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AUDIT OF POSTERIOR URETHRAL VALVE (PUV) IN CHILDREN AT RED CROSS CHILDREN HOSPITAL, CAPE TOWN, JANUARY 2002 – JANUARY 2009

BY

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ANTSAM 003

SUBMITTED TO THE UNIVERSITY OF CAPE TOWN

In fulfilment of the requirements for the degree

MPhil

Faculty of Health Sciences

March, 2009

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DECLARATION

I, Sampson Antwi, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or other university.

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CERTIFICATION

We, the undersigned, jointly certify that the study reported in this dissertation is the original work done by the candidate, Sampson Antwi, under our supervision and that it was conducted as requirement for the award of MPhil by the University of Cape Town. We also supervised the writing of the dissertation.

Signature:……

Professor Mignon McCulloch

Date……..

Signature:……

Dr Priya Gajjar

Date:……

Signature:……

Dr Peter Nourse:

Date:……..

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DEDICATION

This work is dedicated to all the children of the Renal Unit, Red Cross Children Hospital, Cape Town, South Africa, and to the numerous Ghanaian children for whose Healthcare needs I embarked on this postgraduate training.

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ACKNOWLEDGEMENT

I would like to express my sincere gratitude to Professor McCulloch, Dr Gajjar, and Dr Nourse, the supervisors of this project, for their dedication and sacrifice in guiding me throughout the study.

I am also grateful to Dr Isaac Ocheke, my fellow student and registrar, whose has been a source of encouragement to me both in the conduct of this study and during the period of my training.

The staff of the records department of Red Cross Children Hospital deserves commendation for the enormous assistance they gave to me in the retrieval of patient folders.

The input of Dr Samuel Blay of Komfo Anokye Teaching Hospital, Ghana, in the data analysis is highly appreciated.

Finally and above all, the Almighty God is worthy of praise for the strength, character, grace and wisdom he granted me in conducting this research.

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LIST OF ABBREVIATIONS

CIC	Clean Intermittent Catheterisation
CKD	Chronic Kidney Disease
ESRF	End stage renal failure
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
IQR	Inter-Quartile Range
K/DOQI	Kidney Disease Outcome Initiative
KUB	Kidney Ureter Bladder
NAPRTCS	North American Paediatric Renal Transplant Cooperative Study
OU	Obstructive Uropathy
PUV	Posterior Urethral Valve
PUVs	Posterior Urethral Valves
RRT	Renal Replacement Therapy
RXCH	Red Cross Children Hospital
TGF –β	Transforming Growth Factor Beta
USS	Ultrasound scan
UTI	Urinary tract infection
VUR	Vesicoureteric Reflux

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GLOSSARY OF TERMS

Hydronephrosis – dilatation of the kidney by urine accumulation

Hydroureter – dilatation of the ureter

Hydroureteronephrosis – combination of hydronephrosis and hydroureter

Obstructive Uropathy – structural or functional interference with normal urine flow anywhere along the urinary tract from the renal tubule to the urethra.

Ureterostomy –the creation of a stoma (an artificial outlet) for a ureter

Urinary diversion –one of several surgical procedures to re-route urine flow from its normal pathway

Valve ablation – disruption of the obstructing membrane of posterior urethral valve usually under direct vision by cystoscope using an endoscopic loop, Bugbee electrocauterisation, or laser fulguration.

Vesicostomy – a surgically created connection between the urinary bladder and the skin which is used to drain urine from the bladder in an individual with obstruction of normal urine flow.

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ABSTRACT

Posterior urethral valve (PUV) is a congenital obstructing membrane of the male urethra. It is the commonest cause of bladder outlet obstruction in male children. PUV as a cause of obstructive uropathy is an important cause of end stage renal failure (ESRF) in children. Early detection and surgical intervention can slow down progression to ESRF.

A retrospective, folder review of children diagnosed with PUV at Red Cross Children Hospital (RXCH) from January 2002 to January 2009 was undertaken to:

- determine patients' characteristics and method of clinical presentation
- audit timing of diagnosis, and timing and type of surgical intervention and
- determine disease progression

Forty-eight patients were reviewed with median duration of follow up 52 of months (IQR 24 - 107 months).

Nineteen (39.6%) out of the 48 study subjects were diagnosed by prenatal ultrasound scan. Of the remaining 29 (60.4%) who were diagnosed postnatally, age at diagnosis ranged from 1day to 2,950 days (median 17, IQR 1.0 – 90.5 days). On the whole, 17 (58.6%) of the 29 postnatally diagnosed cases were diagnosed within the first 3 months of age.

Racial distribution were 34 (70.83%) Coloured, 13 (27.01%) Blacks and 1 (2.01%) White. None (0.00%) was of Asian origin.

Commonest clinical presentation were urinary tract infection (10 cases), palpable abdominal mass (4 cases), voiding dysfunction (3 cases, 2 as dribbling urine), enuresis (2 cases).

Three types of surgery were identified in the management of PUV in this study either alone or in combination; valve ablation, vesicostomy, and cutaneous ureterostomies. Valve ablation alone was used in 29 (60.4%) patients, vesicostomy alone in 12 (25.0%), and the rest 7 (14.5%) combination surgery.

The median time interval from confirmation of PUV to primary surgical intervention was 8.5 days (IQR 6 - 15days).

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At end of follow up period, estimated glomerular filtration rate and thus stage of chronic kidney disease could be determined for 37 patients of which 20 (54.1%) were in stage 1. Only 1 (2.7%) patient had reached ESRF over time duration of 5 years 3 months. He had subsequently undergone successful renal transplant with graft function preserved after 4 years 2 months (serum creatinine at last follow up is 48 μmol/l). No death had been recorded over the study period but significant numbers (29%) have been lost to follow up for over a year. Prognostic factors identified were serum creatinine at presentation and at 1 year of age, as well as the nadir serum creatinine in the 1st year after surgical relief of the obstruction.

Though significant successes were identified in terms of promptness of diagnosis and surgical intervention, several areas in follow up care need improvement.

PUV could be successfully managed in the African continent to decrease progression to ESRF given the appropriate resources and motivation.

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CHAPTER 1

GENERAL INTRODUCTION

1.0 Introduction

Posterior urethral valve (PUV) is an abnormal congenital obstructing membrane that is located within the posterior urethra of males. Figure 1.1, Appendix 1.

The condition thus occurs exclusively in males.[1] This valve is the most common cause of bladder outlet obstruction in male children.[2] The valve causes mechanical obstruction to normal bladder emptying resulting in increased voiding pressures that may alter normal development of the foetal bladder and kidneys.[2] PUV represents a spectrum of obstructive severity, ranging from disease that may be incompatible with postnatal life due to severe pulmonary hypoplasia, to that which is minimal and may not manifest until later in life. The degree of obstruction caused by this abnormality depends on the configuration of the obstructive membrane within the urethra. Typically, children with higher degrees of obstruction present early in life (outside prenatal detection) with severe symptoms like renal failure and respiratory distress secondary to pulmonary hypoplasia from oligohydramnios whilst those with milder obstruction may present late with mild obstructive symptoms limited to voiding dysfunction.[2] PUV as a cause of obstructive uropathy is an important cause of end stage renal failure (ESRF) in children. Early diagnosis and intervention to decrease bladder pressure and stabilise the upper urinary tract are important to delay or prevent the progression of renal insufficiency with its attendant metabolic complications.

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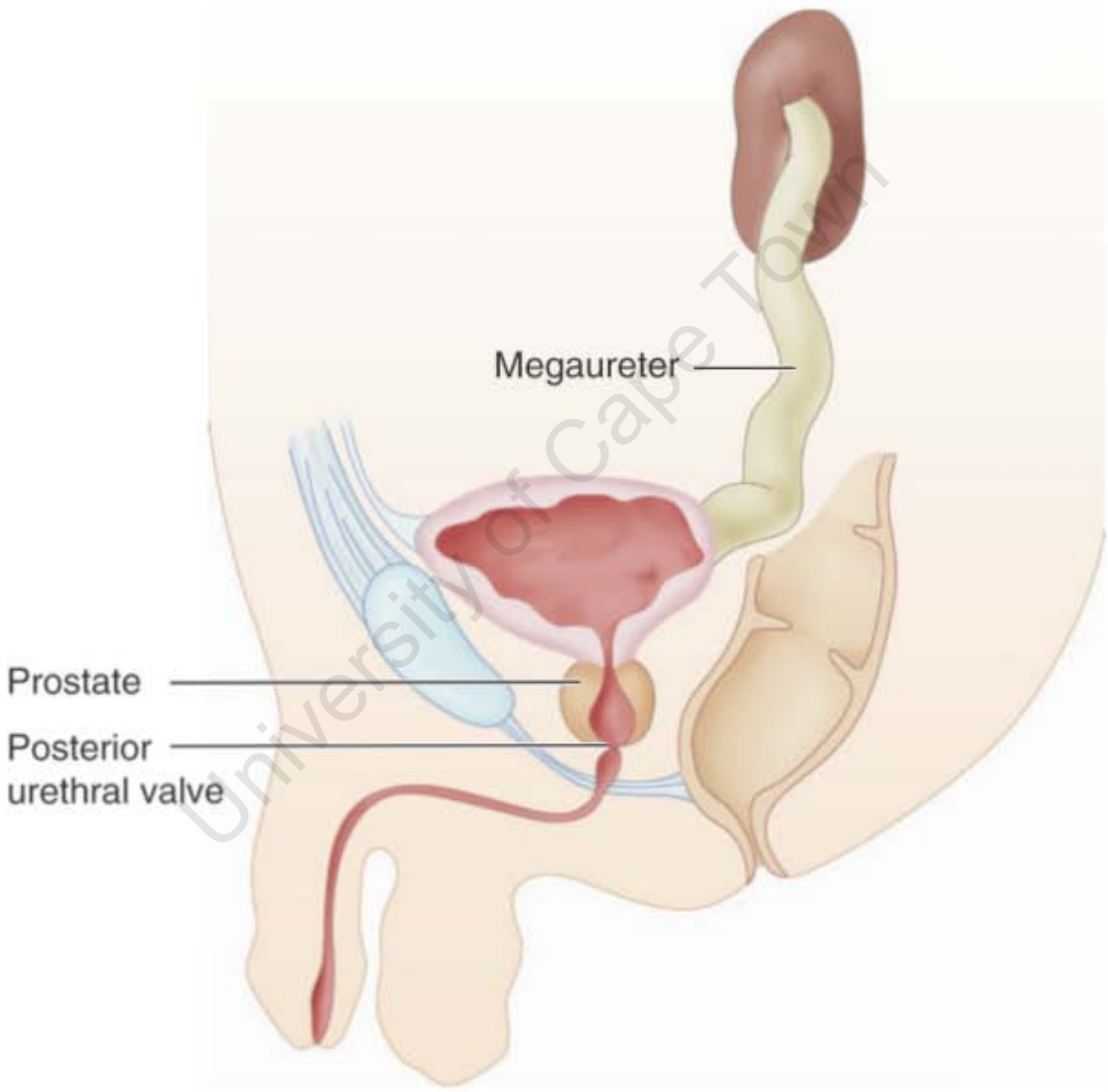

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Figure 1.1: Schematic diagram of the male urethra showing location of PUV

1.1 Overview of functions of the kidney and the metabolic effect of kidney failure

The kidney plays important role in the metabolic processes of the body with respect to the homeostasis of fluid, electrolytes, and acid-base. It is the principal organ responsible for the excretion of the nitrogenous waste products from protein metabolism. Besides these homeostatic roles, the kidney plays central role in erythropoiesis by producing the hormone erythropoietin which is essential for the proliferation of the erythroid precursors. The production of one-alpha (1-α) hydroxylase enzyme by the proximal tubular cells of the kidney makes the kidney a key partner in vitamin D metabolism and, indeed, in bone and mineral metabolism.

In the event of kidney failure, these important homeostatic and endocrine functions become deranged with drastic, and often fatal, consequences:

- Fluid overload occurs if intake is not matched with output
- Electrolyte abnormalities occur with the tendency for life-threatening hyperkalaemia
- There is acid-base derangement with development of metabolic acidosis
- Retention of nitrogenous waste products leads to increased levels of urea and creatinine.

If the kidney failure is persistent or chronic, then the impaired endocrine functions of the kidney manifest clinically with the development of anaemia (with its associated poor quality of life) and renal osteodystrophy. The net effect of renal failure in its advanced form is a poor quality of life in both cognitive and physical functions. Children with chronic renal failure commonly present with growth failure and impaired development.

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1.2 Definition and staging of chronic kidney disease (CKD)

Operationally, CKD is defined by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) as kidney damage persisting for ≥ 3 months or Glomerular filtration rate (GFR) < 60ml/min/1.73m^3, regardless of the underlying diagnosis.[3] Kidney damage in this context is defined as structural or functional abnormalities of the kidney as identified by imaging tests(e.g. hydronephrosis, small hyperechoic kidneys, absence of one kidney), kidney biopsy, or abnormalities in the urine (e.g. proteinuria, microalbuminuria, haematuria) or blood (e.g. elevated blood urea or creatinine). Neonates with prenatal renal abnormalities detected on ultrasound that is confirmed postnatally have CKD because the kidney abnormality started *in utero*.[4] Thus all neonates with congenital kidney malformations in essence have CKD.

