The ABCs of ADPKD: Management of Polycystic Kidney Disease in Primary Care

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Learning Objectives

- By the end of this didactic, the NP Resident will be able to:
  - Discuss the incidence and prevalence of autosomal dominant polycystic kidney disease (ADPKD) and its relevance in primary care.
  - Discuss the pathophysiology of ADPKD.
  - Discuss diagnosis of ADPKD in the primary care setting.
  - Review key components of managing ADPKD in the primary care setting, including determining the risk of disease progression, the role of genetic testing, hypertension management, and the role of specialty referral.
  - Discuss acute and chronic management considerations in ADPKD.

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What is ADPKD

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

- Most common inherited kidney disease
- 5% of ESKD cases in the US
- Affects 1:1000 live births
- Affects all ethnicities and genders
- Systemic disorder affecting multiple organ systems with a multitude of renal and extrarenal manifestations
- Gradual cystic enlargement of both kidneys ultimately resulting in kidney failure

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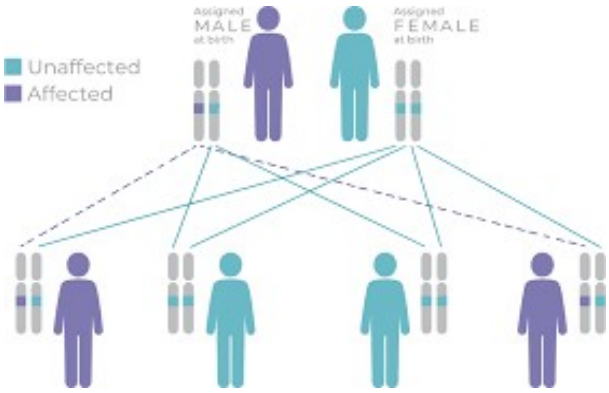
Pathophysiology of ADPKD

Primarily caused by genetic mutations in *PKD1* or *PKD2*
- Code for proteins polycystin 1 and polycystin 2, respectively
- Results in cystogenesis

Cystogenesis begins in utero

Autosomal dominant
- Each child of an affected parent has a 50% chance of inheriting PKD as well
- Infrafamilial variability exists
- De novo mutations can occur



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Pathophysiology of ADPKD

PKD1 mutation
- 85% of cases
- ESKD by 5th decade
- Truncating: bigger kidneys, more complications, most rapid progression
- Non-truncating: milder disease, less rapid progression
  - Polycystin 1 is not entirely inactivated

PKD2 mutation
- 15% of cases
- ESKD by 7th decade
- Milder disease, less complications, later onset
  - Often detected later in life

Rarely, a mutation in *GANAB* can be pathogenic for ADPKD

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Pathophysiology of ADPKD

Epithelial-lined, fluid-filled cysts grow in or on the kidney

- Results in obstructive nephropathy
- Slow, gradual, and massive bilateral kidney enlargement
- Kidneys can become up to 20x normal size

Labs may not show that kidneys are getting bigger

- Require imaging for diagnosis
- Kidney size is a predictor of disease progression
  - Patients with bigger kidneys are more likely to experience more rapid loss of kidney function than patients with smaller kidneys

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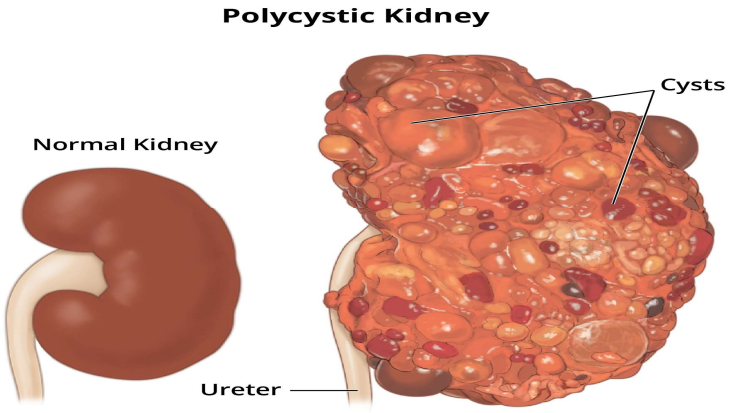
Pathophysiology of ADPKD



