Empiric antibiotic treatment for urinary tract infection in pre-school children: susceptibilities of urine sample isolates

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Abstract

Background

Antibiotic treatment recommendations based on susceptibility data from routinely submitted urine samples may be biased because of variation in sampling, laboratory procedures, and inclusion of repeat samples, leading to uncertainty about empirical treatment.

Aim

To describe and compare susceptibilities of *E. coli* cultured from routinely submitted samples, with *E. coli* causing UTI from a cohort of systematically sampled, acutely unwell children.

Design, setting and participants

Susceptibilities of 1458 *E. coli* isolates submitted during the course of routine primary care for children <5 years (routine care samples), compared to susceptibilities of 79 *E. coli* isolates causing UTI from 5107 children <5years presenting to primary care with an acute illness (systematic sampling: the DUTY cohort).

Results

The percentage of *E. coli* sensitive to antibiotics cultured from routinely submitted samples were; amoxicillin 45.1% (95% CI 42.5% to 47.7%); co-amoxiclav using the lower systemic breakpoint (BP) 86.6% (84.7% to 88.3%); cephalexin 95.1% (93.9% to 96.1%); trimethoprim 74.0% (71.7% to 76.2%); and nitrofurantoin 98.2% (97.4% to 98.8%)..

The percentage of *E. coli* sensitive to antibiotics cultured from systematically sampled DUTY urines considered to be positive for UTI were; amoxicillin 50.6% (39.8% to 61.4%); co-amoxiclav using the systemic BP 83.5% (73.9 to 90.1%); co-amoxiclav using the urinary BP 94.9% (87.7% to 98.4%); cephalexin 98.7% (93.2% to 99.8%); ; trimethoprim 70.9% (60.1% to 80.0%); nitrofurantoin 100% (95.3% to 100.0%); and ciprofloxacin 96.2% (89.4 to 98.7%)..

Conclusion

E. coli susceptibilities from routine and systematically obtained samples were similar. Most UTIs in preschool children remain susceptible to nitrofurantoin, co-amoxiclav, and cephalexin.

***Key words*:** Urinary Tract Infections; Pediatrics; Diagnosis; Anti-Bacterial Agents; antibiotic resistance; surveillance; treatment recommendations

Introduction

Early, effective antibiotic treatment of UTI in young children alleviates acute symptoms, and may also limit long-term sequelae.(1) Antibiotics should ideally be prescribed only to those who have a UTI, using an antibiotic with the narrowest effective spectrum. Empirical treatment is more or less universal in primary care, given that urine culture results take several days, and as yet there are no rapid point of care tests that give a sufficiently robust indication of aetiology and the susceptibility of infecting organisms.

Guidelines generally recommend that choice of empiric antibiotics for suspected urinary tract infection (UTI) in acutely unwell children should depend on local susceptibilities.(1, 2) Such information is usually derived from routinely collected data, and may provide biased estimates because of variation in sampling decisions by individual clinicians, differing laboratory procedures and the inclusion of repeat samples in databases. The susceptibilities of organisms from urines submitted in routine care and in organisms causing UTI from systematically obtained urines in primary care have not been directly compared.

Information about susceptibilities of cultured organisms in urine samples routinely submitted from children in primary care may therefore not be generalizable to the child presenting with acute illness in primary care who has not had recurrent UTIs, who is not known to have a structural renal tract abnormality, or who has complex medical needs. Previous studies have generally focused on epidemiological studies of asymptomatic children(3-6) or on children presenting to health care with symptoms

clearly attributable to UTI.(7) A recent study from the US found that the resistance patterns differed between routinely submitted outpatient and inpatient urine samples.(8) We know of only one large study that has focused on culture results in systematically sampled acutely unwell children, and we know of no study that has analysed systematically sampled urine from acutely unwell children in a central research laboratory using more intensive techniques that are currently undertaken in routine laboratory practice.(9) Susceptibilities of organisms cultured in systematically sampled children in the community with an acute illness (not just those suspected of UTI) have not been compared to sensitivities in urines submitted for routine laboratory culture (which usually includes only those children with a high suspicion of UTI, recurrent UTI and with renal tract abnormalities). Systematic sampling involves taking a urine sample form all eligible children rather than sampling based only clinical suspicion. Such a comparison would help determine the applicability of findings surveillance based on routinely submitted samples to children presenting in primary care with an acute illness.