The NKF-K/DOQI has classified CKD into 5 stages according to its severity as determined by the GFR with stage 1 disease being mild and stage 5 the most severe form.[3] (Table 1). Since GFR increases with maturation from infancy and approaches adult mean value by 2 years of age, it is important to recognise that GFR ranges that define the CKD stages apply only to children 2 years and above. These GFR ranges defining CKD do not apply to infants, since they normally have a lower GFR, even when corrected for body surface area.[3]

According to this nomenclature, patients with stage 5 disease are in end-stage renal failure (ESRF) and thus require a form of renal replacement therapy (RRT) in the form of dialysis or kidney transplant in order to ameliorate the toxic effect of uraemia, improve the quality of life and indeed, to sustain life. But epidemiological studies suggest that patients with ESRF represent just the "tip of the iceberg" of CKD and that patients with earlier stages of CKD (stage 1-4) are likely to exceed those reaching ESRF by as much as 50 times.[5] Since CKD is usually asymptomatic in its early stages, it is often underdiagnosed and underreported.

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Table 1.1: NKF-K/DOQI classification of chronic kidney disease (CKD). Adapted from reference 3.

Stage of CKD	GFR(ml/min/1.73m^2)	Description	Action plan
1	≥ 90	Kidney damage with normal or increased GFR	Diagnose and treat primary & comorbid conditions, slow CKD progression
2	60-89	Kidney damage with mild reduction of GFR	Evaluate rate of decline in GFR
3	30-59	Moderate reduction of GFR	Evaluate & treat complications
4	15-29	Severe reduction of GFR	Prepare for renal replacement therapy
5	< 15	End stage renal failure	Renal replacement therapy

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1.3 Burden of CKD, cost implications and need for early detection.

Worldwide, the number of patients with chronic kidney disease (CKD) is rising markedly, especially in adults, and CKD is now being recognised as a major public health problem that is threatening to reach epidemic proportions over the next decade.[6]
The economic cost of North American ESRF programmes reached $25.2 billion in 2002, an 11.5% increase over the previous year, and is expected to reach $29 billion by 2010.[6]
Given the high cost of treatment for patients in ESRF and the fact that 50 times more patients have milder kidney disease, the diagnostic and therapeutic approach to CKD must emphasise early detection, and aggressive management aimed at slowing the disease progression and avoiding ESRF. This is particularly important in children in whom congenital abnormalities of the kidney and urogenital tract are the main causes of CKD.[7,8,9] Malformations of the urinary tract, obstructive uropathy, and renal hypoplasia/dysplasia is said to account for 36% of children with chronic renal failure worldwide.[10]

1.4 Progression of CKD in PUV to ESRF

The North American Paediatric Renal Transplant Cooperative Study (NAPRTCS)[8] and a population-based registry in Italy (ItalKid)[9] data have demonstrated that patients with congenital anomalies such as PUV have slower progression of early CKD towards ESRF than patients with glomerular disease as the underlying pathology for their CKD.
Malformations of the urinary tract can easily be detected by antenatal ultrasound scan. Given the relatively high incidence of posterior urethral valves (PUV), 1 in 5,000[11] to 1 in 8,000[12] live births, and the fact that early detection and therapeutic intervention can slow down disease progression,[13,14,15] the need for early detection and intervention becomes imperative.

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1.5 Motivation for the study: Importance of early detection and intervention of PUV in Africa.

Africa is a developing country where the resources and expertise to manage terminal CKD are largely lacking. It is therefore of great importance to detect congenital malformations of the urinary tract at the earliest time possible so as to slow down the disease progression and possibly avoid the development of ESRF.

This consideration formed the motivation for this study which looked at the management practices of children with diagnosis of PUV at Red Cross Children Hospital, particularly in auditing the timing of diagnosis and surgical intervention. The documentation of this particular experience at RXCH would therefore be very important in creating future direction for the best care of PUVs in developing countries.

1.6 Research Question

Red Cross Children Hospital (RXCH) is reputed to offer one of the best paediatric renal services in Africa. The renal unit has well laid out treatment protocols for the different categories of renal diseases aimed at offering comprehensive care including longitudinal follow-up. Children with PUV are followed up according to a PUV Protocol (Appendix 2).

This study sets out to address the following questions:

- How many cases of PUV were diagnosed over the period January 2002 to January 2009?
- At what ages were PUVs diagnosed?
- What were the timing and type of surgical interventions used?
- Were there associated urinary tract abnormalities or medical conditions?
- What were the courses of the disease over the time period?
- Were there any factors of prognostic importance?
- To what extent was the departmental protocol adhered in follow-up care?
- What were the outcomes for the patients?

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1.7 Study Objectives

The study objectives are to:

- document characteristics of patients (race and age at diagnosis) and clinical presentation of PUV
- audit timing of diagnosis and surgical intervention
- audit type of surgical procedure used in management
- document associated urinary tract abnormalities
- identify complications associated with PUV.
- identify factors that portend poor prognosis
- determine progression of kidney function deterioration at 1 year and at last follow-up
- identify other medical conditions associated with PUV
- determine the extent of adherence to departmental protocol
- determine outcomes

1.8 Outline of the dissertation

The work conducted in this study is presented in the various chapters. Chapter 1 gives background to PUVs, renal function and the effect of renal dysfunction, and the burden of chronic kidney disease that is becoming an epidemic. The pressing need for early detection and intervention is also highlighted. Finally, the motivation for the research as well as the research objectives is introduced in chapter 1. Chapter 2 reviews the subject of posterior urethral valve from valuable research papers and books. The research methodology used in this study is outlined in chapter 3. The research findings are presented in chapter 4. A detailed interpretation and discussion of the findings from this study in the light of current literature is presented in chapter 5. Conclusions drawn from this study as well as recommendations, and the limitations to the study are presented in chapter 6. All the references cited in this study followed the Vancouver style and are presented after chapter 6. Important documents and radiographs related to this study are then presented in the appendix.

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CHAPTER 2

LITERATURE REVIEW

2.0 Introduction

This chapter reviews posterior urethral valve from current updates, various studies in the literature, and valuable books.

2.1 Structure and development of PUV

The male urethra is composed of posterior and anterior urethral segments. The posterior urethra consists of the prostatic urethra and the membranous urethra whilst the anterior urethra consists of the spongy/penile urethra. Figure 2.1

PUV develops during embryogenesis when the mesonephric (Wolffian) duct insert abnormally anterior on the cloaca before its division into the urogenital sinus and the anorectal canal.[2] Under conditions of normal insertion of the mesonephric duct, the most caudal end of the duct is absorbed into the primitive cloaca at the site of the future verumontanum in the posterior urethra. The remnants of this process are the posterior urethral folds called plicae colliculi that run distally and laterally to the verumontanum. The verumontanum is the midline prominence in the midprostatic urethra where the ejaculatory ducts enter. Abnormal anterior insertion of the mesonephric duct is thought to exaggerate the normal folds, with the distinction of these folds being thicker, more prominent, and fused anteriorly causing PUV.[2]

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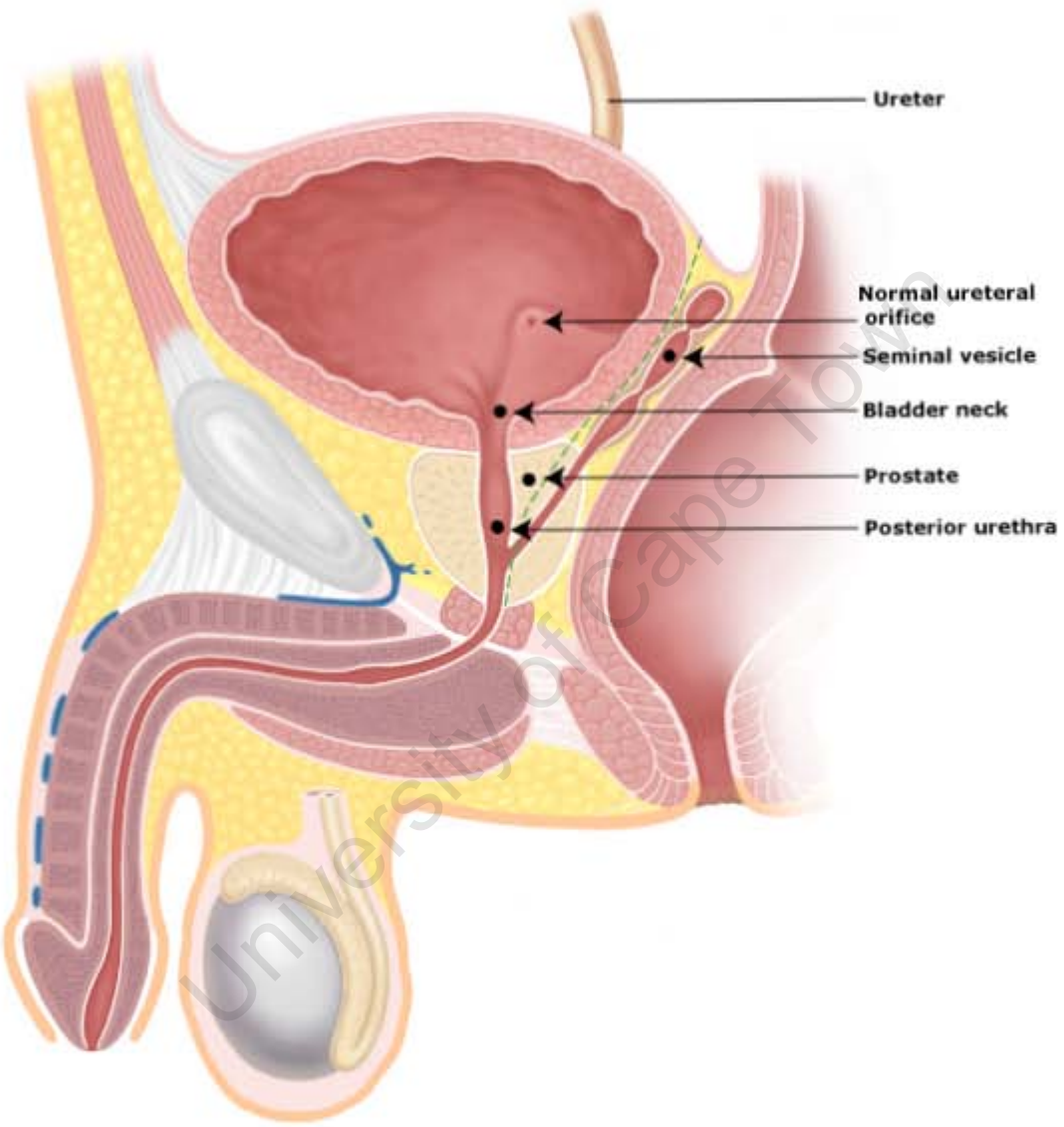

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Figure 2.1: Schematic diagram of the normal male urethra/reproductive tract (Source: http://www.uptodate.com/online/content/topic.do?topicKey=pediatri/5776&view=print)

2.2 Types/Classification of PUV

Posterior urethral valve was first described and classified by Hugh Hampton Young, urology pioneer, in 1919.[16] Young et al initially categorised PUV into 3 types:

- Type I valves: these are bicuspid valves/leaflets that originate at the distal aspect of the verumontanum and fan out to fuse in the midline just proximal to the external striated sphincter. There is a variable aperture to allow urine flow during voiding; however, the fused portion fills with urine and bulges into the membranous urethra. This gives the characteristic sail-in-the-wind finding commonly seen on micturiting cystourethrogram (MCUG). Type I valves account for 95% of all valves.
- Type II valves: are mucosal folds that run along the posterolateral wall of the urethra from the ureteral orifice to the verumontanum. Type II valves are no longer considered as obstructing valves; rather, they are thought to be sequele of voiding dysfunction. They can be differentiated from type I and III valves by their location proximal to the verumontanum.
- Type III valve: is a circumferential membrane or diaphragm that is located at the membranous urethra and is thought to result from incomplete regression of the urogenital membrane during embryogenesis. There is a central aperture, and the central portions of the ring may prolapse into the more distal urethra during voiding, which results in a wind-sock appearance on MCUG. Type III valves account for only 5% of all valves.

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2.3 Pathophysiology/Effects of PUV on the urinary system

Compared with the adult kidney, the developing kidney is highly susceptible to injury from obstruction to urine flow as occurs in PUV.[17] PUV can appear at the earliest stage of development of the urinary system; therefore, the entire developing kidney and the urinary tract develop in an abnormal environment of high intraluminal pressure due to the mechanical obstruction.[2] The occurrence of such obstruction at a critical time in organogenesis can have a profound and permanent effect on the functions of the kidneys (glomerulus, tubules, microvasculature, interstitium), ureters, and the bladder.[2,18] The consequence of such profound and permanent defect on the developing urinary system is that significant malfunction of the kidneys, ureters and bladder may persist despite adequate decompression of the urinary tract. Not surprisingly, therefore, attempt at in utero drainage of the urinary tract through vesicoamniotic shunts at periods when foetal viability can be assured has been met with unfavourable results.[19,20,21] To the contrary, other studies[22] have shown clear benefit of early surgical intervention in slowing progression to ESRF. The outcome of surgical intervention is to a large extent determined by the gestational age of the foetus when obstruction developed, and by the presence of renal dysgenesis (abnormal development of the kidneys).

