

What is the appropriate empiric antibiotic therapy in uncomplicated urinary tract infections in children in developing countries?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: <http://www.ichrc.org>

This review addresses the question: *What is the appropriate empiric antibiotic therapy in uncomplicated urinary tract infections in children in developing countries?*

The **WHO Pocketbook of Hospital Care for Children** recommends for antibiotic therapy –

► Give oral cotrimoxazole (4 mg trimethoprim/20 mg sulfamethoxazole per kg every 12 hours) for 5 days. Alternatives include ampicillin, amoxicillin and cephalexin, depending on local sensitivity patterns of *E. coli* and other Gram-negative bacilli that cause UTI, and on antibiotic availability (see page 325 for details of dosage regimens).

► If there is a poor response to the first-line antibiotic or the child's condition deteriorates, give gentamicin (7.5 mg/kg IM once daily) plus ampicillin (50 mg/kg IM/IV every 6 hours) or a parenteral cephalosporin (see pages 330–331). Consider complications such as pyelonephritis (tenderness in the costo-vertebral angle and high fever) or septicaemia.

Section Editors: Trevor Duke and Julian Kelly

For more information on this project to evaluate the evidence behind the WHO Hospital Care for Children, see *J Trop Pediatr* 2006; 52: 1–2. If you would like suggest a topic or contribute a review, please contact Dr Julian Kelly. E-mail julian.kelly@rch.org.au.

► Treat young infants aged <2 months with gentamicin (7.5 mg/kg IM once daily) until the fever has subsided; then review, look for signs of systemic infection, and if absent, continue with oral treatment, as described above. (Pocketbook chapter 6.8, page 164).

Introduction:

Urinary tract infection (UTI) is an important cause of morbidity and mortality in children.^{1,2} Studies from developing countries show that the around 10% of children with febrile illnesses have UTI.¹² Studies have shown a higher UTI prevalence of 8-35% in malnourished children.¹⁶ The risk of developing UTI before the age of 14 is approximately 1% in boys and 3-5% in girls.¹ Due to lack of overt clinical features in children less than two years, appropriate collection of urine samples and basic diagnostic tests at first-level health facilities in developing countries, UTI are not generally reported as a cause of childhood mortality. If poorly treated or undiagnosed, UTI is an important cause of long-term morbidities such as hypertension, failure to thrive and end-stage renal disease.¹

Unfortunately, many of the organisms responsible for UTI in developing and industrialised countries have become resistant to first-line antimicrobials. It is thus necessary to establish the type of pathogen and antimicrobial sensitivities in the local environment in order to treat the UTI with the appropriate antibiotic.

Methodology

Articles were identified through PubMed by use of the 'Clinical Queries' framework. The clinical search strategy employed was: (Anti-bacterial agents OR antibiotic*) AND (Urinary tract infections OR bacteriuria) AND (child* OR paediatric OR pediatric). The clinical filters for both 'therapy' and 'narrow, specific', as well as 'broad, sensitive' were used. And only 2 articles relating to UTI were identified, one of which was in German. A similar strategy was adopted to search the Global Health (1973 to April 2006) and EMBASE (1980 to 2006 Week 14) databases, and the Cochrane Library (Issue 1, 2006) was also searched. Reference lists were hand-searched, abstracts retrieved and read and articles checked for citations using the Cited Reference Tool on the Web of Science. Where relevance was in doubt, the complete article was sourced.

Articles were restricted to the English language. Trials on non-antibiotic treatment of UTI were excluded, as were those for treatment of complicated UTIⁱ (abnormal renal tract, impaired renal function, impaired host defences), antibiotic prophylaxis for recurrent UTI. We included studies relating to the treatment for UTI in malnourished children, as this is an important high-risk group. UTI prevalence has been reported as high as 8-35% in febrile malnourished children, with the risk of bacteriuria increasing with the severity of malnutrition.²⁻⁷

Methodological quality of selected articles was assessed using the Oxford Centre for Evidence-Based Medicine Levels of Evidence framework. No randomised-control trials were found. However, there were two prospective cohort studies and two case series that were found to be relevant. One systematic review article was found covering all aspects of UTI in both the developed and developing countries.

Results

All of the studies examined patients with suspected UTI and collected data on the infecting organism and subsequent antibiotic sensitivities. (See Tables 1 and 2.)

