RACP Lecture Series - Nephrology

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Topics

1. CAKUT
2. UTI
3. Vesicoureteric reflux
4. Voiding Dysfunction
5. Antenatal hydronephrosis
6. Cystic Kidney disease

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Kidney Development

- Metanephros - E32 human, E10 mouse
- Caudal portion of Wolffian duct invades mesenchyme - metanephric mesenchyme
- Ureteric bud
  - branches within mesenchyme (? Up to and post birth)
  - Becomes collecting duct and extrarenal ureter
- Metanephric mesenchyme
  - Condenses and forms cap over tip of ureteric bud branches
  - Subset transition from mesenchyme to epithelial cells to form renal vesicle
  - Renal vesicle evolves into majority of nephron - glomerulus to distal collecting tubule

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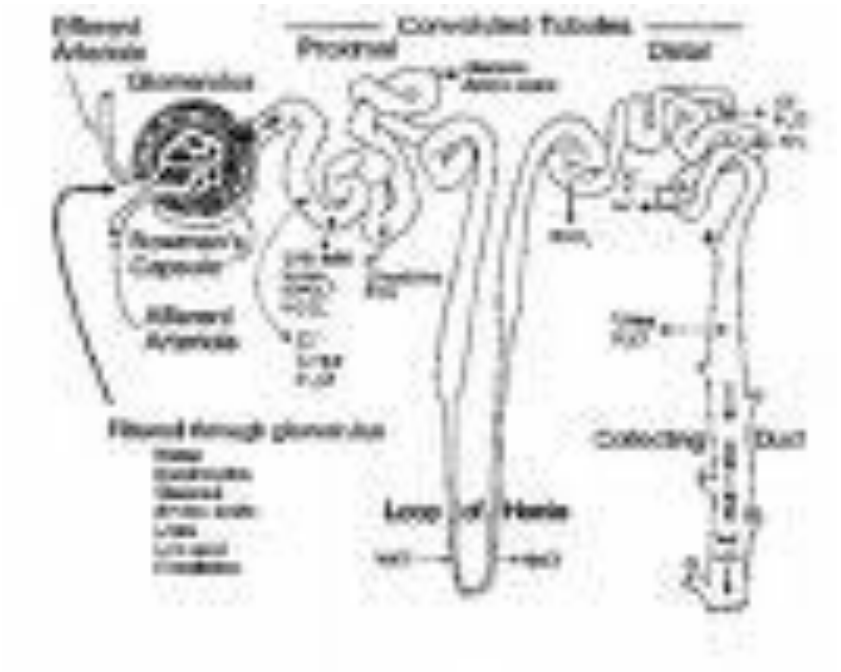
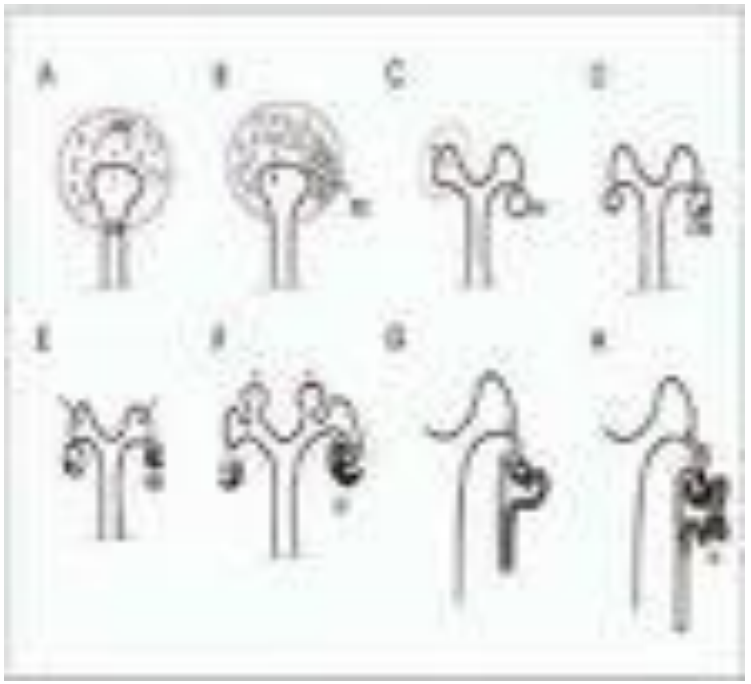
Nephron development





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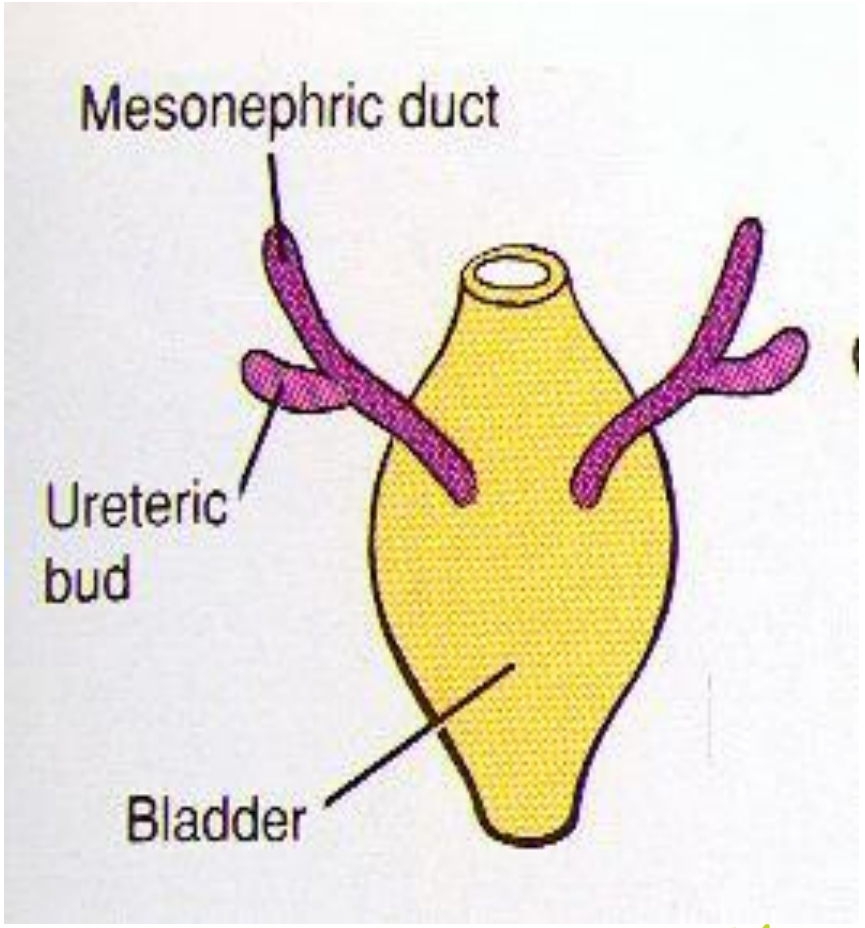
Renal Development

- Renal vesicle
  - Comma shaped body
  - S shaped body
  - Invaded by a capillary to form glomerular tuft
- S shaped body
  - Fuses with tip of ureteric bud - continuous lumen
- Remaining metanephric mesenchyme
  - Smooth muscle
  - Interstitium
  - ? vessels
- Reiterative process - 500,000 - 1,000,000 nephrons in adult kidney

Obstructive uropathy

- Abnormalities of nephrogenesis
  - Hypoplasia, agenesis, duplex
  - Dysplasia
- Obstruction
  - Changes in collecting system resulting from disturbed urinary drainage



Larsen, Human Embryology

- Perinatal obstructive uropathy, RL Chevalier, Sem Perinatol, 28(2),2004, 124-131

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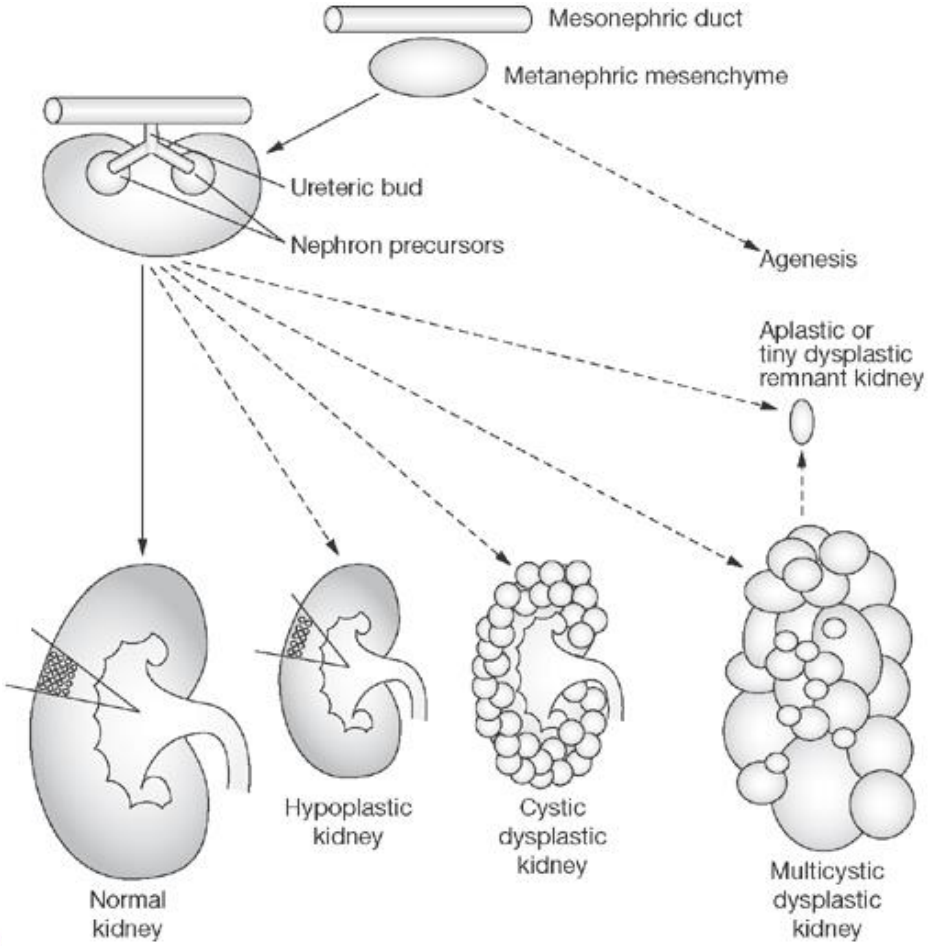
Renal development: Normal & Abnormal



Kerecuk L et al. 2008, Nat Clin Pract Nephrol

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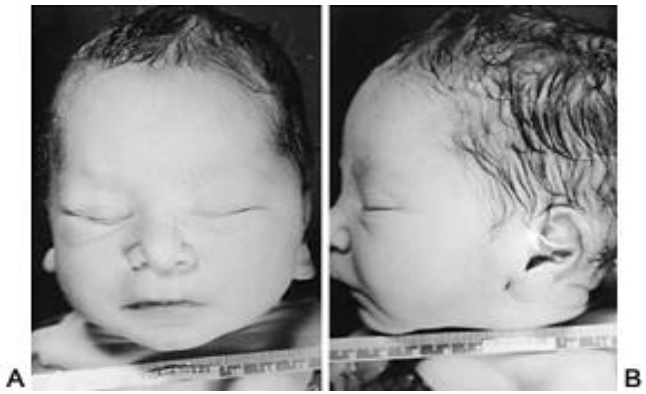
Renal Aplasia

- Bilateral
  - Potter Syndrome
  - 1 in 4000 births
  - incompatible with life
  - Males> females (70%)
  - Oligohydramnios
  - Pulmonary hypoplasia
- Unilateral
- 1/1000, M: F – 1.8 :1
  - ? Associated genitourinary conditions



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Associations of renal hypoplasia/ unilateral agenesis

- Diagnostic Ultrasound
  - Antenatal screen
  - Incidental finding
  - Look for pelvic kidney, horseshoe kidney
- Associations
  - VUR
  - Reduced nephron number
  - Renal enlargement
  - Risk of trauma to larger kidney

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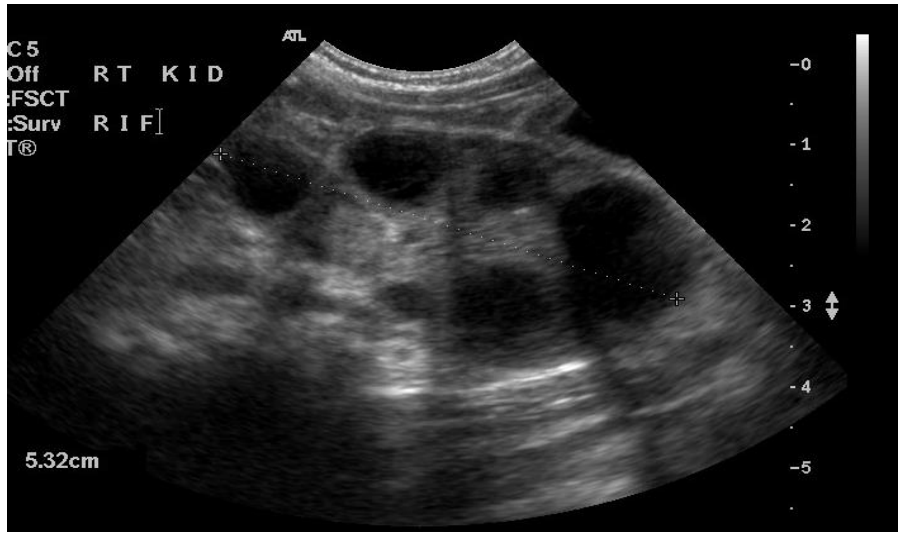
Multicystic Dysplastic Kidney

- Ultrasound
  - cysts vary in size & shape
  - largest are most peripheral
  - no connection between adjacent cysts
  - absence of renal parenchyma surrounding cysts
  - absence of central sonolucency (renal pelvis)
  - echogenic areas (primitive mesenchyme or tiny cysts) in eccentric location
  - adult 1 - 2 calcified cysts in renal fossa
- DTPA / MAG3
  - non functioning renal tissue, no perfusion
- MCU
  - contralateral VUR common



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Multicystic dysplastic kidney

Meta-analysis[1]

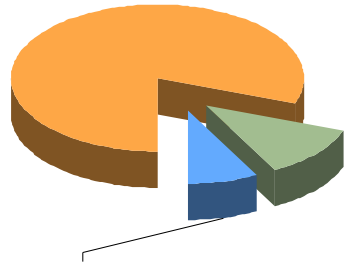
- Incidence 1:4300 live births
  - 130[2] -230[1] patients/ million child population
  - Male >Female 59%: 41%
  - Left > Right 53%: 47%
  - Contralateral kidney abnormal in 33%
    - VUR 19.7%

- presentation
  - antenatal diagnosis 72%
  - unilateral flank mass in neonate 15%
  - UTI 4%
  - haematuria, proteinuria
  - HPT uncommon
- Hypertension & malignant change very rare[3]

1.Schreuder et al., 2009, Nephrol Dial Transplant, epub; 2.Garne et al., 2009, J Pediatr Urol, 5,47-52; 3. Aslam et al., 2006, Arch dis Child, 91, 820-823,

Contralateral kidney

- 33% anomaly
- VUR
  - 19% contralateral kidney (scarring v rare)
  - 16% ipsilateral into atretric ureter
- Obstruction
  - PUJ obstruction
  - ureteric stenosis
  - ectopic ureter, ureterocoele
  - PUV



Careful renal U/s mandatory,

MCU recommendation varies across units

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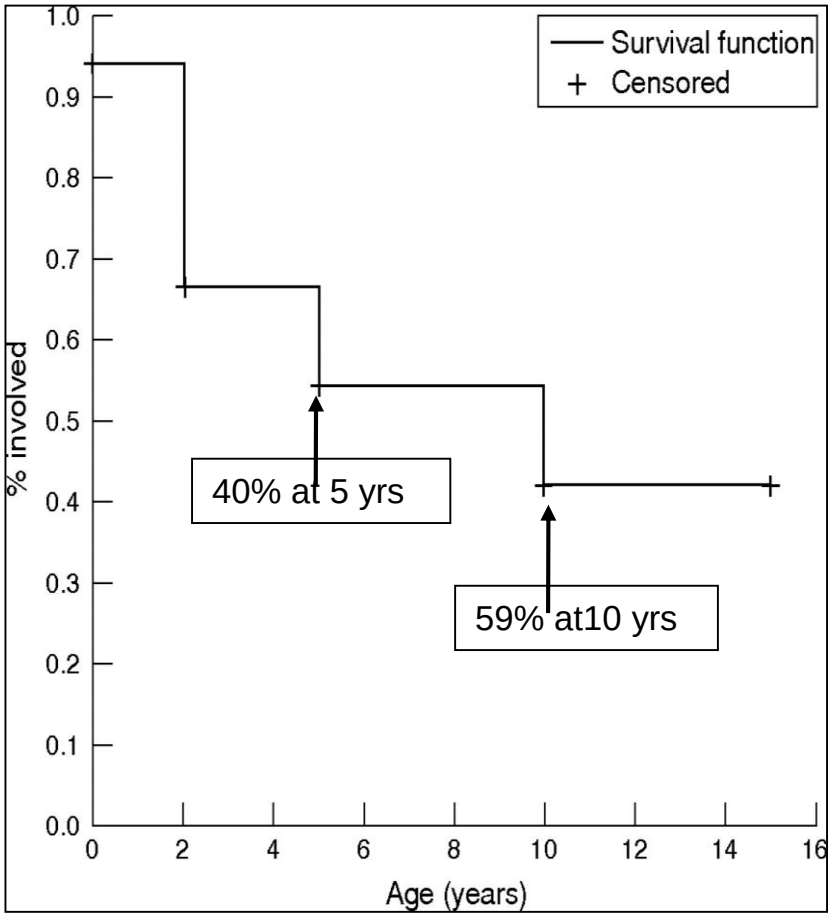
Complete involution of MCDK



- Monitoring[1]
  - U/s at Dx
  - DMSA at 3 months
  - Clinic review (growth, BP, urinalysis)
    - 3, 6, 12 months
    - 2,5 10 yrs
  - U/s 2, 5, 10 yrs
- MMC
  - U/s approx 1 yr, 2, 5, 7 & 10yr
  - Clinic review yearly till 5yr
- Usually good prognosis

1. Aslam, M et al. Arch Dis Child 2006;91:820-823

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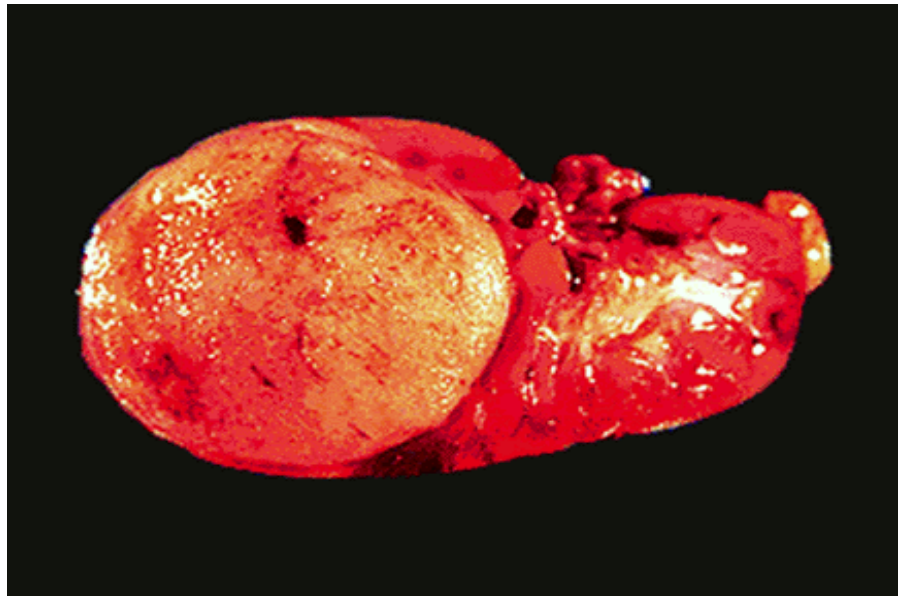
Is Malignancy associated with MCDK?

- 11 cases reported to 1998
  - Wilms: 5 cases
    - 8/12 - 4 yrs at Dx
  - Renal Cell carcinoma: 5 cases
    - 15 - 68 yrs at Dx
  - Mesothelioma: 1 case
    - 68 yrs
- Hypertension in MCDK
  - Rare but usually responds to nephrectomy



Malzoni & Caldmore, 1998, image:http://www.wilmstumour.com/pix/8018b.gif, accessed 20.04.09

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Dysplastic kidneys

- Abnormally developed kidneys (histology)
  - Poorly branched / differentiated nephrons & collecting ducts, increased stroma.
  - Cysts & metaplastic tissue eg cartilage may be present

- Abnormally looking kidneys on Ultrasound
  - Abnormal size or structure
  - Increased echotexture (when compared to liver)

Winyard & Chitty, 2008, Sem Fetal Neon Med, 13,142-151

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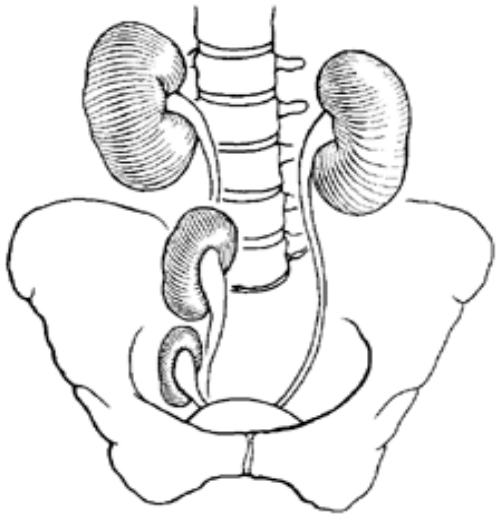
Kidney Position

- Malrotation
- Ectopy
  - Pelvic
  - Thoracic
  - Associated abnormalities
  - UTI, abdominal pain, renal calculi, VUR, obstruction, hydronephrosis



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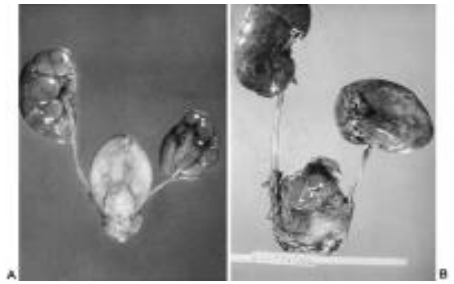
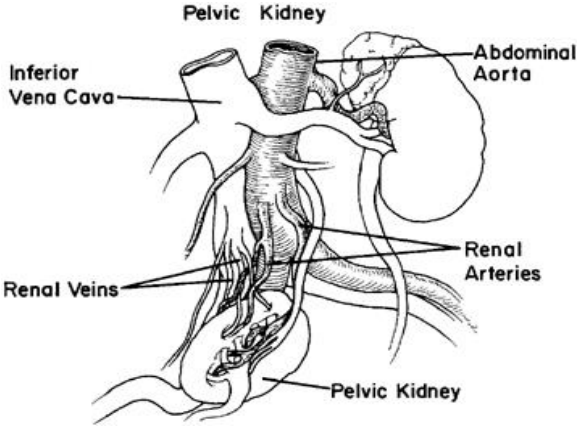
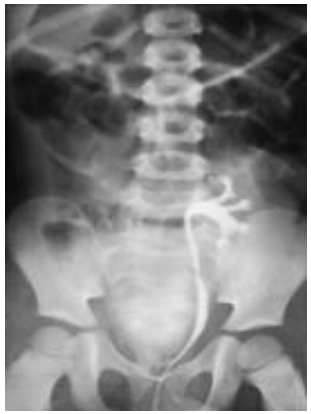
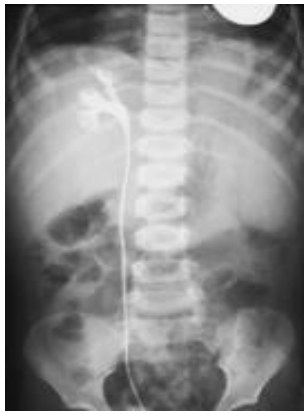
Kidney Position









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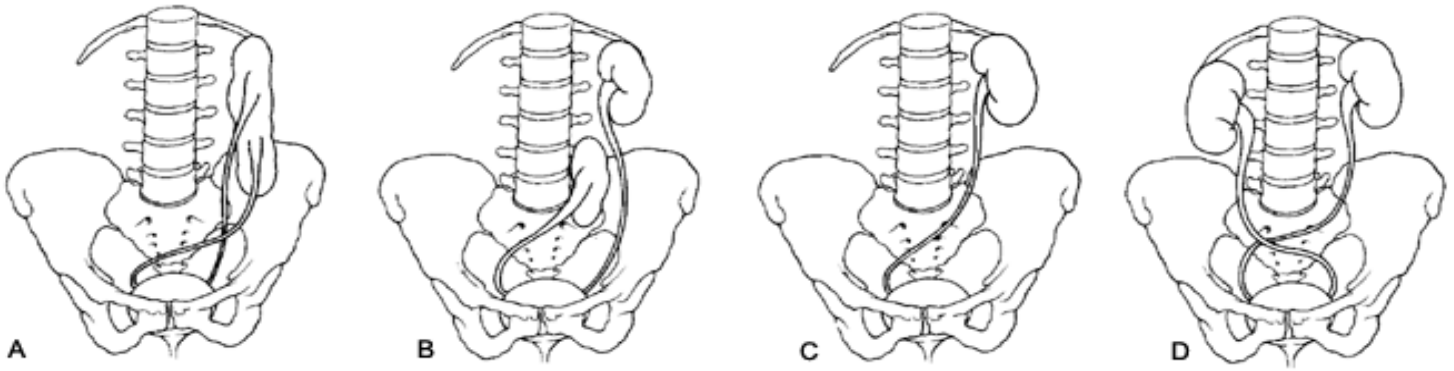
Kidney – Ectopia - Crossed



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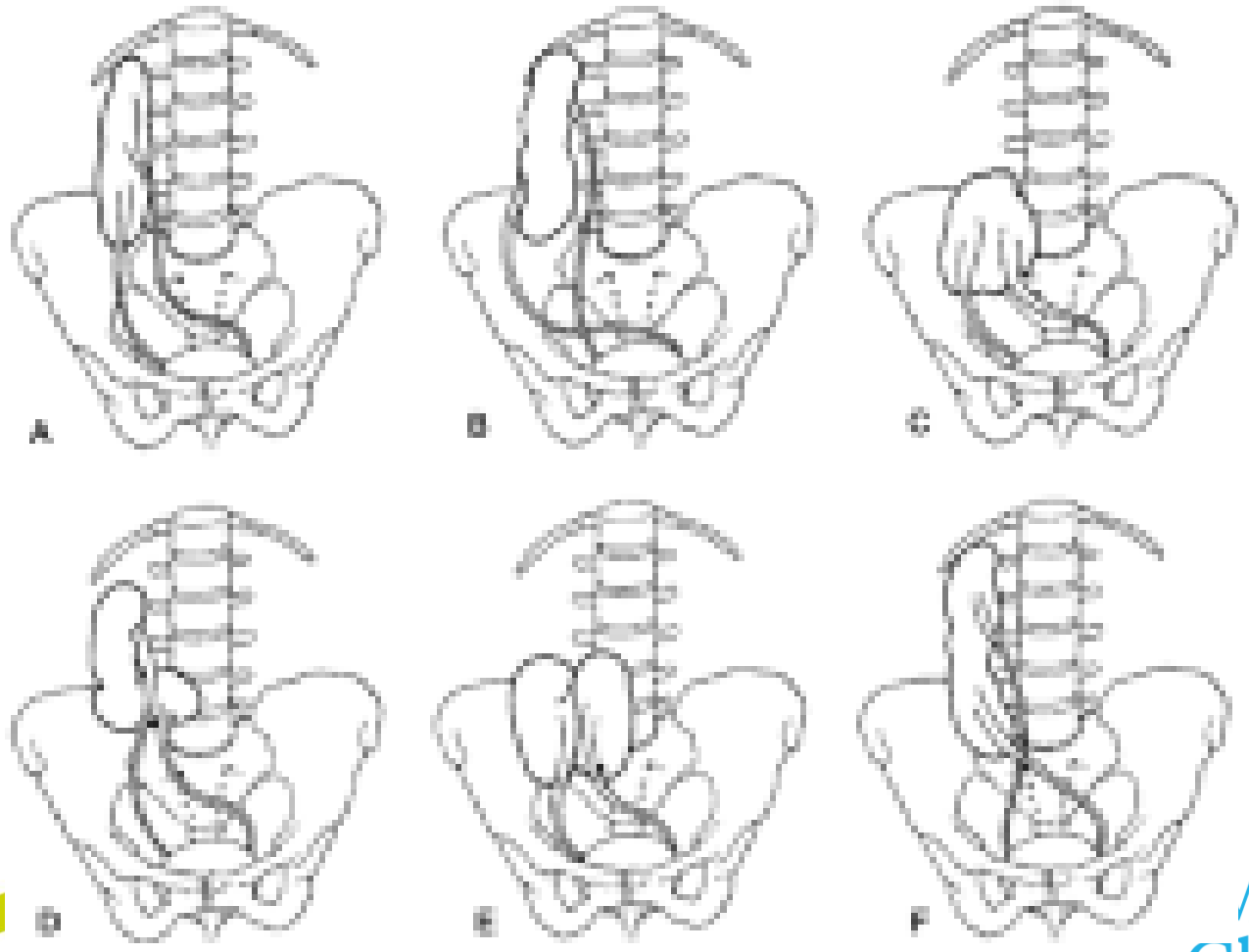
Kidney – Ectopy – Crossed and fused



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Kidney - Horseshoe

- 1 in 400
- Male> female
- Asymptomatic – complicated
  - UTI,
  - Haematuria,
  - obstruction,
  - Hydronephrosis,
  - Calculi
- Associated anomalies – VATER/ VACTERL etc

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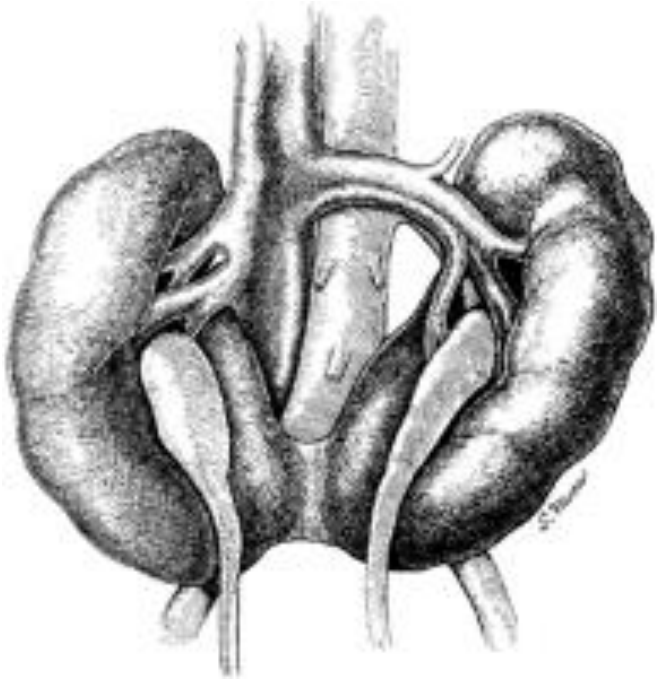
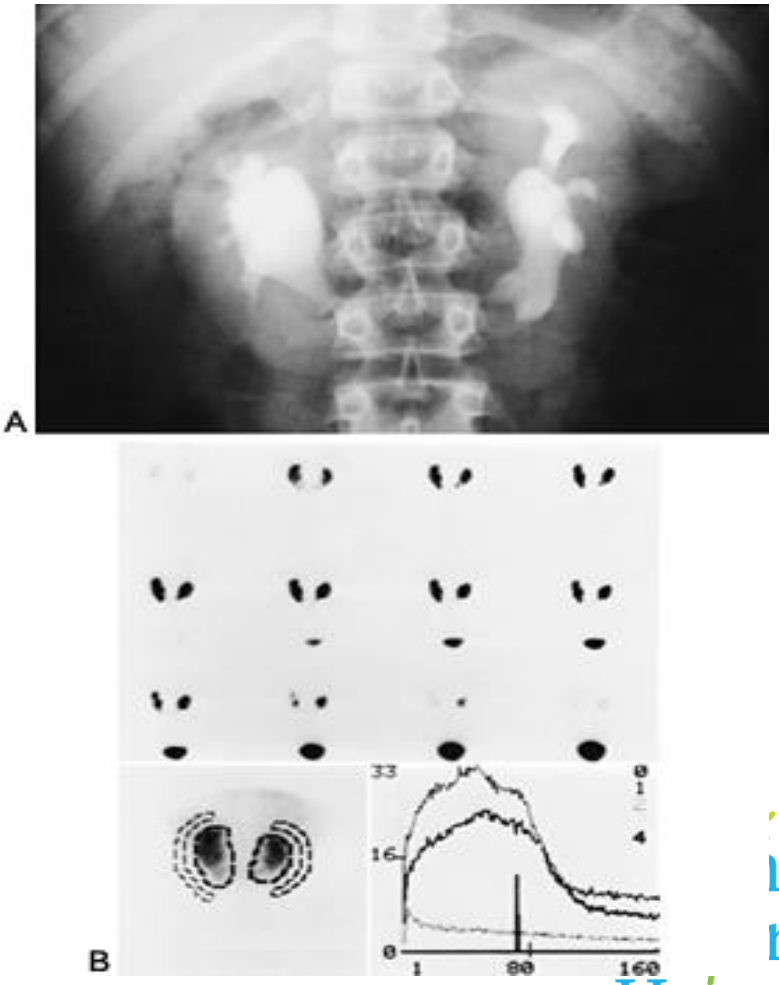
Horseshoe Kidney





Renal Collecting System

- Pelvi-ureteric junction
- Obstruction
  - 1 in 40 live births
  - M>F
  - Abdominal Mass
  - UTI
  - Abdominal pain
  - Haematuria

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PUJ

- ? Other anomalies
- Antenatal finding
- Ix –
  - US, Nuclear medicine
  - Antegrade/ retrograde study
  - Surgery

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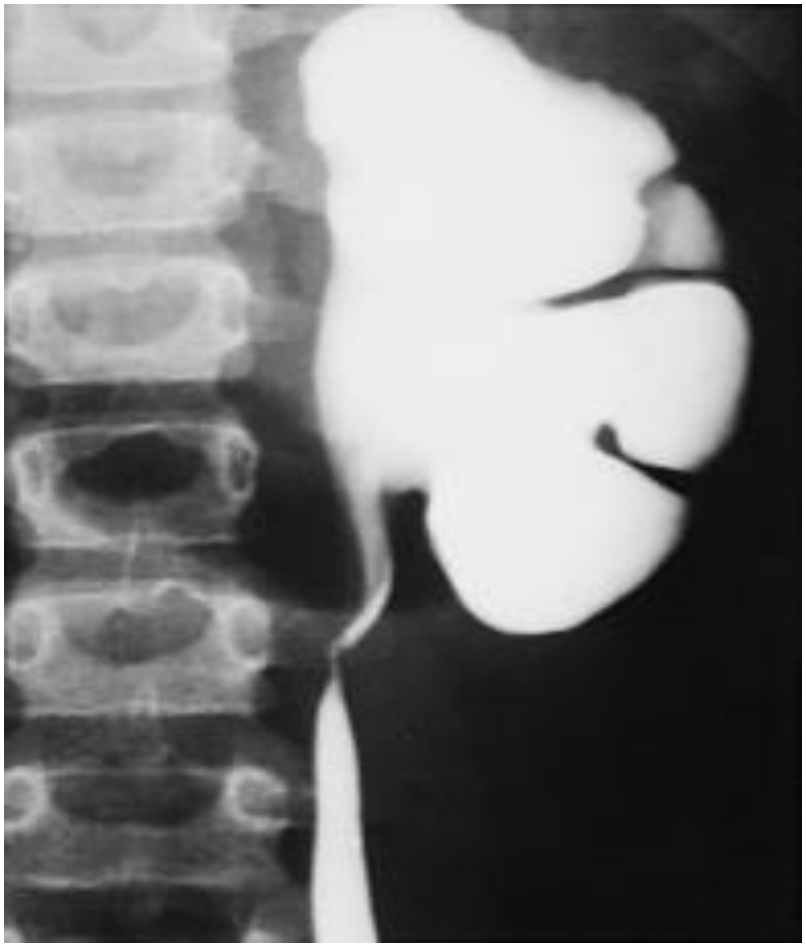