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2.3.1 Effect on the kidney

Renal parenchymal dysgenesis (dysplasia and hypoplasia) is commonly present in patients with PUV and may be due to maldevelopment of the metanephric blastema in an environment of high intraluminal pressure.[2,23,24] Experimental models in animal studies have shown that even temporary complete unilateral ureteral obstruction during nephrogenesis or during nephron maturation can permanently reduce the number of nephrons in the obstructed kidney leading to hypoplasia.[25,26] The kidneys in PUV may function well initially following the relief of the obstruction, but they have reduced renal reserve.[2]

2.3.2 Effect on the tubulointerstitium

The hallmarks of chronic severe obstructive uropathy are the development of tubular atrophy and interstitial fibrosis.[27] Tubular atrophy results from progressive destruction of tubular epithelial cells by programmed cell death (apoptosis).[27] Factors contributing to tubular apoptosis include mechanical stretch of epithelial cells in the dilated tubules, as well as altered gene expression. [18,27] The expression of epidermal growth factor (a survival factor) by the renal tubular cells is reduced, whereas expression of transforming growth factor-β (TGF- β), a proapoptotic factor, is increased, the balance being tipped in favour of cell death. The results is progressive loss of renal mass.[28] Chronic unilateral ureteral obstruction has been shown to lead to infiltration of the interstitium by macrophages and fibroblasts which release fibrogenic cytokines such as TGF-β leading to interstitial fibrosis. The stretched tubular cells themselves under the influence of local growth factors, cytokines and chemokines can undergo epithelial-mesenchymal transformation and differentiate into fibroblasts that augment the progression of interstitial fibrosis.[29,30]

Renal hypoplasia/dysplasia, tubular atrophy, and interstitial fibrosis is commonly associated with PUV. In a study of children with PUV, Heuser and Landing[31] demonstrated that hypoplasia/dysplasia, tubular atrophy, and interstitial fibrosis was present in 39/41 (95.1%) nephrectomy samples.

2.3.3 Impact on tubular function

The consequence of tubular atrophy and interstitial fibrosis as explained above is impaired resorptive capacity of the kidneys. In addition to this tubulo-interstitial defect that distort the medullary architecture, down-regulation of sodium transporters and aquaporins have been described in chronic obstructive uropathy.[32,33] The consequence is poor urinary concentrating ability, resulting in polyuria. These factors contribute to the phenomenon of "postobstructive diuresis" that often follows the relieve of severe

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bilateral urinary tract obstruction such as PUV.[33] Since positive sodium balance is necessary for normal somatic growth in infancy, impaired growth is another consequence of reduced sodium reabsorption in PUV.[34] Thus infants with obstructive uropathy may require sodium supplementation to optimise somatic growth. Distal tubular secretion of potassium and hydrogen ion may also be impaired leading to type 4 renal tubular acidosis.[35]

2.3.4 Effect on ureters and urinary bladder

The bladder outlet obstruction that occurs in PUV, coupled with the high urinary production, places considerable strain on the bladder and ureters. Firstly, the bladder undergoes hypertrophy and hyperplasia in response to the increased workload generating high voiding pressures with near complete emptying initially. There is also increase in collagen deposition. The increased voiding pressures may be transmitted to the upper tract, resulting in dilatation of the ureters, pelvis and calyces, and to the glomeruli contributing to the renal damage. The hypertrophied and hyperplastic bladder may have altered blood flow to the detrusor muscle leading to ischaemic damage and further alteration in collagen deposition.[2] Several authors have noted high pressure, poorly compliant bladder sometimes with uninhibited contraction of the detrusor muscle which may eventually lead to myogenic failure.[2] The term "valve bladder" is used to describe the bladder of patients with PUV who have a fibrotic, poorly compliant bladder. Milder cases may present with isolated urinary incontinence.

There are several causes for dilated ureters which occur in association with PUV. Hydroureter may develop secondary to high retrograde pressure caused by bladder dysfunction. High pressure and large urine volumes may also contribute to deficient muscle development in the walls of the ureters. Large urine volumes due to poor concentration ability can cause the ureters to dilate.[2]

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2.3.5 Adaptive mechanisms in PUV

The impact of urinary tract obstruction may de distributed unequally between the two kidneys.[27] For example; hydroureteronephrosis may occasionally be limited to one side with associated ipsilateral vesicoureteric reflux and dysplastic kidney whilst the contralateral kidney develops normally. This protective mechanism called vesicoureteral reflux and renal dysplasia (VURD) syndrome allows one unit to absorb the brunt of the high pressure and is thus lost in the process while the other unit is spared and undergoes compensatory hypertrophy.[2,36] Other adaptive mechanisms to absorb the high pressure (pop off mechanisms) in PUV include bladder diverticula and urinary ascites resulting from rupture of a calyx.

2.4 Prevalence

The prevalence of PUV worldwide is quoted at between 5,000 [2,11] to 8,000 [12] live births. It is estimated that 10-15% of children undergoing kidney transplantation worldwide have PUV as the cause of their ESRF.[37]

2.5 Race

Though some authors report of no racial predilection,[2] Meyers et al[38] reported of increased prevalence among black children in South Africa.

2.6 Sex

PUV affects only males.[1] The female homolog to the male verumontanum from which the valves originate is the hymen.

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2.7 Clinical presentation of PUV

The clinical presentation of PUV is extremely variable which may be related to the degree of obstruction.[2] In the presonography era, late presentation of PUV was considered a good prognostic sign suggestive of a lesser degree of obstruction. Over the past 2 decades, however, the widespread use of prenatal ultrasound in developed countries has resulted in most cases of PUVs being diagnosed antenatally.[39] Currently, congenital obstructive uropathy is diagnosed before the age of one year in almost 100% of cases. Early diagnosis and early surgical intervention to relieve obstruction, combined with coordinated medical and surgical follow up, has resulted in a significant decline in infant mortality from obstructive uropathies such as PUV.[37]

2.7.1 Features on prenatal ultrasound scan

The classical features on antenatal scan include oligohydramnios, bilateral hydronephrosis and hydroureter, a thick-walled bladder with or without diverticula, and a dilated urethra.[1] The oligohydramnios may result in marked pulmonary hypoplasia causing death shortly after birth, while others already succumb in utero. When a male newborn is found to have bilateral hydronephrosis and hydroureter, he should be regarded as having PUV until proven otherwise.[1]

2.7.2 Clinical presentation in the newborn

Newborns with PUV may present with respiratory distress due to underdevelopment of the lungs (pulmonary hypoplasia) caused by oligohydramnios. An appropriate volume of amniotic fluid largely produced by foetal urine is necessary for complete and proper branching of the bronchial tree and alveoli. Other consequences of oligohydramnios include Potter's facies and limb deformities. Abdominal distension from urinary ascites or urinoma due to calyceal rupture, and a palpable abdominal mass from hydronephrosis or distended urinary bladder may are additional features.[2,40]

If the diagnosis of PUV is not recognised at birth, then severely affected children often present within weeks of birth with urinary tract infection (UTI), dehydration, electrolyte

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abnormalities, renal failure or failure to thrive.[2] A poor, dribbling urine stream may also be noted. The UTI may rapidly disseminate into urosepsis as the infection occurs within the closed system of PUV.[1]

2.7.3 Presentation in infants and toddlers

For children who escape prenatal detection, PUVs are usually discovered during evaluation of UTI, voiding dysfunction, failure to thrive, abdominal mass, or renal failure.[1,2]

2.7.4 Delayed presentation in older children and adults

Children with PUV that were not diagnosed on prenatal ultrasound and who do not manifest overt urinary pathology are at risk of delayed presentation. As stated earlier, such children have been assumed to have milder degree of obstruction. But as expected, such children have often presented in advanced renal failure when much of their function has been lost. Such presentations include UTI, urinary incontinence, particularly daytime wetting in boys older than 5 years, secondary diurnal enuresis, voiding pain or dysfunction, and poor urine stream. Others may be diagnosed incidentally when proteinuria or hydronephrosis is found on examination for unrelated conditions.
Though rare, adult presentation of PUV has been described with symptoms varying from obstructive voiding symptoms to postejaculatory dysuria.[37]

2.8 Diagnosis

2.8.1 Renal and bladder ultrasound scan

Ultrasound is a useful screening tool for all children with suspected PUV. A proper ultrasonographic study to evaluate the urinary tract must include images of kidneys, the ureters, and the bladder (KUB). For every child in whom PUV was suspected based on antenatal hydronephrosis, renal and bladder ultrasound scan should be performed in the early postnatal period to confirm the hydronephrosis and look for additional features of PUV. Typical findings on ultrasound suggestive of PUV include bilateral hydroureteronephrosis with or without cortical thinning, thick-walled bladder with trabeculation and diverticula, and a dilated posterior urethra with a hypertrophic bladder

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neck[2]. The bladder may be of large or small volume, but it is invariably thick-walled. Occasionally, the hydroureteronephrosis is limited to one side with associated cystic or dysplastic-appearing kidney which also has vesicoureteric reflux in what is termed vesicoureteral reflux and renal dysplasia syndrome (VURD). VURD is an adaptive response in which one unit of the urinary system absorbs the brunt of the high pressure and is lost while the other unit is spared and undergoes compensatory hypertrophy. Ultrasound may also pick up complications that may be associated with PUV such as urinary ascites, perinephric collections due to urinomas, and bladder diverticula. These complications act as pop-off mechanisms to also absorb the pressure in the system. Additionally, the parenchyma of the kidney will also be assessed by ultrasound for any evidence of hypoplasia and dysplasia which appear as small kidneys, or hyperechogenic kidneys with small cysts respectively. These numerous findings on ultrasound notwithstanding, micturiting cystourethrogram is necessary to confirm the diagnosis of PUV since ultrasound findings may be normal in mild cases without upper tract abnormality and an essentially normal bladder.[2] Bomalaski et al[37] found as many as 30% of their patients with PUV who had late presentation to have a normal ultrasonography. These cases could all be considered mild as they presented late.

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2.8.2 Micturiting cystourethrogram (MCUG)

MCUG is considered the diagnostic criterion standard imaging modality for PUV.[2] It is important to perform the MCUG during voiding and under fluoroscopy, with imaging of the posterior urethra. The diagnosis of PUV on MCUG is confirmed by visualisation of the valve leaflets and a dilated or elongated posterior urethra. MCUG also assesses the bladder for associated findings of trabeculation, diverticula, and vesicoureteral reflux (VUR). Figure 2.2

2.8.2.1 Limitations of MCUG

Sometimes, normal mucosal folds of the posterior urethra (plicae colliculi) may appear as luscencies on MCUG and suggest the presence of valve leaflets. Conversely, valve leaflets may not be visible on MCUG particularly if improper MCUG techniques are used; such as omission of adequate urethral views during voiding or failure to remove the urinary catheter, which can stent the valves open during voiding.[2]

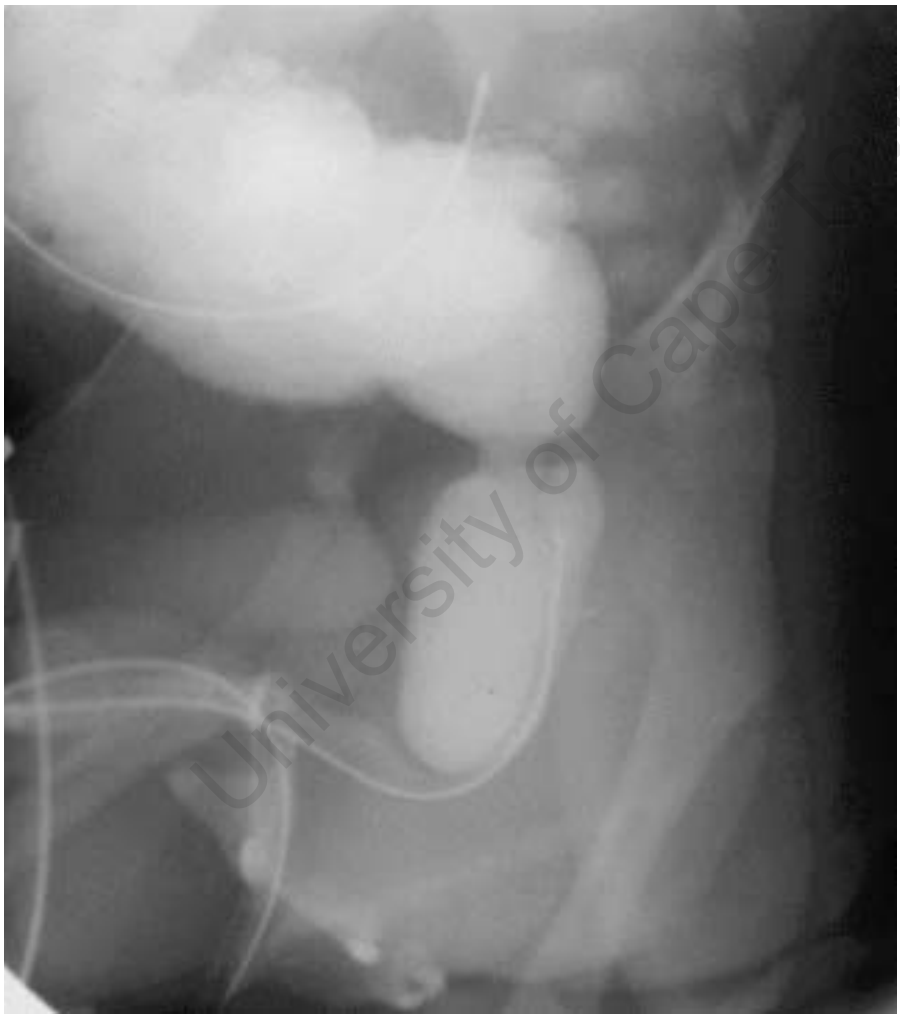

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Figure 2.2: MCUG in a child with PUV showing a dilated posterior urethra, hypertrophied and trabeculated bladder, and hypertrophied bladder neck. (Source: reference 2)

2.8.3 Cystourethroscopy

The limitations of MCUG make it imperative, sometimes, to resort to cystourethroscopy to either confirm or negate the diagnosis of PUV.[2,40] Cystourethroscopic confirmation of PUV should be combined with primary valve ablation.

2.8.4 Other diagnostic tools in PUV

Computed tomography scan and magnetic resonance imaging have sometimes been employed in the diagnosis of PUV but these offer no diagnostic advantage over MCUG except for the rare instance where plicae colliculi are demonstrated with MCUG and not with computed tomography and which may then lead to an incorrect diagnosis of PUV. Nuclear cystography has no role in the diagnosis of PUV. Nuclear renography, however, may be used to assess upper tract consequences of bladder outlet obstruction and to determine relative function of each kidney.[2]

Urodynamic studies are frequently employed to evaluate bladder function.