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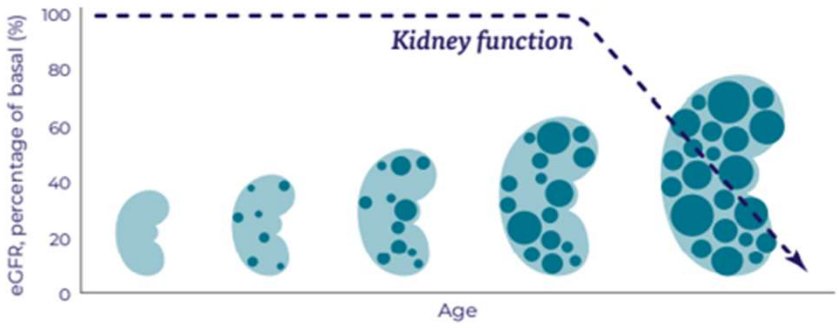
Pathophysiology of ADPKD



Adapted from Grantham JJ, et al. *Nat Rev Nephrol.* 2011;7(10):556-566

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Diagnosing ADPKD

Diagnosis is not always obvious

- Incidental finding
- Lab values do not reflect kidney dysfunction
- Symptoms are not often present
  - Vague
  - Attributable to extrarenal manifestations
- *PKD1* typically present with more symptoms at an earlier age

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Diagnosing ADPKD

Clinical presentation

- Hypertension
- Hematuria
- Urinary tract infection
- Proteinuria
- Back or flank pain
- Kidney stones
- Headaches

Most commonly diagnosed in asymptomatic patients with a positive family history, in an evaluation for secondary hypertension, or as an incidental finding for another concern

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Diagnosing ADPKD

Relevant family history

- Family members affected
- Degree of relation
- Age of onset of ESKD
- Genetic mutation, if available
- Cause of death, if applicable

Prediction of mutation

- *PKD1:* at least one family member who developed ESKD before age 55 years
- *PKD2:* at least one family member who reached age 70 years without ESKD

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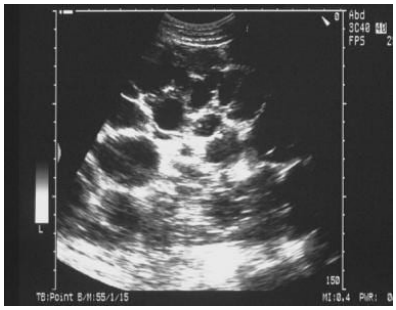
Diagnosing ADPKD



With family history
- Asymptomatic
  - Baseline ultrasound
  - +/- genetic testing
  - If positive, baseline CT or MRI
- Typical findings
  - Baseline CT or MRI

Without family history
- No established imaging-based criteria for diagnosis
- Baseline ultrasound
- Genetic testing

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Diagnosing ADPKD

WITH FAMILY HISTORY

US Criteria for Diagnosis	
Age	# Cysts
15-29	>/= 3 cysts unilaterally or bilaterally
30-39	
40-59	>/= 2 cysts in each kidney
>/= 60	>/= 4 cysts in each kidney

WITHOUT FAMILY HISTORY

>/= 10 cysts each kidney Simple cysts increase with age		
Age	% with Unilateral Cysts	% with Bilateral Cysts
15-29	0	0
30-49	1.7	1
50-69	11.5	4
>/= 70	22.1	9

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Clinical Case Scenario: Amelia

31-year-old AFAB (she/her) with an unremarkable medical history presents to the clinic for blood in her urine for the past three days after a ski trip, she reports multiple falls but did not sustain any injuries

She is not on any medications
- IUD in place

She has a family history of ADPKD
- Father: ESKD at age 49
- Pat. grandmother: ESKD in her 50s

Evaluation
- Exam
  - Well-appearing, no distress
  - No CVA tenderness
  - No palpable cysts on kidneys
  - BP 148/94, P 68
  - Wt 139 lb (63 kg), Ht 5'5" (1.68 m)
- Labs
  - Creatinine 1.1 mg/dL
  - eGFR 69 ml/min
  - Urinalysis, + blood and + protein
- Imaging
  - Renal US: diffuse bilateral cysts

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What Next?

