EXPERIENCE WITH POINT-OF-CARE URINE CULTURE IN CHILDREN AT RAHIMA MOOSA MOTHER & CHILD HOSPITAL, JOHANNESBURG, SOUTH AFRICA.

RESEARCHER:

Dr Ismail MIGAMBI
Student number 394858
Department of Paediatrics & Child Health
University of the Witwatersrand, Johannesburg

CO-SUPERVISORS:

Prof A COOVADIA
Head of Department
Paediatrics & Child Health
Rahima Moosa Mother & Child Hospital

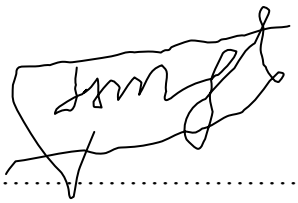
Dr G REUBENSON
Department of Paediatrics & Child Health
Rahima Moosa Mother & Child Hospital

Research report submitted in partial fulfilment of the requirements for the degree of Master of Medicine in Paediatrics.

Johannesburg, 2015.

DECLARATION

I, Ismail MIGAMBI, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.



Signed: ……

The 17th day of February 2015.

To my dear wife Rehma and
Our beautiful children Issa and Izzat
With love and admiration…

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First of all, I would like to express my sincere thanks to Professor A Coovadia, my co-supervisor who provided thoughtful guidance and constructive criticism. His commitment and support were always encouraging.

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ABSTRACT

BACKGROUND: Urinary tract infections (UTIs) are an important cause of morbidity in children in developing countries and increasing antimicrobial resistance is reported in many countries. This retrospective study describes the performance of urine dipsticks, the aetiology and the antimicrobial susceptibility of paediatric UTIs at Rahima Moosa Mother and Child Hospital, Johannesburg.

METHODS: We conducted a retrospective study of results from patients investigated for UTI over a four year period between January 2009 and December 2012 in the Department of Paediatrics & Child Health at Rahima Moosa Mother and Child Hospital.

RESULTS: *Escherichia coli* was the commonest isolated uropathogen. Dipsticks sensitivity to identify UTI was 40% for leucocyte esterase and 34% for nitrites. The specificity was 94.6% for leucocyte esterase and 96% for nitrites. Malnutrition was associated with greater risk of having a UTI, with odds ratio of 2.06 (95% Confidence interval 1.4-2.9). In addition malnourished children tended to present with more resistant uropathogens. Resistance to sulphamethoxasole/trimethoprim and cephalexin has been progressively increasing between 2009 and 2012. From 64% to 79% for sulphamethoxasole/trimethoprim and from 24% to 63% for cephalexin.

CONCLUSION: Positive urine dipsticks results allow immediate patient treatment but negative results need to be interpreted within the clinical context due to a high rate of false negatives. Malnourished children are significantly predisposed to urinary tract infections and tend to have more resistant uropathogens. Resistance to cephalexin is rising and studies to assess patient outcomes are needed to determine whether cephalexin still has a role in the treatment of paediatric UTI.

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ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
CI	Confidence intervals
CFU	Colony forming units
ESBL	Extended Spectrum Beta-lactamase producing
NHLS	National Health Laboratory Service
NPV	Negative predictive value
PPV	Positive predictive value
RMMCH	Rahima Moosa Mother and Child Hospital
UTI	Urinary tract infection
UWFA	Underweight for Age

I. INTRODUCTION

Urinary tract infections (UTIs) are an important cause of morbidity in children in developing countries (1).

Although all individuals are potentially susceptible to UTIs, there are specific higher-risk groups. Risk factors include very young age (neonates/infants), female gender, perineal colonization, urinary tract anomalies and immune deficiency (2).

Patients with UTI may be asymptomatic or present with a wide range of clinical manifestations from mild dysuria to life threatening septic shock. As a result, the true incidence of paediatric UTIs is difficult to determine (3, 4).

Up to 7% of girls and 2% of boys will have symptomatic, culture-confirmed UTI by 6 years of age (5). The prevalence of UTI in febrile infants is higher with younger age, with a rate of nearly 7% among febrile newborns (5).

In a meta-analysis the pooled prevalence rates of febrile UTIs in females aged 0-3 months, 3-6 months, 6-12 months, and >12 months was 7.5%, 5.7%, 8.3%, and 2.1% respectively. Among febrile male infants less than 3 months of age, 2.4% (CI: 1.4-3.5) of circumcised males and 20.1% (CI: 16.8-23.4) of uncircumcised males had a UTI. For the 4 studies that reported UTI prevalence by race, UTI rates were higher among white infants 8.0% (CI: 5.1-11.0) than among black infants 4.7% (CI: 2.1-7.3). Among older children aged 2 to 19 years with urinary symptoms, the pooled prevalence of UTI (both febrile and afebrile) was 7.8% (CI: 6.6-8.9) (6).

Up to one-fifth of children with malnutrition have been reported to have a UTI despite the absence of clinical signs or symptoms (7). Page *et al* studied infections in malnourished children; they found that 16% of children admitted for complicated severe acute malnutrition had a UTI (8).

The bacterial causes of UTI also vary based on a number of factors, predominantly the age of the patient and associated co-morbidities. *E coli* is the most frequently isolated pathogen (2).

UTI is associated with important medical and financial implications. Recurrent UTIs may cause renal scarring. Long-term consequences of renal scarring include hypertension, decreased renal function, and end-stage renal disease (3). Financial implications include the cost of doctors' visits, hospitalisation expenses, antimicrobial prescriptions, as well as transport costs. Days off school are also an important consequence of UTI among school-aged children as are caregivers' missed work days (3).

The standard test for the diagnosis of UTI is a quantitative urine culture (9). UTI is defined as significant bacteriuria in a patient with pyuria (i.e. evidence of an inflammatory response). What constitutes significant bacteriuria depends upon the method of collection and the isolated organism. The distal urethra is usually colonised by the same bacteria that may cause UTI; thus a low colony count may be present in a specimen obtained by voiding or transurethral catheterisation when bacteria are not present in bladder urine. *Lactobacillus spp*, coagulase-negative *staphylococci*, and *Corynebacterium spp* are usually not considered clinically relevant uropathogens (9).

Bacteriuria from a mid-stream urine specimen is considered significant if it grows ≥100 000 cfu/mL. Growth from a catheter specimen is considered significant if ≥10 000 cfu/mL and any number of colonies from suprapubic aspiration is significant (5).
Some studies in adults suggest that lower levels of bacteriuria (100 to 10 000 cfu/mL) should be considered significant for UTI in symptomatic individuals (10).

However, clinicians commonly initiate therapy before final urine culture results become available. To assist in this decision, rapid screening tests have been developed and are widely used (11).

Urine dipsticks include a biochemical analysis of urine for detection of nitrites and leucocyte esterase. Reports on the accuracy of urine dipstick analysis to rule in or out UTI differ widely. In a meta-analysis of the accuracy of urine dipsticks for both children and adults, the reported specificity of the urine dipstick test in detecting UTI was 85-98% for nitrites and 17-93% for leucocyte esterase. Sensitivity for positivity of either is 68-88%. The same study suggests that in children urine dipsticks test alone is useful to rule out infection when both results of leucocyte esterase and nitrites are negative, but recommends that a positive nitrite result need further work up (12).

However there are other reports which concluded that it is unsafe to rely on dipsticks alone to exclude a UTI especially when clinical suspicion is strong (13). In particular, anecdotally, urine dipsticks sensitivity seems to be lower in neonates, malnourished and immune-compromised children.

The dipslide Uricult® is a point-of-care urine culture test that yields results within 16-48 hours (14). The Uricult® is helpful in excluding UTI in febrile infants and may reduce unnecessary hospitalization and antibiotic use. The sensitivity of the dipslide in identifying UTI ranges from 70 to 95%. The reported specificity is 80 to 96% (15).

While children with suspected UTI are often given empiric antibiotic therapy before the causative organism and its antimicrobial sensitivities are known, antibiotic resistance amongst common uropathogens seems to be increasing. Ampicillin resistance was found in more than 75% of isolates and 2 to 40% of uropathogens are resistant to aminoglycosides (16), (17). With regard to these therapeutic challenges it is advised to regularly monitor the antimicrobial susceptibility profiles amongst commonly isolated uropathogens.

II. OBJECTIVES

A. To describe ***the aetiology*** of Uricult®-detected UTIs at RMMCH, Department of Paediatrics & Child Health from January 2009-December 2012.

B. To describe ***the antimicrobial susceptibility*** pattern of Uricult®-detected pathogens at RMMCH, Department of Paediatrics & Child Health from January 2009-December 2012.

C. To evaluate ***the performance*** [sensitivity, specificity, positive and negative predictive values (PPV, NPV)] ***of urine dipsticks*** in Uricult®-detected UTIs at RMMCH, Department of Paediatrics & Child Health from January 2009-December 2012.

III. METHODOLOGY

1. STUDY DESIGN

This is a retrospective descriptive study describing a record review of Uricult® results from the Department of Paediatrics & Child Health (RMMCH) over a 4 year period from January 2009 to December 2012.

2. STUDY POPULATION

Routinely collected clinical information and laboratory results were obtained from the Uricult® database. (See appendix 1 for Uricult® datasheet). The Uricult® dipslide point-of-care urine culture system has been in use within RMMCH, Department of Paediatrics & Child Health for more than 10 years. Urine is collected from all patients considered at risk for UTI. Urine specimens are typically screened by a urine dipstick strip, looking for the presence of leucocytes and/or nitrites, and then 'plated' onto 3 separate culture media on one Uricult® dipslide at the point-of-care. 'Dipsticks-negative' samples (nitrite and leucocyte esterase negative) are often plated, particularly when obtained from neonates, malnourished and immune-compromised individuals. Limited clinical information is routinely recorded into a paper-based database (see appendix 1). The specimen is then incubated at 37°C (also at point-of-care) and read daily, excluding most weekends and public holidays, by an

experienced clinician. Specimens considered to be negative or contaminated at 48-72 hours are discarded. Specimens suspected to have grown a significant pathogen are then submitted to the National Health Laboratory Services (NHLS) for identification and antibiotic sensitivity determination. Figure 1 shows Uricult® dipslides and incubator.

During the period under review the nutritional status of patients was assessed using the Wellcome classification (see appendix 2)

Figure 1: Uricult® slide and incubator

3. SAMPLING

a. INCLUSION AND EXCLUSION CRITERIA

All patients investigated for UTI with the Uricult® dipslide between January 2009 and December 2012 were included. No exclusion criteria were applied. However Uricult® dipslides were unavailable from May to July 2010 and from July to October 2012.

