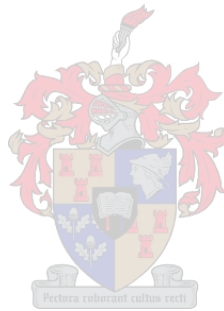


Paediatric Bacterial Urinary Tract Infections in the South African Context

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Thesis presented in fulfilment of the requirements for the degree of Master of Medicine (Paediatrics) in the Faculty of Medicine and Health Sciences at Stellenbosch University

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Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the authorship thereof (unless to the extent explicitly otherwise stated) and that I have not previously, in its entirety or in part, submitted it for obtaining any qualification.

Signature: Dr S. Irušen

Date

Abstract (Chapter 2)

Title: The Microbial Burden and Antibiotic Profile of Pediatric Bacterial Urinary Tract Infections at a Tertiary Hospital in the Western Cape, South Africa

Background: Urinary tract infection (UTI) is a commonly encountered problem in infants presenting to emergency units with fever. Current international data reports that uropathogens and their associated antibiotic susceptibility is evolving. This study describes the organism profile and inherent antibiotic resistance pattern at a tertiary hospital in the Western Cape, South Africa

Methods: A retrospective study on all urine samples sent to the National Health Laboratory Service (NHLS) from 1 January 2012 – 31 December 2013 at Tygerberg Hospital was performed. UTI was defined as a single organism growth $>10^5$ cfu/ml and leukocytes >1000 cells/ml. The organisms and antibiotic sensitivities were described and further correlated with community, hospital associated or hospital acquired infections, HIV status and blood culture results were also determined.

Results: 282 samples met study definitions for inclusion in the study. *E. coli* was cultured most frequently (143/50.7%) followed by *K. pneumoniae* (64/22.7%) and *P. mirabilis* (13/4.6%). Extended spectrum beta lactamase (ESBL) producing organisms accounted for 75/64.1%; *K. pneumoniae* accounted 54/72% of those infections. Most ESBL infections were hospital acquired (32/42.7%). For *E. coli*, 90.8% were resistant to amoxicillin/ampicillin and 71.8% to TMP/SMX. For *K. pneumoniae*, 88.7% were resistant to co-amoxiclavulanic acid and 98.2% to cefotaxime/ceftriaxone. HIV status was not predictive of more resistant organisms; the numbers in the HIV group were too small to be statistically significant.

Conclusion: The organism population and antibiotic sensitivity profile is evolving in line with international data trends. Of ESBL-producing organisms, 1/6.7% of *E. coli* were sensitive to piperacillin-tazobactam and 5/33.3% to amikacin. *K. pneumoniae* displayed 10/18.5% and 37/68.5% sensitivity to piperacillin-tazobactam and amikacin respectively. These antibiograms support current hospital policy to treat hospital associated and acquired infections with piperacillin-tazobactam and amikacin empirically until urine culture and sensitivity are available thereby limiting carbapenem drug pressure. Further data is required looking at the influence of HIV of UTI and risk factors for the development of resistance

Opsomming (hoofstuk 2)

Titel: Die Mikrobiese Lading en Antibiotiese Profiel van Pediatrisse Bakteriese Urienweginfeksies by 'n Tersiêre Hospitaal in die Wes-Kaap, Suid-Afrika

Agtergrond: Urienweginfeksie (UWI) is 'n algemene probleem by babas wat met koors in die noodeenheid beland. Volgens huidige internasionale data evolueer uropatogene en die gepaardgaande antibiotiese vatbaarheid daarvan voortdurend. Hierdie studie beskryf die organisme-profiel en inherente antibiotiese weerstandspatroon by pediatriese UWI-pasiënte in 'n tersiêre hospitaal in die Wes-Kaap, Suid-Afrika.

Metodes: 'n Retrospektiewe studie is uitgevoer met alle urinemonsters wat van 1 Januarie 2012 tot 31 Desember 2013 na die Nasionale Gesondheidslaboratoriumdiens (NHLS) by Tygerberghospitaal gestuur is. UWI is omskryf as 'n enkele organisme met 'n groeitempo van $>10^5$ cfu/ml en 'n leukosietesifer van $>1\ 000$ selle/ml. Die organismes en antibiotiese sensitiwiteit is beskryf en verder gekorreleer met gemeenskaps-, hospitaalverwante en hospitaalverworwe infeksies, MIV-status en bloedkwekingsresultate.

Resultate: Altesaam 282 monsters het aan die vereistes vir insluiting by die studie voldoen. *E. coli* is die gereeldste gekweek (143/50,7%), gevolg deur *K. pneumoniae* (64/22,7%) en *P. mirabilis* (13/4,6%). Organismes wat uitgebreidespektrum-beta-laktamase (ESBL) produseer, was verantwoordelik vir 75/64,1% van die infeksies, en *K. pneumoniae* vir 54/72%. Die meeste ESBL-infeksies was hospitaalverworwe (32/42,7%). *E. coli* was 90,8% weerstandig teen amoksisillien/ampisillien, en 71,8% teen TMP/SMX. *K. pneumoniae* was onderskeidelik 88,7% en 98,2% weerstandig teen ko-amoksiklavulaansuur en kefotaksiem/keftriaksoon. MIV-status was nie 'n aanwyser van weerstandiger organismes nie; die getalle in die MIV-groep was te laag om statisties beduidend te wees.

Gevolgtrekking: Die organismepopulasie en antibiotiese sensitiwiteitsprofiel evolueer in pas met tendense in internasionale data. Onderskeidelik 1/6,7% en 5/33,3% van die UWI-gevalle in hierdie studie wat met ESBL-*E. coli* verband gehou het, was sensitief vir piperasillien-tazobaktam en amikasien. *K. pneumoniae* het in onderskeidelik 10/18,5% en 37/68,5% van gevalle sensitiwiteit vir piperasillien-tazobaktam en amikasien getoon. Hierdie antibiogramme ondersteun huidige hospitaalbeleid om hospitaalverwante en -verworwe infeksies empiries met piperasillien-tazobaktam en amikasien te behandel totdat urinekweking en -sensitiwiteit beskikbaar is, om sodoende karbapenem-middeldruk te beperk. Verdere data oor die invloed

van MIV op UWI, sowel as oor die risikofaktore vir die ontwikkeling van weerstandigheid, word vereis.

Abstract (Chapter 3)

Title: Factors Impacting Positive Urinary Tract Infections in patients (0-5 years) Attending a Paediatric Emergency ward in a Tertiary Care Hospital in the Western Cape, South Africa

Background: Urinary tract infection (UTI) is a commonly encountered problem in infants with fever presenting to emergency units. This study evaluated factors (clinical signs, antibiotic exposure and co-morbid conditions) that influence positive urine cultures in patients presenting to the emergency center at a tertiary hospital in the Western Cape, South Africa. Furthermore, the correlation with urine dipsticks, serum inflammatory marker, and renal imaging studies and UTI was described.

Methods: A convenience sample of children (birth-5 years) presenting to the emergency unit, in whom urine samples were submitted, were prospectively enrolled into the study provided informed individual consent was obtained from the parent/guardian. Patients and caregivers were interviewed using preformed data collections sheets. Patient were further subdivided into those < 3 and > 3 months old; casualty protocols dictate that patients < 3 months old have urine dipsticks +/- formal urine analysis when screening for sites of potential bacterial sepsis.

Results: One hundred and twenty-three samples were included in the study. Twenty-nine (23.6%) samples had culture confirmed UTI and 34 (27.6%) had mixed organism growth on urine culture. *E. coli* was isolated in 12 (41.4%) followed by *Klebsiella pneumoniae* in 9 (31%) cases. *E. coli* and *K. pneumoniae* showed sensitivity rates to ciprofloxacin of 91.7% and 100% respectively. Patients with severe acute malnutrition and acute respiratory tract infections were less likely to have UTI. HIV exposure (this group is over represented in our setting) ($p=0.044$) and urine leukocyte esterase and nitrates ($p=0.018$ and $p=0.043$ respectively) were significantly related with culture confirmed UTI. Renal ultrasound imaging was likely to be normal in patients with confirmed UIT ($p=0.0$).

Conclusion: Twenty-nine (23.6%) urine samples were positive for a urine pathogen. This is markedly higher than international trends. HIV exposure and urine dipsticks were statistically significant for correlating with culture confirmed UTI. These factors must be considered to guide empiric antibiotic administration. Of our cohort, 27.6% of samples were mixed growth, indicating how difficult it is to obtain sterile specimens from a pediatric patients. These specimens were not repeated and therefore clinically significant true UTI was missed. Furthermore, these samples should be repeated if clinically indicated as missed UTI can lead to significant patient morbidity.

Opsomming (hoofstuk 3)

Titel: Faktore met 'n Invloed op Positiewe Kwekings vir Urienweginfeksie by Pasiënte (0 tot 5 jaar) in 'n Pediatriese Noodeenheid in 'n Tersiêresorghospitaal in die Wes-Kaap, Suid-Afrika

Agtergrond: Urienweginfeksie (UWI) is 'n algemene probleem by babas wat met koors in die noodeenheid beland. Hierdie studie het faktore (kliniese tekens, antibiotiese blootstelling en ko-morbiede omstandighede) beoordeel wat 'n invloed het op positiewe urinekwekings by pediatriese pasiënte in die noodeenheid van 'n tersiêre hospitaal in die Wes-Kaap, Suid-Afrika. Daarbenewens is die korrelasie tussen UWI en urinedoopstokkies, seruminflammasiemerkers en nierbeeldingstudies beskryf.

Metodes: 'n Geriefsteekproef van kinders (pasgebore tot 5 jaar oud) wat in die noodeenheid beland het en van wie urinemonsters ingesamel is, is voorlopig in die studie opgeneem, met dien verstande dat hulle ouer/voog se ingeligte individuele toestemming verkry word. Onderhoude is met behulp van voorafopgestelde data-insamelingsvelle met pasiënte en hulle versorgers gevoer. Pasiënte is ook ingedeel in diegene jonger as drie maande en diegene ouer as drie maande; volgens ongevalleprotokol moet pasiënte jonger as drie maande 'n urinedoopstokkietoets en/of formele urine-ontleding ondergaan om moontlike bakteriese sepsis op te spoor.

Resultate: Altesaam 123 monsters het aan die vereistes vir insluiting by die studie voldoen. Van daardie pasiënte het 29 (23,6%) kwekingsbevestigde UWI gehad, en 34 (27,6%) gemengde organismegroei in die urinekweking. *E. coli* is in 12 (41,4%) gevalle geïsoleer, gevolg deur *Klebsiella pneumoniae* in nege (31%) gevalle. *E. coli* en *K. pneumoniae* was onderskeidelik 91,7% en 100% sensitief vir siprofloksasien. Die waarskynlikheid van UWI by pasiënte met erge akute wanvoeding en akute lugweginfeksies was kleiner. MIV-blootstelling (hierdie groep is oorverteenvoerdig in ons omgewing) ($p = 0,044$) en leukosiet-esterase en nitrate in die urine ($p = 0,018$ en $p = 0,043$ onderskeidelik) was statisties beduidend vir korrelasie met kwekingsbevestigde UWI. Die waarskynlikheid van normale nierultraklankbeelding by pasiënte met bevestigde UWI was hoog ($p = 0,0$).

Gevolgtrekking: Altesaam 29 (23,6%) van die urinemonsters het positief getoets vir 'n urinepatogeen. Dít is merkbaar hoër as internasionale tendense. MIV-blootstelling en urinedoopstokkies was statisties beduidend vir korrelasie met kwekingsbevestigde UWI. Hierdie faktore moet as rigsgoere vir die empiriese toediening van antibiotika beskou word. 'n

Totaal van 27,6% van die monsters uit ons kohort het gemengde groei getoon. Hieruit blyk duidelik hoe moeilik dit is om steriele monsters by pediatriese pasiënte te verkry. Hierdie uriene monsters is nie herhaal nie en daareen was kliniese beduidende UWI gemis. Monsters moet herhaal word indien daar kliniese indikasies bestaan, aangesien UWI wat misgekyk word beduidende pasiëntemorbiditeit tot gevolg kan hê.

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Dedication

To my wife and parents, your fierce belief and support of me in pursuit of my dreams is a kindness and strength that I will never adequately be able to describe.

“Have I not commanded you? Be strong and courageous. Do not be afraid; do not be discouraged, for the LORD your GOD will be with you wherever you go.”