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Next Steps

Hypertension management

Role of genetic testing

Determining risk of progression

Specialty referral

Treatment with tolvaptan

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Hypertension Management

Average onset 30 years

Degree of HTN varies

Role of renin
- Byproduct of cystogenesis
- Epithelial lining of cysts
- Cyst fluid

Role of RAAS inhibition

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Hypertension Management

Treatment options
- Nonpharmacological interventions
  - Nutrition
- ACEI or ARB
- Subsequent therapies
- Avoidance of diuretics

Target BP
- < 130/80 vs < 110/75

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Role of Genetic Testing

Critical aspect of patient counseling

Not widely used in the US

Considerations for testing:
- Understanding of genetic testing
- Consequences of results
- Comfort discussing results
- Access to professional genetic counselors

Draws attention to the need for increased education for providers in genetic testing and analysis of results

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Clinical Case Scenario

Amelia had genetic testing done and underwent counseling with a trained genetic counselor

Found to have a truncating *PKD1* mutation

Use this information to determine her risk of progression using the PROPKD score

PROPKD Scoring System			
1 point	Male gender		
2 points	HTN before age 35		
2 points	Urological event before age 35		
0 points	*PKD2* mutation		
2 points	Non-truncating *PKD1* mutation		
4 points	Truncating *PKD1* mutation		
Risk of Progression to ESKD	0-3 Low Risk	4-6 Intermediate Risk	7-9 High Risk

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Clinical Case Scenario

Amelia's PROPKD Score = 8 points			
1 point	Male gender		
2 points	**HTN before age 35**		
2 points	**Urological event before age 35**		
0 points	*PKD2* mutation		
2 points	Non-truncating *PKD1* mutation		
4 points	**Truncating *PKD1* mutation**		
Risk of Progression to ESKD	0-3 Low Risk	4-6 Intermediate Risk	**7-9 High Risk**

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Determining Risk of Progression

Critical aspect of managing ADPKD
- This needs to start in the primary care setting for patients to have the best outcomes possible!

Characteristics associated with more rapid disease progression
- Genetic factors
- Kidney size
- Hypertension
- Early onset of symptoms
- Male gender
- Proteinuria

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Determining Risk of Progression

Renal ultrasound is diagnostic of ADPKD
- Follow up with CT or MRI

Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP)
- Kidney volume as an FDA-approved prognostic biomarker
  - Higher kidney volume = higher risk for progression
- Foundation of ADPKD management
  - Only one FDA-approved pharmacological therapy
  - Individual at high risk for progression

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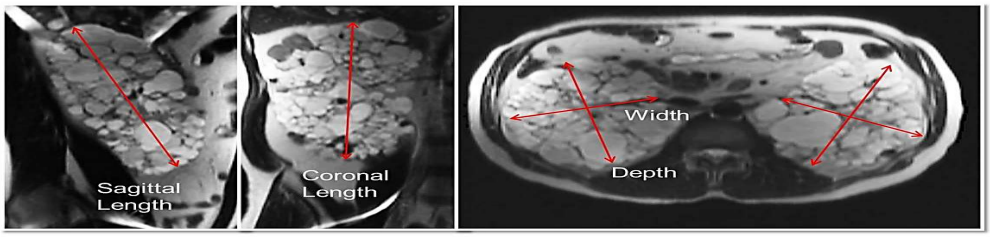
Determining Risk of Progression



Kidney Volume Calculator based on Ellipsoid equation (π/6xLxWxD) from MRI or CT image			
Required Data Entry			
Right Kidney		**Left Kidney**	
Sagittal Length (mm)		Sagittal Length (mm)	
Coronal Length (mm)		Coronal Length (mm)	
Width (mm)		Width (mm)	
Depth (mm)		Depth (mm)	
Calculated Results			
Right Kidney Volume (mL)		**Left Kidney Volume (mL)**	
		Total Kidney Volume (mL)	
Clear All		Calculate Volumes	

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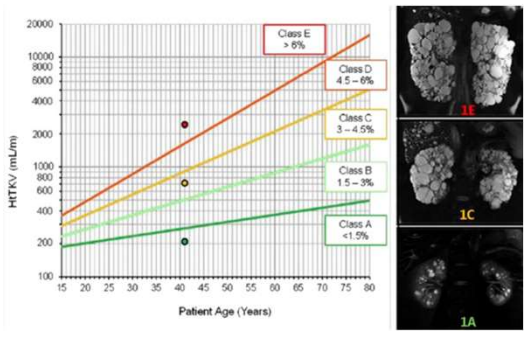
Determining Risk Progression



