COMMENTARY

The Disputed Champion: Ampicillin and Gentamicin for Febrile Young Infants

Tara L. Greenhow, MD,[a] Joseph B. Cantey, MD[b]

The distribution of pathogens and approach to empirical antibiotics in febrile infants aged <90 days has been debated for decades. There is increasing disagreement as to whether the combination of those timeless workhorses ampicillin and gentamicin (A&G) remains appropriate empirical therapy given the changing epidemiology of bacteremia and meningitis in young infants.[1–8] In the article by Feldman et al, researchers used the Pediatric Health Information System to describe regional differences in both pathogens and empirical antibiotic use in previously healthy infants <90 days old who were seen in 1 of 8 US pediatric children's hospital emergency departments and had a positive urine, blood, or cerebral spinal fluid (CSF) culture.[9] Not surprisingly, urinary tract isolates (urinary tract infection [UTI] alone or with associated bacteremia) made up 87% of infections. There was no regional difference in UTI pathogens. Blood and CSF pathogens differed by hospital, but susceptibilities remained constant and *Escherichia coli* and group B *Streptococcus* were the most common organisms. Third-generation cephalosporins (3GCs) were used for empirical therapy in the majority of infants, either alone (43%) or with ampicillin (39%). The combination of A&G was used in only 11% of infants.

We struggle to understand why providers are not using A&G empirically in febrile infants <90 days of age. This choice flies in the face of data. In previous studies, researchers have consistently demonstrated equal, or in some cases superior, efficacy of A&G compared with 3GCs.[3,10] In this study by Feldman et al, for example, A&G would have been adequate in 95% of cases compared with only 90% for 3GC monotherapy.[9] In addition to superior efficacy, A&G offers other advantages over 3GCs (Table 1), including the fact that it drives less bacterial resistance.[11,12] Still, many institutions continue to rely on empirical cephalosporin-based therapy. Aronson et al found low rates of empirical A&G use in febrile infants, with 11% overall (22% ≤28 days old, 3% 29–56 days old, and <1% 57–89 days old).[13] In the current study by Feldman et al, even centers in which group B *Streptococcus* was the predominant cause of bacteremia had low utilization of A&G.[9] We ask, why?

Is it fear of gentamicin toxicity that has limited its routine use? Gentamicin nephrotoxicity appears to be related to the duration of use, the total dose administered,[14] the age of the patient,[15] and factors associated with impaired renal function.[16] With once-daily dosing, the transient high peak level does not cause toxicity.[17] Therefore, the risk of 1 or 2 doses of once-daily gentamicin is highly unlikely to cause nephrotoxicity. Similarly, in numerous studies of infants exposed to gentamicin in the neonatal period, researchers have demonstrated no increased risk for ototoxicity compared with unexposed infants, but the perception of gentamicin as ototoxic has continued. As with nephrotoxicity, once-daily dosing has decreased the risk for gentamicin ototoxicity.

[a]*Division of Infectious Diseases, Department of Pediatrics, Kaiser Permanente Northern California, San Francisco, California; and* [b]*Division of Infectious Diseases and Neonatal/Perinatal Medicine, Department of Pediatrics, Texas A&M Health Science Center and Baylor Scott & White Healthcare, Round Rock, Texas*

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Address correspondence to Tara L. Greenhow, MD, Division of Infectious Diseases, Department of Pediatrics, Kaiser Permanente Northern California, 2238 Geary Blvd, San Francisco, CA 94115. E-mail: tara.greenhow@kp.org

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TABLE 1 Advantages and Disadvantages of Different Empirical Antibiotic Regimens for Suspected Serious Bacterial Infection in Young Infants

Regimen	Advantages	Disadvantages
A&G	Most effective empirical regimen in majority of studies Covers *Enterococcus* and *Listeria* Covers most ESBL-producing Gram-negative rods Narrower spectrum	Does not cover ampicillin-resistant pathogens in cerebrospinal fluid
Third-generation cephalosporin monotherapy	Simple dosing Penetrates CSF well	Does not cover *Enterococcus* Does not cover *Listeria* Does not cover ESBL-producing Gram-negative rods May promote bacterial resistance
Third-generation cephalosporin with ampicillin	Simple dosing Penetrates CSF well Covers *Enterococcus* and *Listeria*	Double β-lactam therapy may lower seizure threshold Does not cover ESBL-producing Gram-negative rods May promote bacterial resistance Unnecessarily broad in many cases

CSF, cerebral spinal fluid; ESBL, extended-spectrum beta-lactamase.