Joshua 1: 9

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Abbreviations

UTI: Urinary tract infection

NHLS: National Health Laboratory Service

HIV: Human immunodeficiency virus

CFU: Colony forming unit

MSU: Midstream urine

CRP: C-reactive protein

TMP/SMX: Trimethoprim/Sulphamethoxazole

VUR: Vesicoureteric reflux

MDR: Multi-drug resistance

XDR: Extreme drug resistance

ESBL: Extended spectrum B-lactam

IBL: Inducible B-lactam

KUB US: Kidney Ureter Bladder Ultrasound

IMCI: Integrated management of childhood illness

Chapter 1: An Overview of Paediatric Urinary Tract Infection

Epidemiology:

Urinary tract infections (UTI) are an important consideration in all children presenting to an emergency unit with unexplained pyrexia(1). UTI is defined as the presence of a uropathogen in the urinary tract resulting in symptoms, signs with or without deranged inflammatory markers (2). It differs from asymptomatic bacteriuria, which indicates colonization of the urinary tract and requires no treatment. UTIs are classified into infections of the lower (urethra and bladder) and upper (ureter, renal pelvis and renal parenchyma) urinary tract. This distinction has implications on initial management, investigation and follow-up (1,2). Infections of the upper tract are termed pyelonephritis.

Lower tract infections are generally treated as simple infections. However, upper tract infections, especially if recurrent, have significant morbidity and mortality. They may lead to acute kidney injury (especially in neonates and infants) renal scarring, hypertension, renal/perinephric abscesses, bacteraemia with systemic inflammation and chronic renal disease (1–3). Recurrence of UTI is a recognised complication with higher rates amongst those patients experiencing their first infection after the age of 1 year. Boys have a recurrence rate of 32% compared to girls at 40%. Each prior infection increases the inherent risk by 25% (1).

A meta-analysis on the prevalence of UTI showed that rates vary by age, gender, race and circumcision status (4,5). UTI is more common amongst pre-school children compared to school-age children with rates of 1-3% and 0.7-2.3% respectively(1). The overall incidence is 6.6-8% of girls and 2% of boys by the age of 7 years (1,6). Furthermore, 5-14% of emergency room visits by children can be attributed to UTI (4). Shaik *et al* conducted a metanalysis and found that the prevalence rates of UTI in 2008 were higher compared to a study conducted by the American Academy of Paediatrics in 1999. Females with fever have higher rates of UTI in the first year of life and these decline over the following 2 years: 7.5% (0-3 months), 5.7% (3-6 months), 8.3% (6-12 months) and 2.1% (>12 months) (5).

Circumcision reduces to the incidence of UTI by 90% in normal boys (4). The prevalence of UTI in circumcised compared to uncircumcised infants is 2.4% and 20.1% respectively (5). Although randomised controlled trials are required to show the efficacy of circumcision in reducing the rate of UTI in children with urinary tract abnormalities, it can be considered a therapeutic intervention in this setting (4). There is emerging controversy surrounding routine

circumcision and potential infringement upon the child's rights and exposure to unnecessary procedures.

Microbiology:

Current international research shows that the microbiological profiles in lower and upper urinary tract infections are similar. *Escherichia coli* (*E. coli*) is the most common uropathogen, found in 90% of culture positive samples. Other organisms identified from community acquired UTI are *Enterobacter aerogenes*, *Enterococcus* species, *Proteus vulgaris*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Klebsiella oxytoca* (6–9). A retrospective study conducted by Mirsoleymani et al showed that gender influences the microbial profile. *E. coli* is more common amongst females whereas *Klebsiella spp.* infections are more likely to occur in males (10).

Pathophysiology:

The pathophysiology has been well described with structural and physiological abnormalities predisposing to infection. Unidirectional flow of urine, Tamm-Horsfall proteins and immune function are important in preventing UTI. These mechanisms interact with bacterial adhesion molecules and virulence properties to prevent ascending infection (2,11). Haematological spread from skin lesions, abscesses and cardiac vegetations are also implicated but are rare. Indwelling catheters are associated with an increased incidence of hospital associated and hospital acquired urinary tract infections (12). This has been attributed to the development of a bacterial biofilm inherent to long term catheter use. The bacteria become integrated into the catheter and tissue; quorum sensing allows for modulation gene responses coding for antibiotic targets thereby increasing their resistance profile (12).

Clinical assessment of UTI is difficult as younger patients are unable to voice their symptoms. Older children may complain of dysuria, frequency, vomiting, rigors, fever and flank/loin pain. A fever $>38^{\circ}\text{C}$ and irritability in infants and toddlers are highly suggestive signs of pyelonephritis (1). Inflammatory markers are able to predict the site of infection. Elevated procalcitonin (PCT) levels have a sensitivity and specificity of 94.1% and 89.7% respectively for the diagnosis of acute pyelonephritis (3). C-reactive protein (CRP) has a sensitivity of 100% and specificity of 18.5% (3).

Diagnosis:

In emergency units, rapid reagent urinary dipsticks are readily available. Zorc *et al* conducted a meta-analysis of various modalities commonly used in UTI diagnosis. Leukocyte esterase has a sensitivity of 83% and specificity of 84%. Nitrates are not very sensitive (50%) but are

highly specific 98% (2). The gold standard for diagnosing a UTI is a positive urine culture. Specimens must be collected in a sterile manner using a midstream urine collection, suprapubic aspiration or sterile catheter. Single organism growth of $>10^4$ CFU/ml from a sterile catheter collection is considered positive, whilst any growth from a suprapubic aspirate can be considered positive (2). Microscopy with gram stain has a sensitivity of 93% and specificity of 95% for UTI (2). Standard microscopy showing >5 white cells/high powered field has a sensitivity of 67% and specificity of 79% (2).

Clinical practice guidelines published by the American Academy of Paediatrics noted that culture from urine [perineal] bags have a worryingly high rate of false positives: approximately 88% (13). This has significant implications for patients as unsterile cultures lead to unnecessary hospital admissions, investigations and antibiotic use, therefore predispose to antibiotic resistance.

Management in an Era of Increasing Resistance

There is a paucity of South African paediatric data on the organism profile in UTI. Published results relate to adult female patients and correlate with international paediatric data. *E. Coli* is the most common organism isolated amongst adult patients. The other urinary isolates occurred in various frequencies (14,15). In a study published in 1994, Maartens and Oliver found that the incidence of antibiotic resistance to amoxicillin (65.1%) and co-trimoxazole (47.3%) amongst urinary isolates was present amongst community-acquired infections in Cape Town (16).

A study by Habte et al in 2009 examined urinary isolates in hospital and community isolates in adult patients and found that gram-negative pathogens had a high level of resistance to amoxicillin (43-100%) and co-trimoxazole (29-90%). Resistance to gentamicin (0-50%) and ciprofloxacin (0-33%) was lower. Importantly, extended-spectrum beta lactamase (ESBL) organisms were more prevalent in hospital patients (15). In 2013, Lewis et al showed similar results amongst adult female patients with high levels of resistance to co-amoxiclavulenic acid (82.8% CI 77.5-88) when compared to fluoroquinolones and fosfomycin. Furthermore, trimethoprim/sulphamethoxazole (TMP/SMX) was the least effective agent in the treatment of UTI (44.3% susceptible; CI 37.4-51.2) (14).

When comparing these South African results to international data, a similar trend of resistance to TMP/SMX, amoxicillin and co-amoxiclavulenic acid is apparent. In addition, increasing resistance to cephalosporins amongst *E. coli* isolates has been observed. Fortunately, nitrofurantoin remains an efficacious agent in the treatment of UTI (7,8,17,18). A study in North

India showed in-vitro resistance to imipenem amongst *Enterobacteriaceae*. Enterococci were more common amongst nosocomial UTI and 12% of those strains were vancomycin resistant (9). With the widespread, often indiscriminate use of antibiotics, one can postulate that rates of resistance have increased over the last two decades and that updated paediatric data in South Africa is a necessity as this is a complex evolving issue.

Nosocomial infections are associated with increased morbidity, mortality and health care cost, comprising 10% of hospital acquired infections amongst children (19,20). Prolonged indwelling catheters are directly associated with nosocomial UTI. This is compounded by antibiotic misuse resulting in a higher incidence of candida infections as well (20). Garraffo et al looked at how antibiotic exposure in the previous 12 months influenced resistance profiles with UTI. The study found a statistically significant relationship between antibiotic exposure and subsequent development of resistance: amoxicillin (71% vs 46%), first generation cephalosporins (65% vs 46%) and TMP/SMX (36% vs 15%) (18).

Current guidelines for treating pyelonephritis recommend 7-10 days of appropriate, culture guided antibiotics. Children less than 3 months should be admitted for intravenous antibiotics whereas those over 3 months of age are adequately treated with an oral course (21). A three-day course of antibiotics will suffice for an uncomplicated lower UTI. Longer course therapy has fewer treatment failures without a rise in reinfection (22). All children with first time UTI should have a screening ultrasound within 6 weeks to rule out anatomical anomalies (21). Children with recurrent infections, renal dysfunction, septicaemia or infection with non-*E.coli* organisms are recommended to have a dimercaptosuccinic acid scan within 4-6 months to rule out renal scarring (21). A micturating cystourethrogram (MCUG) may be done when vesicoureteric reflux (VUR) is suspected but is not recommended routinely (23). MCUG is costly, exposes the patient to considerable amounts of ionizing radiation and reflux correlates poorly with renal scarring (23). Contrast enhanced ultrasound is a more accurate alternative.

Co-morbid Conditions:

A study by Jeena *et al* retrospectively evaluated children admitted to King Edward VIII Hospital in Durban, South Africa between 1985-1992. UTI was the final diagnosis in only 4-17% of cases but, importantly, occurred frequently as part of other clinical presentations (24). UTI was found in 20-50% of acute diarrhoeal illness, 11-22% of acute respiratory illness and 23-44% of cases of protein energy malnutrition. Furthermore, only 13% of children had identifiable urinary tract signs (24). Kala *et al* also evaluated South African children with malnutrition and showed that UTI was present in 34.7% of cases (25). These findings concur with a similar study performed from in Turkey with UTI being prevalent in 30% of children (26). Human

Immunodeficiency Virus (HIV) is often associated with malnutrition in children. Asharam *et al* retrospectively evaluated 55 patients (29 children with HIV positive) admitted to King Edward Hospital in Durban, South Africa but failed to show an association with HIV and UTI. This can be attributed to the small sample size and therefore further investigation is warranted (27).

Rationale for further investigation:

South Africa is a developing country with a gross discrepancy between private and government medical resources. Understanding the microbial profile will help optimize these resources in the South African context and give insight into the burgeoning issues of resistant organisms in community infections. Furthermore, UTI often co-exists with other medical conditions. It is therefore important to assess these conditions and examine factors that influence positive urine cultures in patients presenting to emergency departments. Understanding the uropathogen profile in the South African context is of critical importance as this influences protocol implementation and antibiotic choice. Indiscriminate antibiotic usage has led to increased pressure on classes of antibiotic and, subsequently, an increase in pharmacotherapy resistance. The inherent public health burden requires that judicious treatment practices be implemented.

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Chapter 2: The Microbial Burden and Antibiotic Profile of Paediatric Bacterial Urinary Tract Infections at a Tertiary Hospital in the Western Cape, South Africa

Introduction

Paediatric urinary tract infection (UTI) is defined as the bacteriuria (bacterial growth of $>10^5$ colony forming units/milliliter is regarded as the threshold) in the presence of signs and symptoms (1). The overall incidence of UTI's in infants presenting with fever is 7% and accounts for 5-14% of visits to emergency departments annually (2). Uropathogenic *Escherichia coli* (*E.coli*) accounts for 60-70% of community acquired infections (1). Alberici et al reviewed the data found by the ESCAPE (Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Failure in Paediatric Patients) study group and showed that the uropathogen profile is evolving in both hospital and community settings. *E.coli* caused $<50\%$ of UTI's and *Klebsiella* spp, *Enterococci* with *Proteus* and *Pseudomonas* are emerging as community acquired uropathogens (3).

