Vancomycin Should Be Part of Empiric Therapy for Suspected Bacterial Meningitis

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The use of empiric vancomycin plus a third-generation cephalosporin for suspected bacterial meningitis has been recommended since 1997. Although the prevalence of ceftriaxone-nonsusceptible pneumococcal meningitis has decreased, vancomycin should still be included as empiric therapy for bacterial meningitis.

Keywords. bacterial meningitis; pediatric; Streptococcus pneumoniae; vancomycin.

Streptococcus pneumoniae is the most common cause of bacterial meningitis among children aged >1 month in the United States [1]. Pneumococcal meningitis (PM) is associated with higher rates of long-term neurological sequelae and case-fatality than are other causes of bacterial meningitis [1, 2]. Thus, optimal antibiotic therapy should be provided promptly to prevent delayed cerebrospinal fluid sterilization [3].

The 2018 Red Book [4] and the Infectious Diseases Society of America (IDSA) practice guidelines for the management of bacterial meningitis [5] recommend using vancomycin and a third-generation cephalosporin for children aged >1 month with suspected bacterial meningitis, and they recommend this same combination as definitive therapy for ceftriaxone-nonsusceptible PM [5]. The addition of vancomycin was implemented in 1997 to provide coverage for ceftriaxone-nonsusceptible (ceftriaxone or cefotaxime minimum inhibitory concentration, ≥1 μg/mL) S pneumoniae isolates that were associated with ceftriaxone treatment failures.

After the first reports of ceftriaxone-nonsusceptible PM in the early 1990s, the 7-valent (PCV-7) and then 13-valent (PCV-13) pneumococcal conjugate vaccines were introduced in 2000 and 2010, respectively. Most β-lactam–nonsusceptible pneumococcal infections in the pre–PCV-7 era were caused by 1 of 5 serotypes (6B, 9V, 14, 19F, or 23F), all of which were included in the PCV-7 vaccine. In the post–PCV-7/pre–PCV-13 era, 19A emerged as a multidrug-resistant serotype and is now included in the PCV-13. The sequential implementation of these vaccines substantially decreased the rates of invasive pneumococcal infections, vaccine-serotype colonization, and pneumococcal antibiotic resistance. However, S pneumoniae has the ability to evade environmental stressors such as vaccines and antibiotics through frequent genetic recombination with other pneumococci and the Streptococcus mitis group in the nasopharynx; thus, its epidemiology (eg, serotype, genotype, antibiotic susceptibility profile) is changing constantly.

Ceftriaxone-nonsusceptible S pneumoniae was responsible for 12% of PM cases among pediatric and adult patients between 1998 and 2005 in the United States [6]. A US pediatric multicenter pneumococcal surveillance study that included 8 children’s hospitals found a decrease in ceftriaxone-nonsusceptible PM cases from 13% in 2007–2009 to 3% in 2011–2013, all of which were caused by serotype 19A [7]. Recent data from the same study group revealed that ceftriaxone-nonsusceptible S pneumoniae was responsible for 5% of PM cases between 2014 and 2017. These infections were caused by vaccine serotypes 19A and 23F and nonvaccine serotypes 35B and 10A (S. L. Kaplan and K. G. Hulten, personal communication). These results are not surprising, because serotype 35B has emerged as the predominant β-lactam–nonsusceptible serotype among invasive isolates collected from pediatric patients in the post–PCV-13 era in the United States, followed by 15B/15C, 15A, and 23B [8]. Only time will tell if any of these nonvaccine β-lactam–nonsusceptible serotypes will be as successful as the widely disseminated post-PCV-7 clone 19A-ST320.

In addition, global spread of pneumococcal clones with a selective advantage has been reported (eg, Spain23F-1, France23F-3). Emergence of the meropenem-nonsusceptible 15A-ST63 pneumococcal clone among Japanese children was reported recently [9]. Results of genomic analysis suggested that this emergence was the result of recombination of the penicillin-binding protein 1a region between the serotype 15A-ST63 and serotype 19A-ST320 strains. Nonsusceptibility to meropenem was observed to a lesser extent among serotypes 6A, 6B, 6D, 15B/15C, 19A, 19F, 23F, and 35B in Japan [9].

The number of cases of ceftriaxone-nonsusceptible PM has certainly decreased in the United States, but the disease has not been eliminated. As long as we continue to use serotype-based...
pneumococcal vaccines with a limited valency, circulation of antibiotic-resistant pneumococcal strains will always occur. Some might argue that, on the basis of current PM epidemiology and the fact that vancomycin can be nephrotoxic, vancomycin should no longer be used as part of empiric therapy for bacterial meningitis. However, an increased risk of vancomycin-induced nephrotoxicity, which frequently is reversible, has not been observed with ≤48 hours of therapy [10]. Is a prevalence of 3% to 5% of ceftriaxone-nonsusceptible PM low enough to discontinue the use of empiric vancomycin? How many patients with ceftriaxone-nonsusceptible PM are we willing to let be undertreated for 48 to 72 hours if empiric vancomycin is not used? Given that the case-fatality rate in pediatric patients with PM is ~9% [1] and more than half of PM survivors have long-term sequelae despite optimal antibiotic therapy [7], we need to consider carefully the potential devastating consequences of delaying optimal therapy for 48 to 72 hours. Instead of advocating for discontinuation of the empiric use of vancomycin, we should focus on optimizing its use in children with suspected bacterial meningitis. Distinguishing bacterial and viral meningitis is essential for decreasing unnecessary vancomycin use. In patients with cerebrospinal fluid pleocytosis who have not been pretreated with antibiotics, tools such as the bacterial meningitis score can help identify patients at very low risk for bacterial meningitis [11]. If patients classified as being at very low risk for bacterial meningitis are otherwise healthy and fully vaccinated, ceftriaxone alone might be considered. So far, we have won many battles against *S. pneumoniae* but not yet the war. We need to remain vigilant and monitor the activity of β-lactam-nonsusceptible serotypes under the current vaccine pressure.

**Notes**

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**References**