Prune Belly Syndrome: A 31 year experience at the Chris Hani Baragwanath Academic Hospital, South Africa

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Medicine in Paediatrics

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I, Shannon Dale Leahy declare that this research report is my own work. It is being submitted for the degree of Masters of Medicine in the branch of Paediatrics in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

22 day of September , 2017

This work is dedicated to my parents,

Bev and Rory Leahy,

for all their support during my journey through medicine.

To my husband,

Tyran Van Lieshout,

for his love and patience.

Presentations arising from this study

- Poster presentation:

  Faculty Research Day, University of the Witwatersrand, Medical School.

  1 September 2016

- Oral Presentation:

  South African Renal Congress, Cape Town.

  10 September 2016

- Oral Presentation:

  WITS Paediatrics Research Day, University of the Witwatersrand, Medical School.

  26 November 2016

Abstract

Background: PBS is a rare congenital disorder with a triad of signs: absent abdominal wall musculature, urinary tract malformations, cryptorchidism.

Objectives: Describe the patient profile, management, and outcome of patients attending the Paediatric Nephrology clinic at Chris Hani Baragwanath Academic Hospital.

Methods: Retrospective descriptive record review.

Results: 44 patient files were analysed. Median duration of follow up: 24 months (1.7–130). Median age at presentation was 5.5 days (1–730). Associated conditions included: urological 48%, orthopaedic 11%, congenital heart disease 7%, gastrointestinal 4.5%. Medical management included prophylactic antibiotics and intermittent bladder catheterisation. Surgical management included abdominoplasty with orchidopexy (3 years) and circumcision (7.7 years). Patients over the age of 2 years had a better overall outcome. There was a high default rate of 57%.

Conclusion: Patient profile and management is comparable to other reported series. Deterioration in renal function to ESRD was observed less in this review possibly due to the high default rate.

Acknowledgements

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GLOSSARY

cGFR:	Calculated glomerular filtration rate
CHBAH:	Chris Hani Baragwanath Academic Hospital
CHD:	Congenital heart disease
CKD:	Chronic kidney disease
ESRD:	End stage renal disease
HNF-1β:	Hepatocyte nuclear factor – one beta
ICU:	Intensive care unit
IQR:	Interquartile range
OR:	Odds ratio
PBS:	Prune Belly Syndrome
PUV:	Posterior urethral valves
UTI:	Urinary tract infection
VCU:	Voiding cystourethrogram
VUR:	Vesicoureteric reflux
WHO:	World Health Organisation

Chapter 1

1.0 Introduction:

1.1 Definition

The Prune Belly Syndrome (PBS) is a rare congenital disorder characterised by a triad of signs with a wide variability of clinical manifestations and severity.[1, 2]

PBS was first reported by FrÖhlich in 1939.[3] Osler then assigned the syndrome its current title in 1950 owing to its characteristic appearance of the abdominal wall.[3-6] Later nine cases were reported by Eagle and Barret and it was then alternatively called the Eagle-Barret Syndrome.[6] Other synonyms seen in the literature include the triad syndrome and abdominal musculature deficiency syndrome.[6] The complete syndrome is only seen in males which consist of: deficient or absent abdominal wall musculature, malformations in the urinary tract, specifically megacystis, megaureters, hydronephrosis and renal dysplasia, and bilateral cryptorchidism.[1, 2, 6, 7, 8, 9]

Male patients make up between 90 - 95% of the cases of PBS.[1, 8] Female patients have the characteristic abdominal wall appearance as well as malformations of the urinary tract.[6] Patients with urinary tract abnormalities with or without cryptorchidism, but intact abdominal wall musculature are referred to as “pseudo-prunes”.[10]

1.2 South African setting

There is currently no published articles regarding PBS in South Africa and very few recent articles published from other countries. The Chris Hani Baragwanath Academic Hospital (CHBAH) is a tertiary institution mainly serving the community of Soweto. It is a referral centre for patients within the Gauteng province and surrounding provinces and countries. The majority of patients are referred from the North West province. The Paediatric Nephrology unit at the CHBAH attends to paediatric patients with a variety of renal conditions needing specialised care.

1.3 Epidemiology

The incidence of PBS in the United States of America is 3.76 – 3.8 / 100 000 live births.[2, 6] No local data has been published. Little is known about the epidemiology. Racial incidence depends on population demographics. [2] Most cases of PBS occur sporadically, however familial cases of PBS suggest an X-linked mode of inheritance in a few cases.[11-14]

1.4 Aetiology

There are two main theories regarding the aetiology of the PBS.[7, 11] The first theory is explained by an early functional urethral obstruction by a valve-like mechanism which causes a sequence of events including megacystis, megaureter and hydronephrosis.[7, 11, 15] This then eventually leads to abdominal expansion and an absent or deficient abdominal wall formation.[7, 11, 14, 16] The cause of the

functional urethral obstruction is largely unknown.[6, 11] A focal insult during the development of the urogenital sinus mesoderm has been proposed.[6, 11]

The second theory suggests a mesenchymal developmental arrest during early embryogenesis, causing the genitourinary characteristics seen in PBS.[1, 15] The transcription factor, HNF 1β, is implicated in early embryogenesis in the kidneys, genital tract, abdominal wall and gut, which regulates tissue specific gene expression in these organs.[6, 7, 17] Abnormal gene expression or deletion of the HNF-1β gene on chromosome 17 causes disruption of development of the mesonephric duct derivatives, renal tubules, prostate gland and maldevelopment of the abdominal wall leading to abnormalities seen in PBS.[6, 7,16]

1.5 Clinical findings

The urinary system in PBS reveals varying degrees of parenchymal dysplasia, together with ureteropelvic dilatation, mega-ureters and a high capacity bladder.[1, 7, 15] Ultimately the urinary system in PBS is a low pressure, dilated and generally of a non-obstructive nature.[1] The kidneys themselves may be small in size with both the cortex and medulla showing varying degrees of dysplasia.[11] This all contributes to progressive renal dysfunction, and together with recurrent damage from infection and scarring of the kidney, could lead to end stage renal disease (ESRD).[7] Vesicoureteric reflux (VUR) is seen in up to 66-75% of the cases.[1, 6, 17]

The abdomen has a wrinkled, drooping appearance due to partial or total dysplasia of the muscular wall, figure 1.5.[1] Microscopic evaluation of the muscular abdominal wall shows atrophy, shrunken muscle fibres and fibrous tissue with some areas of the wall replaced with collagen.[11,16]

The failure of descent of the testicles is probably due to a mechanical barrier attributable to the dilated urinary system.[11] This can be explained by both aetiological theories.[11] The testes are small in size and the development of the epididymis and vas deferens may be abnormal, which is predominately explained by the mesenchymal theory.[1, 6, 7] Due to the abnormal development of the testes these patients are infertile.[17]

Figure 1.5: Typical appearance of the PBS. Note the wrinkled appearance of the skin overlying the abdomen and bilateral undescended testes. Image courtesy of Anatomy Box.[18]

1.6 Diagnosis

A diagnosis of PBS can be suspected antenatally using ultrasound with certain features suggestive of the condition, for example a bulging abdomen, lack of abdominal wall musculature, dilatation of the urinary systems, cystic kidneys, oligohydramnios, foetal ascites and hypoplastic lungs.[3, 6] The main differential diagnosis antenatally is posterior urethral valves (PUV) which must be differentiated postnatally by a voiding cystourethrogram (VCU).[9]. The diagnosis of PBS is usually made postnatally in South Africa due to the fact that less than 50% of pregnant mothers in the urban government hospitals have access to an antenatal ultrasound before 24 weeks of gestation.[19]

1.7 Associated abnormalities

Associated abnormalities are a frequent occurrence in PBS which can affect the outcome of patients.[1] Prematurity has been described in studies as one of the most common associated factors in patients with PBS (40%).[2, 8, 16]

Respiratory system complications are frequently encountered in PBS.[1] The weak diaphragmatic muscle as well as pulmonary hypoplasia resulting from oligohydramnios in utero contributes to the morbidity and mortality in the early phase of life as an infant.[1, 7, 20] In addition, spinal and thoracic problems from the lack of abdominal wall musculature contribute to the respiratory complications.[1, 20]

Gastrointestinal problems are seen in up to 30% of patients with the PBS, these include atresias and malrotations.[1, 7] Omphalocoeles have also been described in a few patients.[2]

Skeletal abnormalities are also present in 30-40% of patients depending on the degree of oligohydramnios in utero.[1] Club feet and congenital dislocation of the hip have been associated with this syndrome.[7]

Acyanotic and cyanotic congenital heart disease (CHD) have also been associated with PBS.[1, 7, 8]

Cystic kidney disease, posterior urethral valves (PUV) and urachal abnormalities have also been related with PBS.[2, 6, 13] Functional complications such as acute and chronic renal failure, urinary tract infection have also been implicated in patients with PBS. [2, 6, 13]