Microbial resistance is a growing problem that requires standardized definitions and nomenclature. An international group of experts from the European Centre of Disease Prevention and Control (ECDC) and the Centre of Disease prevention and Control (CDC) came together to create standardized terminology to describe antimicrobial resistance. Multi-drug resistance (MDR) is acquired resistance to at least one agent in three or more antibiotics categories. Extreme drug resistance (XDR) is acquired resistance to at least one agent in all but two or fewer antimicrobial categories (i.e. pathogens remain susceptible to at least two agents) (4).

Calzi et al conducted a study in Genoa, Italy looking at resistance trends to oral antibiotics amongst gram negative rods from 2007 till 2014. Here, *E. coli* UTI had rates of resistance to co-amoxiclavulenic acid and ciprofloxacin of 23.6% and 6.5 % in 2007 and 35.6% and 9.4% in 2011-2014 respectively ($p<0.0001$). Similar trends were seen amongst *Enterobacteriaceae* spp to trimethoprim/sulphamethoxazole (TMP/SMX) and ciprofloxacin with resistance rates of 9,6% and 1.2% in 2007 and 18.1% and 6.1 % in 2011-2014 ($p= 0.02$ and $p=0.0007$) (5). Chen et al showed that *E.coli* extended spectrum beta-lactamase (ESBL) activity at a tertiary hospital in Taiwan was 2% in 2003 but increased to 11% in 2012; *E.coli* overall drug sensitivity was 20% to ampicillin, 61% to co-amoxiclavulenic acid, 85% to ceftriaxone, 68.7% to ceftazidime and 54.6% to cefotaxime (6). Another study conducted at 2 tertiary level hospitals in Northern Taiwan showed that cephalosporin prophylaxis increased rates of ESBL UTI (compared to TMP/SMX) and that antimicrobial susceptibility decreased to almost all antibiotic

classes. This was further aggravated by the use of repeated courses of different antibiotics (7).

Maartens et al conducted a retrospective study looking at antimicrobial susceptibility in community acquired isolates causing UTI in adult females at Groote Schuur Hospital, Western Cape South Africa in 1991. The overall antibiotic resistance in *E.coli* and *Enterobacteriaceae* isolates to amoxicillin, co-amoxiclavulinate and TMP/SMX was 65.1%, 18.7% and 47.3% respectively (8). A study conducted in Gauteng, South Africa in 2011 described the overall susceptibility of uropathogens, causing UTI in adult female patients, to TMP/SMX (44.3%), co-amoxiclavulnic acid (82.8%), ciprofloxacin (94.1%) and nitrofurantoin (91.7%) (9).

Microbial resistance poses a challenge to South Africa's health system. This problem is compounded by overuse and inappropriate prescription of antibiotics in the South African paediatric population. This study will evaluate the uropathogen population in paediatric (birth to 14 years) bacterial UTI and the respective antibiotic susceptibility profile and compare this to international data and trends. Furthermore, UTI will be classified into community, hospital associated and hospital acquired infections. These infections will then be linked to Human Immunodeficiency Virus (HIV) status and concurrent blood culture results (if applicable).

Definitions

Urinary tract infection: Single organism growth >100 000cfu/ml and leukocytes >1000cells/ml in urine specimens sent to the laboratory

Community Acquired Infection: Infection identified on presentation to the paediatric emergency unit in the absence of any prior admission in the preceding 30 days

Hospital Associated Infection: Infection identified on presentation to the paediatric emergency unit with prior hospital admission in the preceding 30 days

Hospital Acquired Infection: Infection after 72 hours post admission

* Mono-drug resistance: Acquired resistance to 1 drug category

* Multi-drug resistance: Acquired resistance to at least 1 agent in >3 antibiotic categories

* Extreme drug resistance: Acquired resistance to >1 agent in all but <2 categories

* Extended spectrum B-lactam producer: Organism resistant to 1st-3rd generation cephalosporin [class] antibiotics

* Definitions taken from Magiorakas et al (4)

Materials and Methods

Setting:

This study was conducted at Tygerberg Hospital, a tertiary hospital in the Western Cape, South Africa; this hospital serves the Northern and Eastern rural districts of the Western Cape. The paediatric service comprises 309 beds providing neonatal, general and sub-specialist care. All urine cultures are performed on site at the medical microbiology laboratory of the National Health Laboratory Service (NHLS).

Study Design:

A retrospective descriptive analysis of all urine cultures, taken from patients aged birth-14 years, from the NHLS databases between 1 January 2012 and 31 December 2013 was performed. This study was undertaken from 2015-2016. Samples included were those from children aged birth to 14 (completed) years with a positive pure [single] growth of a uropathogen. There were no interventions or diagnostic methods implemented for this study.

Investigation of UTI:

Urine samples were collected and sent to the laboratory based on clinical suspicion of UTI or if clinicians were investigating sources of pyrexia in paediatric patients. The methods of sample collection were often not recorded on the laboratory request form.

The NHLS reports cell counts, presence of crystals and debris (if applicable) and the culture results of all urine specimens sent for analysis. Identification and microbial susceptibility is performed using the automated Vitek II platform and interpreted using annually published Clinical and Laboratory Standards Institute (CLSI) breakpoints.

It should be noted that the NHLS at the study center did not release the uropathogens full antimicrobial sensitivity if the organism was sensitive to penicillin and cephalosporin antibiotics. This is done to limit prescription of unnecessary broad spectrum antibiotics by treating physicians.

The data provided by the NHLS was cross referenced with data on the electronic Clinicom Data Management system to stratify the specimens into community, hospital associated and hospital acquired infections by looking at the date of admission compared to the date when the sample was taken, as described previously.

Samples were further linked with concurrent blood culture and human immunodeficiency virus (HIV) tests/results. Voluntary counselling and testing for HIV is routinely offered to patients and parents. If the HIV status of patient was known during initial assessment, then formal HIV testing was not performed. HIV exposure and HIV results at the time of admission or from previous admission to Tygerberg hospital were not accessible in the NHLS during this investigation.

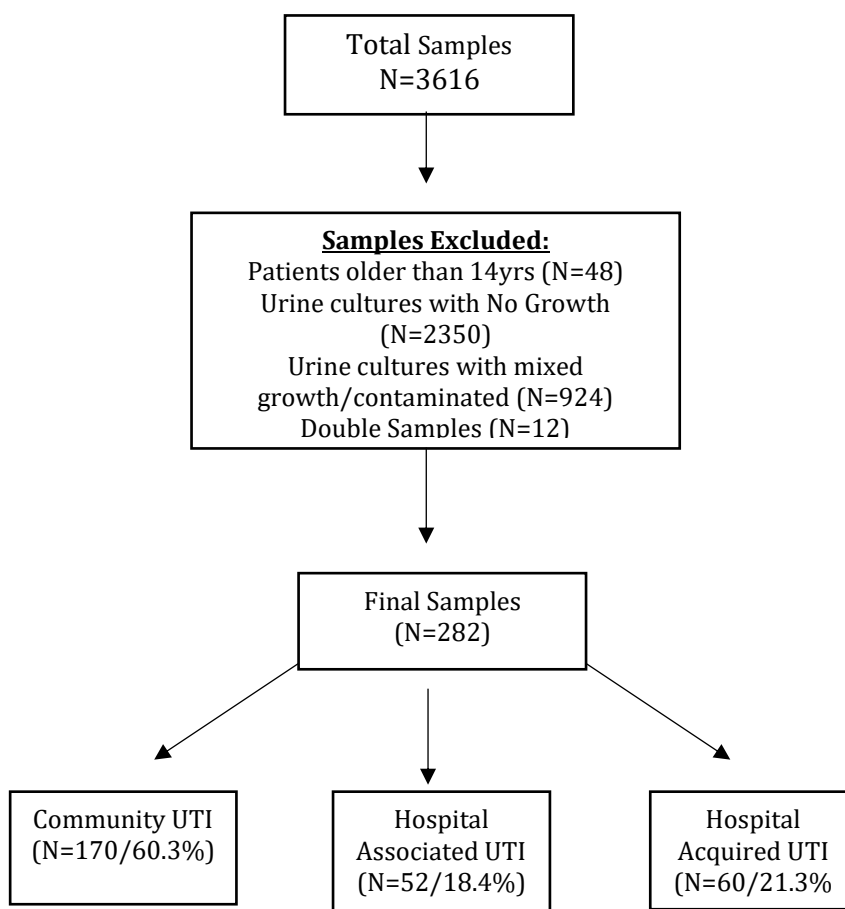
Statistical Analysis:

All data received from the laboratory was captured on electronic spread sheets. Data variables were allocated numerical codes and exported to statistical software (STATA v12; Statacorp) for further analysis. Complex analysis was done in partnership with the Department of Biostatistics at Stellenbosch University. Factors associated with positive culture was assessed bivariately using Pearson's chi square test and Fisher's test for categorical variables. Statistical significance was accepted if $p < 0.05$.

Ethics:

The research Protocol "Paediatric Bacterial Urinary Tract Infections in the South African Context" (S14/09/182) was approved by the Human Research and Ethics Counsel (HREC) of Stellenbosch University.

Figure 1: Patient Recruitment Flow Diagram



Results

A total of 3616 samples from 1 January 2012 till 31 December 2013 were reviewed for inclusion. Forty-eight samples were from patients above 14 years old, 2350 urine samples had no growth, 924 samples were mixed growth/contaminated (i.e. multiple organisms were cultured) and 12 samples were submitted twice for the same patient during the index UTI. 282 samples met the study definition and were included in the study. The median age for the group was 12.1 months (IQR: 2.9-42.3). These were further stratified into community UTI (170/60.3%), hospital associated UTI (52/18.4%) and hospital acquired UTI (60/21.3%) (figure 1).

Table 1 describes the overall and uropathogen specific demographic data of the samples included in the study. The mean age of the patients was 27.8 months with a male predominance (56.74%; $p=0.004$). One hundred and forty-two (50.4%) samples were from patients below 1 year old; of whom, 90/63.4% were male. Of the culture confirmed UTI's, 235/83.3% were sourced from the general and specialist paediatric wards. The most common

organism was *E. coli* (143/50.7%) followed by *Klebsiella pneumoniae* (64/22.7%), *P. mirabilis* (13/4.6%) and *Enterococcus* species (13/4.6%).

In 186 samples (65.9%) the patients did not have HIV serology results available. Only 115/40.8% of the samples had a concurrent blood culture performed. Of those, 9 (3.2%) had a positive blood culture with their concurrent UTI. Of positive cultures, 77.8% were attributed to *E. coli* UTI complicated with a concurrent bacteraemia.

A total of 75/26.6% cultured organisms were positive for ESBL production. Of those, 19/25.3% of samples were community acquired vs 24/32% which were hospital associated vs 32/42.7% which were nosocomial ($p=0.0$). *E. coli* displayed high level resistance to amoxicillin (90.8%), ampicillin (90.8%) and TMP/SMX (71.8%). *K. pneumoniae* showed high level resistance to the penicillin, penicillins with B-lactam antagonists, all cephalosporin's categories, folate pathway inhibitors and nitrofurantoin (table 2). There was also marked resistance to gentamicin (76.6%) but was 74.5% sensitive to amikacin. Similar levels of resistance were seen in the *Enterobacter* spp group.

Resistance amongst *E. coli*, *K. pneumoniae* and *P. mirabilis* infections were further described according to proposed definitions by the European Centre of Disease Prevention and Control (ECDC) and the Centre of Disease prevention and Control (CDC) (table 2 and 3) (4). *K. pneumoniae* was more frequent with hospital associated and nosocomial infections ($p=0.006$). Although multi- and extremely drug resistant *P. mirabilis* ($n=13$) showed higher rates of resistance to penicillins and penicillins with Beta-lactams amongst males and in community infections, but not reaching statistical significance due to small numbers.

