Urinary tract infection. Interstitial nephritis. Tubulopathies. Polycystic kidney disease.

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Epidemiology

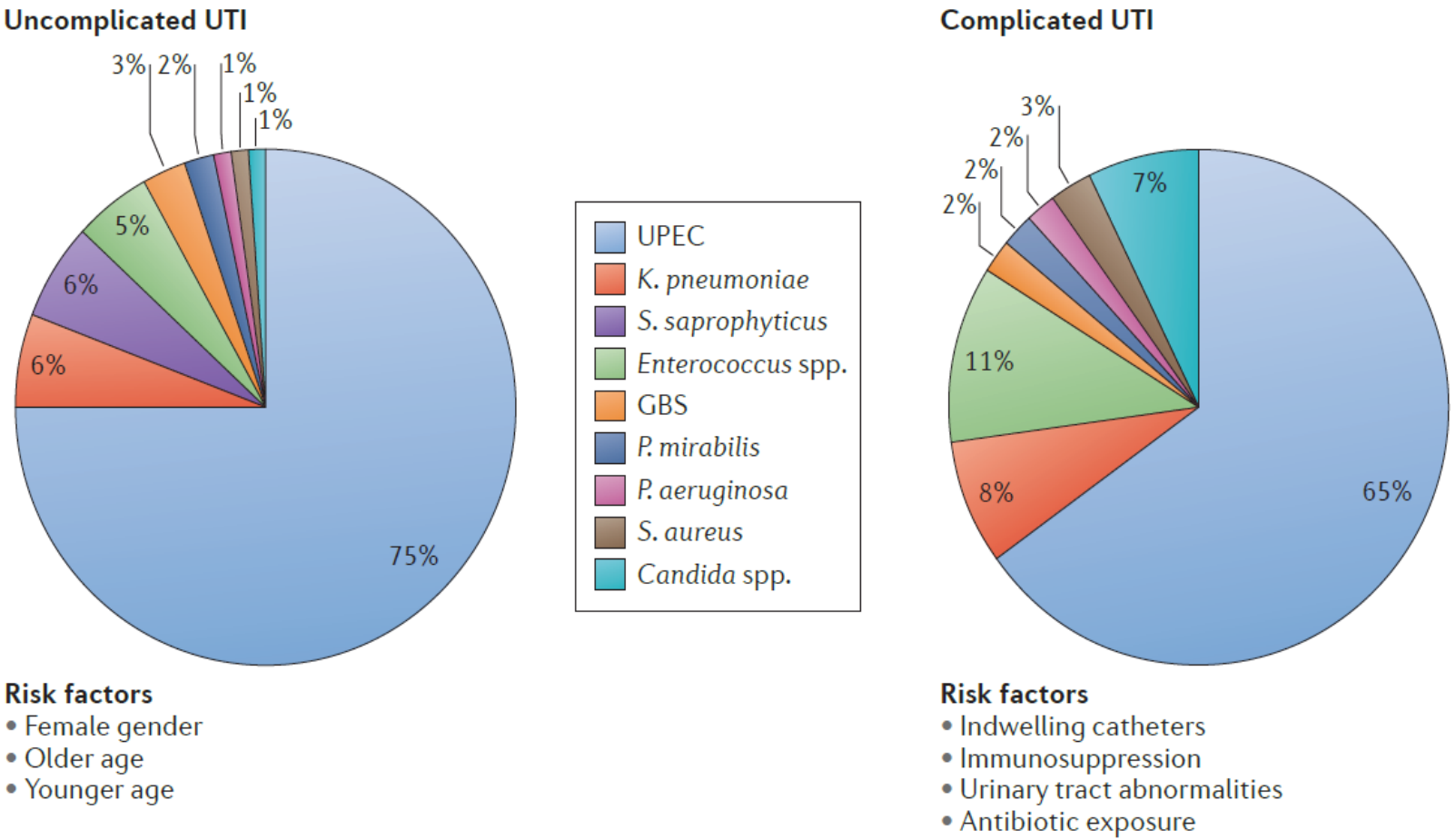
- **Urinary tract infections are the most common bacterial infections, affecting 150 million people each year worldwide**
- **Among sexually active young women, the incidence of symptomatic urinary tract infection is high;**

  0.5 to 0.7 UTIs per person-year
- **Acute cystitis- 0.07 episodes per person per year**
- **Annual incidence of acute pyelonephritis - 12 to 13 cases per 10,000 women**

Urinary tract infections

- **Uncomplicated UTI- healthy nonpregnant adults**
- **A complicated urinary tract infection, whether localized to the lower or upper tract, associated with an underlying condition that increases the risk of failing therapy:**
  - **Diabetes**
  - **Pregnancy**
  - **Hospital acquired infection**
  - **Renal failure**
  - **Urinary tract obstruction (urolithiasis, malignacies, ureteral or urethral strictures, bladder diverticula, renal cysts, fistulas, ileal conduits)**
  - **Presence of an indwelling urethral catheter, stent, nephrostomy tube or urinary diversion**
  - **Functional or anatomic abnormality of the urinary tract (neurogenic bladder, vesicoureteral reflux)**
  - **Renal transplantation**
  - **Immunosuppression**

Microbiology



Risk factors
- Female gender
- Older age
- Younger age

Risk factors
- Indwelling catheters
- Immunosuppression
- Urinary tract abnormalities
- Antibiotic exposure

Microbiology

- **For uncomplicated UTIs (in order of prevalence) *Escherica coli*, *Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterococcus faecalis, group B Streptococcus (GBS), Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus and Candida spp*.**
- **For complicated UTIs, (in order of prevalence) *Escherica coli, Enterococcus spp., K. pneumoniae, Candida spp.,S. aureus, P. mirabilis, P. aeruginosa and GBS.***

