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URINARY TRACT INFECTION IN CHILDREN WITH CONGENITAL ANOMALIES OF THE KIDNEY AND URINARY TRACT ATTENDING THE DIVISION OF PAEDIATRIC NEPHROLOGY AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL, SOUTH AFRICA

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Dissertation submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Master of Science in Medicine

Johannesburg, 2016

Declaration

I, Nneka Chioma Okoronkwo, declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in the branch of 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.

Signature of candidate: _____

November 7th, 2016

Dedication

This work is dedicated to my God who made my journey to Paediatric Nephrology possible against all odds.

Abstract

Background:

Both CAKUT and UTI can independently cause renal insufficiency with ultimate progression to ESRD, and CAKUT is a well-documented risk factor for UTI in children.

Aim:

To describe CAKUT in a cohort of children, between 2 weeks and 18 years of age, and to document the patterns of UTI in this group.

Method:

A retrospective medical record review was performed on all patients with documented CAKUT managed between January 2005 and December 2014.

Results:

The prevalence of CAKUT was 20% and the male: female ratio was 4.4:1. The median age at presentation was 8.4 months and the median duration of follow up was 39 months. At presentation 57% were under the age of one year and 21% were above the age of 5 years. PUV was the commonest type of CAKUT and a very low rate of VUR was noted.

The incidence of UTI was 41.8% and the odds of getting a UTI were significantly increased among children with bladder anomalies, PUV and collecting system anomalies. *Escherichia coli* and *Klebsiella pneumonia* were the commonest bacteria isolated and, although more than 90% of both *E. coli* and *Klebsiella pneumoniae* were sensitive to amikacin, meropenem, imipenem and

ertapenem, more than 40% were resistant to commonly used oral antibiotics such as amoxicillin/clavulanate and trimethoprim-sulphamethoxazole.

Prophylactic antibiotic use was highest among patients with PUV (35%) and, overall, patients who were not on a prophylactic antibiotic were five times more likely to have a UTI. The association between antibiotic prophylaxis and the development of antibiotic resistance could not be explored but there was a statistically significant association between the type of bacteria isolated and the use of antibiotic prophylaxis.

Conclusion:

Delayed presentation, the high rate of UTI and the high rate of antibiotic resistance to many first line oral antibiotics are all of concern. The study highlights the effectiveness of antibiotic prophylaxis in this group. Future research topics include determining the long term outcome, and the long term effects of antibiotic prophylaxis on renal function, in our cohort.

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My parents and siblings, who are a family worth having.

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NOMENCLATURE

CAKUT	Congenital Anomalies of the Kidney and the Urinary Tract
CDW	Corporate Data Warehouse
CFU	Colony forming unit
CKD	Chronic kidney disease
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
DK	Duplex kidney
eGFR	Estimated glomerular filtration rate (bedside Schwartz formula)
ESRD	End stage renal disease
HIV	Human Immunodeficiency Virus
IVU	Intravenous urography
MCDK	Multicystic Dysplastic Kidney
NHLS	National Health Laboratory Services
PBS	Prune Belly Syndrome
PUV	Posterior urethral valves
PUJ	Pelviureteric junction obstruction
SLE	Systemic Lupus Erythematosus
SK	Single kidney
TMP/SMX	Trimethoprim-sulphamethoxazole
Tc99-MAG3	Technetium 99 Mercaptoacetyltriglycine
UTI	Urinary tract infection
VUR	Vesicoureteral reflux
VUJ	Vesicoureteric junction obstruction
VCUG	Voiding cystourethrogram

1. Introduction

Urinary tract infection (UTI) is defined as the presence of micro-organisms in the urinary tract, with clinical signs and symptoms.[1] Boys are more affected than girls in infancy, with a tenfold increased risk for uncircumcised compared to circumcised boys.[1] However, after the first year of life and all through childhood, UTI affects 1-2% of boys and 5-8% of girls.[1, 2] UTI is uncommon in the first two weeks of life, with an incidence of only 2% even in neonates who are bacteraemic.[3] Any pathogenic micro-organism can cause UTI, but bacteria are the aetiology in more than 90% of cases. Gram negative bacteria are the leading cause of UTI in children, with *Escherichia coli* (*E. coli*) alone accounting for 75-90% of childhood UTIs worldwide.[1-5] Other common causative organisms include *Pseudomonas aeruginosa, Klebsiella pneumoniae, Proteus mirabilis, Streptococcus agalactiae (Group B Streptococcus), Streptococcus viridans, Enterobacter species and Staphylococcus aureus* amongst others.[1-5]

1.1 The clinical features of UTI

The anatomical location of the UTI, the age of the child and the severity of the infection all determine the symptoms and signs of the illness.

Lower tract UTI refers to bladder infection (cystitis), while upper tract UTI includes pyelonephritis and perinephric or renal abscess.

Neonates can present with fever, hypothermia, apnoeic spells, poor perfusion, abdominal distension, diarrhoea, vomiting, lethargy, irritability, and convulsions. Other common signs in this age group are poor weight gain, palpable kidneys, jaundice, acidosis and electrolyte imbalance.[5, 6]

Older infants may present with difficulties in feeding, failure to thrive, diarrhoea, fever, malodorous urine, weak urinary stream, dribbling, pallor, irritability, lethargy and suprapubic and abdominal tenderness. [5, 6]

Older children are more likely to present with frequency, dysuria, enuresis, hesitancy, malaise, fever, flank pain, nausea and vomiting.[5, 6]

1.2 The diagnosis of UTI

Culture of bacteria from a correctly collected urine specimen is the gold standard for the diagnosis of UTI.[1-3, 6] Suitable specimens for urine culture may be collected by "clean catch" mid-stream urine (MSU), urethral catheter or via suprapubic aspiration.[1-3]

UTI is clinically defined as the presence of significant bacteriuria with symptoms of illness. Significant bacteriuria is defined as the culture of one properly obtained, clean-voided, midstream urine specimen growing greater than 100,000 colony forming units (CFU) per milliliter (ml) of a single uropathogenic organism, a catheterized specimen growing greater than 10,000 CFU per ml of a single uropathogenic organism; or a specimen obtained by suprapubic tap growing greater than 1,000 CFU per ml of a single uropathogenic organism.[6-9]

1.3 The complications of UTI

UTI is often associated with significant morbidity, with some cases progressing to renal scarring, hypertension and renal insufficiency.[4, 5] UTI may even result in complications such as septicaemia and death.[4, 5] A 27 year follow-up study from Sweden showed that focal renal scarring due to pyelonephritis in a child carried a 23% risk for hypertension and a 10% risk for end stage renal disease.[10]

1.4 The management of UTI

As soon as a clinical diagnosis of UTI is made, a correctly collected urine specimen should be timeously sent to a laboratory for microscopy, culture and sensitivity testing.[6] Thereafter, empirical antibiotic treatment is started and the antibiotic choice reviewed after the culture and sensitivity results are available.[2, 6] The choice of empiric antibiotic should be based on local antimicrobial sensitivity patterns.[1, 2, 5] The prompt and adequate treatment of an episode of UTI is crucial in order to prevent complications and long term sequelae.[1, 5]

The duration and route of antibiotic therapy depends on the clinical severity of the infection, the age of the child, the location of the infection and the presence of underlying structural abnormalities.[1-5]

Neonates with UTI should be treated with parenteral antibiotics for 7-10 days, and a combination of ampicillin or cephalosporin, along with aminoglycosides, is usually used.[2, 5] Infants and older children with acute pyelonephritis require initial intravenous antibiotics and a combination of aminoglycosides and ampicillin (or a cephalosporin) can also be used.[5, 6, 11]

Children with symptomatic lower urinary tract infections are treated with oral antibiotics for seven days. [5-7]

Asymptomatic bacteriuria is only treated if the child is younger than five years, has a structural urinary tract abnormality, or if symptomatic UTI develops.[5]

A urine culture should be done 3-7 days after the completion of therapy to exclude a relapse.[1-5]

It is standard practice to screen for congenital anomalies of the kidney and the urinary tract **(**CAKUT) in certain groups of children with UTI. These include children with a delayed or

unsatisfactory response to treatment of the first febrile UTI, the presence of an abdominal mass or abnormal voiding pattern, and the presence of causative organisms other than *Escherichia coli*. [1, 2, 5]

Clinical follow-up is important for children with recurrent UTI, CAKUT or renal scarring. Urine should be screened for UTI at subsequent episodes of febrile illness following the first febrile UTI in a young child.[6]

1.5 Congenital Anomalies of the Kidney and the Urinary Tract (CAKUT)

CAKUT comprises a wide range of renal system structural and functional malformations that may occur at the level of the kidney (e.g. hypoplasia and dysplasia), collecting system (e.g. hydronephrosis and megaureter), bladder (e.g. ureterocoele, vesicoureteral reflux and vesicoureteral junction obstruction) or urethra (e.g. posterior urethral valves).[12]

CAKUT results from faulty development of the renal system which may occur in isolation, confined to the kidney and urinary tract, or may manifest as part of a syndrome with additional congenital malformations found outside the kidney and urinary tract.[12] CAKUT constitutes about 20 to 30% of all anomalies identified in the pre-natal period, and its prevalence among the general paediatric population ranges between 3.5-43%.[13-17]

