Renal cystic disease

Cyst = abnormal fluid-filled space lined by epithelial cells
Diverticulum = abnormal outpouching of hollow organ into surrounding tissues
Many renal 'cysts' actually diverticula, or formed by dilatation/ectasia of tubules and collecting ducts
Majority of cystic conditions arise from nephrons after they have formed: exception is multicystic kidney disease, where cysts arise in dysplastic tissue formed due to irregular metanephric blastema and multiloculated cystic nephroma, which is a benign tumour
Renal cystic disease divided into genetic and non-genetic:

Genetic	Non-genetic
ARPKD	Multicystic kidneys
ADPKD	Medullary sponge kidney
Juvenile nephronopthisis	Multiple benign cysts
Congenital nephrosis	Acquired renal cystic disease
Von Hippel Lindau disease	Multiloculated cystic nephroma
Tuberous sclerosis	Calyceal diverticulum

Genetic renal cystic disease

<u>ARPKD</u>
Incidence 1:10,000 – 1:40,000
Mutation of PKHD1 gene on chromosome 6 (protein product fibrocystin)
Small cysts (usually < 2mm) arising from collecting ducts, with associated dilatation of portal tracts (congenital hepatic fibrosis)
Severity increases with earlier age:

Infancy	Severe renal dysfunction; mild CHF. High risk of death due to pulmonary complications. 2yr survival 50%. 15yr survival 46%
Childhood	Mild renal disease [but still 50% ESRF in adolescence and 100% by adulthood]. Severe CHF and hepatic complications (fibrosis, portal HT, bleeding varices: liver failure very rare) Continued development of cysts up to age of 13, or rarely 20 years of age – usually more discrete cysts

Diagnosis on prenatal USS in ~50%. Symmetrical very large homogenous hyperechogenic kidneys due to multiple small cysts.
No known cure. Supportive treatment only (pulmonary, hepatic and GI etc)

Item	Autosomal Recessive Polycystic Kidney Disease (ARPKD)	Autosomal Dominant Polycystic Kidney Disease (ADPKD)
Gene defect	Chromosome 6	Chromosomes 4 and 16
Incidence	1:5,000 to 1:40,000	1:500 to 1:1,000
Usual age at clinical presentation	Perinatal	Third to fifth decades
Typical sonographic appearance of kidneys	Symmetrically enlarged, homogeneous, hyperechogenic kidneys	Large cystic kidneys, sometimes asymmetrical
Histology	Collecting duct ectasia; cysts derived principally from collecting duct	Microcysts and macrocysts derived from entire nephron
Liver	Always congenital hepatic fibrosis but of varying severity	Cysts, mostly in adults (on very rare occasions a newborn may have congenital hepatic fibrosis)
Other system involvement	None	Intracranial aneurysms; colonic diverticuli; mitral valve regurgitation; cysts of other organs

ADPKD

Autosomal dominant with almost 100% penetrance: 96% of patients with disease by 90 yrs (Gabow 1991)
Variable expression of disease + 10% spontaneous mutation rate means that up to half of patients have no family history of disease
Incidence 1:500 – 1:1000 live births
Accounts for 10-15% of all patients on haemodialysis in US
3 gene defects:

PKD 1	Chromosome 16p13.3	polycystin-1	89%
PKD 2	Chromosome 4q13.23	polycystin-2 `	10%
PKD 3	Unknown chromosome	unknown	1%

Type 1 defects progress more rapidly than type 2 defects
Typical presentation 30-40 yrs; very occasionally in children
Bilateral asymmetrically enlarged kidneys with large cysts
Cysts form from all segments of nephron (cf. ARPKD). Pathogenesis unknown but associated with increased tubular epithelial cell proliferation, loss of cell polarity, fluid accumulation ECM remodelling
Associated features:

Hepatic cysts	very common
Pancreatic cysts	10%
Splenic cysts	5%
Berry aneurysms	0-41% [more common if FHx aneurysm]
Diverticulosis	uncommon
Mitral valve regurgitation	uncommon
Other cysts and vascular aneurysms	uncommon

Clinical features:

Palpable mass	
Loin pain	60% patients
Haematuria	50% patients
Hypertension	60% patients
UTI	50% patients
Stones	20% patients; uric acid or oxalate
Renal failure	50% patients (Churchill1984)

NB. increased incidence of renal adenoma but NOT renal cell carcinoma

Diagnosis
- Genetic linkage studies
- USS-defined – three or more cysts in each kidney
- Negative studies in patients aged 35-40 indicate absence of disease

Management
- Preservation of renal function – ACEI [no evidence that routine cyst decompression useful in preventing renal deterioration]
- A number of agents have been trialled, including vasoproessin II antagonists (tolvaptan) and mTOR inhibitors (sirolimus) without much efficacy
- Treatment of complications – UTI, stones, etc.