4. DATA COLLECTION

Permission was sought from the then Head of the Department of Paediatrics & Child Health at RMMCH as well as the Medical Superintendent of the hospital to access the database.
The paper-based Uricult® database was searched by the principal investigator to identify all culture positive specimens and the antimicrobial susceptibilities of the cultured organisms. Additionally from the same database the urine dipsticks results for nitrite and leucocyte esterase were extracted. Variables were then captured into an Excel spread sheet (Microsoft Office). Patient anonymity was maintained by excluding patients' names and hospital numbers.

5. DATA ANALYSIS

Data in the MS-Excel spreadsheet were exported to statistical software (STATA version 12) for analysis purposes.

Absolute and relative frequency of different microorganisms cultured was determined. The frequency of resistance to specific antibiotics was also determined. The performance of urine dipsticks was determined in comparison with laboratory confirmed cases of UTI.

6. LIMITATIONS

The retrospective design of our study is such that we relied upon the available data in the database. Hence for some patients data were incomplete. Furthermore, a patient record review was not undertaken and so no additional clinical information was obtained.

The brands of urine dipsticks used over this period are not known and there may have been more than one supplier.

IV. ETHICS CLEARANCE

The study proposal was submitted to the Human Research Ethics Committee of the University of the Witwatersrand for approval before commencing the study. The application was considered on 30 November 2012 by Human Research Ethics Committee (Medical) and clearance certificate M121139 was issued as shown in Appendix 3. As this is a case review, there was no risk to the study participants.

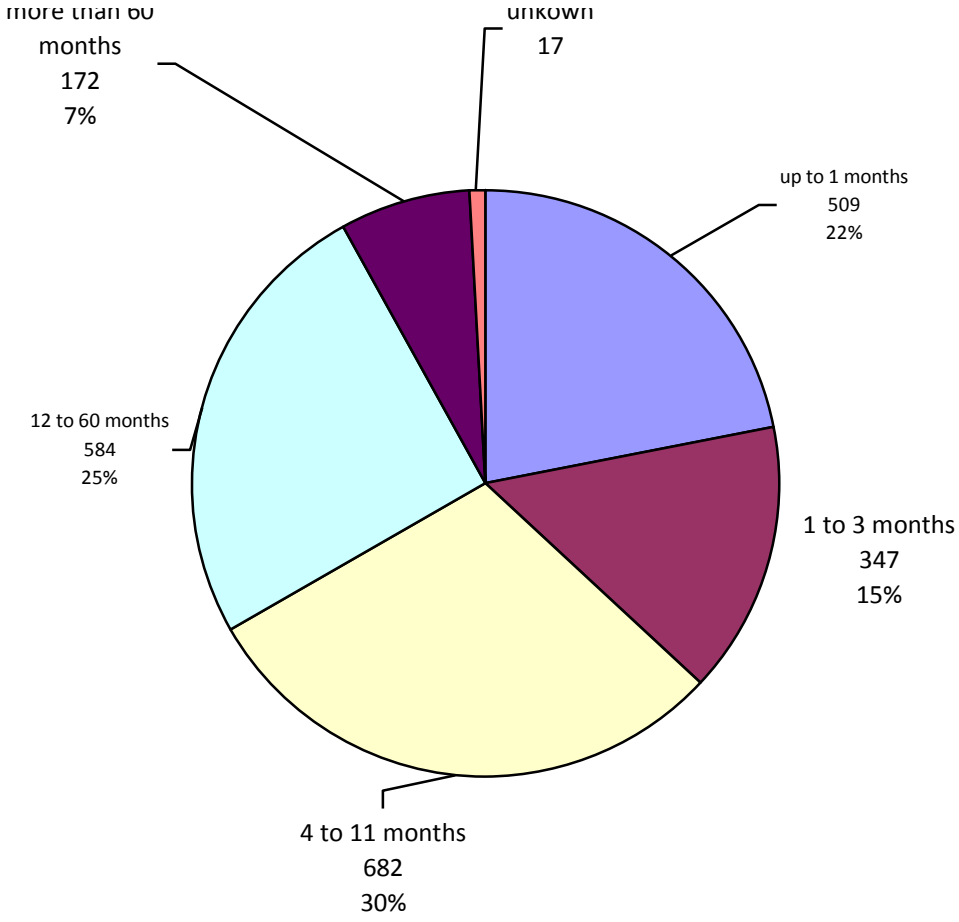
V. RESULTS

About 6000 patients are seen annually in the admission ward at RMMCH Paediatric department and approximately 10% of these patients are investigated for UTI with a urine specimen obtained and 'plated' onto a Uricult® dipslide. Most are done during the months of March to July with 12% of patients getting a urine specimen 'plated'.

1. DESCRIPTION OF THE POPULATION

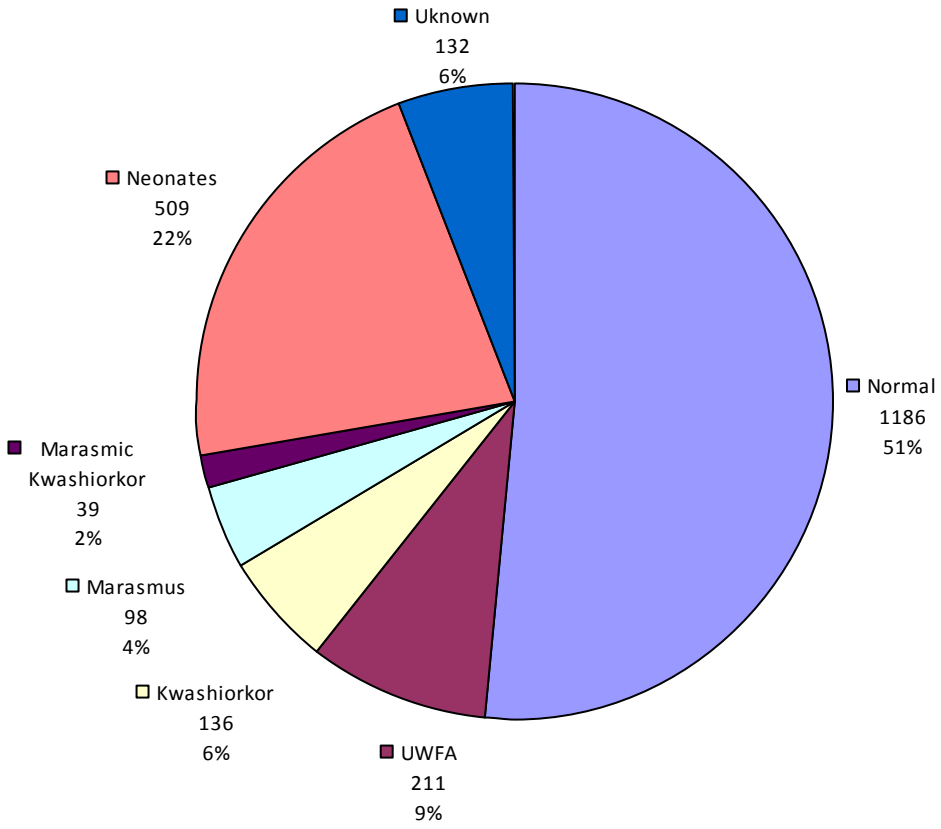
Data from a total of 2311 urine cultures were reviewed. Samples from the same patient on different days were included as separate samples. There were 1030 (44.5%) girls and 1195 (51.7%) boys. For 86 (3.8%) entries the patient sex was not recorded. Patients' age ranged from 0 to 13 years. The age distribution is shown in figure 2.

Figure 2: Participant age distribution



Of 2311 children studied, there were 136 (5.9%) with kwashiorkor, 98 (4.2%) with marasmus, 39 (1.7%) with marasmic kwashiorkor, 211 (9.1%) underweight for age (UWFA) and 1186 (51.3%) well-nourished. There were 509 (22%) neonates and 132 (5.7%) had no nutritional status recorded. Neonates were considered a nutritional group on its own besides the Wellcome classification due to their unique age-weight relationship. The nutritional status of participants is shown in figure 3.

Figure 3: Participant nutritional status



Of 2311 specimen that were plated onto the Uricult® culture media, 1736 (75.1%) were negative whereas 228 (9.9%) were discarded after 48-72 hours because they were considered contaminated. A total of 324 (14.0%) samples cultured a laboratory confirmed uropathogen; 43.2% (n=140) from female patients and 56.7% (n=184) from males. Six (1.8%) patients who had a confirmed UTI did not have their sex documented.

There were 23 specimens submitted to NHLS that were reported as contaminated. Of all 251 contaminated specimens, 36% were collected by urinary catheterization, 24% by mid-stream urine, 9.5% by suprapubic aspiration and 11.5% by non-documented methods. Urine bag specimens contributed to 24% of contaminated specimens; however considered alone, 62% of all bag specimens were contaminated.

The highest prevalence of UTI was found in infants aged 4-11 months (16.6%), followed by neonates (14.9%). The lowest prevalence was in children older than 60 months (11%). (Figure 4). Forty seven percent (n=152) of patients with UTI had normal nutritional status, 15.4% (n=50) were underweight for age, 10.8% (n=35) had kwashiorkor, 3% (n=10) had marasmus, and 4.3% (n=14) had marasmic kwashiorkor. Neonates made up 17.2% (n=56) of patients with culture confirmed UTI and 7 patients with UTI had no nutritional status documented (Figure 5). For kwashiorkor and marasmic kwashiorkor patients the odds ratio of having a UTI compared to normal nutritional status was 2.06 [95% Confidence interval 1.4-2.9]; for UWFA patients the odds ratio was 1.5 [95% Confidence interval, CI 1.2-2.1].