1.8 Classification

Patients can be classified into mild, moderate and severe forms of the syndrome directed by their renal function.[17] This classification system helps to prognosticate the general outcome of patients.[17] Twenty percent fall into the severe category presenting with severe renal dysplasia, oliguria and pulmonary hypoplasia.[1, 17] There is a high incidence of stillbirth and early neonatal mortality in this category.[1, 21] Thirty to forty percent of the cases display a moderate severity with marked renal dysplasia and progressive renal failure.[1, 17] One third of patients in the moderate category will die within two years of life without intervention.[17] The mild group accounts for 40% of the cases with mild renal dysplasia and varying degrees of urinary collecting system enlargement.[1, 17] Up to 30% of patients who survive infancy in the mild and moderate categories can develop ESRD due to the intrinsic renal dysplasia despite management procedures that try to improve drainage of urine and prevent infection of the urinary system.[22]

1.9 Management

The management of PBS has evolved through the years.[1] The main aim of management is to preserve renal function and prevent infection in the urinary tract.[6] Cosmetic and preventative management in terms of the abdominal wall and testes respectively are also priorities.[6]

Some centres advocate for early aggressive surgical management which include temporary urinary diversion and major corrective surgery of the urological system in order to decrease the size of the dilated system and improve urinary drainage.[1, 8, 23] Later abdominal wall reconstruction and orchidopexy can be considered.[1, 8]

More recently an individually tailored approach that encompasses urinary tract reconstruction, bilateral orchidopexy and abdominoplasty in one operation has been proposed.[17] Circumcision has been shown to prevent colonisation of the urinary tract and together with antibiotic prophylaxis may reduce urinary tract infection (UTI) rates.[24]

Urinary tract infections are treated with the appropriate antibiotics. Conservative management includes prophylactic antibiotics, double voiding with or without intermittent catheterisation.[6, 8] The aim is to achieve complete bladder emptying and thus avoiding urinary stasis and overgrowth of bacteria leading to infection.[6, 8] The use of prophylactic antibiotics is to prevent urinary tract infections. Recently the use of prophylactic antibiotics has come under debate.[8, 25]

Managing the abdominal wall defect is not just for cosmetic reasons but also to improve the daily function of the patient with PBS.[4] The lack of the abdominal wall contributes to scoliosis of the spine, backache and difficulty in mobilisation that may impact on motor development and contribute to respiratory compromise.[4, 16]

Orchidopexy is important to attempt to prevent malignancy as the testes are exposed to high temperatures in the abdominal cavity with potential malignant transformation.[17] If malignant transformation in the testes does occur, early detection is possible after orchidopexy.[17]

Peritoneal dialysis has been successful in patients with PBS and end stage renal disease.[22] Although the deficiency of the abdominal musculature potentially can be a problem with peritoneal dialysis catheter insertion, a laparoscopic technique has been shown to be effective.[22] Renal transplantation has also been shown to be successful in patients with PBS who require renal replacement therapy.[23]

1.10 Outcome

Due to the rarity of the condition and paucity of literature on the outcome of PBS is difficult to predict.[2, 8] The severity of the condition, associated features and the initial and long term management impact on the outcome of patients with PBS.[2, 8, 15]

1.11 Aims and objectives

The aims of this study were to describe the epidemiology, management and outcome of patients with PBS at the Chris Hani Baragwanath Academic Hospital (CHBAH), South Africa.

The objectives of this study were as follows:

- To describe the patient profile at presentation, including age, gender, race, anthropometry, renal function, associated anomalies.
- To describe the medical and surgical management offered.
- To describe the frequency and the indications for hospitalisation.
- To describe the renal and ultimate outcome of the patients.

Chapter 2

2.0 Materials and Methods:

2.1 Materials and study design

This study was a retrospective descriptive record review of patients diagnosed with PBS over 31 years. Patients with PBS who attended the CHBAH's Paediatric Nephrology clinic from 01 January 1984 to 31 December 2014 were included in this study. The files were identified using the renal clinic filing system and were retrieved physically. Data from the files was entered into an electronic data sheet using the REDCap^{TM} programme (appendix A).

2.2 Ethics clearance and permission

Ethics clearance was obtained from the Human Research Ethics Committee (Medical) of the University of the Witwatersrand. Clearance number M141113 (appendix B). The Chief Executive Officer of the hospital as well as the Paediatric Nephrology Unit gave permission for this study and to access the patient files. Due to the retrospective nature of the study patient consent to access information in the files was not required. All patient identifying information was kept anonymous.

2.3 Demographics and anthropometry

Gender, race and age of presentation at the clinic were documented for each patient. The mean follow up duration in months was calculated.

Weight (kg) and length (cm) was documented at birth and at each clinic visit. Z scores for weight and height were calculated using the World Health Organisation (WHO) Anthro version 3.2.2 anthropometric calculator.[26] Patients less than five years of age were analysed using the WHO growth standard charts and patients over the age of five, the WHO body mass index chart.[27]

2.4 Renal function

The renal function was evaluated and compared at the first clinic presentation and at the last clinic visit, using the calculated GFR (cGFR).

cGFR (ml/min/1.73m^2) was calculated using the Schwartz formula[28-30]:

cGFR = *k* x length (cm) x 88.5 / serum creatinine (*u*mol/L).

K is an age and sex specific constant that varies with muscle mass.[28] Where heights/lengths were not documented in the patient's files, the closest height/length documented to the date of the creatinine value was used. Serum creatinine is measured by the National Health Laboratory Service at the CHBAH using the modified Jaffe method via the Roche Cobas® 8000 machine.[31]

The cGFR was categorised into five stages using the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Classification of the stages of chronic kidney disease (CKD) for patients over the age of two years (table 2.4.1).[28, 29] The cGFR for children under the age of two years does not fit the above mentioned classification.[30, 32] The equation incorrectly places these patients in a worse category of CKD staging.[30, 32] This is due to the immaturity of the developing kidneys.[30, 32] For children under the age of two years the cGFR

was calculated and then stratified using standard deviations with population norms. They were classified according to moderate (-1 to -2 SD) and severe (> -2 SD) reduction in their GFR (table 2.4.2).[29, 30, 32]

Table 2.4.1: Stages of CKD[30]:

Stage	**Description**	**GFR (ml/min/1.73m^2)**
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	<15 or dialysis

Table 2.4.2: Normal GFR in children less than two years of age[29, 30, 32]:

Age and sex	**Mean GFR (SD)**
1 week, male and female	40.6 (14.8)
2-8 weeks, male and female	65.8 (24.8)
>8 weeks, male and female	95.7 (21.7)

Table 2.4.3 categorises the two age groups concurrently in a normal cGFR, moderate reduction and severe reduction in cGFR. These categories were used to stratify patients into severity categories (mild-severe).

Table 2.4.3: Categories of cGFR:

	Normal cGFR	**Moderate reduction cGFR**	**Severe reduction cGFR**
< 2 years of age	0 to -1 SD	>-1 to -2 SD	> -2 SD
> 2 years of age	CKD 1	CKD 2 CKD 3	CKD 4 CKD 5

There are limitations to the Schwartz formula regarding nutritional state and ethnicity.[32] Although adjustments to the constant value for muscle mass helps to make the estimation more accurate, there is a lack of data available for the cGFR estimation for different ethnic groups.[32] Nevertheless, when using the Jaffe method to measure serum creatinine the Schwartz formula is recommended.[28, 30]

2.5 Associated conditions

Associated conditions were classified into different anatomical systems commonly seen with PBS. Radiological findings of the genitourinary system were documented.

2.6 Medical and surgical management

The age at initiation of prophylactic antibiotics and intermittent catheterisation was documented. The type of antibiotic used and pathogen causing UTI's was also documented. Screening dipstick by bag collection, microscopy and cultures by suprapubic and midstream urine collection are used at the clinic to get accurate results.

The different surgical management options and the age of intervention were documented.

2.7 Hospital admissions

The frequency, reason and outcome of hospital admissions were assessed. The total number of admissions for each patient was divided by the number of years that a patient followed up to get a rate of hospital admissions per year.

Patients with significant respiratory infections included patients who required hospital admission or intensive care support. Patients who had multiple respiratory tract infections that were treated as outpatients were not included in this category. The number of UTI's per patient (in-patient and out-patient) per year was documented.

2.8 Outcome

The outcome was classified into four broad categories: active, demised, transferred, and defaulted. The active category included all the patients currently seen at the nephrology clinic. Patients between the ages of 16-18 years were transferred to the adult nephrology services. Patients who defaulted scheduled appointments were contacted telephonically however this proved difficult as the majority of the contact numbers had changed.

The categories were then further analysed into renal outcome as normal or reduced cGFR. The use of prophylactic antibiotics and intermittent catheterisation was evaluated with the final renal outcome to establish odds ratios.

2.9 Statistical analysis

The information captured from the data sheets was analysed using both Microsoft Excel 2010® and the Statistica 12® statistical programme. Means and standard deviations (SD) were used to represent normally distributed data, whereas medians and interquartile ranges (IQR) represented non-parametric data. Tables, bar graphs, pie charts and box-whisker plots were used to represent data.

2.10 Limitations

Due to the retrospective nature of this study the following limitations were encountered:

- Missing data from files, especially anthropometry and biochemistry results
- Anthropometry measurements not being standardised

Other limitations included neonates not represented in this study due to an early neonatal death and thus not referred to the renal unit. This may underestimate the severe group of patients in this record review.