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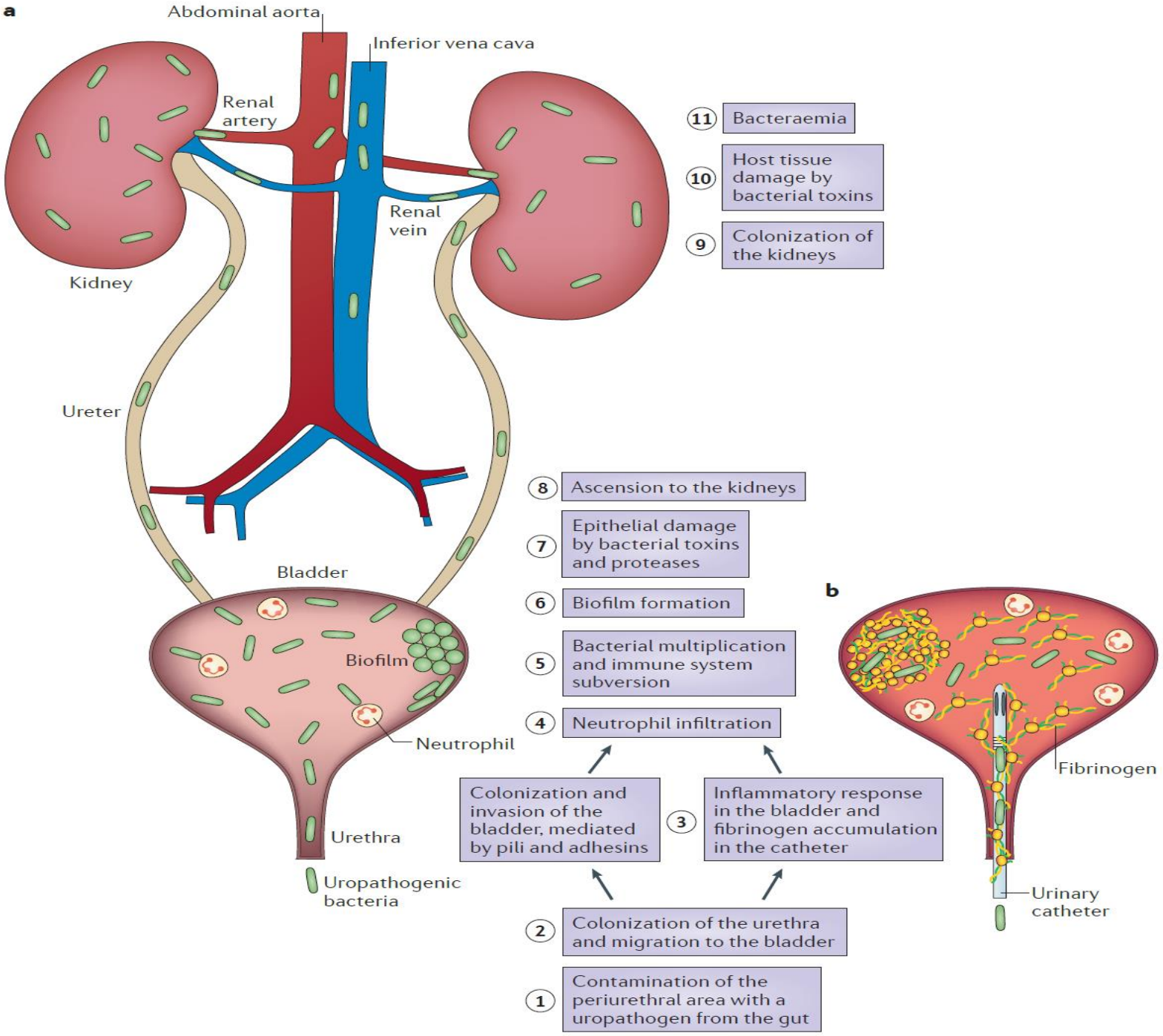
Risk factors for UTI

- female gender
- prior UTI
- sexual activity
- vaginal infection
- diabetes,
- obesity
- genetic susceptibility

Table 1 | **Classification of UTIs, symptoms, host risk factors and treatment**

Parameter	Cystitis (bladder infection)	Pyelonephritis (kidney infection)
Classification	Uncomplicated UTI; complicated UTI	Complicated UTI
Symptoms	Painful urination (dysuria); urinary frequency; urinary urgency; suprapubic pain; bloody urine (haematuria)	Fever; flank pain; costovertebral angle tenderness
Host risk factors	Individual UTI history; family history; sexual activity; new sexual partner; postmenopausal age; vaginal dysbiosis; recent antibiotic use	Individual UTI history; family history; sexual activity; new sexual partner; postmenopausal age; vaginal dysbiosis; recent antibiotic use; anatomic urogenital abnormalities; vesicoureteral reflux; diabetes mellitus; pregnancy; catheterization; urolithiasis; immunosuppression; history of pyelonephritis
Diagnosis	Positive urine culture; pyuria; haematuria[b]	Positive urine culture; pyuria; haematuria[b]
Treatment (low MDR risk)[a]	Empiric treatment with nitrofurantoin or fosfomycin	Treatment with ciprofloxacin or levofloxacin
Treatment (high MDR risk)[a]	Treatment with oral β-lactams and fluoroquinolones until culture sensitivity results are acquired	Treatment with ceftriaxone or ertapenem and trimethoprim–sulfamethoxazole, amoxicillin–clavulanic acid or a third-generation cephalosporin

Pathogenesis


a
Abdominal aorta
Inferior vena cava
Renal artery
Renal vein
Kidney
Ureter
Bladder
Biofilm
Neutrophil
Urethra
Uropathogenic bacteria
11 Bacteraemia
10 Host tissue damage by bacterial toxins
9 Colonization of the kidneys
8 Ascension to the kidneys
7 Epithelial damage by bacterial toxins and proteases
6 Biofilm formation
5 Bacterial multiplication and immune system subversion
4 Neutrophil infiltration
3
Colonization and invasion of the bladder, mediated by pili and adhesins
Inflammatory response in the bladder and fibrinogen accumulation in the catheter
2 Colonization of the urethra and migration to the bladder
1 Contamination of the periurethral area with a uropathogen from the gut
b
Fibrinogen
Urinary catheter

Uncomplicated urinary tract infections (UTIs)

- **uropathogens that reside in the gut contaminate the periurethral area (step 1) and are able to colonize the urethra.**
- **Subsequent migration to the bladder (step 2) and expression of pili and adhesins results in colonization and invasion of the superficial umbrella cells (step 3).**
- **Host inflammatory responses, including neutrophil infiltration (step 4) begin to clear extracellular bacteria. Some bacteria evade the immune system, either through host cell invasion or through morphological changes that result in resistance to neutrophils, and these bacteria undergo multiplication (step 5) and biofilm formation (step 6).**
- **These bacteria produce toxins and proteases that induce host cell damage (step 7), releasing essential nutrients that promote bacterial survival and ascension to the kidneys (step 8).**
- **Kidney colonization (step 9) results in bacterial toxin production and host tissue damage (step 10). If left untreated, UTIs can ultimately progress to bacteraemia if the pathogen crosses the tubular epithelial barrier in the kidneys (step 11).**