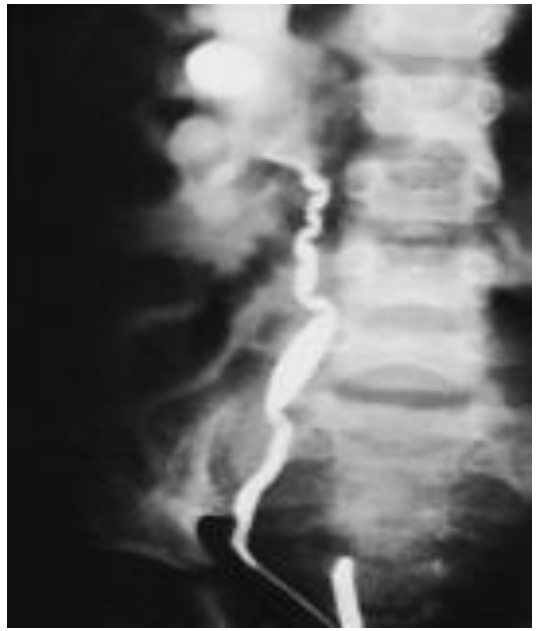

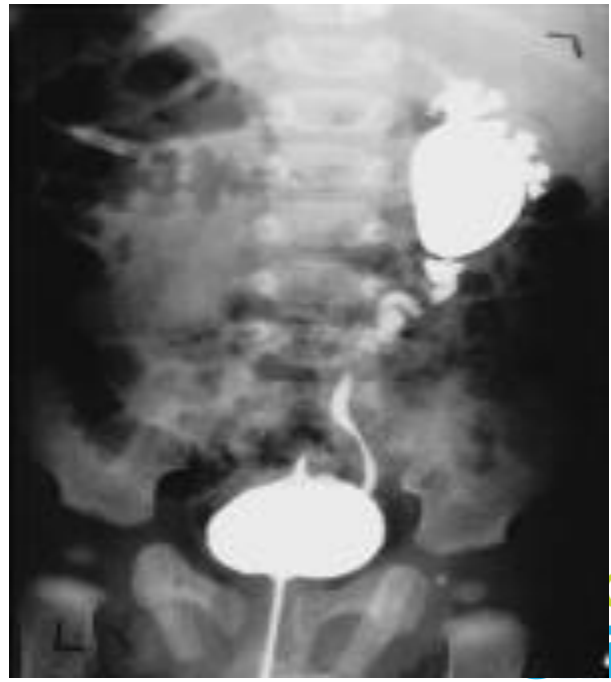

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Ureter - Duplication

- 1 in 125 births
- 40% bilateral
- F>M
- Complete duplication
- Incomplete duplication
- Bifid Ureter
- Clinically – asymptomatic, UTI, Mass, VUR, Obstruction

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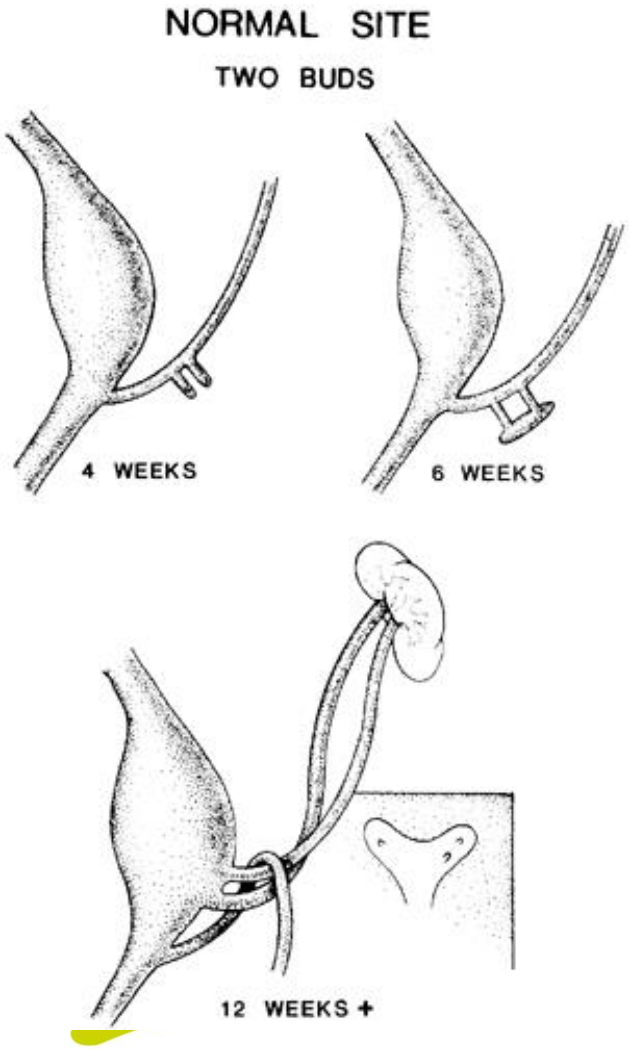
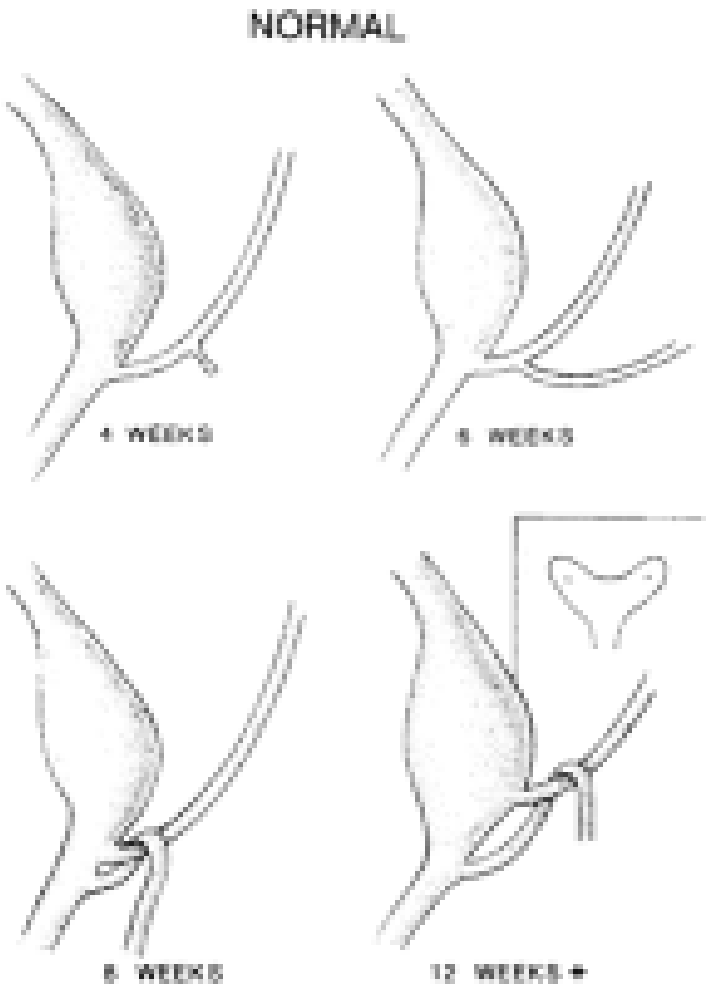
Ureteric development





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Duplex Kidney

- Upper Moiety
- Loewr Moiety
- Associated
  - VUR – usu lower
  - Obstruction – usu upper

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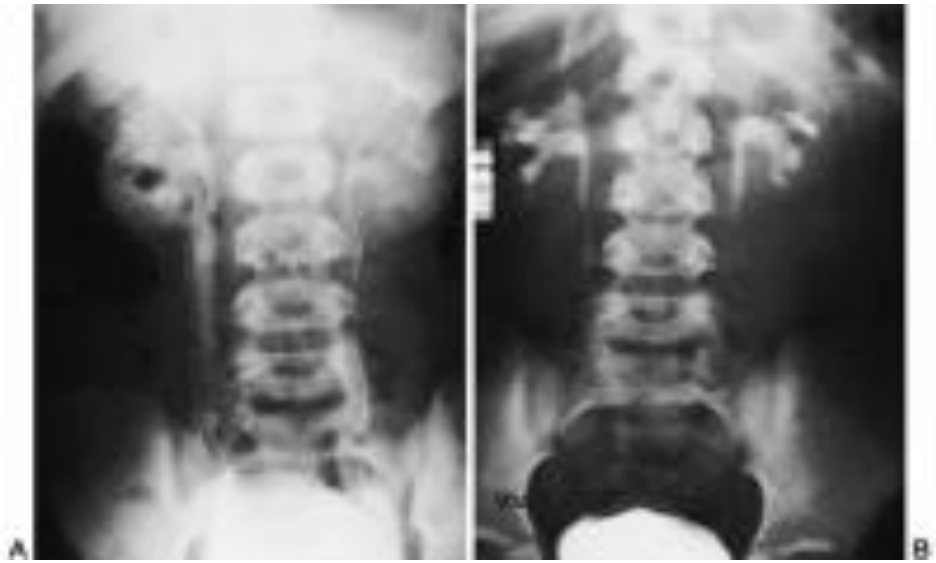
URETEROURETERAL
REFLUX



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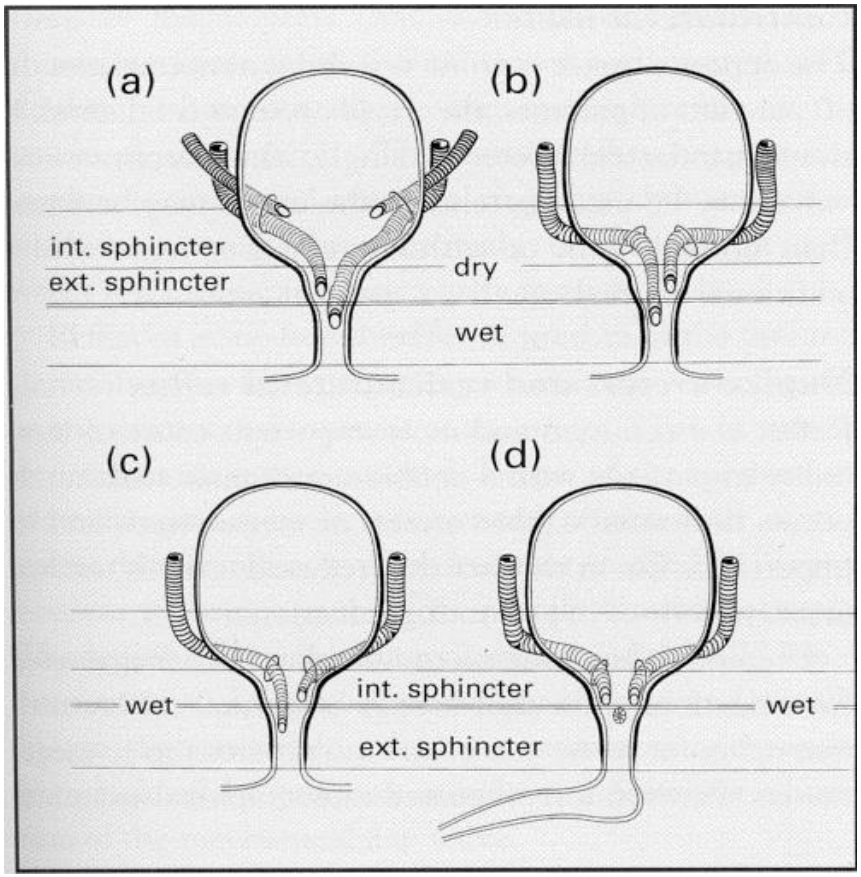
Ectopic ureters



- Ureter may be part of a duplex but may be single system
- Ureter may end in
  - bladder (N continence)
  - Urethra
  - Seminal vesicle/vagina
- If bypass sphincter

  = incontinence (dribbling)

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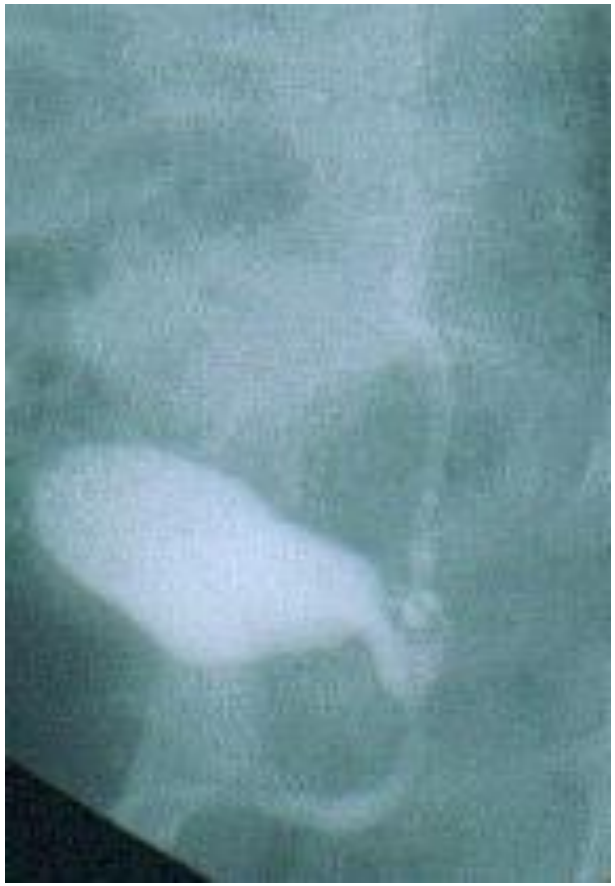
Ectopic ureter



- May be seen on IVP
  - May be missed
- If strong clinical suspicion (persisting dribbling)
  - Cystoscopy
  - Dye IV to pass into urine
    - Identify ectopic ureter
- Surgery can be curative

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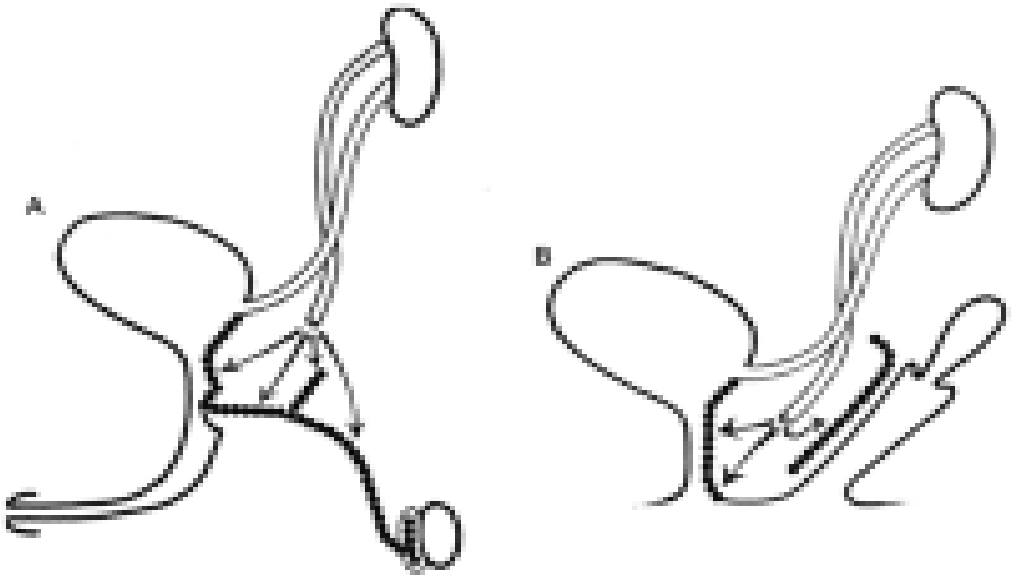
Ectopic ureter – possible insertion – male, female



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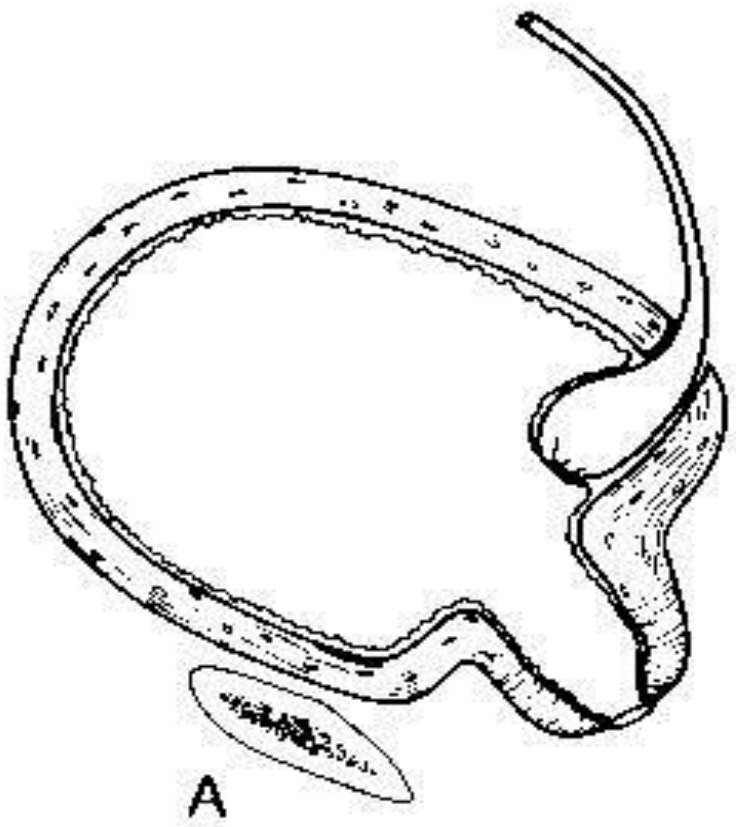
Ureterocoele



- Balloon like dilatation of distal ureter with pin-hole opening
- Usu upper half of duplex system
- Bladder consequences
  - Dec functional bl cap
  - Obstruction to emptying
  - Distortion of bladder neck after surgery
  - Assoc VUR --- UTI's

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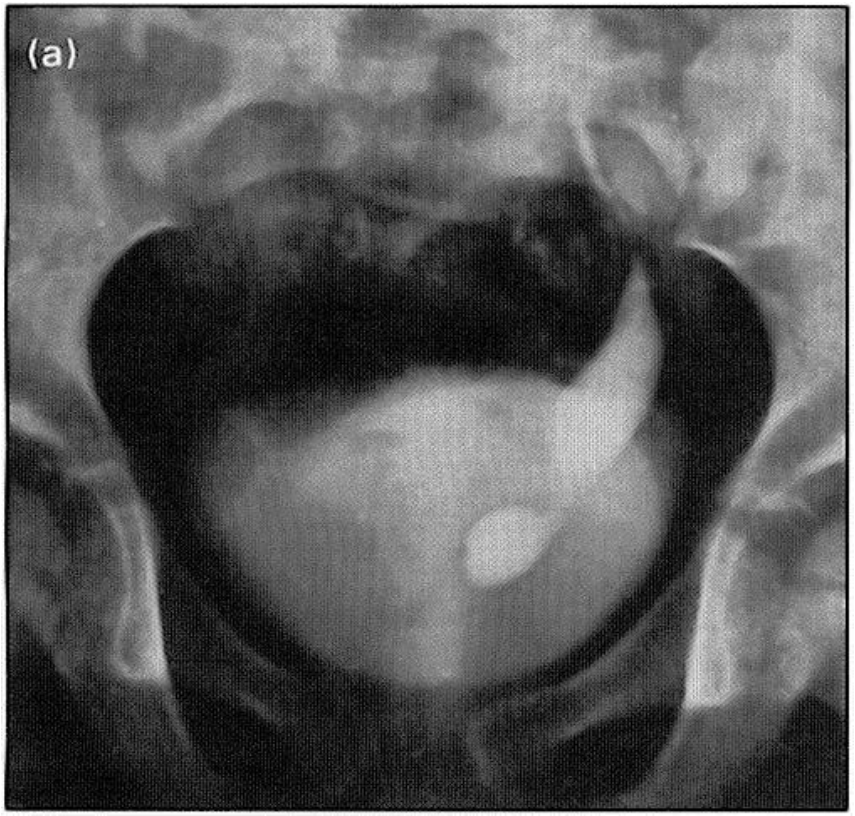
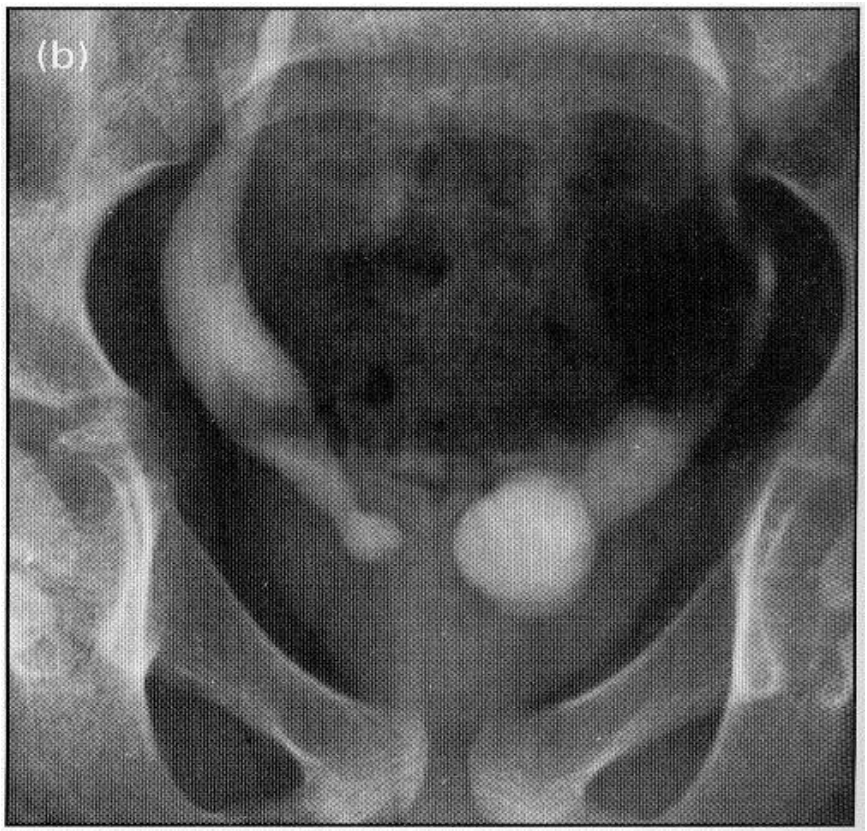
Ureterocoele





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Bladder exstrophy

- Bladder open
  - lower ant abdo wall absent
  - Bladder visible through “hole”,
    - May turn inside out
    - Small bladder
    - Detrusor, bladder neck, ext sphincter abn
- Assoc abn pelvis
  - Symphysis pubis widely separated
- Perineum usu short
  - Anus more anterior
  - Occ anal stenosis
- Male>female
  - Undescended testes
    - Short penis
  - Usu N uterus, ovaries
    - Short vagina, uterine prolapse

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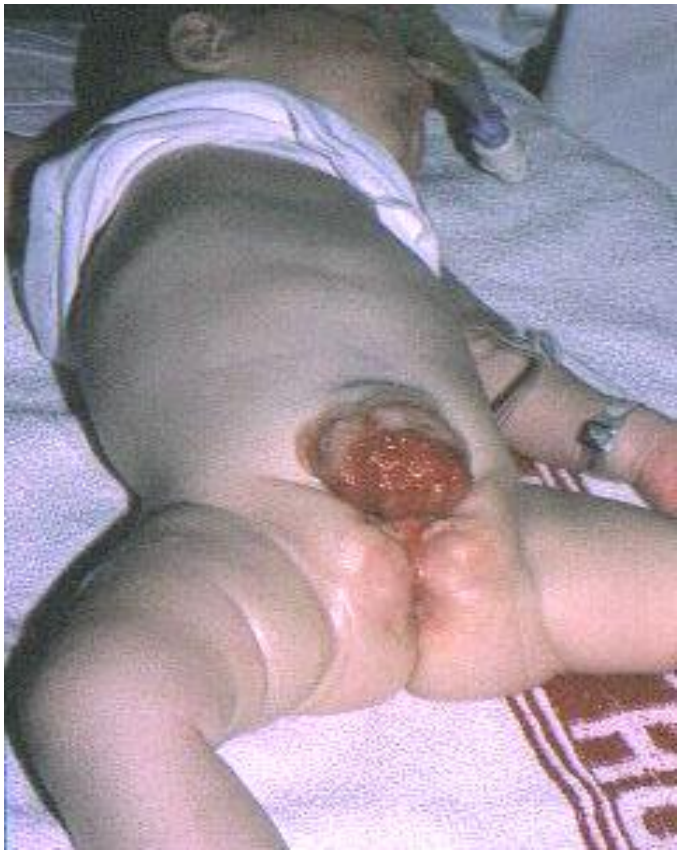
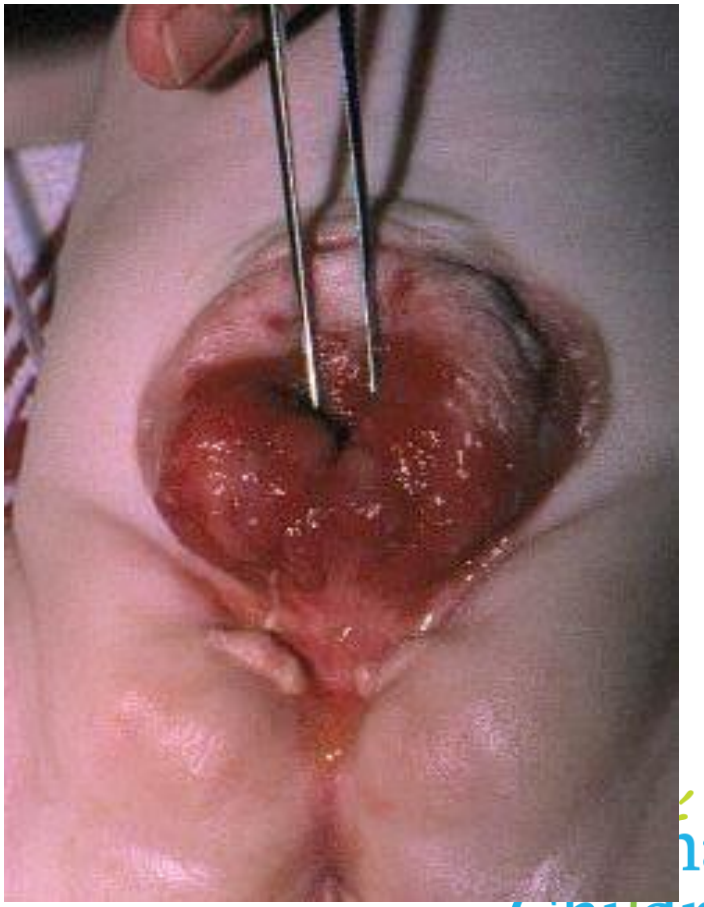
Bladder exstrophy





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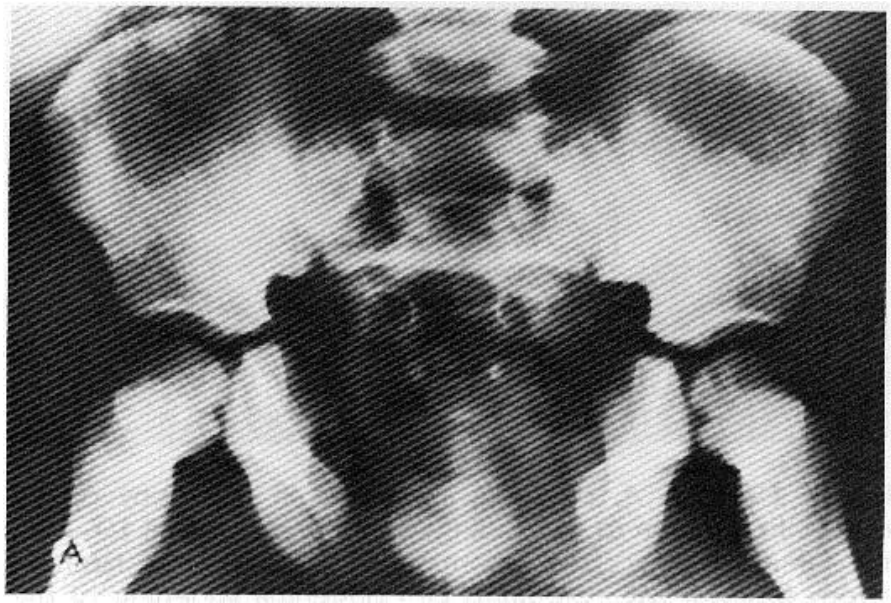
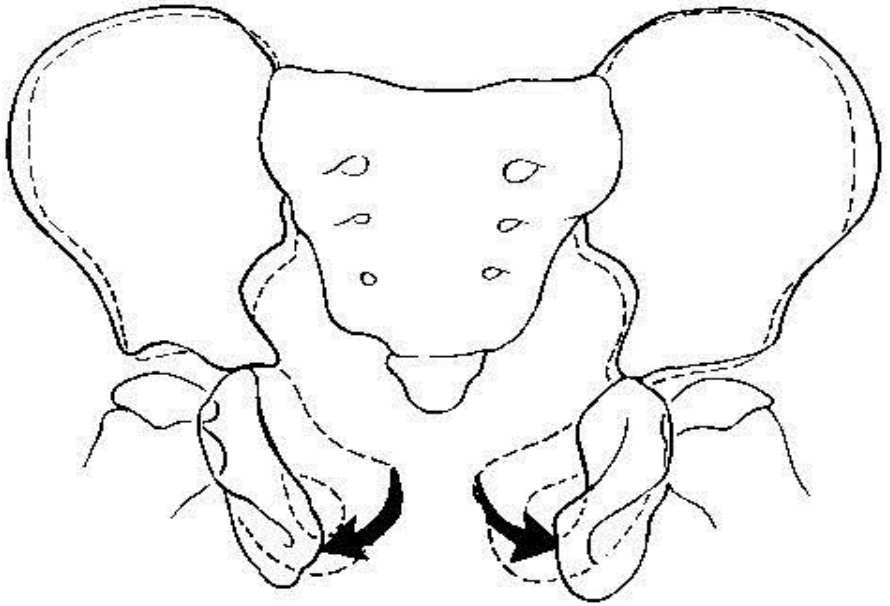
Bladder exstrophy





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Kidney – Vascular malformations

- Renal Artery Stenosis
- Renal AVM
- Renal artery aneurysm
- Mid aortic syndrome

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Hypospadias and Epispadias

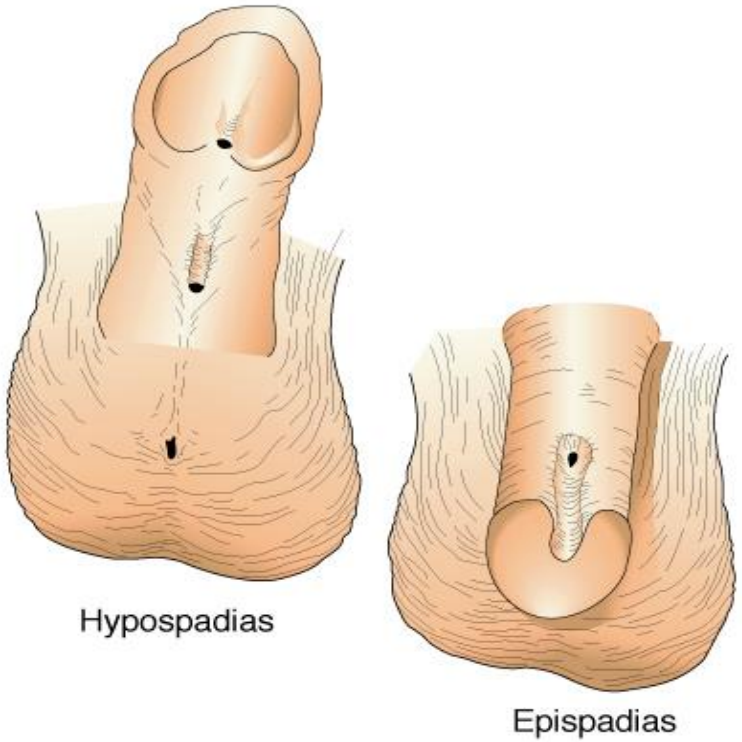

Figure 45-1 Hypospadias and epispadias.