Figure 4: Frequency of UTI within age groups

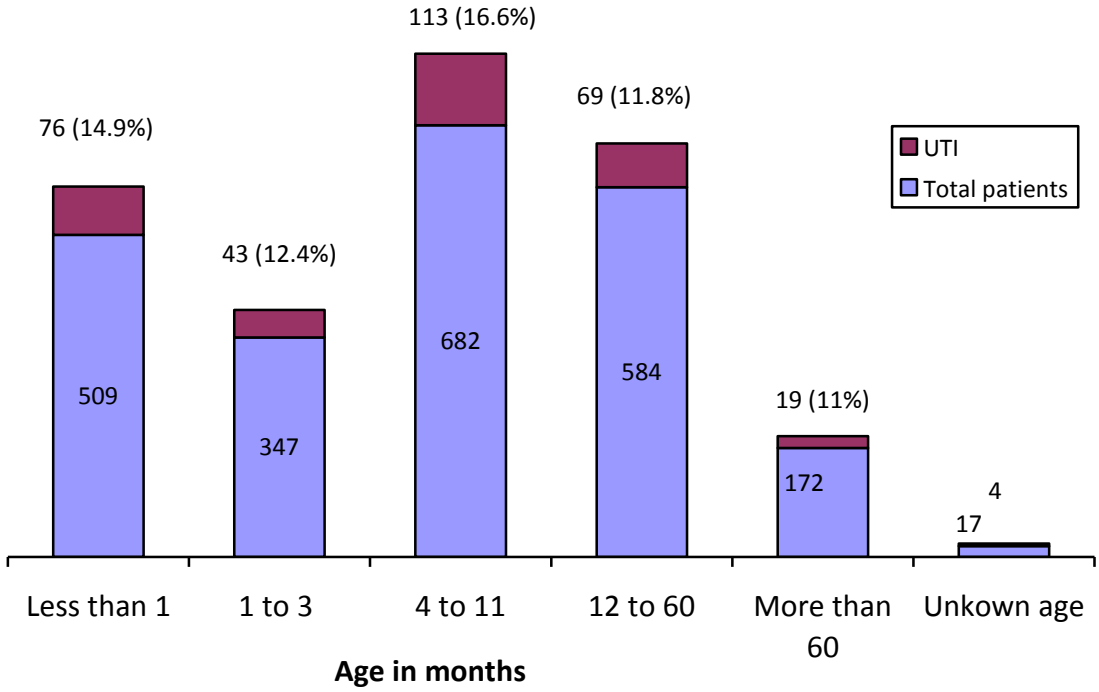
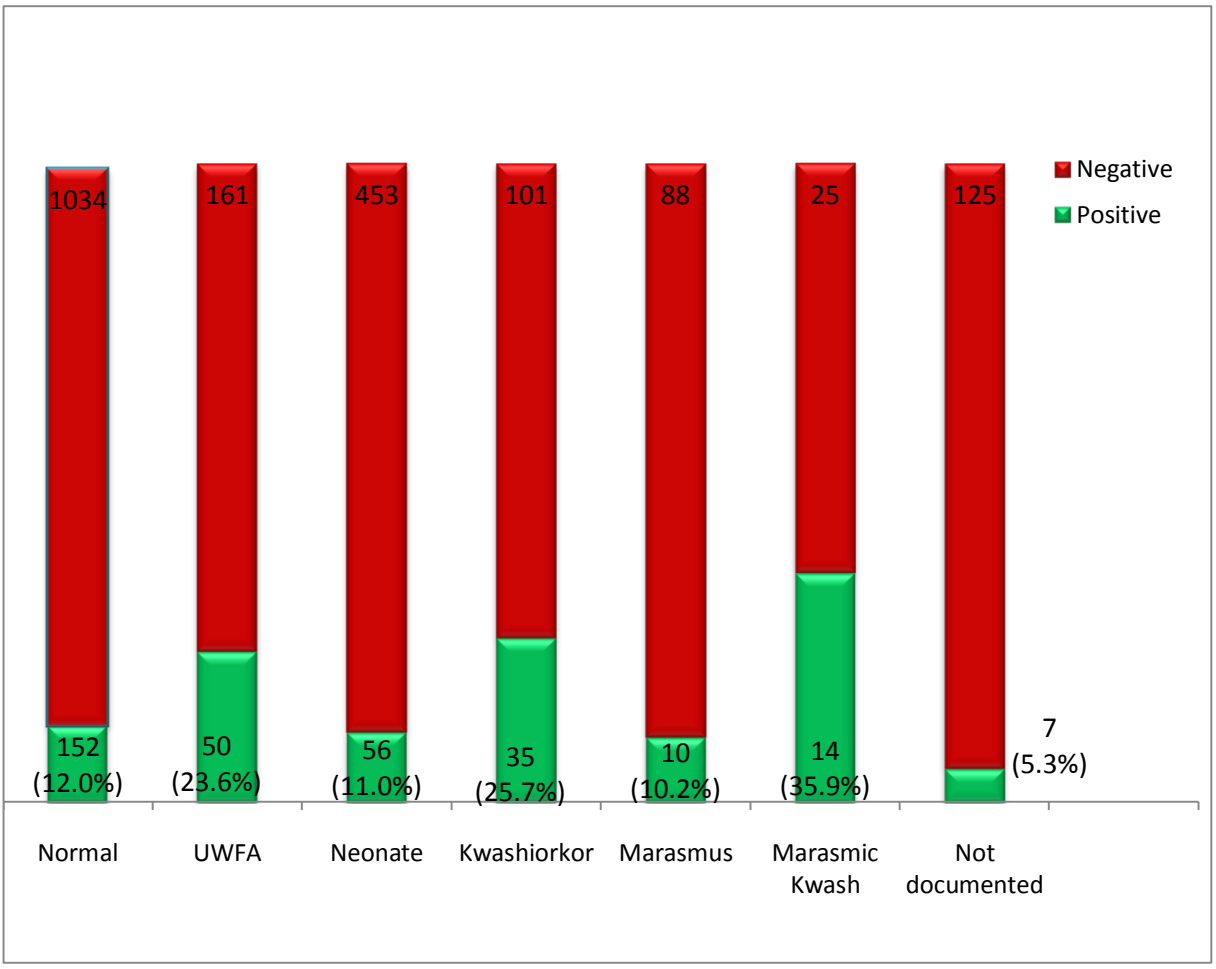


Figure 5: UTI and nutritional status



2. FREQUENCY OF UROPATHOGENS

A total of 14 different uropathogens were isolated. *Escherichia coli* was the most commonly isolated uropathogen detected in 67.5% of infected specimens, followed by *Klebsiella pneumoniae* (14.8%). Coagulase-negative *Staphylococcus* grew in 2.4% and *Candida albicans* in 1.5% of infected specimens. There were 23 Extended Spectrum Beta-lactamase producing (ESBL) pathogens; 5 *E coli* and 18 *Klebsiella pneumoniae.*

One specimen grew Methicillin-resistant *Staphylococcus aureus* (MRSA). Seven specimens grew more than one uropathogen, e.g. *E coli* with *Klebsiella pneumoniae* or *Klebsiella with Enterobacter sp.* The frequency of the uropathogens isolated is shown in Table 1.

Table 1: Frequency of uropathogens

Isolate	Frequency
E coli	219 (67.6%)
Klebsiella pneumoniae	48 (14.8%)
Klebsiella oxytoca	3 (0.9%)
Proteus mirabilis	7 (2.1%)
Enterobacter cloacae	7 (2.1%)
Citrobacter species	4 (1.2%)
Pseudomonas aeruginosa	7 (2.1%)
Morganella morgani	1 (0.3%)
Enterococcus faecalis	5 (1.5%)
Coagulase-negative *Staphylococcus*	8 (2.4%)
MRSA	1 (0.3%)
Acinetobacter baumanii	1 (0.3%)
Serratia	1 (0.3%)
Mixed growth	7 (2.1%)
Candida albicans	5 (1.5%)
Total	**324**

3. URINE DIPSTICKS

a. Nitrites

Nitrites were detected in 102 of 324 samples with a uropathogen identified; sensitivity 31.4% (95% CI 26.6-37%). Nitrites were positive in 68 (3.5%) cases out of 1964 culture-negative samples; specificity 96.5% (95% CI 95.6-97.3%), PPV 60% (95% CI 52.4-67.3%) and NPV 90.3% (95% CI 88-90.8 %). Eleven specimens tested positive for nitrites but were found contaminated when cultured.

b. Leucocyte esterase

The sensitivity of dipsticks detected leucocyte esterase was 36.1% (95% CI 31-41.6%). (117/324 culture-positive samples were positive for leucocytes esterase). Of 1964 culture-negative samples, 103 (5.3%) were positive for leucocyte esterase with a specificity of 94.7% (95% CI 93.7-95.7%), PPV 53% (95% CI 46.3-60%) and NPV 90% (95% CI 88.6-91.2%). Seven specimens tested positive for leucocyte esterase but were contaminated when cultured.

When leucocyte esterase and nitrite results were combined, specificity increased to 97.7% but sensitivity remained low; 31.4% (PPV 62.0%, NPV 92.3%).

Of 509 urine specimens collected from neonates, 76 (14.9%) were culture-positive. Among these, leucocyte esterase was positive in 18 cases with 23 false positives. Specificity 94.6% (95% CI 92.1-96.6%), sensitivity 23.6% (95% CI 14.6-34.8%), PPV 43.0% (95% CI 28.4-60.2%) and NPV 87.6% (95% CI 84.2-90.45%). Nitrites were positive in 19 cases of confirmed UTI with 20 additional false positives. Specificity 95.3% (95% CI 93-97%), sensitivity 25% (95% CI 15.7-36.2%), PPV 48.7% (95% CI 32.4-65.2%) and NPV 89.0% (95% CI 84.5-94.6%). Table 2 illustrates the performance of urine dipsticks within nutritional categories.

Table 2: Performance of urine dipsticks within nutritional categories

		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Overall Study Population	Leucocytes	36.1 (30.8-41.1)	94.6 (93.6-95.7)	53.0 (46.3-60.0)	89.9 (88.6-91.0)
	Nitrite	31.4 (26.4-36.8)	96.1 (95.6-97.3)	60.1 (52.2-67.0)	89.5 (88.0-90.8)
	Leucocytes and Nitrite	31.4 (25.3-38.0)	97.7 (97.0-98.3)	62.0 (52.0-71.0)	92.3 (91.0-93.4)
Well-nourished	Leucocytes	41.0 (32.7-50.0)	94.6 (92.8-96.1)	52.1 (50.0-59.2)	92.1 (90.3-93.6)
	Nitrite	34.9 (26.0-43.0)	94.0 (92.2-95.2)	44.7 (36.0-53.5)	92.1 (90.3-93.6)
	Leucocytes and Nitrite	36.4 (29.3-44.1)	97.1 (95.8-99.3)	69.8 (58.1-77.4)	93.1 (91.4-95.0)
Kwashiorkor	Leucocytes	42.8 (26.0-56.1)	94.5 (87.0-97.6)	75.0 (50.7-91.1)	81.2 (72.8-88.1)
	Nitrite	48.5 (31.9-63.5)	92.3 (86.1-96.7)	68.1 (45.7-87.9)	81.2 (72.8-88.1)
	Leucocytes and Nitrite	30.4 (23.3-39.7)	95.4 (95.0-96.1)	76.0 (66.0-83.6)	85.1 (82.4-89.0)
Marasmus	Leucocytes	35.7 (12.7-64.9)	91.4 (78.0-95.8)	50 .0 (18.7-81.3)	84.0 (71.6-92.4)
	Nitrite	42.8 (17.6-71.1)	85.3 (75.7-91.4)	33.3 (13.0-56.5)	89.7 (80.8-95.5)
	Leucocytes and Nitrite	26.4 (19.3-36.7)	92.4 (91.0-95.1)	59.0 (51.3-72.0)	90.1 (88.4-92.2)
Marasmic Kwashiorkor	Leucocytes	40.0 (12.1-73.7)	92.8 (74.0-99.0)	66.6 (23.0-95.0)	79.3 (60.3-92.0)
	Nitrite	50.0 (18.8-81.3)	92.8 (74.0-99.0)	71.4 (29.0-96.0)	82.1 (63.1-94.0)
	Leucocytes and Nitrite	31.4 (26.3-42.7)	93.4 (92.1-94.7)	71.2 (59.8-74.0)	86.1 (83.4-91.0)

4. ANTIMICROBIAL SENSITIVITY

In this study the highest rates of antimicrobial resistance were observed for ampicillin and sulphamethoxazole/trimethoprim (93.8% and 72.8% respectively). Only 2 isolates were resistant to amikacin and three isolates were resistant to colistin. None of the isolates was found to be resistant to carbapenems. Table 3 shows the frequency of resistance to different antibiotics. Resistance to most antibiotics was higher in 2012 than in the previous 3 years (Table 4). However only resistance to sulphamethoxazole/trimethoprim and cephalexin showed a significant increase over the study period (Figures 6, 7).

