Antibiotics for acute pyelonephritis in children

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For the current issue of the *Journal*, we asked Dr Jennifer M Walton to comment on, and put into context, the recent Cochrane Review on antibiotics for acute pyelonephritis in children.

Background

Urinary tract infection (UTI) is one of the most common bacterial infections in infants. The most severe form of UTI is acute pyelonephritis, which results in significant acute morbidity and may cause permanent kidney damage. There remains uncertainty regarding the optimum antibiotic regimen, route of administration and duration of treatment. This is an update of a review that was first published in 2003 and updated in 2005 and 2007.

Methods

Search methods: The Cochrane Renal Group's Specialised Register, CENTRAL, MEDLINE, EMBASE, reference lists of articles and conference proceedings were searched, without language restriction, to April 10, 2014.

Selection criteria: Randomized and quasi-randomized controlled trials comparing different antibiotic agents, routes, frequencies or durations of therapy in children zero to 18 years of age with proven UTI and acute pyelonephritis were selected.

Data analysis: Four authors independently assessed study quality and extracted data. Statistical analyses were performed using the random-effects model, and the results were expressed using risk ratio (RR) for dichotomous outcomes or mean difference for continuous data, with 95% CI.

Results

This updated review included 27 studies (4452 children). It incorporated evidence from three new studies, and following re-evaluation, a previously excluded study was included because it now met the inclusion criteria.

Risk of bias was assessed to be low for sequence generation (12 studies), allocation concealment (six studies), blinding of outcome assessors (17 studies), incomplete outcome reporting (19 studies) and selective outcome reporting (13 studies). None of the studies were blinded for participants or investigators. The 27 included studies evaluated 12 different comparisons. No significant differences were reported for duration of fever (two studies, 808 children: mean difference 2.05 h [95% CI –0.84 h to 4.94 h]), persistent UTI 72 h after commencing therapy (two studies, 542 children: RR 1.10 [95% CI 0.07 to 17.41]) or persistent kidney damage at six to 12 months (four studies, 943 children: RR 0.82 [95% CI 0.59 to 1.12]) between oral antibiotic therapy (10 to 14 days) and intravenous (IV) therapy (three days) followed by oral therapy (10 days). Similarly, no significant differences in persistent bacteriuria at the end of treatment (four studies, 305 children: RR 0.78 [95% CI 0.24 to 2.55]) or persistent kidney damage (four studies, 726 children: RR 1.01 [95% CI 0.80 to 1.29]) were reported between IV therapy (three to four days) followed by oral therapy and IV therapy (seven to 14 days). No significant differences in efficacy were reported between daily and three times daily administration of aminoglycosides (one study, 179 children, persistent clinical symptoms at three days: RR 1.98 [95% CI 0.37 to 10.53]). Adverse events were mild and uncommon, and rarely resulted in discontinuation of treatment.

Conclusion

This updated review increases the body of evidence supporting that oral antibiotics alone are as effective as a short course (three to four days) of IV antibiotics followed by oral therapy, for a total treatment duration of 10 to 14 days for the treatment of acute pyelonephritis in children. When IV antibiotics are adminstered, a short course (two to four days) of IV therapy followed by oral therapy is as effective as a longer course (seven to 10 days) of IV therapy. If IV therapy with aminoglycosides is chosen, single daily dosing is safe and effective. Insufficient data are available to extrapolate these findings to children <1 month of age, or to children with dilating vesicoureteric reflux (grades III-V). Further studies are required to determine the optimal total duration of antibiotic therapy required for acute pyelonephritis.

The full text of the Cochrane Review is available in The Cochrane Library: Strohmeier Y, Hodson EM, Willis NS, Webster AC, Craig JC. Antibiotics for acute pyelonephritis in children. Cochrane Database of Systematic Reviews 2014, Issue 7. Art. No.: CD003772. DOI: 10.1002/14651858.CD003772.pub4.