2.9 Differential diagnosis of PUV

These include anatomic obstructive disorders and functional voiding disorders.[2]

Anatomic obstructive disorders:

- Urethral atresia
- Anterior urethral valves
- Urethral duplication
- Congenital urethral polyp
- Ureterocele
- Congenital urethral stricture (Cobb collar)
- Prune-belly syndrome
- Plicae colliculi (normal anatomic structure)

Functional voiding disorders

- Neuropathic bladder
- Detrusor Sphincter Dyssynergia (DSD)

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- Nonneurogenic neurogenic bladder (Hinman syndrome)
- Small capacity hypertonic bladder

2.10 Treatment of PUV

Treatment of PUVs is broadly divided into medical and surgical care.

2.10.1 Medical care

Though corrective surgery remains the definitive treatment of PUV,[1,40,41] some children may present in metabolically unstable state with severely impaired renal function, electrolyte and acid-base abnormalities, dehydration, or infection that requires initial medical stabilization.[1,40] Newborn babies with severe PUV may require pulmonary resuscitation due to pulmonary hypoplasia. Under such circumstances, immediate relief of urethral obstruction should be instituted by placement of urethral catheter either transurethrally,[1,40] or suprapubically through a wide intravenous canula.[1] This will allow drainage of the obstructed system, may improve renal failure, reduce risk of infection as well improve treatment response, and thereby reducing the opportunity for further renal damage.[1] After relief of the obstruction there will often be a diuretic phase as a consequence of the associated tubular dysfunction and solute diuresis, resulting in salt and water loss which will require careful replacement and monitoring for some days.

The second phase of medical management of PUVs is follow-up care after surgical intervention. Unrelenting progression of renal dysfunction has been widely associated with some cases of obstructive uropathy even after surgical correction that requires long-term follow-up and optimal care so as to slow the progression. Areas of particular importance include prevention and efficient treatment of UTI, blood pressure control, monitoring for and control of proteinuria, optimal management of renal failure, and management of bladder problems. Identification and management of any bladder dysfunction is particularly important as it has implications for graft survival following transplant. Thus, urodynamic studies should be considered in any boy with PUV with suspected bladder dysfunction. In general, urinary incontinence beyond the age of 5 years should prompt evaluation of bladder dysfunction.[1] The fibrotic, poorly compliant bladder that is often associated with severe PUV require optimal management with anticholinergics, clean intermittent catheterization with or without continent appendicovesicostomy (Mitrofanoff principle), and sometimes augmentation cystoplasty.

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2.10.2 Surgical intervention

Surgery remains the definitive treatment of PUV to ablate this congenital membrane. However, in certain situations primary valve ablation may have to be deferred. In such situations, urinary diversion procedures will have to be performed to provide a more lasting drainage of the obstructed system beyond that provided by the initial catheterization. Surgical management of PUV is thus divided into 2;

- Corrective surgery
- Urinary diversion

2.10.2.1 Corrective surgery

Primary valve ablation is the treatment of choice in PUV[42] and is recommended soon after confirmation of PUV. Various surgical approaches that have been described include:[40]

- disrupting the obstructing membrane by the blind passage of a valve hook.
- rupture of the valves with a Forgarty catheter under radiologic control
- a perineal urethrostomy approach particularly when there are difficulties with instrumentation
- Direct transvesical approach
- Diathermy of the valves with a D. I. W. Hook especially in the preterm infant

Currently, however, valves are disrupted under direct vision by urethrocystoscopy using an endoscopic loop, Bugbee electrocauterisation, or laser fulguration.[1,2] The objective is to relieve the obstruction by cutting the valves at the 12-, 5-, and 7- o'clock positions.

2.10.2.2 Urinary diversion

Urinary diversion may be used in situations where primary valve ablation is not feasible e.g. urethral size too small for available cystoscopic instrumentation. In such situations, valve ablation is deferred until adequate growth of the urethra has occurred, usually by age 1 year. The diversionary stoma is then closed when secondary valve ablation is carried out. Three methods of urinary diversion have been described and they may be used either alone, or in combination:

- Vesicostomy[2,40]

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- Bilateral cutaneous ureterostomies[40,42]
- Nephrostomy[40,42]

2.11 Long term outcome of PUV

Several studies have confirmed that children with PUV progress to ESRF, albeit slowly, despite corrective surgical intervention.[1,41,43,44] This calls for a prolonged and coordinated medical and surgical follow-up care so that evolving clinical problems can be identified and managed early so as to slow progression. Several factors account for this progressive nature of renal insufficiency in PUV. As enumerated under section 2.3 above, the obstructive pathology occurring in intra-uterine life during critical period of nephrogenesis leads to parenchymal dysgenesis and nephron loss. These children are therefore born with reduced renal reserve and are at risk of CKD particularly during adolescence when the increase in body mass places enormous metabolic burden on the stressed kidney. Bladder dysfunction as well as ureteral abnormalities that are commonly associated with PUV may contribute significantly to deteriorating renal function if they are not identified and managed optimally.

2.12 Prognostic factors

Factors that have been cited as portending poor long-term outcome in PUV include:

- Early presentation outside prenatal detection.[45] It is argued that severe obstructive disease will manifest early in life
- Nadir serum creatinine > 80 µmol/l at 1 year of age after relief of obstruction.[46,47] or within 5 days of relief of obstruction
- Proteinuria at age 5 years.[45]
- Daytime incontinence after 5 years of age, indicating bladder dysfunction.[45]

Identification of these prognostic factors may be useful in planning further management and discussions with parents.

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CHAPTER 3

STUDY SUBJECTS AND METHODS

3.0 Introduction

This chapter captures the description of the study site and the study design. Statistical tools used in data collection and analysis, and ethical issues in this study are also described in this chapter

3.1 Study site

The study was carried out at Red Cross Children Hospital (RXCH), Cape Town, South Africa.

South Africa is the southern-most part of Africa with a total land area of 1,219,090 square kilometres.[48] It has only northern borders, being bordered from north east to north west by Mozambique, Zimbabwe, Botswana, and Namibia. Figure 3.1 Uniquely, South Africa shares 2 oceans in its coast; the Atlantic Ocean and the Indian Ocean. It has 9 administrative provinces (Figure 3.1) with a total national population of 40.5 million.[48] It is a multiracial country consisting of Blacks, Whites, Coloured, Asians, and others unspecified.

Cape Town is the provincial capital of the Western Cape, where RXCH is located. The dominant racial group in the Western Cape are the Coloured with a population of 2,146,109 (54.2%) out of the provincial total of 3,956,875. The black and the White form almost equal proportion of 20.8% and 20.7% respectively, corresponding to nominal figures of 826,691 and 821,551. Asians constitute 40,376 (1.0%) of the provincial total of 3,956,875. Table 3.2

Red Cross Children Hospital is a specialist, teaching hospital affiliated to the University of Cape Town. It serves as the main tertiary referral center to the whole of the Western and Northern Cape Provinces and also receives referrals from other provinces and abroad. It has units for all the major paediatric sub-specialist disciplines and has a total bed capacity of 290. It is famous for its paediatric organ transplant programme. Until

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recently, it was the only center where paediatric combined kidney-liver transplantation was done. It thus receives referrals from all over the country and beyond.

Children with posterior urethral valves are followed up according to a departmental protocol. See Appendix 2.

The renal unit combines harmoniously with the urology and radiology units through a weekly joint renal-urology ward round and a weekly renal-urology and radiology conference. Such collaboration affords the opportunity for joint treatment approach for children with urological disorders such as PUV.

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Figure 3.1: South African Provincial Map (Source: Reference 48)

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Table 3.1: Population by province and population group (percentages). (Source: Ref 48)

Population Group	Eastern Cape	Free State	Gauteng	Kwazulu-Natal	Limpopo	Mpuma-Langa	Northern Cape	North West	Western Cape	South Africa
Black African	87.5	88.0	73.8	84.9	97.2	92.4	35.4	91.5	26.7	79.0
Coloured	7.4	3.1	3.8	1.5	0.2	0.7	51.6	1.6	53.9	8.9
Indian or Asian	0.3	0.1	2.5	8.5	0.2	0.4	0.3	0.3	1.0	2.5
White	4.7	8.8	19.9	5.1	2.4	6.5	12.4	6.7	18.4	9.6
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

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3.2 Study Design

This was a retrospective study of all children with diagnosis of PUV who were captured on the hospital's database from the period January 2002 to January 2009.

3.2.1 Inclusion criteria

- All patients with diagnosis of posterior urethral valve, as established by micturating cystourethrogram or urethrocystoscopy, who were captured on the hospital's database from January 2002 to January 2009.

3.2.2 Exclusion criteria

- Causes of bladder outlet obstruction other than PUV
- PUVs hooked to the database after 31st January, 2009.

3.3 Method of data collection

The medical records of all children who satisfied the inclusion criteria were retrieved. A case report form (Appendix 3) was used for data capturing. Information extracted from the records included:

- age at which diagnosis was suspected
- race
- clinical presentation
- time interval to confirmation of diagnosis
- time interval between confirmation of diagnosis and surgical intervention
- type of surgical procedure used to relieve obstruction
- documented complications associated with PUVs
- co-morbid conditions identified
- serum creatinine values at time of diagnosis, nadir value after surgical relief of obstruction, and value at 1-year of age and at last follow up.

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- Outcome of patient at last follow up in terms of stage of chronic kidney disease, renal replacement therapy, and patient's survival.

3.4 Estimation of glomerular filtration rate (eGFR)

The GFR of study subjects were estimated from the Haycock - Schwartz formula[49] as follows:

$$eGFR(ml/min/1.73m^2) = k \times \text{height (cm)/serum creatinine (}\mu\text{mol/l)}$$

where k = 24 for preterm neonates
33 for term neonates
40 for normal infants (0 – 12 months)
49 for boys and girls (2-12 years)
49 for girls 13 – 21 years
60 for boys 13 – 21 years

3.5 Data management and analysis

After completion of the datasheet, the data was double entered using Epi info version 3.2.2. It was checked for inconsistencies on a weekly basis. Upon completion of the data entry, data was transported to Stata® intercool version 10 for analysis. Continuous variables such as the age at diagnosis and length of follow-up were analysed and reported as median with their inter-quartile range. Categorical data were analysed and presented as frequencies with their respective percentages. Spearman's correlation was used to determine the correlation between the stage of kidney disease and the various continuous variables. For dichotomous variables however, the chi-square tests for trend was used. For both tests a p-value of less than 0.05 was considered statistically significant.

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3.6 Ethical Consideration

3.6.1 Access

Ethical approval (REC REF: 061/2009) was obtained from the Faculty of Health Sciences Research Ethics Committee of the University of Cape Town. Appendix 4. Written approval to perform the research was obtained from the medical superintendent of RXCH. Appendix 5.

3.6.2 Ethical Principles guiding the conduct of the research

To ensure maximum protection and confidentiality of patients who were enrolled into this study, patient names were not included on the case report forms. Data collected from each study subject was kept in a binder in a locked cabinet. Data entered into the computer were not released to others except the statistician who was in a foreign country. The foreign location of the statistician together with the anonymous label of the data ensured maximum protection of patient's confidentiality.

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CHAPTER 4

RESULTS

4.0 Study subjects

A total of forty-nine children with the diagnosis of posterior urethral valve were analysed over the study period. A review of one child however showed that he had idiopathic urethral bulbar stricture, and not PUV. He was subsequently excluded from the study. Forty-eight children were thus eligible for analysis.

4.1 Age at diagnosis

Nineteen (39.6%) out of the 48 study subjects had the diagnosis of PUV made by prenatal ultrasound scan whilst the remaining 29 (60.4%) were diagnosed postnatally. Age at diagnosis in the latter group ranged from 1day to 2,950 days. The mean age at diagnosis was 241.2 days and the median age was 17days (IQR 1.0 – 90.5 days).

On the whole, 22 (75.8%) of the 29 postnatally diagnosed cases were diagnosed within 1 year of age.

The age ranges at which diagnosis were made are shown in figure 4.1.

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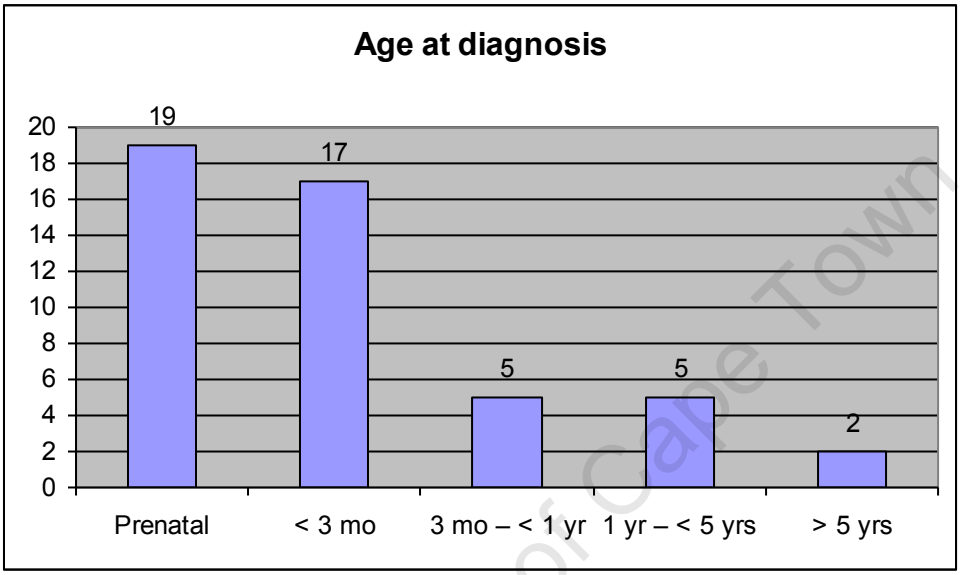

Figure 4.1: Age at diagnosis of PUV in study subjects.