Short-course gentamicin exposure did not increase rates of sensory neural hearing loss in a premature infant population.[18] High peak levels are not ototoxic, but rather it is the total dose, concomitant use of other ototoxic medications (eg, loop diuretics and platinum-based chemotherapy agents), and genetic propensity.[19] Therefore, we suggest caution in using gentamicin for those rare infants on other ototoxic medications or with a family history of hearing loss. Finally, the only infants who are exposed to prolonged gentamicin therapy are those with sepsis because of ampicillin-resistant, Gram-negative rods, which makes up a tiny fraction of the infants started on empirical therapy.

Are providers concerned about missing meningitis? To be fair, the increasing proportions of ampicillin-resistant, Gram-negative rods and the poor penetration of aminoglycosides into CSF make A&G suboptimal for suspected meningitis. Therefore, we fully endorse the use of 3GCs for suspected meningitis with 1 major caveat: infants with suspected meningitis must undergo lumbar puncture for CSF analysis and culture. Otherwise, empirical cephalosporins have a tendency to become 3 weeks of "definitive" treatment of suspected meningitis that is never proven. For young infants, lumbar puncture and appropriate diagnostic testing is a critical aspect of antimicrobial stewardship.

If providers are not convinced by the evidence supporting A&G and instead insist on 3GCs, we echo the conclusions by Feldman et al in not recommending the addition of ampicillin.[9] Combining ampicillin (another β-lactam agent) with a third-generation cephalosporin adds to neurotoxicity and the possibility of antagonistic effects in certain situations.[20] The only additional pathogens covered by the addition of ampicillin are *Listeria monocytogenes* and *Enterococcus* spp. For a decade, researchers have reported on the rarity of *L monocytogenes*,[1–3,5–7] but the concern for this pathogen has persisted. In a 2016 meta-analysis, Leazer et al[20] reported on the rarity of *L monocytogenes* and *Enterococcus* spp. infections. In several large regional studies,[1,3,5–7] a national study,[2] the above meta-analysis,[21] and the current article by Feldman et al,[9] there were no cases of late-onset *Listeria*.

Optimization of antibiotic use in young infants must address not only overuse but also underuse of antibiotics. In the current study by Feldman et al, many febrile infants (hospital range, 20%–50%) with proven infection did not receive any empirical antibiotics at the time of presentation.[9] This rate is higher than the 10.9% overall and 27.1% in those 57 to 89 days old who were not empirically treated in another national study.[12] While we await the American Academy of Pediatrics' guidelines on the "Approach to the Febrile Infant," we are reminded of risk stratification. For decades, providers were hesitant to withhold antibiotics in young febrile infants. The concept of stratifying selected infants into low-risk categories to safely withhold empirical antibiotic therapy emerged ~25 years ago with the Philadelphia and Rochester criteria.[22,23] Risk stratification has evolved to include newborns[24] but remains elusive for infants 3 to 28 days old. Although we fully support assessing febrile infants and placing them in high- or low-risk strata, a meaningful percentage in this study who had serious bacterial infections were correctly stratified into a low-risk category and had antibiotics withheld, given that the negative predictive value of risk stratification exceeds 99%.[22,23,25]

In conclusion, we prefer the use of empirical A&G in febrile infants because of its proven efficacy and narrower spectrum, with use of 3GCs reserved for suspected or proven meningitis. If providers insist on using a 3GC, there is no evidence to support the routine addition of ampicillin in infants 7 to 90 days old. Finally, we further support a standardized approach to empirical antibiotics. The similar distribution of infections (predominantly UTIs) and pathogens (predominantly group B *Streptococcus* along with *E coli* and other Gram-negative rods) across geographically diverse sites in this study and others, suggests that selection of empirical antibiotics in young infants with a suspected bacterial infection is a question in search of a national answer. We feel strongly that the answer should be A&G.

REFERENCES

1. Greenhow TL, Hung YY, Herz AM, Losada E, Pantell RH. The changing epidemiology of serious bacterial infections in young infants. *Pediatr Infect Dis J*. 2014;33(6):595–599
2. Biondi E, Evans R, Mischler M, et al. Epidemiology of bacteremia in febrile infants in the United States. *Pediatrics*. 2013;132(6):990–996
3. Cantey JB, Lopez-Medina E, Nguyen S, Doern C, Garcia C. Empiric antibiotics for serious bacterial infection in young infants: opportunities for stewardship. *Pediatr Emerg Care*. 2015;31(8):568–571