NB. Infections in renal cysts usually respond to fat-soluble antibiotics (TMP, quinolones, chloramphenicol)
Pre-transplant Nx avoided unless very symptomatic (haematuria, stone load) or interferes with Tx (massive size), as native kidneys a/w continued epo production and fluid balance.
Survival of patients with ESRF as good if not beter than age-matched pts. Cardiovascular (40%) and intracranial haemorrhage (10%) main causes of death

Juvenile nephronopthisis

Responsible for ~10-20% of renal failure cases in children
Autosomal-recessive inheritance of mutations of NPH gene on chromosome 2
Typically presents with renal failure, interstitial fibrosis and cysts at corticomedullary junction. Tubular salt-wasting leads to polydipsia and polyuria.
16% have retinitis pigmentosa (Senior-Loken syndrome)
Related autosomal dominant condition known as Medullary cystic disease complex – virtually identical anatomic/pathological features but adult onset.

Item	Juvenile Nephronophthisis	Medullary Cystic Disease
Inheritance	Autosomal recessive (chromosome 2)	Autosomal dominant (chromosome ?)
Incidence	1:50,000	1:100,000
End-stage renal disease	By age 13yr	20–40yr
Medullary cysts	Develop after renal failure	May develop before onset of renal failure
Tubular basement membrane	Thickened	May not be thickened
Symptoms	Polyuria, polydipsia, anemia, growth retardation (usually after age 2)	Polyuria, polydipsia, anemia; may have hematuria and proteinuria (symptoms usually appear after patient is fully grown)

Congenital nephrosis

2 types: Finnish type (CNF) and diffuse mesangial stenosis (DMS).
CNF is associated with huge kidneys and a large placenta at birth.
DMS is sometimes associated with Drash syndrome (nephrotic syndrome, Wilms' tumor, and male pseudohermaphroditism).
Both have profound proteinuria and dilated proximal tubules.
No Rx except RRT and, ultimately renal transplantation

Tuberous sclerosis

Autosomal dominant with variable penetration; occasionally sporadic
1:10,000 live births
Mutation of TSC1 gene on chromosome 9 or TSC2 gene on chromosome 16 (adjacent to PKD1 – may be some crossover)
Hamartomas in CNS (tuber-like), skin, eyes, and kidneys. Also renal cysts
Presentation with epilepsy (fits), mental retardation (twits), adenoma sebaceum (zits). Also ash-leaf patches.
Renal cysts in 20% (eosinophilic lining), AML in 40-80%, and RCC in 2%

Von Hippel Lindau disease

Autosomal dominant
1 in 36,000 live births
Mutation of VHL tumour suppressor gene on short arm of chromosome 3
Disease results from inactivation or silencing of normal (wild-type) allele
25-50% of VHL ‘carriers’ will get RCC in lifetime. 70% risk aged 60.

3 major manifestations of VHL disease: Clear-cell RCC; CNS haemangio-blastomas [retina, cerebellum]; phaeochromocytoma. Also renal, pancreatic and epididymal cysts

VHL classification

Type	1	Clear-cell RCC with CNS haemangioblastoma
Type	2a	Phaeo and CNS haemangioblastoma
	2b	Phaeo, clear-cell RCC and CNS haemangioblastoma
	2c	Phaeo alone

Non-genetic renal cystic disease

Multicystic dysplastic kidney (MCDK)

Congenital

Sporadic, rarely inherited (AD variable penetrance)

Dysplastic non-functioning kidney; thought to be due to either fetal ureteric obstruction or failed interaction of ureteric bud and metanephric blastema