Table 1: Total and Specific Uropathogen Demographic data

	Total (n=282)	E.coli (n=143)	K.pneum (n=64)	P.mirabilis (n=13)	Enterococ spp (n=13)	Enterobact spp (n=6)	Candida spp (n=20)	Other (n=22)	
Gender (n/%)									
Male	160/56.7%	69/43.1%	34/21.3%	9/5.6%	13/8.1%	4/2.5%	13/8.1%	18/11.3%	p=0.004
Female	122/43.3%	74/60.7%	30/24.6%	4/3.3%	1/0.8%	2/1.6%	7/5.7%	4/3.3%	
Ward (n/%)									
General	235/83.3%	136/95.1%	46/71.9%	11/84.6%	11/84.6%	4/66.7%	11/55%	16/72.7%	
Neonatal	27/9.6%	3/2.1%	13/30.3%	2/15.4%	2/15.4%	1/16.7%	2/10%	4/18.2%	
ICU	20/7.1%	4/2.8%	5/7.8%	0/0%	0/0%	1/16.7%	7/35%	2/9.1%	
HIV Status (n/%)									
Positive	16/6.7%	3/18.8%	9/56.3%	0/0	2/12.5%	0/0	1/6.3%	1/6.3%	p=0.0
Negative	80/28.4%	30/37.5%	24/30%	3/3,75%	2/2,5%	1/1,25%	13/16,25%	7/8,75%	
Not tested/done	186/66%	110/59,14%	31/16,67%	10/5,38%	10/5,38%	5/2,69%	6/3,23%	14/7,53%	
Blood Culture (n/%)									Sample too small
Positive	9/3.2%	7/77.8%	0/0	0/0	0/0	0/0	0/0	2/22.2%	
Negative	91/32.3%	32/35.2%	32/35.2%	3/3,3%	7/7.7%	3/3.3%	9/9.9%	5/5.5%	
Not done	167/59.2%	97/58.1%	28/16.8%	10/6%	7/4.2%	3/1.8%	8/4.8%	14/8.4%	
Contaminated	10/3.6%	5/50%	3/30%	0/0	0/0	0/0	1/10%	1/10%	
Positive; Alternative Org	5/1.8%	2/40%	1/20%	0/0	0/0	0/0	2/40%	0/0	
Type Infection (n/%)									Sample too small
Community	170/60.3%	114/67.1%	17/10%	9/5.3%	8/4.7%	3/1.8%	8/4.7%	11/6.5%	
Hosp associated	52/18.4%	20/38.5%	22/42.3%	0/0%	1/1.9%	1/1.9%	4/7.7%	4/7.7%	
Nosocomial	60/21.3%	9/15%	25/41.7%	4/6.7%	5/8.3%	2/3.3%	8/13.3%	7/11.7%	
ESBL (n/%)	75/26.6%	15/20%	54/72%	0/0%		3/4%		3/4%	p=0.0
Community	19/25.3%								
Hosp associated	24/32%								
Nosocomial	32/42.7%								p=0.0
HIV Positive	11/14.7%								
HIV Negative	28/37.3%								
HIV Not Tested/Done	36/48%								p=0.022

* Enterococcus spp includes Enterococcus faecalis (1/0.35%), Enterococcus faecium (1/0.35%) and Enterococcus species (13/4.61%)

** Enterobacter spp includes Enterobacter aerogenes (3/1.06%) and Enterobacter cloacae (3/1.06%)

*** Candida spp includes Candida albicans (16/5.67%) and Candida species (4/1.42%)

**** Other includes Acinetobacter baumannii complex (1/0.35%), Acinetobacter baumannii (4/1.42%), Citrobacter freundii (1/0.35%), Hafnia alvei (2/0.71%), Klebsiella oxytoca (3/1.06%), Klebsiella pneumoniae spp ozaen (1/0.35%), Morganella morganii (3/1.06%), Pseudomonas aeruginosa (2/0.71%), Raoultella planticola (1/0.35%), Serratia marcescens (2/0.71%), Serratia spp (1/0.35%), Staphylococcus aureus (2/0.71%) and Staphylococcus saprophyticus (1/0.35%)

Table 2: *In vitro* Uropathogen Resistance to Tested Antibiotics

Antibiotic Categories		E. coli (n=143)		K. Pneum (n=64)		P. Mirabilis (n=13)		Enterobacter spp. (n=6)	
		Tested	Resistance (n/%)	Tested	Resistance (n/%)	Tested	Resistance (n/%)	Tested	Resistance (n/%)
Penicillin	Amoxicillin	142	129 (90.8)	64	64 (100)	13	11 (84.6)	4	4 (100)
	Ampicillin IV	142	129 (90.8)	64	64 (100)	13	11 (84.6)	4	4 (100)
Penicillin + β -Lactam Inhib)	Co-amoxicillin	129	49 (38)	62	55 (88.7)	7	3 (42.9)	6	6 (100)
	Piperacillin-tazobactam	15	9 (60)	38	28 (73.7)	2	2 (100)	2	2 (100)
1st/2nd Gen Cephalosporin	Cefuroxime PO	138	26 (18.8)	64	55 (85.9)	13	0 (0)	5	5 (100)
	Cefuroxime IV	137	18 (13.1)	64	55 (85.9)	13	0 (0)	4	4 (100)
3rd/4th Gen Cephalosporin	Cefotaxime	52	15 (28.8)	55	54 (98.2)	3	0 (0)	3	3 (100)
	Ceftriaxone	52	15 (28.8)	55	54 (98.2)	3	0 (0)	3	3 (100)
	Ceftazidime	19	15 (78.9)	55	54 (98.2)			3	3 (100)
	Cefepime	18	15 (83.3)	51	50 (98)			5	2 (40)
Cephamycins	Cefoxatin			2	0 (0)			1	1 (100)
Aminoglycosides	Gentamicin	141	18 (12.8)	64	49 (76.6)	13	3 (23.1)	6	3 (50)
	Amikacin	22	4 (18.2)	51	13 (25.5)	3	0 (0)	3	1 (33.3)
	Tobramycin	4	4 (100)						
Fluoroquinolones	Ciprofloxacin	52	11 (21.2)	48	23 (47.9)	7	1 (14.3)	4	2 (50)
	Nalidixic Acid	2	0 (0)	7	7 (100)			2	1 (50)
Carbapenems	Imipenem	13	0 (0)	36	1 (2.8)			3	0 (0)
	Ertapenem	14	0 (0)	47	0 (0)			4	0 (0)
	Meropenem	16	0 (0)	41	0 (0)			3	0 (0)
Folate Pathway Inhib	Trimethoprim-sulphamethoxazole (cotrimox)	142	102 (71.8)	64	49 (76.6)	11	6 (54.5)	6	4 (66.7)
Nitrofuran Derivatives	Nitrofurantoin	6	1 (16.7)	14	12 (85.7)	5	5 (100)	2	2 (100)
Glycylcyclines	Tigecycline			2	0 (0)	3	3 (100)		
Polymyxins	Colistin			2	0 (0)	1	1 (100)		

Table 3: Uropathogen Antibiotic Category Resistance

	E. coli (n=143)						K. pneumoniae (n=64)						P. mirabilis (n=13)					
	Sensitive	Mono	Dual	MDR	XDR		Sensitive	Mono	Dual	MDR	XDR		Sensitive	Mono	Dual	MDR	XDR	
Gender:																		
Male (n=69)	3/4.4%	9/13.0%	25/36.2%	19/27.5%	13/18.8%	p=0.542	0/0%	3/8.8%	2/5.9%	6/17.7%	23/67.7%	p=0.726	1/11.1%	1/11.1%	3/33.3%	0/0%	4/44.4%	p=0.225
Female (n=74)	5/6.8%	12/16.2%	33/44.6%	13/17.6%	11/14.9%		0/0%	3/10%	0/0%	6/20%	21/70%		0/0%	0/0%	3/75%	1/25%	0/0%	
Ward:																		
General (n=136)	8/5.9%	19/14%	56/41.2%	31/22.8%	22/16.2%		0/0%	5/10.9%	2/4.4%	11/23.9%	28/60.9%		1/9.1%	1/9.1%	4/36.4%	1/9.1%	4/36.4%	
Neonatal (n=3)	0/0%	0/0%	1/33.3%	1/33.3%	1/33.3%		0/0%	0/0%	0/0%	1/7.7%	12/92.3%		0/0%	0/0%	2/100%	0/0%	0/0%	
ICU (n=4)	0/0%	2/50%	1/25%	0/0%	1/25%	p=0.537	0/0%	1/20%	0/0%	0/0%	4/30%	p=0.366	0/0%	0/0%	0/0%	0/0%	0/0%	p=0.692
HIV Status																		
Positive (n=3)	0/0%	0/0%	1/33.3%	2/66.7%	0/0%		0/0%	0/0%	0/0%	1/11.1%	8/88.9%		0/0%	0/0%	0/0%	0/0%	0/0%	
Negative (n=30)	0/0%	2/6.7%	9/30%	12/40%	7/23.3%		0/0%	4/16.7%	0/0%	5/20.8%	15/62.5%		0/0%	1/33.3%	2/66.7%	0/0%	0/0%	
Not tested/done (n=110)	8/7.3%	19/17.3%	48/43.6%	18/16.4%	17/15.5%	p=0.037	0/0%	2/6.5%	2/6.5%	6/19.4%	21/67.7%	p=0.674	1/10%	0/0%	4/40%	1/10%	4/40%	p=0.241
Blood Culture:																		
Positive (n=7)	0/0%	2/28.6%	0/0%	4/57.1%	1/14.3%	p=0.475	0/0%	0/0%	0/0%	0/0%	0/0%	p=0.975	0/0%	0/0%	0/0%	0/0%	0/0%	p=0.241
Negative (n=32)	1/3.1%	4/12.5%	13/40.6%	8/25%	6/18.8%		0/0%	4/12.5%	1/3.1%	6/18.8%	21/65.6%		1/33.3%	0/0%	2/66.7%	0/0%	0/0%	
Not done (n=97)	7/7.2%	14/14.4%	42/43.3%	18/18.6%	16/16.5%		0/0%	2/7.1%	1/3.6%	6/21.4%	19/67.9%		0/0%	1/10%	4/40%	1/10%	4/40%	
Contaminated (n=5)	0/0%	1/20%	1/20%	2/40%	1/20%		0/0%	0/0%	0/0%	0/0%	3/100%		0/0%	0/0%	0/0%	0/0%	0/0%	
Positive; Alternative drug (n=2)	0/0%	0/0%	2/100%	0/0%	0/0%		0/0%	0/0%	0/0%	0/0%	1/100%		0/0%	0/0%	0/0%	0/0%	0/0%	
Type of Infection																		
Community (n=114)	6/5.3%	19/16.7%	48/42.1%	25/21.9%	16/14%		0/0%	5/29.4%	2/11.8%	3/17.7%	7/41.2%		1/11.1%	1/11.1%	3/33.3%	1/11.1%	3/33.3%	
Hospital associated (n=20)	2/10%	2/10%	8/40%	4/20%	4/20%		0/0%	1/4.6%	0/0%	5/22.7%	16/72.7%		0/0%	0/0%	0/0%	0/0%	0/0%	
Nosocomial (n=9)	0/0%	0/0%	2/22.2%	3/33.3%	4/44.4%	p=0.380	0/0%	0/0%	0/0%	4/16%	21/84%	p=0.006	0/0%	0/0%	3/75%	0/0%	1/25%	p=0.656

Monodrug resistance (Mono): Acquired resistance to 1 drug category

Multi-drug resistance (MDR): Acquired resistance to at least 1 agent in >3 antibiotic categories

Extreme drug resistance (XDR): Acquired resistance to >1 agent in all but <2 categories

Discussion:

The majority of urine samples sent to the NHLS were sterile and did not culture a uropathogen (n=2350). Of samples considered a UTI in this study, 170/60.3% were community derived, 52/18.4% hospital associated and 60/21.3% hospital acquired infections. The median age for the group was 12.1 months (IQR: 2.9-42.3); data reports that patients younger than 5 years old are at higher risk of UTI (10). Gram negative enteric bacteria predominated in line with international data. *E. coli* remains the dominant organism (50.7%) in this study followed by *K. pneumoniae*, *P. mirabilis* and *Enterococcus* spp. Rates of *E. coli* infection causing UTI have been reported to be between 60% - 80.3% and 7% - 26% for *K. pneumoniae* (1,5,11–13). The lower rates of *E. coli* infection demonstrate a loss of supremacy and emergence of newer organisms possibly due to drug selection pressure. Further reasons for this are not immediately apparent.

E. coli and *K. pneumoniae* accounted for 69/92% of total ESBL infections. Of ESBL infections, 19/25.3% were attributed to community acquired infections. The rates of hospital acquired ESBL infection from a tertiary hospital in Pretoria, South Africa for *E. coli* and *K. pneumoniae* are 11.9% and 40.6% respectively (14). Rates of *E. coli* ESBL infections range from 11% - 39.4% (6,12).