We therefore set out to compare the susceptibilities of *E. coli* in samples positive for UTI in routinely submitted samples from children in the community and compare these to those cultured from systematically obtained samples considered positive for UTI in acutely unwell pre-school children presenting to primary care.

Methods

Samples submitted during the course of routine care

Antimicrobial susceptibility data for urines submitted to microbiology laboratories across Wales in 2011 was extracted from DataStore, a data repository that extracts all results from the laboratory information management systems into a common searchable format. DataStore was searched for all urines submitted from general practice from children in the first five years of life with an *E. coli* UTI (identified directly using UTI Chromogenic agar) that had susceptibility testing performed from any of the 10 laboratories in Wales. Culture and susceptibilities were performed using common standard operating procedures, based on the National Standard Method (BSOP 41).(10) Susceptibilities were performed by BSAC disc diffusion tests.(12) The data do not differentiate between mid-stream, clean-catch, nappy pad or catheter urines. Data from duplicate isolates were removed prior to analysis. Organisms from the same patient, with the same identification and susceptibility pattern isolated ≤ 91 days from the date of the initial isolate were excluded. To reduce the effect of variable susceptibility testing rates to different antibiotics, individual hospital or laboratory sensitivities are only presented for organisms where ≥80% of such isolates from the given sample type was tested and where the number of isolates tested exceeds 10. In the case of first generation cephalosporins, eight laboratories reported cephalexin and two laboratories cefradine. For the purposes of this analysis the results have been combined and reported as cephalexin. For co-amoxiclav a systemic breakpoint (BP) was used for interpretation. We were not able to obtain culture results for urine submitted UK wide.

Samples from children undergoing systematic urine sampling (The DUTY Cohort)

The Diagnosis of Urinary Tract infection in Young children (DUTY) study was a multicentre, prospective, diagnostic cohort study that recruited children aged under

five years, between April 2010 to April 2012.(11) Multi-centre ethical approval was granted by the South West Southmead Research Ethics Committee (previously Southmead Research Ethics Committee, then South West 4 REC), Ref #09/H0102/64.

DUTY Cohort Participants

Children presenting unwell to primary care with an acute illness episode of up to 28 days duration, even where the responsible clinician was confident of the diagnosis (e.g. a child with bronchiolitis), or with urinary symptoms, were eligible to take part in the study. The sample therefore included all children with an acute illness, not just those at high risk of UTI. Children were excluded if: they were neither constitutionally unwell (e.g. acute conjunctivitis only) or an absence of urinary symptoms; they were known to have a neurogenic or surgically reconstructed bladder; they were using a permanent or intermittent urinary catheter; the main presenting problem was trauma; or antibiotics had been taken within seven days.

DUTY cohort procedure

Urine samples were obtained by clean catch, where possible, for children who were toilet trained or for whom the parent or DUTY Study Research Nurse was happy to attempt collection. For children still using nappies (diapers) whose parents did not think clean catch would be successful, Newcastle Nappy Pads were used. Nappy pads were inserted into the nappy (diaper) then removed as soon as the child urinated to reduce the risk of contamination. Once the child had urinated the nappy pad was removed and the urine was extracted with a syringe into a sterile container.

If it was not possible to obtain a sample before the child left the primary care site, the parent was given the necessary equipment and advice on taking the sample at home. They were given a labelled Sterilin™ bottle into which to transfer the urine, and asked to write the time and date the sample was obtained. They were advised to store the sample in the refrigerator and return it to the primary care site (directly or via collection by the DUTY Study Research Nurse/Clinical Studies Officer) as soon as possible, preferably within 24 hours.