1.6 The diagnosis of CAKUT

With improved prenatal screening many cases of CAKUT are diagnosed by antenatal ultrasonography performed at 18-20 weeks of gestation.[18, 19] The most common antenatal manifestations of CAKUT include variations in gross morphology of the kidney, ureter or bladder with, or without, oligohydramnios. Postnatal manifestations can be the presence of a

palpable abdominal mass or a single umbilical artery, feeding difficulties, decreased urinary output, deficient abdominal wall musculature and undescended testes in a male infant, or multi organ birth defects.[18] Ultrasonography, contrast radiography (e.g. VCUG and IVU), cystoscopy and Tc99- MAG3 scanning are all used in the post natal investigation of antenatally detected renal tract abnormalities or CAKUT.[2]

Urinary tract infection in children is well recognized as a marker for CAKUT in the postnatal period, and most children with CAKUT which is not detected antenatally are only referred for investigation after a diagnosis of UTI is made.[16] Other possible reasons for referral, especially in those without urinary tract symptoms, are detection of CAKUT as an incidental finding during a routine examination or while the child is undergoing investigation for an unrelated complaint. For this reason, the diagnosis of CAKUT is often missed in otherwise seemingly healthy children who come from areas where routine, high standard, antenatal screening policies are not in place. Unfortunately, such patients are at risk for presenting later with chronic kidney disease.[20]

1.7 The association of CAKUT and UTI

Congenital anomalies of the kidney and urinary tract (CAKUT) are a well-documented risk factor for the development of UTI in children.[1-5] CAKUT is thought to alter the natural free unidirectional flow of urine causing stasis and thereby enhancing the growth of pathogenic micro-organisms.[16, 19]

The incidence of CAKUT among patients with UTI ranges from 25-55%.[16] Ring and Zobel found CAKUT in 42% of infants with UTI, with obstructive uropathy and vesicoureteral reflux (VUR) accounting for 37% and 59% of all the anomalies respectively.[21] Also, in that study 61% of infants with CAKUT had UTI.[21]

In addition to predisposing patients to UTI, some forms of CAKUT may also predispose to renal scarring, calculus formation, hypertension and renal failure, even in the absence of recurrent UTI.[11, 12, 20, 22] CAKUT is responsible for 34-59% of CKD and 30-50% of cases of end-stage renal disease (ESRD) in children.[13-15]

1.8 The management of UTI in children with CAKUT

The importance of prompt treatment of acute episodes of UTI in this cohort of patients cannot be over-emphasized.[23] As mentioned previously, hospital admission and parenteral antibiotics may be required in certain circumstances such as cases of severe illness and suspected pyelonephritis.[2, 5]

Prevention of UTI in this group of patients is advocated due to their increased risk of renal scarring, hypertension and end stage kidney failure. [2, 24-26]

In addition to enhancing personal hygiene and prevention of constipation, some clinicians place a selected group of CAKUT patients onto continuous antibiotic prophylaxis. Indications for continuous antibiotic prophylaxis include children less than 5 years with VUR, or other structural anomalies, and those who have had three documented UTIs in one year.[2, 5, 24, 25]

The use of antimicrobial prophylaxis in patients with CAKUT and recurrent UTI is still controversial. [26-29] Those opposing the use of prophylactic antibiotics voice the concern that this practice may breed resistant strains of pathogens, increase the risk of breakthrough infections, and encourage adverse drug reactions. They also argue that the effectiveness of antibiotic prophylaxis is questionable, and that many patients will need to be treated to benefit one child. Finally, they fear that any benefit from this practice may be interrupted by low adherence of patients to the prescribed medication.[26-29]

All the aforementioned concerns are due to the fact that previous studies on the use of prophylactic antibiotics were rife with contradictory results and divergent conclusions. However, some well controlled and randomized studies, including the PREVENT and RIVUR trials, have documented some benefits of antibiotic prophylaxis use in select groups of patients.[24, 28, 30, 31]

Although prophylactic antibiotics have been recommended for children with grades IV and V VUR and other significant urological anomalies, the current recommendation is to discourage prophylactic antibiotic use in children with recurrent UTI who do not have CAKUT. Rather, they should be treated promptly and adequately whenever they get UTI. [6, 29]

Both CAKUT and UTI can independently cause renal insufficiency with ultimate progression to ESRD.[4, 20, 26] A large body of literature exists on UTI in children, including documenting the presence of CAKUT among patients with UTI.[1-5, 16, 17, 21] Also, previous studies on CAKUT have dealt with its prevalence and pattern among general paediatric populations, antenatal diagnosis, reviews and outcomes, methods of diagnosis, and recently its genetic aetiology.[11-18, 20-22]

Finally, the author is not aware of any literature on CAKUT and its relationship to UTI in South Africa.

We hope that this study on UTI and CAKUT will be useful in helping us to develop new recommendations and management guidelines aimed at preventing, or reducing, the rate of progression to ESRD in this group of children. In addition, the knowledge gained will also be useful in guiding subsequent antibiotic prescribing protocols.

Finally, this review aims to expand the knowledge of these conditions, specifically with relation to our own unique South African paediatric population.

1.9 The aims and objectives of the study

1.9.1 Aim

The study aimed to describe CAKUT in a cohort of children who attended the Division of Paediatric Nephrology at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), and the study also aimed to document the patterns of UTI in this group of patients.

1.9.2 Objectives

(1) To determine the prevalence of CAKUT amongst children attending the renal clinic at CMJAH.

(2) To describe the different types of CAKUT seen in the study population.

(3) To determine the rate of UTI, the types of causative organisms and the antimicrobial sensitivity patterns seen in the study population.

(4) To determine the association between prophylactic antibiotic use and the rate of UTI in the study population.

(5) To determine the association between prophylactic antibiotic use and the causative organisms of UTI in the study population.

CHAPTER 2

2. Materials and methods

2.1 Ethics clearance

The study was conducted in full conformance with the principles of the Declaration of Helsinki, Good Clinical Practice and within the laws and regulations of South Africa. The interests of the patients were safeguarded and their anonymity guaranteed.

Permission was obtained from the Chief Executive Officer of CMJAH.

Ethical approval for this study was obtained from the Human Research Ethics Committee and the Postgraduate Committee of the University of Witwatersrand before commencement of the study. Ethics Clearance number: M150709 (Appendix A)

2.2 Study design and study population

The study was a retrospective review of the medical records of all patients between 2 weeks and 18 years of age with documented congenital anomalies of the kidney and urinary tract being managed by the Division of Paediatric Nephrology at CMJAH between January 2005 and December 2014.

The following groups of patients were excluded from the study:

1. Neonates less than 2 weeks of age.
2. Patients with confirmed retroviral infection.
3. Patients with Diabetes Mellitus.
4. Solid organ transplant recipients.

5. Non-transplant patients on immunosuppressive therapy (e.g. those with SLE, nephrotic syndrome and patients requiring plasma exchange)

2.3 Study procedure

The details of all patients cared for by the Division of Paediatric Nephrology at CMJAH are recorded in hard copy patient files which are kept in a secure filing room, located inside the division.

The total number of all the patients that attended the division between January 2005 and December 2014 was retrieved from the hospital statistical unit. Files of patients that met the selection criteria were retrieved, and information relevant to the study was extracted (see attached Data Capture Sheet, Appendix B).

2.3.1 Definition of terms

1. UTI

The presence of a UTI was defined as finding significant bacteriuria with symptoms and signs of infection in the patient as charted in the files.[6-9]

Significant bacteriuria was defined as:

A. The culture of one properly obtained, clean-voided, midstream urine specimen growing greater than 100,000 colony forming units (CFU) per milliliter (ml) of a single uropathogenic organism.[6-9]
B. The culture of one properly obtained catheterized urine specimen growing greater than 10,000 CFU per ml of a single uropathogenic organism.[6-9]

C. The culture of a urine specimen obtained by suprapubic tap growing greater than 1,000 CFU per ml of a single uropathogenic organism.[6-9]

2. Contaminated urine specimen

A contaminated urine specimen was defined as one manifesting any growth of two or more different organisms, or the growth of *Enterococcus faecalis* or *coagulase negative Staphylococcus.*[32,33]

3. Classification of CAKUT

CAKUT was classified into anomalies of the kidney, anomalies of the collecting system, anomalies of the bladder, and anomalies of the urethra as suggested by Song and Yosypiv.[12]

2.3.2. Microbiology of the UTIs

Details on the microbiology of the UTIs of the study population and their complete sensitivity patterns was obtained by submission of an application to the Corporate Data Warehouse (CDW) of the National Health Laboratory Service (NHLS) requesting extraction of data from the Laboratory Information System (LIS) at the CMJAH NHLS laboratory. The application requested data on the organism type and the susceptibility patterns of the UTIs diagnosed in the patients of our cohort (see attached NHLS Approval and Form, Appendix C).

2.3.3. Recording of patients' information

Each patient was allocated a study number. Patients' names and hospital numbers were not written on the data base. Information was recorded on the study proforma (Appendix B) by the primary investigator and then de identified and keyed into a data base using a study number.

2.4 Data analysis

After data collation and cleaning, analysis was done using the Stata 13 statistical package.[34] Data analysis was performed by the primary investigator and the results were re-checked by a statistician. Frequency tables and percentages were generated for all the major variables of interest. Continuous variables were described using median and interquartile range. Categorical variables were presented as percentages, pie and bar charts and comparisons between such variables were done using the Pearson Chi Square test and the Fisher's exact test where appropriate. Regression analysis was used to assess the relationship between the different CAKUT classes and UTI, and also to assess the relationship between antibiotic use and UTI. A confidence interval of 95% was used, and for all analyses a p-value < 0.05 was taken as statistically significant.