Hospital acquired ESBL UTI represented 42.7% of total ESBL infections (p=0.0); *E. coli* represented 20% and *K. pneumoniae* 72%% of ESBL UTI in this study (p=0.0). Dramowski et al reported that *Klebsiella* spp accounted for 16% of community acquired and 51% of hospital acquired bacteraemias. E (15). This reflects an increase in *Klebsiella* spp infection in our environment. There is a global increase in both community and hospital acquired ESBL UTI infections. Dayan et al showed that community ESBL infection increased from 1% in 2007 to 5.8% in 2012 in Israel (16). A retrospective study in Thailand found the prevalence of community ESBL producing organisms to be 19.2% (95% CI: 13.8-25.7) (17). Factors implicated in exacerbating community ESBL infections were previous hospital admissions, previous use of penicillins or fluroquinolones, recurrent UTI and genitourinary tract anomalies (18). We did not assess risk factors for community acquired ESBL infection due to the retrospective nature of this study.

The pooled prevalence of ESBL *Enterobacteriaceae* is 14% (95% CI: 8-21), however the actual incidence may be as high as 40% in Europe; vesico-ureteric reflux (OR 2.79), history of UTI (OR 2.89) and recent antibiotic use (OR 2.92) were risk factors identified (19).

Of ESBL *E. coli* UTI in this study, 1/6.7% and 5/33.3% was sensitive to piperacillin-tazobactam and amikacin respectively. ESBL *K. pneumoniae* displayed 10/18.5% and 37/68.5% sensitivity to piperacillin-tazobactam and amikacin respectively. These antibiograms support current hospital policy to treat hospital associated and acquired infections with piperacillin-tazobactam and amikacin until urine culture and sensitivity are available, thereby limiting carbapenem drug pressure.

Table 4 displays *E. coli* resistance rates from this study compared to data from a European multicenter study, data from Taiwan and two studies performed in India (3,6,20,21). The antibiotics listed are those commonly used at primary and secondary level health services.

Study	Site	<i>E. coli</i> Drug Resistance							
		Amoxicillin	Co-amoxicillin	TMP/SMX	Cefotaxime	Ceftriaxone	Ciprofloxacin	Amikacin	Piptaz
Index Study	South Africa	90.8%	38%	71.8%	28.8%	28.8%	21.2%	18.2%	9%
Alberici et al	European Multicentre	>50%	20-50%	>50%			0-50%		
Chen et al	Taiwan	80%	39%	53%	55.4%	15%			
Rajiv et al	India	98%	88%		73.5%	73.5%	63.3%	21.4%	
Mishra et al	India	39%	36%	31%		36%		31%	38%

Table 4: *E. coli* Resistance Rates from Index study Compared to International Data

Cheng et al further described decreasing sensitivity rates for *K pneumoniae* and *Proteus* spp to cefazolin; sensitivity was 72% and 60% in 2008 and 44% and 10% in 2012 respectively (6). The author found that *K. pneumoniae* exhibited 85.9% resistance to first and second generation cephalosporins and >98% resistance to third and fourth generation cephalosporins. This is of relevance as 64/22.7% of UTI's were attributed to *K. pneumoniae*; 17/26.5% of which are community and 22/34.4% hospital associated UTI. *P. mirabilis* showed 100% sensitivity to all cephalosporins tested by the NHLS.

Blood for cultures are only drawn if the treating physician deems them clinically indicated; 9 (3.2%) patients with UTI had a positive blood culture but 167 (59.2%) had no culture sample drawn. There was no statistically significant correlation with causative organisms and antibiotic resistance against patients with positive blood cultures. Megged et al showed that male gender, age <3 months, higher creatinine and underlying urological abnormalities were significant risk factors for the development of bacteraemia (22). A retrospective study conducted at the same study site looking at blood stream infections in paediatric patients from January 2008 till December 2013 reported a 5.5% pathogen yield from all blood cultures drawn (23).

Further investigation is warranted to look at the true influence of HIV infection and risk of UTI as the numbers were too small in the present study. Asharam et al showed no significant impact of HIV/AIDS on antibiotic sensitivity, response to therapy or duration of hospitalization (24).

Our study provides an insight into the changing UTI organism population as well as antibiotic resistance/susceptibility profile. Antibiotic resistance is a developing challenge that requires use of judicious use of antimicrobial therapy. Future studies would be required to further explore resistance profiles as to better guide clinician's antibiotic prescription practices.

The major limitation to this study was that we were unable to assess for risk factors predisposing to UTI organism resistance. This included recent hospital exposure/admission for both patients and family members and underlying urinary tract anomalies.

Conclusion

The results evidenced in this study show that the organism profile of paediatric UTI is changing in line with international data trends. *K. pneumoniae* underlies 10% of culture positive infections. ESBL producing organisms were noted in 75 (64.1%) of UTI, of which *K. pneumoniae* accounted for 54. Furthermore, 25.3% of ESBL producers arise from the community setting. Extremely drug resistant *K. pneumoniae* species were significantly more likely to originate from hospital acquired infections. Health care practitioners should demonstrate judicious antibiotic practices to curb growing resistance by prescribing appropriate antibiotics and rationalize therapy based on urine microscopy culture and sensitivity results.

Funding and Conflict of Interest:

No external funding was provided for this study. The authors declare no conflict of interests.

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Chapter 3: Factors Impacting Positive Urinary Tract Infections in patients (0-5 years) Attending a Paediatric Emergency ward in a Tertiary Care Hospital in the Western Cape, South Africa

Introduction

Paediatric urinary tract infection (UTI) is defined as the presence of organisms in the urine with $> 10^5$ colony forming units/milliliter (cfu/ml) considered significant. UTI accounts for 5-14% of emergency department visits annually (1). The pooled prevalence rates of febrile UTI in female infants aged 0-3, 3-6 and 6-12 months was 7.5%, 5.7% and 8.3% respectively and remains more common amongst pre-school children compared to school age children with rates of 1-3% and 0.7-2.3% respectively (2). Risk factors for UTI in the febrile infant are age, gender, circumcision status in boys, race and duration of fever (3).

The most common bacterial pathogens are gram negative enteric organisms such as *Escherichia coli* (*E. coli*) and *Klebsiella* species; virulence factors (adhesins and haemolysins) allow these organisms to damage the uroepithelium (4). Adenovirus and Candida infection has also been implicated in causing haemorrhagic cystitis (5). Urine culture is the gold standard for diagnosis as signs and symptoms in the younger patient can often be non-specific (6).

Pyelonephritis can lead to significant morbidity. Shaikh et al, in a systematic review, reported that of children presenting with a first UTI, 57% (95% CI: 50-64) had changes consistent with acute pyelonephritis on the acute phase dimercaptosuccinic acid (DMSA) scan renal scan. On follow up scan, and 15% (95% CI: 11-18) had evidence of renal scarring on the follow up scan (7). UTI is the first presentation in 30% of children urinary tract anomalies (8). This includes vesico-ureteric reflux and obstructive uropathies predispose patients to pyelonephritis (9). The American Academy of Paediatrics recommends that patients diagnosed with a UTI, receive 7-14 days of antibiotics, and are monitored for recurrent infections and an ultrasound evaluation of the renal tract to rule out structural anomalies (3). However, these recommendations are quality B evidence for antibiotic use quality C evidence for imaging studies. UTI may progress and result in complications that include renal abscesses, septicaemia, renal scarring, hypertension and chronic kidney disease (10).

This study evaluated factors that influence positive urine cultures in patients from birth till 5 years at Tygerberg Hospital paediatric emergency room and to describe the correlation with urine dipsticks, serum inflammatory marker and renal imaging studies. Factors considered are clinical signs, antibiotic exposure and spectrum of co-morbid conditions.

Materials and Methods

Setting:

The study was conducted at Tygerberg Hospital, a tertiary level hospital in the Western Cape, South Africa. The paediatric emergency room protocols dictate that patients younger than 3 months old, patients with suspected bacteraemia or those with pyrexia of unknown origin have urine dipsticks +/- formal laboratory based urine analysis when screening for potential sites of sepsis. At the time of the study, urine dipsticks +/- formal analysis was done at the discretion of the attending clinician in patients older than 3 months of age. All urine cultures are performed on site at the medical microbiology laboratory of the National Health Laboratory Service (NHLS).

Study Design and Data Management:

A convenience sample children (birth-5 years) presenting to the emergency unit, in whom urine samples were submitted, were prospectively enrolled into the study provided informed individual consent was obtained from the parent/guardian. Patients were further subdivided into those below or above 3 months of age. The casualty protocols at the study site dictate that patients younger than 3 months have urine dipsticks +/- laboratory based urine analysis when screening patients for potential sites of sepsis. Patients that presented to the hospital on multiple occasions were eligible for re-recruitment into the study. Data was collected using preformed collections sheets. Patients were randomly allocated predetermined study numbers to ensure anonymity and confidentiality. These numbers were used to link patients to the electronic sheet. Data sources further included patient files/records, NHLS and radiology electronic databases and Clinicom and ECM electronic patient information.

We defined UTI as culture of a single organism from a urine sample sent to the NHLS. Mixed growth on urine samples were treated as contaminates by the attending doctors; these samples were not repeated. Nutritional definitions were according to the World Health organisation (WHO) (11).

Statistical Analysis:

In consultation with the Department of Biostatistics, a power analysis showed that a sample size of 100 patients would be adequate for statistical significance to correlate co-morbidities with UTI. The characteristics of the patients were described using standard descriptive analysis. Data analysis was performed using Stata version 12 (StataCorp). Factors associated with positive culture were assessed bivariate using Pearson's chi square test for categorical variables and t-tests for continuous variables. Binary logistic regression analysis was used to adjust the estimates for confounding.

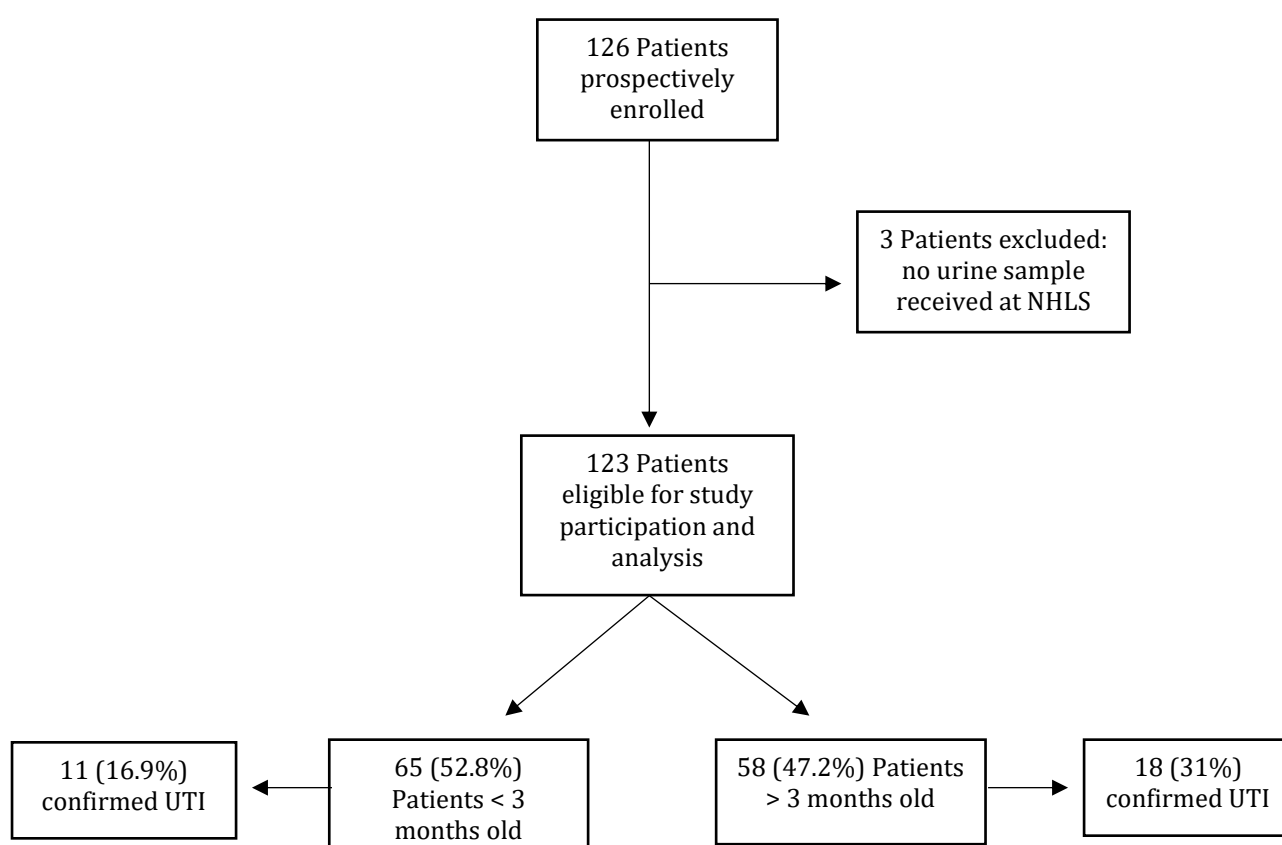
Ethics:

The research Protocol "Paediatric Bacterial Urinary Tract Infections in the South African Context" (S14/09/182) was approved by the Human Research and Ethics Counsel (HREC) of Stellenbosch University.