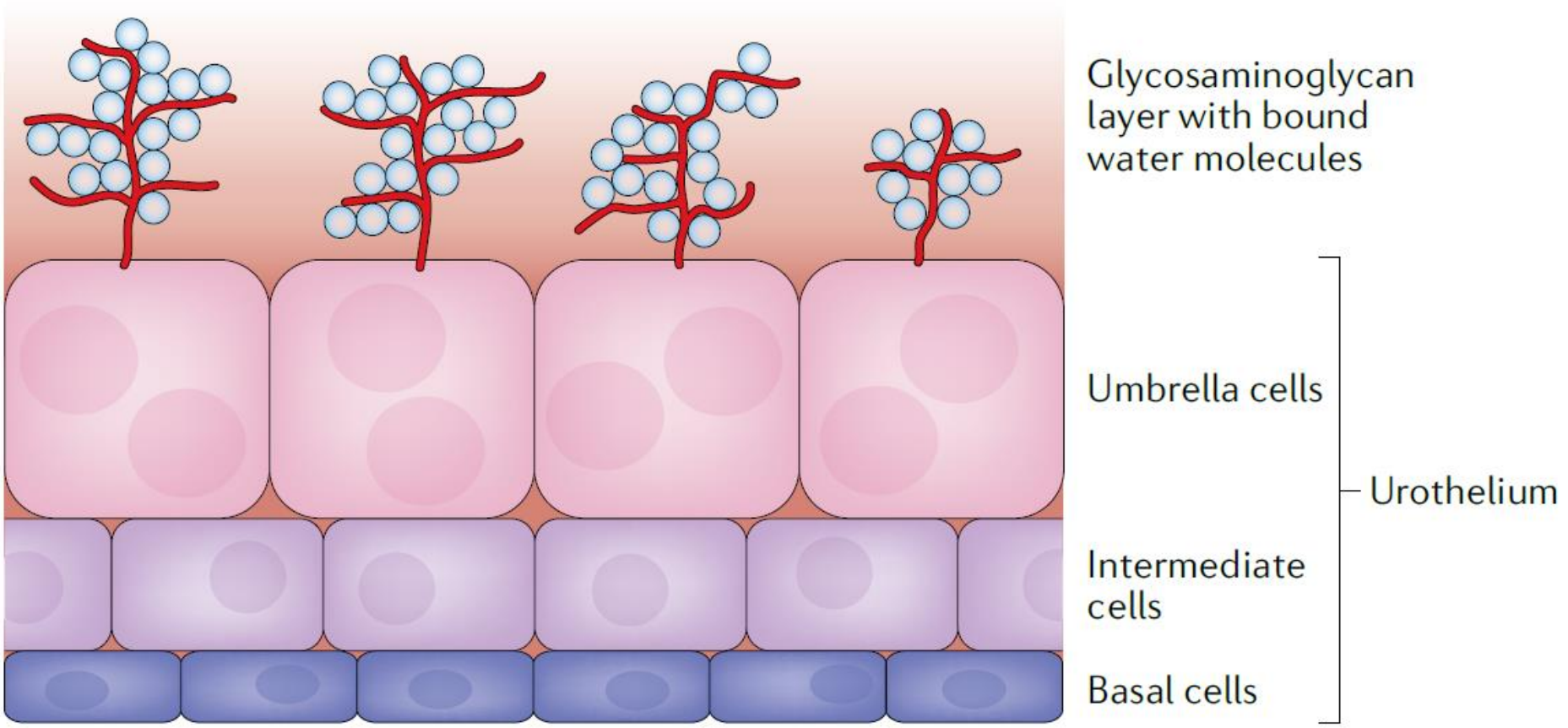


Fig. 2 | **Structure of the glycosaminoglycan layer of the bladder wall.** The

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The immune response to infection in the bladder

Livia Lacerda Mariano[1,2] *and Molly A. Ingersoll*[1,2] ✉

Key points

- The bladder contains constitutive passive defences, such as mucus and immunoglobulins, to protect it against colonization.
- Robust cytokine expression and inflammatory cell infiltration into the bladder during urinary tract infection are dependent on bacterial species and sex.
- Uropathogenic *Escherichia coli* induces a non-sterilizing adaptive immune response in the bladder.
- Uropathogenic *Escherichia coli* causes long-lasting changes in the bladder urothelium, conferring resistance or increased susceptibility to subsequent infections depending on the outcomes of the first infection.
- Vaccines and other non-antibiotic-based therapies in development might provide therapeutic relief to those suffering from recurrent or chronic urinary tract infection.

https://doi.org/10.1038/s41585-020-0350-8

Classification

Infection with a uropathogen with broad-spectrum antimicrobial resistance is also considered complicated although there are no data to suggest that such infections are more likely to fail if an antimicrobial to which the infecting pathogen is susceptible is used.

Lower urinary tract

- **Cystitis**
- **Urethritis**

Upper urinary tract

- **Acute pyelonephritis**

Clinical manifestations

- **Cystitis - dysuria, frequency, urgency, suprapubic pain, and/or hematuria. Symptoms of cystitis can be subtle in the very young and very old women**
- **Pyelonephritis- symptoms of cystitis may or may not be present together with fever (>38ºC), chills, flank pain, costovertebral angle tenderness, and nausea/vomiting.**
- **Patients with acute pyelonephritis present with sepsis- multiple organ system dysfunction, shock, and/or acute renal failure.**

Diagnosis of UTI

- **Signs and symptoms of urinary tract infections supported by laboratory evidence of pyuria and/or bacteriuria**
  - **Urinalysis (either by microscopy or by dipstick)**
  - **Urine culture with susceptibility data**

In healthy ambulatory women, laboratory evaluation is not necessary to make the diagnosis of uncomplicated cystitis

Diagnosis

- **Pyuria is the most valuable laboratory diagnostic test for UTI**
- **The most accurate method for assessing pyuria is to examine an unspun voided midstream urine specimen with a hemocytometer; an abnormal result is ≥10 leukocytes/microL**
- **Hematuria is common in the setting of UTI**
- **Dipsticks are commercially available strips that detect the presence of leukocyte esterase (an enzyme released by leukocytes, reflecting pyuria) and nitrite (reflecting the presence of Enterobacteriaceae, which convert urinary nitrate to nitrite). Dipsticks are generally performed whenever UTI is suspected**
- **Leukocyte esterase may be used to detect >10 leukocytes per high power field (sensitivity of 75 to 96 percent; specificity of 94 to 98 percent)**

Diagnosis

- **Negative nitrite test despite the presence of bladder bacteriuria include insufficient bladder incubation time for conversion of nitrate to nitrite, low urinary excretion of nitrate, inability of some organisms to convert nitrate to nitrite (*Enterococcus faecalis* S.saprophyticus, Acinetobacter, Candida), and decreased urine pH (due to cranberry juice or other dietary supplements**).
- **Urine dipstick test alone is useful when both nitrite and leukocyte esterase tests are positive (sensitivity 68 to 88 percent)**
- **Dipstick results can modestly improve diagnosis, but cannot adequately rule out infection**
- **In truly infected patients, a significant number of leukocytes (>10/microL or 10,000/mL) should generally be present. Absence of pyuria on microscopic assessment can suggest colonization instead of infection when there is bacteriuria**
- **Bacteriuria and pyuria does not necessarily signify infection, particularly if there are no symptoms.**

Diagnosis

- **Sterile pyuria**
  - **Contamination of the urine sample with vaginal leukocytes from vaginal secretions**
  - **Chronic interstitial nephritis**
  - **Nephrolithiasis**
  - **Uroepithelial tumor**
  - **Painful bladder syndrome/interstitial cystitis**
  - **Intra-abdominal inflammatory process adjacent to the bladder**
  - **Infection with atypical organisms, such as *Chlamydia*, *Ureaplasma urealyticum*, or tuberculosis**
  - **Autoimmune diseses: SLE, ANCA vasculitis**

Urine culture

- **Indications for urine culture**
  - **to confirm the presence of bacteriuria and to identify and provide antibiotic susceptibility information on the causative organism**
  - **Culture of a clean-catch voided urine specimen**
  - **except for healthy non-pregnant young women with typical symptoms of non-febrile cystitis (uncomplicated UTI)**

Diagnosis

Because of the difficulty in obtaining uncontaminated voided midstream urine specimens, quantitative thresholds have been established to distinguish bladder bacteriuria from urethral contamination

- **Suprapubic aspiration → any number**
- **Acute cystitis in nonprgnant young women: $10^3 \geq$ CFU/ml**
- **UTI in men: $\geq 10^3$ CFU/ml**
- **Acute pyelonephritis in women: $\geq 10^4$ CFU/ml**
- **Complicated UTI: $\geq 10^5$ CFU/ml**
- **Recurrent, noncomplicated UTI in women: $\geq 10^5$ CFU/ml**
- **Patients with UTI symptoms, with indwelling bladder catheters: $\geq 10^3$ CFU/ml**
- **Asymptomatic bacteriuria in patients with indwelling bladder catheters $\geq 10^5$ CFU/ml**
- **Asymptomatic bacteriuria without indwelling bladder catheters:**
  - **Women $\geq 10^5$ CFU/ml – two positive cultures**
  - **Men $\geq 10^5$ CFU/ml – one positive culture**