The use of the Schwartz formula has not been validated in the South African population which may impact on the overall classification of the patient in a CKD stage. The formula was initially tested on patients with normal body habitus and in a normal state of health.[30]

Chapter 3

3.0 Results:

3.1 Demographics

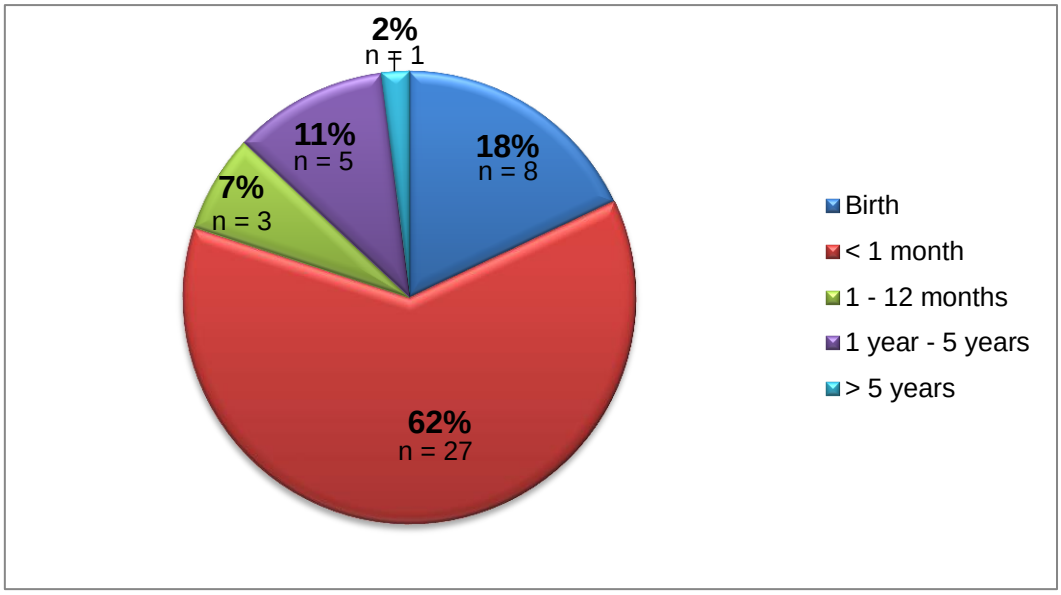
Fifty five patients diagnosed with PBS were identified that attended the paediatric renal clinic between January 1984 and December 2014. Records were available for 44 patients. During this 31 year review there was an average of 1.8 patients per year with PBS seen at the clinic. Of the 11 patient files not located, 10 were male and one was female. No other information was available for these patients and thus these patients were excluded from this study.

Only available records were analysed for this review (N=44). Male patients accounted for 90.9% (n = 40) and 9.1% (n = 4) were female. Of the 44 patients the majority were Black (n = 42, 95.5%), with one Caucasian and one mixed race patient.

Twenty two (50%) patients attending the clinic were referred from an outside referring hospital. Fourteen patients (32%) were referred from hospitals within the Gauteng province; seven patients (16%) were referred from the North West province. One patient (2%) was transferred from Mozambique.

The median duration of follow up was 24.5 $\pm$ 81 months (IQR 1.7 – 130 months).

Graph 3.1 represents the age categories when patients presented to the renal clinic with the diagnosis of PBS. The diagnosis was already established in the patients presenting after the age of 1 year. The records did not document the reason for the delay in specialist referral.



Graph 3.1: Age categories at presentation to the renal clinic

Birth weight, presentation and last clinic visit anthropometry are shown in table 3.1. Seven (16%) of the patients were of low birth weight (<2.5kg). At presentation three (7%) of the patients were moderately wasted (weight for height < -2 Z scores) and five (11%) were severely wasted (weight for height < -3 Z scores).

Table 3.1: Anthropometry

	Mean ± SD
Birth weight for age (Z score)	-0.94 ± 1.08
Presentation weight for age (Z score)	-1.35 ± 1.25
Presentation weight for height (Z score)	-0.96 ± 1.69
Weight for height Z score last visit (<5 years)	-1.24 ± 2.02
BMI last visit (>5 years)	0.03 ± 1.23

3.2 Associated conditions

The gestational age for 36 (81%) patients was available. Of those patients 33 (92%) were born at term and three (8%) patients were born with a gestational age of less than 37 weeks.

Table 3.2 displays the types and frequencies of common associated conditions with PBS.

Table 3.2: Associated conditions

System	n	%	Type	N
Urological	21	47.7%	Vesicoureteral reflux Patent urachus Suspected Posterior urethral valves	12 5 4
Orthopaedic/ Musculoskeletal	5	11.4%	Bilateral clubbed feet Congenital hip dysplasia Spina bifida occulta	3 1 1
Cardiovascular	3	6.8%	Patent ductus arteriosus Supravalvular pulmonary stenosis	2 1
Gastrointestinal	2	4.5%	Omphalocoele	2

3.3 Radiology

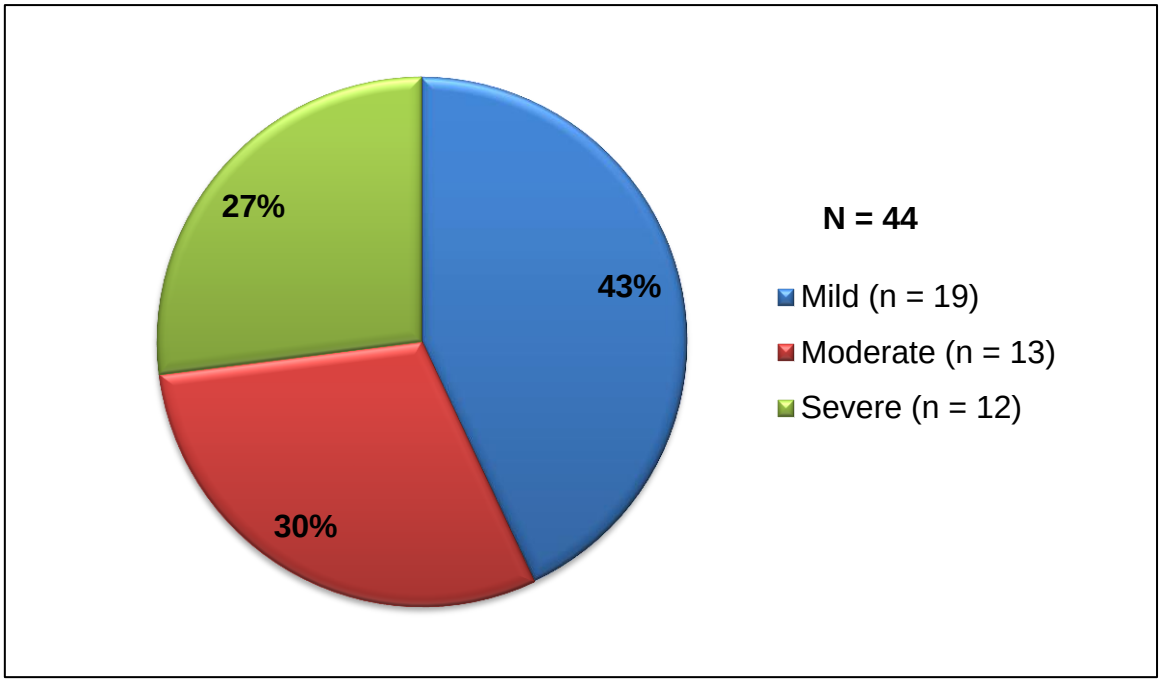
Ultrasound of the urinary system and voiding cystourethrograms (VCU) reports were analysed. Table 3.3 shows the frequency of structural renal abnormalities seen either on ultrasound or VCU.

Table 3.3: Radiological abnormalities

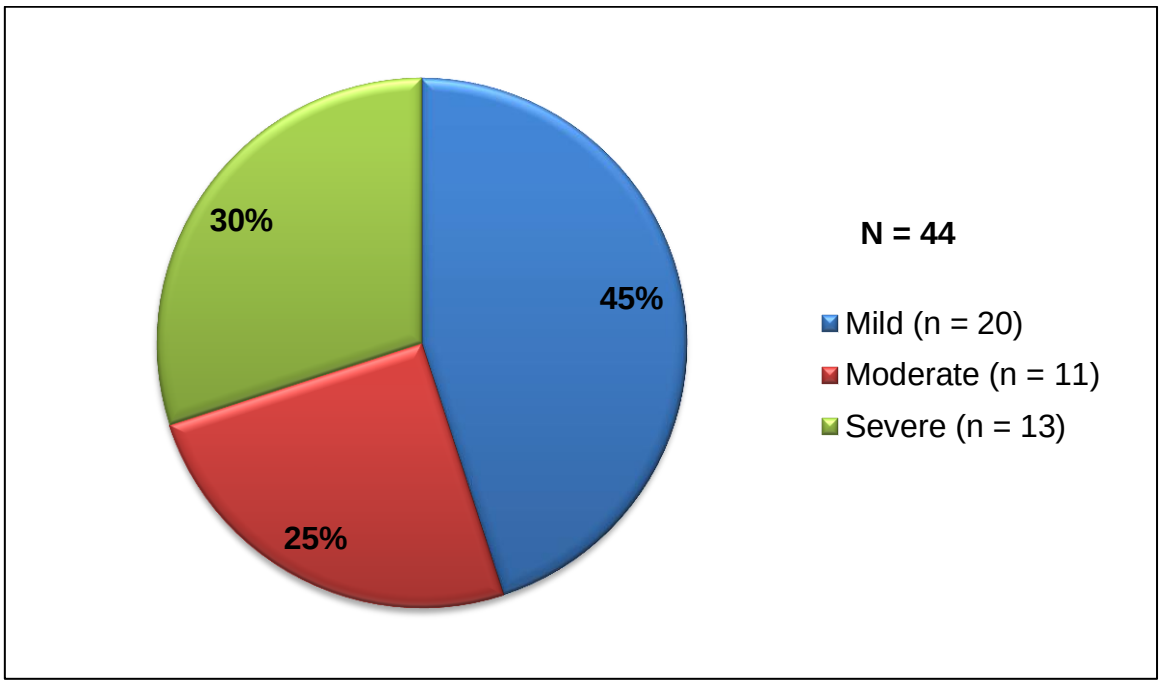
Results:	**N**	**%**
Hydronephrosis: Bilateral Unilateral	 21 6	 47 14
Hydro/Megaureter	19	43
VUR: Bilateral Unilateral	 8 4	 18 9
Bladder: Large volume Trabeculated wall	 8 7	 18 16
Suspected PUV	4	9
Torturous/Megaurethra	5	11
Renal cysts	2	4.5