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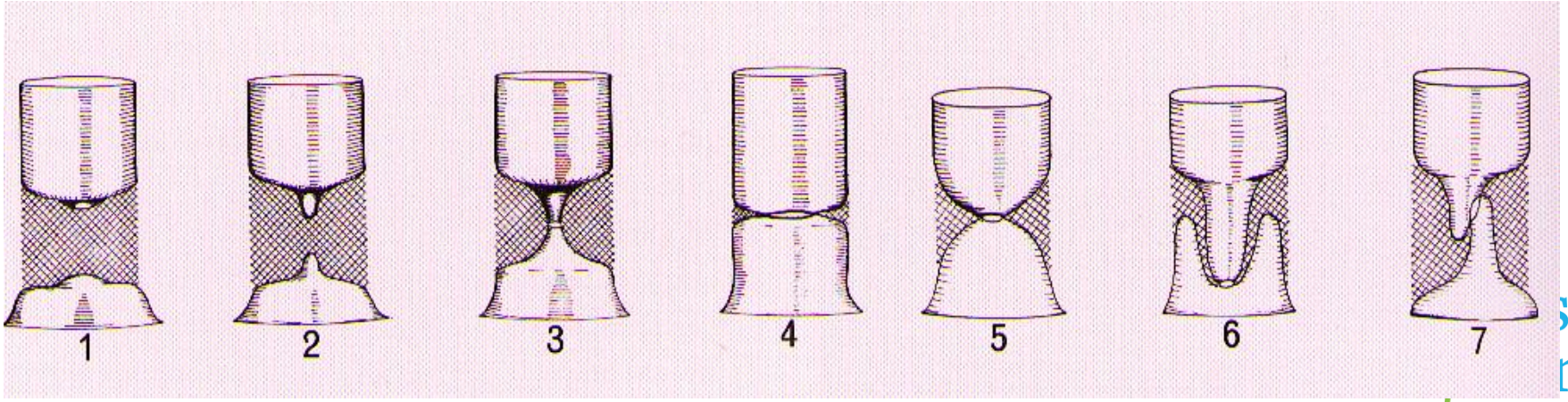
Posterior Urethral Valve

- Proximal male urethra blocked by fine membrane (valve)
- Presentation
    - Antenatal hydronephrosis
    - UTI in boy
    - Delayed day time continence



Posterior Urethral Valve

- Incontinence
  - Urethral sphincter distorted
  - Bladder
    - Noncompliant hypertonic bladder
    - Incomplete emptying
    - High pressure storage
  - Ureters
    - Vesicoureteric reflux (often high grade) - UTI’s
  - Kidneys
    - Obstructive uropathy - high volume urine prod’n

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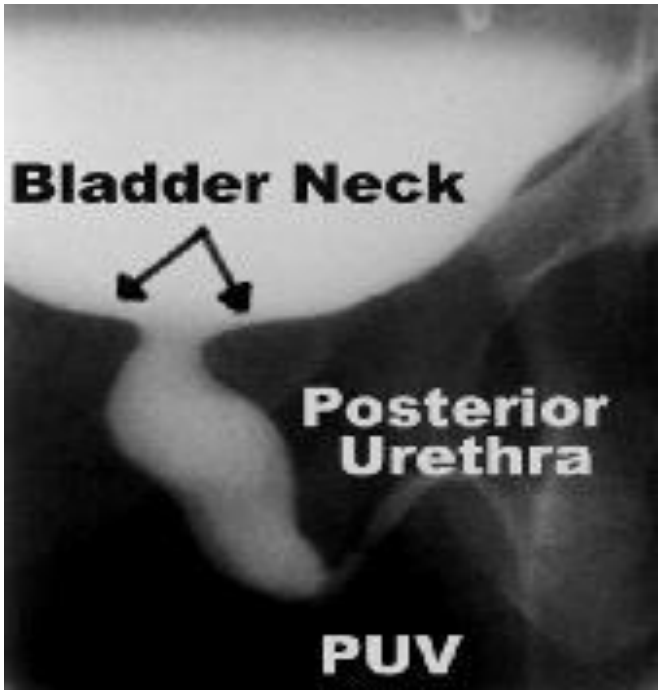
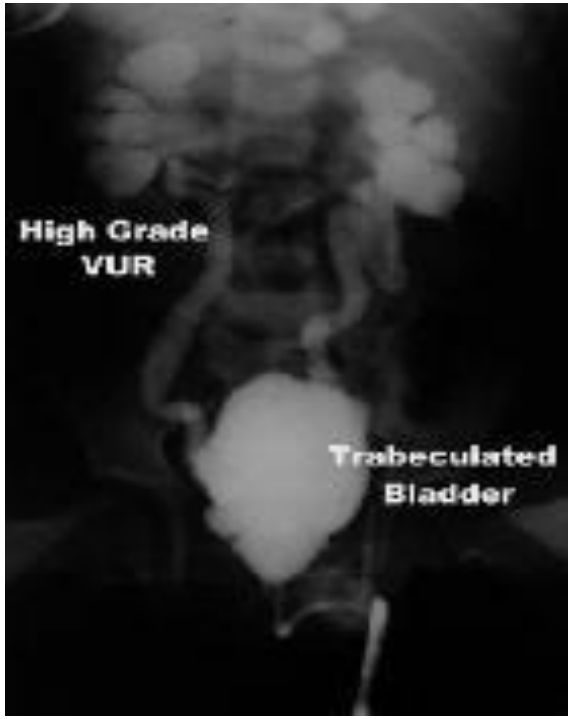
Posterior urethral valve





http://www.emedicine.com/ped/topic2357.htm#Target2

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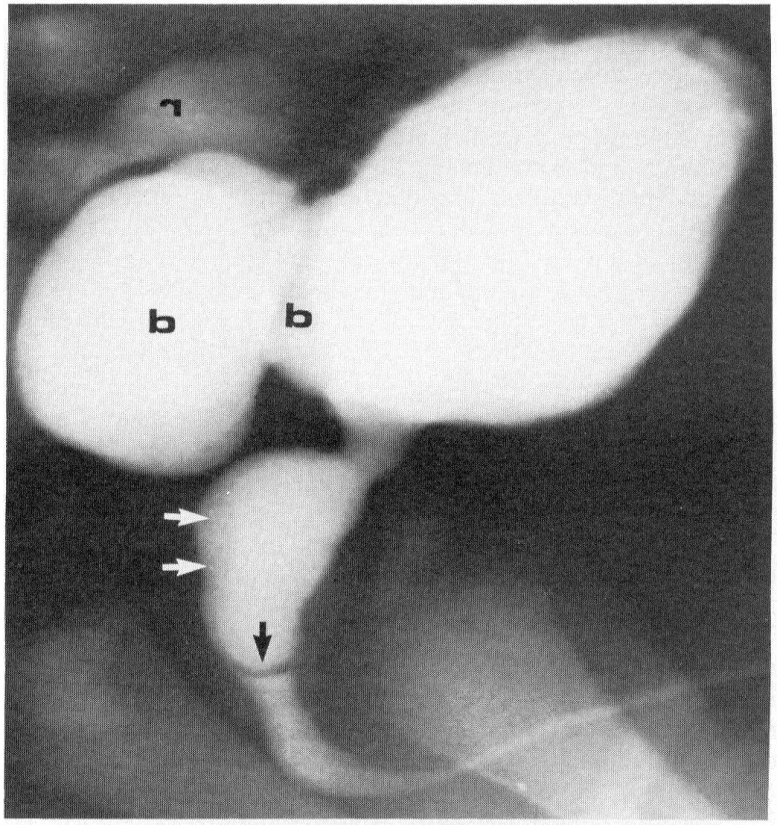
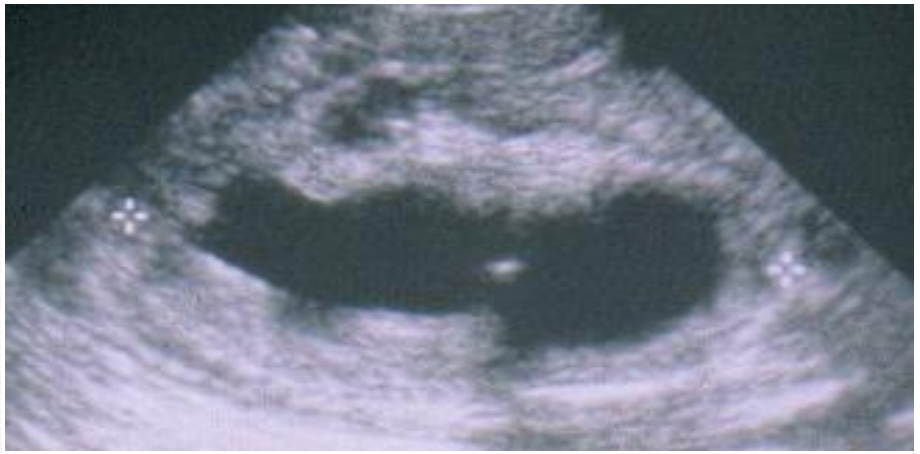
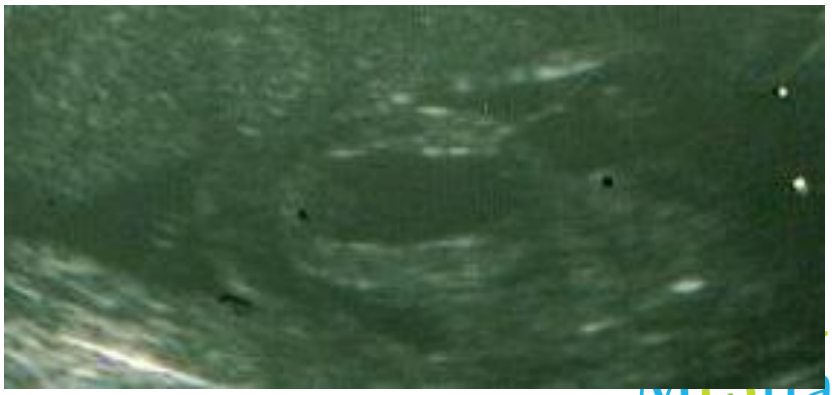
Posterior urethral valve







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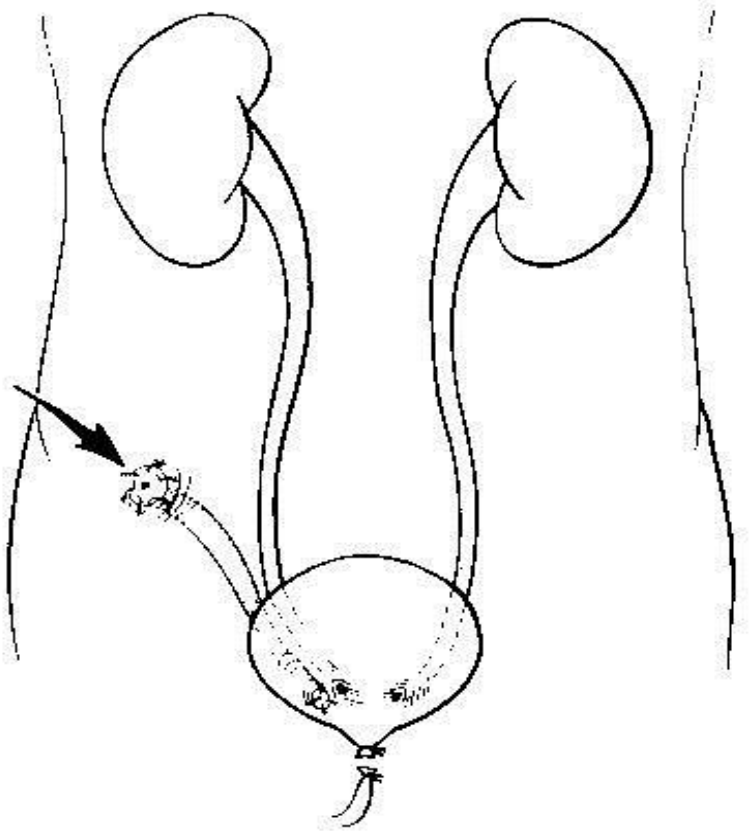
Mitrofanoff procedure

- Management
  - Remove obstruction
  - Mx VUR/UTI’s
  - Mx renal damage
    - Renal impairment
    - Salt & bicarb wasting
  - Bladder compliance
    - Ditropan
    - Bladder augmentation
      - CIC/stoma



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UTI - epidemiology

- 2nd most common bacterial infection after otitis media
- Overall prevalence -approximately 7 % in febrile infants and young children
  - varies by
    - age,
    - race/ethnicity,
    - sex,
    - circumcision status
  - White children: two- to four-fold higher prevalence than black children.
  - Girls: two- to four-fold higher prevalence of UTI than circumcised boys.
  - White girls with a temperature of >39^{o}C have a UTI prevalence of 16 percent.

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Urinary Tract Infections

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UTI - epidemiology

- 0.3 - 1.3% of all infants have UTI
- Males = females < 12 months of age
- Males> females < 3 months of age
- Females > males after 12 months
- Symptomatic UTI before puberty
  - Girls – 3-5%
  - Boys - 1-2%
- Recurrence
  - girls – 50%
  - Boys – uncommon, rare after 2 years

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UTI - pathophysiology

- Defense against bacterial invasion
- Physical
  - Unidirectional urinary flow
  - Uroepithelium
  - Local proteins that inhibit/ impede bacterial attachment - Tamm Horsfall protein
- Innate and adaptive immunity
  - Uroepithelial cell activation and transmembrane signalling
  - Production of distinct inflammatory mediators, and inflammatory cell recruitment
  - Cell and bacterial destruction

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UTI - pathogenesis

- Bacterial properties
  - Attachment - fimbriae - E coli - internalised in transitional epithelial cells in vacuoles equivalent to phagocytosis
  - Induces inflammatory response - this response results in renal damage

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UTI - pathogenesis

- Toll like receptors - recognise pathogen associated molecule patterns
  - TL 2 - detect lipoproteins from Gram positive bacteria
  - TL 4 - lipopolysaccharide signalling receptor - lower urinary tract and bladder
  - TL11 - kidney - recognises uropathogenic E coli (UPEC) and inhibits ascent of micro-organisms
- Tamm Horsfall protein - ascending Loop of Henle - prevents UPEC colonization, impedes fimbrial attachment, activates innate and adaptive immunity

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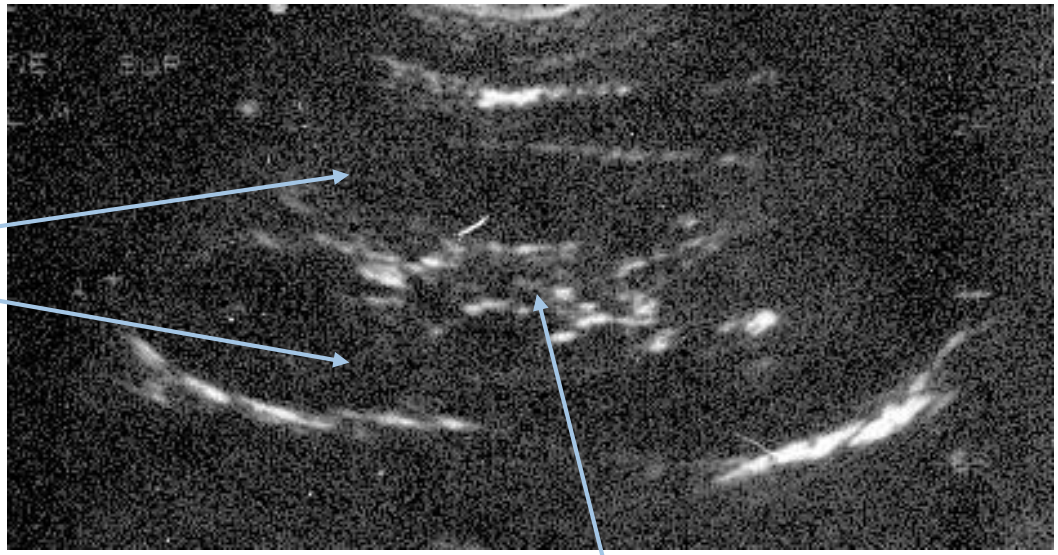
Normal renal ultrasound

Kidney cortex

Normal echotexture



Renal pelvis, no hydronephrosis

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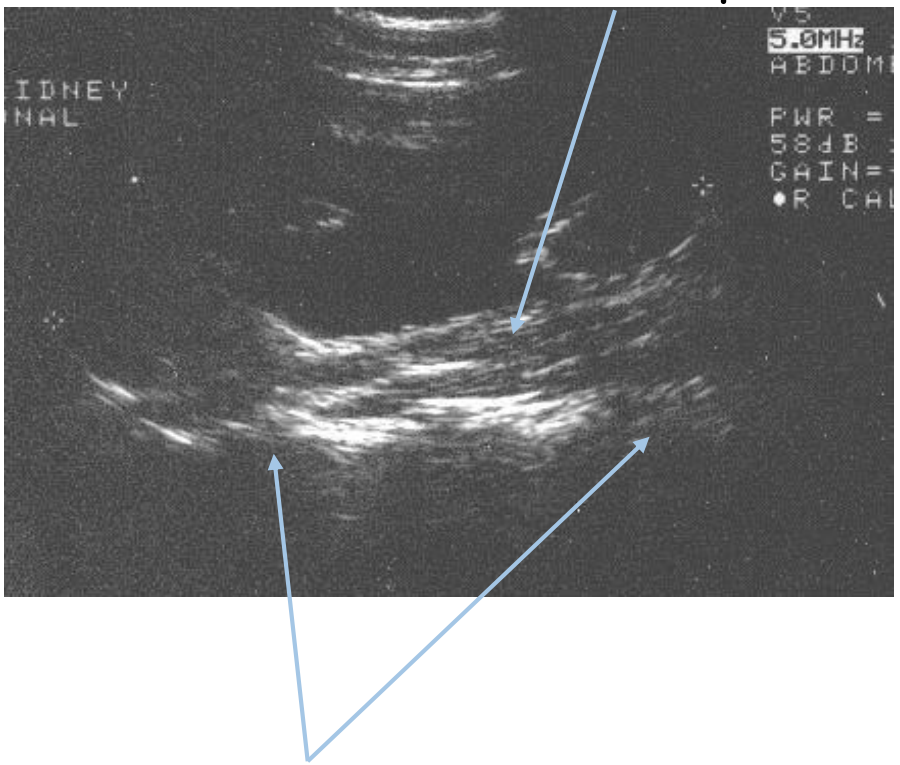
Hydronephrosis U/s

- Hydronephrosis
  - Dilated renal pelvis and ureters on both sides
  - Normal bladder



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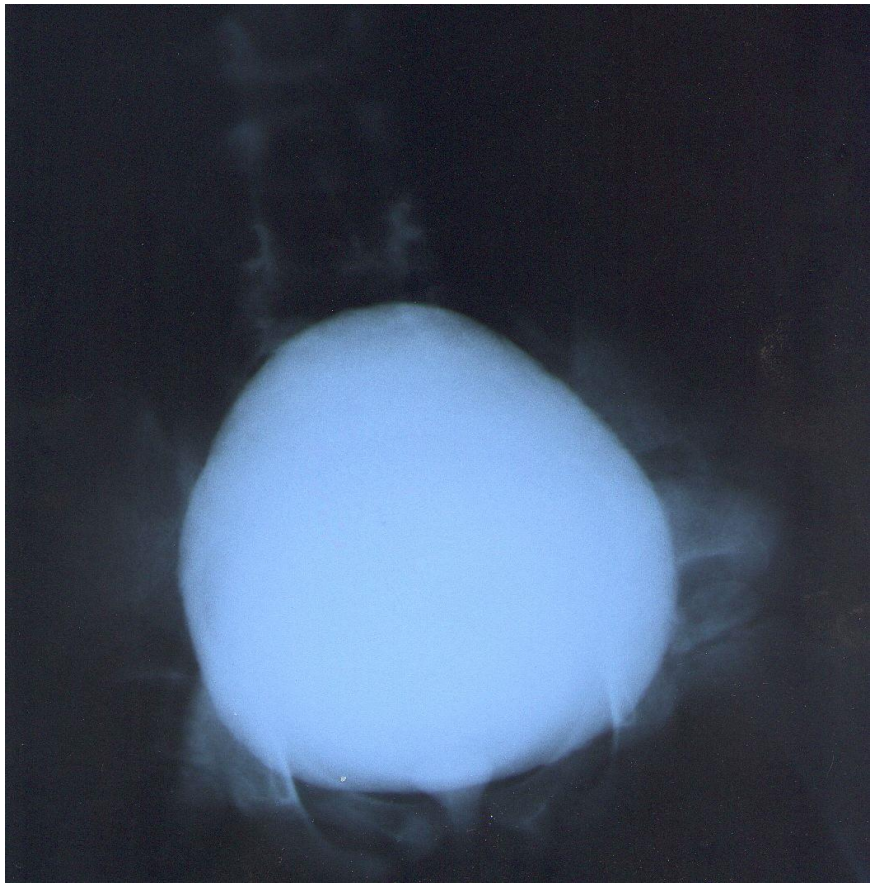
Micturating cystourethrogram

- Insert catheter into bladder
  - Fill with radio opaque dye
  - X ray during filling & voiding
- Catheter may be inserted under sedation, then awake for voiding phase
  - MMC only



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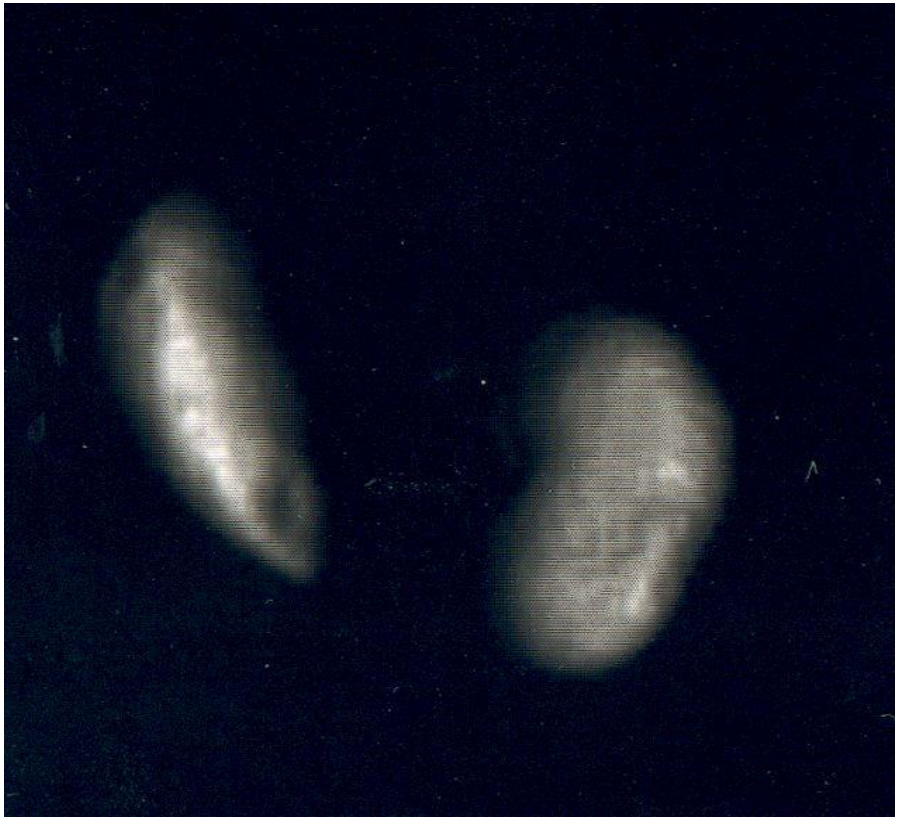
DMSA

- Dimercaptosuccinic acid scan
- Radio isotope injected IV
- Taken up by renal distal tubular cells
- Areas of poor uptake = tubular atrophy & interstitial fibrosis

  = renal scarring or reflux nephropathy



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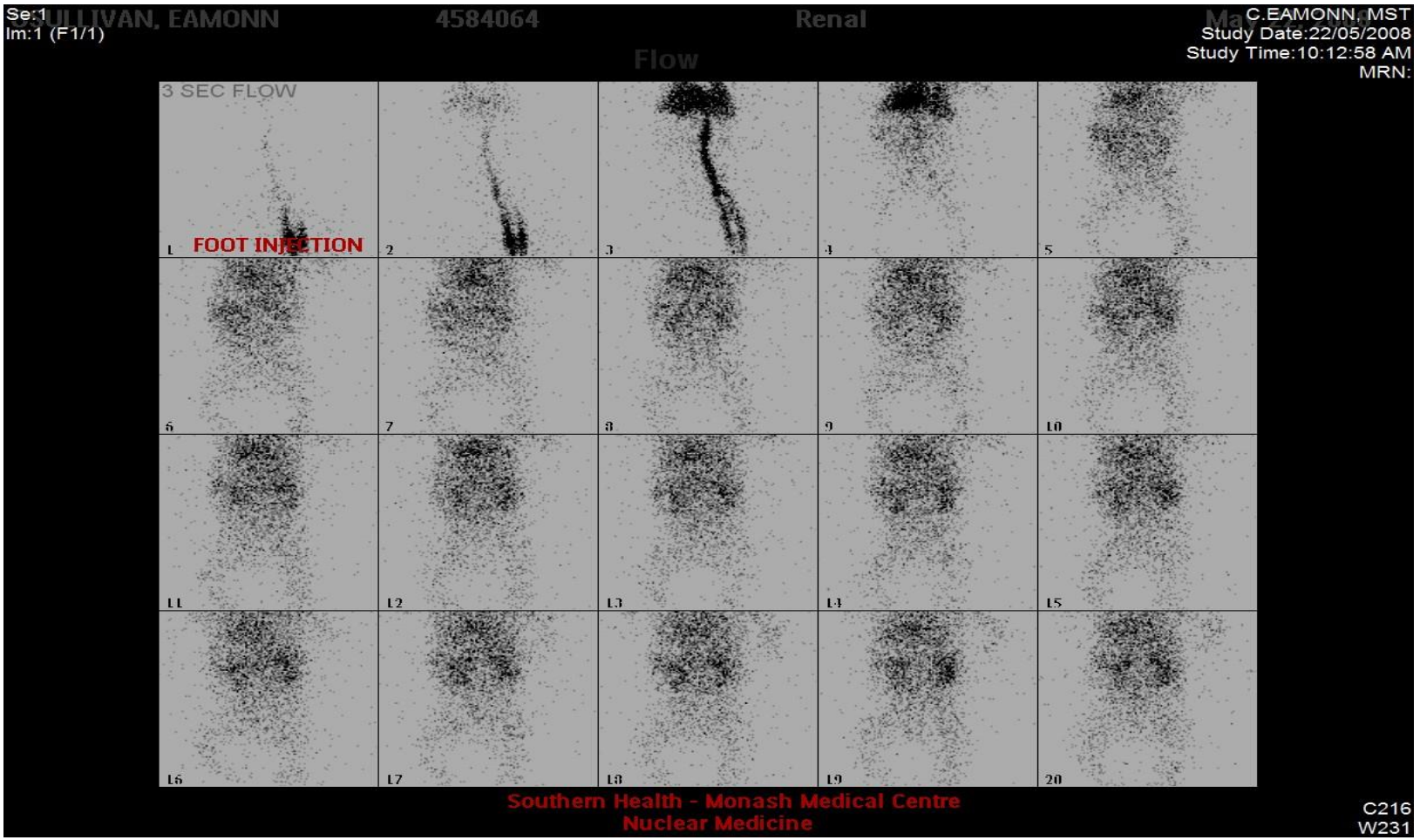
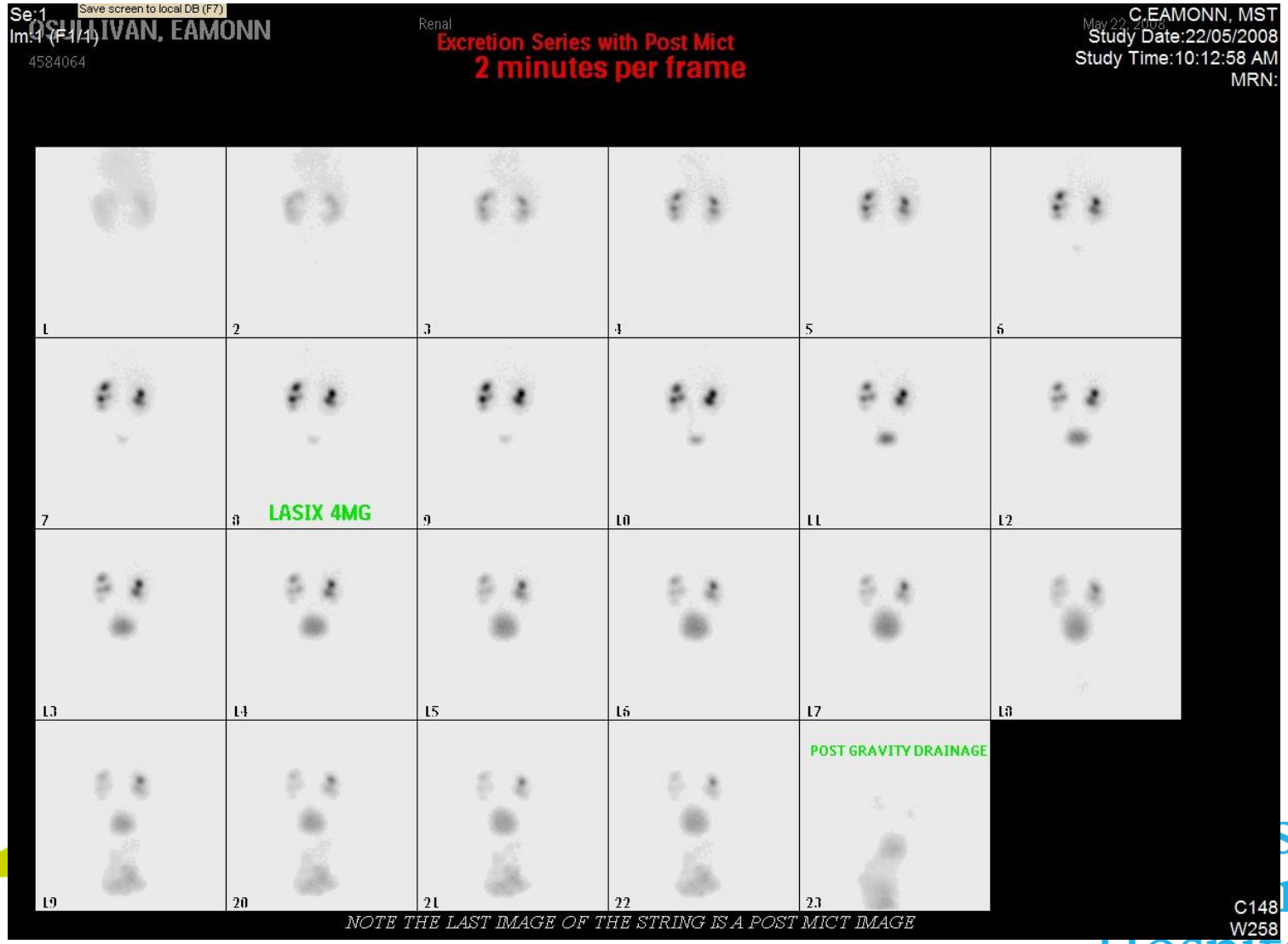
DTPA/ MAG - 3 - perfusion

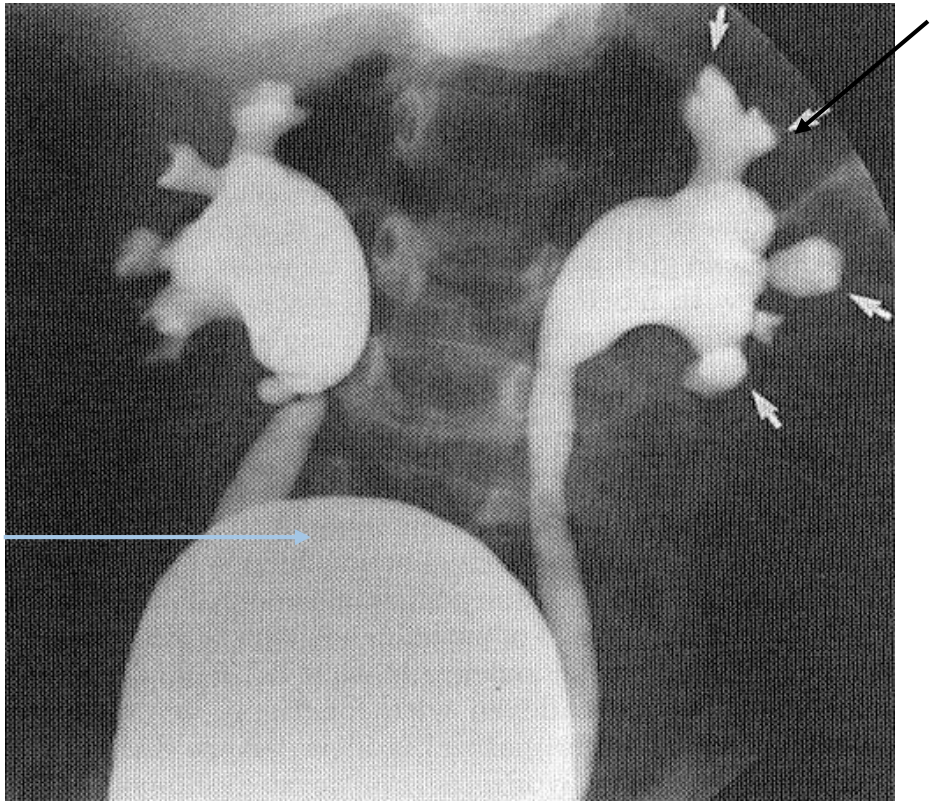


DTPA/ MAG - 3 - excretion



Vesicoureteric reflux

- Renal pelvis
  - Dilated
  - Calyceal dilatation or clubbing
- Ureters
  - V-U reflux (severity)
  - Dilatation/tortuousity
- Bladder
  - size, shape, thickened wall
- Urethra
  - Obstruction, stenosis



From Clinical Urography, ed Pollack, H.M., 1990

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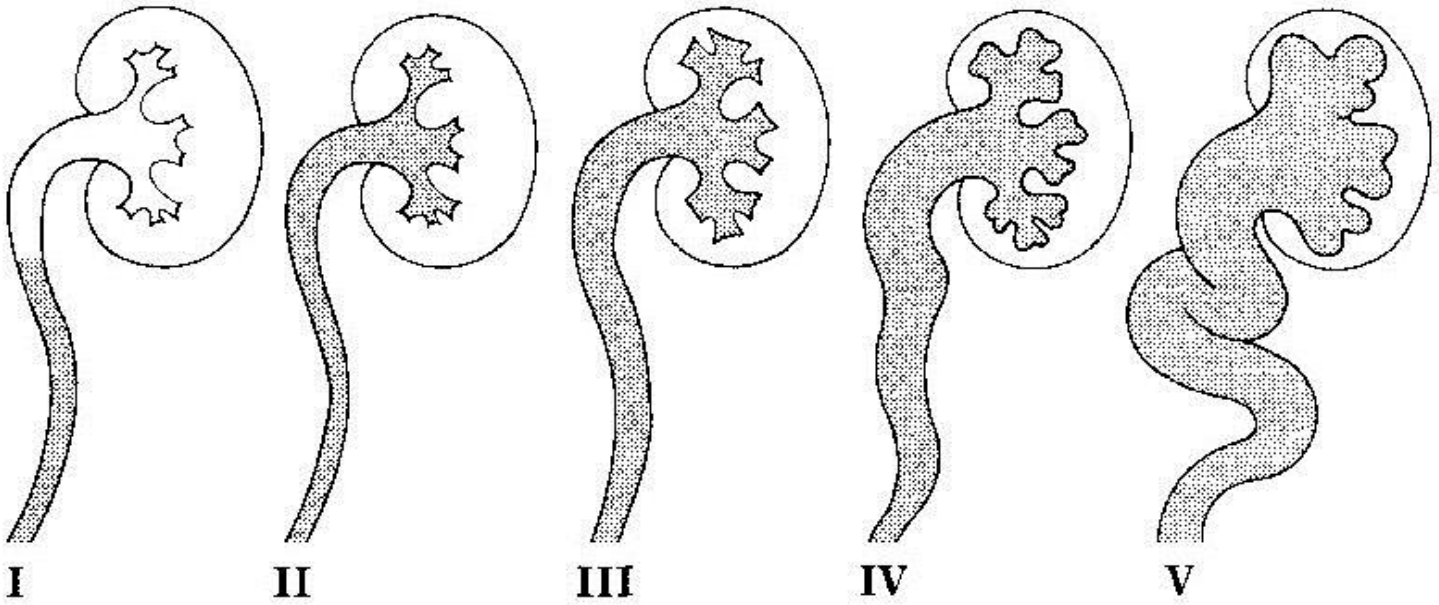
Classification of VUR severity



From Pediatric Nephrology, Barratt, Avner & Harmon

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Importance of VUR

- Recurrent UTI’s
  - Often pyelonephritis
    - Fever, dysuria, urinary frequency, loin pain,
    - Septicaemia
- Associated reflux nephropathy
    - Hypertension, renal impairment,
    - Occasional kidney failure

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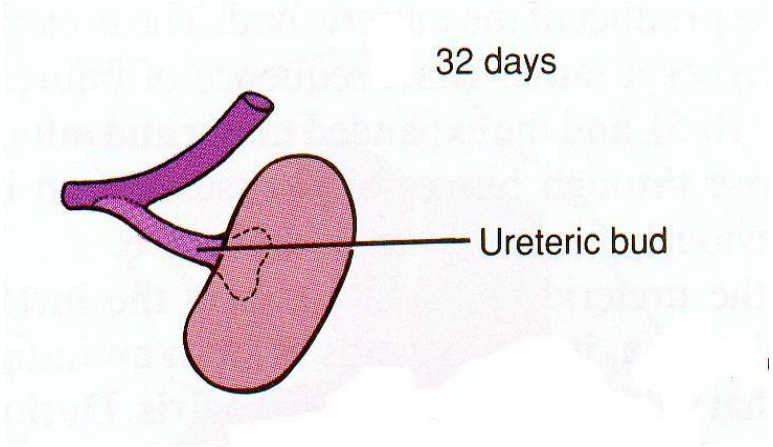
Reflux nephropathy

- Congenital
  - Abnormal development as ureteric bud penetrates metanephric blastema
- Acquired
  - from pyelonephritis



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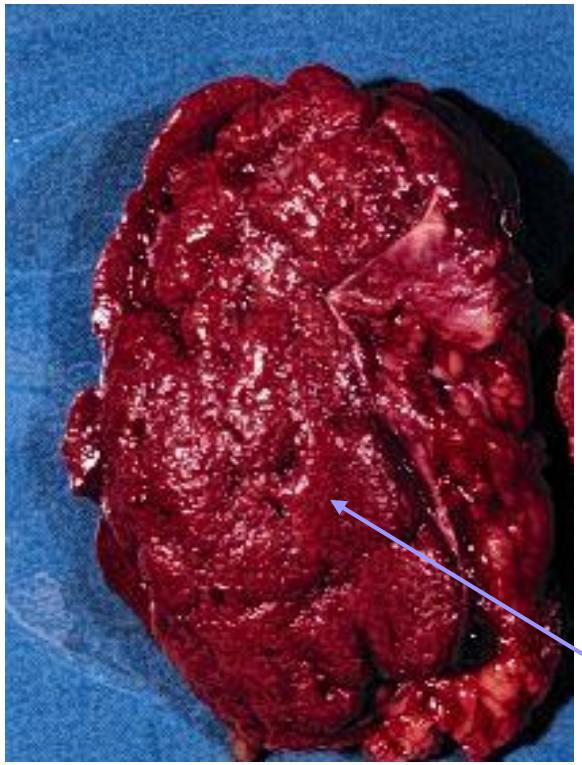
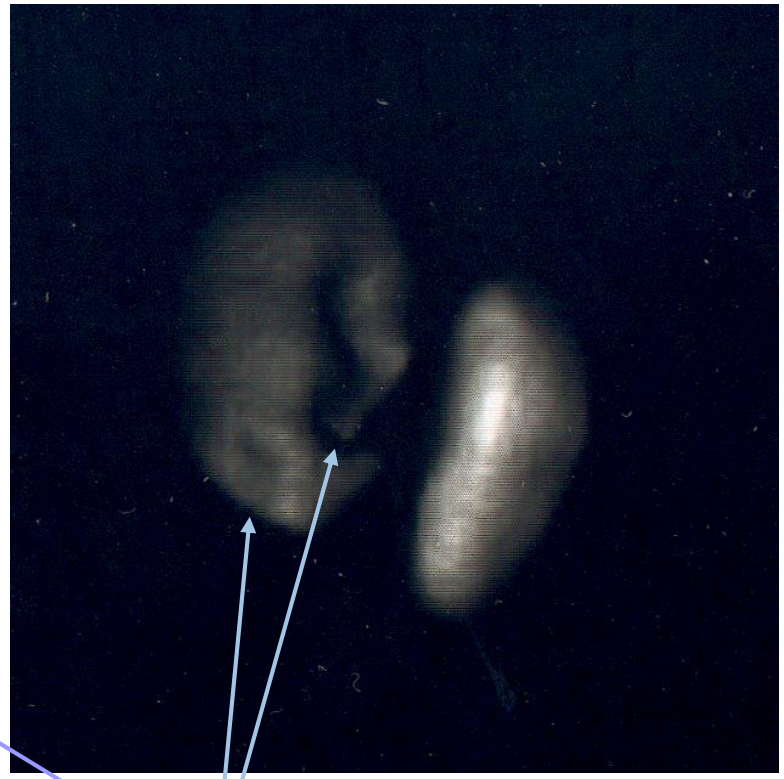
Reflux nephropathy





Renal scarring

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- Majority of VUR resolves or improves with bladder growth
  - Reduce UTI (lower & upper) whilst resolution occurs
  - Importance during own pregnancies

- Renal impairment
  - Relatively uncommon
- Severe reflux nephropathy
  - 20% of children and adolescents with ESRF have reflux nephropathy
  - 5-10% of adults with ESRF have reflux nephropathy
- Hypertension
  - Reflux nephropathy most common cause in kids

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- Medical
  - prophylactic antibiotics
    - Trimethoprim/ Cotrimoxazole
    - Nitrofurantoin
    - Not Kelfex, Amoxil, Augmentin
  - urinary surveillance
    - Regular FWT urine for leukocytes & nitrites
    - Urine M & C
    - Commence Antibiotics immediately
    - Review for sensitivities
  - how long for?
    - at least till fully toilet trained
- Surgical
  - Deflux
  - reimplantation of ureters

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Controversies

- Imaging
  - What imaging?
  - Who?
  - When
  - Do you need to image?