Incidence

Unilateral	1:2500 – 1:4000
Bilateral	1:20,000

Males > females

Left > right

Pre-natally diagnosed on USS; occasionally present with abdominal mass or as an incidental finding post-natally. Only incidental finding in patients with unilateral disease: bilateral disease a/w anhydramnios and fatal pulmonary hypoplasia

Imaging

USS	Non-communicating cysts (cf. PUJO)
DMSA	Non-functioning
MCUG	30-40% have mild VUR on MCUG, but significance unclear

Management

(i) Observation	30% involute on serial imaging
(ii) Nephrectomy	Massive Development of hypertension No role for prophylactic Nx for either hypertension or malignancy (Manzoni 1998) – incidence < 1% for each

Medullary sponge kidney

Originally described by Bietzke in 1908

Dilated distal collecting ducts with ectasia, diverticula and stones.

No stones = ‘bristles of brush’; stones = ‘bouquet of flowers’

Incidence 1:5000 to 1:20,000

75% bilateral

Clinical features

Renal colic	60% patients [calcium phosphate/oxalate]
UTI	30%
Visible haematuria	10%
Hypercalciuria	30%

Diagnosis

Medullary or clayceal contrast blush on IVU
Differential diagnosis = nephrocalcinosis (calcium deposition in non-dilated collecting ducts: a/w hyperparathyroidism, malignancy, sarcoidosis, TB, vitamin D intoxication)

Treatment
Symptomatic
Thiazides for hypercalciuria

Simple renal cysts

Common
USS criteria simple cyst:
1. spherical or ovoid
2. sharply defined, thin wall
3. absence of internal echoes
4. good transmission of sound waves with acoustic enhancement

Absence of above predicates Bosniak categorisation, now typically via CT
Logitudinal studies in adults and children show enlargement in 20-25% of cases on follow-up

Acquired cystic disease of the kidney (ARCD)

Association with ESRF first described by Dunnill 1977
Prevalence 28-47% in patients with ESRF (post-mortem), increasing with age
More common in pts with tubulointerstitial disease; uncommon in DM
Cysts accumulate on dialysis (either HD or peritoneal); usually improve with transplantation, although the risk of cancer persists
Typically located at corticomedullary juction – always in continuity with tubule, unlike genetic renal cystic disease
Pathogenesis unknown: theories = occlusive, toxic, hormonal, immune, growth factor and ischaemia. May induce ectopic luminal position of Na+/K+ ATPase
No specific number for diagnosis – typically 4 or more encompassing at leat 25% of renal mass, unilaterally or bilaterally
Associated increased risk of renal adenoma and renal cell carcinoma. Risk of renal cell carcinoma:

General popn.	1.3/1000
Renal insufficiency	1.5/1000
ESRF	6.0/1000
Kidneys with cysts	23/1000
ESRF with ARCD	46/1000

Visible haematuria complicates ~50% patients with ARCD
Surveillance for renal tumours controversial (5 yr survival low; mRCC = 2% deaths, compared with high background death rates on dialysis anyway).USS scanning at diagnosis of ESRD and q. 3 yrs reasonable option. No surveillance policy in UK however.

Cystic nephroma

AKA multiloculated cystic nephroma
Benign tumour
Bimodal age distribution: 2-3 yrs; 30-50 yrs
Commoner in male children and adult females

Macro: well circumscribed, encapsulated, multiloculated with intervening septa
Micro: cuboidal cells lining cysts with hobnail appearance
Asymptomatic in kids; haematuria, pain, hypertension in adults
Virtually all have appearances of Bosniak III/IV cysts on imaging – therefore usually post-surgery finding. May be suspected by finding of curvilinear calcification and herniation into renal pelvis
If suspected on imaging - partial OK in adults; radical nephrectomy in kids as differentiation from cystic Wilm's tumour difficult

Calyceal diverticulum
First described by Rayer in 1841
Incidence 5:1000 (IVUs)
Typically located adjacent to upper pole calyx
Differentiated from cyst by lining of transitional epithelium, separated from calyx by narrow neck
Management
- Asymptomatic – no treatment
- Symptomatic
  - (i) PCNL and ablation of lining
  - (ii) Endoscopic retrograde laser infundibulotomy and stone removal
  - (iii) Laparoscopic excision/marsupialisation
  - (iv) Open partial nephrectomy