Are oral antibiotics equivalent to intravenous antibiotics for the initial management of pyelonephritis in children?

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PART A: EVIDENCE-BASED ANSWER AND SUMMARY

Urinary tract infection (UTI) is a common bacterial infection in infants and children. In a Swedish study (1), the attack rate for at least one UTI by seven years of age was 8.4% in girls and 1.7% in boys. In young children, UTIs typically present as pyelonephritis (2,3), which has been associated with renal scarring. Long-term effects of renal scarring are decreased renal function and hypertension (4). The optimal route for antibiotic therapy – oral (PO) or intravenous (IV) versus intramuscular administration – is not clear. Consensus guidelines (5,6) from the 1990s still recommend IV antibiotics. The present review summarizes studies comparing PO antibiotics with initial IV antibiotics for children diagnosed with pyelonephritis, with the primary outcome being renal scarring for six months or more post-therapy.

A literature search of the PubMed, EMBASE and Cochrane databases was performed on December 2008. In a Cochrane review, Hodson et al (7) identified three studies – Hoberman et al (8), Montini et al (9) and Buechner et al (10) – that met the inclusion criteria. Data from the Buechner et al (10) abstract has since been published by Neuhaus et al (11).

All studies were randomized controlled trials (8,9,11). The studies stratified children by hospital, sex and age (9), and age and duration of fever (8). Hoberman et al (8) recruited children from the emergency departments of four tertiary care children's hospitals in the United States. Neuhaus et al (11) recruited from three paediatric hospitals and two community hospitals in Switzerland, while Montini et al (9) recruited from 28 paediatric inpatient units in northeast Italy. The age range was one to 24 months of age (8), one month to six years of age (9), and six months to 16 years of age (11). Only one study (8) reported the mean age (eight months), while the median age was eight months (9), 1.6 years (IV/PO) (11) and 2.2 years (PO) (11). The studies' exclusion criteria were clinical assessment of sepsis, PO intake and dehydration (8,9,11). Clinical assessment can be subject to interpretation. The number of excluded children was not cited before the time of enrolment (8,9,11).

All studies enrolled children who had a combination of fever, urinalysis results, inflammatory markers and a single organism from a urine culture (8,9,11). Two studies (8,9) excluded children with renal abnormalities by history or prenatal ultrasound. Neuhaus et al (11) allowed enrolment of children with isolated vesicoureteric reflux, megaureter or duplex kidney, independent of antibiotic prophylaxis.

The standard antibiotic therapy was sequential IV cefotaxime (8) or ceftriaxone (9,11) for three days, followed by cefixime (8), coamoxiclavulanate (9) or ceftibutin (11) for either seven days (9) or 11 days (8,11) versus the same total duration with PO antibiotics alone. The studies' definitions for renal scarring, parenchymal volume loss or renal contour distortions, and pyelonephritis were consistent (8,9,11). Two nuclear radiologists interpreted the renal scans independently and resolved any discrepancies by consensus (8,9,11). Two studies (8,11) measured the rate of renal scarring after six months from antibiotic therapy, while Montini et al (9) measured the rate after 12 months.

All studies (8,9,11) demonstrated no statistical differences in the rates of renal scarring between PO and IV/PO treatment groups. Hoberman et al (8) demonstrated that renal scarring occurred in 9.8% in the PO group and 7.2% in the IV/PO group (P=0.21). Among those children with acute pyelonephritis defined as a positive renal scan, renal scarring occurred in 16.9% in the PO group and 13.6% in the IV/PO group (P=0.18) (8). Montini et al (9) demonstrated renal scarring in 13.7% in the PO group and 17.7% in the IV/PO group. The absolute mean difference was 4% (95% CI –11.1 to 3.1). Among those children with acute pyelonephritis defined as a positive renal scan, the incidence of renal scarring was 27.8% in the PO group and 33.0% in the

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IV/PO group. The mean difference was 5.8% (95% CI –18.7 to 6.9). Finally, Neuhaus et al (11) demonstrated renal scarring in 26.2% in the PO group and 45.8% in the IV/PO group (P=0.2), adjusted for C-reactive protein and size of acute phase renal lesion.

There were no severe adverse reactions in the three studies (8,9,11). One child was switched from PO medication to IV medication because of vomiting (8). The bacteremia rate was 4.3% (13 of 298, of which five received PO antibiotics) and repeat blood cultures were sterile. The rate of symptomatic UTI reinfection was similar in both treatment groups; all repeat urine cultures were sterile. No antibiotic changes were required (8). In the Montini et al (9) study, coamoxiclavulanate was changed to another PO antibiotic in 10 children because of gastrointestinal upset and in two children because of antibiotic resistance. No child treated with ceftriaxone required an antibiotic switch. Repeat urine cultures after three days of treatment were positive for only two specimens, were considered contaminated and no antibiotic change was required. No blood cultures were drawn in the study (9). Neuhaus et al (11) identified one patient who was randomly assigned to the IV group with bacteremia and did well. All repeat urine cultures were sterile. All children in the study tolerated the antibiotics without side effects.

Equal numbers of children failed to complete the study in each treatment group, with these rates being approximately 10% (8), 20% (9) and 30% (11). The majority of dropouts were due to parental withdrawal of consent.

PART B: CLINICAL COMMENTARY

PO antibiotic therapy for children with UTIs has the advantages of ease and cost over IV therapy (12). All three studies (12-14) showed comparable renal scarring between IV and PO antibiotic groups without serious adverse events, suggesting that PO therapy has the potential to improve and simplify treatment. Although a significant number of children (25% to 30%) dropped out before the final renal scan, the children were similar because the dropout rates were comparable between the two therapy groups (13,14). Vesicoureteric reflux (VUR), rather than antibiotic choices, affected renal scarring. There was no risk difference in renal scarring between treatment groups, despite the presence of VUR. However, these children have a higher risk of renal scarring than children without VUR (12,14).

There are no data on PO antibiotics for UTIs in infants younger than one month of age. With higher risks of bacteremia, meningitis and nonspecific findings, these children would benefit from conservative IV antibiotics. Yet, Hoberman et al (12) suggested that it was probably safe to switch to PO antibiotics for children who responded to IV antibiotics.

The applicability of these studies to children with known structural urological abnormalities is not clear. Only Neuhaus et al (14) enrolled these children. Nine children required surgery, dropping them from the study. Three children completed the study, yielding no meaningful results. There are no randomized trials examining PO antibiotics therapy in children taking prophylactic antibiotics. Resistance to common PO antibiotics may be greater in this population. However, children with urological abnormalities and children on prophylactic antibiotics would probably respond to appropriately broad-spectrum PO antibiotics.

Barriers to adapting new therapies are limited dissemination and synthesis of information, and poor quality indicators (15). Recently, the National Institute for Health and Clinical Excellence (16) published treatment guidelines advocating PO antibiotics in uncomplicated patients as young as three months of age. Clinician compliance is to be determined.

A structured outpatient follow-up is required to ensure optimal therapy. This would include tracking and defining community antibiotic sensitivities and microorganisms. Common empirical antibiotic choices are cefixime or amoxicillin/clavulanic acid. Although ceftibutin performed well in one study (14), it is not licensed in Canada.

SUMMARY

PO antibiotics appear to be as effective as initial IV antibiotics for UTIs in children older than one month of age with no known structural urological abnormality. Therefore, clinicians should consider PO antibiotics for these children who are nontoxic and have close parental and follow-up care.

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