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4.2 Race of study subjects

The prevalence of PUV among the various racial groups was as follows:

Thirty four of 48 patients (70.83%) were of the Coloured race whilst 13 (27.01%) were Blacks. Only one subject (2.01%) was White. There were no Asian patients. Figure 4.2.

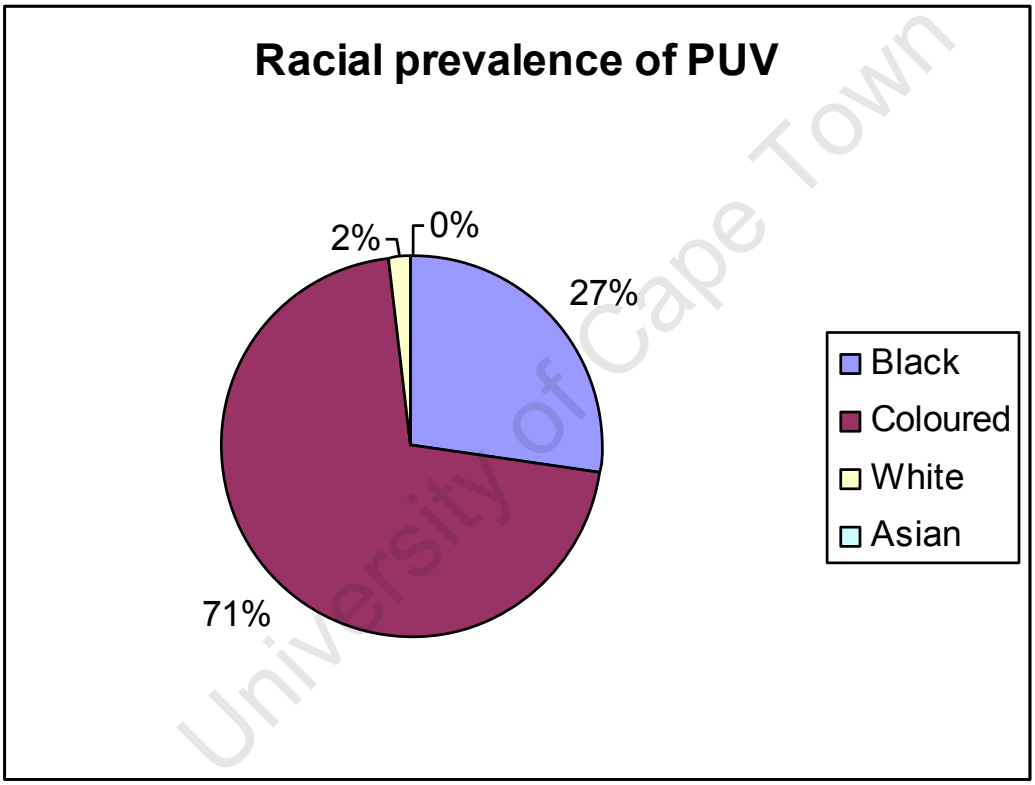

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Figure 4.2: Prevalence of PUV among the 4 racial groups in South Africa.

4.3 Method of diagnosis of PUV

Three main diagnostic investigatory methods of PUV were identified in this analysis; ultrasound, MCUG, and urethrocystoscopy. All cases had kidney, ureter, and bladder (KUB) ultrasound done largely as screening method. The study subjects would then subsequently have MCUG to confirm the diagnosis. The diagnoses of 3 cases were however based solely on ultrasound studies. In 1 case, MCUG could not confirm the presence of the valves when the KUB ultrasound had suggested PUV. PUV was however confirmed on urethrocystoscopy.

4.4 Time interval to confirmation of diagnosis

The median time interval from clinical suspicion of PUV and/or ultrasound screen to confirmation by MCUG and/or urethrocystogram was 5 days (median 5, IQR 1.0 – 10.2 days). In seventeen (35.4%) of the 48 cases, the diagnosis was confirmed within the first 24 hours of life. In 32 patients (66.6%), the diagnosis was confirmed within the first 7 days of initial suspicion and in 2 patients (4.1%) after 30 days.

4.4.1 Some reasons for delayed MCUG confirmation

Some reasons that were identified for delayed confirmation of PUV by MCUG were:

- Fluoroscopic machine has broken down
- Patient missed appointment
- On-going urinary tract infection

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4.5 Time interval to primary surgical intervention

The median time interval from confirmation of PUV to primary surgical intervention was 8.5 days (IQR 6 - 15days). Except for 2 cases whose surgery were delayed beyond 30 days at 40 and 120 days respectively, all cases (95.8%) had primary surgical intervention within the first 30 days of confirmation of PUV.

4.5.1 Some reasons for delayed primary surgery

Some of the reasons attributed to delayed surgery identified in this audit were:

- Urethra too small for the available cystoscope
- On-going urinary tract infection

Interestingly for one particular child, the initial MCUG was postponed due to breakdown of the Fluoroscope. When it was fixed and the diagnosis was confirmed on MCUG, an attempted valve ablation was unsuccessful due to hypertrophied bladder neck. He had to be rescheduled again for temporary urinary diversion by vesicostomy and only had valve ablation done at a later date.

4.6 Treatment of PUV

4.6.1 Initial medical management

It is the practice at this study site to insert an initial urinary catheter in all cases of suspected obstructive uropathy secondary to PUVs. Thus all cases of PUV identified in this audit had initial transurethral catheter placement to drain the urinary tract while awaiting confirmation. Screening and treatment for urinary tract infection was routinely done. MCUG was done only after the UTI has been well treated. The electrolyte and acid-base abnormalities that were associated with the renal failure were treated according to standard treatment of renal failure. Intravenous fluid replacement was done for post-obstructive diuresis according to the age-specific urine output/kg/hr.
Since Red Cross Children's Hospital had no neonatal unit, all cases with initial respiratory problems at birth were firstly managed at the neonatal intensive care unit at the provincial maternity hospital.

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4.6.2 Type of surgical intervention

Three types of surgery were identified in the management of PUV in this study either alone or in combination;

- Valve ablation
- Vesicostomy
- Cutaneous ureterostomies

Thirty-five (72.9%) out of the 48 cases had valve ablation as the primary surgical intervention whilst the remaining 13 (27.1%) had preliminary urinary diversion by

vesicostomy. Secondary vesicostomy was performed on 3 cases on account of incomplete primary valve ablation. Four (8.3%) out of the 48 cases had secondary cutaneous ureterostomies to augment urinary drainage on account of secondary vesicoureteral junction obstruction.

Two children had their valves ablated incidentally during passage of urethral catheter; 1 completely and the other partially.

Table 4.1 shows the various surgical methods employed n this audit.

Table 4.1: Types of surgical interventions in treatment of PUV

Type of Surgery	**Frequency**	**Percentage**
Valve ablation only	29	60.4
Primary vesicostomy only	12	25.0
Valve ablation + secondary ureterostomies	3	6.3
Valve ablation + secondary vesicostomy	3	6.3
Primary vesicostomy + secondary ureterostomies	1	2.0
Total	48	100.0

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4.6.3 Other surgical interventions

Besides the definitive treatment of valve ablation and temporary diversionary methods, other surgical interventions that were carried out in patients' management included:

- Bladder augmentation (2 cases)
- Appendicovesicostomy (Mitrofanoff principle) for CIC of the bladder (2 cases)
- Nephrectomy for non-functioning kidney (2 cases), and severe pyonephrosis (1 case)

Histology of the 3 nephrectomised kidneys showed renal dysgenesis with interstitial nephritis in two, whilst the other showed end stage renal disease with hydropyonephrosis from long standing hydronephrosis and pyelonephritis.

4.7 Primary Methods of Clinical Presentation

The 48 cases of PUVs studied in this audit presented variably with some presentations unrelated to the urinary system. The various modes of clinical presentation are shown in Table 4.2.

It is significant to note that dribbling of urine on micturition as a presenting complaint was identified in only 2 (4.17%) out of the 48 study patients.

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Table 4.2: Methods of Clinical Presentation of PUV*

Clinical Presentation	Frequency	Percentage
Prenatal hydronephrosis	17	35.41
UTI	10	20.83
Palpable abdominal mass	4	8.33
Voiding difficulties	3	6.25
Gastroenteritis	3	6.25
Renal cysts detected on ultrasound	2	4.17
Enuresis	2	4.17
E. coli sepsis	1	2.08
Meningitis	1	2.08
Necrotising enterocolitis	1	2.08
Pneumonia	1	2.08
Renal failure	1	2.08
Failure to Thrive	1	2.08
Upper respiratory infection	1	2.08
Total	48	100.00

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* The clinical presentation identified in this audit may be biased due to the absence of neonatal unit at RXCH. Thus patients with severe symptoms related to pulmonary hypoplasia either died or were too ill to be referred.

4.8 Associated urinary tract abnormalities

Every segment of the urinary tract from the posterior urethra through the bladder, ureters, and the renal pelvis were affected in all the 48 cases studied. The renal parenchyma was not spared the secondary effects of this obstructive disease with 6 (12.5%) cases of renal dysplasia being recorded. Thirty-eight (79.1%) of the 48 cases had bilateral hydroureteronephrosis whilst 4 (8.3%) had unilateral pathology. Thirty-six (75.0%) had demonstrable bladder pathology of various degrees ranging from thickened wall through trabeculations to formation of diverticula. Thirteen (27.0%) cases had vesicoureteric reflux which could be demonstrated on MCUG whilst 6 (12.5%) cases had dysplastic kidneys, 2 of which were associated with unilateral VUR in Vesicoureteral Reflux and Dysplasia syndrome (VURD).

The various abnormalities of the urinary system that were associated with PUV are depicted in figure 4.3.

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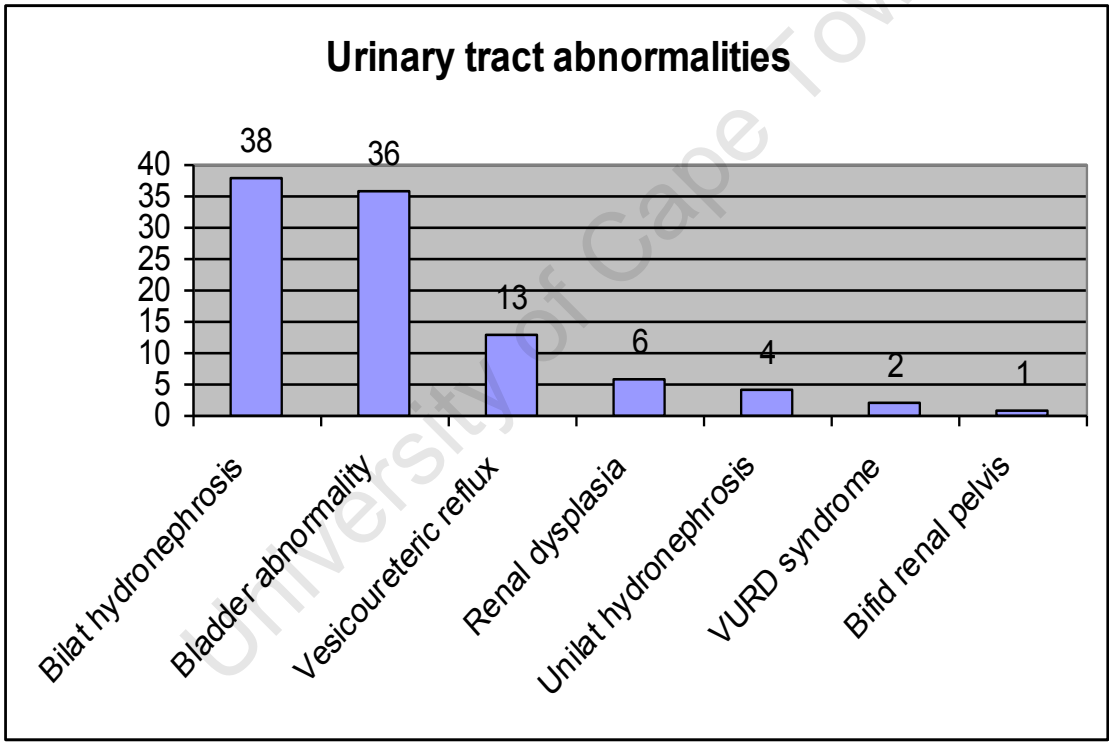

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Figure 4.3: Urinary tract abnormalities associated with PUV

4.9 Complications

Complications of PUV identified in this audit were:

- Urinary ascites (3)
- Urinoma (2)
- Oligohydramnios with lung hypoplasia (2)
- Unilateral non-functioning kidney (2)
- Potter's sequence (1)
- Perinephric abscess (1)
- Pyonephrosis (1)
- Acute renal failure (1)
- Hypertension (1)
- Ruptured bladder during MCUG (1)

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4.10 Other associated medical conditions

Other medical conditions that were identified to be associated with PUV in this study are presented below:

- Inguinal hernia (3 cases)
- Bilateral squint (1 case)
- Attention Deficit Hyperactive Disorder (1 case)
- Polydactyly (1 case)
- Trisomy 21 (1 case)
- Dysmorphism with macrocephaly, mental retardation and atrial septal defect (1 case)
- Maternal systemic lupus erythematosis (1 case)
- Right undescended testes (1 case)

- Pulmonary tuberculosis (1 case)

4.11 Serum creatinine estimations

4.11.1 Creatinine at diagnosis (pre-surgery)

Records of serum creatinine at diagnosis (pre-surgery) were available for 40 (83.3%) out of the 48 studied subjects. The median creatinine value was 86 μmol/l (IQR 67.5 - 146.7μmol/l).