EXPERT COMMENTARY

Treatment of pyelonephritis remains a relatively common reason for admission to hospital, with an overall estimated annual admission rate in the United States of 18 to 20 per 100,000 pediatric patients, with rates of up to 2.5 times higher than this for infants (1). When confronted with a child with a febrile UTI, the primary treatment goals are to treat the underlying infection and minimize the risks for complications, such as sepsis or permanent kidney damage. There is a growing body of evidence that early, versus delayed, initiation of antibiotics does not reduce the risk for renal scarring (2); therefore, it appears unlikely that the route of initial antibiotic administration will affect the incidence of scarring. Furthermore, there is accumulating evidence that many cases of uncomplicated pyelonephritis can be successfully treated using oral antibiotics alone. While outpatient oral treatment is now common practice for older patients with febrile UTIs, when encountering a young infant with a febrile UTI, many clinicians are still apt to admit the patient to hospital for observation and initial empirical IV therapy.

Current Canadian Paediatric Society (CPS) guidelines (3) recommend that nontoxic children >2 months of age, with no known underlying urinary tract pathology, be treated with a seven-to-10 day course of appropriate oral antibiotics, as long as there is no other indication for admission to hospital, and they are likely to receive and tolerate every dose of oral therapy. The CPS recommendations are less definitive regarding treatment of infants one

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to two months of age because of their higher risk for sepsis and meningitis. The CPS guideline does not address infants <1 month of age; however, most experts would recommend that all undergo a full septic work up and admission for IV antibiotics. In terms of choice of antibiotics for infants >2 months of age with a probable UTI who require admission to hospital and parenteral therapy, the CPS recommends that initial empirical treatment with once-daily dosing of aminoglycoside can be considered a safe and effective alternative to broader-spectrum third-generation cephalosporins.

The results of the recent Cochrane review are generally aligned with the CPS guidelines. For patients >1 month of age with no known urinary tract anomalies presenting with uncomplicated pyelonephritis, the review demonstrated that oral and IV therapy were equally effective. If IV therapy is used, once-daily aminoglycoside is safe and effective, and a short course of IV therapy with completion of 10 to 14 days total therapy with an oral antibiotic is appropriate (4). However, it is important to note that there are some key limitations of the current review that clinicians should be aware of before deciding to change current practice. The 27 studies included were quite heterogeneous in design, study population and definitions. Furthermore, 10 studies excluded children who were "seriously ill or unstable", but did not provide consistent definitions for these terms. The evidence is only of moderate quality for the route of antibiotic administration, and is even lower quality for once-daily aminoglycoside therapy. There is very limited evidence regarding the optimal treatment duration. Most importantly, the review was unable to analyze outcomes according to age, leaving lingering doubt as to whether oral therapy is truly safe and effective in young infants.

In conclusion, the results of this Cochrane review are unlikely to change my current practice significantly. Older children who have a febrile UTI (presumed pyelonephritis), but who are clinically stable and able to tolerate oral medication will still be treated with oral outpatient antibiotics for approximately 10 days. However, given the lingering questions regarding the applicability of this review to very young infants, I remain wary of discharging a younger infant (<3 months of age) who presents with fever and urinalysis consistent with a UTI home on oral antibiotics without a period of observation, and likely a short course of IV treatment until the source of infection is confirmed. In my experience, vomiting is not uncommon in infants with pyelonephritis, and I remain concerned about the possibility of missed oral doses, particularly early in the course of illness. Furthermore, although the risk for concomitant bacterial meningitis in infants with UTI has been demonstrated to be quite low (<0.5%) (5), the spectre of missing or undertreating a case of Gram-negative meningitis in a young infant continues to haunt clinicians caring for paediatric patients. On the other hand, the Review findings that a short course of IV antibiotics followed by completion of the 10 to 14 day total course with oral therapy is safe, is consistent with my current practice of rapidly transitioning to oral antibiotics once the child is clinically improving, which is usually within 48 h to 72 h, and treating for a total of 10 days. In terms of antibiotic selection, given recent shortages of various antibiotics, my choice of therapy is dictated as much by which antibiotic is available that the isolate is susceptible to, as what is 'most' evidence based.

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