Estimated eGFR decline in mL/min per year		
	AMAB	AFAB
Class 1A	-0.23	0.03
Class 1B	-1.33	-1.13
Class 1C	-2.36	-2.43
Class 1D	-3.48	-3.29
Class 1E	-4.78	-4.59

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Treatment With Tolvaptan

Two branded formulations: Jynarque vs Samsca
- Jynarque=approved to reduce rate of progression of ADPKD
- Samsca=approved to treat hyponatremia

Selectively inhibits binding of vasopressin at V2 receptor sites in the kidney
- Vasopressin plays a role in cyst growth
- Decreases cell proliferation and fluid secretion in cysts

TEMPO 3:4 and REPRISE studies
- Use of tolvaptan in individuals with ADPKD can result in ~1 ml/min difference in eGFR decline compared to placebo

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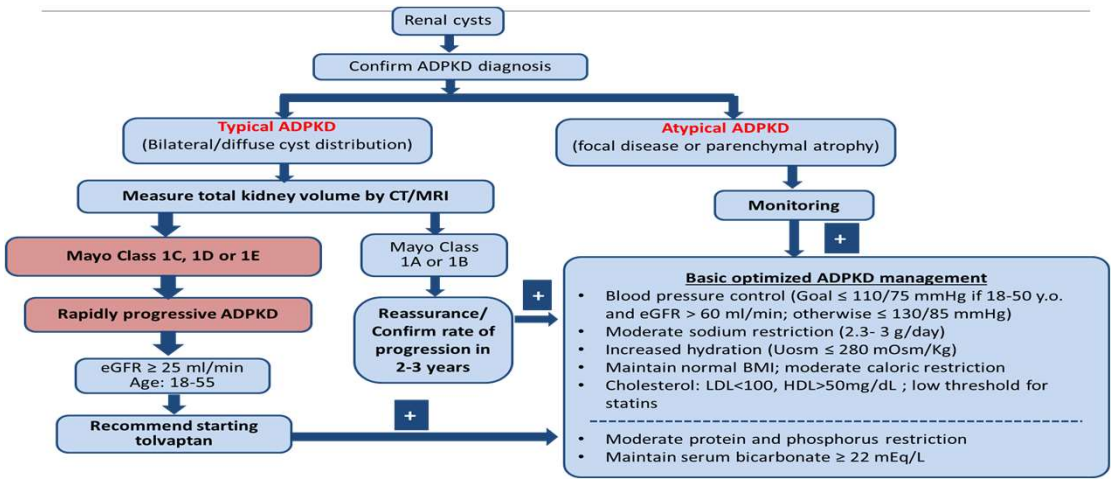
Treatment With Tolvaptan



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Treatment with Tolvaptan

Hepatotoxicity
- 4.9% of patients experienced mild liver injury
- 0.2% of patients experienced serious liver injury

Can only be prescribed by certified prescribers

Can only be dispensed by certified pharmacies

Patient status forms required regularly to monitor safety of therapy

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Clinical Case Scenario

You order a follow up MRI to determine TKV and the radiologist provides the dimensions for you to enter in the Mayo calculator
- TKV=1884 ml
- htTKV=112.4 ml/m
- You use the second stage of the calculator to determine her classification

Is Amelia at high risk for disease progression?

Does she qualify for treatment with tolvaptan?

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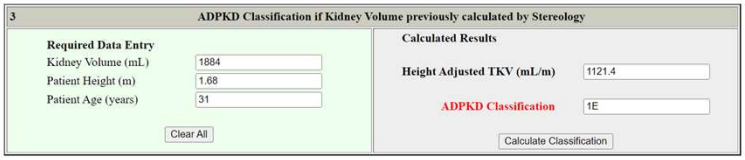
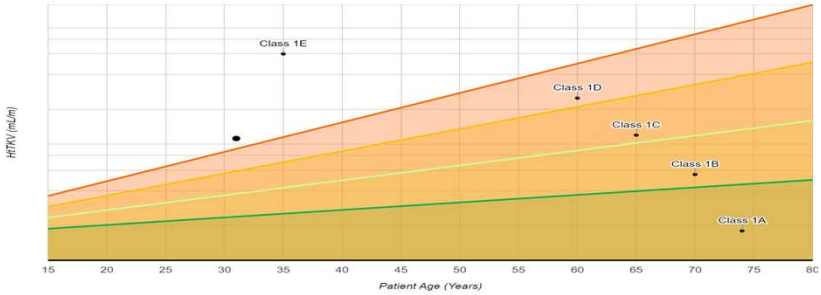
Clinical Case Scenario