Table 3: Antibiotic resistance of urinary isolates

Antimicrobial	Frequency of resistance
Sulphamethoxasole/trimethoprim	236 (72.8%)
Ampicillin	304 (93.8%)
Amoxicillin/clavulanate	71 (21.9%)
Piperacillin/tazobactam	48 (15.0%)
Cephalexin	131 (40.4%)
Cefuroxime	30 (9.4%)
Ceftazidime/ceftriaxone/cefotaxime	28 (8.7%)
Cefepime	22 (7.0%)
Gentamicin	49 (15.1%)
Tobramycin	43 (13.5%)
Amikacin	2 (0.6%)
Nalidixic acid	30 (9.4%)
Nitrofurantoin	28 (8.7%)
Ciprofloxacin	12 (4.3%)
Colistin	3 (0.9%)
Meropenem/Ertapenem	0

Figure 6: Rate of antimicrobial resistance (%)

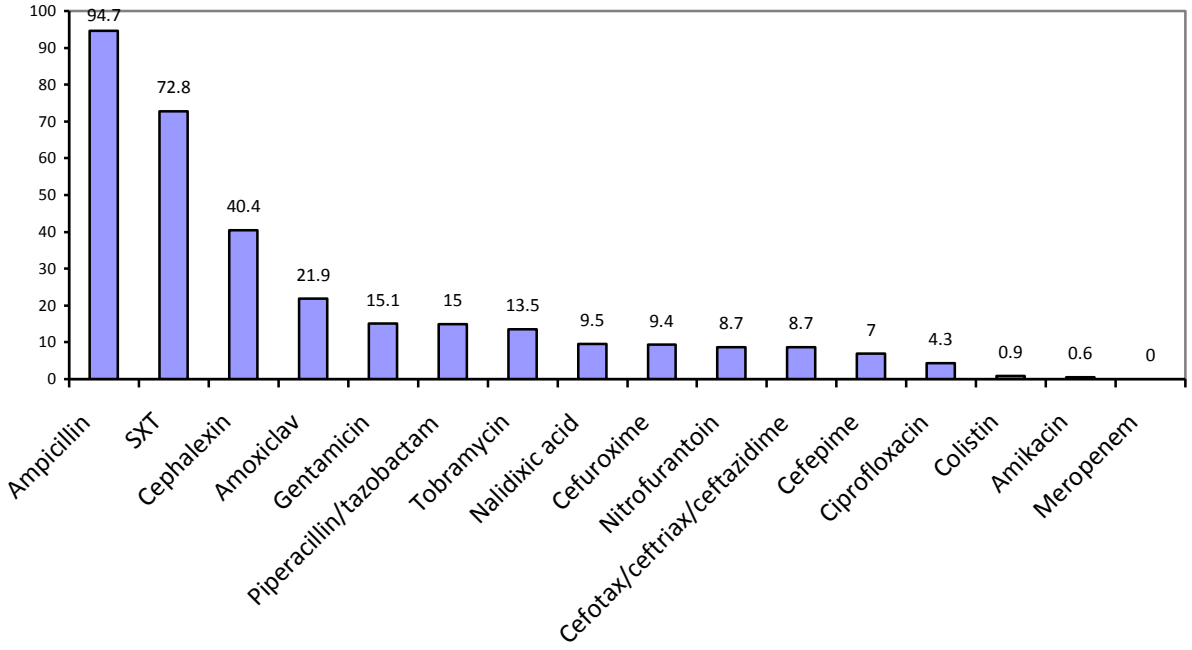
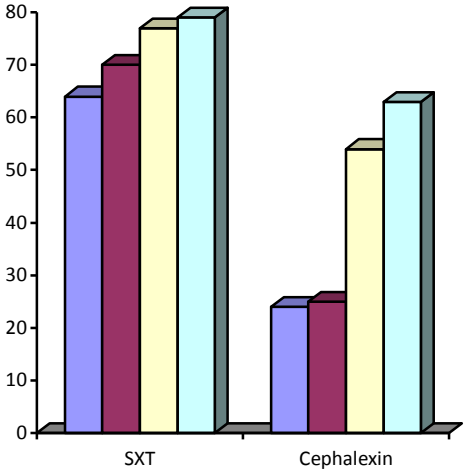


Table 4: Antimicrobial resistance by year of study

Antimicrobial	2009	2010	2011	2012
Sulphamethoxasole/trimethoprim	64.0%	70.0%	77.1%	79.0%
Ampicillin	88.7%	97.7%	91.2%	98.1%
Amoxicillin/clavulanic acid	26.0%	19.1%	17.0%	25.1%
Piperacillin/tazobactam	15.8%	4.5%	4.5%	18.7%
Cephalexin	24.0%	25.0%	54.0%	62.9%
Cefuroxime	9.1%	9.1%	7.8%	12.5%
Ceftazidime/ceftriaxone/cefotaxime	9.1%	6.8%	5.8%	12.5%
Cefepime	8.1%	4.5%	4.4%	12.5%
Gentamicin	20.0%	12.0%	15.1%	17.1%
Tobramycin	18.1%	13.6%	7.3%	12.5%
Nalidixic acid	12.2%	4.5%	4.8%	14.0%
Nitrofurantoin	8.1%	9.0%	5.8%	12.5%
Ciprofloxacin	5.1%	3.0%	4.9%	4.0%

Figure 7: Rate of resistance to Sulphamethoxazole/trimethoprim and cephalexin



E coli and *K pneumoniae* made up 82.4 % of all isolates**.** Compared to *E coli*, *K pneumoniae* showed greater resistance to all antimicrobials with the exception of sulphamethoxasole/trimethoprim.

Table 5: Antibiotic resistance rates of *E coli* and *K pneumoniae*

Antimicrobial	***E coli***	***K pneumoniae***
Sulphamethoxasole/trimethoprim	83.7%	68.7%
Ampicillin	76.2%	95.0%
Amoxicillin/clavulanate	17.3%	39.3%
Piperacillin/tazobactam	14.3%	21.0%
Cephalexin	32.0%	45.7%
Cefuroxime	5.9%	25.5%
Ceftazidime/ceftriaxone/cefotaxime	5.4%	23.2%
Cefepime	4.0%	21.0%
Gentamicin	13.7%	21.0%
Tobramycin	12.8%	18.6%
Nalidixic acid	8.9%	16.2%
Nitrofurantoin	5.4%	20.9%
Ciprofloxacin	1.2%	6.6%

Patients with malnutrition tended to have more resistant uropathogens detected. However this was statistically significant only for gentamicin.

Table 6: Frequency of resistant UTI pathogens in various nutritional categories

Antimicrobial	Normal	UWFA	Marasmus	Kwashiorkor	Marasmic kwashiorkor	P value, Normal nutrition versus malnutrition[1]
Sulphamethoxasole/trimethoprim	74.0%	80.1%	97.3%	92.3%	97.0%	0.07
Ampicillin	92.0%	96.1%	97.3%	97.3%	95.0%	0.20
Amoxicillin/clavulanate	22.5%	34.0%	46.1%	25.7%	26.0%	0.09
Piperacillin/tazobactam	14.4%	11.1%	30.7%	24.4%	25.5%	0.18
Cephalexin	39.4%	34.0%	64.2%	60.0%	65.0%	0.10
Cefuroxime	6.7%	11.0%	23.0%	12.2%	11.0%	0.09
Ceftazidime/ceftriaxone/cefotaxime	6.7%	11.0%	15.4%	9.7%	10.0%	0.31
Cefepime	5.3%	6.5%	15.4%	7.3%	10.0%	0.27
Gentamicin	14.7%	20.0%	69.2%	20.0%	20.0%	0.01
Tobramycin	12.0%	13.0%	38.5%	17.0%	20.0%	0.07
Nalidixic acid	8.2%	11.0%	15.4%	12.2%	10.0%	0.11
Nitrofurantoin	6.0%	13.0%	23.1%	12.2%	9.1%	0.11
Ciprofloxacin	3.7%	8.7%	15.4%	2.4%	3.2%	0.03

[1] Malnutrition group comprises patients with kwashiorkor, marasmic kwashiorkor and marasmus.

VI. DISCUSSION

Point-of-care testing for UTIs has a number of benefits including lower cost, more rapid availability of data and consequent more rapid clinical decision making. Disadvantages may include relying on non-microbiologists for interpretation, lack of microscopy results, and intermittent non-availability of stock.

1. UTI PREVALENCE AND UROPATHOGENS

Paediatric UTI is a common reason for seeking medical attention (6). Effective management relies on the identification of the causative organism and the appropriate choice of antimicrobials.

The prevalence of UTIs in our study is higher than that in most reported studies. However the prevalence of risk factors for UTI among our study population was substantial. Twenty two percent of patients were neonates and a further 11.7% had severe malnutrition (kwashiorkor, marasmus, marasmus kwashiorkor). While HIV status may impact on the epidemiology of paediatric UTIs, this was not recorded in the database used for this study.

Nader Shaikh *et al* in a meta-analysis reported a pooled prevalence of UTIs of 7% among febrile infants less than 24 months. For those aged between 2 and 19 years the pooled prevalence was 7.8% (6). There are other studies that have reported significantly higher prevalence of UTIs. Up to 28.6% of 1878 urine samples from children with suspicion of UTI were positive for pathogenic organisms in a hospital based study in Nepal (18).

While UTI is said to be a common complication of severe malnutrition, reported prevalence varies between 3 and 35% in malnourished paediatric in-patients (19). Previous studies have also shown that UTI is an important occult infection in malnourished children. The majority of malnourished patients diagnosed with UTI are admitted for reasons other than UTI. It has been recommended that all severely malnourished children have a urine specimen cultured (20). Our isolation rates among patients with kwashiorkor and marasmic kwashiorkor were significantly higher than among those with normal nutritional status. UWFA patients were also found to be at a greater risk of having UTIs.