2.5 Limitations of the study

Being a retrospective case review, some data were incomplete.

The presence of co morbid conditions, which may have predisposed to UTI independent of the presence of CAKUT, such as chronic constipation, primary bladder dyssynergia, spina bifida and cerebral palsy were not taken into account.

Although the protocol of the Division of Paediatric Nephrology is that all children referred for an evaluation have an abdominal ultrasound performed, not all get a MAG 3 scan and so, it is possible that patients with minor grades of reflux may have been missed.

It is also possible that some children who attended our clinic may inadvertently not have had an abdominal ultrasound performed, and that some of the routine abdominal ultrasounds preformed during the study period may, due to technical error, have missed cases of CAKUT. These factors might affect the true prevalence of CAKUT in this study.

Finally, patients such as those with Down's syndrome and ano-rectal anomalies (managed by the paediatric surgical team), who may not have been referred to our clinic, were not traced and reviewed for this study due to logistical and time constraints. Exclusion of these children may also have affected the prevalence of CAKUT in this study.

3. Results

3.1 The general characteristics and prevalence of CAKUT

Over the study period 691 new patients were seen at the clinic and, of those, 138 were diagnosed with CAKUT. This gave a prevalence of 20% for CAKUT in children referred to the Division of Paediatric Nephrology of CMJAH over the study period.

Four records were excluded from analysis because they were lost to follow up after their diagnosis was made (they visited the clinic only once).

Of the remaining 134 patients there were 109 males and 25 females giving a male: female ratio of 4.4:1 (Table 3.1). The median age at presentation was 8.4 months (IQR 1.9 - 47.7) and the median duration of follow up was 39 months (IQR = 12.5-81.7).

Table 3.1 The age at presentation and sex distribution of the study population

Age (months)	**Males**		**Females**		**Total**	
	%	**N**	**%**	**N**	**%**	**N**
< 12	56.0	61	60.0	15	56.7	76
12-59	22.0	24	24.0	6	22.4	30
60-120	19.3	21	0.0	0	15.7	21
>120	2.8	3	16.0	4	5.2	7
Total	100.0	109	100.0	25	100.0	134

3.2 The types of CAKUT

The different types of CAKUT were classified into anomalies of the kidney, anomalies of the collecting system, anomalies of the bladder, and anomalies of the urethra. Figure 3.1 shows the distribution of the different classes of CAKUT among the study population. Anomalies of the urethra were the most common, while anomalies of the bladder were the least common anomaly seen.

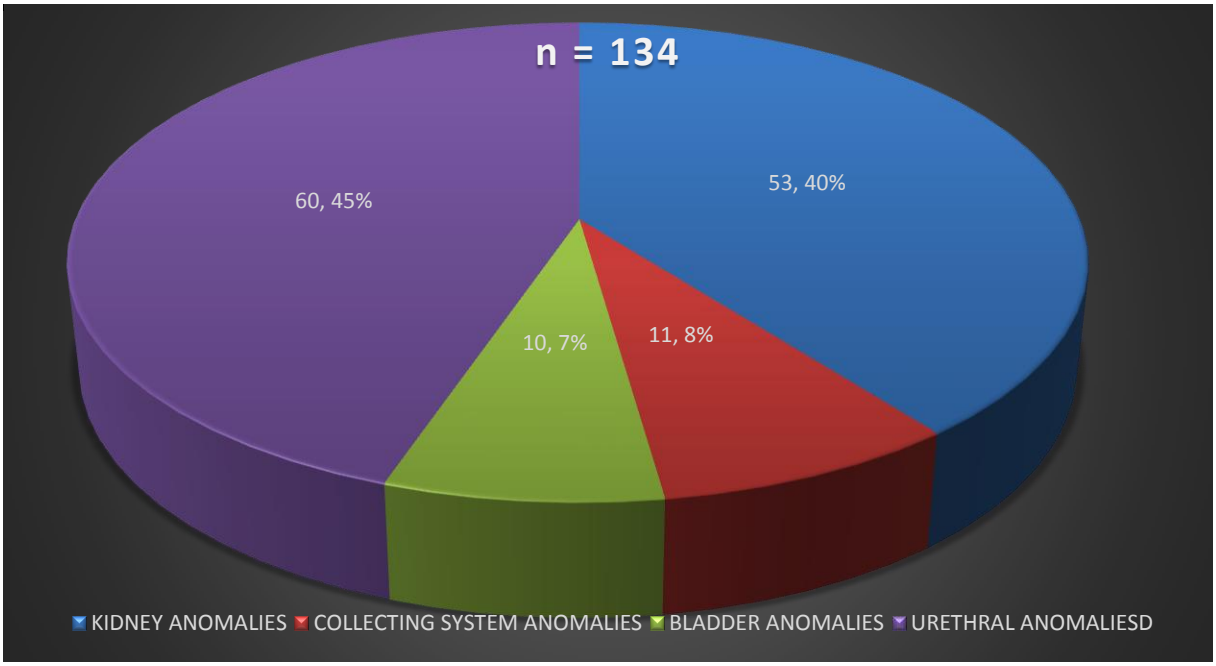

Figure 3.1 A pie chart showing the frequency of the different classes of CAKUT among the study population

3.2.1 The subgroups of CAKUT in each class.

A detailed breakdown of the different types of CAKUT found in the study population is shown in Table 3.2 below.

Table 3.2 A detailed breakdown of the different types of CAKUT

CAKUT CLASS	PERCENTAGE (%)	FREQUENCY
KIDNEY ANOMALIES		
Horse shoe kidney	**0.7**	1
Hypoplastic kidney	**5.2**	7
Duplex kidney	**6.0**	8
Single kidney	**13.4**	18
Multicystic Dysplastic kidney	**14.2**	19
COLLECTING SYSTEM ANOMALIES		
Pelviureteric junction obstruction	**7.5**	10
Vesicoureteric junction obstruction	**0.7**	1
BLADDER ANOMALIES		
Prune Belly Syndrome	**3.0**	4
Vesicoureteric reflux	**4.5**	6
URETHRAL ANOMALIES		
Posterior urethral valves	**44.8**	60
TOTAL	**100.0**	**134**

3.2.2 The age at presentation and sex distribution among the different types of CAKUT

Fifty seven percent (76/134) of the patients with CAKUT were under the age of one year when they first presented to the clinic, and 21% (28/134) presented above the age of 5 years. There was a significant statistical association between the age at presentation and the different types of CAKUT (p=0.024). Figure 3.2 below summarizes the sex and age groups of the different types of CAKUT at presentation.

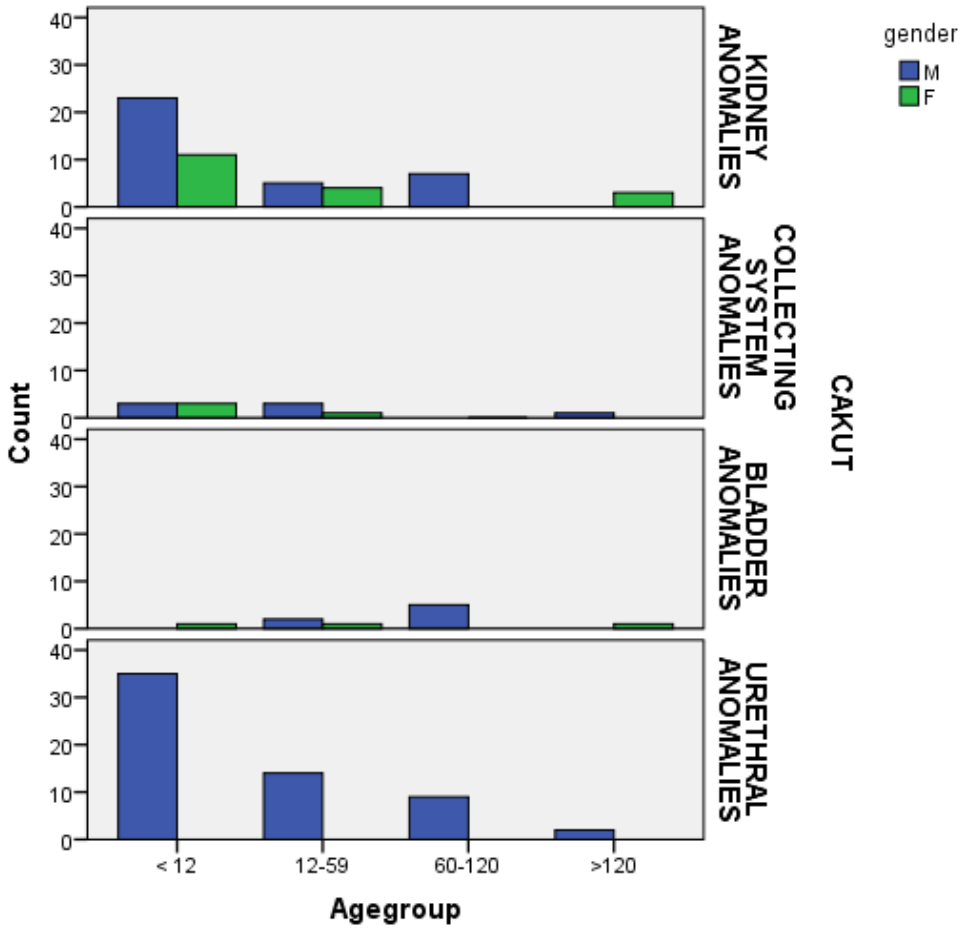

Figure 3.2 The age at presentation and the sex distribution of the different types of CAKUT

3.3 UTI in the patients with CAKUT

3.3.1 The incidence of UTI

Fifty-six (41.8%) of the patients with CAKUT had a culture proven UTI. The distribution of UTI among the main classes of CAKUT is shown in Table 3.3 below. There was a statistically significant difference in the rate of UTI among the different types of CAKUT (p=0.002). Bladder anomalies had the highest rate of UTI followed by collecting system anomalies.