Treatment

Acute uncomplicated cystitis in young women

Empiric therapy

First line therapy

- **TMP-SMX (trimethoprim + sulfamethoxazole) 960 mg (160 mg + 800 mg) orally twice daily for 3-5 days**
- **Trimethoprim 100 mg orally twice daily for 3-5 days**
- **Nitrofurantoin 100 mg orally twice daily for 5 days**
- **Furazydyna 100 mg orally three times daily for 5 days**
- **Fosfomycin 3 grams single dose**

In empiric therapy there is restriction for use fluoroquinolones for uncomplicated infections

Acute uncomplicated cystitis in young women

Second line therapy

- amoxicillin-clavulanate 625 mg twice daily for 3-7 days
- ciprofloxacin 250 mg twice daily for 3 days
- ofloxacin 200 mg twice daily for 3 days
- levofloxacin 250 mg once daily for 3 days

Recurrent UTI

- **Recurrent UTI- ≥2 infections in six months or ≥3 infections in one year. Recurrent UTIs -young, healthy women with anatomically and physiologically normal urinary tracts**
- **Reinfection- recurrence is caused by a different strain of microorganism than the one responsible for the original infection.**
- **Relapse-infecting strain is the same and the recurrence occurs within two weeks of the completion of treatment for the original infection.**
- **Recurrent UTI arising more than two weeks after treatment is considered to be a reinfection, even if the infecting pathogen is the same as the original. When a sterile urine culture is documented between the two UTIs in a patient off antibiotics, the recurrence is also classified as a reinfection.**
- **Recurrent cystitis- reinfection. The initially infecting strain can persist in the fecal flora after elimination from the urinary tract, subsequently recolonizing the introitus and bladder and causing recurrent UTI, most recurrences occur in the first three months after the initial infection.**

Antimicrobial prevention of recurrent cystitis

Choice of antibiotic should be based upon the susceptibility patterns of the strains causing the patient's previous UTIs

- **TMP-SMX 240 mg 1 x day or 3 x week**
- **Trimethoprim 100 mg 1 x day**
- **Nitrofurantoin 50-100 mg 1 x day**
- **furazydyna 50-100 mg 1 x day**
- **cefaklor 250 mg 1 x day**
- **cefaleksin 250 mg 1 x day**
- **norfloxacin 200 mg 1 x day**
- **fosfomycin 3,0 g every 10 days**

Bed time dose

Noantimicrobal prevention

Table 4. Strategies for Nonantimicrobial Prevention of Recurrent Acute Uncomplicated Cystitis.*

Strategy	Comments
Behavioral counseling	
Recommend abstinence or reduction in frequency of intercourse	Sexual intercourse is the strongest risk factor for uncomplicated UTIs; often this behavioral strategy is not feasible
If spermicides are used, recommend changing to another method for contraception or prevention of infection	Spermicide use, including use of spermicide-coated condoms, is a strong risk factor, especially if used with a diaphragm; spermicides alter the vaginal flora and favor the colonization of uropathogens
Recommend that patient urinate soon after intercourse, drink fluids liberally, not routinely delay urination, wipe front to back after defecation, avoid tight-fitting underwear, avoid douching	In case–control studies, none of these strategies have been shown to be associated with a reduced risk of recurrent UTIs, and none have been studied prospectively; however, it is reasonable to suggest them to the patient, since they pose a low risk and might be effective
Biologic mediators	
Cranberry juice, capsules or tablets	Biologic plausibility is based on the inhibition of uropathogen adherence to uroepithelial cells; clinical data supporting a protective effect have been limited by design flaws[40]; a recent randomized, placebo-controlled trial showed no benefit from cranberry juice[41]
Topical estrogen	In some postmenopausal women, topical estrogen normalizes the vaginal flora and reduces the risk of recurrent UTIs[42]; oral estrogens are not effective
Adhesion blockers (D-mannose, available in health-food stores and online, is occasionally used as preventive therapy)	UTIs caused by *E. coli* are initiated by adhesion of the bacteria to mannosylated receptors in the uroepithelium by means of FimH adhesin located on type 1 pili; theoretically, mannosides could block adhesion; however, D-mannose has not been evaluated in clinical trials

Cranberry

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The New England Journal of Medicine

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Inhibition of the Adherence of P-Fimbriated *Escherichia coli* to Uroepithelial-Cell Surfaces by Proanthocyanidin Extracts from Cranberries

TABLE 1 Phytochemical content of cranberry foods

Food source	Flavan-3-ol monomers and dimers (28,49)	Proanthocyanidins (28,34)	Anthocyanins (26,34)	Hydroxybenzoic acids (49,50)	Hydroxycinnamic acids (49,50)	Terpenes (51)	Flavonols (50)
Cranberry fruit							
mg/100 g	7–33	133–367	13–171	503–602	73–82	65–125	20–40
mg/serving[1]	5.6–26.4	106–293	10.4–136.8	402–482	57.6–65.6	52–100	16–32
Cranberry juice							
mg/L	6–35	89–230	27–132	64	12–19	Trace	11–58
mg/serving[2]	7	17.8–46	5.4–26.4	12.8	2.4–3.8	Trace	2.2–11.6
Canned cranberry sauce							
mg/100 g	112.8	16–54.4	0.6–11.8	476	47.5	1.1–22.8	—[5]
mg/serving[3]	78.9	11.2–38	0.4–8.3	333.2	33.2	0.8–16	—
Sweetened, dried cranberries							
mg/100 g	—	64.2	10.3	—	—	98.5	—
mg/serving[4]	—	25.6	4.1	—	—	39.4	—

[1] 80 g whole fruit.
[2] 200 mL juice.
[3] 70 g sauce.
[4] 40 g dried fruit.
[5] No data available.

Uncomplicated acute pyelonephritis

Urine culture and susceptibility testing should be performed, initial empiric therapy. Outpatient management is acceptable for patients with mild to moderate illness.

First line therapy

- **Ciprofloxacin 500 -750 mg orally twice daily for 7 – 10 days or 1000 mg once daily for 7 days**
- **Lewofloxacin 250-500 mg once daily for 7-10 days or 750 mg once daily for 5 days**

Second line therapy (beat-lactams)

- **cefpodoksym 200 mg twice daily for 10 days**
- **ceftybuten 400 mg once daily for 10 days**

Subsequent therapy should be guided by susceptibility data

- **TMP-SMX 960 mg twice daily for 14 days**
- **amoxicillin-clavulanate 625 mg three times daily for 10-14 days**

Uncomplicated UTI

Follow-up urine cultures are not needed in patients with acute cystitis or pyelonephritis whose symptoms resolve on antibiotics

Complicated UTI

- **Etiology- organisms resistant to commonly used oral antimicrobials recommended for uncomplicated cystitis.**
- **Colonization and infection with antibiotic-resistant organisms- exposure to antimicrobials or contact transfer of resistant organisms between patients because of poor infection control practices.**
- **The prevalence of drug resistance among pathogens causing complicated urinary tract infections is growing.**

Complicated UTI

- **Empiric antimicrobial therapy should be initiated promptly, taking into account previous antimicrobial use and results of recent urine cultures, with subsequent adjustment guided by antimicrobial susceptibility data.**

- **Patients with persistent clinical symptoms after 48 to 72 hours of appropriate antibiotic therapy for acute uncomplicated urinary tract infection should undergo radiologic evaluation of the upper urinary tract.**
- **In addition, radiologic evaluation is warranted for patients with pyelonephritis who are severely ill or who also have symptoms of renal colic or history of renal stones, diabetes, history of prior urologic surgery, immunosuppression, repeated episodes of pyelonephritis, or urosepsis.**
- **CT scanning is the study of choice to detect anatomic or physiologic factors associated with complicated urinary tract infection.**