As expected, Gram-negative bacteria were the most commonly isolated uropathogens with *E coli* isolated in 67.5% of all positive cultures. The second most common pathogen was *Klebsiella pneumoniae* (14.8%). Gram-positive organisms have received more attention recently as a cause of bacteriuria and UTIs. Some studies have reported them to cause 0.7 to 12.2% of UTIs (18). Gram-positive organisms were identified in 3% of positive specimens in this study.

2. URINE DIPSTICKS

Misdiagnosing UTI can lead to a failure of appropriate antibiotic prescription or prescription of unnecessary treatment and inappropriate investigations. Dipsticks are cheap, rapid and easy to perform (12).

In this study the sensitivity of leucocyte esterase to identify UTI was 31.4% with a specificity of 94.8%. For nitrites the sensitivity was only 36.1% with a specificity of 96.6%.
These results show that a positive urine dipstick reasonably reliably detects UTI but a negative result needs to be more carefully considered; it is important to interpret a negative result within the clinical context of the patient. This result is in concordance with the conclusion drawn by Coulthard MG *et al* but it is in contrast with a meta-analysis by Deville LJM *et al* which suggested that a dipstick negative for both leucocyte esterase and nitrites reliably rules out a UTI in children (12), (13).

The high proportion of young patients in our study may play a role in the poor performance of urine dipsticks. The sensitivity of dipsticks in neonates was particularly low; 23.6% for leucocyte esterase and 25% for nitrites. It is believed that frequent voiding in non toilet-trained infants leads to decreased time for production of nitrites by nitrate-reducing organisms in the bladder (21).

In this study dipsticks did not show better performance within a particular nutritional category and performed poorly even in well-nourished children.

We were not able to assess a possible impact of HIV infection as the HIV status of each patient was not recorded in the Uricult® database. Some other situations that can affect the performance of urine dipsticks were not assessed in our study; for example sensitivities of

dipsticks may be falsely high as many dipsticks negative samples may not have been cultured. Conversely, prior exposure to antibiotics may result in falsely low dipstick specificity as patients exposed to antibiotics may be culture-negative despite having UTI and positive urine dipstick.

3. ANTIMICROBIAL SUSCEPTIBILITY

It was not recorded in the database whether community acquired or nosocomial infection was suspected, thus drug susceptibility results reflect a combination of community and nosocomially-acquired organisms.

Increasing antibiotic resistance among urinary tract isolates has been reported from many countries (16). In our study, for most antibiotics we found a higher antimicrobial resistance in 2012 than in previous years. However it is only for sulphamethoxasole/trimethoprim and cephalexin that the resistance has been significantly increasing over the study period.

Resistance to sulphamethoxasole/trimethoprim was higher than in most other reports. One explanation may be the increasing use of sulphamethoxasole/trimethoprim for prophylaxis against opportunistic infections in HIV-infected and HIV-exposed individuals.

Resistance to cephalexin has been steadily increasing over the study period. Cephalexin is often used empirically for first-line treatment of community-acquired UTIs and if our results are representative of district or national resistance patterns this practice needs to be reconsidered. Cephalexin is also commonly used for chemoprophylaxis against subsequent UTIs. While our results raise concerns with regard to the role of cephalexin in the management of paediatric UTIs, we did not collect patient outcomes; therefore we could not establish the proportion of patients with clinical treatment failure. Many antimicrobials concentrate in the urine and patients may clinically respond even when their isolate shows resistance to the antibiotic used.

Resistance to amoxicillin/clavulanic acid, another antibiotic that is empirically used to treat community-acquired UTIs, was found in 21.9% of isolates. However some of these may be from patients with nosocomial UTI and so may not accurately reflect the prevalence of resistance in community-acquired infections.

Isolates from malnourished patients showed higher resistance to antibiotics as compared to well-nourished patients, but the difference was statistically significant only for gentamicin.

VII. CONCLUSION

Urine dipsticks positive for leucocytes AND nitrites reliably detects UTIs in children, however urine culture in these patients is still recommended to identify the causative pathogen and its antimicrobial resistance. Any other pattern on urine dipsticks screening was unable to reliably exclude or identify UTIs in this study. Urine culture is therefore recommended regardless of dipsticks results, when there is a reasonable clinical suspicion for UTI. We did not identify a difference in the performance of urine dipsticks between well-nourished and severely malnourished children.

Patients with severe malnutrition showed significantly higher rates of UTI. We recommend the assessment of the possible impact of HIV infection on the prevalence of paediatric UTIs as well as on the identity of their causative organisms and antibiotic susceptibility of UTI in HIV-infected children. This was not possible in our study since participant HIV status was not documented in the Uricult® database.

A high rate of antimicrobial resistance to both sulphamethoxasole/trimethoprim and cephalexin was identified. In addition the resistance to these two antibiotics has been rising over the study period. Since clinical response to cephalexin in those patients with cephalexin-resistant UTI was not recorded it is difficult to know whether cephalexin still has a role in the treatment of paediatric UTIs. Similar concerns exist for amoxicillin/clavulanic acid. Patients with malnutrition showed higher rates of antimicrobial resistance to all first line drugs including amoxicillin/clavulanic acid and gentamicin.

Point-of-care urine culture is an attractive alternative to off-site culture, particularly in settings with poor or delayed access to laboratory-based urine cultures. Our study demonstrates the feasibility of this in a busy, developing world, paediatric setting. While not assessed in this study it is also likely to be cost saving and efforts to make it more widely available are to be encouraged.

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APPENDIX 1. URICULT DATASHEET

DATE	NAME	HOSPITAL NUMBER	UNIT	AGE	SEX	PRIMARY DIAGNOSIS	NUTRITIONAL STATUS	DIPSTICKS	URICULT RESULT	SENT TO LAB (YES/NO)	LAB RESULT

APPENDIX 2. WELLCOME CLASSIFICATION OF PROTEIN ENERGY MALNUTRITION

Weight (% of standard)	Oedema	
	Yes	No
60-80	Kwashiorkor	Under Weight for Age (UWFA)
<60	Marasmic kwashiorkor	Marasmus

APPENDIX 3. ETHIC CLEARANCE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Ismail Migambi

CLEARANCE CERTIFICATE	**M121139**
PROJECT	Experience with Point-of-Care Urine Culrure in Children at Rahima Moosa Mother & Child Hospital, Johannesburg, South Africa
INVESTIGATORS	Dr Ismail Migambi
DEPARTMENT	Department of Paediatrics Rahima Moosa Mother & Child Hospital
DATE CONSIDERED	30/11/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 18/11/2013 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof Ashraf Coovadia

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

APPENDIX 4: PLAGIARISM DETECTION REPORT

Turnitin Originality Report

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EXPERIENCE WITH POINT-OF-CARE URINE CULTURE IN CHILDREN

25**AT RAHIMA MOOSA MOTHER & CHILD HOSPITAL, JOHANNESBURG, SOUTH AFRICA.**

RESEARCHER: Dr Ismail MIGAMBI Student number 394858

41**Department of Paediatrics**& Child **Health University of the Witwatersrand,**

Johannesburg

CO-SUPERVISORS: Prof A COOVADIA Head of Department

19**Paediatrics & Child Health Rahima Moosa Mother & Child Hospital**

Dr G

19**REUBENSON Department of Paediatrics & Child Health Rahima Moosa Mother & Child Hospital**

Research report submitted

3**in partial fulfilment of the requirements for the degree of Master of Medicine in Paediatrics. Johannesburg,** 2015. i **DECLARATION I,** Ismail MIGAMBI, **declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university. Signed:**

…….. The 17th day of February 2015. ii To my dear wife Rehma and Our beautiful children Issa and Izzat With love and admiration… iii ACKNOWLEDGEMENTS

36**First of all, I would like to express my** sincere thanks **to** Professor A Coovadia, **my** co- **supervisor**

who provided thoughtful guidance and constructive criticism. His commitment and support were always encouraging. Next, my special thanks go to my co-supervisor, Dr G Reubenson for his useful comments, constructive suggestions, and the gifts he offered in terms of scientific thinking and challenges. I would like to thank Professor P Cooper and all in the Department of Paediatrics & Child Health for the training opportunity. I also would like to express my gratitude to Tabby Gitau for her sensitive support. My sincere gratitude goes to the Government of Rwanda for the scholarship that enabled me to train in Paediatrics. iv ABSTRACT

38**BACKGROUND: Urinary tract infections (UTIs) are** an **important cause of morbidity** in children **in**

developing countries and increasing antimicrobial resistance is reported in many countries. This retrospective study describes the performance of urine dipsticks, the aetiology and the antimicrobial susceptibility of paediatric UTIs

25**at Rahima Moosa Mother and Child Hospital, Johannesburg.**

24**METHODS: We conducted a retrospective study of** results from **patients**

investigated for UTI over a four year period between January 2009 and December 2012 in

31**the Department of Paediatrics & Child Health at Rahima Moosa Mother and Child Hospital.**

RESULTS: Escherichia coli was the commonest isolated uropathogen. Dipsticks sensitivity to identify UTI was 40% for leucocyte esterase and 34% for nitrites. The specificity was 94.6% for leucocyte esterase and 96% for nitrites. Malnutrition was associated with greater

16**risk of having** a UTI, **with odds ratio of 2.** 06 **(95% Confidence interval**

1.4-2.9). In addition malnourished children tended to present with more resistant uropathogens. Resistance to sulphamethoxasole/trimethoprim and cephalexin has been progressively increasing between 2009 and 2012. From 64% to 79% for sulphamethoxasole/trimethoprim and from 24% to 63% for cephalexin. CONCLUSION: Positive urine dipsticks results allow immediate patient treatment but negative results need to be interpreted within the clinical context due to a high rate of false negatives. Malnourished children are significantly predisposed to urinary tract infections and tend to have more resistant uropathogens. Resistance to cephalexin is rising and studies to assess patient outcomes are needed to determine whether cephalexin still has a role in the treatment of paediatric UTI.

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26**resistance rates of E coli and K pneumoniae.....**

16 Table 6: Frequency of resistant UTI pathogens in various nutritional categories ..... 17 viii ABBREVIATIONS AIDS CI CFU ESBL NHLS NPV PPV RMMCH UTI UWFA Acquired Immune Deficiency Syndrome Confidence intervals Colony forming units Extended Spectrum Beta-lactamase producing National Health Laboratory Service Negative predictive value Positive predictive value Rahima Moosa Mother and Child Hospital Urinary tract infection Underweight for Age I.