Table 3.3 The different types of CAKUT and the presence of UTI

	PRESENCE OF UTI		**NO UTI**		
CAKUT TYPE	**%**	**n**	**%**	**n**	**TOTAL**
Kidney	22.6	12	77.4	41	53
Duplex	25.0	2	75.0	6	8
Single	16.7	3	83.3	15	18
MCDK	31.6	6	68.4	13	19
Others	12.5	1	87.5	7	8
Collecting system	54.5	6	45.5	5	11
PUJ	60.0	6	40.0	4	10
VUJ	0.0	0	100.0	1	1
Bladder	70.0	7	30.0	3	10
PBS	100.0	4	0.0	0	4

VUR	50.0	3	50.0	3	6
Urethra	51.7	31	48.3	29	60
PUV	51.7	31	48.3	29	60
Total	41.8	56	58.2	78	134

p = 0.002

To further assess the relationship between CAKUT types and UTI, a logistic regression model was employed as shown in Table 3.4 below. When compared with the group with kidney anomalies the odds of getting a UTI were increased approximately 9 fold among children with bladder anomalies, followed by those with urethral anomalies and then collecting system anomalies.

Table 3.4 The logistic regression model for UTI occurrence in the different CAKUT types

	UTI	
EXPOSURE	**OR (95% CI)**	**P Value**
Kidney anomalies	1	
Bladder anomalies	9.3 (1.9600 - 44.1378)	0.005
Collecting system anomalies	4.8 (1.1367 - 20.2983)	0.033
Urethral anomalies	5.4 (2.0219 - 14.5381)	0.001

3.3.2 The causative organisms

Two hundred and ninety-one (291) bacteria were isolated from 56 patients with 291 episodes of urinary tract infections. *Escherichia coli* was the commonest bacteria isolated, while *Acinetobacter baumanni* was the least common of the top five bacteria isolated. (Figure 3.3)

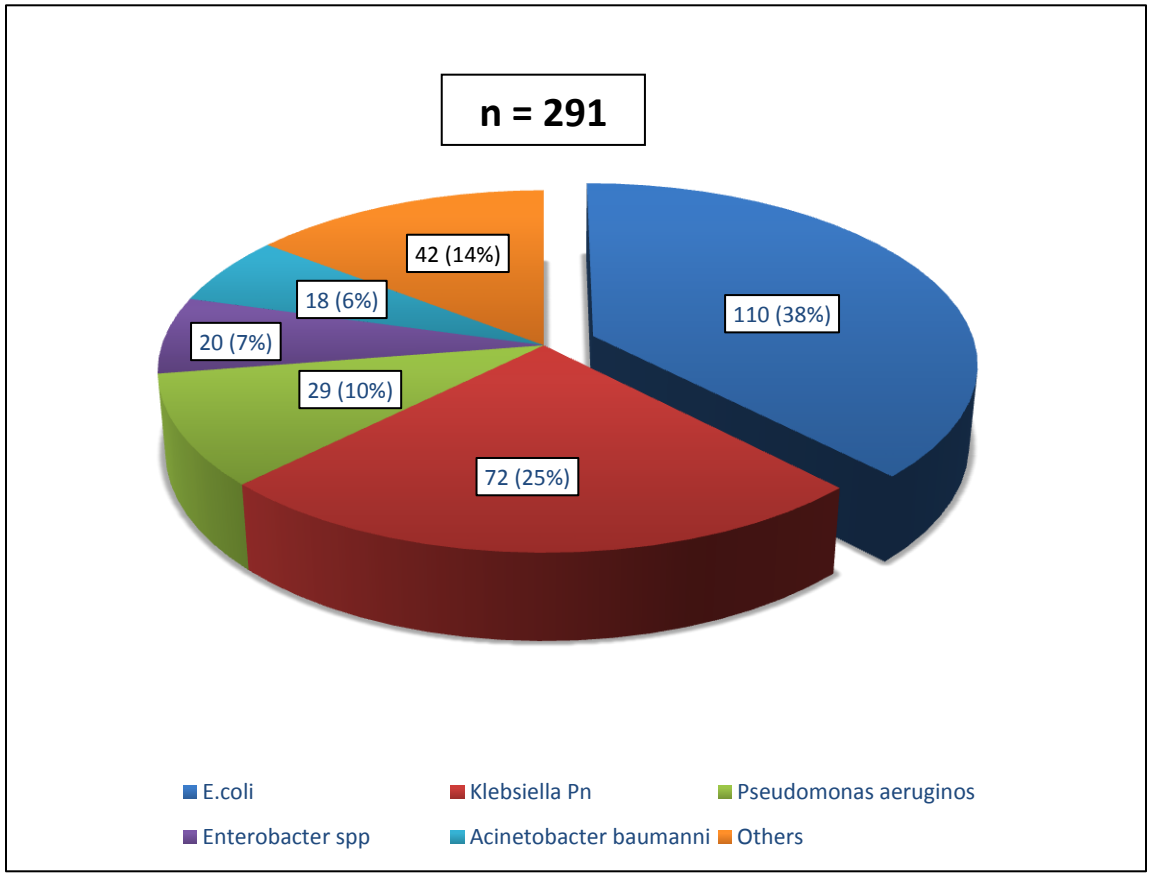

Figure 3.3 Pie chart showing the different causative bacteria

3.3.3 The antibiotic sensitivity patterns

For each bacterium isolated in this study, the antibiotic used for the sensitivity testing was reported as either 'sensitive', 'resistant' or 'not tested'. Table 3.5 below reflects the cases where

the antibiotics were tested and reported as sensitive. More than 90% of both *E. coli* and *Klebsiella pneumoniae* were sensitive to amikacin, meropenem, imipenem and ertapenem.

More than 40% of *E. coli* and *Klebsiella pneumoniae* were resistant to amoxicillin/clavulanate and trimethoprim-sulphamethoxazole.

3.3.4 The causative organisms and the different types of CAKUT

3.3.4.1 The distribution of the causative organisms among the different types of CAKUT

Table 3.6 shows that PUV had the highest number of episodes of UTI (162) followed by MCDK and PBS respectively. *E. coli* was the most common causative organism in most of the CAKUT patients with the exception of MCDK, duplex kidney and hypoplastic kidney. There was a statistically significant association between the different CAKUT types and the bacteria isolated. ($p < 0.001$)

Table 3.5 The antibiotic sensitivity patterns of the bacterial isolates

The major causative bacteria

Antibiotics	**E.C**	**E.C**	**Kle**	**Kle**	**Pseu**	**Pseu**	**Ente**	**Ente**	**Aci**	**Aci**	**Oth**	**Oth**
	%	**n= 110**	**%**	**n= 72**	**%**	**n= 29**	**%**	**n= 20**	**%**	**n= 18**	**%**	**n= 42**
Amikacin	99.1	110	97.2	72	93.1	29	95.0	19	44.4	18	97.6	41
Meropenem	99.1	109	98.6	72	93.1	29	90.0	19	50.0	17	88.1	38
Imipenem	93.6	104	98.6	71	93.1	28	85.0	18	27.8	16	90.5	38
Colistin	89.1	98	90.3	67	86.2	26	90.0	18	77.8	14	47.6	31
Ertepenem	90.9	100	91.7	67	41.4	12	85.0	19	16.7	4	69.0	30
Gentamicin	78.2	105	41.7	72	93.1	29	75.0	19	16.7	16	57.1	29
Ciprofloxacin	65.6	106	41.7	72	89.7	28	80.0	20	16.7	18	71.4	38
Cefoxitin	75.5	94	80.6	67	31.0	10	15.0	18	16.7	5	40.5	26
Ceftazidime	70.9	106	38.9	71	79.3	29	55.0		38.9	18	45.2	28
Cefixime	66.4	97	48.6	70	82.8	27	45.0	18	16.7	17	52.4	26
Nitrofurantoin	85.5	102	52.8	65	0.0	3	35.0	20	0.0	7	9.5	19
Ceftriazone	66.4	102	37.5	71	6.9	7	40.0	18	16.7	6	50.0	28
Cefotaxime	66.4	102	37.5	71	6.9	7	40.0	18	16.7	6	50.0	28
Cefuroxime	60.0	107	34.7	69	0.0	15	10.0	18	0.0	8	23.8	28
Amoxicillin/ clavulanate	47.3	105	27.8	71	0.0	7	5.0	19	0.0	3	23.8	17

Cephalexin	36.4	89	16.7	63	0.0	7	0.0	17	0.0	3	9.5	22
TMP/SMX	15.5	106	31.9	70	6.9	27	55.0	19	11.1	18	40.5	33

E. C = *Escherichia coli*, Kle = *Klebsiella pneumoniae*, Pseu = *Pseudomonas aeruginosa*, Ente=

Enterobacter species, Aci = *Acinetobacter baumanni*, Oth = Others

Table 3.6 The distribution of the bacterial isolates among the different types of CAKUT