3.4 Renal function

GFR was calculated and categorised for patients at the first and last clinic visits. The pie graphs (graph 3.4.1 and 3.4.2) represent the severity category according to the cGFR of all the patients at presentation and at their last clinic visit respectively.



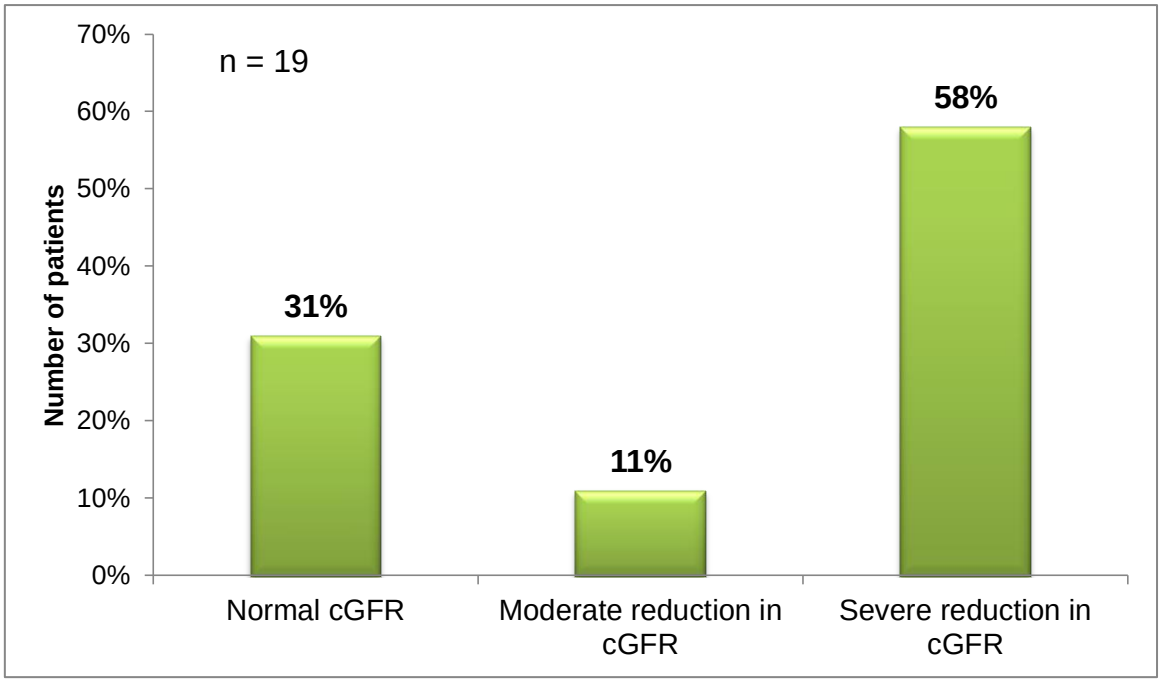
Graph 3.4.1: Categories of patients with PBS at presentation.



Graph 3.4.2: Categories of patients with PBS at the last clinic visit.

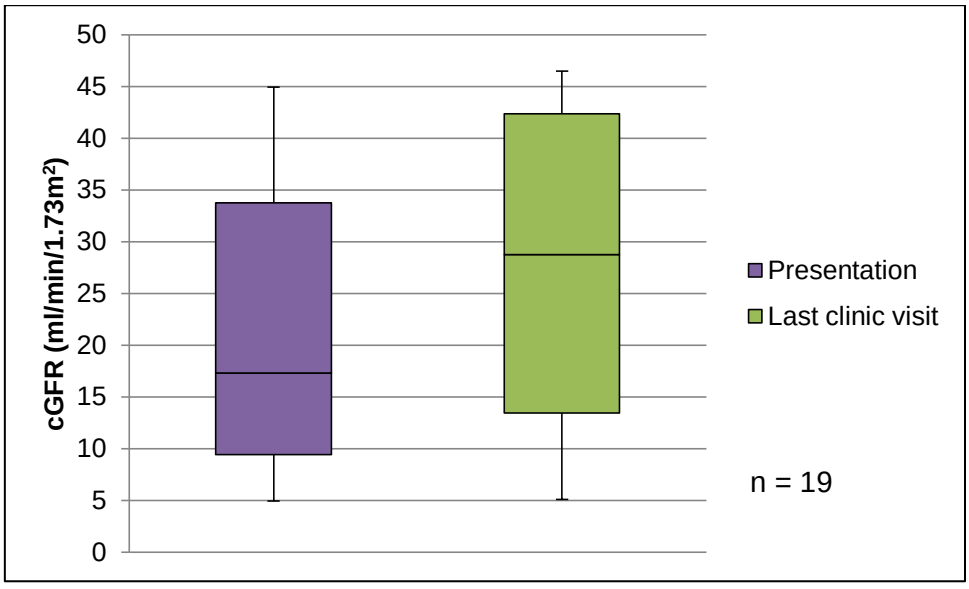
Nineteen (43%) patients were less than two years of age at the last clinic visit.

The cGFR is represented in the graph 3.4.3.



Graph 3.4.3: Categorised cGFR of patients less than two years of age at the last clinic visit.

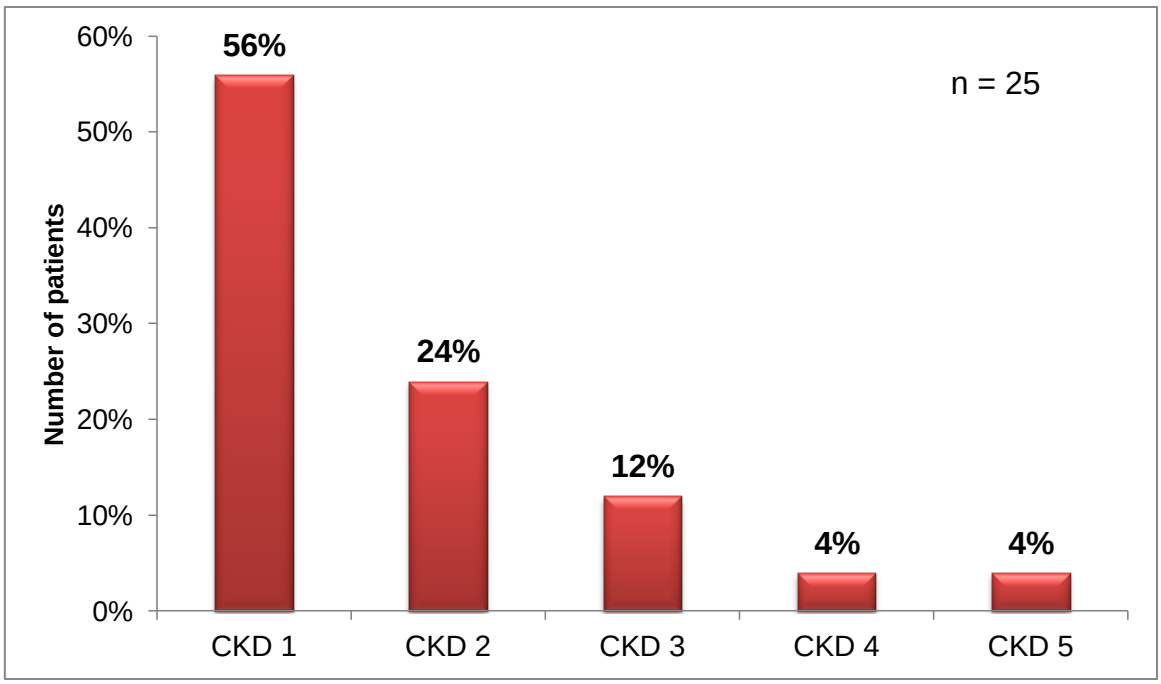
Comparing the progression of the patient less than two years of age from the first clinic visit to the last an improvement of cGFR was shown (graph 3.4.3).



Graph 3.4.4: Box and whisker plot of cGFR of patients less than two years of age at presentation and the last clinic visit.

Twenty five (57%) patients were over the age of two years at the last clinic visit.