In a study by Jeena *et al*¹² (n=94), set in a primary health care clinic, Gram-negative pathogens accounted for 87.5% of cases, *E. coli* and

Klebsiella pneumoniae being the pathogens most common (56% and 19%, respectively). It was found that these pathogens were most sensitive to gentamicin (100%), nalidixic acid (100%), augmentin (96%), and cephalexin (96%). A previous hospital-based study by the same authors¹³, looked at bacteriuria and pyuria in catheter specimens from 180 hospitalised children. The bacteria detected (mainly *E.coli*) were found to be sensitive to nalidixic acid (100%), amikacin (100%), cephalexin (91%) and augmentin (94%).

A study by Musa-Aisien *et al*¹⁴ (n=300), described the prevalence and antimicrobial sensitivity pattern in UTI in febrile under-5s at children's emergency unit in Nigeria. *E.coli* was yet again the most common pathogen (58%). Other isolates were *Klebsiella pneumoniae* (23%), and *Staphylococcus aureus* (19%). All isolates were moderately-to-highly sensitive to gentamicin (80%), augmentin (81%), ceftriaxone (77%), and ciproxin (77%). Of the 26 children who were commenced on augmentin, 16 (62%) responded to treatment, with resolution of fever and any other symptoms within 72 hours.

In a study of 185 children with UTIs by Wammanda *et al*¹⁵, *E. coli* constituted 59.5% of the isolates and *Klebsiella* and *Enterobacter species* caused 10.6%. *E.coli* was sensitive to augmentin and gentamicin in 60% and 80%, respectively. Similar susceptibility results were observed for *Klebsiella* and *Enterobacter species*.

Discussion

This review highlights a lack of a large body of evidence to address a very common problem: the appropriate empiric antibiotic therapy for uncomplicated UTI.

Nalidixic acid, aminoglycosides including gentamicin, amikacin and streptomycin, 3rd generation cephalosporins and augmentin were suggested by the studies found in this review as possible treatment for resistant pathogens.

There was a paucity of literature for antibiotic therapy for uncomplicated UTI in the developing world. Each of the four studies was a case series or a prospective review. In most of the papers, efficacy of antibiotics was not the main objective of the study, which meant that the studies did not include any follow-up and there was little detail about the doses and durations given.

Summary

The available evidence indicates that local sensitivity patterns should be the final arbiter in determining empiric guidelines. In those children who fail to improve or deteriorate with initial therapy, or who are very young, then Gram-negative coverage with an aminoglycoside is important.

References

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Table 1 summarising the sensitivities of Gram negative organisms to various antibiotics:

	Study			
	Wammanda (2002) Hospital based study <i>E. Coli</i>	Jeena (1995) Hospital based study All organisms	Jeena (1996) PHC based study All organisms	Musa-Aisen (2003) Hospital based study <i>E. Coli</i>
Antibiotic	Gram negative organisms sensitivity to antibiotic			
Ampicillin	15%	14%	7%	13%
Cotrimoxazole	16.7%	42%	28%	40%
Amoxycillin-clavulanic acid	60%	94%	96%	80%
Gentamicin	80%	-	100%	80%
Nalidixic acid	-	100%	100%	-
Amikacin	-	100%	-	-
Cephalexin	-	91%	96%	-
Sulpahamethoxazole	-	-	14%	-
Trimethoprim	-	-	21%	-
Chloramphenicol	33%	-	-	20%
Ciprofloxacin	-	-	-	80%
Ceftazidime	-	-	-	27%
Erythromycin	-	-	-	0%
Azithromycin	-	-	-	40%
Ceftriaxone	-	-	-	67%

Table 2 summarising the range of urinary tract pathogens found:

Pathogen	Wammanda (2002) hospital- based study Nigeria	Jeena (1995) hospital- based study South Africa	Jeena (1996) PHC based study S.A.	Musa-Aisien (2003) hospital- based study Nigeria
Gram-negative organisms	70.1%	79%	87.5%	81%
E. coli	59.5%	53%	56%	58%
Klebsiella	10.6%	-	19%	23%
Enterobacter	10.6%	-	-	-
Staph. aureus	-	-	-	19%
Alkaligenes faecalis	-	-	-	-