Parenteral regimens for empiric tratment of complicated pyelonephritis

Antimicrobial agent	Dose, interval
Mild to moderate pyelonephritis*	
Ceftriaxone	1 g every 24 hours
Ciprofloxacin	400 mg every 12 hours
Levofloxacin	750 mg every 24 hours
Aztreonam¶	1 g every 8 to 12 hours
Severe pyelonephritis	
Cefepime	2 g every 12 hours
Piperacillin-tazobactamΔ	3.375 g every 6 hours
Ceftolozane-tazobactam	1.5 g every 8 hours
Ceftazidime-avibactam	2.5 g every 8 hours
MeropenemΔ	500 mg every 8 hours
Imipenem	500 mg every 6 hours
Doripenem	500 mg every 8 hours

Complicated pyelonephritis

- **Underlying urinary tract anatomic or functional abnormalities (such as obstruction or neurogenic bladder) should be addressed in consultation with a urologist. Antibiotics alone may not be successful unless such underlying conditions are corrected.**
- **Antibiotics are generally administered for 5 to 14 days. For patients who are treated with a fluoroquinolone and have a mild infection and quick clinical response, five days may be adequate. Longer course of therapy is indicated for patients with more severe infection, resistant organisms, or abnormal anatomy or obstruction. Depending on patient circumstances, a duration of therapy beyond 14 days may be warranted.**
- **If antimicrobial susceptibility data and clinical circumstances permit, treatment may be completed with oral therapy; acceptable agents include levoflxacin, ciprofloxacin, or TMP-SMX**

Asymptomatic bacteriuria

Isolation of a specified quantitative count of bacteria in an appropriately collected urine specimen from an individual without symptoms or signs of urinary tract infection. The quantitative thresholds are different for voided clean catch specimens and catheterized specimens. The presence of pyuria (≥10 leukocytes/mm^3 of uncentrifuged urine) is not sufficient for diagnosis of bacteriuria. Pyuria with asymptomatic bacteriuria is not indication for therapy.

Women- two consecutive clean-catch voided urine specimens with isolation of the same organism in quantitative counts of ≥10^5 cfu/mL

Men- single clean-catch voided urine specimen with isolation of a single organism in quantitative counts of ≥10^5 cfu/mL

Catheterized specimen with isolation of a single organism in quantitative counts of ≥10^5 cfu/mL

Asymptomatic bacteriuria -epidemiology

Women

- **prevalence of asymptomatic bacteriuria among healthy women increases with advancing age, from about 1 percent among schoolgirls to >20 percent among women over 80 years residing in the community, it correlates with sexual activity**
- **Pregnant and non-pregnant women have a similar prevalence (2 to 7 percent)**
- **In young healthy women, asymptomatic bacteriuria is transient; it rarely lasts longer than a few weeks.**
- **Prevalence among diabetic women is 8 to 14 percent**

Men

- **Asymptomatic bacteriuria is rare among healthy young men**
- **Among men older than 75 years residing in the community, prevalence is 6 to 15 percent**
- **Diabetic men do not appear to have a higher prevalence of bacteriuria than nondiabetic men**

Asymptomatic bacteriuria

Whom to treat

- **Pregnancy (beta-lactams,nitrofurantoin, fosfomycin) - asymptomatic bacteriuria occurs in 2 to 7 percent of pregnant women. It typically occurs during early pregnancy. Without treatment, 30 to 40 percent of pregnant women with asymptomatic bacteriuria will develop a symptomatic UTI, including pyelonephritis, risk is reduced by 70 to 80 percent if bacteriuria is eradicated. Most cases of pyelonephritis occur during the second and third trimesters. Untreated bacteriuria has been associated with an increased risk of preterm birth, low birth weight, and perinatal mortality.**
- **Urologic intervention — patients undergoing transurethral resection of the prostate and other urologic procedures in which mucosal bleeding is anticipated.**
- **Renal transplant recipients — in the first three months following transplantation?**

Asymptomatic bacteriuria

Whom not to treat

- **Nonpregnant premenopausal women,**
- **Diabetics,**
- **The elderly (in community and in health care facilities),**
- **Nursing home residents,**
- **Patients with spinal cord injury,**
- **Patients with indwelling urethral catheters,**

Treatment of asymptomatic bacteriuria does not reduce the incidence of symptomatic UTI, recurrent asymptomatic bacteriuria, complications (chronic kidney disease) or death compared with no treatment or placebo.

Avoiding treatment of asymptomatic bacteriuria is important for reducing development of antibiotic resistance.

Acute interstitial nephritis (AIN)

Acute interstitial nephritis (AIN) is a renal lesion that causes a decline in renal function and is characterized by an inflammatory infiltrate in the kidney interstitium.

- **Drugs (with antibiotics responsible for 30 to 49 percent of these cases) – 70 to 75 %**
- **Infections – 4 to 10 %**
- **Tubulointerstitial nephritis and uveitis (TINU) syndrome – 5 to 10 %**
- **Systemic disease including sarcoidosis, Sjögren's syndrome, systemic lupus erythematosus (SLE), and others – 10 to 20 %**

AIN -drugs

Any drug can cause AIN, although only a few have been reported with any frequency.

- **Nonsteroidal anti-inflammatory agents (NSAIDs), including selective cyclooxygenase (COX)-2 inhibitors**

- **Penicillins and cephalosporins**
- **Rifampin**
- **Antimicrobial sulfonamides, including trimethoprim-sulfametaxazole**
- **Diuretics, including loop diuretics such as furosemide and bumetanide, and thiazide-type diuretics**
- **Ciprofloxacin and, perhaps to a lesser degree, other quinolones**
- **Cimetidine (only rare cases have been described with other H-2 blockers)**
- **Allopurinol**
- **Proton pump inhibitors (PPIs) such as omeprazole and lansoprazole**
- **Indinavir**
- **5-aminosalicylates (eg,mesalamine)**

The development of drug-induced AIN is not dose dependent, and recurrence or exacerbation can occur with a second exposure to the same or a related drug

Clinical manifestation

Patients may present with nonspecific signs and symptoms of acute renal dysfunction. Acute or subacute onset of nausea, vomiting, and malaise, many patients are asymptomatic. Patients may be oliguric or nonoliguric. Signs and symptoms of an allergic-type reaction may be present.

- **Rash – 15 %**
- **Fever – 27 %**
- **Eosinophilia – 23 %**
- **Triad of rash, fever, and eosinophilia – 10%**

The prevalence of AIN caused by PPIs, 5-aminosalicylates, and NSAIDs often without obvious associated symptoms is increasing. Skin rash and eosinophilia are significantly less common with these drugs than in antibiotic-induced AIN.

Laboratory findings

- **Acute kidney injury (AKI) may be severe**
- **Eosinophilia and eosinophiluria**
- **A characteristic urine sediment – white cells, red cells, and white cell casts**
- **A variable degree of proteinuria – proteinuria can range from none or minimal to >1 g/day. NSAID- NEPHROTIC SYNDROME**
- **Radiographic findings – no radiographic findings that are diagnostic for AIN**

Diagnosis

A definitive diagnosis of AIN is made by renal biopsy. It is often considered unnecessary to make a definitive diagnosis, such as among patients who have clearly documented onset of renal failure after initiation of a common culprit drug and who improve immediately upon stopping the offending agent.