DUTY cohort laboratory analysis

Urine samples were split into two fractions. Since results might be needed for clinical management, the priority fraction was sent to the local NHS laboratory routinely used by the recruiting primary care site for routine diagnostic processing. If sufficient urine was available, the second fraction was sent to the Specialist Antimicrobial Chemotherapy Unit, Public Health Wales Microbiology Laboratory, Cardiff (Central Research Laboratory). A minimum of 1ml volume was required for analysis. Urine samples were transported to the central laboratory in a urine monovette containing boric acid (Sarstedt) using standard biological sample post office Safeboxes^{TM}. In the central research laboratory, microscopy was performed using an IQ200 automated urine analyser (Iris Diagnostics Ltd, UK) to determine counts of white blood cells, red blood cells, squamous epithelial cells, bacteria and other artefacts. Quantitative total and species-specific counts were recorded for all organisms present. Disc susceptibilities were performed on any organism present at $>10^3$ cfu/mL according to BSAC guidelines.(12) Antimicrobials tested for all isolates were trimethoprim, nitrofurantoin and amoxicillin. Gram negative and positive isolates were further tested with co-amoxiclav, cephalexin, ciprofloxacin, cefpodoxime and cefoxitin,

vancomycin, novobiocin respectively. Oral doses of co-amoxiclav are in 2:1 ratio amoxicillin/clavulanate. Susceptibility testing is performed according to standardized methods; the British Society for Antimicrobial Chemotherapy (BSAC) standardized method uses 2:1 ratio and the European Committee for Antimicrobial Susceptibility Testing (EUCAST) standardized method uses a 2mg/L fixed concentration of clavulanate. The BSAC method was the most used method in the UK whilst the EUCAST method is the method due to be adopted by UK labs in the future. In this study, we used both discs to cover any differences that may be highlighted.

Urinary breakpoints are employed when the UTI is uncomplicated, as in most adult community patients. Systemic breakpoints are used when the UTI may be more complicated (i.e. causing a systemic infection). In the DUTY children we thought it advisable to interpret using both breakpoints to cover the possibility that a system infection could be present.

The definition of UTI in the Central Research Laboratory was $\geq 10^5$ CFU/mL of a pure or predominant uropathogen (where predominant was defined as a 3 $\log_{10}$ difference in growth between the predominant and next organism). For the purposes of the DUTY study, an uropathogen is defined as any *Enterobacteriaceae*. We used the cut point of $\geq 10^5$ CFU/mL to reduce risk of including false positives.

Results

Samples submitted during the course of routine care

In the routine database analysis, we identified 1458 urine samples for children in the first five years of life in 2011 that were submitted from general practices in the course

of routine care, which grew *E. coli* and were tested for antimicrobial susceptibility (only 1343 were tested against amoxicillin). We do not have data for the total number of samples that were submitted for children in this age group, only those growing *E. coli* on culture. 45.1% (95% CI 42.5% to 47.7%) were susceptible to amoxicillin, 86.6% (84.7% to 88.3%) to co-amoxiclav, 95.1% (93.9% to 96.1%) to cephalexin, 74.0% (71.7% to 76.2%) to trimethoprim, and 98.2% (97.4% to 98.8%) to nitrofurantoin.

Systematically sampled dataset (DUTY cohort)

A total of 6390 urine samples were obtained from the 7163 recruited children. The majority of samples (73.5%) were successfully split into two fractions and were sent to both the local NHS and central research laboratories, but there was insufficient urine for a fraction to be sent to the Central Research Laboratory in 1073 (15.0%) of cases and 64.2% had arrived by two days, 80.4% by 3 days, and 91.1 by 4 days.

5231 (73.0%) samples were received at the Central Research Laboratory, 124 could not be processed (e.g. the sample leaked in transit or there was insufficient urine), and 5107 (71.3%) were cultured and had a 'UTI status' result. 94 of these sample culture results were considered to indicate a UTI according to the definition of UTI we used, giving a prevalence of 1.8%.

Table 1 provides demographic features of the 5107 children from the DUTY cohort who had samples cultured in the research laboratory. 19.7% (n=1006) were between 1 and 2 years old, with 8.1% (n=412) less than 6 months old. There were equal numbers

of males and females (49.1% vs. 50.9% respectively). Most were ethnically 'white' (82.9%, n=4235).

Table 2 shows the comparative susceptibility of *E. coli* considered the causative agent for UTI isolated from community urines from across Wales in 2011, in patients aged 0-5 years inclusive (n=1458) and from urines obtained by systematically sampling children presenting to primary care with an acute illness (the DUTY study samples).

The online supplementary table provides details of sensitivities to all *Enterobacteriaceae* (n=94) including the *E. coli* (n=79) cultured from urines samples of acutely unwell children (DUTY Cohort) in the first five years of life considered positive for UTI.