	BACTERIA						
CAKUT	**E.coli %**	**Klebs %**	**Pseudo %**	**Enterobacter %**	**Acineto %**	**Others %**	**Total n**
KIDNEY ANOMALIES							
DK	22.2	0.0	27.8	5.6	22.3	22.2	18
MCDK	34.4	37.5	0.0	9.4	12.5	6.3	32
Hypoplastic	0.0	0.0	100.0	0.0	0.0	0.0	2
SK	55.0	25.0	15.0	0.0	5.0	0.0	20
COLLECTING SYSTEM ANOMALIES							
PUJ	62.5	18.8	6.3	6.3	0.0	6.3	16
VUR	58.8	11.8	0.0	17.6	0.0	11.8	17
BLADDER ANOMALIES							
PBS	33.3	16.7	4.2	4.2	8.3	33.3	24
PUV	34.6	28.4	10.5	6.8	4.3	15.4	162
TOTAL	**37.8**	**24.7**	**10.0**	**6.9**	**6.2**	**14.4**	**291**

$p<0.001$

3.4 The use of prophylactic antibiotics and their relationship to UTI

Out of the 134 patients with CAKUT, 36 patients had been started on prophylactic antibiotics after the diagnosis of CAKUT was made. Figure 3.4 below shows the types of CAKUT on prophylactic antibiotics. The frequency of prophylactic antibiotic usage was highest among patients with PUV (35%).

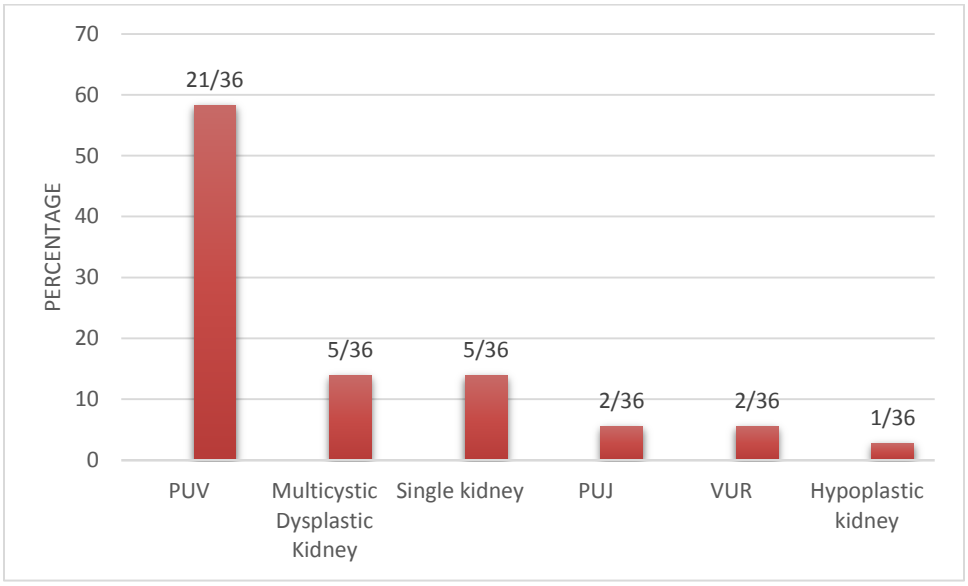

Figure 3.4. The pattern of antibiotic prophylactic use amongst the different types of CAKUT

Ninety-eight (98) patients were not commenced on any prophylactic antibiotic. Forty-nine (50%) of those who were not given prophylactic antibiotics had at least one episode of UTI on follow up, while only seven (19.4%) of those on antibiotic prophylaxis developed a UTI. The association between UTI and prophylactic antibiotic use is shown in Table 3.7 below. There was

a statistically significant association between the use of prophylactic antibiotics and the rate of UTI ($p < 0.001$). Patients who were not on a prophylactic antibiotic were five times more likely to have a UTI than those who were on a prophylactic antibiotic (OR = 5.21, P = 0.001, 95% CI: 1.9906 – 13.6277).

Table 3.7 The association between antibiotic prophylactic use and UTI

		UTI		
		YES **n (%)**	**NO** **n (%)**	**TOTAL** **n (%)**
ANTIBIOTIC PROPHYLAXIS	**YES**	7 (19.4)	29 (80.6)	36(100.0)
	NO	49 (50.0)	49 (50.0)	98 (100.0)
	TOTAL	56 (41.8)	78 (58.2)	134 (100.0)

p<0.001

A more detailed breakdown of the use of prophylactic antibiotic and the rate of UTI among the different classes and sub groups of CAKUT can be seen in Table 3.8. There was a decreased frequency of UTI in patients on antibiotic prophylaxis in all the different classes and sub groups of CAKUT.

Table 3.8. A breakdown of the CAKUT subgroups, the use of antibiotic prophylaxis and the rate of UTI.

UTI					
CAKUT	**On Prophylaxis**		**No Prophylaxis**		**Total**
	%	**n**	**%**	**n**	**n**
Kidney	18.2	11	23.8	42	**53**
Duplex	0.0	0	25.0	8	**8**
Single	40.0	5	7.7	13	**18**
MCDK	0.0	5	42.9	14	**19**
Others	0.0	1	14.3	7	**8**
Collecting system	0.0	2	66.7	9	**11**
PUJ	0.0	2	75.0	8	**10**
VUJ	0.0	0	0.0	1	**1**
Bladder	0.0	2	87.5	8	**10**
PBS	0.0	0	100.0	4	**4**
VUR	0.0	2	75.0	4	**6**
Urethra	23.8	21	66.7	39	**60**
PUV	23.8	21	66.7	39	**60**
Total	19.4	36	50.0	98	**134**

3.4.1. The association between prophylactic antibiotic use and the bacteria isolated

Table 3.9 shows the effect of prophylactic antibiotics on the pattern of the bacteria isolated among the different types of CAKUT. Patients who were on prophylactic antibiotics showed an altered pattern of bacteria isolated, with *Klebsiella pneumoniae* being the most common organism isolated, rather than *E coli,* when compared to the group that were not on prophylactic antibiotics. There was a statistically significant association between the type of bacteria isolated and the use of antibiotic prophylaxis (p= 0.031).

Table 3.9. The association between prophylactic antibiotic use and the bacteria isolated from the different types of CAKUT.

	Antibiotic prophylaxis			
Bacteria	**YES**		**NO**	
	%	n	%	n
E. Coli	25.0	13	41.0	97
Klebs	36.0	19	22.0	53
Pseudo	13.0	7	9.0	22
Entero	11.0	6	6.0	14
Acineto	2.0	1	7.0	17
Others	13.0	7	15.0	35
TOTAL	100.0	53	100.0	238

p= 0.031

4. DISCUSSION

4.1 Underestimation of the prevalence of CAKUT

CAKUT constitutes about 20 to 30% of all anomalies identified in the pre-natal period[13-15] and its reported prevalence among the general paediatric population ranges between 3.5 and 43%.[16,17]

The prevalence of CAKUT in this study (20%) falls within the range of results (3.5 – 43%) reported from other studies around the world. [16-18,35,36] The study which reported a prevalence rate of 43% was from a unit in Iraq. This study was a case control study in a general paediatric setting where 128 children (64 with UTI, and 64 without UTI) were screened for CAKUT using abdominal ultrasound.[16] Other studies obtained their study populations from the general paediatric setting, including urology clinics, and prospectively screened all children who presented to hospital for CAKUT, and not only those with UTIs or renal pathologies.[16-18,35,36]

Although our study reflects the incidence of CAKUT in a select group of patients (i.e. those referred to a specialist paediatric nephrology clinic) in whom we could expect to find a higher incidence of CAKUT compared to the general paediatric population, there are a number of reasons that our results may nevertheless still underestimate the true prevalence of CAKUT in our population;

- It is well recognized that some forms of CAKUT remain asymptomatic throughout life and may never be detected except through screening.[16,20,21] Our clinic only sees children who have been referred for a nephrology evaluation and it is likely that many children in the general paediatric population which our unit serves may have asymptomatic CAKUT and so would not have been diagnosed and referred for investigation.

- Patients with CAKUT who were seen primarily at the urology or paediatric surgery clinics at our hospital may not have been referred to us for follow up, despite this being the protocol in place.
- Some cases of CAKUT may not have had an ultrasound performed by our clinic, despite this being the protocol in place, and some of the routine abdominal ultrasounds that were performed during the study period may have missed some cases of CAKUT due to technical error
- In our study 159 different anomalies were documented for the 134 patients. However, as part of our study protocol we labeled any patient with two or more types of CAKUT as having only one type of CAKUT. This was based on the methodology used in a study reported from Egypt.[37] We chose the 'primary' CAKUT and ignored the extra anomaly which was assumed to have developed secondary to the 'primary' CAKUT.

