Randomized Trials in Children With UTI

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Randomized trials have played a pivotal role in shaping the management of pediatric urinary tract infections (UTIs). In important recent trials, authors have demonstrated that oral antibiotics are as effective as intravenous (IV) antibiotics[1] and that prophylactic antibiotics do not prevent renal scarring.[2] Given multiple ongoing controversies in the diagnosis and management of UTIs, however, still more trials are needed. In this issue of *Pediatrics*, Basmaci et al[3] report a systematic review of 40 trials published between 1990 and 2016 involving 4381 UTI cases. They highlight the numerous inconsistencies in inclusion criteria and choice of end points in published UTI antibiotic trials and suggest that more uniformity is required.

INCONSISTENT UTI-DEFINING INCLUSION CRITERIA

The lack of uniform inclusion criteria across trials reflects an ongoing controversy over the definition of UTI.[4] Because of fear that some UTIs will be missed,[5] there is reluctance to incorporate pyuria as a diagnostic criterion,[6] despite the latest recommendation from the American Academy of Pediatrics UTI clinical practice guideline[7] and subsequent supportive data that the urinalysis is more reliable than previously estimated.[8] Additionally, there is uncertainty over appropriate colony-count thresholds, interpretation of multiple organisms on urine culture, how the method of urine collection impacts results, and whether cystitis can and should be differentiated from pyelonephritis. Until consensus can be reached in these areas, uniform inclusion criteria may be an elusive goal. Published guidelines such as those from the American Academy of Pediatrics can be used as a guide, although the narrow age range (2 months–2 years) of this guideline limits its utility for all children.

These ambiguities in disease definition are not unique to UTIs. In pneumonia, for example, chest radiograph results, lung examination findings, clinical symptoms, inflammatory markers, and sputum analyses are all used to define disease. Even when there is near-certainty that pneumonia exists, most cases are caused by viruses,[9] and differentiating viral from bacterial pneumonia remains a challenge. Similarly, there is substantial variability in the diagnosis of acute otitis media (in which viral etiologies are also common), and streptococcal pharyngitis, which is clouded by asymptomatic bacterial carriage. Inclusion of patients without bacterial disease is likely to attenuate differences in outcomes between groups in any antibiotic trial.

VARIABILITY OF CLINICAL END POINTS

Variability in choice of clinical end points in UTI trials is expected given the heterogeneity of the clinical questions at hand. For example, time to resolution is a reasonable outcome when comparing oral and IV antibiotics, or comparing 1 oral antibiotic to another. In contrast, symptomatic relapse is a more appropriate outcome for a trial comparing 7 versus 14 days of the

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same oral antibiotic because it is rare for clinical resolution to take longer than 7 days, and the importance of asymptomatic microbiologic relapse is unclear. Although Basmaci et al[3] reference adult Food and Drug Administration and European Medicines Agency guidelines suggesting microbiologic cure as an end point, this end point is less well-suited to pediatric UTIs given the challenges of obtaining a clean sample in children. Similarly, radiographic outcomes are of unclear diagnostic utility because abnormalities of questionable clinical relevance are common. Therefore, time to improvement and symptomatic relapse may be the best candidate end points depending on the clinical question being studied. A validated tool to assess clinical improvement is needed.

THE NEXT FRONTIER OF UTI TRIALS

Basmaci et al[3] call for the harmonization of future pediatric UTI trial design methodologies. What questions remain to be answered in future trials? From our perspective, several knowledge gaps exist that could be informed by well-designed trials. The first surrounds young infants (<2 months), in which there is evidence of substantial variability in duration of parenteral antibiotic durations.[10–12] Further evidence that short IV or all oral courses are safe even in the youngest infants could have a meaningful impact on harms and costs associated with long IV courses (including adverse effects of central catheters) and extended hospitalizations. The second gap involves the approach to highly resistant UTIs, which are often treated with prolonged parenteral courses of broad spectrum antibiotics, despite evidence from small studies that most patients improve despite receiving antibiotics to which their organisms are resistant.[13,14]