Discussion

Urine sampling rates from primary care are variable and may be biased towards recurrent and more severe cases, and so antibiotic susceptibilities from routinely submitted samples may not be representative of organisms causing urinary tract infection (UTI) in children presenting with acute illness in the course of routine care, and this may bias treatment recommendations that are based on routinely submitted samples. We found that the antimicrobial susceptibilities of organisms considered to be causing a UTI cultured in routinely submitted samples was remarkably similar to susceptibilities of organisms considered to be causing a UTI cultured from urine in systematically sampled children under the age of five. Most UTIs in preschool

children remain susceptible to nitrofurantoin, co-amoxiclav (using the urinary BP in uncomplicated UTI), and cephalexin.

Our systematically sampled data set was obtained from the largest prospective study of UTI in children presenting to primary care with acute illness. We recruited large numbers and had over 5000 centrally analysed urine results. All of these urine samples were processed according to the same standard operating procedures, and cultured using sensitive methods.

For the analysis presented in this paper, we based our definition of a microbiologically diagnosed UTI on culture results and did not include clinical factors in this definition. Our UTI prevalence (1.8%) was lower than found in previous studies.(13) Our definition included only significant growths of Enterobacteriaceae UTI, which may have missed some UTI caused by non-Enterobacteriaceae. Urine samples were often difficult to obtain and the nappy pad method was commonly used in the younger children, and this may be associated with greater levels of contamination and increased risk of false negative and false positive results. Some urine volumes were insufficient to be split to allow for Research Laboratory analysis, which may have resulted in risk of selection bias. We did not use methods such as suprapubic aspiration or catheterisation, as these are not feasible for large numbers of children in primary care. Urine samples were transported to the Central Research Laboratory by post and most had arrived in the lab by 2 days after the sample was taken.

Heginbothom and colleagues found no evidence that screening and duplicate samples materially affected estimates of levels of resistance in routinely submitted samples for all age groups.(14) We are not aware of any study that has compared the culture results of systematically sampled urines from acutely unwell children who are found to have laboratory proven UTI with data derived from samples submitted during the course of routine care.

NICE guidelines for managing children under 3 months and those with suspected upper urinary tract infection state "consider referral and treat with 7 to 10 days of oral antibiotic such as co-amoxiclav or cephalosporin (IV if oral not possible)". For older children and those with lower UTI, NICE recommends treating with oral antibiotics for 3 days, and that "the choice of antibiotics should be directed by locally developed multidisciplinary guidance. Trimethoprim, nitrofurantoin, cephalosporin or amoxicillin may be suitable."(1) High rates of resistance to amoxicillin should be borne in mind when making decisions about empiric therapy. The American Academy of Pediatrics clinical practice guideline for the diagnosis and management of the initial UTI in febrile infants and children 2 to 24 months states that the usual choices for oral treatment of UTIs include a cephalosporin, amoxicillin plus clavulanic acid, or trimethoprim- sulfamethoxazole, but recommend against nitrofurantoin because serum and parenchymal antimicrobial concentrations may be insufficient to treat pyelonephritis or urosepsis.(15) Adverse effects include anorexia, nausea, vomiting, and diarrhoea, and acute and chronic pulmonary reactions have been reported.(16) Nitrofurantoin should not be used when pyelonephritis is suspected

We do not have clinical details for the children in the routinely submitted dataset, and

so are not able to make detailed comparisons between these children and the children in the DUTY cohort. The children who had their urine sampled during the course of routine care have had urine sampled based on clinical suspicion of a UTI, whereas the basis for sampling in the DUTY cohort was systematic, in that we asked clinicians to submit a sample on all sequential eligible children. Despite this difference in approach to identifying children for sampling in the two dataset, we found that most organisms in routinely submitted samples positive for UTI from children in the first five years of life and from those samples positive from systematically sampled acutely unwell children aged from three months until five years in primary care produced remarkably similar results.

This suggests that estimates of antimicrobial susceptibilities derived from surveillance using routinely submitted samples from young children are applicable to empirical treatment decision for acutely unwell children in primary care.

