistance concerns, especially in pneumococcus, said Dr. Stechenberg.

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.

"Also, 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. We're used to using it in patients with genital herpes and immunocompromised patients with zoster," 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 said. For this reason, "it's important not to have rapid infusions and to make sure patients are well hydrated before treatment starts, to give enough hydration along with treatment, and to look for underlying renal disease."

Dr. Stechenberg reported having no disclosures related to her presentation. ■

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