4.11.2 Nadir serum creatinine

The lowest level of serum creatinine (nadir) achieved in the first year following surgical drainage ranged from 21μmol/l to 146 μmol/l with a median value of 40 (IQR 31.2 - 49.5 μmol/l).

4.11.2.1 Duration to nadir creatinine

The time interval to achieve the nadir value ranged from 4 days to 210 days, with a median of 30 days (IQR 14.0 – 48.5 days).

4.11.3 Serum creatinine at 1 year of age

Records for serum creatinine at age 1 year were available for 18 (39.1%) out of the 46 study subjects who were aged ≥ 1 year. The median value was 48 μmol/l (range 25 – 219, IQR 38.2 – 63.7μmol/l).

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4.11.4 Serum creatinine at last follow up

Thirty-nine (81.2%) of the 48 study subjects had their creatinine determined at the last follow up. The median value was 57µmol/l (IQR 43-73µmol/l).

4.12 Length of, and age at, follow up

The median duration of follow up was 52 months (IQR 24 - 107 months).

At the last follow up, patients' ages ranged from 1 month – 221 months (median 100, IQR 47.5 – 128.7%).

4.13 Outcome of study subjects

4.13.1 Stage of chronic kidney disease

The stage of chronic kidney disease at last follow up based upon the estimated glomerular filtration rate (GFR) according to the K/DOQI guideline are presented in Figure 4.4 below. Staging of CKD could be determined for 37 (77.0%) out of the 48 study subjects. Two children were < 2 years and were therefore not eligible for CKD staging according to K/DOQI guidelines.[3] For nine (19.5%) others, the eGFR could not be determined because of incomplete data; either lack of height measurement or no determination of serum creatinine at the last follow up.

At the end of the follow up period, only one (2.7%) patient had reached ESRF at a time interval of 5 years 3 months.

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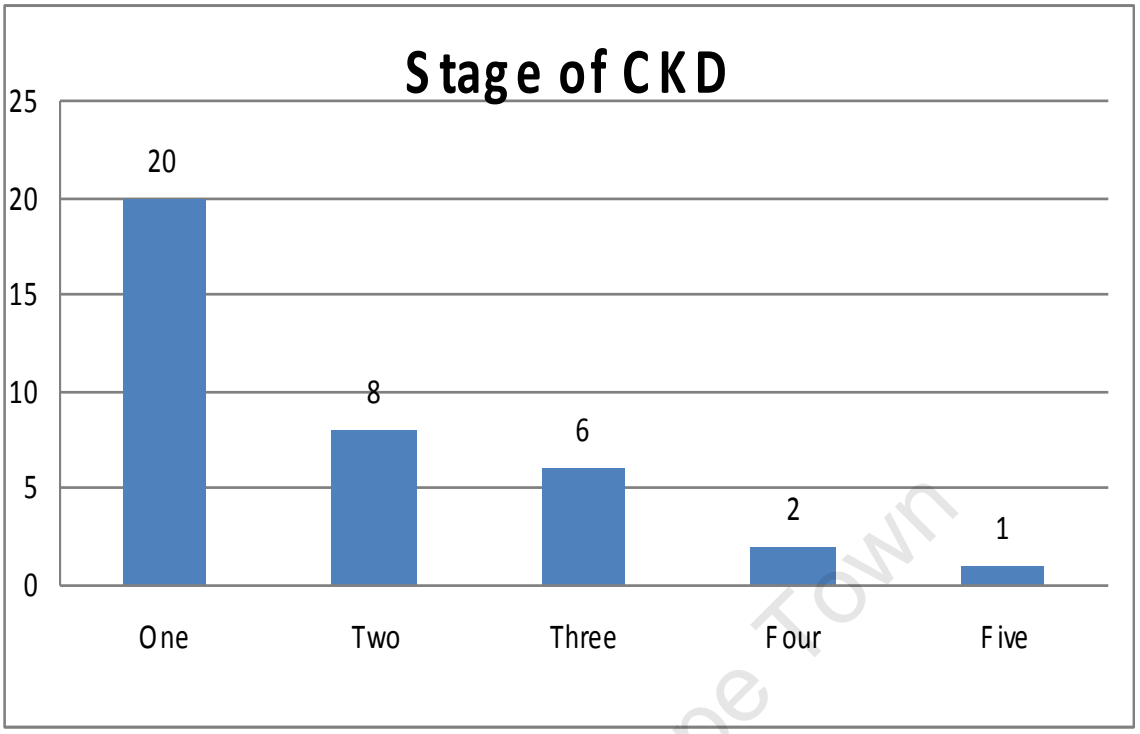

Figure 4.4: Stage of chronic kidney disease at last follow up

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4.13.2 Type of Renal Replacement Therapy (RRT)

The sole patient who had reached ESRF and therefore needed RRT had peritoneal dialysis for 5 months and was successfully transplanted thereafter at age 5 years 9 months. The transplanted kidney has survived 4 years 2 months with a serum creatinine at last follow up of 48 µmol/l.

4.13.3 Survival outcomes

No mortality had been recorded in the cases reviewed during the study interval. However, for 14 cases, more than 1 year has elapsed since they were last reviewed. Their appointment schedules could not be determined from their folders to know whether they were still within appointment time or have defaulted follow up. The survival outcome of such patients may not be accurately determined.

4.14 Correlation of various parameters of patients with the stage of CKD.

Tests for correlations between various aspects of patients' characteristics and stage of CKD were performed using either Spearman's rank correlation or Chi (X-) squared. The results are presented in Table 4.3 below.

Table 4.3: Statistical significance

Characteristic	**Spearman's rho**	**Chi squared**	**p - value**
Age at diagnosis (outside prenatal)	0.0923484	-	0.592 (NS)
Age at surgery	0.06209948	-	0.719 (NS)
Presence of bladder pathology	-	1.0676	0.301(NS)
Presence of VUR	-	0.2385	0.625 (NS)
Serum creatinine at diagnosis(presurgery)	**0.4563161**	**-**	**0.008***
Nadir creatinine (in 1st year)	**0.5183205**	**-**	**0.003***
Time interval to nadir creatinine	0.1382254	-	0.458 (NS)
Serum creatinine at 1 year	**0.6815544**	**-**	**0.002***

NS = not significant

* = statistically significant

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4.15 Adherence to departmental protocol on PUV

The departmental protocol on follow up management of children with PUV (see Appendix 2) stipulates a scheduled annual review tied with various investigations aimed at staging the CKD for the appropriate therapeutic action to be instituted as per K/DOQI guidelines (Table 1).

This well scheduled follow up protocol was largely not adhered to. For example, only 25 (54.3%) of 46 children aged ≥ 1 year were scheduled for the 1 year follow up appointment of whom 18(72%) had their serum creatinine determined. Height measurements, which serve both as index for growth monitoring and a factor in the computation of the estimated glomerular filtration rate (see Schwartz formula in section 3.5), were inconsistently taken. For example, 9 patients (25%) had no height measurements at the last follow up.

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CHAPTER 5
DISCUSSION

5.0 Age at diagnosis of PUV and the need for universal prenatal ultrasound scan.

For all forms of obstructive uropathies including PUVs, the goal of therapy is to relieve the obstruction in the earliest possible time. Such a goal can only be met if the condition is diagnosed early. Since urinary tract dilatation is generally regarded as one of the foetal abnormalities that could easily be identified prenatally, the tendency in the present decade in most first world countries is towards a 100% diagnosis of all obstructive uropathies prenatally.[37,38,50] In developing countries, however, the often poor maternal health care services with its attendant lack of prenatal ultrasound scan leaves most children with obstructive uropathies to be identified only postnatally; sometimes quite late with advanced renal dysfunction. In this audit, more than 60% of children with PUV escaped prenatal detection. One child was diagnosed as late as 2,950 days (8 years). The ages at which PUV were diagnosed in this audit parallels that of a series in the British Isles conducted in the presonographic era in the 1970s.[40] Even when all the cases of PUV diagnosed in the last 3 years of the audit (from January 2006 to January 2009) were analysed, only 6 (42.8%) out of 14 cases were identified prenatally. Considering the fact that this audit covers a relatively recent period, 2002 to 2009, the finding of < 40% cases of prenatally detected PUV highlights the generally suboptimal maternal health care services that often confront developing countries like Africa.

Compared to other African countries south of the Sahara, South Africa has a strong economy with probably the best healthcare services. The Western Cape province, and Cape Town Metropolis in particular where RXCH is situated, has one of the best healthcare services in South Africa, and so by extension the whole of Africa. If only 35.41% of PUVs were detected prenatally in this study in this province/metropolis, then the situation could be worse for less endowed provinces and probable the rest of Sub-Saharan Africa. More effort therefore needs to be put into improving maternal healthcare

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services in Africa, particularly in terms of universal access to prenatal ultrasound scan. Such an intervention could improve significantly, the number of congenital obstructive uropathies like PUV that are detected and treated early. The intervention will lead to improvement in the quality of life of the affected child. Also, some economic gains could be made to the state in terms of resources saved in averting the high cost of treatment for ESRF.

5.1 Methods of clinical presentation

Outside prenatal detection of PUV, the methods of presentation of PUV identified in this audit is consistent with reports in the literature.[1,2,19,40] A palpable abdominal mass (bladder or kidney) has been described as a common finding in patients with PUV[39]. In this audit, 4 (8.33%) patients presented that way and stress the importance of the routine examination of newborns. In this way it may be possible to make diagnosis before UTI occurs and thus lessen the severity and possibly the deterioration of renal function. Daytime wetting and nocturnal enuresis as presentations of PUV in older boys as identified in this audit have been reported by Bomalaski et al[37] as the leading methods of late presentation of PUV and stresses the need for thorough investigation of this social disorder.

Obtaining a history of dribbling of urine in a boy is undoubtedly one of the most important clues to the diagnosis of PUV. There is therefore a false conception among doctors that a good urine stream excludes PUV. In this audit, only 2 (4.17%) of the 48 study patients presented with dribbling of urine. In analysing 108 children with PUVs from 7 surgical centers in the British Isles, Atwell found only 5.5% of the children to have reported poor urine stream as a primary complaint.[40] Thus, this widely held belief of "no urine dribble in a boy, no PUV" should be discarded. Instead, any symptom referable to the urinary tract in a boy, including bedwetting in a boy more than 5 years of age, should warrant some investigation to rule out PUV.

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5.1.1 The need for radiological evaluation for ALL boys with UTI

Of the 29 postnatally diagnosed PUVs in this audit, 10 (34.4%) were identified during evaluation for UTI. In his series, Atwell JD[40] identified UTI as the most common method of presentation of PUV in 7 paediatric surgical centers in the British Isles, accounting for 34.2% of all methods of presentation. Because UTI is a common presenting feature in boys with PUV, universal radiological investigation is recommended in all boys who were not screened antenatally, after their first UTI. Such a recommendation though at variance with the NICE guideline[51] on evaluation of UTI is still relevant in the Africa where most children never had a prenatal ultrasound scan.

The NICE guidelines on UTI stipulate a mandatory radiological evaluation only for children less than 6 months of age diagnosed with UTI. For children older than 6 months, there should be additional features to warrant further diagnostic imaging.

In this audit, an eight year old with history of failure to thrive and previous UTI who was never evaluated radiologically presented with advanced chronic renal failure and a non-functioning left kidney. Histology on his nephrectomised kidney showed hydropyonephrosis from long standing hydronephrosis and pyelonephritis.

5.2 Prevalence and Racial distribution of PUV

Since RXCH receives referrals from outside the Western Cape Province, the prevalence of PUV in the population could not be determined in this audit. However, among the four racial groups in the Western Cape, PUV appears to be relatively commoner among the Coloured race accounting for 70.8% of all cases. This is against the background that the Coloured, though in the majority within the Western Cape Province, constitutes 53.9% of the total population of the province (Table 3.1). When the distribution of PUV among the Whites and Blacks who have population distribution in the Western Cape of 18.7% and 26.7% respectively (i.e. White : Black ratio of 1 : 1.42) were compared, 13x as many Blacks compared to Whites were affected. This finding may give credence to the report by Meyers et al[36] who found PUV to be more prevalent among Blacks in South Africa. This racial distribution of PUV may, however, be biased considering the well known fact that in South Africa, more White patients than Blacks and Coloured have private medical

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insurance and are thus managed by the private sector. Some authors have reported of no racial predilection of PUV.[2]

5.3 Diagnostic tools in PUV

In this audit, 3 main diagnostic tools for PUV were identified namely KUB USS, MCUG, and urethrocystoscopy which is in keeping with the practice elsewhere.[2,43] MCUG was the standard tool used in confirmation of PUV as has been the practice internationally.[43] The limitation of MCUG as cautioned by Wienner JS[2] was demonstrated in this audit when a patient with a negative MCUG film was later confirmed to have valves on urethrocystoscopy. Thus a proper MCUG technique must be employed at all times with adequate urethral views as well as removal of the urethral catheter during the voiding phase. Where the suspicion of PUV is strong on account of clinical and sonographic features, a negative MCUG should prompt urethrocystoscopic evaluation. The consequence of a missed diagnosis based upon false negative MCUG could be disastrous for the individual child and his family. The converse is also true for MCUG leading to false positive results. Bomalaski et al[37] insists that all cases of PUVs suspected on MCUG must be confirmed by cystoscopy. Also in this audit, 3 cases of PUVs were diagnosed solely on ultrasound findings. Tejani et al demonstrated that a good sonographic technique could actually establish the diagnosis of PUV.[43]

5.4 Time interval to confirmation of diagnosis and surgical intervention

For all obstructive uropathies including PUV, the importance of prompt diagnosis and subsequent definitive treatment cannot be overemphasised.[1,2] In this audit, the median time to confirmation of diagnosis was 5 days, with more than one-third of cases (35.4%) being confirmed in the first 24 hours of presentation. In all, 66.6% of all cases were confirmed in the first 7 days of presentation.