20**INTRODUCTION Urinary tract infections (UTIs)** are an important **cause of** morbidity **in children in**

developing countries (1). Although all individuals are potentially susceptible to UTIs, there are specific higher-risk groups. Risk factors include very young age (neonates/infants), female gender, perineal colonization, urinary tract anomalies and immune deficiency (2). Patients with UTI may be asymptomatic or present

13**with a wide** range **of clinical manifestations from** mild dysuria **to**

life threatening septic shock. As a result, the true incidence of paediatric UTIs is difficult to determine (3, 4).

2**Up to 7% of girls and 2% of boys will have symptomatic, culture-confirmed UTI by** 6 **years of age** (5). **The prevalence of UTI in febrile infants is** higher **with younger age, with a rate of nearly 7% among febrile newborns** (5). **In**

a meta-analysis

1**the pooled prevalence rates of febrile UTIs in females aged 0-3 months, 3- 6 months, 6-12 months, and >12 months was 7.5%, 5.7%, 8.3%, and 2.1% respectively. Among febrile male infants less than 3 months of age, 2.4% (CI: 1.4-3.5) of circumcised males and 20.1% (CI: 16.8-23.4) of uncircumcised males had a UTI. For the 4 studies that reported UTI prevalence by race, UTI rates were higher among white infants 8.0% (CI: 5.1- 11.0) than among black infants 4.7% (CI: 2.1-7.3). Among older children**

aged 2 to

1**19 years with urinary symptoms, the pooled prevalence of UTI (both febrile and afebrile) was 7.8% (CI: 6.6-8.9)**

(6). Up to one-fifth of children with malnutrition have been reported to have a UTI despite the absence of clinical signs or symptoms (7). Page et al studied infections in malnourished children; they found that 16% of children admitted for complicated severe acute malnutrition had a UTI (8). The bacterial causes of UTI also vary based on a number of factors, predominantly the age of the patient and associated co-morbidities. E coli is the most frequently isolated pathogen (2). UTI is associated with important medical and financial implications. Recurrent UTIs may cause

28**renal scarring. Long-term consequences of renal scarring include hypertension,** de- creased **renal function, and end-stage renal**

disease (3). Financial implications include the cost of doctors' visits, hospitalisation expenses, antimicrobial prescriptions, as well as transport costs. Days off school are also an important consequence of UTI among school-aged children as are caregivers' missed work days (3).

30**The standard test for the diagnosis of UTI is a quantitative urine culture**

(9).

27**UTI is defined as significant bacteriuria in a patient with pyuria** (i.e. **evidence of an inflammatory response).**

What constitutes significant bacteriuria depends upon the method of collection and the iso- lated organism.

7**The distal urethra is** usually colonised **by the same bacteria that may cause UTI; thus a low colony count may be present in a specimen obtained by voiding or** transure- thral catheterisation **when bacteria are not present in bladder urine.**

Lactobacillus spp, coagu- lase

39**-negative staphylococci, and Corynebacterium spp are** usually **not considered clinically relevant**

uropathogens (9). Bacteriuria from a mid-stream urine specimen is considered significant if it grows ≥100 000 cfu/mL. Growth from a catheter specimen is considered significant if

2**≥10 000 cfu/mL** and **any number of colonies**

from suprapubic aspiration is significant (5). Some studies in adults suggest that lower levels of bacteriuria (100 to 10 000 cfu/mL) should be considered significant for UTI in symptomatic individuals (10). However, clinicians commonly initiate therapy before final urine culture results become available. To assist in this decision, rapid screening tests have been developed and are widely used (11). Urine dipsticks include a biochemical analysis of urine for detection of nitrites and leucocyte esterase. Reports on

49**the accuracy of urine dipstick** analysis **to**

rule in or out UTI differ widely.

44**In a meta-analysis of the accuracy of**

urine dipsticks for both children and adults, the reported specificity of the urine dipstick test in detecting UTI was 85-98% for nitrites and 17- 93% for leucocyte esterase. Sensitivity for positivity of either is 68-88%. The same study suggests that in children urine dipsticks test alone is

45**useful to rule out infection** when both **results of** leucocyte esterase and **nitrites**

are negative, but recommends that a positive nitrite result need further work up (12). However there are other reports which concluded that it is unsafe to rely on dipsticks alone to exclude a UTI especially when

clinical suspicion is strong (13). In particular, anecdotally, urine dipsticks sensitivity seems to be lower in neonates, malnourished and immune- compromised children. The dipslide Uricult® is a point-of-care urine culture test that yields results within 16-48 hours (14). The Uricult® is helpful in excluding UTI in febrile infants and may reduce unnecessary hospitalization and antibiotic use. The sensitivity of the dipslide in identifying UTI ranges from 70 to 95%. The reported specificity is 80 to 96% (15). While children with suspected UTI are often given empiric antibiotic therapy before the causative organism and its antimicrobial sensitivities are known, antibiotic resistance amongst common uropathogens seems to be increasing. Ampicillin resistance was found in more than 75% of isolates and 2 to 40% of uropathogens are resistant to aminoglycosides (16), (17). With regard to these therapeutic challenges it is advised to regularly monitor the antimicrobial susceptibility profiles amongst commonly isolated uropathogens. II. OBJECTIVES A. To describe the aetiology of Uricult®-detected UTIs at RMMCH, Department of Paediatrics & Child Health from January 2009-December 2012. B. To describe the antimicrobial susceptibility pattern of Uricult®-detected pathogens at RMMCH, Department of Paediatrics & Child Health from January 2009-December 2012. C. To evaluate the performance

40**[sensitivity, specificity, positive and negative predictive values (PPV, NPV)] of**

urine dipsticks in Uricult®-detected UTIs at RMMCH, Department of Paediatrics & Child Health from January 2009-December 2012. III. METHODOLOGY 1. STUDY DESIGN

47**This is a retrospective descriptive study** describing a record **review of**

Uricult® results from the Department of Paediatrics & Child Health (RMMCH) over a 4 year period from January 2009 to December 2012. 2. STUDY POPULATION Routinely collected clinical information and laboratory results were obtained from the Uricult® database. (See appendix 1 for Uricult® datasheet). The Uricult® dipslide point-of- care urine culture system has been in use within RMMCH, Department of Paediatrics & Child Health for more than 10 years. Urine is collected from all patients considered at risk for UTI. Urine specimens are typically screened by a urine dipstick strip, looking for the presence of leucocytes and/or nitrites, and then 'plated' onto 3 separate culture media on one Uricult® dipslide at the point-of-care. 'Dipsticks-negative' samples (nitrite and leucocyte esterase negative) are often plated, particularly when obtained from neonates, malnourished and immune-compromised individuals. Limited clinical information is routinely recorded into a paper-based database (see appendix 1). The specimen is then incubated at 37°C (also at point-of-care) and read daily, excluding most weekends and public holidays, by an experienced clinician. Specimens considered to be negative or contaminated at 48-72 hours are discarded. Specimens suspected to have grown a significant pathogen are then submitted to the National Health Laboratory Services (NHLS) for identification and antibiotic sensitivity determination. Figure 1 shows Uricult® dipslides and incubator. During the period under review the nutritional status of patients was assessed using the Wellcome classification (see appendix 2) Figure 1: Uricult® slide and incubator 3. SAMPLING a. INCLUSION AND EXCLUSION CRITERIA All patients investigated for UTI with the Uricult® dipslide between January 2009 and December 2012 were included. No exclusion criteria were applied. However Uricult® dipslides were unavailable from May to July 2010 and from July to October 2012. 4. DATA COLLECTION Permission was sought from the then

43**Head of the Department of Paediatrics & Child Health at**

RMMCH as well as the Medical Superintendent of the hospital to access the database. The paper-based Uricult® database was searched by the principal investigator to identify all culture positive specimens and

the antimicrobial susceptibilities of the cultured organisms. Additionally from the same database the urine dipsticks results for nitrite and leucocyte esterase were extracted. Variables were then captured into an Excel spread sheet (Microsoft Office). Patient anonymity was maintained by excluding patients' names and hospital numbers. 5. DATA ANALYSIS Data in the MS-Excel spreadsheet were exported to statistical software (STATA version 12) for analysis purposes. Absolute and relative frequency of different microorganisms cultured was determined. The frequency of resistance to specific antibiotics was also determined. The performance of urine dipsticks was determined in comparison with laboratory confirmed cases of UTI. 6. LIMITATIONS The retrospective design of our study is such that we relied upon the available data in the database. Hence for some patients data were incomplete. Furthermore, a patient record review was not undertaken and so no additional clinical information was obtained. The brands of urine dipsticks used over this period are not known and there may have been more than one supplier. IV. ETHICS CLEARANCE The study proposal was submitted to

37**the Human Research Ethics Committee of the University of the Witwatersrand**

for approval before commencing the study. The application was considered on 30 November 2012 by Human Research Ethics Committee (Medical) and clearance certificate M121139 was issued as shown in Appendix 3. As this is a case review, there was no risk to the study participants. V. RESULTS About 6000 patients are seen annually in the admission ward at RMMCH Paediatric department and approximately 10% of these patients are investigated for UTI with a urine specimen obtained and 'plated' onto a Uricult® dipslide. Most are done during the months of March to July with 12% of patients getting a urine specimen 'plated'. 1. DESCRIPTION OF THE POPULATION Data from a total of 2311 urine cultures were reviewed. Samples from the same patient on different days were included as separate samples. There were 1030 (44.5%) girls and 1195 (51.7%) boys. For 86 (3.8%) entries the patient sex was not recorded. Patients' age ranged from 0 to 13 years. The age distribution is shown in figure 2. Figure 2: Participant age distribution more than 60 unkown months 17 172 7% up to 1 months 509 22% 12 to 60 months 584 25% 1 to 3 months 347 15% 4 to 11 months 682 30% Of 2311 children studied, there were 136 (5.9%) with kwashiorkor, 98 (4.2%) with marasmus, 39 (1.7%) with marasmic kwashiorkor, 211 (9.1%) underweight for age (UWFA) and 1186 (51.3%) well-nourished. There were 509 (22%) neonates and 132 (5.7%) had no nutritional status recorded. Neonates were considered a nutritional group on its own besides the Wellcome classification due to their unique age-weight relationship. The nutritional status of participants is shown in figure 3. Figure 3: Participant nutritional status Uknown 132 6% Neonates 509 22% Marasmic Kwashiorkor 39 2% Marasmus 98 4% Kwashiorkor 136 6% Normal 1186 51% UWFA 211 9% Of 2311 specimen that were plated onto the Uricult® culture media, 1736 (75.1%) were negative whereas 228 (9.9%) were discarded after 48-72 hours because they were considered contaminated. A total of 324 (14.0%) samples cultured a laboratory confirmed uropathogen; 43.2% (n=140) from female patients and 56.7% (n=184) from males. Six (1.8%) patients who had a confirmed UTI did not have their sex documented. There were 23 specimens submitted to NHLS that were reported as contaminated. Of all 251 contaminated specimens, 36% were collected by urinary catheterization, 24% by mid-stream urine, 9.5% by suprapubic aspiration and 11.5% by non-documented methods. Urine bag specimens contributed to 24% of contaminated specimens; however considered alone, 62% of all bag specimens were contaminated.