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Post UTI imaging

- AAP – US and VCUG (MCU) in all children up to 2 years of age

- NICE
  - US if less than 6 months or older if atypical UTI or recurrent UTI
  - MCU – if less than 6 months and atypical or recurrent UTI

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Post UTI imaging

- What are we trying to diagnose?
- Renal damage (40% post UTI)
- VUR – 30%
- Obstruction 1%

- ? Best test for those indications
- DMSA
- MCU

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GUIDELINES

Diagnosis and management of urinary tract infection in children: summary of NICE guidance

Rintaro Mori,[1] Monica Lakhanpaul,[2] Kate Verrier-Jones[3] on behalf of the Guideline Development Group

BMJ 2007;335:395-7
doi:10.1136/bmj.39286.700891.AD

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- High Risk
  - Recurrent UTI
  - Clinical signs – poor stream, palpable kidneys/ Bladder
  - Unusual organism
  - Bacteraemia/ septicaemia
  - Prolonged clinical course
  - Unusual presentation eg older boy
  - Known antenatal abnormality

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Box 1 | Initial management of children 3 months or older but younger than 3 years: use urgent microscopy and culture to diagnose urinary tract infection

Specific urinary symptoms

- Send urine sample for urgent microscopy and culture; if urgent microscopy is not available, send a urine sample for microscopy and culture
- Start antibiotic treatment

Non-specific symptoms

High risk of serious illness

- Refer child urgently to paediatric specialist care
- Send urine sample for urgent microscopy and culture
- Manage in line with NICE clinical guideline on feverish illness in children[2]

Intermediate risk of serious illness

- Consider urgent referral to a paediatric specialist (see NICE guideline[2])
- When specialist paediatric referral is not required:

- arrange urgent microscopy and culture
- start antibiotic treatment if microscopy is positive
- consider dipstick testing if urgent microscopy is not available
- start antibiotic treatment if nitrites are present (these suggest the possibility of infection)

- In all cases, a urine sample should be sent for microscopy and culture

Low risk of serious illness:

- Send urine sample for microscopy and culture
- Start antibiotic treatment if microscopy or culture is positive

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Box 2 | Initial management of children 3 years or older: use dipstick test to diagnose urinary tract infection

If leucocyte esterase and nitrite are positive

- Start antibiotic treatment for urinary tract infection
- If child has high or intermediate risk of serious illness or a history of infection, send urine sample for culture

If leucocyte esterase is negative and nitrite is positive

- Start antibiotic treatment if fresh sample was tested
- Send urine sample for culture

If leucocyte esterase is positive and nitrite is negative

- Send urine sample for microscopy and culture
- Only start antibiotic treatment for urinary tract infection if there is good clinical evidence of such infection
- Result may indicate infection elsewhere
- Treat depending on results of culture

If leucocyte esterase and nitrite are negative

- Do not start treatment for urinary tract infection
- Explore other causes of illness
- Do not send urine sample for culture unless recommended (see recommendations on urine culture

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Imaging strategies*

- Children of all ages with atypical urinary tract infection (box 3): perform ultrasonography of the urinary tract during the acute infection to identify structural abnormalities of the urinary tract.
- Infants younger than 6 months with first time urinary tract infection that is responsive to treatment: do ultrasonography within six weeks of the infection.
- Children younger than 3 years with atypical and/or recurrent urinary tract infection (box 3): do a DMSA (dimercaptosuccinic acid) scan 4-6 months after the acute infection to detect renal parenchymal defects.
- Do not do routine imaging to identify vesicoureteral reflux.

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Pediatr Nephrol (2008) 23:9–17
DOI 10.1007/s00467-007-0552-9

REVIEW

Imaging in childhood urinary tract infections: time to reduce investigations

Stephen D. Marks · Isky Gordon · Kjell Tullus

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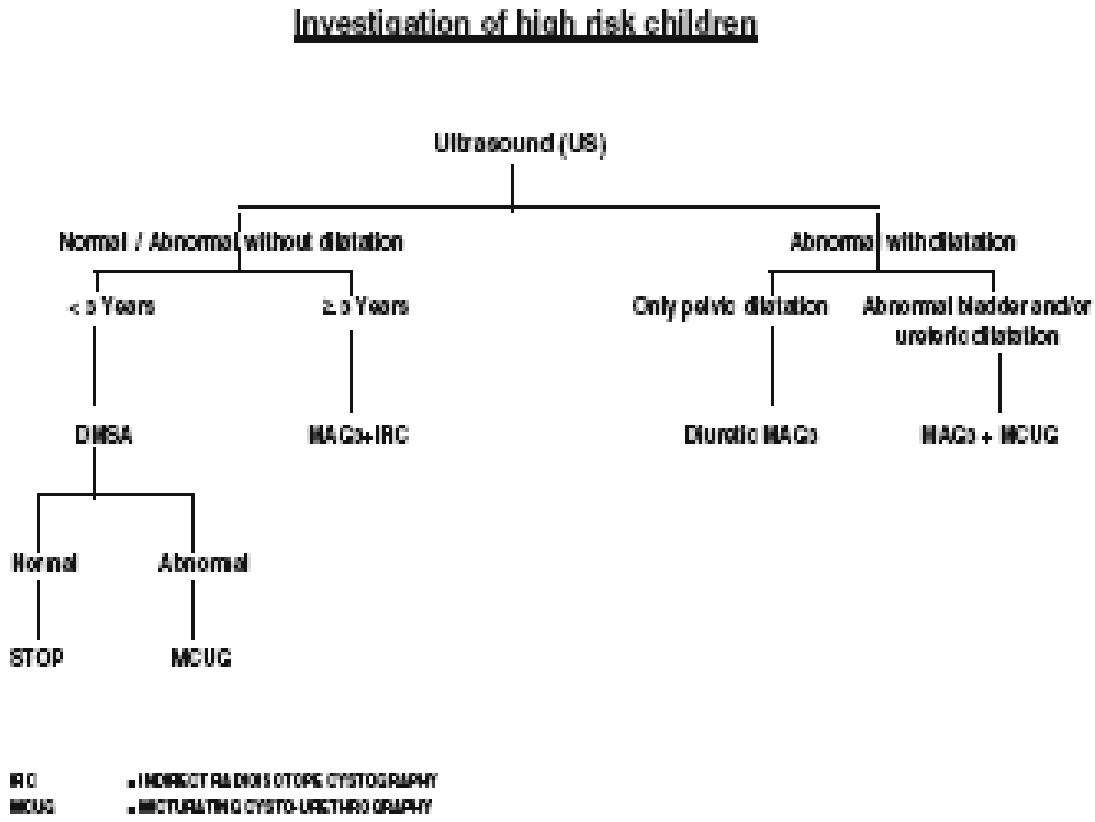
Fig. 2 Investigation of children with febrile UTI. This protocol should be followed only for children who are deemed "high risk"



IRC = INDIRECT RADIONUCLIDE CYSTOGRAPHY
MCUG = MICTURATING CYSTO-URETHROGRAPHY

Controversies

- Treatment
  - Which antibiotic?
  - How delivered?
  - How long to treat?

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Antibiotic treatment

- Children with a high risk of serious illness[2] and/or younger than 3 months: refer immediately to secondary care
- Children aged 3 months and older with acute pyelonephritis or upper urinary tract infection:
  - consider referral to secondary care
  - treat with 10 days of oral antibiotics, or if child is unable to tolerate oral antibiotics, start treatment with intravenous antibiotics until oral intake is possible
  - repeat culture if no response within 24-48 hours
- Children aged 3 month and over with cystitis or lower urinary tract infection:
  - treat with three days of oral antibiotics according to local guidance
  - advise carers to return for review if the child remains unwell after 24-48 hours.

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Preventing recurrence

- Do not prescribe antibiotic prophylaxis routinely.

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Box 3 | Main characteristics of patients with atypical or recurrent urinary tract infection

Atypical (any of the following)

- Septicaemia or patient who looks seriously ill (see NICE guideline[2])
- Poor urine flow
- Abdominal or bladder mass
- Raised creatinine concentration
- Failure to respond to treatment with suitable antibiotics within 48 hours
- Infection with non-*Escherichia coli* organisms

Recurrent (any of the following)

- Two or more episodes of urinary tract infection with acute pyelonephritis or upper urinary tract infection
- One episode of urinary tract infection with acute pyelonephritis or upper urinary tract infection plus one or more episode of urinary tract infection with cystitis or lower urinary tract infection
- Three or more episodes of urinary tract infection with cystitis or lower urinary tract infection

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Vesico-ureteric reflux – does it matter?

- CKD – chronic malformed kidneys
  - Obstructive uropathy – 22%
  - Hypoplasia/ dysplasia/ aplasia – 18%
  - Reflux nephropathy – 8%

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VUR, reflux nephropathy

- Prevalence
  - 24% - 30% of young people < 21 years with UTI
  - 8% Grade IV or V
- Resolution
- 13% per year – Grade I, II, III
- 73% of children have no VUR or Grade I after 10 years

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VUR, reflux nephropathy

- Postnatal acquisition of scars is rare with VUR even with febrile UTI
- Acute pyelonephritis can cause renal scarring with or without reflux present
- Is reflux a surrogate marker of an abnormal urinary tract?
- Reflux increases risk of new scars developing in abnormal kidneys
- VUR without infection rarely causes new scars

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UTI/ VUR/ RN

- Long term complications
  - CKD
  - Hypertension
  - Pregnancy associated complications

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Short versus standard duration oral antibiotic therapy for acute urinary tract infection in children (Review)

Michael M, Hodson EM, Craig JC, Martin S, Moyer VA

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PLAIN LANGUAGE SUMMARY

Short courses of antibiotics (2–4 days) are as effective as longer treatment for bladder infections in children.

Bladder and kidney infections (urinary tract infections - UTI) are common in children. Bladder infections cause pain on passing urine and frequency of urination. Some children keep getting repeat bouts. Standard courses of antibiotics (7-10 days) are used to clear the infection. Shorter courses may reduce adverse effects and costs, but there has been concern that they might reduce the chances of clearing the infection and increase the risk of recurrence. A review of studies found that short courses of antibiotics (2-4 days) used for bladder infections are as effective as standard courses at clearing UTI, with no increase in recurrence.

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Long-term antibiotics for preventing recurrent urinary tract infection in children (Review)

Williams G, Wei L, Lee A, Craig JC

Monash Children's Hospital

PLAIN LANGUAGE SUMMARY

Long-term antibiotics for preventing recurrent urinary tract infection in children

Bladder and kidney infections (urinary tract infection - UTI) are common in children, especially girls. They cause an uncomfortable illness that can include vomiting, fever and tiredness. In some children kidney damage may occur, as can repeat illnesses. With repeated infections the risk of kidney damage increases. Some doctors prescribe long-term antibiotics to try to prevent infections recurring, but this may cause the child to be unwell in other ways, e.g. vomiting. This review of trials found evidence that long-term antibiotics did prevent some infections, but these infections occurred without the child being unwell, that is they may not be real illnesses and thus don't need prevention. Nitrofurantoin was more effective than trimethoprim but had more adverse effects.

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Cranberries for preventing urinary tract infections (Review)

Jepson RG, Craig JC

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There is some evidence that cranberry juice may decrease the number of symptomatic UTIs over a 12 month period, particularly for women with recurrent UTIs. It's effectiveness for other groups is less certain. The large number of dropouts/withdrawals indicates that cranberry juice may not be acceptable over long periods of time. It is not clear what is the optimum dosage or method of administration (e.g. juice, tablets or capsules). Further properly designed studies with relevant outcomes are needed.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antibiotic Prophylaxis and Recurrent Urinary Tract Infection in Children

Jonathan C. Craig, M.B., Ch.B., Ph.D., Judy M. Simpson, Ph.D., Gabrielle J. Williams, Ph.D., M.P.H., Alison Lowe, B.Sc., Graham J. Reynolds, M.B., B.S., Steven J. McTaggart, M.B., B.S., Ph.D., Elisabeth M. Hodson, M.B., B.S., Jonathan R. Carapetis, M.B., B.S., Ph.D., Noel E. Cranswick, M.B., B.S., Grahame Smith, M.B., B.S., Les M. Irwig, M.B., B.Ch., Ph.D., Patrina H.Y. Caldwell, Ph.D., Sana Hamilton, M.P.H., and Leslie P. Roy, M.B., B.S., for the Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts (PRIVENT) Investigators

N Engl J Med 2009;361:1748-59.

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METHODS

We randomly assigned children under the age of 18 years who had had one or more microbiologically proven urinary tract infections to receive either daily trimethoprim–sulfamethoxazole suspension (as 2 mg of trimethoprim plus 10 mg of sulfamethoxazole per kilogram of body weight) or placebo for 12 months. The primary outcome was microbiologically confirmed symptomatic urinary tract infection. Intention-to-treat analyses were performed with the use of time-to-event data.

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RESULTS

From December 1998 to March 2007, a total of 576 children (of 780 planned) underwent randomization. The median age at entry was 14 months; 64% of the patients were girls, 42% had known vesicoureteral reflux (at least grade III in 53% of these patients), and 71% were enrolled after the first diagnosis of urinary tract infection. During the study, urinary tract infection developed in 36 of 288 patients (13%) in the group receiving trimethoprim–sulfamethoxazole (antibiotic group) and in 55 of 288 patients (19%) in the placebo group (hazard ratio in the antibiotic group, 0.61; 95% confidence interval, 0.40 to 0.93; P=0.02 by the log-rank test). In the antibiotic group, the reduction in the absolute risk of urinary tract infection (6 percentage points) appeared to be consistent across all subgroups of patients (P≥0.20 for all interactions).

CONCLUSIONS

Long-term, low-dose trimethoprim–sulfamethoxazole was associated with a decreased number of urinary tract infections in predisposed children. The treatment effect appeared to be consistent but modest across subgroups. (Australian New Zealand Clinical Trials Registry number, ACTRN12608000470392.)

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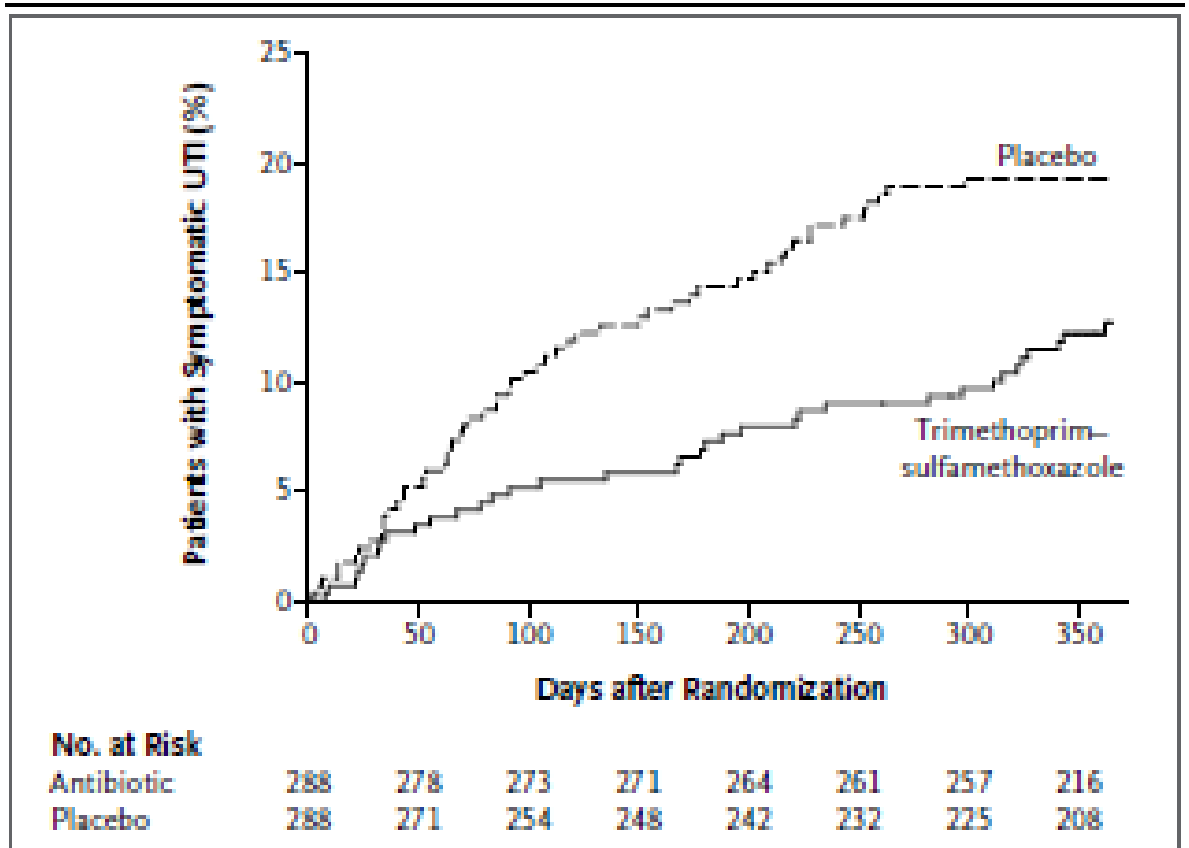

Figure 2. Time to Symptomatic Urinary Tract Infection (UTI) (Primary Outcome).

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 19, 2014 VOL. 370 NO. 25

Antimicrobial Prophylaxis for Children with Vesicoureteral Reflux

The RIVUR Trial Investigators*

Monash Children's Hospital

BACKGROUND

Children with febrile urinary tract infection commonly have vesicoureteral reflux. Because trial results have been limited and inconsistent, the use of antimicrobial prophylaxis to prevent recurrences in children with reflux remains controversial.

METHODS

In this 2-year, multisite, randomized, placebo-controlled trial involving 607 children with vesicoureteral reflux that was diagnosed after a first or second febrile or symptomatic urinary tract infection, we evaluated the efficacy of trimethoprim–sulfamethoxazole prophylaxis in preventing recurrences (primary outcome). Secondary outcomes were renal scarring, treatment failure (a composite of recurrences and scarring), and antimicrobial resistance.

RESULTS

Recurrent urinary tract infection developed in 39 of 302 children who received prophylaxis as compared with 72 of 305 children who received placebo (relative risk, 0.55; 95% confidence interval [CI], 0.38 to 0.78). Prophylaxis reduced the risk of recurrences by 50% (hazard ratio, 0.50; 95% CI, 0.34 to 0.74) and was particularly effective in children whose index infection was febrile (hazard ratio, 0.41; 95% CI, 0.26 to 0.64) and in those with baseline bladder and bowel dysfunction (hazard ratio, 0.21; 95% CI, 0.08 to 0.58). The occurrence of renal scarring did not differ significantly between the prophylaxis and placebo groups (11.9% and 10.2%, respectively). Among 87 children with a first recurrence caused by *Escherichia coli*, the proportion of isolates that were resistant to trimethoprim–sulfamethoxazole was 63% in the prophylaxis group and 19% in the placebo group.

CONCLUSIONS

Among children with vesicoureteral reflux after urinary tract infection, antimicrobial prophylaxis was associated with a substantially reduced risk of recurrence but not of renal scarring. (Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; RIVUR ClinicalTrials.gov number, NCT00405704.)

Voiding Disorders

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What is it?

- Day wetting
- Night wetting
- Urge
- Urge incontinence
- Stress incontinence
- Dysfunctional voiding
- Dysfunctional elimination syndrome
- Detrusor dyssynergia
- Unstable bladder
- Hinman Bladder
- Non-neurogenic bladder
- Ectopic ureter
- Neurogenic bladder
- ?????

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What do you want to do?

- Diagnose wetting problem
- Confirm or exclude ‘organic’ disease
- Develop a treatment plan

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What are we talking about?

The International Children's Continence Society terminology

The Standardization of Terminology of Lower Urinary Tract Function in Children and Adolescents: Report from the Standardisation Committee of the International Children's Continence Society

Tryggve Nevéus,* Alexander von Gontard, Piet Hoebeke, Kelm Hjälmås,†
Stuart Bauer, Wendy Bower, Troels Munch Jørgensen, Søren Rittig, Johan Vande Walle,
Chung-Kwong Yeung and Jens Christian Djurhuus

J Urol 176, 314-324, 2006

www.i-c-c-s.org

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Incontinence

- involuntary wetting
- at an inappropriate time and place
- in a child 5 years old or more

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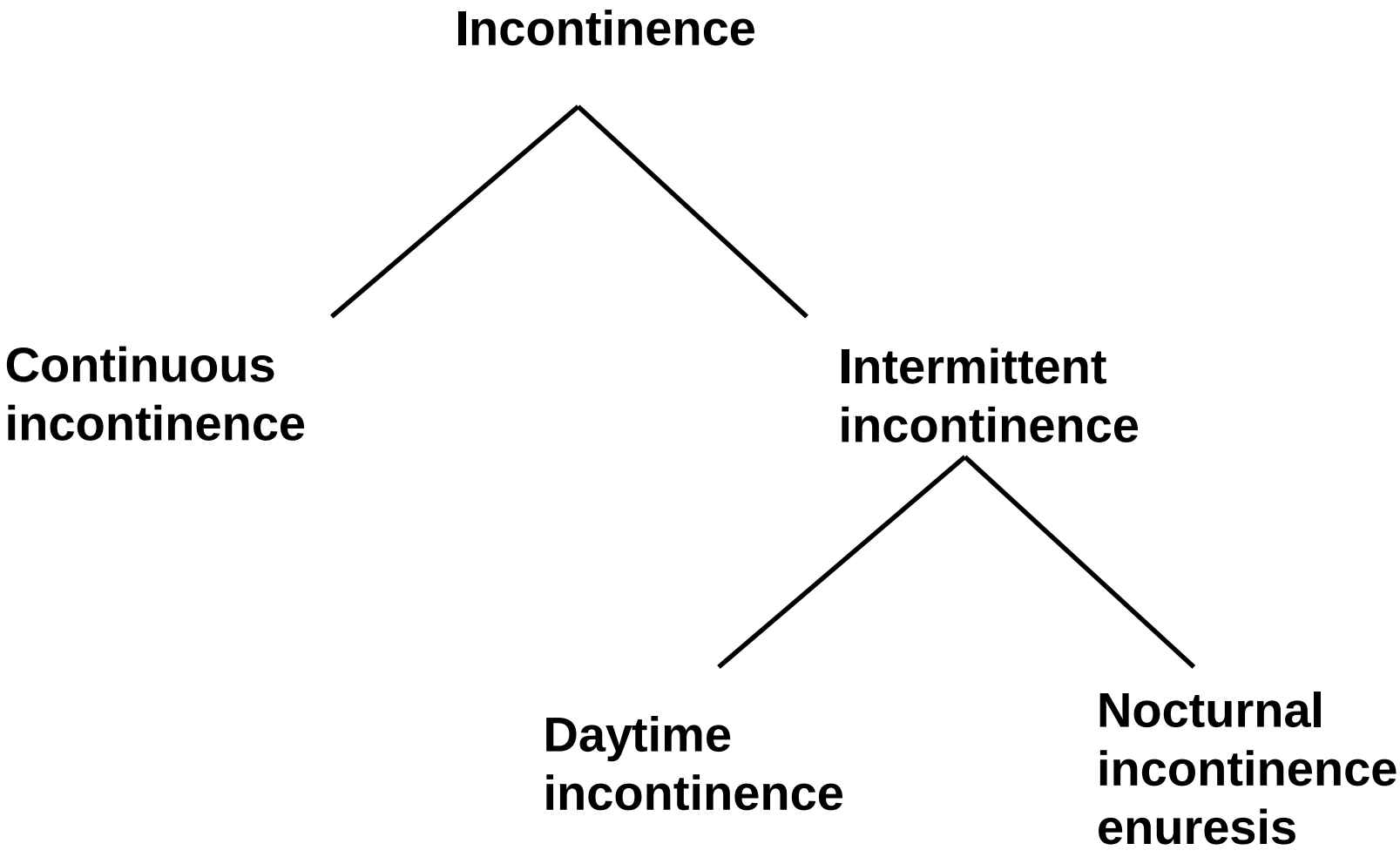

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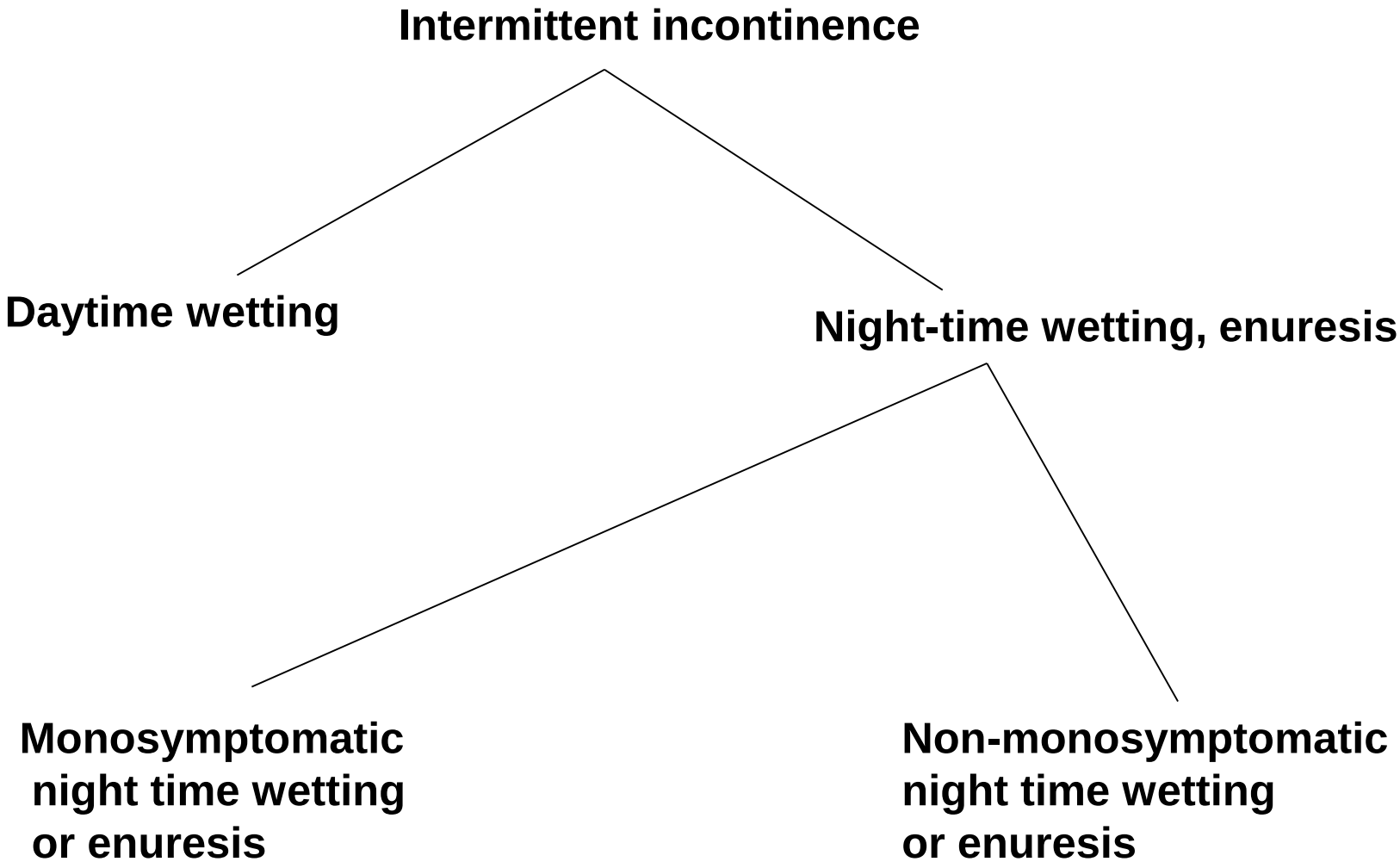

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Enuresis

Intermittent incontinence while asleep

- Regardless of
  - whether cystometry reveals that the voiding is complete and normal or not
  - whether the child also suffers from day-time incontinence or not
  - what we think the cause is
- Monosymptomatic enuresis
  - Enuresis in a child without daytime bladder symptoms
    - i.e. enuresis without
      - Urgency
      - Incontinence
      - Increased/decreased voiding frequency
      - Voiding postponement
      - Holding manoeuvres
      - Interrupted flow

Otherwise - Non-monosymptomatic enuresis

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Intermittent nocturnal incontinence - (enuresis)

- Children with enuresis and daytime incontinence have enuresis* and daytime incontinence
- We do not change the name of the disorder just because the child also suffers from another disorder, even though it gives clues regarding pathogenesis (compare: asthma and hay-fever)
- The coexistence of the two may also be just coincidence. Both conditions are common!
- *Of the nonmonosymptomatic subtype

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Bladder Findings (Descriptors)

- Increased daytime voiding frequency
  - 8 voidings or more per day
- Decreased daytime voiding frequency
  - 3 voidings or less per day
- Voided volume
  - Was bladder capacity
- Residual Volume
  - > 20 ml is abnormal, also use <10% of prevoid bladder volume
- Polyuria
  - >2 l/m^2 per 24 hours

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Bladder Findings

- Maximum voided volume
  - Was ”Functional bladder capacity” as measured from a voiding diary
- Expected bladder capacity
  - deduced from the standard formula
  - EBC (ml) = 30 + (30 x age (years))
  - Use until 12 years of age (390 ml)

- Compare MVV and EBC
  - Small Bladder is MVV < 65% of EBC
  - Large Bladder is MVV> 150% EBC

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More findings related to the bladder

- Terms deduced from history and voiding diary
  - Overactive bladder
  - Underactive bladder

- Determined from cystometry
  - Detrusor overactivity
  - Detrusor instability
  - Detrusor underactivity

- We cannot speak about the detrusor without having performed a cystometry
- This is in accordance with ICS adult terminology
- Instability is an ambiguous word

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Daytime wetting

- Storage/ Filling
- Voiding/ emptying

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Day-time LUT conditions

- Overactive bladder
  - children with urgency
  - (increased voiding frequency and/or incontinence often present but not required for use of the term)
- Urge incontinence
  - children with incontinence and urgency
- Voiding postponement
  - children who are observed to habitually postpone voiding using holding manoeuvres
- Underactive bladder
  - Children with low voiding frequency who need to use raised intraabdominal pressure to void
- Dysfunctional voiding
  - children who habitually contract the sphincter during voiding, producing uroflow curves of a staccato type

Note:

- This term says nothing about the storage phase.
- Dysfunctional voiding or voiding dysfunction is not the same as ”any bladder disturbance”