Management of Acute Tubulointerstitial Nephritis

- In cases of acute tubulointerstitial nephritis due to hypersensitivity reactions (allergic interstitial nephritis), early recognition and prompt discontinuation of the offending drug are helpful; cessation of the offending agent usually, but not always, results in complete recovery in patients.
- Rate of recovery is variable, and, in some patients, renal failure persists for many weeks before renal function improves. Some patients may progress to chronic renal insufficiency.
- If no sign of improvement is observed within a few days of discontinuation of the offending agent, consider therapy with steroids. Although controlled trials are lacking, many authors suggest using prednisone at relatively high doses (eg, 1 mg/kg for 4-6 wks with rapid tapering of the dose). This intervention may improve the outcome, speeding renal recovery and reducing the requirement for dialysis.

Chronic tubulointerstitial nephritis

Chronic tubulointerstitial nephritis is usually asymptomatic, presenting with slowly progressive renal impairment. Urinalysis may be normal or show low-grade proteinuria (<1.5 g/day) and/or pyuria. Diagnosis depends on renal biopsy, which reveals variable cellular infiltration of the interstitium, tubular atrophy, and fibrosis.

Causes: sarcoidosis, drugs (prescribed and nonprescribed), irradiation, toxins, and metabolic disorders.

Characteristics of the different types of renal tubular acidosis

	Hypokalemic RTA		Hyperkalemic RTA	
	Type 1 RTA	**Type 2 RTA**	**Hypoaldosteronism (Type 4 RTA)**	**Distal tubule volume defects**
Primary defect	Impaired distal acidification.	Reduced proximal HCO_3 reabsorption.	Decreased aldosterone secretion or aldosterone resistance.	Reduced sodium reabsorption.
Plasma HCO_3	Variable. May be below 10 mEq/L.	Usually 12 to 20 mEq/L.	Usually greater than 17 mEq/L.	Usually greater than 17 mEq/L.
Urine pH	Greater than 5.3.	Variable. Greater than 5.3 if the serum HCO_3 exceeds the tubule's HCO_3 reabsorptive threshold. Less than 5.3 when the serum HCO_3 is reduced to levels that can be largely reabsorbed despite defective proximal tubule reabsorptive mechanisms.	Variable. Usually greater than 5.3.	Variable. Usually greater than 5.3.
Plasma potassium	Usually reduced, but hyperkalemic forms exist; hypokalemia largely corrects with alkali therapy.	Reduced; made worse by bicarbonaturia induced by alkali therapy.	Increased; correcting the hyperkalemia alone will improve the acidosis by increasing ammonium availability.	Increased; correcting the hyperkalemia alone will improve the acidosis by increasing ammonium availability.
Urine anion gap	Positive	Negative	Positive	Positive
Urine calcium/creatinine ratio	Increased	Normal	Normal	Normal
Nephrolithiasis/nephrocalcinosis	Yes	No	No	No

RTA: renal tubular acidosis; HCO_3: bicarbonate.

RTA

- **Distal (type 1) RTA — The major causes of distal RTA in adults are autoimmune diseases (eg, Sjögren's syndrome and rheumatoid arthritis) and hypercalciuria (which is the primary defect in some families). Hereditary distal RTA is most common in children.**
- **Proximal (type 2) RTA — Proximal RTA can occur as an isolated defect in proximal bicarbonate reabsorption or in association with other defects in proximal tubular function that impair reabsorption of other solutes such as phosphate, glucose, uric acid, and amino acids. The major cause of proximal RTA in adults is proximal tubular toxicity related to increased excretion of immunoglobulin light chains due to monoclonal gammopathies that may be latent.**

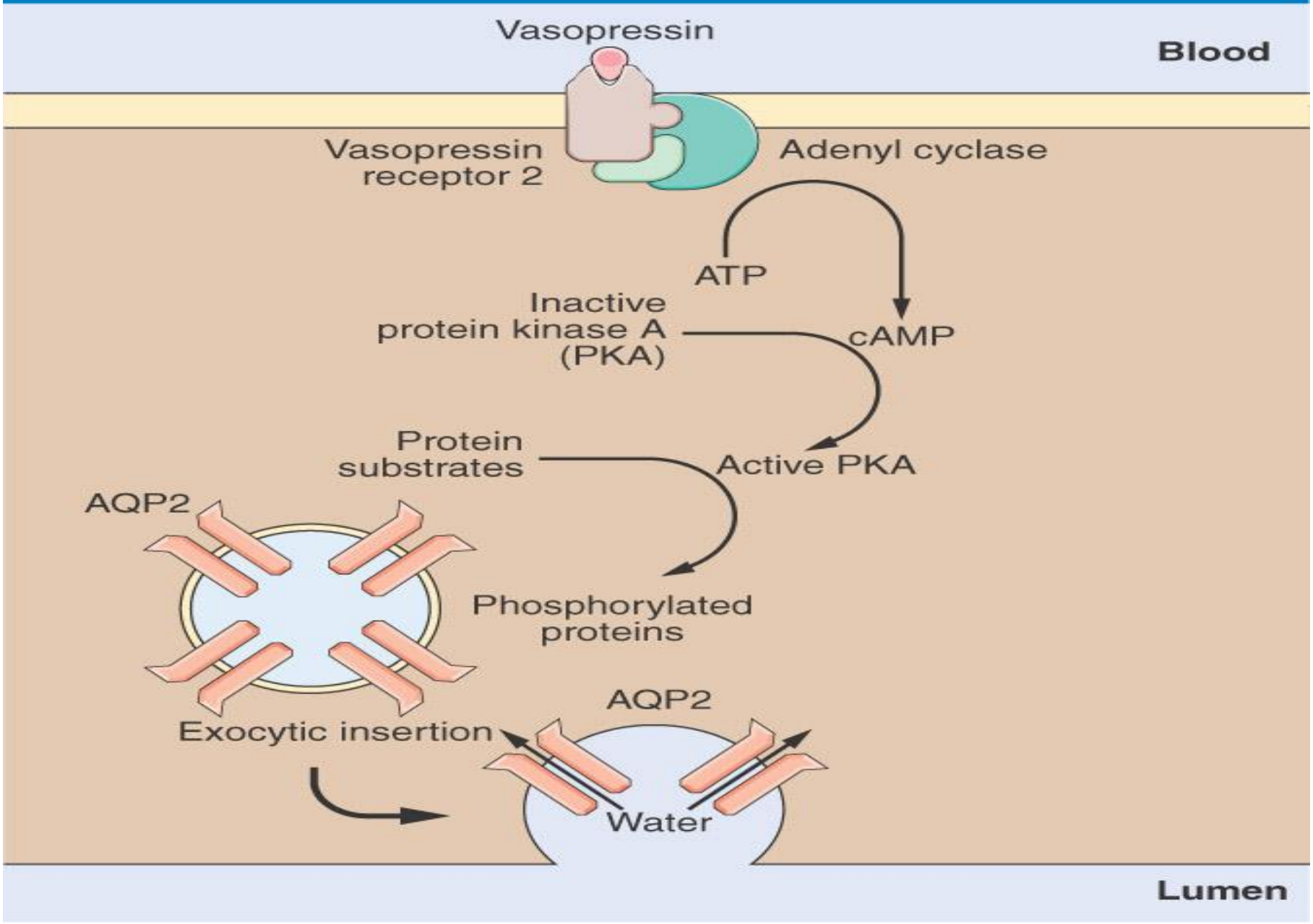
Causes of Fanconi syndrome

Inherited Causes
Cystinosis
Hereditary fructose intolerance
Tyrosinemia
Wilson's disease
Lowe syndrome
Glycogenosis
Mitochondrial cytopathies
Idiopathic
Acquired Causes
Drugs: *cisplatin*, *ifosfamide*, gentamicin, azathioprine, valproic acid (sodium valproate), suramin, streptozocin (streptozotocin), ranitidine
Dysproteinemias: multiple myeloma, Sjögren syndrome, light-chain proteinuria, amyloidosis
Heavy metal poisoning: lead, cadmium
Other poisonings: glue sniffing, diachrome, Chinese herbal medicine
Other: nephrotic syndrome, renal transplantation, mesenchymal tumors