4. Cantey JB, Baldridge C, Jamison R, Shanley LA. Late and very late onset group B Streptococcus sepsis: one and the same? *World J Pediatr*. 2014;10(1):24–28
5. Greenhow TL, Hung YY, Herz AM. Changing epidemiology of bacteremia in infants aged 1 week to 3 months. *Pediatrics*. 2012;129(3). Available at: www.pediatrics.org/cgi/content/full/129/3/e590
6. Watt K, Waddle E, Jhaveri R. Changing epidemiology of serious bacterial infections in febrile infants without localizing signs. *PLoS One*. 2010;5(8):e12448
7. Byington CL, Rittichier KK, Bassett KE, et al. Serious bacterial infections in febrile infants younger than 90 days of age: the importance of ampicillin-resistant pathogens. *Pediatrics*. 2003; 111(5 pt 1):964–968
8. Stoll BJ, Hansen NI, Sánchez PJ, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Early onset neonatal sepsis: the burden of group B Streptococcal and E. coli disease continues. *Pediatrics*. 2011;127(5):817–826
9. Feldman EA, McCulloh RJ, Myers AL, et al. Empiric antibiotic use and susceptibility in infants with bacterial infections: a multicenter retrospective cohort study. *Hosp Pediatr*. 2017;7(8)
10. Ashkenazi-Hoffnung L, Livni G, Amir J, Bilavsky E. Serious bacterial infections in hospitalized febrile infants aged 90 days or younger: the traditional combination of ampicillin and gentamicin is still appropriate. *Scand J Infect Dis*. 2011; 43(6–7):489–494
11. de Man P, Verhoeven BA, Verbrugh HA, Vos MC, van den Anker JN. An antibiotic policy to prevent emergence of resistant bacilli. *Lancet*. 2000;355(9208): 973–978
12. Tsai MH, Chu SM, Hsu JF, et al. Risk factors and outcomes for multidrug-resistant gram-negative bacteremia in the NICU. *Pediatrics*. 2014;133(2). Available at: www.pediatrics.org/cgi/content/full/133/2/e322
13. Aronson PL, Thurm C, Alpern ER, et al; Febrile Young Infant Research Collaborative. Variation in care of the febrile young infant <90 days in US pediatric emergency departments. *Pediatrics*. 2014;134(4):667–677
14. Bertino JS Jr, Booker LA, Franck PA, Jenkins PL, Franck KR, Nafziger AN. Incidence of and significant risk factors for aminoglycoside-associated nephrotoxicity in patients dosed by using individualized pharmacokinetic monitoring. *J Infect Dis*. 1993;167(1): 173–179
15. Sawyers CL, Moore RD, Lerner SA, Smith CR. A model for predicting nephrotoxicity in patients treated with aminoglycosides. *J Infect Dis*. 1986; 153(6):1062–1068
16. Bygbjerg IC, Moller R. Gentamicin-induced nephropathy. *Scand J Infect Dis*. 1976;8(3):203–208
17. Nicolau DP, Freeman CD, Belliveau PP, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother*. 1995;39(3):650–655
18. Fuchs A, Zimmermann L, Bickle Graz M, et al. Gentamicin exposure and sensorineural hearing loss in preterm infants. *PLoS One*. 2016;11(7):e0158806
19. Lanvers-Kaminsky C, Zehnhoff-Dinnesen AA, Parfitt R, Ciarimboli G. Drug-induced ototoxicity: mechanisms, pharmacogenetics, and protective strategies. *Clin Pharmacol Ther*. 2017; 101(4):491–500
20. Chow KM, Hui AC, Szeto CC. Neurotoxicity induced by beta-lactam antibiotics: from bench to bedside. *Eur J Clin Microbiol Infect Dis*. 2005;24(10):649–653
21. Leazer R, Perkins AM, Shomaker K, Fine B. A meta-analysis of the rates of Listeria monocytogenes and Enterococcus in febrile infants. *Hosp Pediatr*. 2016;6(4):187–195
22. Baker MD, Bell LM, Avner JR. Outpatient management without antibiotics of fever in selected infants. *N Engl J Med*. 1993; 329(20):1437–1441
23. Jaskiewicz JA, McCarthy CA, Richardson AC, et al; Febrile Infant Collaborative Study Group. Febrile infants at low risk for serious bacterial infection–an appraisal of the Rochester criteria and implications for management. *Pediatrics*. 1994;94(3):390–396
24. Kuzniewicz MW, Puopolo KM, Fischer A, et al. A quantitative, risk-based approach to the management of neonatal early-onset sepsis. *JAMA Pediatr*. 2017;171(4):365–371
25. Gomez B, Mintegi S, Bressan S, Da Dalt L, Gervaix A, Lacroix L; European Group for Validation of the Step-by-Step Approach. Validation of the "step-by-step" approach in the management of young febrile infants. *Pediatrics*. 2016;138(2):e20154381

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