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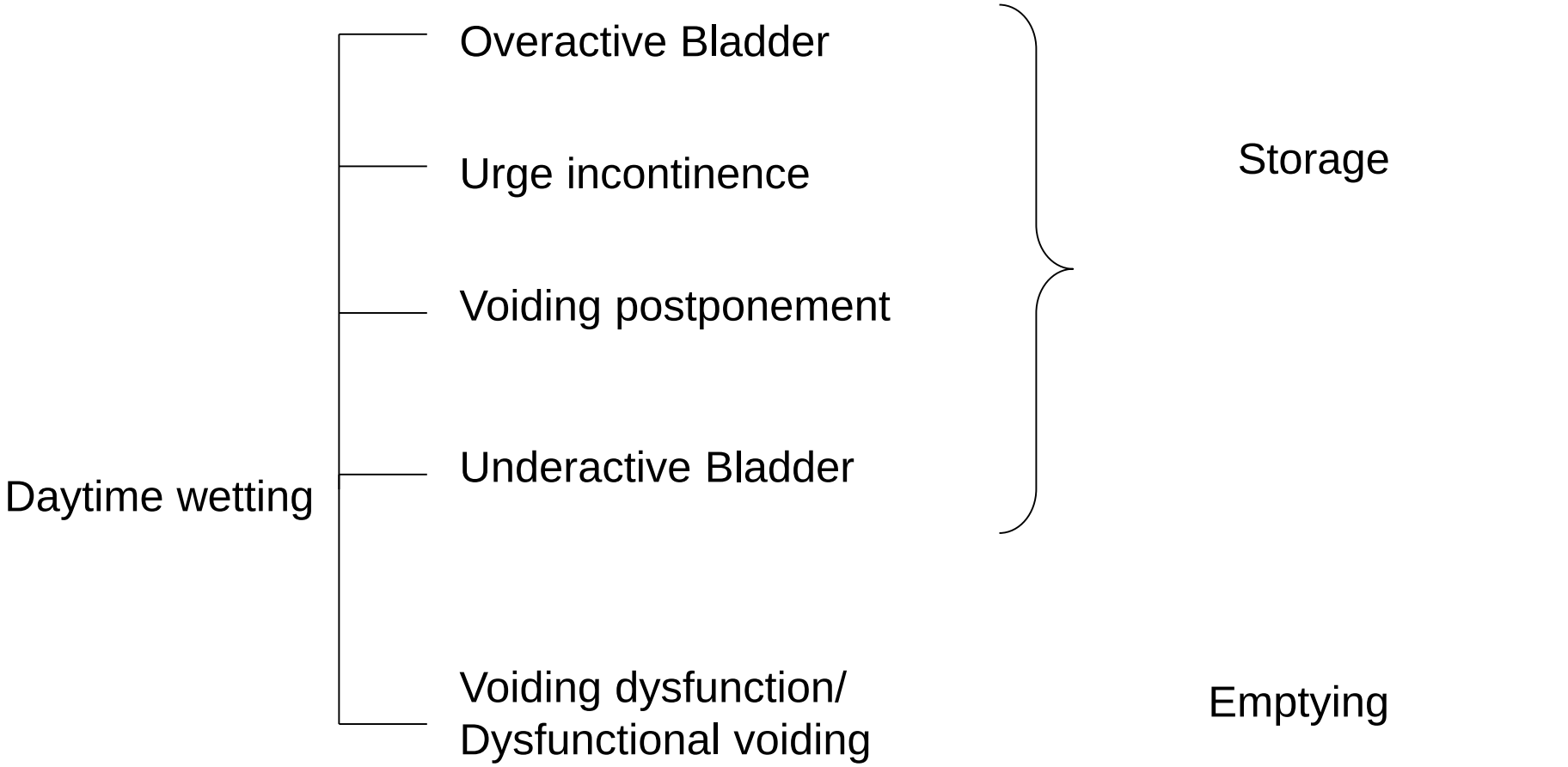
Daytime wetting
Overactive Bladder
Urge incontinence
Voiding postponement
Underactive Bladder
Voiding dysfunction/
Dysfunctional voiding
Storage
Emptying

Daytime LUT Conditions

- Obstruction
- Stress Incontinence
- Vaginal Reflux
- Giggle Incontinence
- Extraordinary Urinary Daytime Frequency

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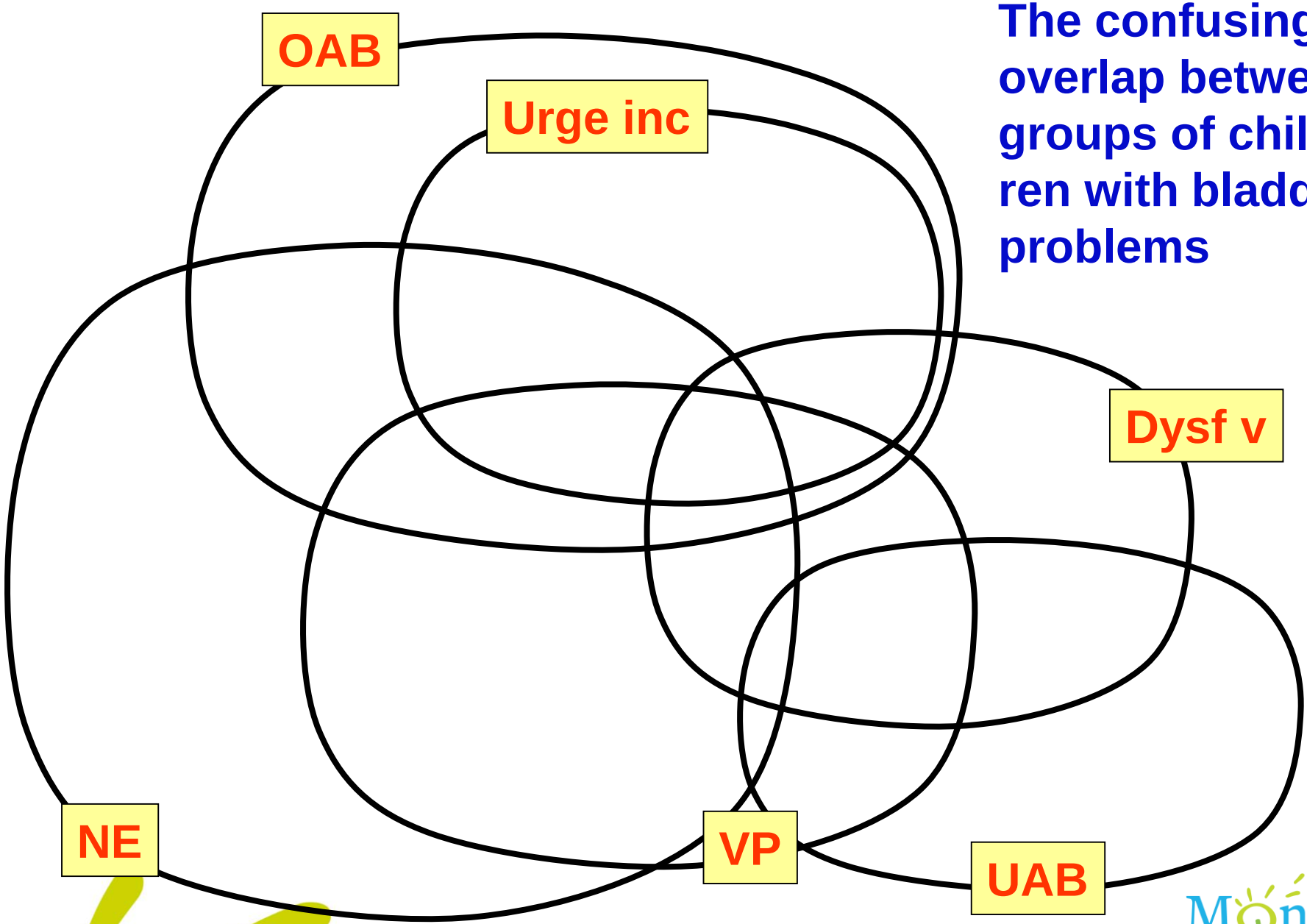
The confusing overlap between groups of child-ren with bladder problems



… and this is *after* we have simplified the subgrouping!

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What do you want to know?

- History
  - When wet?
    - Number of times, pre void, post void, unassociated with voiding
  - How wet?
    - Small / large volumes, need to change, does or doesn't, ? Quantify with pad test
  - Pattern of wetting
  - school toileting routines
  - primary/secondary
  - ?UTI/ ?bowels/ ?sexual history
  - Urinary stream, straining during voiding
  - Associations?
    - School, home, activities
  - Toilet training?
    - Easy/ hard/ successful
  - Observed behaviours?
    - Holding on, 'wiggle', "curtsey", urge
  - Drinking?
    - How much, what, when
  - Concern?
    - Who is worried? What are they worried about?

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Further evaluation

- History
- General
- Perinatal
- Developmental including toilet training history
- Bowels
- Family history, family function

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EVALUATION

- Physical examination
  - BP
  - Genitalia
  - Perineal and perianal sensation
  - Spine and sacrum
  - Anal tone
  - Reflexes
  - Gait/limb asymmetry
  - Urinalysis and culture

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Investigation

- Urine culture and analysis
- Renal US
- Bladder US with pre and post micturition volumes
  - Residual volume <20 ml
  - Or < 10% of CBC
- Bladder diary (frequency volume chart)

J Urol 2010; 183:699 - 703.

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Frequency Volume Chart

- 2 day frequency volume chart or voiding diary
  - Time and volume of drinks
  - Time and volume of voids
  - Time and amount of wetting
  - Presence of urgency
- Provides
  - Voiding frequency
  - Total volume voided in 24 hours
  - Average volume voided
  - Largest and smallest volume voided
  - Distribution of urine volume over day and night
  - Urine loss
  - Fluid intake

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Frequency Volume Chart

Date	Drinks - time	Drinks (mL)	Void - time	Void (mL)	Urgency	Wet/ Dry
	0800	150	0730	200	N	D
			0930	50	N	D
			1100	50	N	D
	1200	150	1230	30	Y	W
	1500	150	1400	60	Y	D
			1600	30	Y	W
			1630	50	Y	D
			1700	25	Y	W
	1800	150	1800	50	Y	D

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Frequency Volume Chart

Date	Drinks - time	Drinks (mL)	Void - time	Void (mL)	Urgency	Wet/ Dry
	0800	300	0730	400	N	W
			1100		N	W
	1200	300				
	1500	400	1400	200	N	W
	1800	450	1800	300	N	D

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Cystometric Bladder Capacity

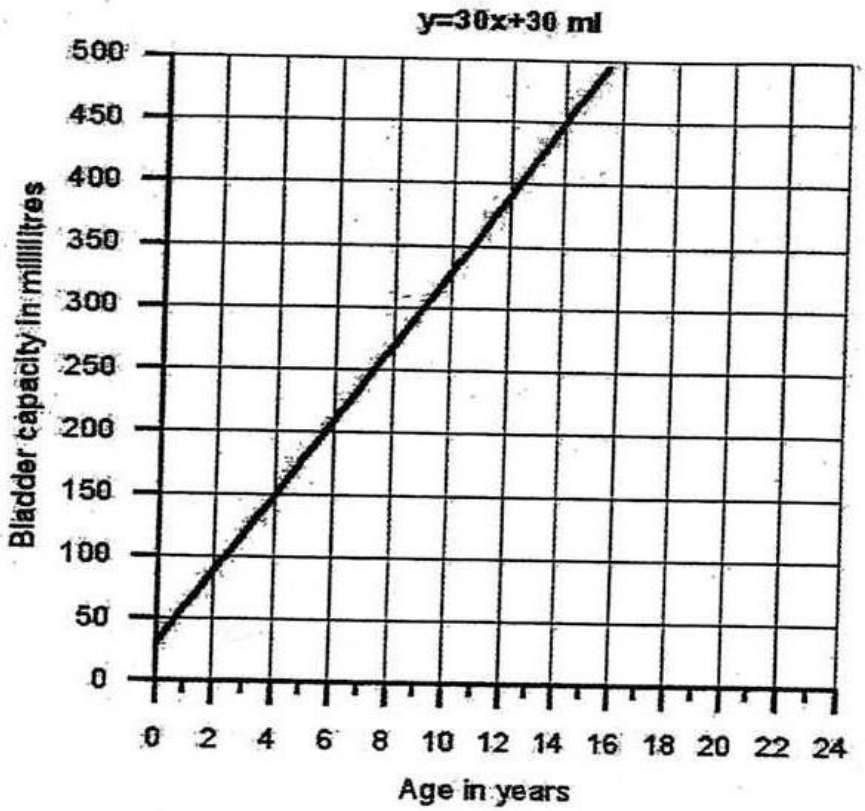

Figure 1 : Bladder capacity using the formula Y = 30 + 30 X (Y= capacity in ml, X = age in years)

- CBC (ml)
  = 30 + (30 x age (yrs))
  OR
  = (age (yrs) +2) x 30

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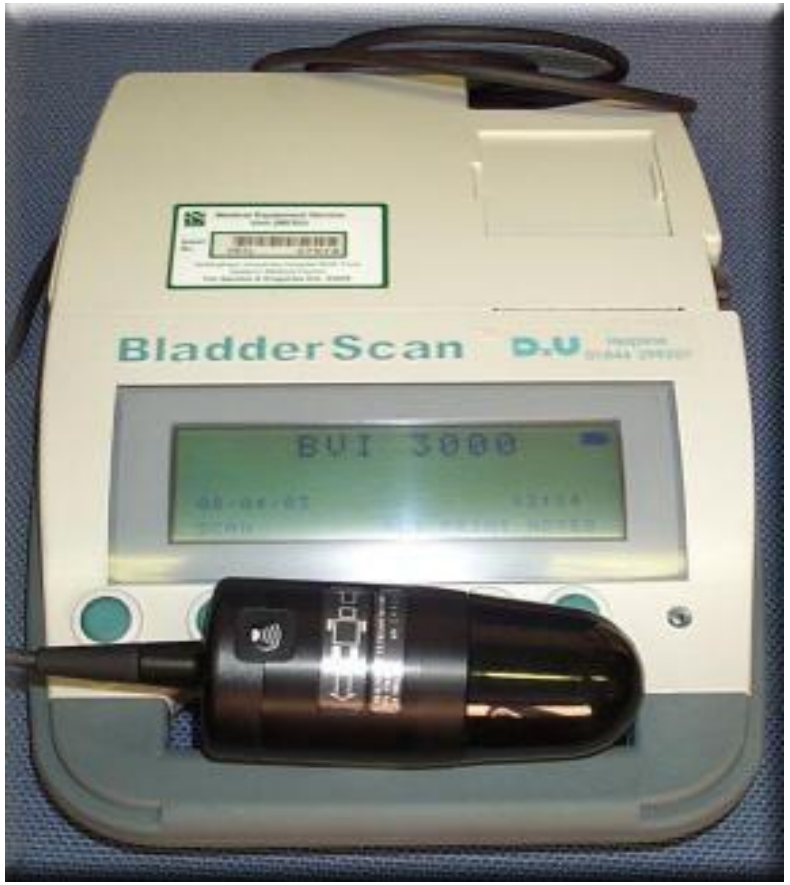
Investigation

- Urine flow study
- Bladder scan
- Urodynamics
- ? MCU
- ? MR spine



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Uroflow

- Measurement of urine flow during voiding
- Rate and pattern
- Least invasive
- Age>4 years, 3 curves prior to interpretation
- Appropriate sitting position

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Uroflow

- Useful for follow up of bladder training
- Useful for biofeedback training in dysfunctional voiding
- Facilitates selection for UD

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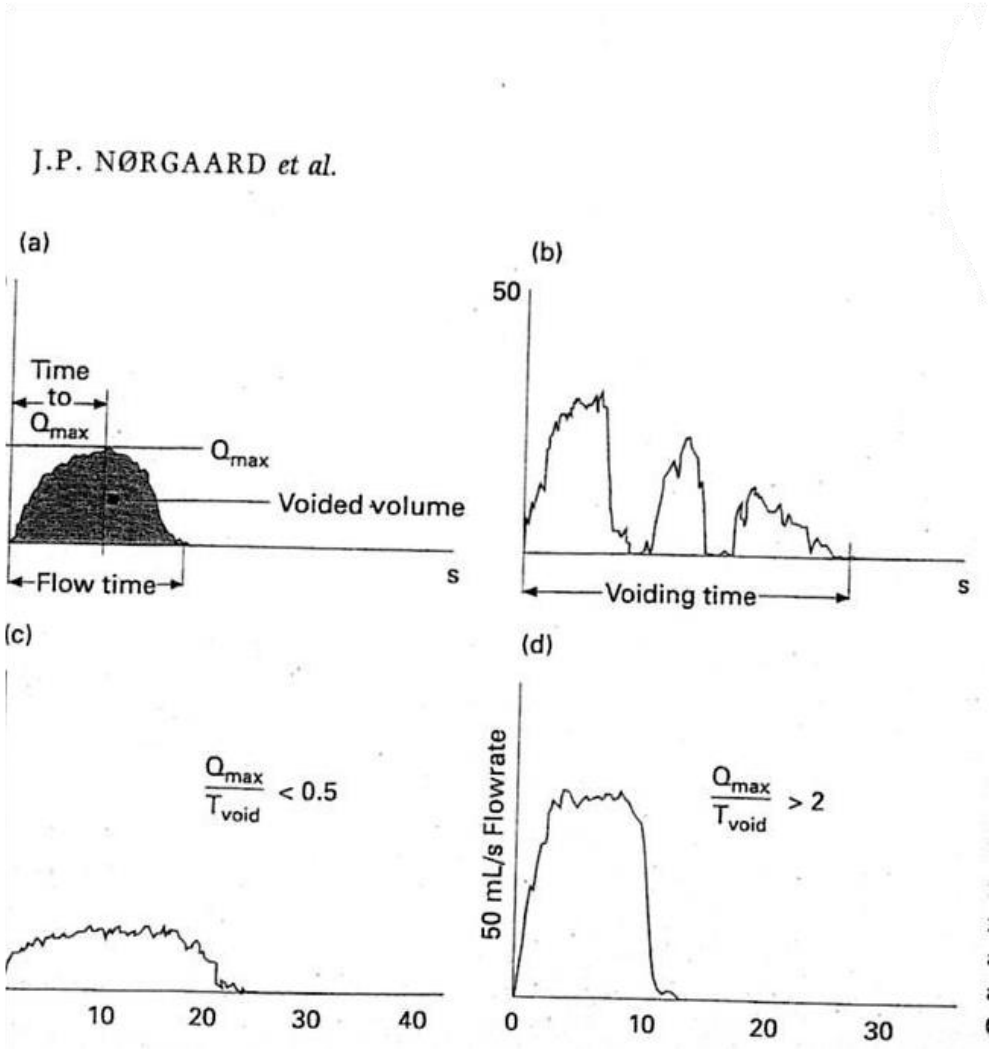
Uroflow patterns



(a) Normal
(b) Interrupted
(c) Obstructive
(d) 'Tower' - urgency

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Uroflow patterns

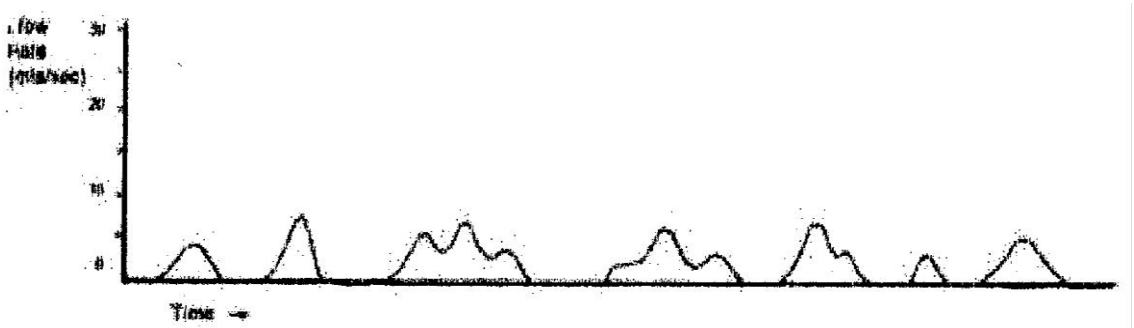

Figure 3.5 *Common flow-rate abnormalities. (a) Typical of an underactive bladder. Note the unsustained pattern of voiding. Bladder emptying is by abdominal effort, which cannot be sustained for more than a few seconds.*

Underactive Bladder

Norgaard et al ICCS, BJU, 1998, 81, S3

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Urodynamics

- Measure pressure/volume relationship of bladder
- Continuous study of filling and emptying
- Transurethral or suprapubic approach
- Rectal probe for abdominal pressure
- Combine with fluoroscopy – video UD
  - Provides VCUG –
    - Anatomical info – bladder shape, VUR, configuration and behaviour of bladder neck and pelvic floor
- EMG – assess sphincter activity
- OR
- Intraluminal urethral pressure

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Urodynamics

- Filling
  - Detrusor activity
  - Bladder sensation
  - Bladder capacity
  - Bladder compliance
    - C = Δ Volume/ Δ P Detrusor (ml/cm H2O)
    - Varies with age as bladder volume varies with age
  - Detrusor pressure
- Emptying
  - Contractility of detrusor
  - Pressure flow relationship

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Urodynamics - indication

- Neuropathic bladder – sphincter dysfunction
  - Spina bifida, cerebral palsy
- Bladder outlet or urethral anomalies
- obstructive flow patterns
- Non neuropathic bladder – sphincter dysfunction
  - Dysfunctional voiding ?? Fail to respond to treatment
  - Underactive Bladder
  - Overactive Bladder - failure to respond to traditional treatment ??
  - Guide to treatment – pharmacotherapy or urotherapy
  - Recurrent UTI

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Urodynamics

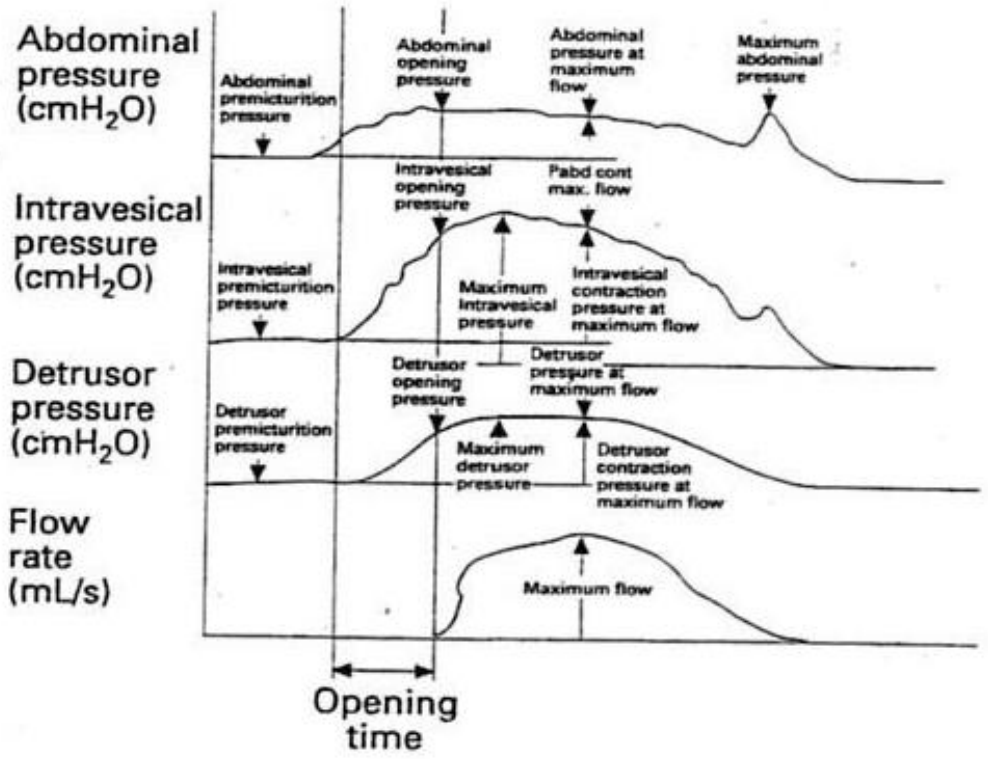

Fig. 6. A pressure/flow/EMG recording of micturition using IC recommended nomenclature for all variables.

Norgaard et al ICCS, BJU, 1998, 81, S3

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Staccato

Underactive Bladder

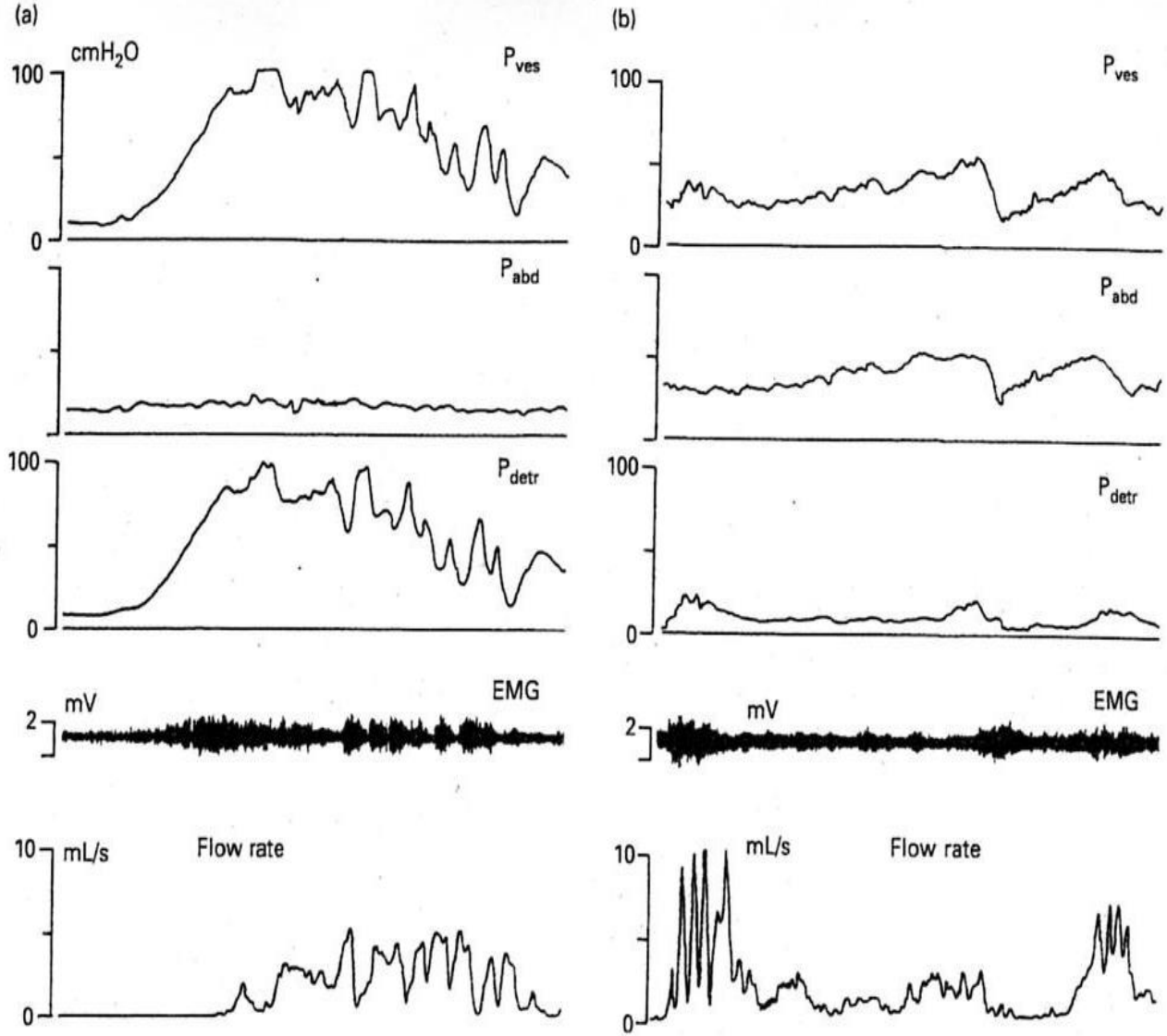

Fig. 2. Urodynamic recording of (a) staccato voiding in a 9-year-old girl. Flow is interrupted by short bursts of pelvic floor activity, resulting in high bladder pressures, prolonged flow time and poor flow rate; and (b) voiding in 'lazy bladder syndrome'. Abdominal pressure is the driving force, resulting in a very fractionated flow pattern, caused by reflex activity of the pelvic floor muscles with each abdominal 'push'. The recording was made during the urodynamic investigation of a 6-year-old girl with daytime and night-time wetting, who tried to comply with every parental demand to void.

Norgaard et al ICCS, BJU, 1998, 81, S3

Urge incontinence

- Involuntary loss of urine assoc with urgency
- Imperative urge to void
- Frequency
- Holding on – squat, curtsey
- Worse in afternoon
- Usually small volume incontinence
- Can have night wetting
- UTI
- constipation

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Urge incontinence - pathogenesis

- Habitual non physiological responses to signals from bladder and urethra
- Fail to obtain, or lose CNS control
- Detrusor instability – involuntary phasic detrusor contraction of any pressure during filling phase whilst attempting to inhibit micturition - no relevant neuropathy
- (if neuropathy present, same phenomenon is detrusor hyperreflexia)

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Urge incontinence - Investigations

- FVC
    - Small bladder capacity
    - Frequency
- US – small bladder capacity, complete emptying
- Flow, PVR - Normal micturition with complete emptying
- UD - Overactive detrusor contraction in early filling phase

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The Myths…

- Incontinence is caused by
- the child is disturbed / expressing anger
- The child is not expressing anger
- the child is lazy / attention seeking
- the child is slow to develop
- the child is ‘not bright’
- the family is dysfunctional
- toilet training too early /too late /badly handled ie a parenting problem

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Growing out of it…

- NE
  - 7 years – 8%
  - 11-12 years – 3%
  - 16 years – 0.8%

- Functional incontinence
  - 7 years – 3.2 – 6.7%
  - 15-17 years – 1.2-3%

The association with adult continence problems

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Epidemiology

- Australia
  - 2292 children, 5 – 12 year olds
  - 458 had wetting
  - Prevalence
    - Nocturnal enuresis alone 15% (60% M)
    - Isolated day wetting 2% (50% M)
    - Combined day and night wetting 4%
  - Marked wetting (> 2/week)
    - Day 1.4% of sample (34), night 5.1% (119)

- Bower et al, BJU, 1996, 78

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Epidemiology

- Belgium
- 4332 children 10 -14 years
- Prevalence
  - MNE 1% (n = 62, 47 M)
  - Isolated daytime wetting 4% (192, 68 M)
  - Day and night wetting 3.5% (151, 89 M)
  - Soiling 3% (120, 45 M)

- Bakker et al, Scand J Urol Nephrol 2002, 36

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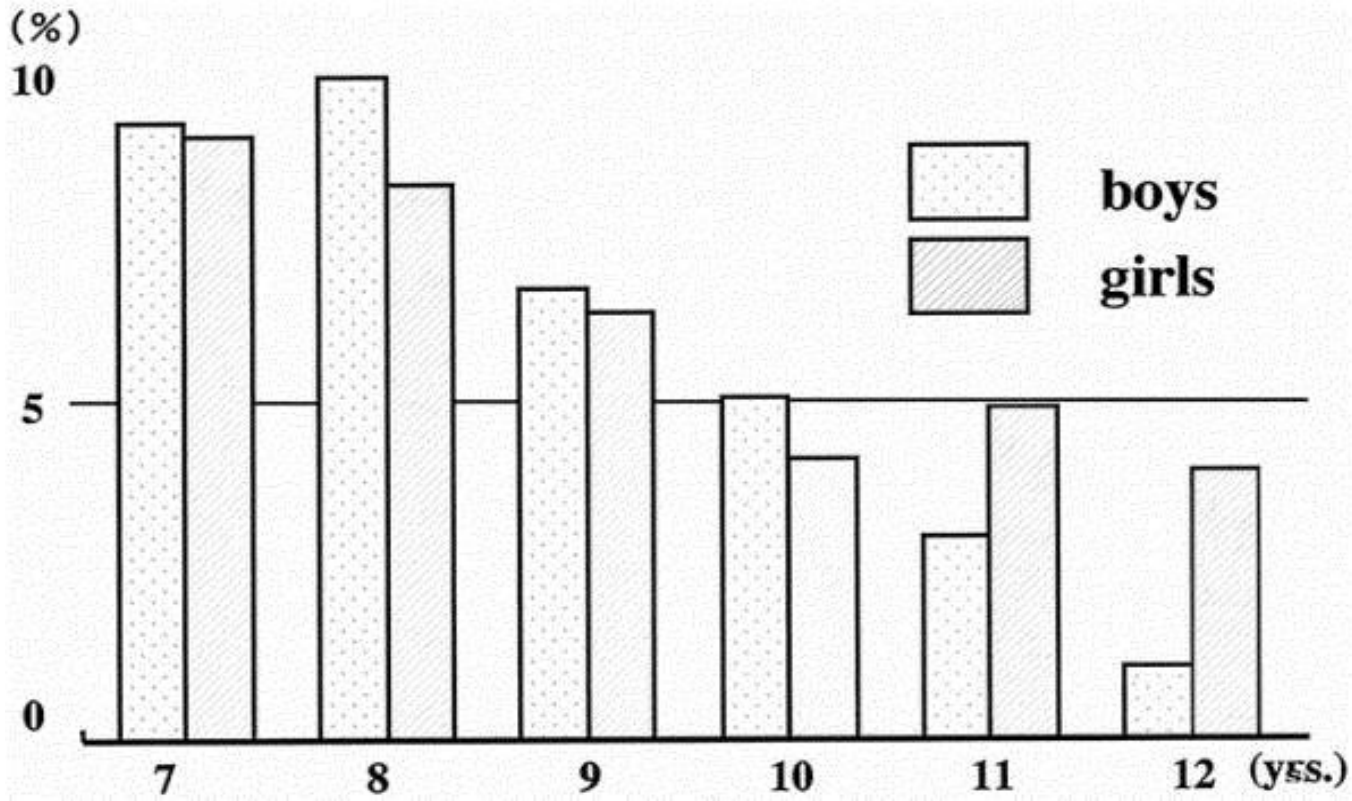
Prevalence incontinence by day



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- “the fact that nobody has died as a direct result of wetting themselves and the widely recognized association of the symptoms of detrusor instability with affective disorders, has generated a wide degree of apathy or antipathy toward the subject amongst many urologists”

- Mundy, AR. BJU, 1988, 62

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Normal bladder function

- Adequate storage capacity
- Efficient emptying capability

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INFANT

- Pathways are intact
- Bladder capacity increases in first 2 years with improved regulation by brainstem inhibitory centre
- Frontal and parietal development allows sensation of bladder fullness, then ability to inhibit micturition, then facilitate voiding

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Epidemiology of bladder control

- Usually day control first
- 20% of children become dry per year between 18 months and 4.5 years

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Normal bladder function

- Bladder fundus -3 layers of smooth muscle that criss-cross
- Internal urethral sphincter - interdigitated smooth muscle bundles around bladder neck and extending to posterior urethra
- External urethral sphincter - smooth and skeletal muscle at level of pelvic floor

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Normal bladder function - nerve supply

- Autonomic nervous system
- Sympathetic
  - Stimulates α and β receptors in smooth muscle
  - α receptors : trigone, bladder neck and distal portion urethra
  - β receptors: bladder fundus

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Normal bladder function - nerve supply

- Neurotransmitter: noradrenaline
- Action:
  - NA and α receptors: contraction of smooth muscle of bladder neck and posterior urethra
  - NA and β receptors: relaxation of bladder fundus
- Regulates bladder function during filling by allowing bladder to enlarge without increasing tension within bladder wall, ie facilitates storage of urine

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Normal bladder function - nerve supply

- Parasympathetic
- Neurotransmitter: acetylcholine
- Receptors: bladder fundus and posterior urethra
- Pelvic N stimulation - ACh release by postganglionic cells - detrusor contraction, inhibition of sym NS - relaxation of smooth Mm at trigone, bladder neck and posterior urethra
- Sustained contraction of bladder until empty

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Normal bladder function - nerve supply

- Somatic nerves
- From sacral cord via pelvic plexus and pudendal nerve to skeletal muscle of external urinary sphincter

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Normal bladder function - CNS role

- Bladder distension - impulses along afferent pathways via pelvic nerves to sacral cord with stimulation of Sympathetic, Parasympathetic and somatic nerves back to bladder.
- Messages between sacral and thoracolumbar areas and brainstem
- Communication between brainstem and frontal and parietal lobes

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Normal bladder function - CNS role

- Brainstem inhibition facilitates urine storage - stim S nerves to fundus and bladder neck, and stim somatic nerves to ext sphincter

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Dysfunctional voiding

- Abnormality of voiding
- Overactivity of pelvic floor during voiding

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Dysfunctional voiding

- Staccato voiding
  - Incomplete relaxation of urethral sphincter during voiding
  - bladder emptying prolonged and incomplete
  - Flow – dips in flow rate
  - UD – dips in flow rate coinciding with high bladder pressure
  - Pathophysiology – flow rate above certain threshold triggers pelvic floor contraction. Contraction reduces flow rate so pelvic floor relaxes

Dysfunctional voiding

- Fractionated voiding
  - Hyperactivity of pelvic floor that stops flow rate so voiding occurs in portions.
  - detrusor hypo contractile, flow due to weak detrusor contraction. Strain to increase speed of micturition. Incomplete voiding.
  - Bladder instability present but easily inhibited
  - Incontinence due to overflow

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Dysfunctional voiding

- Lazy bladder syndrome
  - long term dysfunctional voiding
  - absent detrusor contractions
  - empty by abdominal pressure – straining
  - Absent normal bladder sensation
  - recurrent UTI
  - large residual volumes
  - low voiding frequency – micturition postponed

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Management incontinence

- Address
  - UTI
  - Fluid intake
  - Voiding frequency
  - Constipation

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Management – Day Wetting

- Pharmacotherapy (mainly urge syndrome)
  - Anticholinergics – oxybutinin, propantheline, tolterodine
- Urotherapy (mainly dysfunctional voiding)
  - Voiding frequency
  - Bladder training incl cognitive bladder training school
  - pelvic floor relaxation
  - Biofeedback
- Others
  - Psychologist
  - CIC
  - TENS
  - PENS

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Outcomes

- Sureshkumar et al J Urol, 2003, 170
- Systematic review of RCT
- Only 5 trials suitable for review – all with inherent errors
- Terodiline - ? Most effective

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Outcomes - reality

- Frustrating
- Slow
- Intensive

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Antenatal Hydronephrosis

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Antenatal Hydronephrosis

- Postnatal US
- ? Hydroureter – MCU
- ? Obstruction
  - MAG 3 < 6 weeks of age,
  - DTPA > 6 weeks of age
- Cystoscopy +/- retrograde pyelogram

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Postnatal Differential Diagnosis of Antenatal Hydronephrosis

- Normal: resolved
- Hydronephrosis without ureteric dilatation
  - Transient hydronephrosis
  - Pelvi-ureteric obstruction
  - VUR: mild,mod, severe
- Hydronephrosis with ureteric dilatation
  - Non obstructive congenital megaureter
  - Ureteric obstruction
  - VUR: mod - severe
  - Abnormal bladder
  - Posterior urethral valve

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Antenatal Hydronephrosis – postnatal management

The goal of postnatal evaluation is not necessarily to achieve a definitive diagnosis, but to distinguish clinically significant pathology requiring close follow-up or early intervention from clinically unimportant dilatation.