Results

A total of 126 patients were screened and prospectively enrolled from the paediatric emergency unit at Tygerberg Hospital from February – June 2015. Informed individual consent was obtained for all patients. No parent refused participation. Three patients were excluded as their respective urine samples were not received by the NHLS (figure 1).

Figure 1: Study Sampling Flow Diagram



The median age was 83 days (IQR: 29-320); 59/48% were from males. Sixty-five (52.8%) were submitted from children < 3 months old (Figure 1 and Table 1). Patients < 3 months old had median age 32 days (IQR 21-50) and those > 3 months had a median age 345.5 days (IQR 182-468).

Twenty-nine (23.6%) of those patients had culture confirmed UTI, 34 (27.6%) had mixed organism growth on urine culture; 21 (61.8%) of those samples were sourced from infants < 3 months old. Thirty-eight (58.5%) patients with UTI younger than 3 months old were male (OR 3.88 95%CI: 0.77-19.66; $p=0.102$), whilst those older than 3 months were female

(37/63.8%); there was no statistical significance in gender in these sub groups ($p=0.08$ and $p=0.776$ respectively).

The indications for sending urine samples for culture varied and included investigation for suspected source of bacteraemia in 63 (51.2%) children, suspected UTI in 34 (27.6%) and acute gastroenteritis in 10 (8.1%). Specimens were obtained via sterile in and out catheter in 101 (82.1%) children and 9 (7.3%) samples were collected via perineal bag collection.

The most common co-morbidity was acute gastro-enteritis; 46 (37.4%) patients presented with diarrhoeal disease but this was not predictive for the confirmed UTI ($p=0.344$). Forty-five (36.6%) of patients were assessed as having possible occult bacteraemia. Twenty-five (20.3%) children had a lower respiratory tract infection; these patients were less likely to have concurrent UTI (OR 0.23 95% CI: 0.05-1.04; $p=0.056$). This was also demonstrated amongst patients younger than 3 months (OR 0.09 95%CI: 0.01-1.63; $p=0.103$).

E. coli was isolated in 12 (41.4%) followed by *Klebsiella pneumoniae* in 9 (31%) cases. Three *E. coli* and 4 *K. pneumoniae* samples were extended spectrum beta lactamase (ESBL) producers. Other organisms identified included *Candida albicans* 4 (13.8%), non-*Candida albicans* species 1 (3.4%), *S. marcescens* 1 (3.4%), *E. faecalis* 1 (3.4%) and *Acinetobacter baumannii* 1 (3.4%). Of the fungal UTI's, 3 (60%) patients had $> 50\ 000$ cells/mm² and 3 (60%) had severe acute malnutrition.

E. coli was 100% resistant to amoxicillin, 66.7% to cefuroxime, 25% to ceftriaxone/cefotaxime and 75% and 66.7% resistant to trimethoprim/sulphamethoxazole (TMP/SMX). *K. pneumoniae* showed 100% resistance to amoxicillin, 44.4% resistance to cefuroxime and ceftriaxone/cefotaxime and 66.7%. *E. coli* and *K. pneumoniae* sensitivity to co-amoxiclavulenic acid and ciprofloxacin was 25% and 91.7% and 44.4% and 100% respectively. ESBL *E. coli* was 33.3% and 66.7% resistant to ciprofloxacin and amikacin respectively. ESBL *K. pneumoniae* was 100% sensitive to these drugs.

Of the samples with mixed growth on urine culture, 8 were positive for leukocyte esterase (on urine dipsticks), 1 was positive for nitrates and 1 sample had both leukocyte esterase and nitrate. None of these samples had repeated urine samples sent for culture.

Eighteen (14.6%) patients had severe acute malnutrition but this was not statistically significant for predicting confirmed UTI ($p=0.391$); 2 (11.1%) had a positive urine culture. There was no difference in the ratio of malnutrition in children < 3 and those > 3 months old. Patient's > 3 months old were less likely to have a concurrent UTI ($p=0.023$).

Twenty-six children (21.1%) were HIV exposed. Of those, 10 (47.6%) patients had culture confirmed UTI; 1 (10%) was HIV positive, 7 (70%) was HIV negative and 2 (20%) patients' HIV status was not yet tested. Patients who were HIV exposed from the total patient population (OR 2.57 95% CI: 1.01-6.54; $p=0.048$) and those > 3 months old (OR 4.45 95% CI: 1.17-16.89; $p=0.028$) were less likely to have a UTI. The patient's HIV status did not influence the development of UTI; only 3 patients (2.4%) in the study were HIV positive. A total of 69 (56.1%) patients did not have HIV status documented.

Table 2 illustrates the relationship between signs and symptoms, co-morbidities and previous antibiotic exposure on the development of UTI. Sixty-one (49.6%) patients presented with fever (either on history or documented pyrexia >37.5 °C) and 77 (62.6%) had irritability as presenting complaint. Duration of pyrexia was not documented. The major sign that attending clinicians found on initial assessment was suprapubic pain. There was no statistically significant correlation between signs and symptoms and culture confirmed UTI.

Thirty-three (26.8%) caregivers reported their children receiving antibiotics in the previous year, of whom, 21 received amoxicillin. Nine parental caregivers were not sure what type of antibiotic was prescribed; it was not documented in the Road to Health Card either). Forty-two (34.1%) children received intramuscular ceftriaxone according to the integrated childhood management of illness (IMCI) algorithms; patients were less likely to have confirmed UTI but this was not statistically significant (OR 0.47 95% CI: 0.14-1.57; $p=0.22$). Twenty-eight (22.8%) children had received antibiotics in the casualty at the study site prior to the urine sample being sent to the laboratory.

Urine dipstick positive for nitrates ($p=0.043$) and leukocytes (0.018) correlated with positive urine culture (table 3). This was not statistically significant in patients less than 3 months old; only 46 (70.8%) patients had urine dipstick analysis prior to a urine sample being sent to the laboratory.

C-reactive protein (CRP) was drawn on 38 patients from the study population at presentation. The mean CRP in patients with confirmed UTI ($n=7$) was 67.4 (IQR: 19.6-95.1) and was 37.6 (IQR: 12.5-48.8) in those without UTI ($n=31$) ($p=0.19$). Two patients had confirmed concurrent bacteraemia with UTI. Kidney, ureter and bladder (KUB) ultrasound was likely to be normal in patients with UTI for the total sample and subdivided population ($p= 0.0$).

Table1: Demographic data of the Study Population

	Total (n=123)				<3 months old (n=65)				>3 months old (n=58)			
	Total (n=123)	UTI (n=29)	NoUTI (n=94)		Total (n=65)	UTI (n=11)	NoUTI (n=54)		Total (n=58)	UTI (n=18)	NoUTI (n=40)	
Age, days: median (IQR)	83 (29-320)	125 (49-364)	66 (27-310)		32 (21-50)	42 (21-55)	31 (21-50)		345.5 (182-468)	293.5 (170-421)	357.5 (185-554)	
Gender (n/%)												
Male	59 (48)	16 (27.1)	43 (72.9)	p=0.374	38 (58.5)	9 (23.7)	29 (76.3)	p=0.08	21 (36.2)	7 (33.3)	14 (66.7)	p=0.776
Female	64 (52)	13 (20.3)	51 (79.7)		27 (41.5)	2 (7.4)	25 (92.6)		37 (63.8)	11 (29.7)	26 (70.3)	
Nutrition: weight (n/%)												
Severe	21 (17.1)	4 (19)	17 (81)	p=0.471	6 (9.2)	1 (16.7)	5 (83.3)	p=0.813	15 (25.9)	3 (20)	12 (80)	p=0.42
Moderate	15 (12.2)	2 (13.3)	13 (86.7)		10 (15.4)	1 (10)	9 (90)		5 (8.6)	1 (20)	4 (80)	
Normal	87 (70.1)	23 (26.4)	64 (73.6)		49 (75.4)	9 (18.4)	40 (81.6)		38 (65.5)	14 (36.8)	24 (63.2)	
Nutrition: height (n/%)												
Severe	18 (14.6)	2 (11.1)	16 (88.9)	p=0.391	7 (10.8)	2 (28.6)	5 (71.4)	p=0.346	11 (19)	0 (0)	11 (100)	p=0.038
Moderate	13 (10.6)	3 (23.1)	10 (76.9)		7 (10.8)	0 (0)	7 (100)		6 (10.3)	3 (30)	3 (50)	
Normal	92 (74.8)	24 (26.1)	68 (73.9)		51 (78.4)	9 (17.7)	42 (82.3)		41 (70.7)	15 (36.6)	26 (63.4)	
Nutrition: length/height (n/%)												
Severe	18 (14.6)	2 (11.1)	16 (88.9)	p=0.391	7 (10.8)	2 (28.6)	5 (71.4)	p=0.346	11 (19)	0 (0)	11 (27.5)	p=0.023
Moderate	13 (10.6)	3 (23.1)	10 (76.9)		7 (10.8)	0 (0)	7 (100)		6 (10.3)	3 (16.7)	3 (7.5)	
Normal	92 (74.8)	24 (26.1)	68 (73.9)		51 (78.5)	9 (17.7)	42 (82.4)		41 (70.7)	15 (36.6)	26 (63.4)	
HIV Exposure (n/%)												
Exposed	26 (21.1)	10 (38.5)	16 (61.5)	p=0.044	14 (21.5)	3 (21.4)	11 (78.6)	p=0.438	12 (20.7)	7 (58.3)	5 (41.7)	p=0.022
Not Exposed	97 (78.9)	19 (19.6)	78 (80.4)		51 (78.5)	8 (15.7)	43 (84.3)		46 (79.3)	11 (23.9)	35 (76.1)	
HIV Status (n/%)												
Test not done	69 (56.1)	13 (18.8)	56 (81.2)	p=0.448	38 (58.5)	4 (10.5)	34 (89.5)	p=0.206	31 (53.5)	9 (29)	22 (71)	p=0.825
Positive	3 (2.4)	1 (33.3)	2 (66.7)		1 (1.5)	0 (0)	1 (100)		2 (3.5)	1 (50)	1 (50)	
Negative	50 (40.7)	15 (30.0)	35 (70)		26 (40)	7 (26.9)	19 (73.1)		24 (41.4)	8 (33.3)	16 (66.7)	
Indeterminate	1 (3.2)	0 (0)	1 (100)		0 (0)	0 (0)	0 (0)		1 (1.7)	0 (0)	1 (100)	

Table 2: Variables (history, co-morbidities and antibiotic exposure) and the influence on UTI in Paediatric Patients