Median time to initial surgical intervention was equally short, 8.5 days, with the IQR being 6 - 15days.

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Considering the fact that in Africa health resources, in terms of personnel and equipment, are often over-stretched by the low physician to patient ratio, such promptness in establishing diagnosis and subsequent surgical management identified in this audit is highly commendable.

This commendation notwithstanding, the delay in confirmation of diagnosis as well as surgical intervention in some patients on account of broken down fluoroscopic machine and lack of appropriate endoscopic equipment (urethra too small for the available cystoscope) stresses the need for strengthening of the health systems in Africa. This is particularly important for RXCH considering its status of as a major paediatric referral center in South Africa and beyond. It may be argued though that equipment and technological failure are not unique to Africa.

5.5 Differential diagnosis of PUV

A case initially diagnosed as PUV was found to be idiopathic bulbar urethral stricture (Cobb collar) and underwent a successful urethral dilatation. This case highlights the importance of keeping in mind the differential diagnosis of PUV and the need for a pragmatic approach to investigation since the treatment for each condition is different.

5.6 Management practices of PUV

The management practices identified in this audit is consistent with the literature and can be compared to that of the developed world.[1,40,52]

It has been a standard practice to place urethral catheter at the time of diagnosis to offer quick drainage of the system (which is often infected) while surgical intervention is being planned.[1, 40,52,53] As Postlethwaite and Dickson put it; *infection occurring within the closed system of posterior urethral valves can be lethal.*[1] In this audit, all patients had initial urethral catheter drainage. This is a commendable practice that can improve renal function and the long-term outcome of PUV. It should be embraced by all. For physicians operating in the peripheral institutions, this placement of urethral catheter to promote drainage prior to referral to higher centers should be a routine practice.

The RXCH protocol recommends fluid replacement to manage post obstructive diuresis following relief of obstruction, which if overlooked, could lead to severe fluid deficit and

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worsening of renal failure. The institution of such practice at RXCH is also commendable.

Overall, many aspects of the management practices identified in this audit is standard in keeping with practices elsewhere in the developed world except for the deficiencies in follow up care.

5.6.1 Modalities of surgical interventions

The variety of surgical treatment of PUV described in the literature were employed in the management of study subjects.[41,43,50] Preliminary urinary diversion has been an age old surgical practice particularly where the definitive treatment by valve ablation cannot be performed for medical and or technical reasons.[1,40,50,52,54] In this audit, both lower and upper tract diversionary procedures, by way of vesicostomy and ureterostomies respectively, were employed as has been the practice elsewhere.[40,41,43,52,54] It is significant to note that majority (60.4%) of the study patients identified in this audit had the definitive surgical treatment of valve ablation as the primary and sole surgical treatment. This drive is consistent with the literature[40,55] and is particularly important since urinary diversionary procedures have been reported to jeopardise the potential for bladder healing and normal bladder function.[55,56] Puri et al[55] identified in their study that primary valve ablation is associated with better bladder function than vesicostomy and recommended it to be the surgical treatment of choice.

This audit identified surgical bladder augmentation for patients with failed medical treatment of bladder dysfunction, similar to what was practiced elsewhere.[52] Obsolete valve ablation procedures like disruption of valve by blind passage of a valve hook[52], perineal urethrostomy[40], and transvesical approach to valve ablation[40] were not identified in this audit. Instead, Bugbee electrocauterisation was the main method used which is in keeping with modern methods.[52]

5.7 Urinary tract abnormalities associated with PUV

The pathological effect of this obstructive membrane on the entire segment of the urinary tract proximal to it, including the developing kidney, has made PUV the worse type of

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congenital obstructive uropathy as opined by Casale.[53] Unlike most upper tract obstruction like pelvi-ureteral junction obstruction that tends to affect one unit of the system, PUV commonly exerts its effect on both units of the urinary system. In this audit, abnormalities were identified in every segment of the tract as has been documented in several studies.[12,50] Bladder abnormalities were detected in 75% of cases, VUR in 27.0%, hydroureteronephrosis in 87.4%, bifid renal pelvis 2.0%, and renal dysplasia in 12.5% of cases. The association of these abnormalities with PUV has well been described.[12,37,50] Two patients had myopathic bladder that were severe enough to require augmentation cystoplasty. This procedure has been employed elsewhere[43] and confirms the diverse technical expertise available at RXCH. Appendicovesicostomy (Mitrofanoff principle) for CIC of the bladder was similarly identified in 2 cases.

Though bilateral hydronephrosis was the leading abnormality of the urinary tract identified (79.1%), it is significant to note that 8.3% of patients presented with unilateral hydronephrosis. Warshaw et al[13] similarly identified unilateral hydronephrosis in 18.1% of their patients with PUV. Though bilateral hydronephrosis often with hydroureters has been the sonographic clue to the diagnosis of PUV, the finding of unilateral hydronephrosis in this study as well as elsewhere emphasise the need for any male child with dilatation of the urinary tract, be it unilateral or bilateral, to have MCUG study in order to rule out PUV.

Six patients had renal dysplasia 2 of whom had associated unilateral vesicoureteral reflux with normal contralateral kidneys. This unequal distribution of the pressure effect of PUV among the 2 kidneys is an adaptation mechanism called vesicoureteral reflux and renal dysplasia (VURD) syndrome and has been described in the literature.[13,36]

5.8 Associated medical conditions

A number of medical conditions identified to be associated with PUV in this audit have been described in other studies.[50] The association with inguinal hernia (3 cases in this study) is probably due to the high intraabdominal pressure that is generated during voiding in a bid to overcome the bladder outlet obstruction.

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5.9 Complications

5.9.1 Pop-off mechanisms

Urinary ascites and urinomas are rare complications that may be associated with PUV. They result from the rupture of a calyx as a direct consequence of the high pressure build up in the urinary collecting system as a result of the obstructing membrane of PUV. In this audit, 2 each of urinary ascites and urinomas were identified. Urinary ascites, urinomas, together with VURD and bladder diverticula have been reported to be protective mechanisms (pop-off adaptive mechanisms) in PUV that serve to lower the intraluminal pressures and allow at least one renal unit to develop normally.[2,36]

5.9.2 Complications from decreased foetal urine production (oligohydramnios)

Three children had pulmonary hypoplasia and one had Potter's sequence. Potter's sequence and pulmonary hypoplasia are recognised complications that occur in PUV and result from oligohydramnios secondary to decreased foetal urine output.[52,57] An appropriate volume of amniotic fluid largely produced by foetal kidney is necessary for complete and proper branching of the bronchial tree and alveoli.[52] Modern neonatal intensive care units have led to dramatic reduction in neonatal mortality from obstructive uropathy.[50] But in their study, Nakayama et al[57] were of the opinion that survival from pulmonary hypoplasia depends on the severity of the PUV obstruction which may lead to irreversible pulmonary hypoplasia with fatal outcomes. They emphasised what they called hidden mortality of PUV on the basis that babies with severe PUV may die soon after birth from irreversible, fatal pulmonary hypoplasia without the underlying PUV being recognised. Thus, the true case fatality of PUVs may not be represented in the literature. In this audit, all 3 cases of PUV with pulmonary hypoplasia survived the neonatal period. Whether the survival is due to improvement in neonatal intensive care management or milder PUV cannot be determined. Again since RXCH does not have a neonatal unit and only receives referrals from the provincial neonatal unit, the number of

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cases of PUVs who did not survive the neonatal period cannot be determined in this audit.

5.9.3 Other complications

The other complications identified in this audit namely non-functioning kidney, pyonephrosis, hypertension, perinephric abscess have all been described elsewhere.[40,41,50] An iatrogenic complication occurred in one patient when the bladder was ruptured during performance of the MCUG. Care should be taken during bladder catheterization in patients with PUV, because of the associated bladder pathology. Histology of 3 nephrectomised kidneys for non-functioning (2 cases) and severe pyonephrosis (1 case) showed end stage renal failure with hydropyonephrosis in one specimen from long standing hydronephrosis and pyelonephritis obviously from a missed diagnosis of the PUV whilst the other 2 showed renal dysgenesis with interstitial nephritis. The finding of non-functioning kidney in PUV even after surgical decompression of the system is not uncommon and has been described elsewhere.[40,58] Treatment of the non-functioning kidneys with nephrectomy is in keeping with standard practice and is aimed at reducing the risk of further infection in an already damaged urinary tract.[13,40] Other studies have equally demonstrated renal dysgenesis (dysplasia) and interstitial nephritis in such damaged, non-functioning kidneys.[40,41] Obstructive uropathy has been shown in animal studies to lead to loss of nephrons[25,26] and the release of fibrogenic cytokines such as TGF – β which leads to tubular atrophy and interstitial fibrosis.[28,29,30]

5.10 Progression of CKD

The progression of CKD associated with PUV was determined based on the K/DOQI staging of CKD at the last follow up. At the end of the follow up period ranging from 1 month to 216 months (median 52 months), 20 (54.1%) out of the 37 patients whose CKD stage could be determined were in stage 1 and therefore not in chronic renal failure. Sixteen (43.2%) patients had chronic renal failure, stage 2 – 4.

Only one (2.7%) patient had ESRF (i.e. stage 5) and needed RRT. Thus, altogether, 36 (97.3%) out of the 37 patients were in early stages of CKD over the median duration of

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follow up of 52 months and did not require RRT. This slow progression of CKD towards ESRF identified in this audit could be attributed to a number of factors:

- Firstly, a population-based registry in Italy[9] and the NAPRTCS[8] data have both demonstrated that patients with congenital anomalies generally have slower progression of early CKD towards ESRF compared to patients with glomerular disease as has been demonstrated in this study. Other studies have similarly demonstrated that the evolution of renal failure in children with obstructive uropathy may be extremely prolonged.[41] The duration of follow up in this audit (median 52 months) was not long enough to witness sizable proportion of the study subjects to be in ESRF.
- Secondly, the prompt diagnosis and therapeutic intervention employed in the management of cases in this audit could substantially delay progression to ESRF. The 5 days median time duration to confirmation of diagnosis by MCUG, the 35.4% confirmation within the 1st 24 hours, the median time interval to surgery of 8.5 days, the comprehensive initial medical management identified in this study, and the collaborative team approach to management between nephrology, urology and radiology could all contribute to the slowing of disease progression towards ESRF.

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5.10.1 Time interval to ESRF

The time interval to the development of ESRF in this audit was 5 years 3 months.
It appears though that the progression to ESRF is quite variable and may be related to multiple factors including the time when intrauterine tract obstruction developed, the severity of obstruction, associated renal dysplasia, and timing and type of treatment instituted. Tejani et al found varying time interval from 6 months to 14 year to ESRF. They therefore suggested prolonged follow up care for children with PUV since ESRF can occur many years later.[43]

5.11 Prognostic factors

Factors that have been cited to portend poorer long-term outcome in PUV include:

- early presentation outside prenatal diagnosis,[37,40,45]

- nadir serum creatinine (post surgery) in the first year of life,[13]
- serum creatinine at age 1 year[59]
- presence of VUR,[37]
- age at surgery.[22]

In this audit, 3 factors were identified to have prognostic value of significance namely;

- nadir serum creatinine in the first year of life following surgical relief of the obstruction (Spearman's rho 0.5183204, p-value 0.003),
- serum creatinine at age 1 year (Spearman's rho 0.6815544, p-value 0.002),
- serum creatinine at diagnosis (Spearman's rho 0.4563161, p-value 0.008).

Nadir serum creatinine within the first year as well as creatinine level at age 1 year as prognostic indices have been confirmed in this study. Both may reflect the functional reserve of the kidney following the relief of the obstruction and hence their prognostic value.

Though age at presentation has been cited to have prognostic significant with those presenting early representing severe disease that often show little improvement in renal function after surgery,[45] this could not be confirmed in this study. A previous study similarly failed to show any association of age at presentation with renal outcome.[37] Instead, Tejani et al[43] and El-Sherbiny et al[60]found worse outcomes in children in whom diagnosis was made beyond 2 years and 1 year of age respectively.

Surgical intervention prior to age 1 year as a factor conferring good prognosis as put up by Mayor et al[22] was not confirmed in a study by Warshaw et al[41] when they demonstrated that some patients will ultimately progress to ESRF despite surgical intervention during the first year of life. In this study also, age at surgery as prognostic index could not be confirmed so were presence of VUR, bladder pathology, time interval taken to achieve nadir creatinine.

Serum creatinine at diagnosis as a prognostic factor identified in this study has also been reported elsewhere[61] though other studies have not confirmed that.[13]

Thus several prognostic factors in PUV seem to vary among different studies. It seems though that the most consistent factor of prognostic significance from the literature are the nadir creatinine following relief of obstruction and the creatinine level at 1 year of age.

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5.12 Adherence to departmental protocol

Though a comprehensive departmental protocol for PUV management is in place (Appendix 2), this audit identified several weaknesses in its implementation. For example, height measurement could not be done for 9 (25%) of the 48 patients at the last follow up. While it is generally accepted that height measurements could be problematic in children especially young infants, the importance of such measurements in assessing nutritional status and growth of such children with chronic kidney disease cannot be over-emphasised. Height measurements are also vital input in estimating GFR for classification of CKD as well as appropriate interpretation of blood pressure. Efforts should therefore be made to strengthen anthropometric measurements at both the nephrology and urology clinics.

Another reason that might have accounted for this low adherence to the PUV protocol may be the non-availability of the protocol at the clinics. Most clinicians may not be aware of the protocol details off hand.