Resistance to trimethoprim in *E. coli* from both systematically sampled urines and routine care urines was between 26% and 29%. This is equivalent to the proportion trimethoprim resistance in *E. coli* from a UK multicentre study (26.7%) in 2003. (21) However trimethoprim resistance levels may vary depending on locality; a report published for the London area reported trimethoprim resistance 40% for *E. coli*.(20) It is difficult to know what level is too high to continue to recommend trimethoprim as a first line empirical therapy as there is not always a clear correlation between a resistant UTI organism and a treatment failure.(17) This is thought to be partly due to high concentrations of antimicrobial agents which can be reached in the urine.(17) It has been estimated that a resistance proportion of 30% would still be associated with

an 85% clinical success rate.(17) Co-amoxiclav and cephalexin are broader spectrum alternatives, albeit at the increased risk of generating subsequent antimicrobial resistance. These results also support the recommendation to use nitrofurantoin. (10) This agent does not reach therapeutic concentrations in the blood or other tissues so is less likely to drive resistance in commensal organisms or be effective in pyelonephritis.(18) Increases in resistance to nitrofurantoin are less marked than to other commonly used antimicrobials.(19) However, when renal involvement or sepsis is suspected, in younger children or in children with known renal impairment, an alternative should be used.(1, 16)

Ethical approval

Multi-centre ethical approval was granted by the South West Southmead Research Ethics Committee (previously Southmead Research Ethics Committee, then South West 4 REC), Ref #09/H0102/64.

Transparency Declarations

The study was funded by a grant from the NIHR Health Technology Assessment Programme (project number 08/66/01). The funders had no editorial control over the data.

No conflicts of interest have been declared by the authors except for P. Little who is a member of the NIHR Journals Library Board and has provided consultancy work to Bayer Pharmaceuticals. All authors have completed the unified competing interest form at www.icje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare (1) no financial support for the submitted work from anyone other than their employer; (2) no financial relationships with commercial entities that might

have an interest in the submitted work (3) no spouses, partners, or children with relationships with commercial entities that might have an interest in the submitted work; and (4) no non-financial interest that might be relevant to the submitted work.

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Contributorship statement

CCB and AH won the funding and designed the study. CCB led the drafting of this manuscript and all authors contributed to the final paper. All authors contributed to planning and implementation the study, data collection and interpretation.

Table 1: Demographic features of 5017 children presenting to primary care with an acute illness and enrolled in the DUTY study between April 2010 and April 2012 for whom a urine sample was analysed by the research laboratory[1]

		n	%
Age	Less than 6 months	412	8.1
	6 months to less than 12 months	675	13.2
	1 year to less than 2 years	1006	19.7
	2 years to less than 3 years	989	19.4
	3 years to less than 4 years	1138	22.3
	4 years plus	887	17.4
Gender	Male	2507	49.1
	Female	2600	50.9
Ethnic groupings	White	4235	82.9
	Mixed	261	5.1
	Asian	203	4.0
	Black	325	6.4
	Other	33	0.6
	Missing	50	1.0

[1]. No similar data available for the routinely collected samples

Table 2: Comparison of susceptibilities for *E. coli* considered the causative agent of UTI from samples collected as part of routine care (Wales 2011) and part of a systematic urine sampling (DUTY cohort).

	Wales 2011 (n=1458)		DUTY (n=79)	
	% Susceptible	95% CI	% Susceptible	95% CI
Co-amoxiclav	86.6	84.7 to 88.3	[1]89.9	81.3 to 94.8
			[2]100.0	95.3 to 100.0
			[3]83.5	73.9 to 90.1
			[4]94.9	87.7 to 98.4
Amoxicillin	45.1	42.5 to 47.7	50.6	39.8 to 61.4
Cephalexin	95.1	93.9 to 96.1	98.7	93.2 to 99.8
Nitrofurantoin	98.2	97.4 to 98.8	100.0	95.3 to 100.0
Trimethoprim	74.0	71.7 to 76.2	70.9	60.1 to 80.0
Ciprofloxacin	N/A	N/A	96.2	89.4 to 98.7

[1]2:1 ratio with systemic breakpoint of S≤8 mg/L
[2]2:1 ratio with urinary breakpoint of S≤32 mg/L
[3]fixed 2mg/L with systemic breakpoint of S≤8 mg/L
[4] fixed 2mg/L with urinary breakpoint of S≤32 mg/L

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