Features of Fanconi syndrome

Metabolic Abnormalities
Hyperaminoaciduria
Glucosuria
Hypophosphatemia
Hypokalemia
Hypouricemia
Hypocarnitinemia
Clinical Features
Rickets, osteomalacia
Growth retardation
Polyuria
Dehydration
Proteinuria
Acidosis

Water reabsorption in the distal tubule

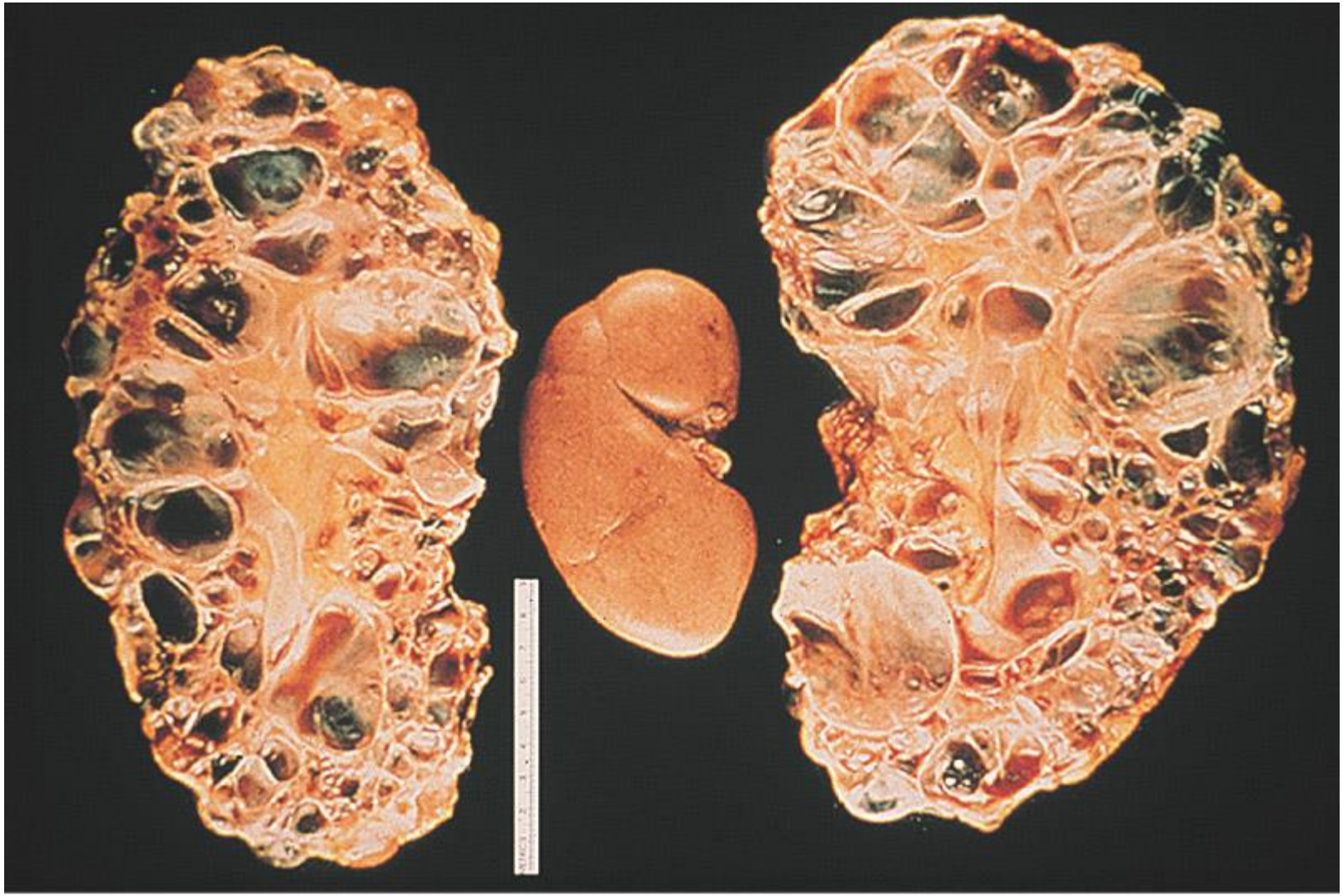


Nephrogenic diabetes insipidus

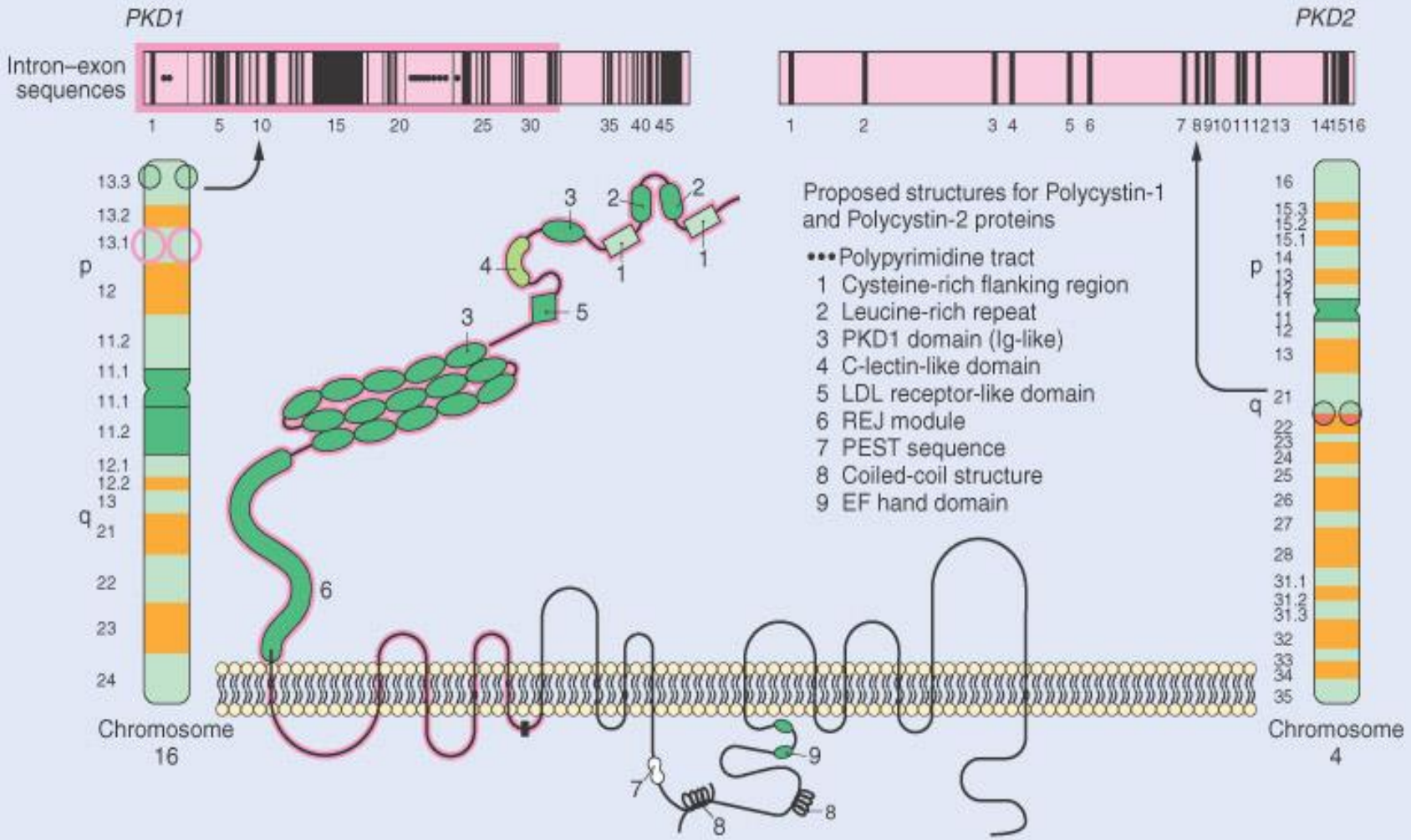
- **Nephrogenic diabetes insipidus (DI) refers to a decrease in urinary concentrating ability that results from resistance to the action of antidiuretic hormone (ADH). This problem can reflect resistance at the ADH site of action in the collecting tubules, or interference with the countercurrent mechanism due, for example, to medullary injury or to decreased sodium chloride reabsorption in the medullary aspect of the thick ascending limb of the loop of Henle .**
- **Patients with moderate to severe nephrogenic or central DI typically present with polyuria, nocturia, and polydipsia. The first manifestation of a mild to moderate loss of concentrating ability is often nocturia**
- **Hereditary nephrogenic DI**
  - **Vasopressin V2 receptor gene mutations**
  - **Aquaporin-2 gene mutation**