4.2 The types of CAKUT

PUV was the commonest type of CAKUT in this study. Most reports estimate the incidence of PUV to be in the range of 1:5000 to 1:8000 live births. However, estimates have varied as widely as 1:2000 and 1:25000 live births. [38] In a study from Australia, a live-birth incidence of 1.28 per 10,000 was reported. In that study, 53% of cases were suspected on antenatal ultrasound and of the remaining cases, 45% were detected in the neonatal period, with 50% of all postnatal cases presenting with urinary tract infection. [38]

The prevalence of PUV in our study was close to 45%. This is in keeping with the findings from the study from Egypt where PUV was the commonest (36.4%) among the 107 different types of

CAKUT reviewed by Soliman *et al*.[37] In contrast, two other studies showed "kidney anomalies" as being the leading type of CAKUT[20,39], and a study from Iraq documented "bladder anomalies" as the most common CAKUT.[16]

Differences in the classification of CAKUT, methodology and study design make it difficult to compare our study results with those of other studies. While Gupta *et al* used both children and adults as their study population, Bondagi reviewed only antenatally diagnosed CAKUT within a perinatal population. [20,39]

The reason for the high prevalence of PUV in our study could be due to their tendency to present early with symptoms of obstructive uropathy and UTI, whereas patients with other forms of CAKUT, e.g duplex collecting system, are often asymptomatic and so may not be referred for investigation.[20]

Previous review articles on VUR suggest the general occurrence of VUR in healthy children to be 1-2%.[40,41] However, primary studies report a frequency of 0-30%.[42] Studies from developed countries have found high rates of VUR in the general paediatric population.[42,43] A study from Finland reported a prevalent rate of 35% among 406 children with UTI while a Canadian study found a rate of 17.2% and 31% in a general paediatric population with normal kidneys and in children with UTI respectively.[42,43] This is in contrast with much lower prevalence rates for VUR previously documented in black South African children.[44,45]

The prevalence of primary VUR in our study was 4.5%. This is in keeping with the 2 previous studies from South Africa. [44,45] We postulate that reasons for the much lower rates in black African children are most likely due to genetic factors.[46]

4.3 The age at presentation and the sex distribution of CAKUT

Males were more likely to develop CAKUT than females which is in keeping with previous studies from the developing world.[21, 37,39, 47-50] The male:female ratio in our study was 4.4:1 and sex was significantly associated with development of CAKUT (P<001). This highlights the need to have a high index of suspicion for CAKUT in every male child who presents with urinary symptoms.

The median age at presentation in our study was 8.4 months (IQR 1.9 - 47.7). This is of real concern as it reflects late presentation of many patients with CAKUT for investigation. Ideally, significant congenital anomalies should be diagnosed during the prenatal period and then followed up postnatally.

In our setting, a combination of poor rates of routine antenatal screening, and also late booking for antenatal care, results in few cases being referred as a result of detection by antenatal anomaly screening programs. In addition in some cases, even when a diagnosis had been made antenatally, parents still did not bring their children to hospital until they develop symptoms. In some extreme cases, some mothers delayed coming to the nephrology clinic even after being referred from the general paediatric clinics This underscores the need for proper counseling of the parents by the referring doctor about their child's illness.

4.4 UTI in CAKUT

4.4.1 The incidence of UTI in patients with CAKUT

UTI remains an important pointer to CAKUT in children.[16,19,21] Every child with CAKUT should be screened for UTI and vice versa and, since both CAKUT and UTI can independently cause

renal insufficiency with ultimate progression to ESRD, the need to minimize or prevent their co-existence cannot be over-emphasized.[4,20,26]

There is a paucity of data on the prevalence of UTI among patients with CAKUT. Previous studies have generally focused on the prevalence of CAKUT among children with UTI which ranges between 25 – 59 %.[16,17,21,51]

The prevalence of UTI in our study was 41.8%. This is lower than the 61% found among infants with CAKUT in Austria.[21] Regardless of the differences in the study population and methodology employed in both studies, it is clear that the prevalence of UTI in patients with CAKUT is high.

4.4.2 The CAKUT types with the highest rates of UTI

The differences in the rates of UTI among the different CAKUT types reached statistical significance ($p = 0.002$). Bladder anomalies as a group were the CAKUT type with the highest rate for UTI followed by PUV and collecting system anomalies respectively. When compared to kidney anomalies, the likelihood of getting a UTI was increased approximately nine fold among children with bladder anomalies and fivefold among those with PUV and collecting system anomalies.

We are not aware of any previously published work specifically looking at which type of CAKUT is associated with the highest rate for UTI, using our classification, but severe grades of VUR have been shown to be associated with recurrent UTI and subsequent scarring and PBS has also been associated with increased rates of UTI.[24,29-31,52,53] Posterior urethral valves also been shown to exhibit a high rate for UTI as reflected in the study by Bomalaski et al.[54]

All these study findings reinforce the fact that many types of CAKUT have a significant tendency to predispose to UTI. A diagnosis of collecting system and bladder anomalies, or PUV, should raise the suspicion of UTI in the index patient.

4.5 The causative organisms for UTI in patients with CAKUT

Studies done on UTI have shown that E.coli is the commonest causative organism in children with and without CAKUT. [1-5, 55-59] In our study, overall, *E. coli* was the commonest isolated bacteria, followed by *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* respectively. This finding is in keeping with other studies on CAKUT which also identified *E coli* as the predominant organism isolated.[16,17,60] As in our study, a report from London also found that *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* respectively were the next most common bacteria causing UTI in children with CAKUT after *E.coli*.[60] In contrast however, Alkhateeb et al from Iraq documented *Proteus mirabilis* as their second most frequent bacteria, before *Klebsiella pneumoniae.*[16]

E. coli was the most common causative organism in most of the CAKUT patients with the exception of MCDK, duplex kidney and hypoplastic kidney, and, although previous studies did not evaluate the relationships between different types of CAKUT and types of causative organism isolated, [16,17,37,60] we found that there was statistically significant association between the different CAKUT types and the bacteria isolated ($p<0.001$).

Our findings support recommendations that the isolation of organisms other than E Coli should be an indication for ultrasound screening for CAKUT during acute infections.[61]

4.6 The antimicrobial sensitivity patterns of the isolated bacteria

Ceftriaxone, ceftazidime, cefotaxime, gentamicin and amikacin are among the highly recommended parenteral antibiotics for the treatment of childhood UTI, and recommended oral antibiotics for UTI treatment in children include amoxicillin/clavulanate, cefixime, cefuroxime, cefpodoxime and cephalexin.[6,7,58] Previous studies on antimicrobial sensitivity patterns have been done on the general paediatric population although not on children with CAKUT per se, and many older studies did not include antibiotics such the carbapenem group.[55-59,62]

When reviewing our data on antimicrobial sensitivity patterns of the isolated bacteria, it must be kept in mind that, in our study, 41.8% of the children were on prophylactic antibiotics and children on prophylactic antibiotics are often infected with organisms that are resistant to commonly used antimicrobials.[28,59,65,66]

A study from Wisconsin showed that CAKUT was associated with a higher frequency of drug-resistant uropathogen infections.[66] The study also showed a high rate of resistance to 3rd generation cephalosporins in children receiving antibiotic prophylaxis.[66]

The extent to which antibiotic prophylaxis influenced the development of microbial resistance in this study was not explored. Unfortunately, due to technical limitations in the reporting of information requested from the Corporate Data Warehouse (CDW) of the National Health Laboratory Service (NHLS), we could not analyze the effect of antibiotic prophylaxis on antibiotic sensitivity patterns other than to compare the group who had been on prophylaxis with the group who had not (see 4.7 and 4.8 below).

In our study, the antimicrobial sensitivity patterns of the isolated bacteria were tested using 17 different antibiotics. Antibiotics to which the majority of the bacteria isolated were sensitive to

were meropenem (100%), colistin (100.0%), ertapenem (100.0%), amikacin (99.1%), imipenem (99.0%), gentamicin (81.9%), and ciprofloxacin (67.9%). More than 90% of both *E. coli* and *Klebsiella pneumonia* were sensitive to colistin, meropenem, ertapenem, imipenem and amikacin. However, because of their cost, and risk of abuse with subsequent microbial resistance, the carbapenems should not be used as first line drugs in the treatment of childhood UTI.

E. coli also demonstrated high levels of sensitivity to antibiotics like gentamicin, ciprofloxacin, cefixime ceftazidime, ceftriaxone and nitrofurantoin in this study. This finding agrees with previous studies.[55-58]

Antimicrobial resistance varies across regions and is influenced by different local antibiotic practices, but all agree that antibiotic resistance is on the increase worldwide.[58,64] In our study more than 40% of *E. coli* and *Klebsiella pneumoniae* were resistant to both trimethoprim-sulphamethoxazole, amoxicillin/clavulanate and cephalexin. In addition, thirty seven percent of *E. coli* and 61% of *Klebsiella pneumonia* showed resistance to cefuroxime.

Antimicrobial resistance to trimethoprim-sulphamethoxazole by bacteria that cause UTI is widely documented in literature.[55-59,62] The increased rate of resistance to trimethoprim-sulphamethoxazole is thought to be due to its widespread use as a prophylactic antibiotic for UTI and *Pneumocystis jirovici* infections in HIV positive patients,[55-59,62] and in areas with high levels of resistance to trimethoprim-sulphamethoxazole, the drug should no longer be used as the first line of treatment of UTI.[55-59,62] The findings of our study highlight that this also applies to our cohort of patients.