Before you start:

Was there antenatal counseling or antenatal plan constructed? YES → follow antenatal mx plan

Risk stratification

- Broadly, antenatal hydronephrosis can be grouped into high-risk and low-risk groups, depending on severity of dilatation and associated features. The prenatal history determines stratification.
- High risk patients need early involvement of specialist urology or nephrology units, if only to guide individualized postnatal evaluation.
- Low risk patients can be investigated as outpatients and should be spared most invasive, radiation-involved modalities. Surveillance ultrasound is the cornerstone.
- **The single most important postnatal investigation is a physical examination of the neonate – palpable kidney or bladder mandates early review by urology or nephrology**

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Antenatal Hydronephrosis – risk stratification

High Risk

- bilateral hydronephrosis ≥ SFU 3 (mod-severe, APD >10mm)
- unilateral dilatation SFU 4 (severe, APD >15mm)
- single kidney
- duplex system
- ureteric dilatation
- ureterocoele (seen at any point)
- Oligohydramnios

Low Risk

- unilateral hydronephrosis SFU1-3 (mild or mod, APD <15mm)
- bilateral hydronephrosis, SFU 1-2 (mild-mod, APD <10mm)
- no ureteric dilatation
- normal bladder
- no renal anomaly apart from HN

<u>Antibiotic prophylaxis</u>

This is recommended for all patients until the first ultrasound and clinical review.

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SFU grading system guide

Society for Fetal Urology Grading System – congenital hydronephrosis

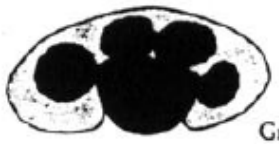

Grade 0


Grade I


Grade II


Grade II


Grade III


Grade IV

Grade	Central renal complex	Parenchyma
0	intact	normal
1	slight splitting of pelvis	normal
2	evident splitting of intrarenal pelvis or dilated extrarenal pelvis *major* calyces dilated	normal
3	wide splitting of pelvis *major and minor* calyces dilated	normal
4	wide splitting of pelvis major and minor calyceal dilatation	thinned or reduced

Postnatal Mx of ANH – low risk

Low-risk, no antenatal plan

- Commence antibiotic prophylaxis
- Examine baby: palpable kidney or bladder? YES → urgent ultrasound and call urology
- NO palpable bladder or kidney:
  - **USS 1 month**:
  - normal → repeat at 6 months
    - stop antibiotics and educate parents on UTI symptoms
  - SFU 1-2 → repeat at 6 months, 12 months and 2 years
    → stop antibiotics and educate parents on UTI symptoms
    → discharge from surveillance once normal, or stable at 2 years
  - SFU 3-4 → refer to nephrourology clinic
    → continue antibiotic prophylaxis

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Postnatal Mx of ANH – high risk

<u>High-risk, no antenatal plan</u>

Commence antibiotic prophylaxis

Examine baby: palpable kidney or bladder? YES → urgent ultrasound and call urology

NO palpable kidney or bladder:

- **USS D4-7**:
- SFU 0 – 2
  - → refer nephro-urology clinic with repeat USS at 1 month
  - → educate parents on UTI symptoms
- SFU 3 – 4
  - → inpatient urology or nephrology consult

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Postnatal hydronephrosis – when to refer?

Referral criteria

- All high-risk; inpatient or at one month depending on first ultrasound
- Low risk; if dilatation increases >50% during surveillance
- Renal size discrepancy >1cm
- UTI

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Antenatal screening

- Principle:
  - Identify patients within the population “at risk”
- Renal
  - Identify patients with CAKUT/ other renal anomalies
    - Reduced nephron number/ renal reserve
  - Antenatal hydronephrosis
    - easiest to identify & measure

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Postnatal U/s requests

Renal size & number

Solitary kidney

Cortex

Thin cortex, Echogenicity increased; AbN corticomedullary diff'n

Pelvis & calyces

Pelvis AP diameter

Calyceal dil'n or pelvis alone

Bilateral

Ureter

Distal dil'n (behind bladder), minor proximal dil'n

Bladder

Thickened bladder wall

Urethra

Dil'n

Ditchfield, Heloury,Johnstone, Walker, 2010

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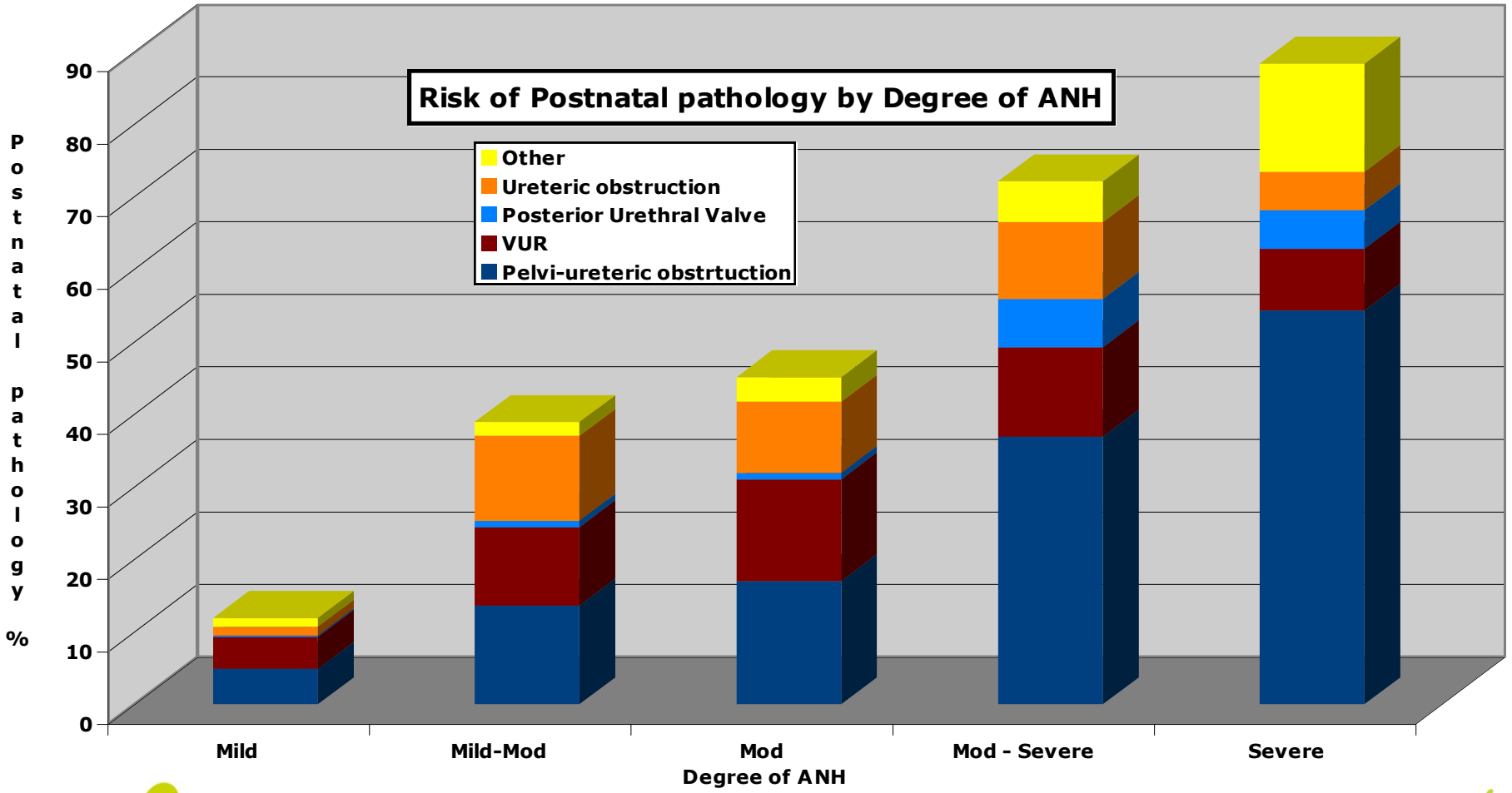
Risk of pathology by degree of ANH



Mild≤7mmT2, ≤9T3; **mild/mod** <10,<15; **mod**7-10,9-15; **mod/sev**≥7, ≥9; **severe** ≥10, ≥15

Adapted from Lee, R.S.,. Pediatrics, 2006. 118(2): p. 586-93.

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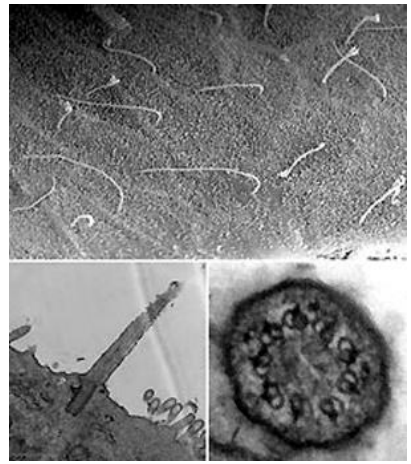
Renal Cystic Disease



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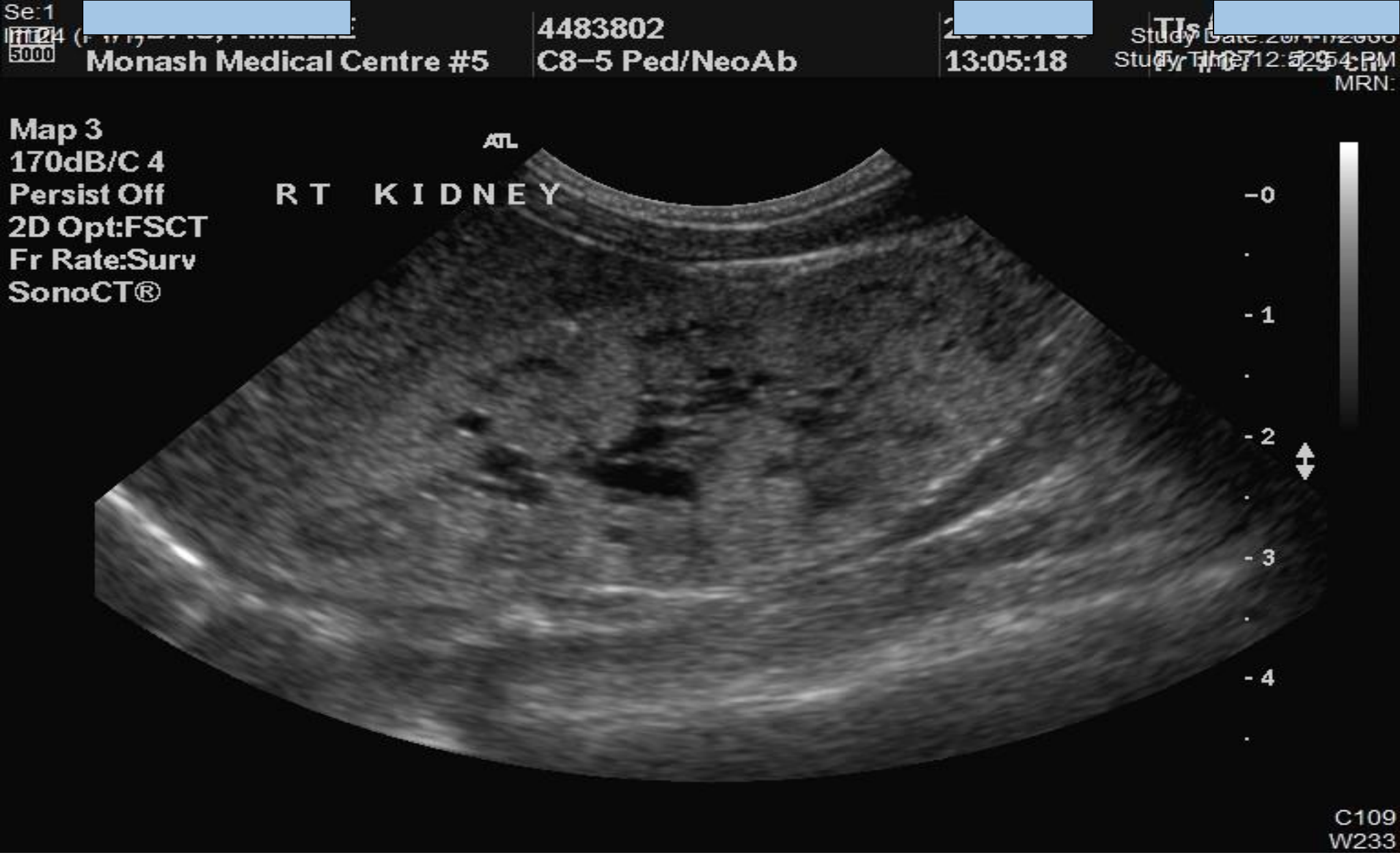

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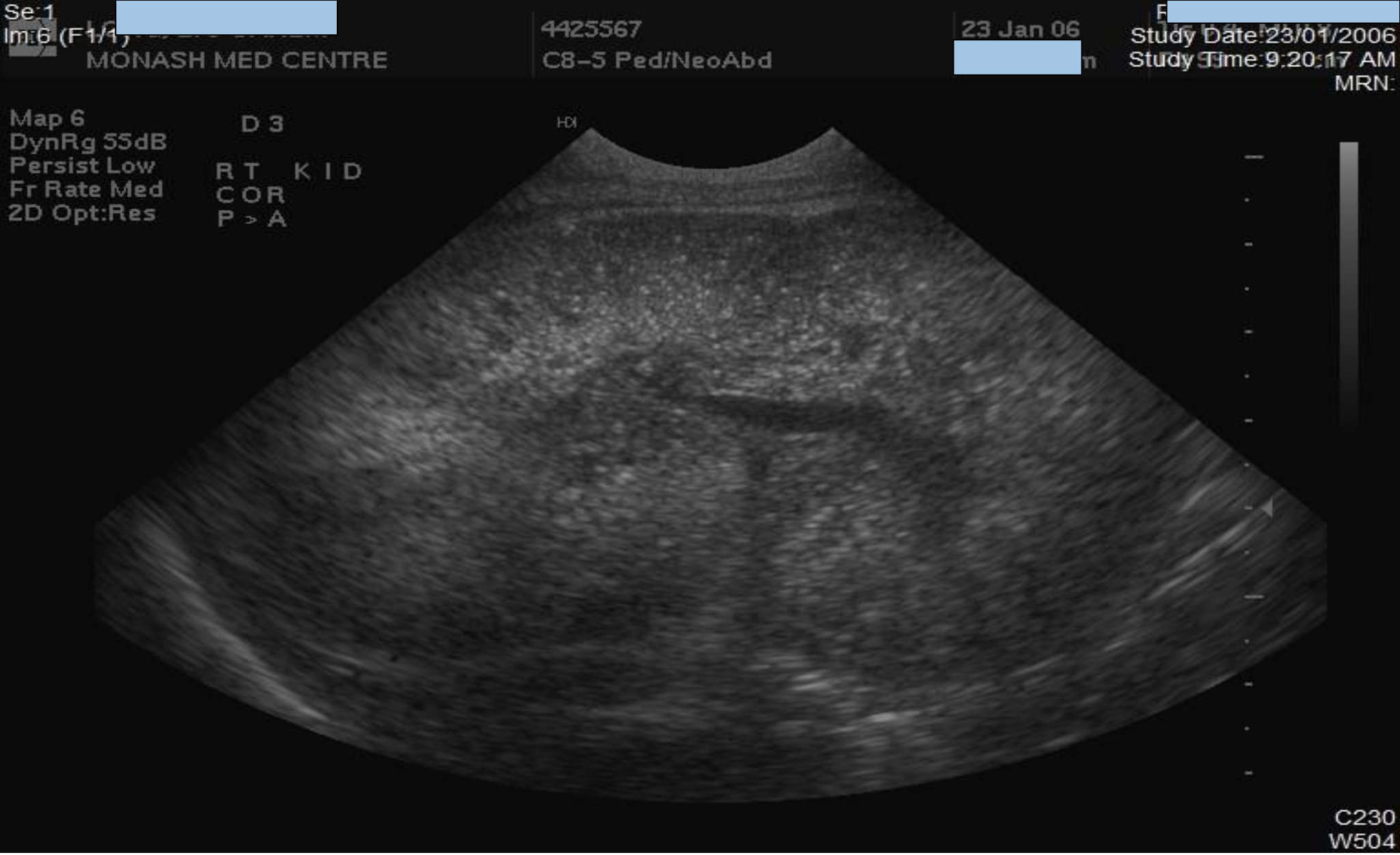

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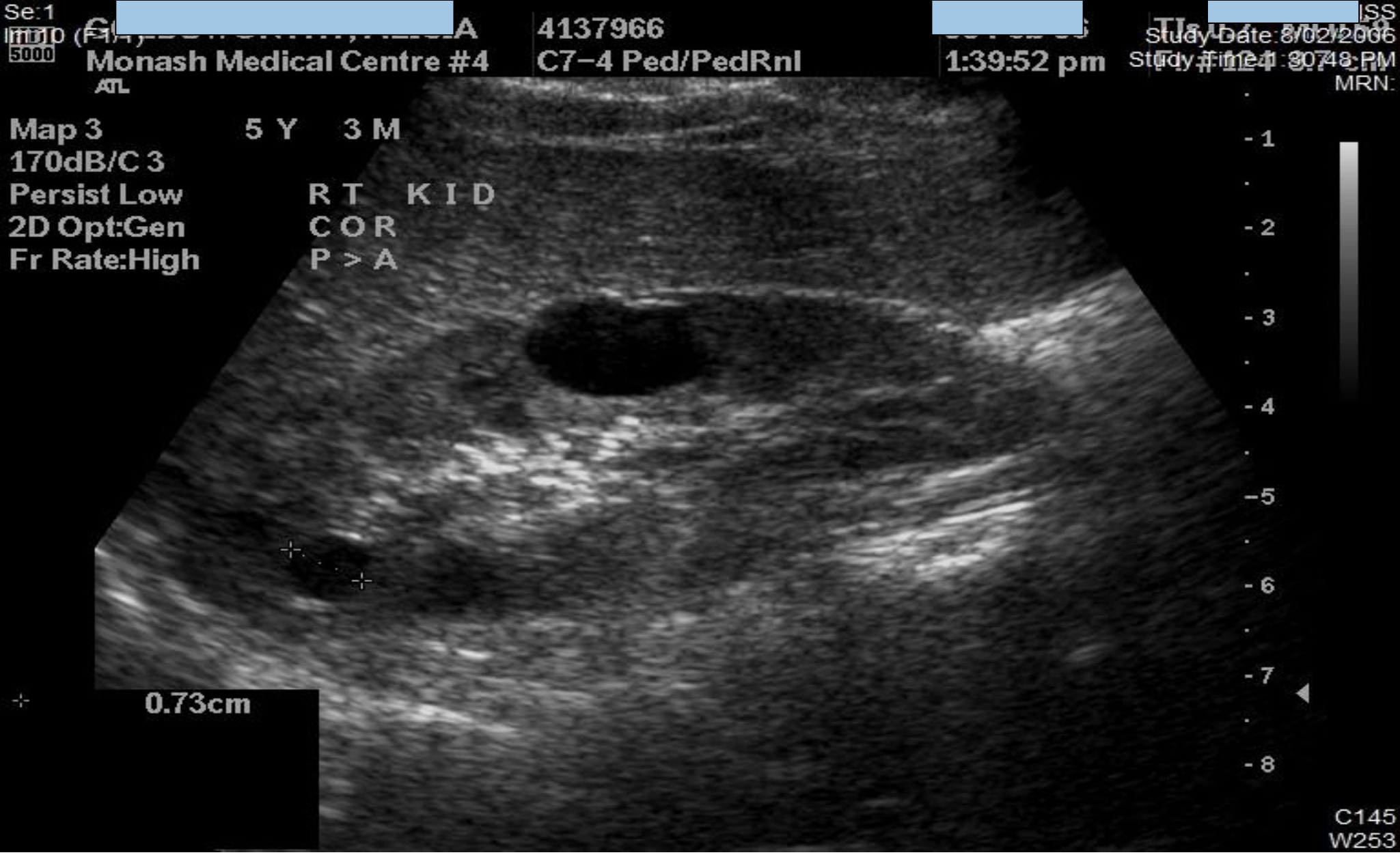

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Cystic Kidney Disease

- Inherited or acquired
- Kidney only or systemic change
- Wide range of age of onset
- Single/ multiple cysts
- Clinically insignificant → End stage renal disease

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Classification of Renal Cysts

- Non hereditary renal malformations
- Genetic
  - Glomerular
    - Glomerular cystic kidney disease
    - RCAD
    - nephronophthisis
  - tubular
- Isolated
- Acquired

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Classification of renal cystic disease

1. Polycystic
2. CAKUT
3. Tubulointerstitial
4. Cystic neoplasms & neoplastic cysts
5. Miscellaneous

Bonsib, 2010, Arch Pathol Lab Med, 134, 554-568

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Classification of renal cystic disease

1. Polycystic
    1. ARPCKD (2): classic in neonates & infants/ childhood
    2. ADPCKD (2): adult form/ early onset childhood
    3. Glomerulocystic (5): PKD/ hereditary/ syndromic/ obstructive/ sporadic
2. CAKUT
3. Tubulointerstitial
4. Cystic neoplasms & neoplastic cysts
5. Miscellaneous

Bonsib, 2010, Arch Pathol Lab Med, 134, 554-568

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Classification of renal cystic disease

1. Polycystic
2. CAKUT
    1. Renal agenesis/dysplasia/adysplasia/ (unilateral/bilateral/syndromic/ non-syndromic/ multiple malformation)
    2. Renal hypoplasia (simple/ oligomeganephronic, reduced nephron generations= cortical hypoplasia/ reduced nephron number.)
    3. Abnormal form, position, number (rotationn/ ectopia/ fusion/ supernumerary/ combination)
    4. Ureteric/urethral: (PUJ/duplication/ VUR/ ectopic ureter/ PUV/ combination)
3. Tubulointerstitial
4. Cystic neoplasms & neoplastic cysts
5. Miscellaneous

Bonsib, 2010, Arch Pathol Lab Med, 134, 554-568

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Classification of renal cystic disease

1. Polycystic
2. CAKUT
3. Tubulointerstitial
    1. Renal tubular dysgenesis: AR/ twin-twin/ACEI
    2. Nephronophthisis: types 1-6
    3. Medullary cystic disease: type 1/ fam juv ↑uricemic nephropathy
    4. Bardet-Beidl: types 1-12
4. Cystic neoplasms & neoplastic cysts
5. Miscellaneous

Bonsib, 2010, Arch Pathol Lab Med, 134, 554-568

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Classification of renal cystic disease

1. Polycystic
2. CAKUT
3. Tubulointerstitial
4. Cystic neoplasm & neoplastic cysts
    1. Cystic nephroma
    2. Cystic partially differentiated nephroblastoma
    3. Multi-locular cystic renal cell carcinoma
    4. Tubulo-cystic renal cell carcinoma
    5. Von-Hippel-Lindau
    6. Lymphangioma/hygroma renalis
5. Miscellaneous
    1. Simple cortical cysts
    2. Medullary sponge kidney
    3. Localized renal cystic disease

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Simple Renal Cysts

- Usually solitary, usually unilateral
- Need to distinguish from complex cysts and malignancy, or potential multicystic or polycystic kidney.
- Autopsy - > 50% of > 50 yo have one or more cysts
- Present at birth – 30,000 antenatal US identified incidence of 0.09% with majority resolving by birth – 2 persisted as benign simple cysts, one evolved into MCDK
- Rare from birth to 20 years, then increased frequency with age
- M:F – 2:1. Prevalence approx 7 – 10%

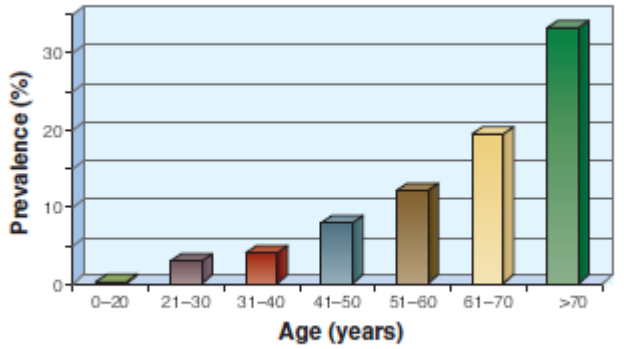

Figure 1. Age-related prevalence of simple renal cysts. Based on data from references[2–4,7–11].

Eknoyan, J Am Soc Nephrol 20, 1874-1876, 2009

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Simple Renal Cysts

- Discrete, cortical, extend to capsule
- 25% increase in size with time esp in younger people
- Asymptomatic
- Symptoms
  - Pain, haematuria, obstruction
- Complications – rupture, infection, haemorrhage

Eknoyan, J Am Soc Nephrol 20, 1874-1876, 2009

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Simple/ complex renal cysts

Table 1. Criteria used in the Bosniak renal cyst classification system

Stage	Cyst Wall	Septae	Calcification	Enhancement
I	Hairline thin	No	No	No
II	Minimal regular thickening	Few, hairline thin	Smooth, hairline thin	No
IIF[a]	Minimal regular thickening	Multiple, minimal smooth thickening	Thick, nodular	No
III	Irregular thickening	Measurably thick, irregular	Thick, nodular, irregular	Yes
IV	Gross irregular thickening	Irregular gross thickening	Thick, nodular, irregular	Yes, tissue and cyst

[a]F in IIF is for follow-up. Cyst size of >3 cm in diameter is another criterion for follow-up and by extension inclusion in class IIF.

Eknoyan, J Am Soc Nephrol 20, 1874-1876, 2009

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Inherited Renal Cystic Disease

Monogenic kidney disease

- More frequent genetic lethal disease in humans
- AD
- AR
- X linked

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Cystic Kidney Disease

- Heterogeneous group of genetic disorders
- Characterized by
  - apparent loss of spatial orientation
  - loss of intercellular communication.
- Outcome: dilatation of the renal tubules and cyst formation.
  - defective tubules that either fail to form correctly,
  - or lose their proper geometry

Wilson PD. Polycystic kidney disease. N Engl J Med 2004; 350: 151-164

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Table 1 Renal cystic diseases: associated genes and protein products

Renal cystic disease	OMIM[a]	Gene	Protein	Subcellular localization
Autosomal dominant polycystic kidney disease (ADPKD)				
ADPKD type 1	601313	*PKD1*	Polycystin 1	Primary cilium, tight junctions, adherens junctions, desmosomes, focal adhesions
ADPKD type 2	173910	*PKD2*	Polycystin 2	Primary cilium, centrosome, endoplasmic reticulum
Autosomal recessive polycystic kidney disease (ARPKD)				
ARPKD	263200	*PKHD1*	Polyductin/fibrocystin	Primary cilium; apical membrane
Nephronophthisis (NPHP)				
NPHP1	256100	*NPHP1*	Nephrocystin 1	Primary cilium, centrosome, adherens junctions, focal adhesions
NPHP2	602088	*NPHP2*; *INVS*	Inversin	Primary cilium, centrosome
NPHP3	604387	*NPHP3*	Nephrocystin 3	Primary cilium/centrosome (predicted)
NPHP4	606966	*NPHP4*	Nephrocystin 4	Primary cilium, centrosome, adherens junctions
NPHP5	609254	*NPHP5*; *IQCB1*	Nephrocystin 5	Primary cilium
Joubert syndrome (JBTS)				
JBTS3	608629	*AHI1*	Jouberin	Undetermined
JBTS4	609583	*NPHP1*	Nephrocystin 1	Primary cilium, centrosome, adherens junctions, focal adhesions
Bardet–Biedl syndrome (BBS)				

Bardet–Biedel syndrome (BBS)				adhesions
BBS1	209901	*BBS1*	BBS1 protein	Centrosome
BBS2	606151	*BBS2*	BBS2 protein	Centrosome
BBS3	608845	*BBS3;ARL6*	ARL6 protein	Centrosome
BBS4	600374	*BBS4*	BBS4 protein	Primary cilium; centrosome
BBS5	603650	*BBS5*	BBS5 protein	Centrosome
BBS6	604896	*BBS6; MKKS*	BBS6 chaperonin	Centrosome
BBS7	607590	*BBS7*	BBS7 protein	Centrosome
BBS8	608132	*BBS8; TTC8*	TTC8 protein	Primary cilium; centrosome
BBS9	607968	*BBS9; PTHB1*	PTHB1 protein	Undetermined
Meckel–Gruber syndrome (MKS)				
MKS1	249000	*MKS1*	MSK1 protein	Primary cilium/centrosome (predicted)
MKS3	607361	*MKS3; TMEM67*	TMEM67 protein	Primary cilium
Orofacial digital syndrome type 1 (OFD1)				
OFD1	311200	*OFD1; CXORF5*	OFD1 protein	Centrosome
Glomerulocystic kidney disease (GCKD)				
Hypoplastic type[b]	137920	*HNF1β*	HNF-1B transcription factor	Nucleus

[a]Online Mendelian Inheritance in Man

Genes and Proteins Implicated in Cystic Diseases of the Kidney

Disease	Gene	Protein	Localization in Renal Epithelial Cells	Renal Symptoms	Extrarenal Symptoms
Polycystic Kidney Disease					
Autosomal dominant PKD1 Autosomal dominant PKD2	*PKD1* 16p13.3 *PKD2* 4q21	Polycystin-1 460 kDa Polycystin-2 110 kDa	Primary cilia Focal adhesions Adherens junctions	Increased kidney size Echogenic kidneys Cortical cysts Cystic dilatation Severe hypertension	Liver and pancreatic cysts Intracranial aneurysms
Autosomal recessive PKD	*PKHD1* 6p12.2	Polyductin/fibrocystin 447 kDa	Primary cilia Apical membrane	Same as autosomal dominant PKD Kidney collecting-duct ectasia	Hepatic fibrosis Facial malformations Pulmonary hypoplasia from oligohydramnios Ductal-palate malformation in the liver
Autosomal Recessive Nephronophthisis					
NPHP 1/JBTS 4/SLSN 1	*NPHP1* 2q13	Nephrocystin-1 83.3 kDa	Primary cilia (β-tubulin) Focal adhesions Adherens junctions Centrosome	Tubular BM thickening Tubular atrophy Diffuse interstitial fibrosis Small corticomedullary cysts Increased or normal kidney size Salt wasting leading to hyponatremia and hypovolemia Polyuria and polydipsia Anemia, anorexia, nausea, metabolic acidosis, weakness ESRD: juvenile form at 13 years, adolescent form at 19 years	Retinitis pigmentosa Truncal cerebellar ataxia Congenital hepatic fibrosis Ocular motor apraxia type Cogan
NPHP 3/SLSN 3	*NPHP3* 3q22.1	Nephrocystin-3 150.8 kDa	Primary cilia		Retinitis pigmentosa Leber congenital amaurosis
NPHP 4/SLSN 4	*NPHP4* 1p36	Nephroretinin 157.8 kDa	Primary cilia axoneme Basal bodies		Retinitis pigmentosa
NPHP 5/SLSN 5	*IQCB1* 3q21.1	Nephrocystin-5 68.9 kDa	Primary cilia		Early onset retinitis pigmentosa Retinal degeneration
NPHP 6/JBTS 5/SLSN 6/MKS 4	*CEP290* 12q21.3	Centrosomal protein 290 kDa	Centrosome of dividing cells		Early onset retinitis pigmentosa Cerebellar vermis aplasia Leber congenital amaurosis
NPHP 7	*GLIS2* 16p13.3	Nephrocystin-7 55.7 kDa	Primary cilia		Not reported
NPHP 8/JBTS 7/MKS 5	*RPGRIP1L1* 16q12.2	Retinitis pigmentosa GTPase regulator interacting protein 1–like 1 130.5 kDa	Ciliary axoneme Basal bodies Centrosome Cytoplasm		Retinitis pigmentosa Hepatic fibrosis
NPHP 9	*NEK8* 17q11.1	NIMA-related kinase 8	Primary cilia		Not reported
NPHP 2	*INVS* 9q31	Inversin 118 kDa	Primary cilia	Increased kidney size Cortical cysts Cystic dilatation Severe hypertension	Situs inversus Retinitis pigmentosa Cardiac ventricular septal defect