A third potentially impactful UTI trial would compare antibiotics to a placebo, at least for low-risk, uncomplicated cases. Resolution of bacterial infections without antibiotics is well-described in 2 of the most common bacterial infections in children: acute otitis media[15] and streptococcal pharyngitis.[16] Data from the Pediatric Research in the Office Setting Febrile Infant Study suggest that the vast majority of UTIs in young infants resolve without treatment.[17] This finding, coupled with the limited data suggesting that many patients with highly resistant UTIs improve despite receiving discordant antibiotics,[13,14] further supports the notion that the immune system can successfully combat bacterial infections in many cases. Given the current global antibiotic resistance crisis, and the decreasing affordability of health care, strategies for safely doing less[18] must be a priority.

ABBREVIATIONS

IV: intravenous
UTI: urinary tract infection

REFERENCES

1. Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC. Antibiotics for acute pyelonephritis in children. *Cochrane Database Syst Rev*. 2014;(7):CD003772
2. Hewitt IK, Pennesi M, Morello W, Ronfani L, Montini G. Antibiotic prophylaxis for urinary tract infection-related renal scarring: a systematic review. *Pediatrics*. 2017;139(5):e20163145
3. Basmaci R, Vazouras K, Bielicki J, et al. Urinary tract infection antibiotic trial study design: a systematic review. *Pediatrics*. 2017;140(6):e20172209
4. Schroeder AR. UTI and faulty gold standards. *Pediatrics*. 2017;139(3):e20163814A
5. Shaikh N, Hoberman A, Martin JM, Shope TR. Author's response: response to comments by Drs Schroeder and Jain. *Pediatrics*. 2017;139(3):e20163814C
6. Shaikh N, Shope TR, Hoberman A, Vigliotti A, Kurs-Lasky M, Martin JM. Association between uropathogen and pyuria. *Pediatrics*. 2016;138(1):e20160087
7. Roberts KB; Subcommittee on Urinary Tract Infection, Steering Committee on Quality Improvement and Management. Urinary tract infection: clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months. *Pediatrics*. 2011;128(3):595–610
8. Schroeder AR, Chang PW, Shen MW, Biondi EA, Greenhow TL. Diagnostic accuracy of the urinalysis for urinary tract infection in infants <3 months of age. *Pediatrics*. 2015;135(6):965–971
9. Jain S, Williams DJ, Arnold SR, et al; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among US children. *N Engl J Med*. 2015;372(9):835–845
10. Brady PW, Conway PH, Goudie A. Length of intravenous antibiotic therapy and treatment failure in infants with urinary tract infections. *Pediatrics*. 2010;126(2):196–203
11. Joshi N, Lucas BP, Schroeder AR. Physician preferences surrounding urinary tract infection management in neonates. *Hosp Pediatr*. 2018;8(1): In press
12. Schroeder AR, Shen MW, Biondi EA, et al. Bacteraemic urinary tract infection: management and outcomes in young infants. *Arch Dis Child*. 2016;101(2):125–130
13. Katsuta T, Shoji K, Watanabe Y, Saitoh A. Treatment of pyelonephritis caused by extended-spectrum β-lactamase-producing Enterobacteriaceae in children. *Pediatr Infect Dis J*. 2013;32(4):417–419
14. Tratselas A, Iosifidis E, Ioannidou M, et al. Outcome of urinary tract infections caused by extended spectrum β-lactamase-producing Enterobacteriaceae in children. *Pediatr Infect Dis J*. 2011;30(8):707–710

15. Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database Syst Rev*. 2015;(6):CD000219

16. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *Cochrane Database Syst Rev*. 2013;(11):CD000023

17. Newman TB, Bernzweig JA, Takayama JI, Finch SA, Wasserman RC, Pantell RH. Urine testing and urinary tract infections in febrile infants seen in office settings: the Pediatric Research in Office Settings' Febrile Infant Study. *Arch Pediatr Adolesc Med*. 2002;156(1):44–54

18. Schroeder AR, Harris SJ, Newman TB. Safely doing less: a missing component of the patient safety dialogue. *Pediatrics*. 2011;128(6). Available at: www.pediatrics.org/cgi/content/full/128/6/e1596

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