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5.13 Outcome of study patients

5.13.1 Stage of CKD

Over the duration of follow up, 36 (97.3%) out of the 37 patients whose eGFR could be determined were in early stages of CKD (i.e. stage 1-4). Only one (2.7%) patient was in ESRF (i.e. stage 5) and needed RRT.

5.13.2 Renal replacement therapy

The sole patient who needed RRT reached ESRF over a follow up period of 5 years 3 months. RRT in the form of peritoneal dialysis was instituted at age 5 years 4 months and was successfully transplanted 5 months later. At 10 years of age during the last follow up, graft function has been preserved with serum creatinine level at 48 μmmol/l.

5.13.3 Survival outcome

Over the duration of follow up, no mortality has been recorded officially. It is significant to note, however, that 14 (29.1%) cases have been lost to follow up for more than a year and therefore survival outcomes could not be accurately determined. Migration out of Cape Town is also a common phenomenon and could account in part for this.

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CHAPTER 6
SUMMARY AND CONCLUSION

6.0 Summary

Posterior urethral valves are common causes of chronic kidney disease in boys.
Close to 40% of children with PUV (35.41%) were prenatally detected based on hydronephrosis (4 unilateral). Though this number could be said to be sub-optimal means of diagnosis of PUV in the light of the near 100% prenatal detection in most developed world, for a developing continent like Africa it offers hope that with little effort at improving antenatal care services in terms of universal access to prenatal ultrasound, more cases of PUVs and other renal congenital abnormalities could de diagnosed prenatally.

For those cases of PUVs that escaped prenatal detection, 75.8% were diagnosed within 1 year of age with variable presentations. Clinical presentations identified in this audit were similar to reports from the literature. The common presentations were urinary tract infection (10 cases), palpable abdominal mass (4 cases), voiding difficulties (3 cases) and enuresis (2 cases). Dribbling of urine at micturition in boys which has long been considered to be an important finding PUV was found in only 2 (4.17%) of the 48 study patients and was consistent with the 5.5% of cases in another study.[40] Thus, this widely held belief of "no urine dribble in a boy, no PUV" should probably be discarded. Instead, any symptom related to the urinary tract in a boy, including daytime wetting or enuresis after the age of 5, warrants some investigation to rule out PUV.

Ten (34.4%) of the 29 postnatally diagnosed PUVs in this study were identified during evaluation for UTI with some more than 5 years of age at presentation (1 case was 8 years old). Thus the NICE guideline on UTI evaluation may not be relevant in the African setting where most children never had a prenatal ultrasound scan.
Though many more Blacks (13x) compared to Whites had PUV in this study (black:white population distribution ratio of 1.42 : 1), this racial distribution may be biased

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considering the well known fact that in South Africa, more White patients than Blacks and Coloured have private medical insurance and are thus managed in the private sector.

Ultrasonography was a useful tool in PUV screening in this study though micturiting cystourethrogram was the main radiological tool used in confirmation of PUVs. There was 1 case with false negative MCUG findings that was confirmed on urethrocystoscopy and highlights the limitation of this radiological method.

The time interval from suspicion of diagnosis to confirmation was swift with seventeen (35.4%) out of the 48 cases being confirmed within the first 24 hours. Overall, the median time to confirmation of diagnosis was 5 days with 66.6% of cases being confirmed in the first 7 days of presentation.

Median time to initial surgical intervention was equally short, 8.5 days, with the IQR being 6 - 15days. Various surgical techniques in the management of PUVs which were in keeping with management practices in the developed world were identified in this study.

Most cases of PUV identified in this study (97.3%) were in earlier stages (stage 1-4) of CKD at the end of duration of follow up which ranged from 1 month to 216 months (median 52 months). Only 1 patient had reached ESRF over a time interval of 5 years 3 months. He has since been transplanted successfully with preserved graft function at 4 years months. No death had been registered during the period of this study but significant number (29%) have been lost to follow up for over a year.

The prognostic indicators identified in this study population were similar to other reports in the literature. There was a coordinated team approach to the management of PUV at RXCH involving the departments of radiology, urology and nephrology.

Though significant successes were identified in this study in terms of promptness of diagnosis and surgical intervention, several areas in follow up care need improvement.

6.1 **Conclusions**

In conclusion, the experience of PUV management at RXCH, Cape Town, gives hope to Africa and the rest of the developing world and highlights the point that with the right priorities given to the health sector by African governments, coupled with a well determined and motivated team of health professionals, congenital kidney anomalies like PUV could be successfully managed in the African continent to decrease progression to

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ESRF. Such an approach will not only improve the quality of life of the African child with chronic kidney disease, but could save our national budgets substantial amount of money in averting the expensive treatment cost of ESRF.

6.2 Recommendations

- With the emerging prenatal ultrasound scan as a routine tool in maternal healthcare services in most part of Africa, there is the need to create the awareness of screening for foetal abnormalities like hydronephrosis among obstetricians and sonographers so that obstructive uropathies like PUVs could be detected prenatally in keeping with modern trends.
- The departmental protocol on PUV needs to be strictly adhered to. The joint nephrology-urology clinical meetings could be used to discuss the protocol to create much awareness of it. Copies of the protocol should be incorporated into the folders of all cases of PUV for easy reference and to promote adherence to its contents among clinicians.
- For every male child who is diagnosed with urinary tract infection irrespective of age, or has daytime incontinence after 5 years, a palpable bladder and/or kidney, PUV should be ruled out through appropriate imaging studies.
- There is the need for up-gradement of the logistics, particularly surgical equipments like cystoscope, to enhance service delivery.

6.3 Limitations of study

- Because this was a retrospective folder review, folders that could not be traced at the time of the audit could not be included and may thus affect the true representation of PUV over the study period.
- The study population may not be true representative of the population of the Western Cape for two reasons:
    i) there is no “onsite” neonatal unit at RXCH. Thus, cases of PUVs with severe respiratory distress from pulmonary hypoplasia either died or were too ill to be referred for investigation and definitive treatment.

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ii) more White patients with private medical insurance might have been managed at the private sector. This is an established practice in South Africa.

- The short duration of follow up in this audit (median 52 months) may not have allowed for the accurate evaluation of treatment outcomes (time to reach ESRF) in the study patients.

6.4 Need for further studies

There is the need to replicate this study in other provinces in South Africa or other African countries considered less endowed than Cape Town to get the true picture of the magnitude of PUV.

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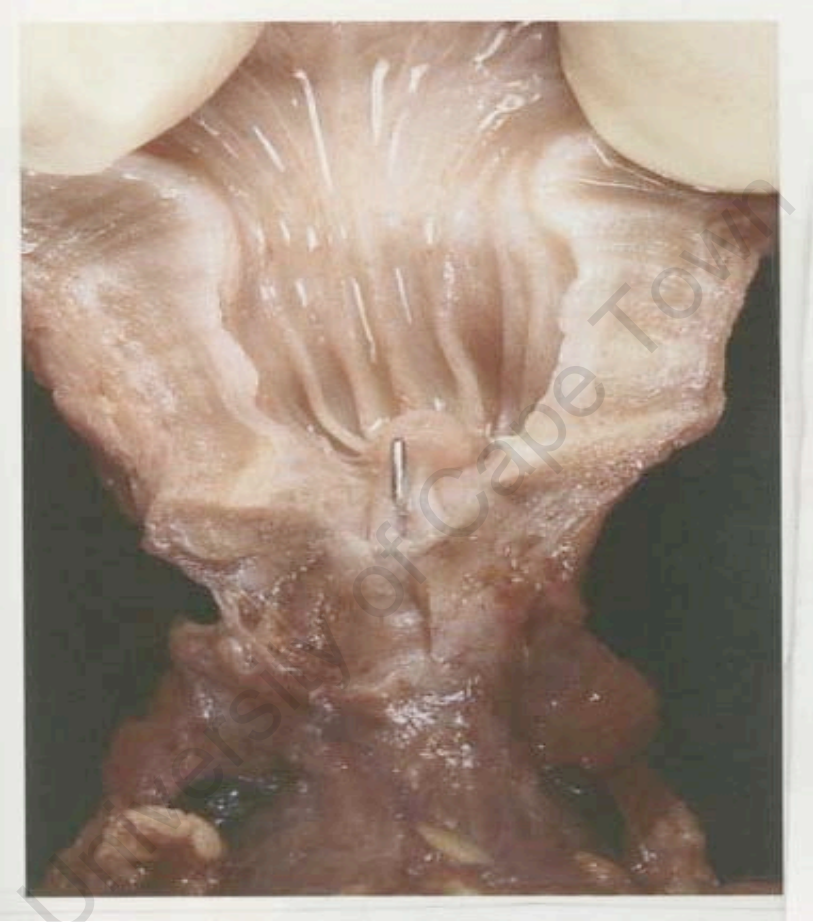
APPENDIX 1

PATHOLOGICAL SPECIMEN SHOWING PUV



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Pathological specimen showing posterior urethral valve. The urethra is obstructed and the bladder wall is markedly thickened. (Source: Paediatric nephrology and urology; the requisites in paediatrics by Bernard S Kaplan and Kevin E. C. Meyers)

APPENDIX 2

Protocol for PUV follow up at Nephrology Unit of RXCH

Posterior Urethral Valve Protocol

At Birth / time of diagnosis _____ Date	Ultrasound KUB, including perineal views Urine biochemistry Suprapubic urine for MC&S FBC, Plasma biochemistry Resection / disruption of valves If discharge plasma creatinine > 60 µmol/l, follow-up at renal clinic
At 3 months _____ Date	Ultrasound KUB, MCUG, Mag3 Urine for MC&S Urine biochemistry Plasma biochemistry: If plasma creatinine > 60 µmol/l, refer renal clinic
At 1 year _____ Date	Mag3 Urodynamics Urine biochemistry Urine MC&S FBC, Plasma biochemistry (If creatinine > 60, refer renal clinic) GFR (If < 50 ml/min/1,73m^2, refer renal clinic)
At 2 years _____ Date	Ultrasound KUB Plasma biochemistry Urine Biochemistry
At 3 years _____ Date	Ultrasound KUB, Mag3 Plasma biochemistry Urine biochemistry GFR (If < 50 ml/min/1,73m^2, refer to renal clinic)
At 4 years _____ Date	Ultrasound KUB Plasma biochemistry Urine biochemistry
At 5 years _____ Date	Ultrasound KUB Mag 3 and indirect cystogram Urine for MC&S FBC Plasma biochemistry Urine biochemistry GFR (If less than 50 ml/min/1,73m^2, refer to renal clinic) Urodynamics

Plasma biochemistry =	Na, K, Cl, TCO_2, Urea, creatinine, albumin, Ca, PO_4, Alk Phos.
Urine biochemistry =	Na, K, Urea, creatinine, protein:creatinine ratio, osmolality

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APPENDIX 3

CASE REPORT FORM

Folder no. ……**DOB……Age diagnosis suspected/confirmed**……/…….

Height at 1-year & at last follow up (cm)……/…..**Race**: white [ ] black [ ] coloured [ ]

Presenting symptoms (tick)

Prenatal HN [ ] UTI [ ] Kidney mass [ ] Weak urine stream [ ] FTT [ ]

Urinary incontinence [ ] Renal failure [ ] Others (state) ……..

Urinary tract abnormalities associated with PUVs (tick):

HN [ ] VUR [ ] Renal dysplasia [ ] Thickened bladder [ ]

Bladder diverticulum's [ ] Others state)……..

Complications associated with PUVs (state)……..

Co-morbid conditions (state): ……..

Age at initial surgical intervention (months): …….

Type of surgery: Vesicostomy [ ] Valve ablation [ ] Ureterostomy [ ] Others

Serum creatinine at:
Diagnosis (pre-surgery)……Nadir value post-surgery……

1-year of age…… Last follow up……..

Patient's outcome at last follow up (tick):

Outcome 1: eGFR…….ml/min/1.73m^2 Stage of CKD……..

Outcme 2: On RRT? Yes [ ] No [ ]

If yes, state type……Time to ESRF…….

Outcome 3: Dead [ ] Alive [ ]

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APPENDIX 4

ETHICAL APPROVAL LETTER

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: nosi.tywabi@uct.ac.za

03 February 2009

REC REF: 061/2009

Dr S Antwi
Renal Unit, Ward E2
Red Cross Children's Hospital

Dear Dr Antwi

PROJECT TITLE: AUDIT OF POSTERIOR URETHRAL VALVES (PUVs) AT RED CROSS CHILDREN HOSPITAL

Thank you for submitting your study to the Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above mentioned study.

Approval is granted for one year until 05 February 2010. Please submit an annual progress report if your study continues beyond the approval period. Alternatively, please submit a brief summary of your findings so that we can close our records.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the REC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

lemjedi

APPENDIX 5

APPROVAL LETTER FROM MEDICAL SUPERINTENDENT, RXCH

Departement van Gesondheid

Department of Health

iSebe IezewMpilo

Verwysing: **Reference:** **Isalathiso:**	**RESEARCH**	**Telefoon:** **Telephone:** **Ifowuni:**	**(021) 658 5383**
Navrae: **Enquiries:**	**Dr. T. Blake**	**Fax:**	**(021) 658 5166**
Datum: **Date:**	**13 February 2009**	**Email:**	**Tblake@pgwc.gov.za**

Dr. Sampson Antwi
Supernumerary Renal Registrar
Ward E2

Dear Dr. Antwi

RESEARCH: RETROSPECTIVE FOLDER REVIEW ON POSTERIOR URETHRAL VALVES FROM JANUARY 2007 – JANUARY 2009

Permission is hereby granted to conduct above-mentioned research at Red Cross War Memorial Children's Hospital.

Yours faithfully,

Dr. T. Blake
Senior Medical Superintendent

Red Cross War Memorial Children's Hospital
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