Studies from Khartoum, Ethiopia and Nigeria have also reported that organisms which cause UTI show high levels of resistance to amoxicillin and amoxicillin/clavulanate.[55-57,62]

Thirty-seven percent of *E. coli* and 61% of *Klebsiella pneumonia* showed resistance to cefuroxime in this study. This can be compared to the findings from Turkey where 38% of *E.coli* and 25% of *Klebsiella pneumonia* showed resistance to cefuroxime. [67]

E. coli showed 44.5% resistance to cephalexin in our study. A previous study reported cephalexin as one of the three antibiotics to which *E. coli* is most resistant.[57] However, they documented a lower rate (26.5%) of resistance to Cephalexin when compared to our current study.[58]

We are concerned that although recommended oral antibiotics for UTI treatment in children include amoxicillin/clavulanate, cefuroxime and cephalexin, our data show high levels of bacterial resistance to these antibiotics.[6,7,58] Our policy has been that CAKUT patients presenting with their first UTI are treated empirically according to the above guidelines and then our treatment of subsequent UTIs is based on the individual patient's prior urine culture results. Re-adjustment in the choice of empirical antibiotics is made once the antimicrobial sensitivity result of the index UTI is available in keeping with recommendations reported elsewhere.[6]

4.7 The association between antibiotic prophylaxis and UTI patterns

Preventing recurrent UTIs in patients with CAKUT is one of the most effective ways of preventing progression to end stage kidney disease in this cohort of children[2,24-26] but, due to conflicting reports on the benefits of antibiotic prophylaxis in preventing UTI, the use of

prophylactic antibiotics to prevent recurrent UTI/renal damage in children is still controversial.[6,7,29,63]

Brandstrom *et al* agreed that antibiotic prophylaxis can protect against recurrent UTI and long-term sequelae in selected groups of patients[28] and other recent studies also advocate the use of prophylactic antibiotics to prevent recurrent UTI in infants with moderate to severe congenital hydronephrosis.[25,27]

Simoese *et al* suggested a subgroup of patients that might benefit from antibiotic prophylaxis. These include those with obstructive uropathy until surgical intervention is achieved, the presence of severely dilated urinary tract, and grades III-V vesicoureteral reflux.[63]

Craig *et al* in Australia showed that low dose antibiotic prophylaxis decreased subsequent UTI episodes in children who had a previous UTI, and recent well designed controlled trials have shown that some subgroups of children do benefit from antibiotic prophylaxis.[24,25,28,30,31,68]

In our study population, the episodes of UTI were significantly decreased among our patients on antibiotic prophylaxis. Thirty-six (26.9%) of the 134 patients with CAKUT were started on prophylactic antibiotics after the diagnosis of CAKUT was made and ninety-eight (73.1%) were not commenced on any antibiotic. Over a follow up period of 39 months (IQR = 12.5-81.7), 7 (19.4%) of those on prophylactic antibiotics developed at least one UTI as compared to 49 (50.0%) of those who were not on prophylaxis ($p = 0.001$). The odds for developing a UTI were increased 5 fold among patients with CAKUT who were not on prophylactic antibiotics (OR = 5.21, $p = 0.001$, 95% CI: 1.9906 – 13.6277)

Craig's study found that 55 (19%) of 288 children without antibiotic prophylaxis developed UTI, while only 36 (13%) of the 288 in the antibiotic group developed UTI (Hazard ratio in antibiotic

group = 0.61; 95% CI: 0.40 - 0.93).[31] Also, in the RIVUR trial, antibiotic prophylaxis with trimethoprim/sulfamethoxazole decreased the risk of UTI recurrence by 50% among 607 children with VUR.[30]

Our results emphasize the positive role that antibiotic prophylaxis can play in the prevention of UTI in children with CAKUT. Unfortunately, due to the retrospective nature of our data collection, we could not analyze the long term effect of antibiotic prophylaxis on renal function but we feel that just to be able to prevent the morbidity of each UTI, it is worthwhile putting at least some children with CAKUT, as suggested by Simoese, on antibiotic prophylaxis.

Currently, the division of paediatric nephrology at CMJAH does not have any antibiotic prophylaxis protocol for the management of patients with UTI and/or CAKUT. Each index patient is treated based on his/her unique clinical condition. The results of this study will help us change this policy to place more patients onto antibiotic prophylaxis

4.8. The association between prophylactic antibiotics use and the bacterial isolates from CAKUT patients with UTI

As mentioned above, the extent to which antibiotic prophylaxis influenced the development of microbial resistance in this study was not explored other than to compare the group who had been on prophylaxis with the group who had not (see 4.6 above).

There was a statistically significant association between the type of bacteria isolated and the use of antibiotic prophylaxis (p= 0.031). In the group who were on antibiotic prophylaxis, *Klebsiella pneumoniae* was the most common organism isolated as opposed to *E coli* in the group that were not on prophylactic antibiotics.

Our study findings are in keeping with other reports which have showed that children on prophylactic antibiotics are often infected with causative organisms other than E. coli.[59,62,65,66]

It is recommended that the urine bacterial profile of CAKUT patients on prophylactic antibiotics be reviewed regularly.[28,61] This will enable physicians to remain ahead of emerging strains of atypical organisms in this cohort of patients.

5. CONCLUSION

As this is the first review that we have performed on our cohort of patients with CAKUT we found our study results to be very enlightening. We are concerned at the delayed presentation of many of our cases of CAKUT, even in circumstances where an antenatal or post natal diagnosis had been made. This highlights the lack of antenatal screening in our facilities and also our poor patient counselling skills.

PUV was the commonest type of CAKUT in our cohort of patients and, as opposed to reports from first world countries, VUR made up a very small part of our cohort. This emphasizes the importance of doing home grown research on our own populations rather than relying on reports of patient populations which may differ from our own.

In light of the fact that UTI among patients with CAKUT predisposes to CKD, we are concerned with the high prevalence of UTI detected in our study (41.8%). Bladder anomalies and PUV were the types of CAKUT with the highest risk for UTI in our center, and doctors caring for children with these anomalies should maintain a high index of suspicion for a UTI whenever such cases are seen.

Escherichia coli was the commonest cause of UTI in our group of patients with CAKUT. Other common bacteria included *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and *Enterobacter Spp* respectively. Meropenem, colistin, ertapenem, amikacin, imipenem, gentamycin and ciprofloxacin were the antibiotics that most of the organisms where sensitive to, and trimethoprim-sulphamethoxazole, cephalexin, amoxicillin/clavulanate and cefuroxime were the antibiotics which demonstrated the highest levels of bacterial resistance. This is of concern as

our current first line of treatment for cystitis is cephalexin or amoxicillin/clavulanate, and for pyelonephritis we use cefotaxime or ceftriaxone as our drugs of choice.

Our results demonstrate that, in cases of CAKUT with a UTI which do not rapidly respond to empiric therapy, doctors should have a high index of suspicion that the causative organism may be resistant to the antibiotic selected for therapy, and should be prepared to rapidly adjust the antibiotic selection accordingly.

Our results showed that antibiotic prophylaxis was very effective in decreasing the rate of UTI in our cohort of patients and, although we could not ascertain which particular subgroup of CAKUT would benefit most from prophylactic antibiotic use, we agree that it is worthwhile putting at least some children with CAKUT on antibiotic prophylaxis.

5.1 Recommendations

- A high index of suspicion for CAKUT should be entertained for all children with UTI, especially if they are boys, infants, or there is recurrence of UTI
- Children with either suspected or confirmed CAKUT should be timeously referred to a paediatric nephrology service for correct management and long-term follow up
- Routine, high quality, prenatal ultrasound examination for all pregnant women should be encouraged to increase the antenatal detection rate for CAKUT
- Parents of children with CAKUT should be properly counselled with regards to follow up appointments and subsequent pregnancies
- It is worthwhile to consider putting at least some children with CAKUT onto antibiotic prophylaxis.

- There should be rapid adjustment of antibiotic selection in patients with poor response to empirically prescribed antibiotics.

5.2 Topics for future research

The results of our study have led us to consider the following topics for future research:

1. To determine the long-term outcome of the CAKUT patients under our care
2. To determine which of the conditions which make up CAKUT are most suitable for antibiotic prophylaxis
3. To determine which antibiotics are most suitable for prophylaxis in these conditions
4. To determine the long term effects of antibiotic prophylaxis on renal function in children with CAKUT
5. To study the long term effects of antibiotic prophylaxis on UTI resistance patterns in children with CAKUT.
6. To study the prevalence of CAKUT in children with ano-rectal anomalies and other syndromes (e.g. Down's syndrome) who may have renal abnormalities as part of the syndrome.