20**The highest prevalence of UTI was found in infants**

aged 4-11 months (16.6%), followed by neonates (14.9%). The lowest prevalence was in children older than 60 months (11%). (Figure 4). Forty seven percent (n=152) of patients with UTI had normal nutritional status, 15.4% (n=50) were underweight for age, 10.8% (n=35) had kwashiorkor, 3% (n=10) had marasmus, and 4.3% (n=14) had marasmic kwashiorkor. Neonates made up 17.2% (n=56) of patients with culture confirmed UTI and 7 patients with UTI had no nutritional status documented (Figure 5). For kwashiorkor and marasmic

kwashiorkor patients the odds ratio of having a UTI compared to normal nutritional status

24**was 2.** 06 **[95% Confidence interval 1.** 4- **2.** 9]; **for** UWFA **patients**

the

16**odds ratio** was **1.5 [95% Confidence interval, CI 1.2-2.**

1]. Figure 4: Frequency of UTI within age groups 76 (14.9%) 43 (12.4%) 509 347 113 (16.6%) 69 (11.8%) UTI Total patients 682 584 19 (11%) 172 4 17 Less than 1 1 to 3 4 to 11 Age in months 12 to 60 More than Unkown age 60 Figure 5: UTI and nutritional status 1034 161 152 50 (12.0%) (23.6%) 453 101 88 25 56 35 10 14 (11.0%) (25.7%) (10.2%) (35.9%) 125 (5.3%) 7 Negative Positive Normal UWFA Neonate Kwashiorkor Marasmus Marasmic Kwash documented Not 2. FREQUENCY OF UROPATHOGENS A total of 14 different uropathogens were isolated. Escherichia coli was the most commonly isolated uropathogen detected in 67.5% of infected specimens, followed by Klebsiella pneumoniae (14.8%). Coagulase-negative Staphylococcus grew in 2.4% and Candida albicans in 1.5% of infected specimens. There were 23

42**Extended Spectrum Beta-lactamase producing** (ESBL) pathogens; 5 **E coli and** 18 Klebsiella **pneumoniae.**

One specimen grew Methicillin-resistant Staphylococcus aureus (MRSA). Seven specimens grew more than one uropathogen, e.g. E coli with Klebsiella pneumoniae or Klebsiella with Enterobacter sp. The frequency of the uropathogens isolated is shown in Table 1. Table 1: Frequency of uropathogens Isolate Frequency E

35**coli Klebsiella pneumoniae Klebsiella oxytoca Proteus mirabilis Enterobacter cloacae Citrobacter** species **Pseudomonas aeruginosa**

Morganella morgani Enterococcus faecalis Coagulase-negative Staphylococcus MRSA Acinetobacter baumanii Serratia Mixed growth Candida albicans 219 (67.6%) 48 (14.8%) 3 (0.9%) 7 (2.1%) 7 (2.1%) 4 (1.2%) 7 (2.1%) 1 (0.3%) 5 (1.5%) 8 (2.4%) 1 (0.3%) 1 (0.3%) 1 (0.3%) 7 (2.1%) 5 (1.5%) Total 324 3. URINE DIPSTICKS a. Nitrites Nitrites were detected in 102 of 324 samples with a uropathogen identified; sensitivity 31.4% (95% CI 26.6-37%). Nitrites were positive in 68 (3.5%) cases out of 1964 culture-negative samples; specificity 96.5% (95% CI 95.6-97.3%), PPV 60% (95% CI 52.4-67.3%) and NPV 90.3% (95% CI 88-90.8 %). Eleven specimens tested positive for nitrites but were found con- taminated when cultured. b. Leucocyte esterase The sensitivity of dipsticks detected leucocyte esterase was 36.1% (95% CI 31-41.6%). (117/324 culture-positive samples were positive for leucocytes esterase). Of 1964 culture- negative samples, 103 (5.3%) were positive for leucocyte esterase with a specificity of 94.7% (95% CI 93.7-95.7%), PPV 53% (95% CI 46.3-60%) and NPV 90% (95% CI 88.6-91.2%). Seven specimens tested positive for leucocyte esterase but were contaminated when cultured. When leucocyte esterase and nitrite results were combined, specificity increased to 97.7% but sensitivity remained low; 31.4% (PPV 62.0%, NPV 92.3%). Of 509 urine specimens collected from neonates, 76 (14.9%) were culture-positive. Among these, leucocyte esterase was positive in 18 cases with 23 false positives. Specificity 94.6% (95% CI 92.1-96.6%), sensitivity 23.6% (95% CI 14.6-34.8%), PPV 43.0% (95% CI 28.4- 60.2%) and NPV 87.6% (95% CI 84.2-90.45%). Nitrites were positive in 19 cases of confirmed UTI with 20 additional false positives. Specificity 95.3% (95% CI 93-97%), sensitivity 25% (95% CI 15.7-36.2%), PPV 48.7% (95% CI 32.4-65.2%) and NPV 89.0% (95% CI 84.5-94.6%). Table 2 illustrates the performance of urine dipsticks within nutritional categories. Table 2: Performance of urine dipsticks within nutritional categories Sensitivity (%) Specificity (%) PPV (%) NPV (%)

Overall Study Population Well- nourished Kwashiorkor Marasmus Marasmic Kwashiorkor Leucocytes Nitrite Leucocytes and Nitrite Leucocytes Nitrite Leucocytes and Nitrite Leucocytes Nitrite Leucocytes and Nitrite Leucocytes Nitrite Leucocytes and Nitrite Leucocytes Nitrite Leucocytes and Nitrite 36.1 (30.8-41.1) 31.4 (26.4-36.8) 31.4 (25.3-38.0) 94.6 (93.6-95.7) 96.1 (95.6-97.3) 97.7 (97.0-98.3) 53.0 (46.3-60.0) 60.1 (52.2-67.0) 62.0 (52.0-71.0) 89.9 (88.6-91.0) 89.5 (88.0-90.8) 92.3 (91.0-93.4) 41.0 (32.7-50.0) 94.6 (92.8-96.1) 52.1 (50.0-59.2) 92.1 (90.3-93.6) 34.9 (26.0-43.0) 94.0 (92.2-95.2) 44.7 (36.0-53.5) 92.1 (90.3-93.6) 36.4 (29.3-44.1) 97.1 (95.8-99.3) 69.8 (58.1-77.4) 93.1 (91.4-95.0) 42.8 (26.0-56.1) 94.5 (87.0-97.6) 75.0 (50.7-91.1) 81.2 (72.8-88.1) 48.5 (31.9-63.5) 92.3 (86.1-96.7) 68.1 (45.7-87.9) 81.2 (72.8-88.1) 30.4 (23.3-39.7) 95.4 (95.0-96.1) 76.0 (66.0-83.6) 85.1 (82.4-89.0) 35.7 (12.7-64.9) 91.4 (78.0-95.8) 50 .0 (18.7-81.3) 84.0 (71.6-92.4) 42.8 (17.6-71.1) 85.3 (75.7-91.4) 33.3 (13.0-56.5) 89.7 (80.8-95.5) 26.4 (19.3-36.7) 92.4 (91.0-95.1) 59.0 (51.3-72.0) 90.1 (88.4-92.2) 40.0 (12.1-73.7) 92.8 (74.0-99.0) 66.6 (23.0-95.0) 79.3 (60.3-92.0) 50.0 (18.8-81.3) 92.8 (74.0-99.0) 71.4 (29.0-96.0) 82.1 (63.1-94.0) 31.4 (26.3-42.7) 93.4 (92.1-94.7) 71.2 (59.8-74.0) 86.1 (83.4-91.0) 4. ANTIMICROBIAL SENSITIVITY In this study the highest rates of antimicrobial resistance were observed for ampicillin and sulphamethoxazole/trimethoprim (93.8% and 72.8% respectively). Only 2 isolates were resistant to amikacin and three isolates were resistant to colistin. None of the isolates was found to be resistant to carbapenems.

21**Table 3 shows the** frequency **of resistance to** different **antibiotics.**

Resistance to most antibiotics was higher in 2012 than in the previous 3 years (Table 4). However only resistance to sulphamethoxazole/trimethoprim and cephalexin showed a significant increase over the study period (Figures 6, 7). Table 3: Antibiotic resistance of urinary isolates Antimicrobial Frequency of resistance Sulphamethoxasole/trimethoprim Ampicillin Amoxicillin/clavulanate Piperacillin/tazobactam Cephalexin Cefuroxime Ceftazidime/ceftriaxone/cefotaxime Cefepime Gentamicin Tobramycin Amikacin Nalidixic acid Nitrofurantoin Ciprofloxacin Colistin Meropenem/Ertapenem 236 (72.8%) 304 (93.8%) 71 (21.9%) 48 (15.0%) 131 (40.4%) 30 (9.4%) 28 (8.7%) 22 (7.0%) 49 (15.1%) 43 (13.5%) 2 (0.6%) 30 (9.4%) 28 (8.7%) 12 (4.3%) 3 (0.9%) 0 Figure 6: Rate of antimicrobial resistance (%) 100 94.7 90 80 70 60 50 40 30 20 10 0 72.8 40.4 21.9 15.1 15 13.5 9.5 9.4 8.7 8.7 7 4.3 0.9 0.6 0 X T A m picillin S phalexin oxiclav G n Piper a cillin/icinzobactaTmobramycainlidixicacideefuforotNaxxiimt/rcoeffutrraianxt/ocienftazidim efepimrofloxacin Colistin ikacineropenem

48**e e e** C **e A** m **e** t **a** m t **a**

C C m N C i p A M C Table 4: Antimicrobial resistance by year of study Antimicrobial Sulphamethoxasole/trimethoprim

13**Ampicillin Amoxicillin/clavulanic acid Piperacillin/tazobactam** Cephalexin Cefuroxime **Ceftazidime/** ceftriaxone/cefotaxime **Cefepime**

Gentamicin Tobramycin Nalidixic acid Nitrofurantoin Ciprofloxacin 2009 2010 64.0% 70.0% 88.7% 97.7% 26.0% 19.1% 15.8% 4.5% 24.0% 25.0% 9.1% 9.1% 9.1% 6.8% 8.1% 4.5% 20.0% 12.0% 18.1% 13.6% 12.2% 4.5% 8.1% 9.0% 5.1% 3.0% 2011 77.1% 91.2% 17.0% 4.5% 54.0% 7.8% 5.8% 4.4% 15.1% 7.3% 4.8% 5.8% 4.9% 2012 79.0% 98.1% 25.1% 18.7% 62.9% 12.5% 12.5% 12.5% 17.1% 12.5% 14.0% 12.5% 4.0% Figure 7: Rate of resistance to Sulphamethoxazole/trimethoprim and cephalexin 80 70 60 50 40 30 20 10 0 SXT Cephalexin E coli and K pneumoniae made up 82.4 % of all isolates. Compared to E coli, K pneumoniae showed greater resistance to all antimicrobials with the exception of sulphamethoxasole/trimethoprim. Table 5: Antibiotic

