PATHOLOGY of CYSTIC KIDNEY DISEASE

Cystic Disease	Etiology	Pathophysiology	Lab Findings, Histology, Diagnosis	Natural History Treatment
AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD) (Type 1)	**Mutation in *PDK1* (Polycystin-1)** Membrane-bound receptor involved in cellular adhesion (epithelial tight junction) Requires Loss of Heterozygosity Constitutes 85% of ADPKD patients	Increased apoptosis of normal parenchyma + proliferation of cyst epithelium → budding and annexing of cyst separation from nephron → involution and reversal of polarity → enlargement Cystic epithelium → secretion of cytokines → interstitial fibrosis Decreased concentrating power Increased renin secretion → hypertension Increased EPO secretion →polycythemia **Renal Anomalies** Flank and back pain Early satiety, GI distress IVC compression → lower extremity edema Pyelonephritis + infection of cystic space Hematuria due to cyst rupture or hemorrhage of renal vessels Nephrolithiasis **Extrarenal Anomalies** Cerebral aneurysm → subarachnoid hemorrhage Massive hepatic cysts Typically not associated with portal HTN or hepatic failure Pancreatic and splenic cysts Mitral valvulopathy Inguinal hernia	**Urinalysis** Early: no changes Progression: microhematuria, subnephrotic proteinuria, increased serum BUN and creatinine, anemia OR polycythemia **Diagnosis** The gold standard is kidney U/S With positive FHx: NOT CARRIER if 0 cysts and <20 yrs R/O Dx if 0 cysts and > 30 yrs Any count and < 18 yrs 2+ total cysts and < 18 – 30 yrs 2+ cysts/kidney and 30 – 59 yrs 4+ cysts/kindey and > 60 yrs Genetic screening	Typically an aggressive disease Mean age to ESRD: 53 years **Treatment** Manage symptoms Maintain BP < 130/80 ACEIs, ARBs, CCBs Diuretics (use sparingly) Avoid renal trauma (e.g. sports) Chronic pain management (do not use NSAIDS!) Dialysis Transplantation (V2 receptor antagonist) (Smoking cessation) **RFs for rapid progression** Male gender *PKD1* mutation UTI Nephrotoxic drug therapy Hypertension
AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD) (Type 2)	**Mutation in *PDK2* (Polycystin-2)** Transmembrane Ca2+ channel, involved in nuclear signaling Requires Loss of Heterozygosity Constitutes 15% of ADPKD patients			Typically a more indolent disease Mean age to ESRD: 69 years

AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE (ARPDK)	**Mutation in** *PKHD1* **(Fibrocystin/Polydyctin)** Large tansmembrane protein; mutation results in loss of intracellular signaling (C-terminal) Dz presents in early infancy	Formation of small cysts in DCT and CD → budding without separation → **fusiform dilation of the CD** **Renal Anomalies** Rapid progression to ESRD **Hepatic Anomalies** Bile duct fibrosis, dilation, and hyperplasia Periportal fibrosis Hepatic cysts Portal HTN without hepatic failure **Pulmonary Hypoplasia**	**Diagnosis** Antenatal U/S with polyhydramnios or oligohydramnios Postnatal U/S: enlarged kidneys with multiple cysts	**Treatment** Maintain BP < 130/80 ACEIs, ARBs, CCBs Sparse diuretic use Hypokalemia can enlarge cysts Tx UTI Tx vesicoureteral reflux Screen renal osteodystrophy EPO Recombinant GH Dialysis Transplantation
NEPHRONOPHTHISIS (NPH)	Inheritance is AR *NPH1* **(Nephrocystin-1)** Juvenile NPH Protein is involved in cell-maxtrix adhesion 85% of NPH *NPH2* **(Inversin)** Infantile NPH Results in rapid decline to renal failure *NPH3***(No known gene product)** ESRD at ~ 19 yrs	Renal cysts are typically small Located in **medulla** and **corticomedullary junction**. Salt wasting Growth stunting Anemia Polyuria **Extrarenal involvement is common**	**Diagnosis** Clinical Hx U/S: small kidneys bilaterally, cysts restricted to subcortical regions	**Common features of NPH and MCKD** *Inherited* *Progress ESRD* (at different ages) *Polyuria* (loss of concentrating power) *Bilateral medullary cysts* **Treatment** Dialysis Transplantation NPH Mean age to ESRD is 13 years MCKD Mean age to ESRD is 20 – 60 years
MEDULLARY CYSTIC KIDNEY DISEASE (MCKD)	Inheritance is AD The mutated locus is unknown	*Presents with nonspecific elevation of serum creatinine* Hypertension Hyperuricemia and gout	**Diagnosis** Clinical Hx U/S: small kidneys bilaterally, cysts restricted to medulla Bx: meduallry cysts + interstitial nephritis, NO thickening of the tubular basement membrane Genetic Screening (Type 2 only)	

MEDULLARY SPONGE KIDNEY (MSK)	A Benign Cystic Disease	Cystic dilation of medulary CD and piricalyceal sinus Typically asymptomatic **Sequelae of MSK** Nephrolithiasis Hematuria UTI Polyuria due to diminished medullary gradient	Highly variable cyst size Diffuse + bilateral distribution The renal parenchyma is NOT sponge-like **Diagnosis** Incidental IV pelography Renal U/S, CT	Mixed inherited and acquired dz (some evidence for AD pattern) DOES not progress to ESRD
TUBEROUS SCLEROSIS	Inheritance is AD Most incidence of Dz is due to *de novo* mutations *Hamartin* and *Tuberin* Regulate cell differentiation and proliferation	A neurocutanous disease with widespread deposition of hamartomas ('tubers') Commonly affects skin (adenoma sebaceum), kidneys, and CNS **Renal Anomalies** *Angiomyolipomas* Bilateral and abundant. Small tumors are asymptomatic. At > 4 cm, increased risk of hemorrhage and hematuria *Benign Cysts* *Renin-dependent hypertension* *CKD* *Renal Cell Carcinoma* (rare) **Presentation** Seizures, MR Adenoma Sebaceum	**Diagnosis** Requires 2 Maj or 1 Maj + 2 Min criteria **Major** Facial angiofibromas (adenoma sebaceum) Cortical tuber Renal angiomyolipoma Subependymal nodule (may be fiant cell astrocytoma) **Minor** Multiple renal cysts Nonrenal hamartoma Bone cysts Hamartomatous rectal polyps Gingival fibroma	**Treatment** Surgical resection Control BP Monitor renal function Annual CT and U/S Progressive disease with variable penetrance and expression Mortality is due to CNS neoplasm and ESRD Mortality is 25% at 10 yrs
Von HIPPEL-LINDAU SYNDROME (VHL)	Inheritance is AD Affects a **tumor suppressor gene** Clinical disease requires Loss of Hetrozygosity (similar to ADPKD)	Widespread distribution of cysts with potential for malignant transformation	**Diagnosis** +FHx CT, MRI, U/S to detect primaries	**Renal-sparing surgery:** Partial nephrectomy Radiofrequency ablation

		CNS and retinal hemangioblastoma **Pheochromocytoma** **Renal Cysts** (premalignant) **Clear-Cell Renal Carcinoma** (causes most mortality)		A progressive disease with average survival ~ 50 years