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.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

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 to:

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).

OR

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.

OR

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] The risk of developing UTI before the age of 14 is approximately 1% in boys and 3-5% in girls.[1] There is a legitimate suspicion that UTI are under-diagnosed and inappropriately managed by children in developing countries. 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 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 UTI (abnormal renal tract, impaired renal function, impaired host defences), antibiotic prophylaxis for recurrent UTI. It is difficult to exclude data relating to the treatment for UTI in malnourished children, as many children in developing countries are moderately malnourished and studies have shown a higher UTI prevalence of 8-35% in malnourished children with the risk of bacteriuria increasing significantly with the severity of malnutrition.[2][3][4][5][6][7]

Methodolological quality of selected articles was assessed using the Oxford Centre for Evidence-Based Medicine Levels of Evidence framework. Unfortunately, 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.

Table 1: Sensitivities of Gram negative organisms to various antibiotics

	Study			
	Wammanda (2002) Hospital based study *E. Coli*	**Jeena (1995) Hospital based study All organisms**	**Jeena (1996) PHC based study All organisms**	**Musa-Aisen (2003) Hospital based study *E. Coli***
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%

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 Jeena et al[13] (n=180), looked at bacteriuria and pyuria in catheter specimens from hospitalised children. The organisms detected (mainly E.coli) were found to be sensitive to nalidixic acid (100%), amikacin (100%), cephalexin (91%) and augmentin (94%).

Another study by Musa-Aisien et al[14] (n=300), looked into 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 by Wammanda et al[15] (n=185), E. coli constituted 59.5% of the isolates, 10.6% isolates being Klebsiella and Enterobacter species. It was observed that E.coli was sensitive to augementin and gentamicin in 60% and 80%, respectively. A similar trend was 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.

Table 2: Urinary tract pathogens found

Pathogen	**Wammanda (2002) hospital-based study Nigeria**	**Jeena (1995) hospital-based study South Africa**	**Jeena (1996) PHC based study South Africa**	**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	-	-	-	-

SUMMARY

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

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