	Total (n=123)				< 3 months old (n=65)				> 3 months old (n=58)			
	Total (n=123)	UTI (n=29)	No UTI (n=94)	p	Total (n=65)	UTI (n=11)	No UTI (n=54)	p	Total (n=58)	UTI (n=18)	No UTI (n=40)	p
Presenting Signs & Symptoms (n/%)												
Fever	61 (49.6)	13 (21.3)	48 (78.7)	p=0.557	28 (43.1)	4 (14.3)	24 (85.7)	p=0.622	33 (56.9)	9 (27.3)	24 (72.7)	p=0.477
Dysuria	13 (10.6)	5 (38.5)	8 (61.5)	p=0.181	1 (1.5)	0 (0)	1 (100)	p=0.649	12 (20.7)	5 (41.7)	7 (58.3)	p=0.371
Irritability	77 (62.6)	19 (24.7)	58 (75.3)	p=0.710	37 (56.9)	7 (18.9)	30 (81.1)	p=0.622	40 (69)	12 (30)	28 (70)	p=0.8
Vomiting	47 (38.2)	15 (31.9)	32 (68.1)	p=0.087	16 (24.6)	2 (12.5)	14 (87.5)	p=0.587	31 (53.5)	13 (42)	18 (58)	p=0.5
Loss of appetite	43 (35)	11 (25.6)	32 (74.4)	p=0.701	15 (23.1)	2 (13.3)	13 (86.7)	p=0.672	28 (48.3)	9 (32.1)	19 (67.9)	p=0.86
Suprapubic Pain	7 (4.9)	3 (42.9)	4 (57.1)	p=0.354					7 (12.1)	3 (42.9)	4 (57.1)	p=0.471
Renal Angle Pain	1 (0.8)	0 (0)	1 (100)	p=0.577					1 (1.7)	0 (0)	1 (100)	p=0.499
Comorbidities (n/%)												
Malnutrition (SAM)	29 (23.6)	5 (17.2)	24 (82.8)	p=0.323	16 (24.6)	2 (12.5)	14 (87.5)	p=0.195	13 (22.4)	3 (23.1)	10 (76.9)	p=0.877
LRTI	25 (20.3)	2 (8)	23 (92)	p=0.04	16 (24.6)	2 (12.5)	14 (87.5)	p=0.587	9 (15.5)	0 (0)	9 (100)	p=0.029
Gastroenteritis	46 (37.4)	13 (28.3)	33 (71.7)	p=0.344	20 (30.1)	6 (30)	14 (70)	p=0.061	26 (44.8)	7 (26.9)	19 (73.1)	p=0.542
Suspected Bacteraemia	45 (36.6)	10 (22.2)	35 (77.8)	p=0.788	39 (60)	8 (20.5)	31 (79.5)	p=0.344	6 (10.3)	2 (33.3)	4 (66.7)	p=0.898
Other	19 (15.5)	4 (21.1)	15 (78.9)	p=0.778	6 (9.2)	1 (16.7)	5 (83.3)	p=0.986	13 (22.4)	3 (23.1)	10 (76.9)	p=0.481
Antibiotic Exposure (n/%)												
In Previous Year	33 (26.8)	11 (33.3)	22 (66.7)	p=0.123	8 (12.3)	2 (25)	6 (75)	p=0.515	25 (43.1)	9 (36)	16 (64)	p=0.477
IMCI Antibiotics	42 (34.1)	6 (14.3)	36 (85.7)	p=0.08	19 (29.2)	1 (5.3)	18 (94.7)	p=0.107	23 (39.7)	5 (21.7)	18 (78.3)	p=0.215
Antibiotic before sample	28 (22.8)	4 (14.3)	24 (85.7)	p=0.188	16 (24.6)	1 (6.3)	15 (93.7)		12 (20.7)	3 (25)	9 (75)	p=0.612

SAM: severe acute malnutrition

LRTI: Lower Respiratory Tract Infection

Other co-morbidities include post-infectious glomerulonephritis (n=1), seizures (n=7), pelviureteric junction obstruction (n=1), VACTERL association (n=1), constipation (n=1), renal failure (n=1), distended abdomen (n=1), patent ductus arteriosus with cardiac failure (n=1), cardiomyopathy (n=1), not documented (n=4)

IMCI: integrated management of childhood illness

Table 3: Investigations and the Correlation with Culture Positive UTI

	Total (n=123)				< 3 months old (n=65)				> 3 months old (n=58)			
	Total (n=123)	UTI (n=29)	No UTI (n=94)	p	Total (n=65)	UTI (n=11)	No UTI (n=54)	p	Total (n=58)	UTI (n=18)	No UTI (n=40)	p
	Urine Dipstick (N=99)				Urine Dipstick (N=46)				Urine Dipstick (N=53)			
Dip: NAD (%)	24 (24.2)	5 (20.8)	19 (79.2)	p=0.567	17 (37)	3 (17.7)	14 (82.4)	p=0,634	7 (13.2)	2 (28.6)	5 (71.4)	p=0,831
Dip: Leukocytes (%)	36 (36.4)	14 (38.9)	22 (61.1)	p=0.018	16 (34.8)	4 (25)	12 (75)	p=0,32	20 (37.7)	10 (50)	10 (50)	p=0,03
Dip: Nitrates (%)	9 (9.1)	5 (55.6)	4 (44.4)	p=0.043	0 (0)	0 (0)	0 (0)		9 (17)	5 (55.6)	4 (44.4)	p=0,126
Dip: Other (%)	56 (56.6)	12 (21.4)	44 (78.6)	p=0.608	19 (29.2)	2 (10.5)	17 (89.5)	p=0,377	37 (63.8)	10 (27)	27 (73)	p=0,381
Blood Culture (n/%)												
Test Not Done	22 (17.9)	6 (27.3)	16 (72.7)		4 (6.2)	0 (0)	4 (100)		18 (31)	6 (33.3)	12 (66.7)	
Positive	8 (6.5)	2 (25)	6 (75)		1 (1.5)	0 (0)	1 (100)		7 (12.1)	2 (28.6)	5 (71.4)	
Negative	91 (74)	20 (22)	71 (78)	p=0.623	58 (89.2)	10 (17.2)	48 (82.8)	p=0,461	33 (56.9)	10 (30.3)	23 (69.7)	p=0,964
Contaminant	2 (1.6)	1 (50)	1 (50)		2 (3.1)	1 (50)	1 (50)		0 (0)	0 (0)	0 (0)	
KUBUS (n=123/%)												
Normal	25 (20.3)	17 (68)	8 (32)	p=0.0	12 (18.5)	7 (58.3)	5 (41.7)	p=0.0	13 (22.4)	10 (76.9)	3 (23.1)	p=0.0
Abnormal	7 (5.7)	1 (14,3)	6 (85,7)		2 (3.1)	0 (0)	2 (100)		5 (8.6)	1 (20)	4 (80)	
Not Applicable	74 (60.2)	0 (0)	74 (100)		45 (69.2)	0 (0)	45 (100)		29 (50)	0 (0)	29 (100)	
Not Done	17 (13.8)	11 (64,7)	6 (35,3)		6 (9.2)	4 (66.7)	2 (33.3)		11 (19)	7 (63.6)	4 (36.4)	
Lost to Follow up (n/%)												
Yes	18 (14.6)	11 (61,1)	7 (38,9)	p=0.0	6 (9.2)	4 (66.7)	2 (33.3)	p=0.01	12 (20.7)	7 (58.3)	5 (41.7)	p=0.067
No	5 (4.1)	1 (20)	4 (80)		2 (3.1)	0 (0)	2 (100)		3 (5.2)	1 (33.3)	2 (66.7)	
Not Applicable	100 (81.3)	17 (17)	83 (83)		57 (87.7)	7 (12.3)	50 (87.7)		43 (74.1)	10 (23.3)	33 (76.7)	

Dip: [Urine] dipstick

NAD: No Abnormality Detected

KUB: Kidney, Ureter and Bladder Ultrasound

Discussion

Paediatric UTI is an important diagnosis to be considered in the febrile patient presenting to the accident and emergency unit. The current paediatric emergency room protocols dictate that patients younger than 3 months old, patients with suspected bacteraemia or those with pyrexia of unknown origin have urine dipsticks +/- formal laboratory based urine analysis when screening patients for potential sites of sepsis. Urine dipsticks +/- microscopy is done at the discretion of the attending clinician in patients above 3 months of age. In this study, 29 (23.6%) patients had culture confirmed UTI. A study done in Ghana on 1393 children <5 years old who had screening urine dipsticks positive for leukocyte esterase and/or urinary nitrates had a 8% positive urine culture with an identified uropathogen (12). This disparity in culture positive rates requires further study and revision of current urine screening protocols at the study site.

The organism profile found in this study is in line with international studies and shows that *K. pneumoniae* is emerging as a significant community acquired pathogen (13,14). This finding is also supported by data presented in the retrospective study (chapter 2) performed by the author. Furthermore, community acquired ESBL infection and drug resistance mirrors international trends (15,16) in this study. Factors predisposing to ESBL infection are recent hospitalization, previous UTI, urinary tract anomalies and antimicrobial prophylaxis (14,15,17,18). This should be considered in guiding appropriate antibiotic choice in patients with suspected UTI. Viral pathogens (adeno-, cytomegalo- and BK virus) have been implicated in causing urinary tract infection in immunocompromised patients (19). A prospective study conducted in Poland followed 102 children undergoing bone marrow transplantation; 25.5% developed haemorrhagic cystitis with BK virus being detected in 80.8% of those samples (20). The present study did not evaluate viral UTI.

Patients who were HIV exposed were more likely to develop UTI however these patients are over represented in the South African setting. Leukocyte esterase and nitrates on urine dipsticks correlated with confirmed UTI. Patients with severe acute malnutrition (weight for height/length <3SD) and having a lower respiratory tract infection (OR=0.23) were less likely to develop a concurrent UTI. However, only 18 (14.6%) of patients had severe acute malnutrition as per WHO definitions. Patients with UTI were more likely to have a normal renal ultrasound.

Paediatric UTI is difficult to diagnose thus making rapid reagent urinary dipsticks an effective tool to assist the clinician. Zorc *et al* conducted a meta-analysis of various diagnostic modalities. Leukocyte esterase has a sensitivity of 83% and specificity of 84%. Nitrates are

not very sensitive (50%) but highly specific 98% (5), supported by the data is in this study. Fitzgerald et al conducted a study at a children's hospital in Dublin using point of care urine microscopy as an adjunct in the diagnosis of UTI. The study team showed a 0.64 correlation between emergency unit and laboratory based diagnosis of UTI (21). This might be a viable option to assist in rapid diagnosis of UTI and earlier initiation of appropriate therapy.

There was no statistically significant correlation between UTI and concurrent bacteraemia. However, it should be noted that 2 (1.6%) patients had a parallel bacteraemia. Megged et al reported that male gender, age <3 months, higher creatinine and underlying urological abnormalities risk factors for UTI with bacteraemia (22).

Asharam conducted a retrospective study on children with HIV infection and UTI co-infection and evaluated clinical presentation, duration of hospitalization, aetiology, antimicrobial susceptibility and renal function. HIV disease had no significant impact on the presentation of UTI (23). Our study showed that HIV exposure was statistically significant for developing culture proven UTI ($p=0,044$) but HIV infection did not affect concurrent UTI; 8 (2.4%) patients had HIV disease. As of 2015, it is estimated that 7 millions South Africans are living with HIV and that adults aged 15-49 have HIV prevalence rates of 19.2% (18.4-20%) (24). Therefore, patients whom are HIV exposed may be over represented in the South African context. Further sub-analysis of patients with HIV was not performed in this study.

Jeena et al conducted a study in Durban, Kwazulu Natal in 1994 and found that patients with acute gastroenteritis, acute respiratory tract infections and protein energy malnutrition had UTI co-infection rates of 20-50%, 11-22% and 23-44% respectively (25). Fifty-four patients with confirmed UTI were retrospectively studied and concurrent illness was described. However, no statistical analysis was performed. Similar rates of infection were found amongst malnourished children in Turkey as 30% of the children had concurrent UTI (26). Kala et al found similar results with UTI being diagnosed in 34.7% of patients admitted with protein energy malnourishment (27). This is contrasted against the data found in the present study demonstrating that UTI was less likely for severe acute malnutrition (previously termed protein energy malnutrition) and lower respiratory tract infections.

Shaikh et al conducted a study at the Children's Hospital of Pittsburgh, Pennsylvania USA and showed that children with *Enterococcus* species, *Klebsiella* species and *Pseudomonas aeruginosa* with significantly less likely to display pyuria than children with *E. coli* (OR of 0.14, 0.34 and 0.19 respectively). This should be noted in cases where clinical suspicion of UTI is high so that early commencement of antibiotics is not delayed (28).

In this study, patients with UTI were statistically more likely to be lost to follow up ($p=0.0$) despite having received dates for outpatient department clinics and ultrasound imaging. The reasons for this are multifactorial: delay in accessing NHLS urine microscopy results, a busy emergency unit and patient financial reasons (e.g. not having transport to attend follow up appointments or no contact details so that follow up can be arranged) and likely reflect larger social challenges in South Africa presently.