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Clinical Case Scenario

Amelia is started on tolvaptan 45 mg/15 mg by her nephrologist

What do you need to know as the PCP?

- REMS protocol
- Changes in labs
- Management of aquaretic effects
  - Polydipsia, polyuria, nocturia
- Travel or sick day management
- Medication interactions

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Specialty Referral

Management of ADPKD may require a full team and each member plays an important role

- Primary care
- Nephrology
  - Consider PKD Foundation Centers of Excellence or Partners in Care
- Hepatology
- Radiology
- Urology
- Mental health specialists
- Neurosurgeons
- Transplant team
- Genetic counselors
- Dietitians

…and so many more!

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Acute and Chronic Management Issues

Planning for progression of CKD

Family planning considerations

Evaluation of acute and chronic pain

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Planning for Progression of CKD

ADPKD is progressive and irreversible

Cystogenesis will result in eventual chronic kidney disease (CKD)

Need to follow normal sequelae of CKD
- Anemia, acidosis, mineral-bone disease, hypertension
- Cardiovascular disease

Planning for eventual ESKD
- Transplant referral
- Dialysis planning
- Palliative care

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Family Planning Considerations

ADPKD is autosomal dominant
- 50% chance each offspring of an affected parent will inherit the mutation

Closely intertwined with fertility
- AMAB: may be prone to infertility
- AFAB: exposure to exogenous estrogen and progesterone may exacerbate cystogenesis
  - Avoid oral contraceptive use

Family planning should be offered to all
- Role for in vitro fertilization with preimplantation genetic diagnosis

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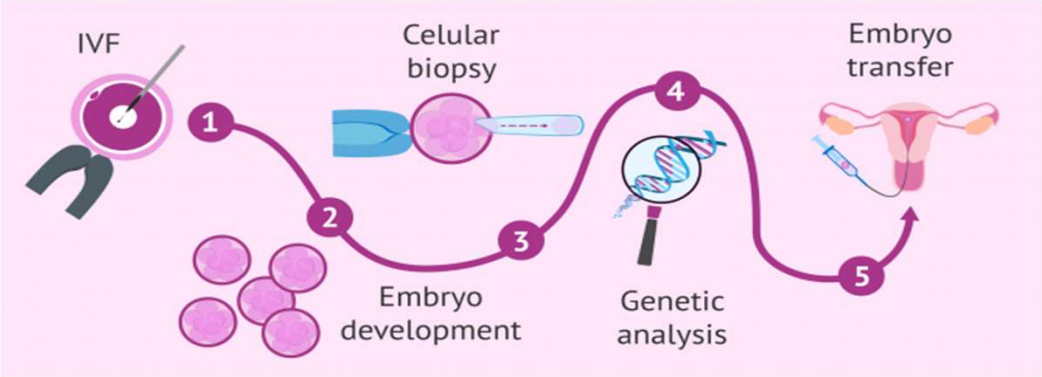
Family Planning Considerations



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Evaluation of Pain

ACUTE PAIN	CHRONIC PAIN
Cyst hemorrhage ◦ Sudden onset of sharp, localized pain ◦ Gross hematuria +/- clots	Daily episodes for more than 4-6 weeks ◦ Often starts as acute episode
UTI/pyelonephritis	Anterior abdomen > back
Nephrolithiasis ◦ 20% incidence in ADPKD	May not correlate with largest cysts ◦ Consider role for cyst aspiration
Headaches ◦ Consider cerebral aneurysm	Early satiety

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Conclusion

ADPKD is a rare condition that is often an incidental diagnosis in the primary care setting

You can play a pivotal role in ensuring optimal care for ADPKD in primary care

- Diagnosis
- Determine risk of rapid progression
- Consider use of genetic testing
- Hypertension management and routine CKD care

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