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 15% 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 vulnerable to GAS infection.
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 VaJact).

The supply of GlaxoSmithKline’s pediatric and adult hepatitis A vaccine (Pediatric and Adult VaJact) has been unavailable for ordering through the rest of 2007, although existing back orders were filled through August. 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 for the ProQuad and Varivax. 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.

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