The categories of the renal function are represented in graph 3.4.5.



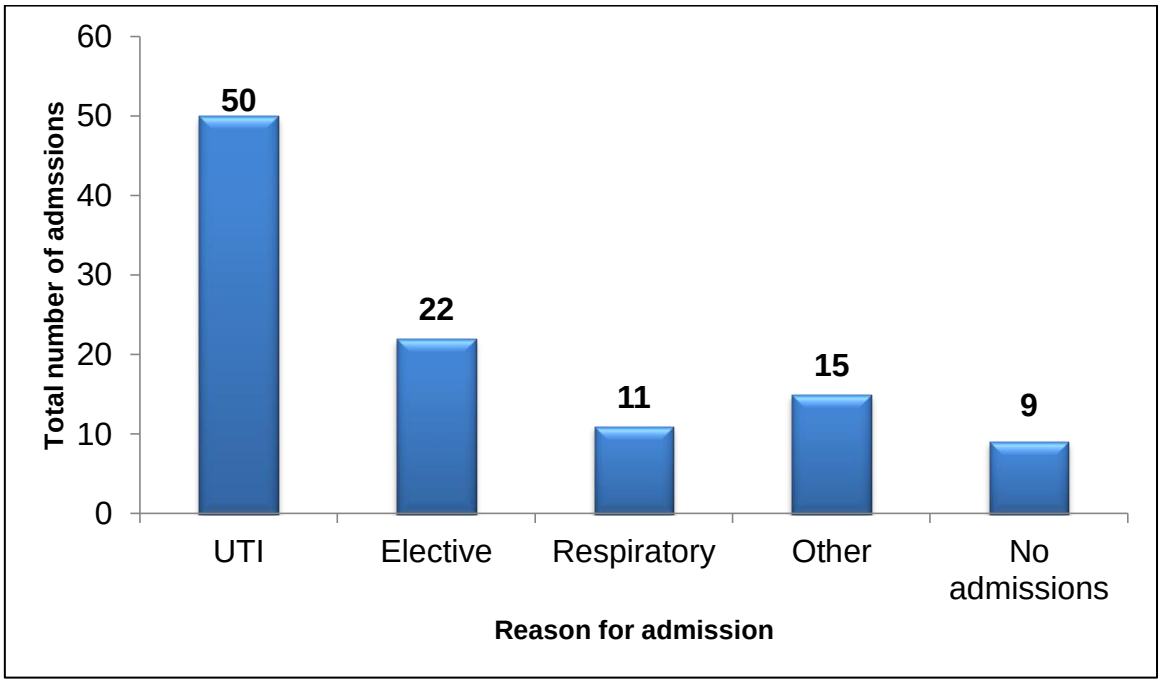
Graph 3.4.5: Categorised cGFR of patients over the age of two years of age at the last clinic visit.

3.5 Hospital admissions

The median admission per patient per year was 0.65 ± 0.98 (IQR 0.34 – 1.00).

The absolute number of hospital admissions is represented in graph 3.5. Patients had admissions in more than one category and multiple admissions in the same category. The majority of the admissions were due to urinary sepsis requiring intravenous antibiotics. There were a total of 272 suspected UTI's in all patients in the review, either by urine culture or urine dipstick from an appropriately collected specimen. Confirmed UTI's is represented in table 3.8.1. Fifty (18%) of the patients with documented UTI's required hospital admission for intravenous antibiotics.

Scheduled surgical interventions made up the elective admission category. The respiratory category comprised of patients that had respiratory tract infections requiring hospital admission. One patient required intensive care support three times for severe community acquired pneumonia. One (2%) patient had severe lung hypoplasia. The category of "other" admissions consisted of patients admitted at birth for further investigations as well as other medical conditions like acute gastroenteritis and hypertension. A total of nine (20%) patients did not require hospital admissions during follow up.



Graph 3.5: Hospital admissions

3.6 Medical management

The median UTI per patient per year was 1.00 ± 0.93 (IQR 0.61 – 2.00). Table 3.6.2 specifies the organism profile that was cultured in the urine. Prophylactic antibiotics were commenced in 38 (86%) of patients attending the renal clinic. The majority of the patients were started during their first clinic visit. Table 3.6.3

reveals the type of prophylactic antibiotics used and the frequencies. The median age of commencement was 26 days of age (IQR 7 – 150 days).

Table 3.6.1 represents the patients with UTI's either commenced on prophylactic antibiotics or not.

Table 3.6.1: Frequency of UTI with or without prophylactic antibiotics

	UTI	**No UTI**	
Prophylaxis	19	19	0.197*
No prophylaxis	1	5	

*Fisher exact test

Intermittent catheterisation was started in 13 (30%) of patients with a median age of 27 months (IQR 11 – 78 months). Four (31%) of the patients started on intermittent catheterisation did not adhere to it.

Table 3.6.2 Organism profile

Organism	**n**	**%**
Gram negative bacteria:		
Escherichia coli	23	31.9
Pseudomonas aeruginosa	9	12.5
Klebsiella species	8	11.1
Enterobactor species (unspecified)	6	8.3
Klebsiella ESBL	5	7.0
Escherichia coli ESBL	2	2.7
Citrobacter diversus	2	2.7
Morganella morganii	2	2.9
Proteus mirabilis	2	2.9
Salmonella	1	1.4
Gram positive bacteria:		
Staphylococcus aureus	2	2.7
Staphylococcus epidermidis	2	2.7
Fungal:		
Candida species (unspecified)	5	7.0
Candida albicans	3	4.2
Total	72	100

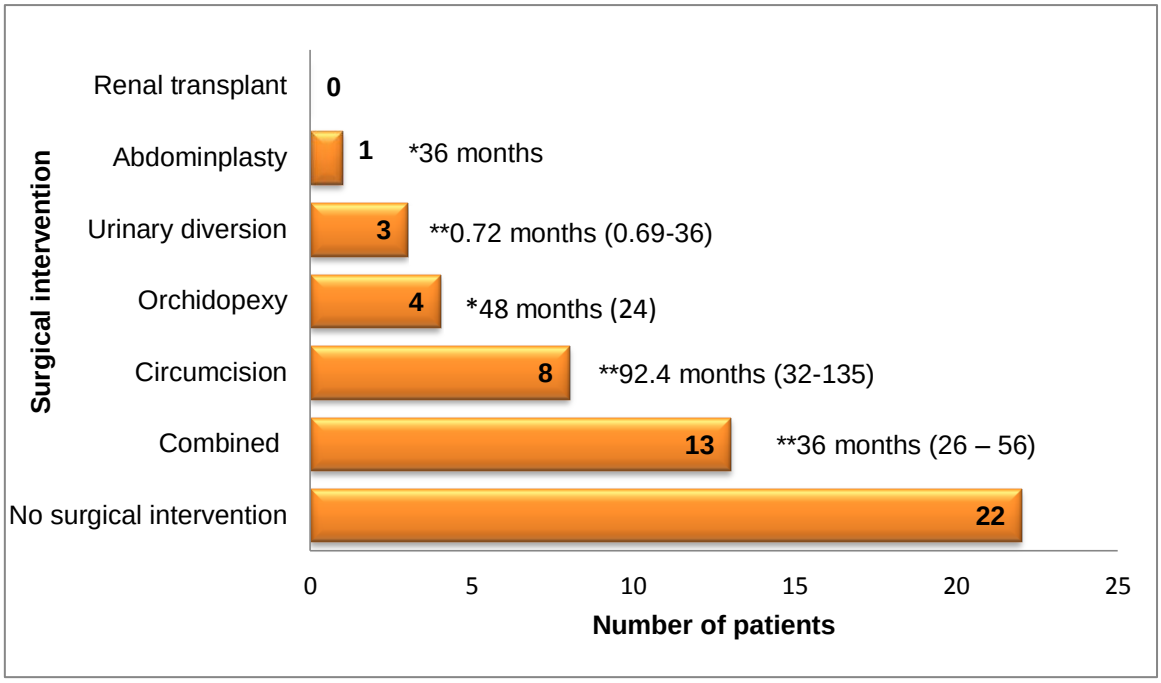
Table 3.6.3: Prophylactic antibiotic choice

Type	**N**	**%**
Trimethoprim/Sulfamethaxole	33	56.9
Nitrofurantoin	17	29.3
Cephalexin	3	5.2
Amoxycillin+clavulanic acid	3	5.2
Nalidixic acid	1	1.7
Antifungal: Fluconazole	1	1.7
Total	58	100

3.7 Surgical management

The type of surgical management, the frequencies and the median age of intervention are represented in graph 3.7. The combined category represents abdominoplasty and orchidopexy being done during one operation. One female patient had an abdominoplasty at the age of three years.

The patients that did not receive surgical intervention include: 2 patients (11%) that are active patients and are under the age of 2 years, 1 patient (4.5%) was transferred to a facility closer to home before surgical intervention was done, another patient (4.5%) demised before any surgical intervention. Eighteen of the 22 (82%) patients that had no surgical intervention had defaulted the clinic.



