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Amoxicillin Failure in Strep Throat

A pair of newly detected actions of Group A streptococci may offer clues as to why penicillin and amoxicillin often fail to eradicate streptococcal pharyngitis in children and adults, and why cephalosporins or macrolides may be better treatment options.

Penicillin failure in eradicating strep throat has been increasingly documented beginning in the 1980s, rising from just 5% in the 1950s to approximately 35% today. My colleague Dr. Janet R. Casey and I have published a series of articles over the years documenting this phenomenon, as have other researchers worldwide. In 2004, Dr. Casey and I conducted two separate meta-analyses demonstrating the clear superiority of cephalosporins—mainly azithromycin and clarithromycin—over penicillin in treating strep throat, both in children (Pediatrics 2004;113:866-82) and adults (Clin. Infect. Dis. 2004;38:1526-34).

Traditional antibiotic resistance does not appear to be the reason. In fact, there is absolutely no in vitro resistance of group A streptococci (GAS) to penicillin or amoxicillin (or cephalosporins).

Some people have theorized that the inadvertent inclusion of strep carriers in many of the studies explains the eradication failure with penicillin, but that has never made sense to me. Why would such inclusion have increased since the 1950s? In fact, the opposite has happened: Efforts have been made in more recent studies to exclude carriers. Our meta-analyses showed that the failure rate remained pretty much rocksolid at 35%, even when we looked at only the 12 most recent studies that did a fantastic job of excluding carriers.

I think the answer lies in considering mechanisms of "resistance" beyond those involving a particular bacterium resisting a particular drug in a test tube. There are two newly appreciated phenomena that I categorize as "in vivo resistance" because they result from a fundamental interaction with the host and can't be measured by a lab test.

About 5 years ago, several researchers published studies showing that streptococci were capable of entering and living inside the epithelial cells of the upper respiratory tract, a process dubbed "internalization." Prior to that time, GAS was thought to be a strictly extracellular pathogen.

Then, just last year, Dr. Edward L. Kaplan of the University of Minnesota and his associates showed for the first time that internalization was a likely explanation for the treatment failure of penicillin and amoxicillin, which are incapable of penetrating the cell wall. In contrast, erythromycin and azithromycin, which enter cells easily, were the most effective at GAS eradication while the first-generation cephalosporin cephalothin and clindamycin had intermediate efficacy (Clin. Infect. Dis. 2006;43:1398-406).

A second mechanism of in vivo resistance, known as "coaggregation," was first described in 2004 by Dr. Eric R. LaFontaine and his associates at the University of Toledo (Ohio). They found that the pathogens *Streptococcus pyogenes* and *Moraxella catarrhalis* colonize overlapping regions of the human nasopharynx, and that *M. catarrhalis* can dramatically increase the adherence of *S. pyogenes* to human epithelial cells (Infect. Immun. 2004;72:6689-93).

Subsequent to that paper, my laboratory group completed a study in which we confirmed Dr. LaFontaine's finding regarding coaggregation of *S. pyogenes* with *M. catarrhalis*, and also for the first time demonstrated the same phenomenon with *S. pyogenes* and *Haemophilus influenzae*.

With coaggregation, the GAS bacteria acquire the ability to attach themselves to the *M. catarrhalis* or *H. influenzae* that already colonize the throat at various times during childhood and adulthood (*H. influenzae* is about 5-6 times more common than *M. catarrhalis*). While these two organisms have long been known to become pathogenic in certain settings, we are now realizing that they also may serve to enhance the attachment of GAS to throat cells.

Indeed, coaggregation is a likely explanation for why some children—such as those more frequently colonized with *M. catarrhalis* or *H. influenzae*—are more vul-

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nerable to strep throat than others. Moreover, it also explains our finding that an individual who is colonized with one of those two organisms and then is exposed to streptococcus has a 10-fold increased likelihood of developing strep throat.

It also helps explain the differential treatment effect of penicillin/amoxicillin versus other antibiotic classes. Both *M. catarrhalis* and *H. influenzae* produce beta-lactamase, which inactivates penicillin and amoxicillin. Cephalosporins, on the other hand, have greater activity in the presence of beta-lactamase, while macrolides such as azithromycin are completely immune to the enzyme.

Thus, it appears that beta-lactamase production, a well-described mechanism for in vitro antimicrobial resistance, is being enhanced by this additional coaggregation mechanism.

Based on this new information, my practice now uses cephalosporins as first-line treatment for strep throat. Cephalexin is a good option because it's generic, and it's first-generation, so it is not as broad-spectrum. We prescribe it twice daily for 10 days.

Second choice would be either a second- or third-generation cephalosporin or azithromycin, depending upon the degree of macrolide resistance in your community. Here in Rochester, where macrolide resistance is about 8%, we normally go with cefprozil, cefdinir, or cefpodoxime. All three are generic, although they're still not cheap— there's currently only one distributor. Cefprozil is the least expensive of the three, and there also is evidence that it eradicates the strep carrier state as well as the active infection (Clin.Ther. 2001;23:1889-900).

The Infectious Diseases Society of America is planning to issue new guidelines for the treatment of streptococcal pharyngitis sometime in 2008. Dr. Kaplan is the chairman of the writing committee, and Dr. Casey is a member. The American Academy of Pediatrics' 2006 Red Book still recommends amoxicillin as first-line therapy, but I'm guessing that will not be the case in the next edition, due out in 2009.

I have no financial conflicts that are relevant to this article. ■

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Merck Updates Vaccine Supply Delays, Shortages

Merck & Co. has issued an update on the status of its vaccine delays and shortages in a letter to physicians.

Merck announced that ProQuad (measles, mumps, rubella, and varicella virus vaccine live) will be unavailable for ordering through the rest of 2007, although existing back orders were filled through August. In the letter, the company said that it was too early to determine if ProQuad will be available in 2008.

Merck had earlier requested that customers transition from ProQuad to M-M-R II and Varivax (varicella vaccine). The Centers for Disease Control and Prevention continues to report that current projections forecast an adequate supply to implement the recommended immunization schedule fully for varicella vaccine for all age groups.

Varivax is currently available in adequate supply, according to Merck, but customers should expect shipping delays of up to 15-20 business days. The company expects to return to normal delivery schedules in late September or early October, but in the meantime two additional shipping days have been added (Thursday for Friday delivery and Saturday for Monday delivery) and at least one order per office is being shipped—instead of the normal first-in, first-out model—to minimize the impact on customers with no supply of Varivax.

Production delays also have plagued Merck in manufacturing its pediatric and adult hepatitis A vaccine (Pediatric and Adult Vaqta). A manufacturing change that is under regulatory review started the delays, which have caused customers to experience 6- to 7-week shipment delays since late July 2007. The company said that orders for the vaccine that it received through early- to mid-September will continue to be filled on a 6- to 7-week back order, but orders that are received after mid-September will not be available for shipment until near the end of the first quarter of 2008.

The supply of GlaxoSmithKline's pediatric and adult hepatitis A vaccine (Pediatric and Adult Havrix) is adequate enough to meet demand; GSK has initiated plans to produce more Havrix to help ensure uninterrupted supply for the U.S. market, according to the CDC.

—Jeff Evans