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Table. Continued

Disease	Gene	Protein	Localization in Renal Epithelial Cells	Renal Symptoms	Extrarenal Symptoms
Additional Autosomal Recessive Syndromes Associated With Nephronophthisis					
JBTS 1	*JBTS1* 9q34.3	Unknown	Unknown	Similar to NPHP when reported	Cerebellar vermis aplasia "Molar tooth" sign Polymicrogyria Hypotonia Ataxia Mental retardation Rod-cone dysfunction Abnormal eye movements Hyperpnea
JBTS 2	*JBTS2* 11p12-13.3	Unknown	Unknown		
JBTS 3	*AHI1* 6q23.3	Jouberin/Abelson helper integration site 137.1 kDa	Nuclear		
JBTS 6/MKS 3	*TMEM67* 8q21.13-q22.1	Transmembrane protein 67 110 kDa	Primary cilia Cytoplasm Endoplasmic reticulum	Bilateral renal cystic dysplasia	Fibrocystic liver Occipital encephalocele Postaxial polydactyly Cleft lip/palate Heart malformations
MKS 1	*MKS1* 17q22	FABB proteome-like protein	Cytoplasm Cytoskeleton Centrosome Basal bodies	Enlarged multicystic kidneys	Liver fibrosis Occipital encephalocele Postaxial polydactyly Cleft lip/palate Heart malformations
BBS 1	*BBS1* 11q13	BBS2-like protein 2 65.1 kDa	Centrosome	Nephronophthisis-similar Urinary tract malformation	Retinitis pigmentosa Anomalies of distal limb Obesity Mental retardation Polydactyly Male hypogenitalism
BBS 2	*BBS2* 16q21	BBS protein 2 79.9 kDa	Centrosome Primary cilia		
BBS 3	*ARL6* 3q21.1	ADP-ribosylation factor–like 6 21.1 kDa			
BBS 4	*BBS4* 15q22.3-q23	BBS protein 4 58.3 kDa			
BBS 5	*BBS5* 2q31.1	BBS protein 5 38.7 kDa	Centrosome		
BBS 6	*MKKS* 20p12	McKusick-Kaufmann syndrome protein 62.3 kDa	Centrosome Primary cilia		
BBS 7	*BBS7* 4q27	BBS2-like protein 1 78.5 kDa			
BBS 8	*TTC8* 14q31.3	Tetratricopeptide repeat domain protein 8			
BBS 9	*PTHB1* 7p14	Parathyroid hormone–responsive B1 protein 99.3 kDa	Unknown		
BBS 10	*C12orf58* 12q21.2	Chromosome 12 open reading frame 58 80.8 kDa	Unknown		
BBS 11	*TRIM32* 9q33.1	Transactivator of transcription–interactive protein 71.9 kDa	Cytoskeleton		
BBS 12	*C4orf24* 4q26-27	Chromosome 4 open reading frame 24 79.1 kDa	Pericentriolar region of basal bodies and centrosomes Cytoskeleton Microtubules		

Table 1 Cystic diseases of the kidney: their causal genes, encoded proteins, localization, and proposed function

Disease	Main features	Genes involved	Corresponding protein	Protein localization	Postulated functions
Autosomal recessive PKD (ARPKD)	Renal cyst, enlarged kidneys, hepatic fibrosis	*PKHD1*	Fibrocystin/polyductin (FPC)	Cilia and secreted	Calcium response; proliferation/ differentiation
Autosomal dominant PKD (ADPKD)	Renal, hepatic, pancreatic and brain cysts	*PKD1*, *PKD2*	Polycystin 1 (PC1) Polycystin 2 (PC2)	Cilia, Golgi apparatus, focal adhesions	Calcium response; proliferation/ differentiation
Nephronophthisis (NPHP) and Senior Løken Syndrome (SNLS)	Renal fibrosis, renal cysts, tubular atrophy, retinal dystrophy (in SNLS)	*NPHP1–NPHP11*	Nephrocystin-1, 2/inversin, 3, 4, 5, 6/CEP290, 7/GLIS2, 8/RPGRIP1L, 9/NEK8, 11/Meckelin	Cilia, basal bodies, centrosomes, focal adhesions.	Cell–cell and cell–matrix adhesion; actin cytoskeleton; cell division; Wnt and Shh signaling
Joubert syndrome (JS)	NPHP and cerebellar ataxia	*AHI1*, *NPHP1*, *CEP290*, *JBTS6/TMEM67*, *RPGRIP1L*, *ARL13B*, *CC2D2A*, *INPP5E*, *JBTS2/TMEM216*	Jouberin, Nephrocystin, CEP290, Meckelin, RPGRIP1L, ARL13B, CC2D2A, INPP5E, TMEM216	Cilia, basal bodies, centrosomes, cell junctions	Ciliogenesis, Sonic Hedgehog signaling
Bardet–Biedl syndrome (BBS)	Renal cysts, obesity, polydactyly, retinal dystrophy, mental retardation	*BBS1-12*, *MKS1*, *CEP290*, *FRITZ*, *SDCCAG8*	BBS1-12, MKS1, CEP290, FRITZ, SDCCAG8	Centrosomes, basal bodies	Pericentriolar organization, ciliogenesis, Wnt signaling
Meckel–Gruber syndrome (MKS)	Occipital meningoencephalocele, cystic kidneys, liver fibrosis, polydactyly	*MKS1*, *MKS3/TMEM67*, *NPHP3*, *CEP290*, *RPGRIP1L*, *CC2D2A*, *MKS2/ TMEM216*	MKS1, meckelin, nephrocystin 3, CEP290, RPGRIP1L, CC2D2A, TMEM216	Centrosomes, cilia, plasma membrane	Basal body localization, ciliogenesis, Hedgehog signaling
Oral–facial–digital syndrome 1 (OFD1)	Malformations of face, oral cavity and digits, renal cysts, polydactyly	*OFD1*	OFD1	Cilia, basal bodies, centrosomes, nucleus	Ciliogenesis, L-R asymmetry, possibly gene regulation
Short-Rib Polydactily (incl. Jeune Asphyxiating Thoracic Dystrophy)	Renal cysts, shortened bones, polydactyly, situs inversus	*DYN2CH1*, *IFT80*	Cytoplasmic dynein 2 heavy chain, IFT80	Chondrocyte cilia, basal bodies	Intraflagelar transport, Hedgehog signaling
Uromodulin-associated kidney diseases (MCKD2, FJHN, GCKD)	Renal cysts, fibrosis, hypertension, hypoeuricemia,	*UMOD*, *MCKD1*, *MCKD2*	Uromodulin	Cilia, basal bodies, centrosomes, secreted	Unknown ciliary role

PKD, Polycystic kidney disease; MCKD2, medullary cystic kidney disease type 2; FJHN, familial juvenile hyperuricemic nephropathy; GCKD, glomerulocystic kidney disease

GENE	Kidney[1]	Eye[2]	Cerebellum[3]	Brain[4]	Liver fibrosis[5]	Heart situs inv.[6]	Bone changes[7]	Literature
NPHP1	100	6	1					21,99,142,143
NPHP2 (INVS)	100	10				10		25,93
NPHP3	100	13			3			24
NPHP4	100	33						23,30
NPHP5	100	100						26,81
NPHP6 (CEP290)	100	100	90	90	10	1	10	27,39,40,80,144-147
Hypomorphic		100						79
NPHP7	100[3]							31
NPHP8 (RPGRIP1L)								32,40
2 truncat	100	100		100	100			
≥1 missense	100	100	100					32,40
NPHP9 (NEK8)	100	30						42
AHI	10	75	100					100,148,149
MKS1	100	5	1	100	90	1	80	110,113,150
MKS3 (TMEM67)	100		50	75	90		20	111,147,150

LEGEND

% involvement	0-5	6-10	11-25	26-50	51-75	76-100

[1]Nephronophthisis or cystic kidney disease.

[2]Mostly retinitis retinal degeneration (RD) in NPHP1-5 (early onset in NPHP5), coloboma (CB) in NPHP6 and 8; oculomotor apraxia type Cogan (OMA) in NPHP1 and 4, Leber congenital amaurosis (LCA) in NPHP6.

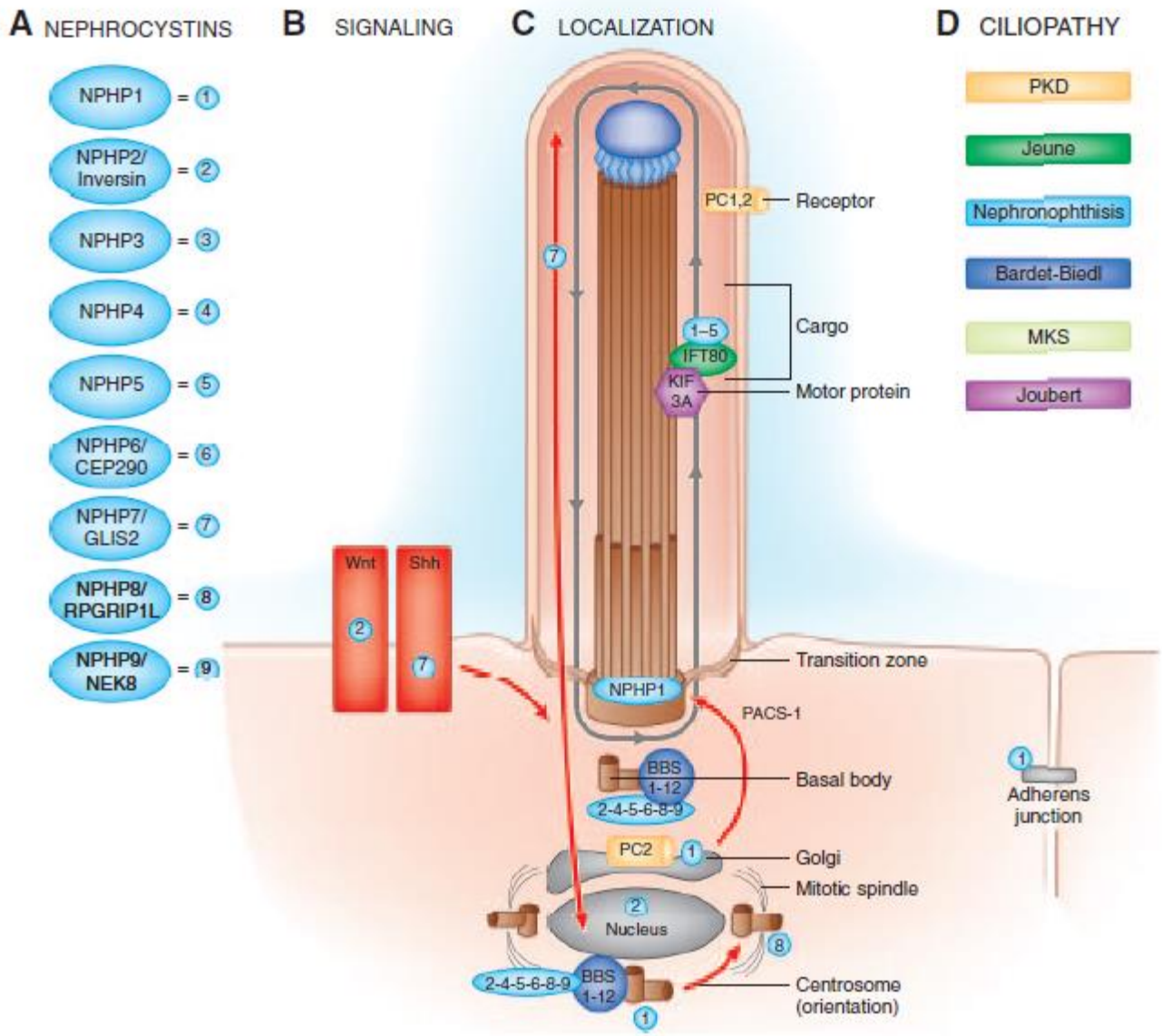
[3]Cerebellar aplasia/hypoplasia (CVA) with radiographic "molar tooth sign": ataxia/hypotonia (AT).

[4]Mental retardation (MR) in NPHP6, NPHP8 with missense mutation, occipital encephaloeele (OE) or aneneephaly (AN) in NPHP8 (2 truncating mutations), MKSl, MKS3; seizures (SZ) in MKS1, BBS.

[5]Liver fibrosis (LF) in NPHP3 and BBS; bile duct proliferation (BDP) in NPHP6, MKS1, MKS3.

[6]Congenital heart defects in NPHP6, MKS, and BBS.

[7]Postaxial polydactyly (PPD) in NPHP6, MKS, and BBS; cleft palate in MKS; scoliosis in NPHP6, NPHP8.



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ADPCKD

- 1 in 400 - 1 in 1,000
- 12.5 million patients worldwide
- Multiple bilateral cysts from all nephron segments
- Renomegaly, progressive renal impairment
- Haematuria, flank pain, UTI, calculi
- Poor urinary concentrating ability
- Hypertension
- Chronic renal insufficiency - 50% by 60 years
- Other organs
  - Liver cysts
  - Pancreas
  - Lung
  - Intestinal diverticulae
  - Cardiac valves abnormalities
  - Intracranial aneurysms

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ADPCKD

- PKD 1 (85%) and PKD 2 encode polycystin 1 and 2 respectively
- Maintain renal tubular cell differentiation, prevent proliferation of epithelial cells, promote epithelial cell migration and branching morphogenesis
- 2 hit hypothesis
  - Germline mutation in PKD1 or PKD 2 segregates within a kindred in an AD fashion
  - Renal cyst occurs if second allele undergoes somatic spontaneous mutation - second hit can be in PKD 1 or PKD 2 - transheterozygote
  - Not all nephrons in ADPKD develop cysts
  - Explains the phenotypic variation

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ADPCKD

- Polycystin 1
  - Integral membrane protein
  - Implicated in cell-cell and cell - matrix interactions
  - Intracellular signalling cascades interacts with polycystin 2
- Polycystin 2
  - Member of transient receptor potential (TRP) channel superfamily of non selective cation channels, permeable for several cations including calcium
    - Plasma membrane
    - Endoplasmic reticulum
    - Apical primary cilia
- Abnormal polarization of transmembrane channels - apical and basolateral - sodium and water actively pumped into cyst

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ADPCKD

- Cysts arise anywhere along nephron
- Eventually separate from tubule
- Expand through accumulation of cyst fluid

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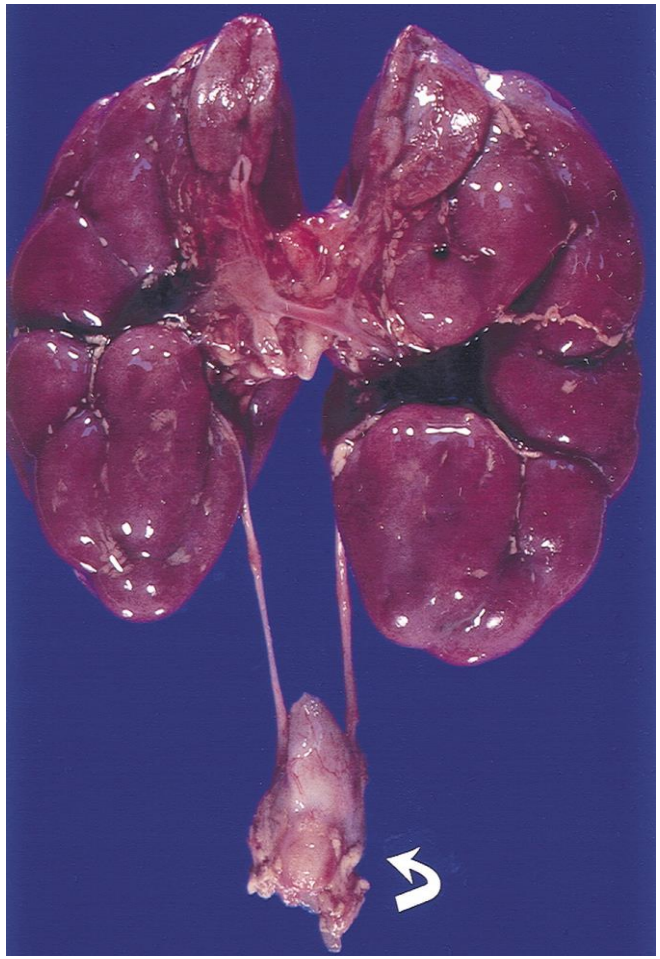

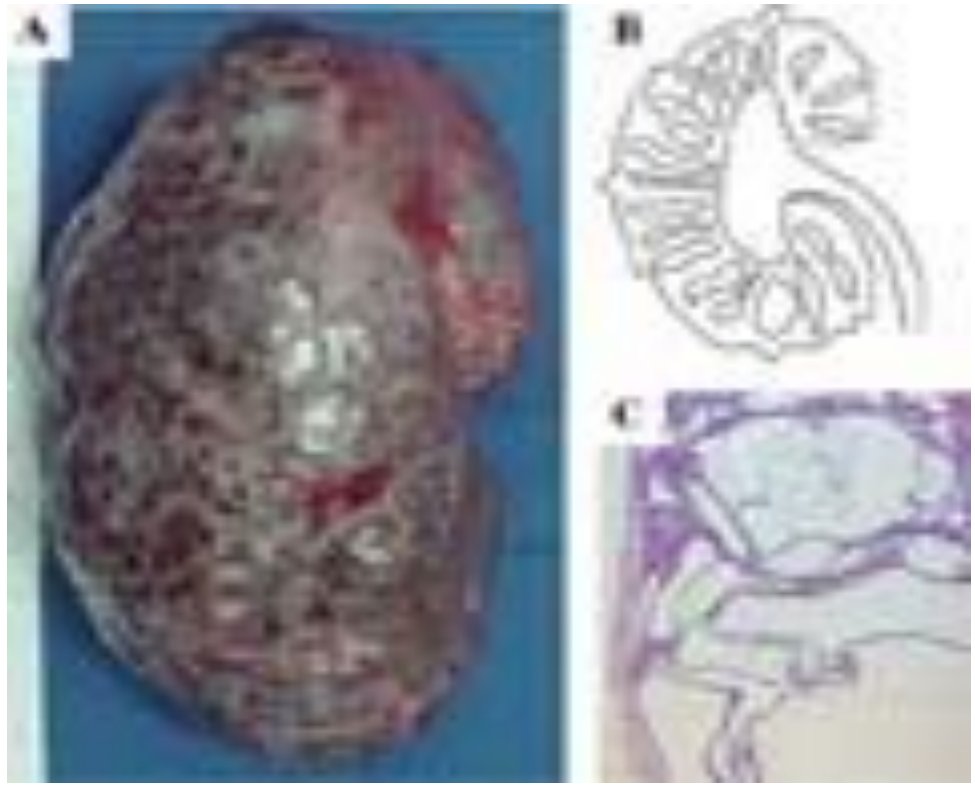

www.scielo.br

diographics.rsnajnls.org

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ARPCKD

- 1 in 20,000 live births
- Wide phenotypic variation
  - FDIU
  - SB/NND - pulmonary insufficiency
  - HT, renal insufficiency, portal hypertension
- Bilateral renal cystic disease in utero
- 30% die in infancy
- 45% liver involvement- Caroli's disease or hepatic fibrosis

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ARPCKD

- Fusiform cysts formed by dilatation of collecting ducts
- Maintain connection to parent nephron

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ARPCKD

- Mutations in PKHD 1
- Protein product - fibrocystin/ polyductin
- Primary cilium and centrosome
- Mediates terminal differentiation of renal collecting duct and intrahepatic biliary ducts
- V large gene, many spliced isoforms - ? Phenotypic variation due to effect of PKHD1 mutations on isoforms

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Nephronophthisis

- AR
- 1 in 50,000
- Thickening and wrinkling of tubular basement membrane with tubular atrophy and interstitial fibrosis
- N/ decreased kidney size
- Few cysts - corticomedullary junction, arise from collecting ducts and distal tubules
- ESRD - adolescence
- Associated features - 10-15%
  - Retinal dystrophy - Senior Loken syndrome
  - Oculomotor apraxia - Cogan syndrome
  - Situs inversus - infantile NPHP
  - Congenital hepatic fibrosis

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Nephronophthisis

- ? Problem of apoptosis cf proliferation
- 6 genes - NPHP1-NPHP6
- Encode cytosolic proteins
  - nephrocystins
- NPHP2 - infantile form
  - encodes inversin - protein critical for left-right patterning
- Nephrocystin-3, -4 and inversin bind to nephrocystin-1 at base of primary cilia
- Also cell-cell junctions, cell-matrix interactions and nucleus - multiple functions according to cell compartment and cell cycle.

Joubert Syndrome

- AR
- Cerebellum
  - Vermal aplasia
- Eye
  - Coloboma
  - Retinitis pigmentosa
- Congenital hypotonia
- Irregular breathing
- Ocular motor apraxia
- Renal - variable - similar to NPHP

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Joubert Syndrome

- Mutations in NPHP1
- 3 other loci
  - JBTS1 - 9q34
  - JBTS2 - 11p11-12
  - JBTS3 - 6q23

  - ? Role of jouberin

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Bardet-Biedl Syndrome

- 1 in 140,000 - 1 in 17,000 (Newfoundland)
- AR - digenic - mutations in 2 genes
- 4 primary features, or 2 primary and 3 secondary
- Renal - 70% - similar to nephronophthisis

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Table 1 Diagnostic criteria for BBS

	Percent prevalence (modified from [4])	Comment
Primary features		
Rod-cone dystrophy	93%	Other ocular defects included: astigmatism, strabismus, cataracts, colour blindness, macular oedema and degeneration, and optic atrophy
Post-axial polydactyly	69%	Present on all four limbs in 21% of patients, only hands in 9% and only feet in 21%. Brachydactyly present in 46% and syndactyly in 9% of patients
Truncal obesity	72%	Mean BMI in males was 31.5 kg/m^2, in females it was 36.6 kg/m^2
Hypogonadism	98%	Males had hypogenitalism and 8% had maldescended testes. Most women reported irregular menstrual cycles
Renal anomalies	24% (only 52% of patients had undergone renal examination)	Renal parenchymal cysts (10%), calyceal clubbing (10%), foetal lobulation (12%), scarring (12%), dysplastic kidneys (5%), unilateral agenesis (4%), renal calculi (2%), vesicoureteric reflux (9%), bladder obstruction (4%), hydronephrosis (4%), horseshoe kidney (2%), ectopic kidney (2%)
Secondary features		
Speech disorder/delay	54%	
Developmental delay	50%	52% showed delay in walking of up to 1 year, speech delayed by up to 2 years in 47%, delay in pubescence in 31% (all males)
Behaviour	33%	Emotional immaturity, outbursts, disinhibition, depression and lack of social dominance, obsessive compulsive behaviour
Ataxia/imbalance	40%	Abnormal gait reported in 33% of patients (see [5])
Diabetes mellitus	6%	
Congenital heart defects	7%	Included: aortic stenosis, patent ductus arteriosis, cardiomyopathy
Liver disease		Hepatic fibrosis
Hearing loss	21%	Predominantly conductive but some sensorineural
Facial features		Deep-set eyes, hypertelorism, long philtrum, thin upper lip, anteverted nares, prominent forehead with male early-onset balding
Situs inversus	Unknown	See [6]
Hirschprung disease	Unknown	See [6]
Polyuria/polydipsia		May be present in the absence of renal abnormality
Dental crowding		Also includes: high arched palate, hypodontia, small roots
Anosmia	~60%	See [11]

Bardet-Biedl syndrome

- 12 genes BBS1 – BBS12
- Each protein is localized to primary cilia, basal bodies, pericentriolar region
- Function
  - Cilia assembly: intraflagellar transport
  - Microtubule dependent trafficking
  - Cell cycle regulation

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Meckel-Gruber syndrome

- AR
- Often lethal
- Bilateral renal cystic dysplasia
- Biliary duct dysgenesis
- Postaxial polydactyly
- CNS
  - Occipital encephalocoele
  - Prosencephalic dysgenesis
  - Rhombic roof dysgenesis
  - Hydrocephalus
  - Dandy-Walker malformation

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Meckel Gruber syndrome

- 3 loci - 17q21-24, 11q13, 8q21-22
- Meckelin - ? Role

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Orofaciodigital syndrome, type 1

- 1 in 250,000
- X linked dominant - lethal embryonically in males
- Malformations of face, mouth, hands and feet
- CNS - hydrocephalus, agenesis of corpus callosum
- Renal cystic disease similar to ADPCKD but no renal enlargement, and cysts mainly of glomerulus
- ESRD - late childhood onwards
- OFD1 gene encodes OFD1 protein
- Important in right-left axis patterning, microtubule organization, cilia formation

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Renal Cysts and Diabetes

- 17cen-q21.3
- Mutation in gene encoding hepatocyte nuclear factor 1β (aka transcription factor 2)
- 9 exon gene
- Role in epithelial differentiation – gene expressed in preglomerular stages of metanephroi, especially medullary and cortical CD branches
- ? Directly regulates transcription of PKHD 1 (? Inhibition of PKHD 1 contributes to cyst formation)
- AD
- Abnormal renal development – non diabetic renal disease – renal cysts, glomerular tufts, abnormal nephrogenesis, small kidney, absent kidney, horseshoe kidney, hyperuricaemic nephropathy
- Diabetes – 25 yrs or earlier (MODY)
- Abnormal genital tract – vaginal aplasia, abnormal uterus, epididymal cysts, atresia of vas deferens

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Renal Cysts and Diabetes

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Approach to cystic renal disease

- Age of initial Dx
  - Antenatal: polycystic/ CAKUT/syndromic/ dysgenesis incl twin-twin & ACEI
  - Early: as above
  - Late childhood: acquired GCKD/ nephronophthisis

- Review family history
  - Cystic kidneys (U/s parents &?siblings)
  - Maturity onset diabetes (renal cysts & diabetes syndrome, may have pyelocalyceal dil'n & ↑urate =HNFβ1 mutation)
  - Gout (Uromodulin disorders: familial juvenile↑Surate nephropathy: infants with ADPCKD)
- Clinical examination (syndrome assoc)
  - Hepatobiliary: cysts/fibrosis/ agenesis GB/ accessory spleen/ situs inversus/ TOFistula
  - Cardiothoracic: cong heart dis/ hypop - Coarct Ao/ lung hypoplasia/ cardiomyopathy
  - Musculoskeletal: prognathism/ clefts/ BOR/ limb abnormalities/ arthrygryposis/
  - CNS: hydrocephalus/ hearing loss
  - Syndromic?

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Approach to cystic renal disease

- Review imaging
  - U/s renal & liver & ?cranial imaging if done ?Dandy Walker cyst/ encephalocoele
    - Number of kidneys affected
      - Both
        - roughly equal: polycystic
        - Assymetric or hydronephrosis/ureter: CAKUT
      - Single kidney: CAKUT/ tumor
    - Cyst size
      - Macroscopic: ADPCKD, simple cyst (1 per decade),
      - Large symmetric echogenic kidneys: ARPCKD/ GCKD
        - If hepatic fibrosis: more likely ARPCKD
        - If normal liver: either ARPCKD or GCKD
  - CxR
- Biochem
  - Uric acid, (child 120-360umol/L), Renal function, ? cytogenetics
- Imaging of parents & siblings, biochemistry parents including uric acid and RBG

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Renal Cystic Disease - Treatment

- Vasopressin V2 receptor antagonists
  - Reduce intracellular cAMP and inhibit cyst development
- Rapamycin - antiproliferative via mTOR inhibition
- Somatostatin

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Pathogenesis of cyst formation

- Increased mitotic rate of cyst epithelia - proliferation
- Increased expression of growth factors
- Loss of apoptosis
- Abnormality of cell transporters
  - Na^+/K^+-ATPase and Na^+ /K^+ /$2Cl^-$ transporter on wrong cell surfaces

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Pediatr Nephrol (2011) 26:1039–1056
DOI 10.1007/s00467-010-1731-7

EDUCATIONAL REVIEW

Ciliopathies: an expanding disease spectrum

Aoife M. Waters · Philip L. Beales

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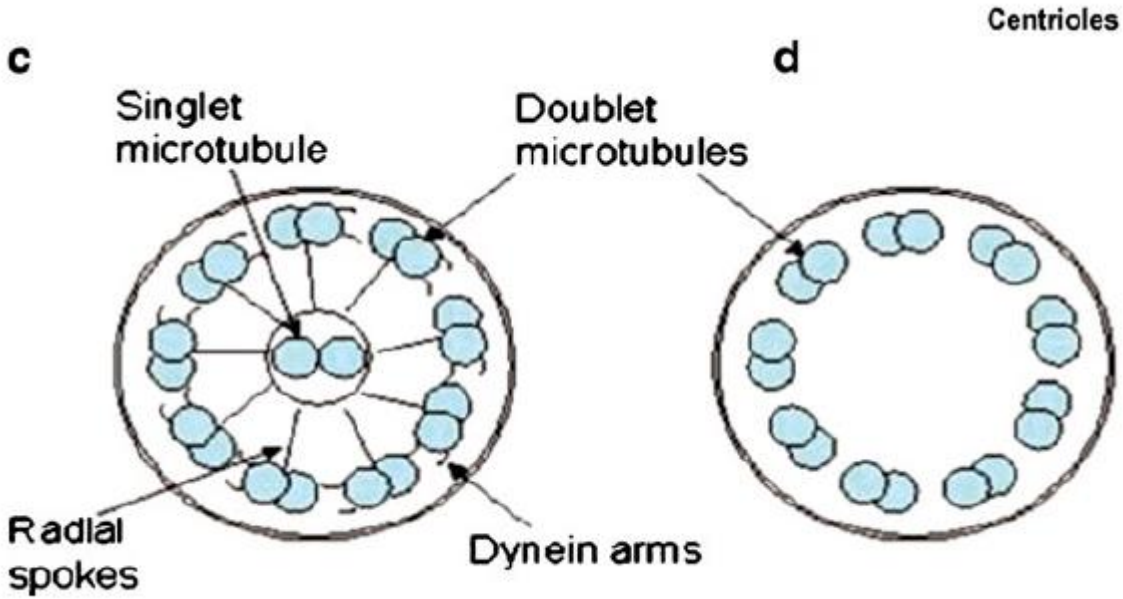

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Table 2 Genotypic overlap in the ciliopathies. (Table modified from Gerdes et al. [130], used with permission)

Gene	LCA	SLS	NPHP	MKS	BBS	JBTS	OFD
CEP290	√	√	√	√	√	√	
NPHP1		√	√			√	
INVS		√	√				
NPHP3		√	√	√			
NPHP4		√	√				
NPHP5		√	√				
GLIS2			√				
NEK8			√				
AHI1						√	
TMEM67			√	√	√	√	
RPGRIPL1	√		√	√		√	
ARL13B						√	
BBS1					√		
BBS2				√	√		
BBS3					√		
BBS4				√	√		
BBS5					√		
BBS6				√	√		
BBS7					√		
BBS8					√		
BBS9					√		
BBS10					√		
BBS11					√		
BBS12					√		
MGC1203					√		
MKS1				√	√		
BBS15					√		
CC2D2A				√		√	
TMEM216				√		√	√
INPP5E						√	
XNPEP3			√				
OFD1[a]						√	√

LCA, Leber's congenital amaurosis; NPHP, nephronophthisis; BBS, Bardet–Biedl syndrome; SLS, Senior–Løken syndrome; JBS, Joubert syndrome, MKS, Meckel–Gruber syndrome, OMA, oculomotor apraxia, OFD, orofaciodigital syndrome

[a] If in males

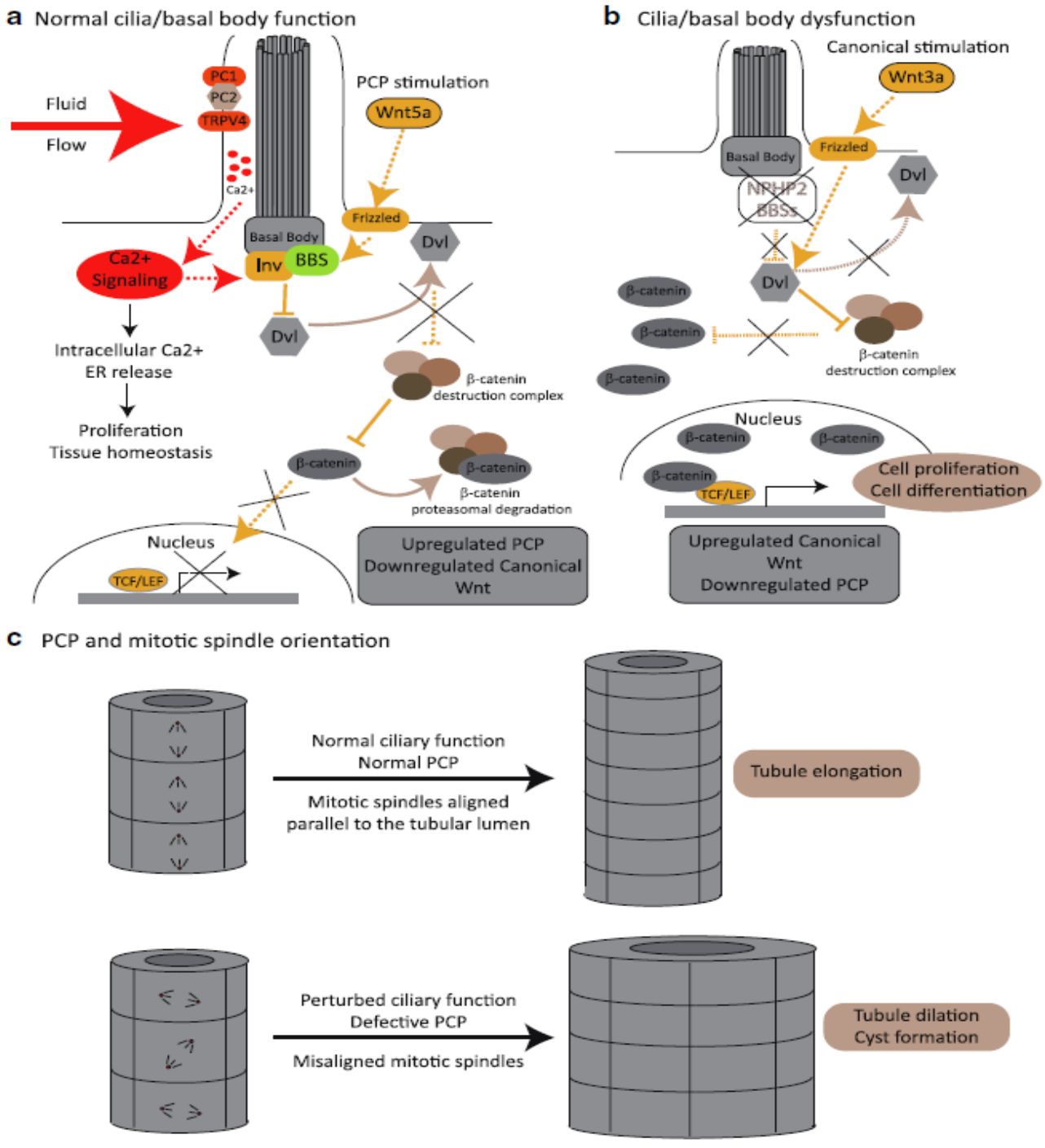
Pediatr Nephrol (2011) 26:1181–1195
DOI 10.1007/s00467-010-1697-5

REVIEW

Cystic diseases of the kidney: ciliary dysfunction and cystogenic mechanisms

Cecilia Gascue · Nicholas Katsanis · Jose L. Badano

Monash Children's Hospital


a Normal cilia/basal body function
Fluid
Flow
PC1
PC2
TRPV4
Ca2+
Ca2+ Signaling
Intracellular Ca2+
ER release
Proliferation
Tissue homeostasis
Basal Body
Inv
BBS
Dvl
PCP stimulation
Wnt5a
Frizzled
β-catenin destruction complex
β-catenin
β-catenin proteasomal degradation
Nucleus
TCF/LEF
Upregulated PCP
Downregulated Canonical Wnt
b Cilia/basal body dysfunction
Canonical stimulation
Wnt3a
Basal Body
Frizzled
Dvl
NPHP2
BBS5
β-catenin
β-catenin destruction complex
Nucleus
Cell proliferation
Cell differentiation
TCF/LEF
Upregulated Canonical Wnt
Downregulated PCP
c PCP and mitotic spindle orientation
Normal ciliary function
Normal PCP
Mitotic spindles aligned
parallel to the tubular lumen
Tubule elongation
Perturbed ciliary function
Defective PCP
Misaligned mitotic spindles
Tubule dilation
Cyst formation

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MECHANISMS OF DISEASE

Robert S. Schwartz, M.D., *Editor*

Ciliopathies

Friedhelm Hildebrandt, M.D., Thomas Benzing, M.D.,
and Nicholas Katsanis, Ph.D.