Graph 3.7: Surgical management with age of intervention

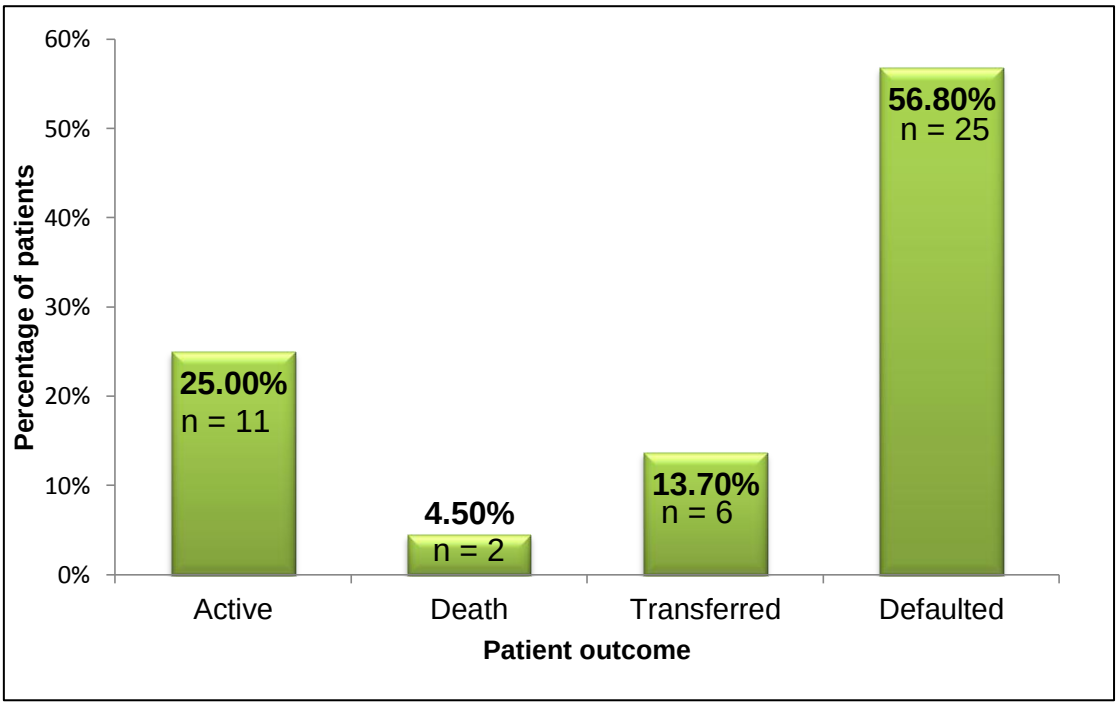
Bold numbers indicate actual number of patients

* Mean age (SD)

** Median age (IQR)

3.8 Outcome

The outcome of patients as per their last clinic visit was broadly classified into categories shown in graph 3.8.1.



Graph 3.8.1: Bar graph representing patient outcome

The two deaths occurred in the hospital setting. The one patient was born with severe lung hypoplasia and demised just over month of age due to overwhelming sepsis. This patient had a nephrostomy done at three weeks of age due to severe hydronephrosis. This patient was managed in the neonatal intensive care unit (ICU). The other patient was nine days old and was admitted for acute gastroenteritis and dehydration. The child later demised after an apnoea in the general ward.

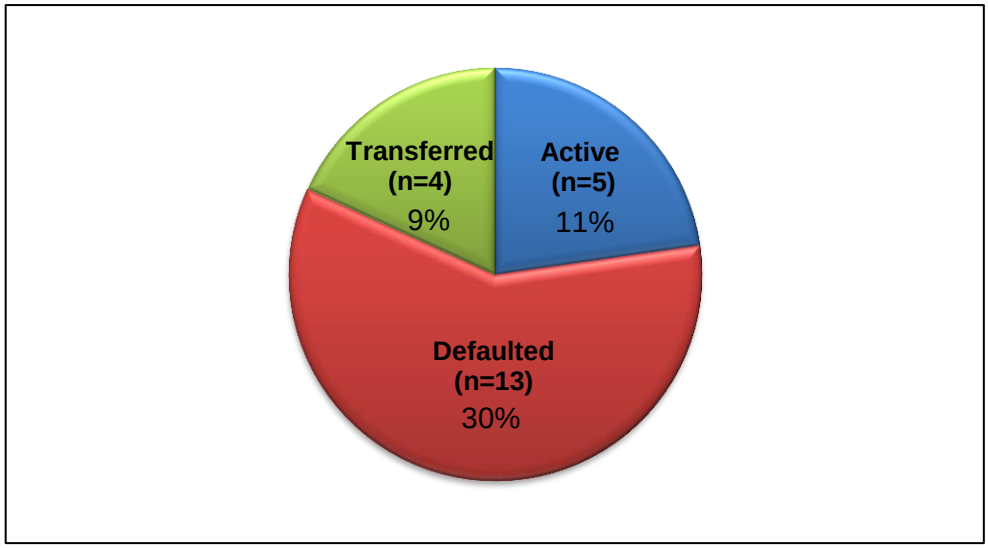
The patient outcome was further analysed into normal and reduced cGFR categories (table 3.8.1).

Table 3.8.1: Patient and final renal outcome at last clinic visit

	Active n (%)	**Transferred** n (%)	**Defaulted** n (%)	**Deaths** n (%)
Number	11 (25)	6 (13.7)	25 (56.8)	2 (4.5)
Normal cGFR	6 (55)	3 (50)	11 (44)	0 (0)
Reduced cGFR	5 (45)	3 (50)	14 (56)	2 (100)
Mean age (SD)	99.3 months (±72.5)	17,7 years (±2.07)	38.7 months (±58.8)	18 days (±12)

The use of prophylactic antibiotics on the final renal outcome had an odds ratio (OR) of 0.8 (95% CI 0.14 - 4.56; p = 0.8). Similarly the use of intermittent catheterisation had an OR of 0.6 (95% CI 0.17 - 2.4; p = 0.5).

As previously mentioned 50% of the patients attending the renal clinic were referred from other hospitals. Graph 3.8.2 represents the referred patients and their outcome at the last clinic visit.



Graph 3.8.2: Pie chart representing number of patients referred-in and their outcome

Table 3.8.2: Patients that defaulted the clinic with their final renal outcome and associated conditions at the last clinic visit

Number	25 (57%)
Mean age	38.7 months (±58.8)
< 2 years	15 (60%)
Normal cGFR	5
Moderate reduction cGFR	2
Severe reduction cGFR	8
> 2 years	10 (40%)
CKD 1	6
CKD 2	3
CKD 3	0
CKD 4	0
CKD 5	1
Associated conditions	9 (36%)

Chapter 4

4.0 Discussion:

Prune Belly Syndrome is a rare disorder with a paucity of local and international studies.[8] Thus this study's aim was to establish a database of patients with PBS at CHBAH, in order to gather information regarding their presentation and management in South Africa and to compare them to existing literature.

4.1 Descriptive analysis

Ninety one percent of the patients in this study were male with the complete triad of signs. Representative of the community that the CHBAH serves, 95.5% of the patients were of Black ethnicity. The gender and race profiles are similar to what is described in the literature.[2, 21]

In this review the diagnosis of PBS was made clinically as opposed to an antenatal diagnosis. Most of the patients were seen for the first time at the clinic before the age of one year with 80% of the patients being neonates. At presentation, 18% of the patients were moderately or severely wasted. At the last clinic visit all patients had normal anthropometry. The reason for this was not established but it can be postulated that regular clinic visits and early intervention, in the form of treating UTIs promptly or introduction of intermittent catheterisation, may have improved the growth of the patients.

There was a wide variation in the duration of follow-up of patients. Some patients defaulted clinic after their first visit whereas others had extensive follow up and subsequently were transferred to the adult nephrology clinic. The high default rate of 57%, possibly due to lack of transport funds, parenteral neglect and/or poor

social support systems, may have contributed to the variability in the duration of follow up. Other articles showed lower default rates with longer follow up times of between 6.8 – 16 years, this can be explained that these studies were done in better resourced countries where health care is more accessible to patients.[8, 21]

4.2 Associated conditions

Seventy percent of the patients had associated abnormalities commonly seen with PBS. Only 4.5% of the patients were born prematurely which is lower than that described in the literature.[2, 16] Early neonatal deaths were not included in the study as they would not have been seen at the renal clinic. This factor could have possibly contributed to the lower rate of premature babies being documented.

Gastrointestinal abnormalities were documented less frequently.[1, 7] Two patients had omphalocoeles which were surgically corrected.

The orthopaedic conditions observed are well described in patients with PBS, of which clubbed feet being the most commonly documented in this review.[7]

4.3 Renal abnormalities

There was a strong correlation with other urological and renal abnormalities which accounted for 48% of the associated conditions. Patent urachus was noted in 11% of the patients. Urachal abnormalities are not well documented in the literature.[13] VUR was seen in 27% of the patients in this review which is lower than in other reports of up to 75%.[2, 6, 17] It has been reported that Black children

generally have decreased rates of primary VUR and this could explain the smaller numbers seen in this review.[33] Hydronephrosis and hydro/megaureters, which is part of the syndrome, were the most commonly seen radiological abnormality, being comparable to other reports.[1, 2, 21] Hydronephrosis was not a universal finding in all the patients in this review. PUV is not reported frequently in the literature. In this review 9% (n=4) of the patients had radiological evidence of PUV. These four patients with suspected PUV did not have cystoscopy to confirm the diagnosis of PUV as they defaulted the clinic and were not contactable.