Appendix A: Ethics Approval Certificate

R14/49 Dr Nneka Chioma Okoronkwo

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150709

NAME: (Principal Investigator)	Dr Nneka Chioma Okoronkwo
DEPARTMENT:	Paediatrics and Child Health/Paediatrics Nephrology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Urinary Tract Infection in Children with Congenital Anomalies of the Kidney and Urinary Tract attending the Division of Paediatric Nephrology at Charlotte Maxeke Johannesburg Academic Hospital, South Africa
DATE CONSIDERED:	31/07/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Cecil S. Levy
APPROVED BY:	Professor P Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	10/02/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004, 10th floor, Senate House/2nd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix B: Data Collection Sheet:

1. **Study No.:**

2. **Date of 1st presentation to the Renal Clinic, CMJAH.**

D	D	M	M	Y	Y

3. **Sex**

Male	

Female	

4. **Age at presentation:**

	Months

5. **Weight at 1st Visit (Kg)…….Z Score…….**

6. **Height at 1st Visit (CM)…… Z Score……**

7. **Any diagnosis of CAKUT?**

YES	

NO	

8. **If yes to Q 7, Any Prenatal diagnosis of CAKUT?**

YES		**NO**		**UNKNOWN**	

9. Type of CAKUT:

S/N	TYPE OF CAKUT	a.Yes	b. No
1	Single kidney	a.Yes	b. No
2	Duplex kidney	a.Yes	b. No
3	Pelvic kidney	a.Yes	b. No
4	Horse-shoe kidney	a.Yes	b. No
5	Hypoplastic kidney	a.Yes	b. No
6	Dysplastic kidney	a.Yes	b. No
7	Multicystic Dysplastic kidney	a.Yes	b. No
8	Hydronephrosis	a.Yes	b. No
9	Pelvi-uretericjunction obstruction	a.Yes	b. No
10	Duplex collecting system	a.Yes	b. No
11	Ureterocoele	a.Yes	b. No
12	Vesicoureteral reflux	a.Yes	b. No
13	Vesicouretericjunction	a.Yes	b. No

	obstruction		
14	**Megacystis**	**a.Yes**	**b. No**
15	**Bladder extrophy**	**a.Yes**	**b. No**
16	**Posterior urethral valve**	**a.Yes**	**b. No**
17	**Congenital urethral stenosis**	**a.Yes**	**b. No**

10. Serum Creatinine at 1st Visit (mmol/l)……

11. GFR@ at First Visit (mls/min/1.73m^2):

GFR	**≥90**	**60 - 89**	**30 - 59**	**12 - 29**	**<15**
CKD STAGE	**1**	**2**	**3**	**4**	**5**

12. Date of last visit:

D	**D**	**M**	**M**	**Y**	**Y**

13. Weight at last Visit (Kg)……..….Z Score……

14. Height at last Visit (CM)…….. Z Score……

15. Serum Creatinine at Last Visit (mmol/l)……..

16. GFR@ at last visit:

GFR	≥90	60 - 89	30 - 59	12 - 29	<15
CKD STAGE	1	2	3	4	5

17. Any UTI?

YES		NO	

18. If yes to Q 17, how many episodes of UTI? .....

19. If yes to Q 17, what was the age at 1st UTI :

	Months

20. Details of U T I.

UTI EPISODE	ORGANISM ISOLATED	SENSITIVE ANTIBIOTICS	RESISTANT ANTIBIOTICS

21. **Any prophylactic antibiotics?**

YES		NO	

22. If answer to Q21 is yes, when was the prophylactic antibiotic started?.....(a) Before first UTI (b) After first UTI

Appendix C: Approval for data collection from NHLS information system

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6142
Fax: +27 (0)11 386 6298
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

05 November 2015

Applicant: Dr Nneka Okoronkwo
Institution: University of the Witwatersrand
Faculty: Health Sciences
Department: Paediatrics
Email: nnekaneo@rocketmail.com
Cell: 074 195 0826

Re: Approval to access National Health Laboratory Service (NHLS) Data

Your application to undertake a research project "**Urinary Tract in Children with Congenital Anomalies of the Kidney and Urinary Tract attending the Division of Paediatric Nephrology at Charlotte Maxeke Johannesburg Academic Hospital, South Africa**" using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be made available to you to conduct the proposed study as outlined in the submitted application.

Please note that the approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met.

- Processes are discussed with the relevant NHLS departments (i.e. Information Management Unit and Operations Office) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- A final report of the research study and any published paper resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research. Any data related queries may be directed to Sue Candy, manager NHLS Corporate Data Warehouse, Tel: (011) 386 6036, Email: sue.candy@nhls.ac.za.

Yours sincerely,

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

NATIONAL HEALTH LABORATORY SERVICE HELPDESK
Tel: (011) 386-6125/6/7/9 Fax: (011) 386-6308 email: helpdesk.1@nhls.ac.za
APPLICATION FOR DATA FROM NHLS INFORMATION SYSTEMS (Q-Pulse FMI0069)

Each application will be approved or rejected subject to the ability to extract this data and the availability of the data, and subject to the intended usage of the requested data. Applications that are incomplete and/or do not contain supporting documentation, will be rejected.

APPLICANT'S DETAILS

Applicant Name	Nneka Chioma Okoronkwo	**Tel No**	(+27)741950826	**Email**	nnekaceo@rocketmail.com
Business Role / Designation			Fellow – Paediatric Nephrology		
Laboratory / Department / Branch / Region (Internal applicants)			Division of Paediatric Nephrology, CMJAH		
Organisation (External applicants)			Department of Paediatrics, CMJAH		
Supervisor Name	Cecil Levy	**Tel No**	(082)7712905	**Email**	cecil.levy@wits.ac.za
Supervisor Designation	Head of the Division of Paediatric Nephrology, CMJAH				

CONDITIONS

- **Data / Information is not to be used in contravention of Sections 14, 15, 16 and 17 of the National Health Act 61 of 2004 and the Promotions of Access to information Act 2 of 2000.**
- **The applicant undertakes to ensure that the data supplied to it by the NHLS is used ethically and solely for the purposes for which it is provided as detailed in this application, and further acknowledges that it shall remain liable for any breaches of this clause by the end user.**
- **If the purpose for the data requested in this application is research or if patient**

identity linked data is required, ethics approval and a one page summary of the protocol shall be attached to this application form. It is the responsibility of the applicant to ensure that their institutions' Human Ethics approval includes explicit authorisation to access the requested NHLS data.

- **The applicant undertakes to store the NHLS data in a confidential manner by separating patient identifying details from laboratory data and storing the master list that links patient identifying details to study patient identifiers in a separate, secure location.**
- **The information is for the private use of the applicant only, unless further approval is obtained from the NHLS. In the event of this, the applicant shall give due credit, including affiliation, of the participation of the NHLS in any such publications or presentations.**
- **The applicant undertakes to provide the Executive Manager: Academic Affairs, Research and Quality Assurance at the NHLS with a copy of any report, presentation or publication emanating from the use of this data.**

ACCEPTANCE OF CONDITIONS

By signing this document we accept the conditions stated above.			
Applicant Signature		**Date**	**27/10/2015**
Supervisor Signature		**Date**	**/ /20**

All fields in this section must be completed

DATA REQUEST DETAILS

Request Type (Tick)	☐ New ☐ Modify	**Data Format (Tick)**	☐ Excel ☐ CSV	**Data Delivery (Tick)**	☐ CD / DVD ☐ Email
Frequency of Extract (Tick)	☐ Once ☐ Repeat	**If Repeat, specify frequency**	☐ Daily ☐ Weekly		☐ Monthly ☐ Annually
DESCRIPTION OF REQUIRED DATA EXTRACT					
Data required	Bacteria isolated and DST patterns (on urine sent for MC&S) for the given list of paediatric patients (see attached) with Congenital Abnormalities of the Urinary Tract (CAKUT)				
Region (for data extract, e.g. Province or Laboratory	CMJAH				
Date range of extract	1st January 2005 – 31st December 2014				
Fields required (e.g. Patient name, Date of Birth, etc)	Please see attached patient list: Hospital ID (GT number); Organism Isolated; Date of Isolation; Resistance Profile for each organism				
ADDITIONAL INFORMATION					
Congenital anomalies of the kidney and urinary tract (CAKUT) are a well-documented risk factor for development of UTI in children.					

There is a paucity of literature on CAKUT and its relation to UTI in South Africa.

In addition to our other study objectives (see attached protocol), we hope to be able to **determine the incidence of UTI, the type of causative organisms and the sensitivity patterns seen in our study population of children with CAKUT.**

DESCRIPTION OF INTENDED USE OF DATA EXTRACT

(e.g. research, epidemiology study, cost analysis of service, drug effectiveness, disease surveillance)

The data will be used as part of Dr Okoronkwo's research towards her MSC dissertation.

We also hope to have the research published in a reputable scientific journal and presented at a relevant forum.

LIST WHO WILL HAVE ACCESS TO THIS DATA

Dr Nneka Chioma Okoronkwo; Dr Cecil Levy

PROJECT NAME AND REGISTRATION NUMBER

(if data is required for a registered research project. Please attach the Ethics Approval.)

Project Name: Urinary tract infection in children with congenital anomalies of the kidney and urinary tract attending the Division of Paediatric Nephrology at Charlotte Maxeke Johannesburg Academic Hospital, South Africa.

Protocol reference number: M150709

Please see the attached confirmation of study approval from the HREC (Medical) of the University of the Witwatersrand: Protocol reference number M150709

NHLS RESPONSIBILITIES

The NHLS will: • **Ascertain if it is possible to extract the required data.** • **Register the application and issue a registration number.** • **Only release the requested data to the applicant whose name is specified on this application form.**
After this application has been completed and approved, please raise a service request with the NHLS IT Service Desk (Contact Number: (011) 386-6125/6/7/9): • **Send an email to helpdesk1@nhls.ac.za, and cc the CDW Manager (sue.candy@nhls.ac.za)** • **Scan this application form and attach it to the email, or fax it to (011) 386-6308.**

FOR OFFICE USE					
APPROVAL BY BUSINESS **(Approval will be obtained by the CDW Manager)**					
INFORMATION MANAGEMENT UNIT APPROVAL (required for external requests and patient identifying data)					
Check list for external applicants	☐ Signed by Supervisor ☐ Ethics Approval attached, if applicable				
Executive Manager: Academic Affairs, Research and Quality Assurance		**Signature**		**Date**	**/ /20**
CEO APPROVAL (required for sensitive data requests)					
Chief Executive Officer		**Signature**		**Date**	**/ /20**
APPROVAL BY IT					

CDW Manager		**Signature**		**Date**	**/ /20**
REQUEST TRACKING					
Service Request Number					
Request Commence Date	**/ /20**				

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