N Engl J Med 2011;364:1533-43

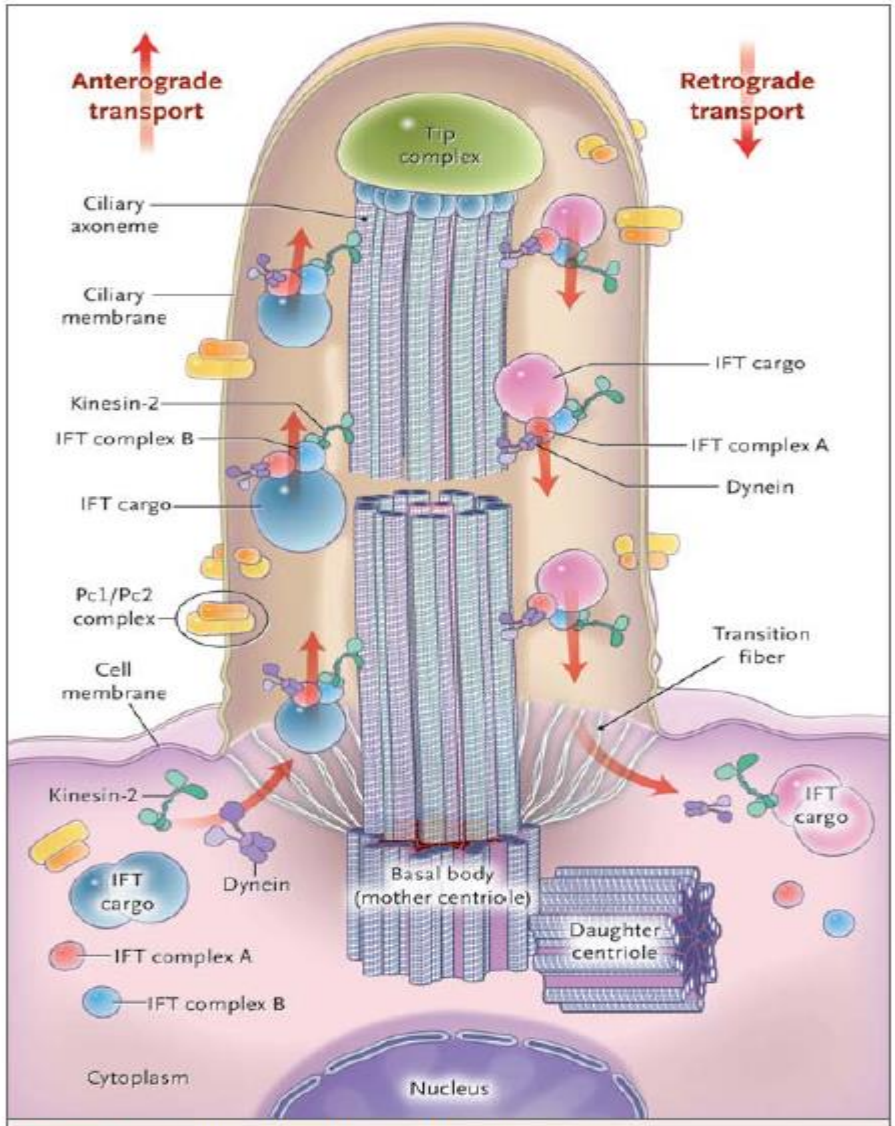


Figure 1. Structure of the Cilium and Intraflagellar Transport.

The cilium is a hairlike structure on the cell surface that consists of a microtubule-based axoneme covered by a specialized plasma membrane, which is assembled from the basal body, or mother centriole. Transition fibers act as a filter for molecules passing into or out of the cilium. Nephrocystin-1 is localized at the transition zone of epithelial cells (not shown).[1] Axonemal and membrane components are transported in raft macromolecular particles (complexes A and B) by means of intraflagellar transport (IFT) along the axonemal doublet microtubules[2] toward the tip complex by heterotrimeric kinesin-2. Mutations of *Kif3a* cause renal cysts and aplasia of the cerebellar vermis in mice.[3] Retrograde transport occurs by means of the motor protein cytoplasmic dynein. (Adapted from Bisgrove and Yost.[4])

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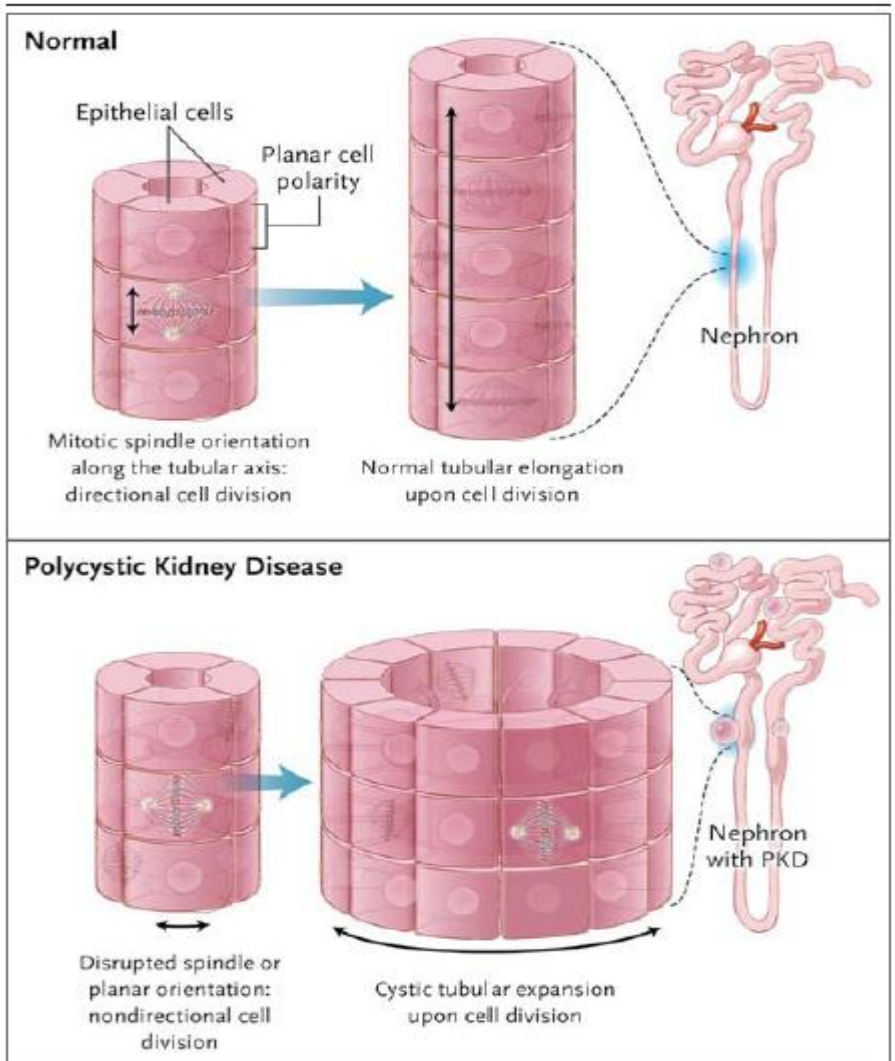

Figure 4. Defects in the Noncanonical Wnt/PCP Pathway Leading to Renal Cysts.

Correct orientation of the mitotic spindle and centrosomes with respect to the longitudinal axis of the tubule is critical for proper planar cell polarity (i.e., the orientation of an epithelial cell layer in three-dimensional space). Noncanonical Wnt/PCP signaling is involved in the regulation of planar cell polarity during renal tubular morphogenesis, when in 2-week-old rodents the tubules still elongate. In this model, if the mitotic spindle is malorient-ed, such as at an oblique angle to (or, to cite an extreme example, perpen-dicular to) the longitudinal orientation of tubule growth, the resulting struc-ture would be a dilated tubule or cyst.

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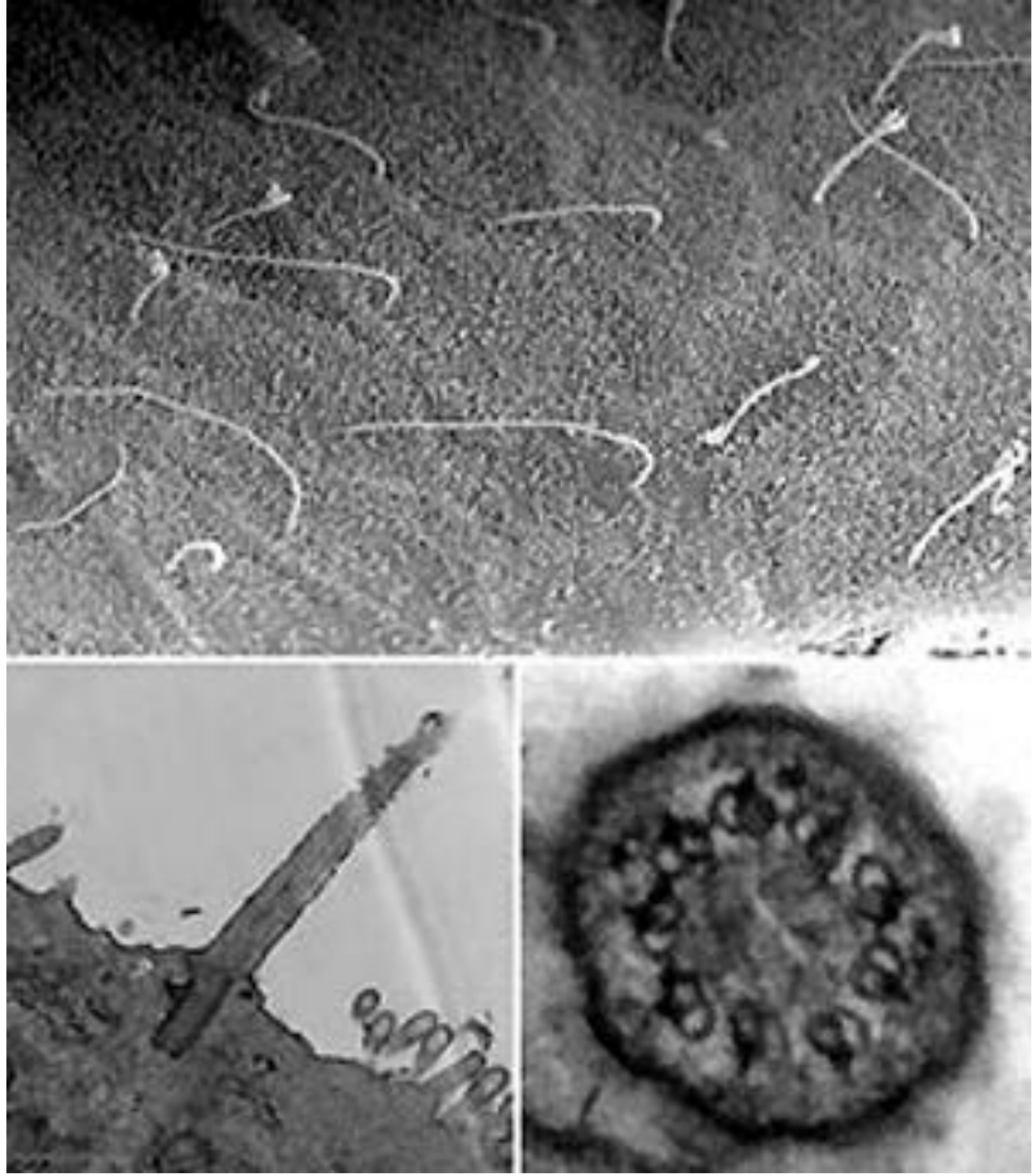

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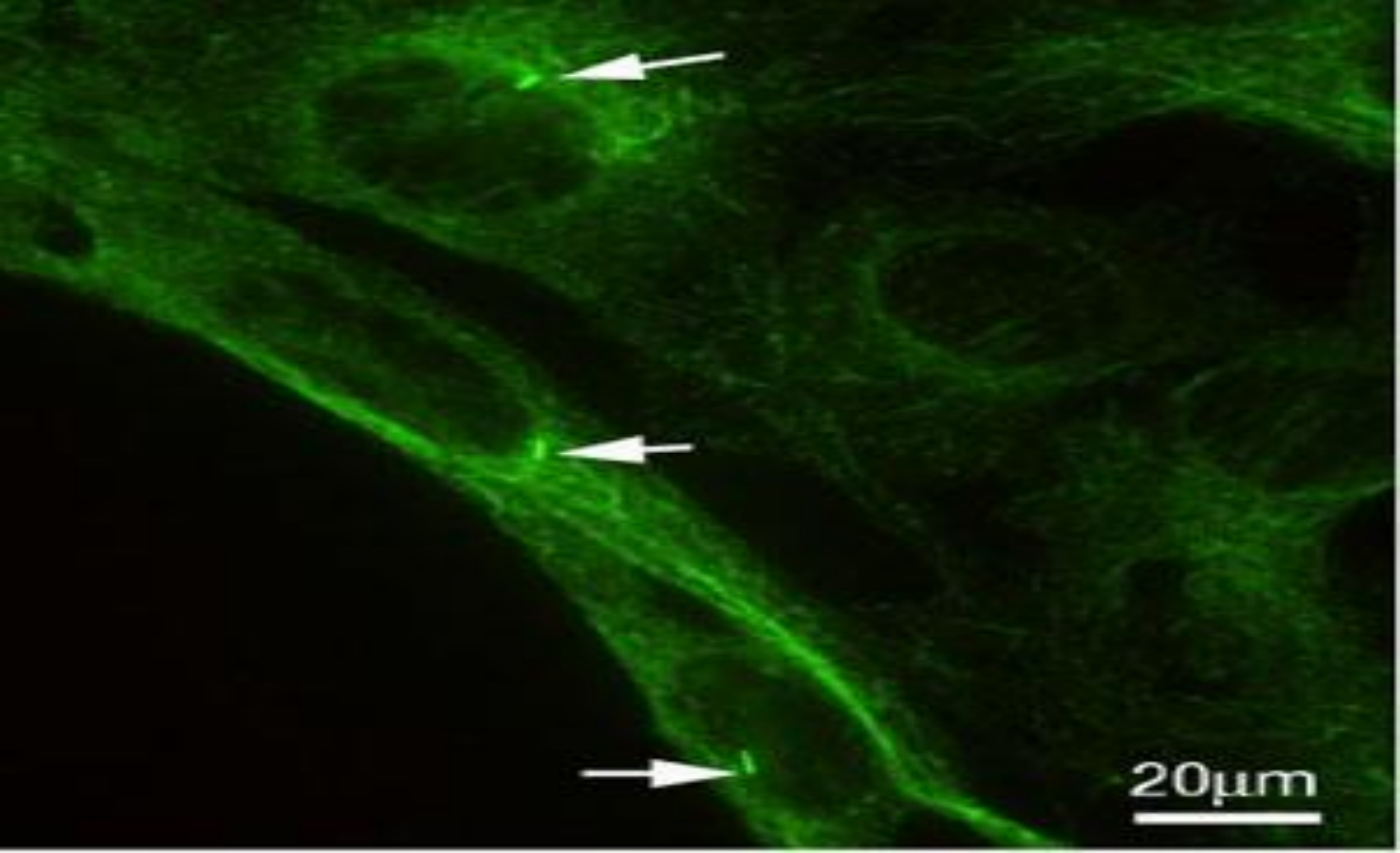

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Primary Cilia - ‘forgotten organelle’

- Single hair like structures
- Protrude from epithelial cells
- Non motile - 9 microtubule doublets with no central doublet cf motile cilia
- Motile - embryonic node - determines right-left patterning
- Grow out from basal bodies or centrosomes
- Most cells- ductal and nonductal epithelial cells, endothelia, neurons, mesenchymal cells, fibroblasts, chondrocytes, osteocytes.

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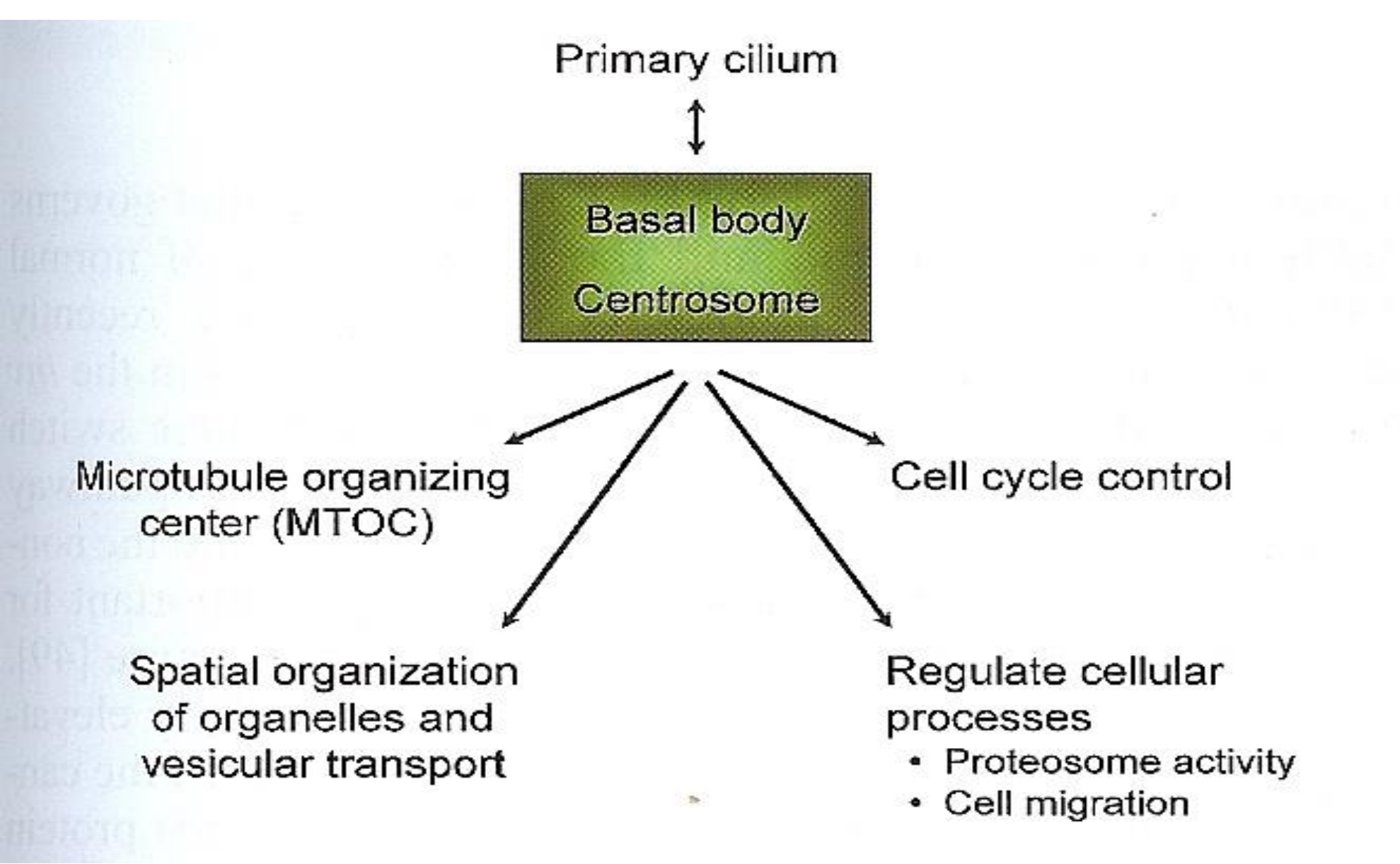

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Primary Cilia

- Motor proteins - kinesins and dyneins transport cargo proteins up and down shaft - intraflagellar rafts
- Modular sensory cellular organelles
- Highly conserved in evolution
- Detect physical and chemical stimuli - mechanical, osmotic, photonic, olfactory and hormonal
- Cells use cilia to detect external stimuli

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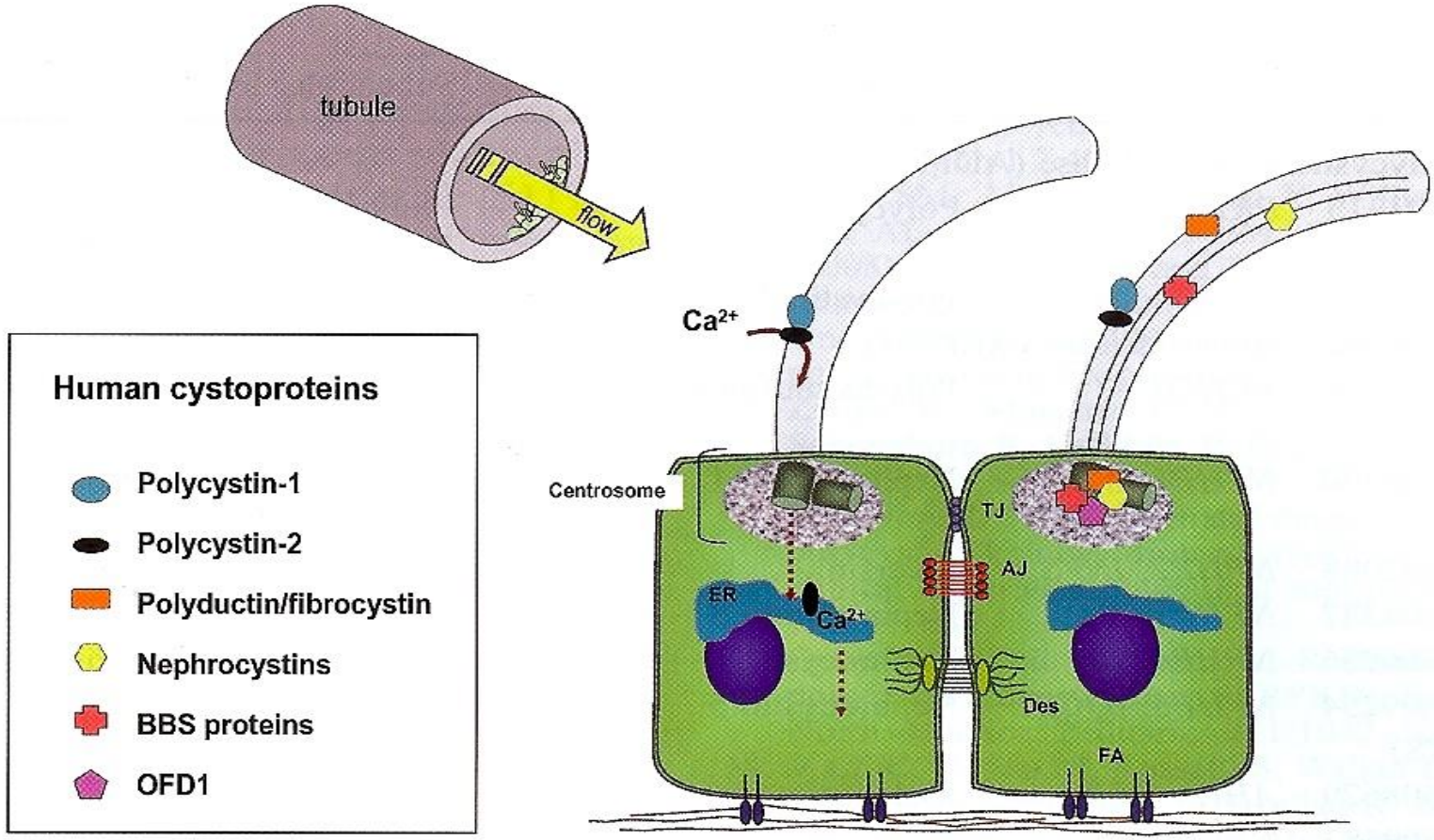

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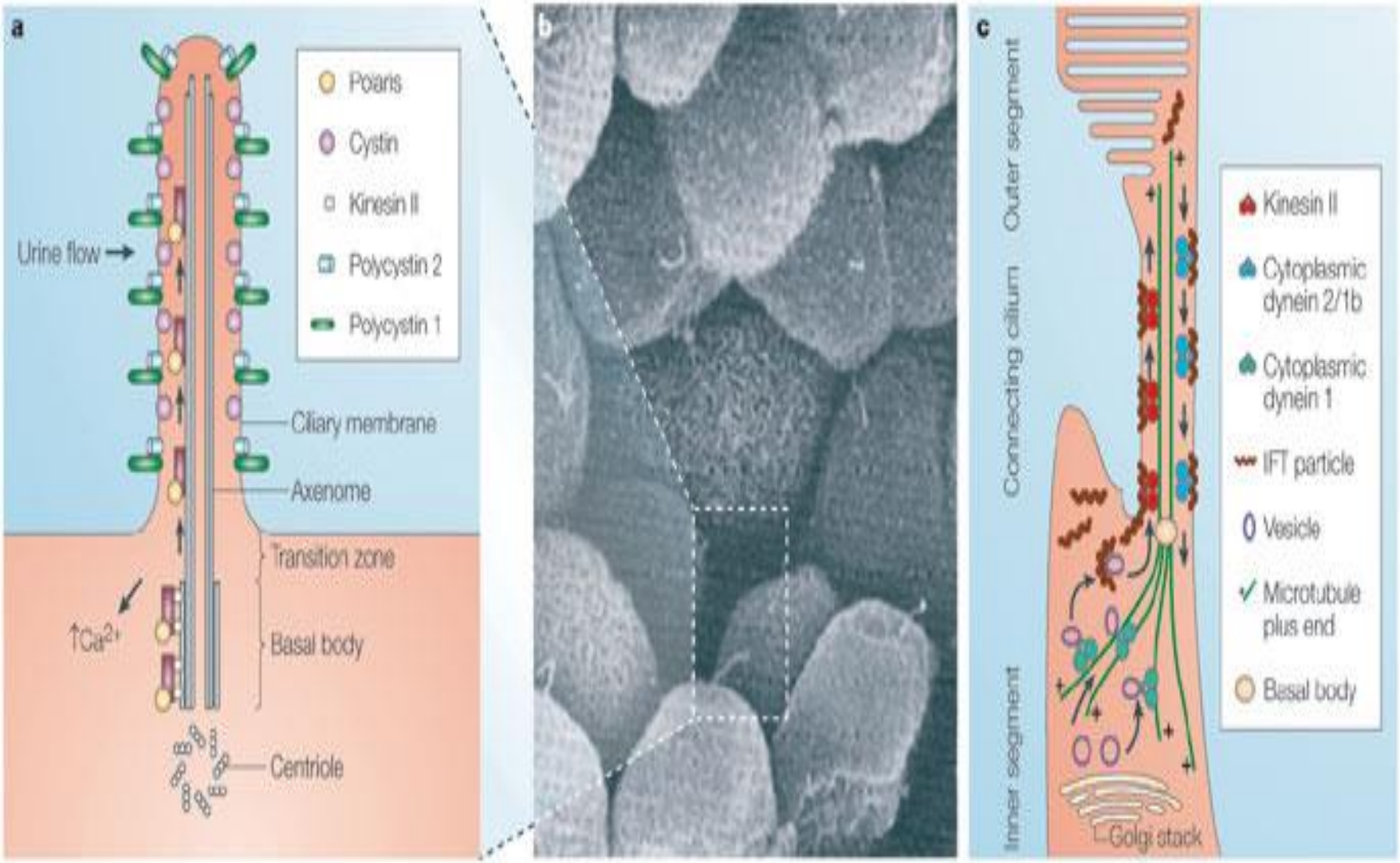

Nature Reviews | Genetics

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Inherited Renal Cystic Disease

- Abnormality of cell proliferation and apoptosis
- Common link is the primary cilia and centrosome
- Yet to unfold
  - Importance of cilia and centriole in cell replication and cyst formation
  - Importance of cilia as means of intracellular signalling (Wnt) in renal development

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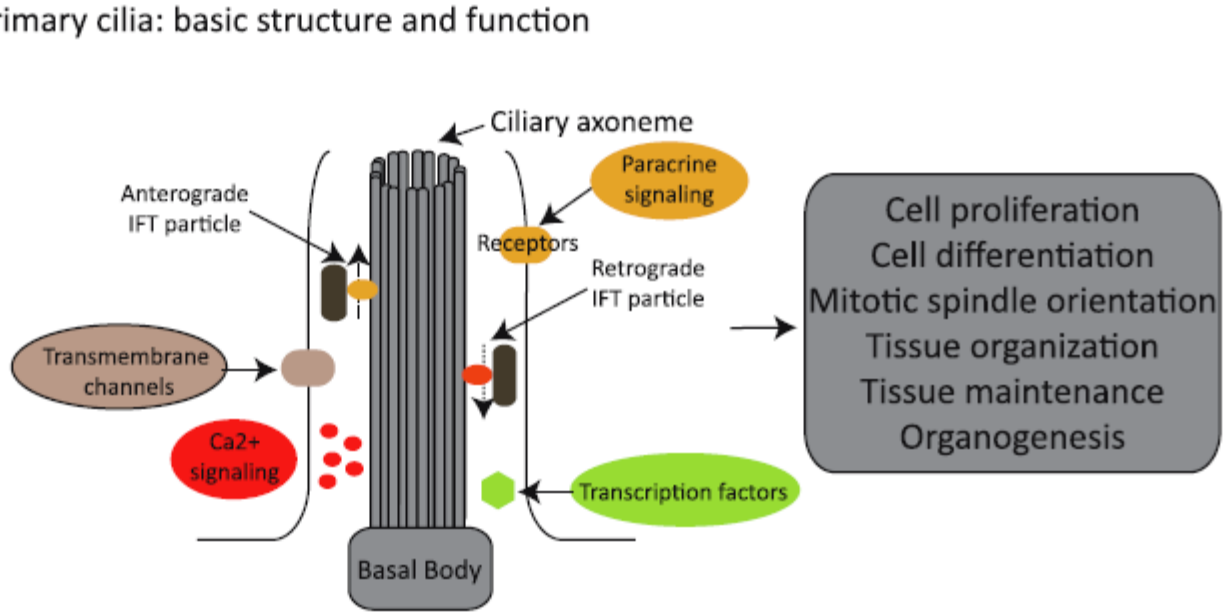
Fig. 1 The cilium: basic structure and function. Cilia are formed by a microtubule core (axoneme) that is organized from a basal body. Along the axoneme, intraflagellar transport (*IFT*) particles are transported in (anterograde) and out (retrograde) of the cilium. The cilium concentrates and organizes a number of channels, receptors, and effectors, therefore playing a critical role in, for example, Ca^{2+} and paracrine signaling, ultimately regulating cellular, tissue, and organ homeostasis



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BRIEF REVIEW www.jasn.org

Nephronophthisis: Disease Mechanisms of a Ciliopathy

Friedhelm Hildebrandt,*†‡ Massimo Attanasio,* and Edgar Otto*

Departments of *Pediatrics and †Human Genetics, University of Michigan, and ‡Howard Hughes Medical Institute, Ann Arbor, Michigan

J Am Soc Nephrol 20: 23–35, 2009. doi: 10.1681/ASN.2008050456

Table. Continued

Disease	Gene	Protein	Localization in Renal Epithelial Cells	Renal Symptoms	Extrarenal Symptoms
Autosomal Dominant Medullary Cystic Kidney Disease/Familial Juvenile Hyperuricemic Nephropathy/ Glomerulocystic Kidney Disease					
ADMCKD1	Unknown 1q21-q23	Unknown	Unknown	Tubular BM thickening Tubular atrophy Interstitial fibrosis Salt wasting Small corticomedullary cysts	
ADMCKD2/FJHN/ GCKD	*UMOD* 16p13.11	Uromodulin/Tamm-Horsfall protein	Cytoplasm Apical vesicles of thick ascending limb of Henle loop		Hypertension Hyperuricemia (gout)
Other Diseases With Cystic Renal Phenotype					
X-linked orofaciodigital syndrome 1	*OFD1* Xp22.2-p22.3	Chromosome X open reading frame 5 116 kDa	Primary cilia Basal body Cytoplasm Cytoskeleton Microtubules Centrosome	Polycystic kidney phenotype with progressive renal failure	Hydrocephalus Malformations of face, oral cavity, and digits
Autosomal recessive Alström syndrome 1	*ALMS1* 2p13	Alström syndrome 1	Cytoplasm Cytoskeleton Microtubules Centrosome Centriole	NPHP phenotype	Progressive visual impairment Cone-rod dystrophy and blindness Diabetes mellitus Truncal obesity Acanthosis nigricans Male hypogenitalism Dilated cardiomyopathy Neurosensory deafness

Abbreviations: ADMCKD, autosomal dominant medullary cystic kidney disease; ADP, adenosine diphosphate; AHI, Abelson helper integration site; ALMS1, Alström syndrome 1; ARL6, ADP ribosylation factor–like 6; BBS, Bardet-Biedl syndrome; BM, basement membrane; C4orf24, chromosome 4 open reading frame 24; C12orf58, chromosome 12 open reading frame 58; CEP290, centrosomal protein 290 kDa; ESRD, end-stage renal disease; FABB, flagella-basal body; FJHN, familial juvenile hyperuricemic nephropathy; GCKD, glomerulocystic kidney disease; GLIS2, glioma-associated similar protein 2; GTP, guanosine triphosphate; INVS, inversin; IQCB1, IQ motif containing B1; JBTS, Joubert syndrome; MKS, Meckel-Gruber syndrome; MKKS, McKusick-Kaufmann syndrome; NEK8, NIMA-related kinase 8; NIMA, never in mitosis gene A; NPHP, nephronophthisis; OFD1, orofaciodigital syndrome 1; PKD, polycystic kidney disease; PKHD1, polycystic kidney and hepatic disease 1; PTHB1, parathyroid hormone–responsive, B1 protein; RPGRIP1L, retinitis pigmentosa GTPase regulator interacting protein 1–like; SLSN, Senior-Løken syndrome; TMEM67, transmembrane protein 67; TRIM32, tripartite motif 32; TTC8, tetratricopeptide repeat domain protein 8; UMOD, uromodulin.