4.4 Admissions and management

Hospital admission rate per patient per year was lower than compared to what is described in other reports.[6, 17, 21] Due to the wide variability of follow up and the high default rate the hospital admission rate could have been under-represented.

Half of hospital admissions were for culture proven urinary tract infections requiring intravenous antibiotics. Uncomplicated urinary tract infections were managed as outpatients. Elective surgical admissions made up 22% of the total admissions. All elective surgical admissions were discharged home.

Admissions due to respiratory illnesses were described less than what is defined in the literature.[1, 16] Respiratory tract infection requiring hospital admission made up eleven percent of the total admissions. One patient was noted to have severe lung hypoplasia. This number could be under represented as patients in the severe category may not be included in this study due to stillbirths or early neonatal deaths. Patients that were accepted into ICU were all discharged home. This highlights that escalation of care for patients with PBS should be

individualised when ICU is required, and not to be excluded for admission solely based on the basis of being a “Prune Belly Syndrome”.

Prophylactic antibiotic therapy to prevent UTI was used in 84% of the patients which is comparable to the conservative management mentioned in other studies.[2, 10] Most patients were started on prophylactic antibiotics at the first visit to the clinic, before imaging was booked. Some patients changed antibiotics mainly due to availability, no dual antibiotics were used. Trimethoprim/Sulfamethaxole and nitrofurantoin was used in 86% of the patients as the prophylactic antibiotic. These antibiotics are commonly used as prophylaxis as they are inexpensive and well tolerated.[25] Nitrofurantoin was used after the age of two years due to its side effect profile. Fluconazole was used as secondary prophylaxis in one patient after recurrent fungal UTI.

Gram negative organisms were found to be the majority of organisms isolated in the urine, i.e. 83% of culture proven UTI’s. Recently there are new recommendations moving away from prophylactic antibiotics in patients with recurrent UTIs with or without structural urological conditions.[25] The risk of antibiotic resistance and the severity of the structural abnormality must be considered when using prophylactic antibiotics.[25] No benefit has been shown in other studies regarding prophylactic antibiotic to reduce renal scarring.[25] Although this review shows that the relationship of prophylactic antibiotic use and prevention of UTI was not statistically significant, the numbers are too small to infer changes in practice.

In the last ten years intermittent catheterisation as a modality has become more utilised in the management of PBS. Intermittent catheterisation was initiated in

30% of the patients. The age of commencing intermittent catheterisation was much later in comparison to the use of prophylactic antibiotics. The reasons for this can be due to the agreement by parents and patients to commence this mode of therapy as well as the training of the patient and/or caregiver. Intermittent catheterisation can be uncomfortable and painful contributing to the patient's unwillingness to initiate or comply with it. Double voiding can be used to completely empty the urinary system. This was not documented in this study.

The odds ratio for the use of prophylactic antibiotics and intermittent catheterisation in preventing deterioration of renal function was not statistically significant. The small study numbers could have contributed to the level of insignificance. However with recent evidence regarding prophylactic antibiotics they are not used at the clinic anymore. The duration of prophylactic antibiotics was not evaluated in the active clinic patients.

Fifty percent of the patients had surgical interventions; this rate is less than in other reports.[1, 2] Elective operations were planned after the age of two years at the clinic in conjunction with the paediatric surgeons. This age requirement and the large default rate seen at the clinic could contribute to the lower surgical rates in this review. Of the active patients (n = 11), six patients are awaiting some or all of the surgical procedures offered. Only one is under the age of two years. The reasons why the surgeries have not yet been done was not established in this study. Abdominoplasty and orchidopexy was done in one combined operation in 30% of the patients. No post-operative complications were reported in any of the operations. A few patients missed their appointment dates for the surgery and needed to be rebooked.

None of the patients in this review received renal replacement therapy. Although one patient was classified at CKD stage five and thus required renal replacement therapy, he defaulted from the clinic at eight years of age and was unable to be contacted.

4.5 Renal function and outcome

At the first clinic visit 19 (43%) of the patients were in the mild category, 13 (30%) were in the moderate category and 12 (27%) were in the severe category.[17] Nineteen patients (43%) remained in the same age category at the last clinic visit (less than two years of age). Fifty eight percent of the patients less than two years were in the severe reduction in cGFR category at the last clinic visit. There was an overall improvement in the actual cGFR in patients less than two years of age which can be explained by the normal maturation of the nephrons. Although there were more patients in the severe cGFR category at the last clinic visit, deterioration in the actual cGFR was not noted.

At the last clinic visit the total number of patients was represented in the following categories: 20 (45%) in the mild category, 11 (25%) in the moderate category and 13 (30%) in the severe category.[17] Twenty five patients (57%) were in the over two years of age group at the last clinic visit. Fifty six percent of these patients had normal renal function with a decreasing frequency of deteriorating CKD staging (CKD 2-5).[30]

Patients less than two years of age in this review had a poorer renal outcome and most likely fall into the severe category. However patients over the age of two years showed a good renal outcome.

Only one patient was in the ESRD category at the last clinic visit. This is significantly lower to what is reported in the literature in that 30% of PBS patients in the mild-moderate category advance to ESRD.[22]

4.6 Patient outcome

Fifty seven percent of the patients during this 31 year review had defaulted the renal clinic. The reasons for defaulting the clinic was not established in each case but it can be postulated that referred patients from peripheral hospitals could have challenges with large travelling distances, financial constraints and lack of social services that are often encountered in developing countries.[34, 35] This review was unable to determine if the defaulted patients had demised. Fifty two percent of the patients who defaulted the clinic were referred from hospitals within the Gauteng province and neighbouring provinces. Over half of the patients that defaulted (56%) had a reduced cGFR at the last clinic visit. Compared to the active and transferred groups of patients, the defaulted category had the higher percentage of patients with a reduced cGFR.

The active patients are seen regularly. Eleven percent of patients were transferred to the adult renal clinic for further care. It was not established in this study if any of these patients went on to have renal replacement therapy. One patient was referred to another tertiary paediatric nephrology clinic closer to that patient's home. Half of the patients had a normal cGFR at the time of transfer.

4.7 Conclusion

Although the numbers in this report are small, it reflects the rarity of PBS. The patient profile is comparable to other reviews however the frequencies of associated conditions in this report differ. Respiratory conditions, VUR and prematurity were noted to be less frequent in this report compared to other reviews. Hydronephrosis was not seen in all patients. Suspected PUV and urachal abnormalities were noted more frequently and thus routine VCU is recommended with subsequent cystoscopy, if required. Medical and surgical management is similar to what is noted in the literature. The frequency of surgical interventions was less. The majority of hospital admissions were for the treatment of urinary sepsis.

There was a good renal outcome in patients over the age of two years, most likely in the mild and moderate categories. Patients less than two years of age had a poorer renal outcome, most likely due to the severe characteristics of the syndrome and urinary sepsis.

An area of concern is the high default rate which is similar to other developing countries.[34, 35] An outreach based care programme is already established as part of the clinic. This can allow further training of health care professionals at peripheral hospitals on the general principles of management and follow-up of these patients. The outreach programme can also manage patients remotely. Patient and staff education is important to improve outcome.

Certain areas can be highlighted despite the limitations to the study, such as the retrospective nature of this study and the small study population. The high default rate is not exclusive to the nephrology clinic but to all specialised clinics especially

in areas of resource constraint. Identification of the main reasons for defaulting follow-up clinics needs to be identified for solution implementation.[34] Antenatal diagnosis should be emphasised. Combined medical and surgical clinics may improve overall patient care.

Patients with PBS have a varied range of presentation and outcomes. Patients with severe disease have a guarded prognosis whilst patients with mild and moderate disease can have minimal comorbidities into adult life. Early referral to a specialised unit and individualised care with a multidisciplinary team can ensure improved outcome for patients with PBS.

Appendix A Data collection sheet

Confidential

Demographics

Record ID	_____
Gender	◯ Male ◯ Female
Race	◯ Black ◯ White ◯ Indian ◯ Coloured ◯ Asian
Age at Presentation (days)	_____
Date of Presenation	_____
Last date seen	_____
Birth weight (kg)	_____
Birth weight Z score	_____
Presentation: Weight (kg)	_____
Weight Z score	_____
Presentation: Height/Length (cm)	_____
Height/Length Z score	_____
Presentation: Head Circumference (cm)	_____
Head Circumference Z score	_____
Weight at last date seen (kg)	_____
Weight Z score at last date seen	_____
Height/Length at last date seen (cm)	_____
Height/Length Z score at last date seen	_____

Renal function

Age Specific Creatinine at Presentation (umol/L)	_____
Actual Creatinine at Presentation (umol/L)	_____
Creatinine at Presentation	◯ Normal ◯ Abnormal (High)
GFR at Presentation (ml/min/1.73m2)	_____
GFR interpretation (< 2 years at presentation)	◯ Normal ◯ Moderate Reduction ◯ Severe reduction
CKD at Presentation (>2 years at presentation)	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
Age Specific Creatinine at Last date seen (umol/L)	_____
Actual Creatinine at Last date seen (umol/L)	_____
Creatinine at Last date seen	☐ Normal ☐ Abnormal (High)
GFR at Last date seen (ml/min/1.73m2)	_____
GFR interpretation (< 2 years at last date seen)	◯ Normal ◯ Moderate Reduction ◯ Severe reduction
CKD at Last date seen (>2 years at last date seen)	◯ 0 ◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5
VUR	◯ Yes ◯ No
VUR	◯ Unilateral ◯ Bilateral
PUV	◯ Yes ◯ No