26**resistance rates of E coli and K pneumoniae**

Antimicrobial E coli Sulphamethoxasole/trimethoprim 83.7% Ampicillin 76.2% Amoxicillin/clavulanate 17.3% Piperacillin/tazobactam 14.3% Cephalexin 32.0% Cefuroxime 5.9% Ceftazidime/ceftriaxone/cefotaxime 5.4% Cefepime 4.0% Gentamicin 13.7% Tobramycin 12.8% Nalidixic acid 8.9% Nitrofurantoin 5.4% Ciprofloxacin 1.2% K pneumoniae 68.7% 95.0% 39.3% 21.0% 45.7% 25.5% 23.2% 21.0% 21.0% 18.6% 16.2% 20.9% 6.6% Patients with malnutrition tended to have more resistant uropathogens detected. However this was statistically significant only for gentamicin. Table 6: Frequency of resistant UTI pathogens in various nutritional categories Antimicrobial Normal UWFA Marasmus Kwashiorkor Marasmic kwashiorkor Sulphamethoxasole/trimethoprim Ampicillin Amoxicillin/clavulanate Piperacillin/tazobactam Cephalexin Cefuroxime Ceftazidime/ceftriaxone/cefotaxime Cefepime Gentamicin Tobramycin Nalidixic acid Nitrofurantoin Ciprofloxacin 74.0% 80.1% 92.0% 96.1% 22.5% 34.0% 14.4% 11.1% 39.4% 34.0% 6.7% 11.0% 6.7% 11.0% 5.3% 6.5% 14.7% 20.0% 12.0% 13.0% 8.2% 11.0% 6.0% 13.0% 3.7% 8.7% 97.3% 92.3% 97.3% 97.3% 46.1% 25.7% 30.7% 24.4% 64.2% 60.0% 23.0% 12.2% 15.4% 9.7% 15.4% 7.3% 69.2% 20.0% 38.5% 17.0% 15.4% 12.2% 23.1% 12.2% 15.4% 2.4% 97.0% 95.0% 26.0% 25.5% 65.0% 11.0% 10.0% 10.0% 20.0% 20.0% 10.0% 9.1% 3.2% P value, Normal nutrition versus malnutrition1 0.07 0.20 0.09 0.18 0.10 0.09 0.31 0.27 0.01 0.07 0.11 0.11 0.03 1 Malnutrition group comprises patients with kwashiorkor, marasmic kwashiorkor and marasmus. VI. DISCUSSION Point-of-care testing for UTIs has a number of benefits including lower cost, more rapid availability of data and consequent more rapid clinical decision making. Disadvantages may include relying on non-microbiologists for interpretation, lack of microscopy results, and intermittent non-availability of stock. 1. UTI PREVALENCE AND UROPATHOGENS Paediatric UTI is a common reason for seeking medical attention (6). Effective management relies on the identification of the causative organism and the appropriate choice of antimicrobials. The prevalence of UTIs in our study is higher than that in most reported studies. However the prevalence of risk factors for UTI among our study population was substantial. Twenty two percent of patients were neonates and a further 11.7% had severe malnutrition (kwashiorkor, marasmus, marasmus kwashiorkor). While HIV status may impact on the epidemiology of paediatric UTIs, this was not recorded in the database used for this study. Nader Shaikh et al in a meta-analysis reported a pooled prevalence of UTIs of 7% among febrile infants less than 24 months. For those aged between 2 and 19 years the pooled prevalence was 7.8% (6). There are other studies that have reported significantly higher prevalence of UTIs. Up to 28.6% of 1878 urine samples from children with suspicion of UTI were positive for pathogenic organisms in a hospital based study in Nepal (18). While UTI is said to be a common complication of severe malnutrition, reported prevalence varies between 3 and 35% in malnourished paediatric in-patients (19). Previous studies have also shown that UTI is an important occult infection in malnourished children. The majority of malnourished patients diagnosed with UTI are admitted for reasons other than UTI. It has been recommended that all severely malnourished children have a urine specimen cultured (20). Our isolation rates among patients with kwashiorkor and marasmic kwashiorkor were significantly higher than among those with normal nutritional status. UWFA patients were also found to be at a greater risk of having UTIs. As expected, Gram-negative bacteria were the most commonly isolated uropathogens with E coli isolated in 67.5% of all positive cultures. The second most common pathogen was Klebsiella pneumoniae (14.8%). Gram-positive organisms have received more attention recently as a cause of bacteriuria and UTIs. Some studies have reported them to cause 0.7 to 12.2% of UTIs (18). Gram-positive organisms were identified in 3% of positive specimens in this study. 2. URINE DIPSTICKS Misdiagnosing UTI can lead to a failure of appropriate antibiotic prescription or prescription of unnecessary treatment and inappropriate investigations. Dipsticks are cheap, rapid and easy to perform (12). In this study the sensitivity of leucocyte esterase to identify UTI was 31.4% with a specificity of 94.8%. For nitrites the sensitivity was only 36.1% with a specificity of 96.6%. These results show that a positive urine dipstick reasonably reliably detects UTI but a negative result needs to be more carefully considered; it is important to interpret a negative result within the clinical context of the patient. This result is in concordance with the conclusion drawn by Coulthard MG et al but it is in contrast with a

33**meta-analysis by Deville** LJM **et al** which suggested **that a dipstick negative for both** leucocyte esterase **and**

nitrites reliably rules out a UTI in children (12), (13). The high proportion of young patients in our study may play a role in the poor performance of urine dipsticks. The sensitivity of dipsticks in neonates was particularly low; 23.6% for leucocyte esterase and 25% for nitrites. It is believed that

4**frequent voiding in non toilet- trained infants leads to decreased time for production of nitrites by** nitrate **-reducing organisms**

in the bladder (21). In this study dipsticks did not show better performance within a particular nutritional category and performed poorly even in well-nourished children. We were not able to assess a possible impact of HIV infection as the HIV status of each patient was not recorded in the Uricult® database. Some other situations that can affect the performance of urine dipsticks were not assessed in our study; for example sensitivities of dipsticks may be falsely high as many dipsticks negative samples may not have been cultured. Conversely, prior exposure to antibiotics may result in falsely low dipstick specificity as patients exposed to antibiotics may be culture-negative despite having UTI and positive urine dipstick. 3. ANTIMICROBIAL SUSCEPTIBILITY It was not recorded in the database whether community acquired or nosocomial infection was suspected, thus drug susceptibility results reflect a combination of community and nosocomially-acquired organisms. Increasing antibiotic resistance among urinary tract isolates has been reported from many countries (16). In our study, for most antibiotics we found a higher antimicrobial resistance in 2012 than in previous years. However it is only for sulphamethoxasole/trimethoprim and cephalexin that the resistance has been significantly increasing

46**over the study period. Resistance to** sulphamethoxasole **/trimethoprim was**

higher than in most other reports. One explanation may be the increasing use of sulphamethoxasole/trimethoprim for prophylaxis against opportunistic infections in HIV-infected and HIV-exposed individuals. Resistance to cephalexin has been steadily increasing over the study period. Cephalexin is often used empirically for first-line treatment of community-acquired UTIs and if our results are representative of district or national resistance patterns this practice needs to be reconsidered. Cephalexin is also commonly used for chemoprophylaxis against subsequent UTIs. While our results raise concerns with regard to the role of cephalexin in the management of paediatric UTIs, we did not collect patient outcomes; therefore we could not establish the proportion of patients with clinical treatment failure. Many antimicrobials concentrate in the urine and patients may clinically respond even when their isolate shows resistance to the antibiotic used. Resistance to amoxicillin/clavulanic acid, another antibiotic that is empirically used to treat community-acquired UTIs, was found in 21.9% of isolates. However some of these may be from patients with nosocomial UTI and so may not accurately reflect the prevalence of resistance in community-acquired infections. Isolates from malnourished patients showed higher resistance to antibiotics as compared to well-nourished patients,

13**but the difference was statistically significant only for**

gentamicin. VII. CONCLUSION Urine dipsticks positive for leucocytes AND nitrites reliably detects UTIs in children, however urine culture in these patients is still recommended to identify the causative pathogen and its antimicrobial resistance. Any other pattern on urine dipsticks screening was unable to reliably exclude or identify UTIs in this study. Urine culture is therefore recommended regardless of dipsticks results, when

there is a reasonable clinical suspicion for UTI. We did not identify a difference in the performance of urine dipsticks between well- nourished and severely malnourished children. Patients with severe malnutrition showed significantly higher rates of UTI. We recommend the assessment of the possible impact of HIV infection on the prevalence of paediatric UTIs as well as on the identity of their causative organisms and antibiotic susceptibility of UTI in HIV-infected children. This was not possible in our study since participant HIV status was not documented in the Uricult® database. A high rate of antimicrobial resistance to both sulphamethoxasole/trimethoprim and cephalexin was identified. In addition the resistance to these two antibiotics has been rising over the study period. Since clinical response to cephalexin in those patients with cephalexin- resistant UTI was not recorded it is difficult to know whether cephalexin still has a role in the treatment of paediatric UTIs. Similar concerns exist for amoxicillin/clavulanic acid. Patients with malnutrition showed higher rates of antimicrobial resistance to all first line drugs including amoxicillin/clavulanic acid and gentamicin. Point-of-care urine culture is an attractive alternative to off-site culture, particularly in settings with poor or delayed access to laboratory-based urine cultures. Our study demonstrates the feasibility of this in a busy, developing world, paediatric setting. While not assessed in this study it is also likely to be cost saving and efforts to make it more widely available are to be encouraged. VIII.

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APPENDIX 1. URICULT DATASHEET DATE NAME HOSPITAL NUMBER UNIT AGE SEX PRIMARY DIAGNOSIS NUTRITIONAL STATUS DIPSTICKS URICULT RESULT SENT TO LAB (YES/NO) LAB RESULT APPENDIX 2. WELLCOME CLASSIFICATION OF PROTEIN ENERGY MALNUTRITION (% of standard) Weight Oedema Yes No 60-80 <60 Kwashiorkor Marasmic kwashiorkor Under Weight for Age (UWFA) Marasmus APPENDIX 3. ETHIC CLEARANCE APPENDIX 4: PLAGIARISM DETECTION REPORT 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27