Limitations to this study were that the method of sample collection was a convenience sample. Therefore, inherently, patients with urine samples sent to the NHLS were potentially missed and not enrolled. Additionally, patients younger than 3 months old are systemically screened for potential sources of sepsis and through inclusion bias skew the results towards this age demographic. It is also noted that there may not be a clinical suspicion of UTI but attending clinicians opt to rule out UTI when managing younger patients. A large proportion of urine samples (34/27.6%) had mixed growth. These urine samples were not repeated and, therefore, potential true UTI were missed. Factors predisposing to mixed growth/contaminated urine cultures are patients < 6months old and uncircumcised male infants (29). In our setting these samples should be repeated if the urine dipsticks screen was abnormal.

Conclusion

We found that 23.6% of the patients had a culture confirmed UTI. Patients with severe acute malnutrition and acute respiratory tract infections were less likely to develop UTI. HIV exposure (this group is likely to over represented in the South African setting because of our high HIV prevalence rates) and urine dipsticks were statistically significant for correlating with culture confirmed UTI. These factors can be used to guide attending health professionals in whom to screen and initiate empiric antibiotic therapy for UTI.

Considering that 27.6% samples yielded a mixed growth on urine culture, further research is need to better understand these factors and their respective impact on developing UTI. Risk factors for antibiotic resistance in UTI also needs further exploration.

Funding and Conflict of Interest

No external funding was provided for this study. The authors declare no conflict of interests.

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Chapter 4: Conclusion – a Unifying Discussion

UTI is a commonly encountered problem in the paediatric patient presenting with fever. There is presently a paucity of South African data on paediatric urinary tract infections. In order to provide local insights into UTI, two studies were conducted with the aim of providing contextual data compared to international trends. The following issues were examined:

- 1) The uropathogens found in urine cultures (viral pathogens were not assessed) in a retrospective cohort of urine cultures and in a prospective cohort of children presenting to the emergency room at Tygerberg Hospital.
- 2) The associated antibiogram profile of significant bacterial urine cultures in community, hospital associated and hospital acquired infections.
- 3) The factors associated with culture positive UTI in children where clinicians sent urine cultures as part of the management protocol for febrile infants and in those whom UTI was suspected.

The organism profile is shifting away from *E. coli* supremacy with *K. Pneumoniae* being another important uropathogen causing UTI; accounting for 50.7% and 22.7% of infections respectively. Furthermore, in keeping with international data trends, *E. coli* exhibited resistance rates to amoxicillin, co-amoxiclavulanic acid and TMP/SMX of 90.8%, 38% and 71.8% respectively. This relevant as these drugs are used in primary care facilities for the empiric treatment of community UTI. *K. pneumoniae* represented 72% of ESBL producers; 25.3% of these infections were derived from the community setting. The current hospital antibiotic guideline for hospital acquired infection is the use of piperacillin-tazobactam and amikacin. The evolution of the organism profile is not unexpected and the role of *Klebsiella* ESBL infection in hospital acquired infection is becoming the norm rather than the exception. Current international studies have shown that recent hospitalization (in the last 6 months), underlying urinary tract structural anomalies and antibiotic exposure are significant risk factors for acquiring inherently resistant urine microbials.

A notable finding is the high rate of contaminated urine cultures in both studies. This clearly illustrates the issues around the importance of sterile urine sample collection. Mixed cultures lead to the added laboratory costs and inherent morbidity in those patients in whom true cases of UTI is missed. Catheter specimens are time consuming and invasive. Presently, studies are evaluating the quality of perineal bag specimens and alternative techniques for urine collection.

A major strength of the retrospective cohort was the inclusion of children with hospital associated and hospital acquired infection, in contrast to the prospective cohort that assessed only community acquired infection. Assessment of the antibiotic profile of the organism population allowed us to test current empiric antibiotic management protocols against local and international data.

In the prospective cohort of children, 23% of urine cultures sent to the laboratory culture a confirmed pathogen. This may suggest strong screening protocols and appropriate request for UTI in suspected cases. Furthermore, one must consider that empiric antibiotic administration at referral clinics and in the emergency unit may reduce the yield of positive cultures. The rates of positive culture in our context is substantially higher than international data and suggests that we are not be screening enough patients. Leukocyte esterase and nitrates on urine dipstick have high sensitivity and specificity for positive urine culture. However, physicians may still need to send urine samples to the laboratory for microscopy in cases where clinical suspicion of UTI is high and urine dipstick is normal.

It was also shown that male patients <3months old, HIV exposure and urine [dipstick] leukocyte esterase and nitrates were associated with positive urine cultures. It should be noted that patients who are HIV exposed are over represented in South Africa. Patients presenting with LRTI as their primary diagnosis were less likely to have concurrent UTI. The results from the retrospective study show statistically significant data on the impact of HIV positive status on acquiring UTI and resistant organisms. This will need further research examining the true role that HIV infection plays.

The data found in this dissertation shows that the organism and resistance profile mirrors that of international studies. This data can be used to guide clinicians as to patients presenting with UTI, antibiotic choices when empirically treating UTI and potential risk factors for resistant organisms. Current literature suggests that prior antibiotic exposure has significant impact on [negatively] selecting for resistant uropathogens. Patients who have risk factors for resistant organism should be considered for empiric therapy with piptazobatem and amikacin. Therefore, clinicians must exercise for caution in antibiotic prescription practices to not exacerbate this evolving problem.

Due to the paucity of South African data on paediatric UTI, further research is required to further explore risk factors for UTI and the development of resistance in our clinical context. The focus should be on the influence of HIV, co-morbid conditions and antibiotic exposure on UTI. In the interim, yearly audits of urine cultures and the respective antibiogram, sent to the

laboratory, can be performed so clinicians can be aware of changing microbial and resistance profiles.

Appendix A:

Informed Individual Consent form (study “Factors Impacting Positive Bacterial and Fungal Urinary Tract Infections in patients (0-5 years) Attending a Paediatric Emergency ward in a Tertiary Care Hospital in the Western Cape, South Africa”)



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PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM

TITLE OF THE RESEARCH PROJECT:

Paediatric Bacterial Urinary Tract Infections in Children

REFERENCE NUMBER:

PRINCIPAL INVESTIGATOR: Dr. S Irusen

ADDRESS: Department Paediatrics
Tygerberg Hospital
Francie van Zijl Drive
Parow
7505

CONTACT NUMBER: Copyright

Dear Parent

You and your child are being invited to take part in a research project. Please take some time to read the information which will explain the details of this project. Please ask questions about any part of this project that you do not fully understand. It is very important that you are satisfied that you clearly understand what this research is about and how you could be involved. Your participation is **entirely voluntary** and you are free to refuse. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part at this stage.

This study has been approved by the **Health Research Ethics Committee at Stellenbosch University** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

Why are we asking you to participate?

You and your child have been invited to participate in this study, because your child had his/her urine sent to the hospitals laboratory to see if there is infection in the bladder or kidneys. All

children, in G-ground, Tygerberg Hospital, that have urine sent for testing will be invited to take part in this study.

What is this research study all about?

We know that bladder and kidney infections are common in young girls and boys. The only way we can be sure that a child has such an infection is by sending the urine to the laboratory. Even then it can be difficult to be sure that the diagnosis was made properly. We want to see when doctors suspect bladder and kidney infections in children and why they send urine. We also want to see what things influence a positive urine result.

What will your responsibilities be?

You and your child will not be expected to perform any tasks or undergo any additional procedures as part of this study. You will be asked a few questions and your blood and urine results and ultrasound images will be looked at.

Will you benefit from taking part in this research?

There is no direct benefit to you for taking part in this study, but the information from this study will help us plan how to take care of children with kidney and bladder infections in the future.

Are there any risks involved in your taking part in this research?

There are no direct risks involved in participating in this study. There will be no additional medical procedures or treatment given. Taking part or not taking part will not affect the medical treatment of your child. Tests are part of normal care and are routinely done whether you take part in the study or not. All information gathered will be kept confidential and anonymous.

If you do not agree to take part, what alternatives do you have?

You are not forced to participate in this study. If you refuse there will be no change in how you are cared for here at the hospital.

Who will have access to your medical records?

The investigators that will have access to your child's medical records and Road-to-Health Booklet are all doctors employed at Tygerberg Hospital in the Department of Paediatrics. They include **Copyright**. All the information we collect will be treated as confidential. No names or hospital numbers will be placed on the information sheet used for collection. The **Health Research Ethics Committee** may inspect the records to ensure that the research is being done correctly and does not harm you.

Will you be paid to take part in this study and are there any costs involved?

No, you will not be paid to take part in the study. Participation in the study is free of charge.

- You can contact **Copyright** if you have any further queries or encounter any problems.
- You can contact the **Health Research Ethics Committee at Copyright** if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- You will receive a copy of this information and consent form for your own records.

Declaration by participant

By signing below, I agree to take part in a research study entitled *Paediatric bacterial urinary tract infections in the South African context*.

I declare that:

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been properly answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.

Signed at (*place*) on (*date*)

.....
Signature of participant

.....
Signature of witness

Declaration by investigator

I (*name*)Dr. S. Irušen..... declare that:

- I explained the information in this document to
- I encouraged her to ask questions and took adequate time to answer them.
- I am satisfied that she adequately understands all aspects of the research, as discussed above
- I did/did not use an interpreter. (*If an interpreter is used then the interpreter must sign the declaration below.*)

Signed at (*place*) on (*date*)

.....
Signature of investigator

.....
Signature of witness

Declaration by Interpreter

I (*name*) declare that:

- I assisted the investigator (*name*) to explain the information in this document to (*name of participant*) using the language medium of Afrikaans/Xhosa.
- We encouraged her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all her questions satisfactorily answered.

Signed at (*place*) on (*date*)

.....
Signature of interpreter

.....
Signature of witness

Appendix B**Data Collection Sheet (study “Factors Impacting Positive Bacterial and Fungal Urinary Tract Infections in patients (0-5 years) Attending a Paediatric Emergency ward in a Tertiary Care Hospital in the Western Cape, South Africa”)****RESEARCH QUESTION 2: Paediatric UTI in children 0-5years: Data Collection sheet**STUDY
NO.**Parental consent obtained:** _____**Demographic Data**

1. Date of Birth/Age: _____
2. Sex: Male Female
3. Weight and height: _____
4. Reason urine sample obtained: _____

Symptoms:

- Fever (specify): _____
- Dysuria
- Frequency
- Irritability
- Vomiting
- Diarrhoea
- Loss of Appetite

Signs:

- Suprapubic pain
- Flank pain
- Renal angle tenderness
- oedema

Comorbid Medical condition:

5. Please specify:
 - Protein Energy Malnutrition
 - Lower Respiratory Tract infection
 - Tuberculosis
 - Acute Gastro-enteritis
 - Meningitis
 - Sepsis (unspecified)
 - Other
6. HIV exposed: Yes/No
7. HIV status:
 - HIV test not done
 - HIV positive
 - i. Viral load _____
 - ii. CD4 count _____
 - iii. ARV's Yes/No
 - HIV negative

Medical History:

8. Previous UTI (when): Yes/No _____
9. ANY antibiotic exposure in previous year: Yes/No
10. If yes, type and duration of antibiotic:
 - Penicillin _____
 - Cephalosporin _____
 - Aminoglycoside _____
 - Carbapenem _____
 - Other _____
11. IMCI antibiotics: Yes/No
12. ON antibiotics before/during urine sample taken: Yes/No
13. If yes, type and duration of antibiotic:
 - Penicillin _____
 - Cephalosporin _____
 - Aminoglycoside _____
 - Carbapenem _____
 - Other _____

Investigations:

14. Urine dipsticks result:
 - Normal
 - Protein
 - Blood
 - Nitrites
 - Leukocytes
 - Glucose
 - Ketones
15. Urine Sampling method:
 - Mid-stream urine sample
 - Suprapubic aspiration
 - Sterile in-out urine catheter
16. FBC: **WCC** _____ **Hb** _____ **Plt** _____
17. Chemistry: **Urea** _____ **Creat** _____ **PCT** _____ **CRP** _____
18. Microbiology:
 - Leukocytes: _____
 - Erythrocytes: _____
 - Other: _____
 - Organism: _____
 - Antibiotic Profile: _____
19. Imaging:
 - Renal ultrasound: _____
 - Other (e.g DMSA): _____
20. Did patients follow up for renal appointments/imaging or lost to follow up?

21. If No, was G ground staff alerted: Yes/No