Associated Anomalies

Recurrent Respiratory Infections	◯ Yes ◯ No
Congenital Heart Disease	◯ Yes ◯ No
Type of CHD	_____
Congenital Gastrointestinal abnormalities	◯ Yes ◯ No
Type of GIT Abnormality	_____
Orthopaedic Malformation	◯ Yes ◯ No
Type of Orthopaedic Malformation	_____

Other

_____

Burden of Disease

Number of Admission per year	_____
Reasons for Admission	☐ Elective ☐ Respiratory ☐ Urinary Sepsis ☐ Other
Outcome of Admission	☐ Discharged ☐ Death

Medical Management

UTI Prophylaxis	◯ Yes ◯ No
Date UTI Prophylaxis started	_____
Age when UTI prophylaxis started (days)	_____
UTI per year	_____
Prophylactic Antibiotic choice	_____
Type organism grown	_____
Intermittent Catherterisation	◯ Yes ◯ No
Intermittent Catherterisation - date started	_____
Age when Intermittent Catherterisation started (months)	_____
Dialysis	◯ Peritoneal ◯ Heamodialysis

Surgical Management

Urinary Diversion	◯ Yes ◯ No
Date of Urinary Diversion	_____
Age of Urinary Diversion (weeks)	_____
Abdominoplasty	◯ Yes ◯ No
Date of Abdominoplasty	_____
Age of Abdominoplasty (months)	_____
Orchidopexy	◯ Yes ◯ No
Date of Orchidopexy	_____
Age of Orchidopexy (months)	_____
Renal Transplant	◯ Yes ◯ No
Date of Renal Transplant	_____
Age of Renal Transplant (years)	_____
Circumcision	◯ Yes ◯ No
Date of Circumcision	_____
Age of Circumcision (months)	_____

Outcome

Outcome	◯ Active ◯ Death ◯ Transferred ◯ Defaulted

Appendix B Ethics clearance certificate

R14/49 Dr Shannon Leahy

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M141113

NAME: (Principal Investigator)	Dr Shannon Leahy
DEPARTMENT:	Paediatrics Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Prune Belly Syndrome : A 31 Year Experience at the Chris Hani Baragwanath Academic Hospital South Africa
DATE CONSIDERED:	28/11/2014
DECISION:	Approved unconditionally
CONDITIONS:	Title Change (06/03/2017)
SUPERVISOR:	Dr KL Peterson and Prof U Kala
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	20/01/2017

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date 6/3/17

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

References

1. Zugor V, Schott GE, Labanaris AP. The Prune Belly syndrome: urological aspects and long-term outcomes of a rare disease. Pediatr Rep. 2012;4(2):e20.

2. Routh JC, Huang L, Retik AB, Nelson CP. Contemporary epidemiology and characterization of newborn males with prune belly syndrome. Urol. 2010;76(1):44-8.

3. Kawamoto K, Ikeda T, Matsuo T, Maeda H, Okamoto N, Satow Y, et al. Prune Belly Syndrome: Report of twelve autopsy cases and possible pathogenesis. Congenit Anom. 1985;25:1-15.

4. Ger R, Coryllos EV. Management of the abdominal wall defect in the prune belly syndrome by muscle transposition: an 18-year follow-up. Clin Anat. 2000;13(5):341-6.

5. Karamanian A, Kravath R, Nagashima H, Gentsch HH. Anaesthetic management of "prune belly" syndrome. Case report. Br Jof Anaesth. 1974;46(11):897-9.

6. Hassett S, Smith GH, Holland AJ. Prune belly syndrome. Pediatr Surg Int. 2012;28(3):219-28.

7. Murray PJ, Thomas K, Mulgrew CJ, Ellard S, Edghill EL, Bingham C. Whole gene deletion of the hepatocyte nuclear factor-1beta gene in a patient with the prune-belly syndrome. Nephrol Dial Transplant. 2008;23(7):2412-5.

8. Seidel N, Arlen A, Smith E, Kirsch A. Clinical manifestations and management of Prune-belly syndrome in a large contemporary pediatric population. Pediatr Urol. 2015;85:211-5.

9. Mesrobian H, Balcom A, Durkee C. Urologic problems of the neonate. Pediatr Clin North Am. 2004;51:1051-62.

10. Woodhouse CR, Ransley PG, Innes-Williams D. Prune belly syndrome--report of 47 cases. Arch Dis Child. 1982;57(11):856-9.

11. Moerman P, Fryns JP, Goddeeris P, Lauweryns JM. Pathogenesis of the prune-belly syndrome: a functional urethral obstruction caused by prostatic hypoplasia. Pediatr. 1984;73(4):470-5.

12. Ramasamy R, Haviland M, Woodard JR, Barone JG. Patterns of inheritance in familial prune belly syndrome. Urol. 2005;65(6):1227.

13. Giuliani S, Vendryes C, Malhotra A, Shaul DB, Anselmo DM. Prune belly syndrome associated with cloacal anomaly, patent urachal remnant, and omphalocele in a female infant. J Pediatr Surg. 2010;45(11):e39-42.

14. Weber S, Thiele H, Mir S, Toliat MR, Sozeri B, Reutter H, et al. Muscarinic Acetylcholine Receptor M3 Mutation Causes Urinary Bladder Disease and a Prune-Belly-like Syndrome. Am J Hum Genet. 2011;89(5):668-74.

15. Zelikovic I, Dabbagh S, Friedman AL, Uehling DT, Chesney RW. Good outcome in prune-belly syndrome despite associated severe anomalies. Pediatr Nephrol. 1988;2(4):512-4.

16. Panitch H. Pulmonary complications of abdominal wall defects. Paediatr Respir Rev. 2015;16:11-7.

17. Denes FT, Arap MA, Giron AM, Silva FA, Arap S. Comprehensive surgical treatment of prune belly syndrome: 17 years' experience with 32 patients. Urol. 2004;64(4):789-93.

18. Figure 1.5. Available from: http://www.anatomybox.com/?s=prune+belly+syndrome. Accessed last on 8/2/2017.

19. Stewart C. The magic of ultrasound. S Afr J Obstet Gynaecol. 2011;17(3):54-55.

20. Crompton CH, MacLusky IB, Geary DF. Respiratory function in the prune-belly syndrome. Arch Dis Child. 1993;68(4):505-6.

21. Zugor V, Gunter S, Labanaris A. The Prune Belly Syndrome: urological aspects of a rare disease. Pediatr Rep. 2012;4(20):781-811.

22. Crompton CH, Balfe JW, Khoury A. Peritoneal dialysis in the prune belly syndrome. Perit Dial Int. 1994;14(1):17-21.

23. Fontaine E, Salomon L, Gagnadoux MF, Niaudet P, Broyer M, Beurton D. Long-term results of renal transplantation in children with the prune-belly syndrome. J Urol. 1997;158(3 Pt 1):892-4.

24. Gucuk A, Burgu B, Gokce I, Mermerkaya M, Soygur T. Do antibiotic and/or circumcision change periurethral uropathogen colonization and urinary tract infection rates in boys with VUR? J Pediatr Urol. 2013;9:1131-6.

25. Robinson J, Finlay J, Lang M, Bortolussi R. Prophylactic antibiotics for children with recurrent urinary tract infections. Paediatr Child Health. 2015;20(1):45-7.

26. World Health Organisation Anthro. 3.2.2 ed. 2011 Available from: http://www.who.int/childgrowth/en/. Accessed last on 8/2/2016.

27. The WHO child growth standards. Available from: http://www.who.int/childgrowth/en/. Accessed last on 8/2/2016

28. Gao A, Cachat F, Faouzi M, Bardy D, Mosig D, Meyrat B, et al. Comparison of the glomerulare filtration rate in children by the new revised Schwartz formula and a new generalized formula. Kidney Int. 2012;83:524-30.

29. Hogg R, Furth S, Lemley K, Portman R, George J, Schwartz J et al. National Kidney Foundation's Kidney Disease Outcomes Quality Intiative Clinical Practice Guidelines for chronic kidney disease in children and adolescents: evaluation, classification and stratification. Pediatr. 2003;111:1416-21.

30. Schwartz G, Brion L, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filrtration rate in infants, children, and adolescents. Ped Clin N Am. 1987;34(3):571-90.

31. Package insert for Roche machine: Systems Cobus C. CREJ2, Creatinine Jaffe Gen,2. 2011;4 ed:1-5.

32. KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. Am J Kidney Dis. 2002;39:S1-S266.

33. Kala UK, Jacobs DW. Evaluation of urinary tract infection in malnourished black children. Ann Trop Paediat. 1992;12(1):75-81.

34. Chatterjee SK, Banerjee S, Basak D, Basu AK, Chakravarti AK, Chatterjee US, et al. Posterior urethral valves: the scenario in a developing center. Pediatr Surg Int. 2001;17(1):2-7.

35. Orumuah AJ, Oduagbon OE. Presentation, management, and outcome of posterior urethral valves in a Nigerian tertiary hospital. Afr J Paediatr Surg. 2015;12(1):18-22.