ADPKD

- **Autosomal dominant polycystic kidney disease (ADPKD) is a common disorder, occurring in approximately 1 in every 400 to 1000 live births.**
- **Approximately 78% of families with ADPKD have an abnormality on chromosome 16 (*PKD1* locus) . Most of the remaining families (14 percent) have a different defect that involves a gene on chromosome 4 (the *PKD2* locus).**
- **The diagnosis of ADPKD relies principally upon imaging of the kidney. Typical findings include large kidneys and extensive cysts scattered throughout both kidneys.**

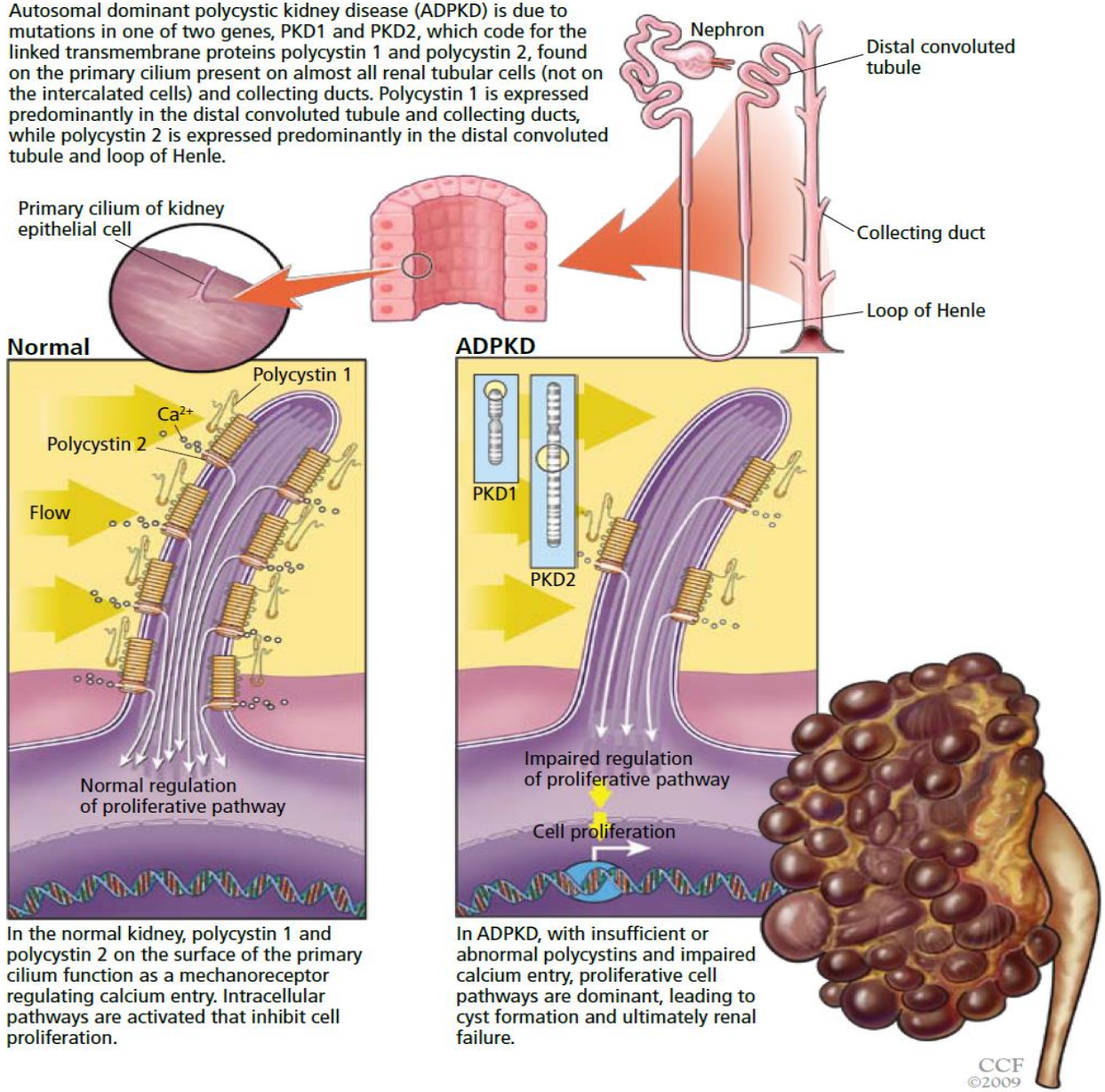


Polycystins



Polycystin and ADPKD

Autosomal dominant polycystic kidney disease (ADPKD) is due to mutations in one of two genes, PKD1 and PKD2, which code for the linked transmembrane proteins polycystin 1 and polycystin 2, found on the primary cilium present on almost all renal tubular cells (not on the intercalated cells) and collecting ducts. Polycystin 1 is expressed predominantly in the distal convoluted tubule and collecting ducts, while polycystin 2 is expressed predominantly in the distal convoluted tubule and loop of Henle.



In the normal kidney, polycystin 1 and polycystin 2 on the surface of the primary cilium function as a mechanoreceptor regulating calcium entry. Intracellular pathways are activated that inhibit cell proliferation.

In ADPKD, with insufficient or abnormal polycystins and impaired calcium entry, proliferative cell pathways are dominant, leading to cyst formation and ultimately renal failure.

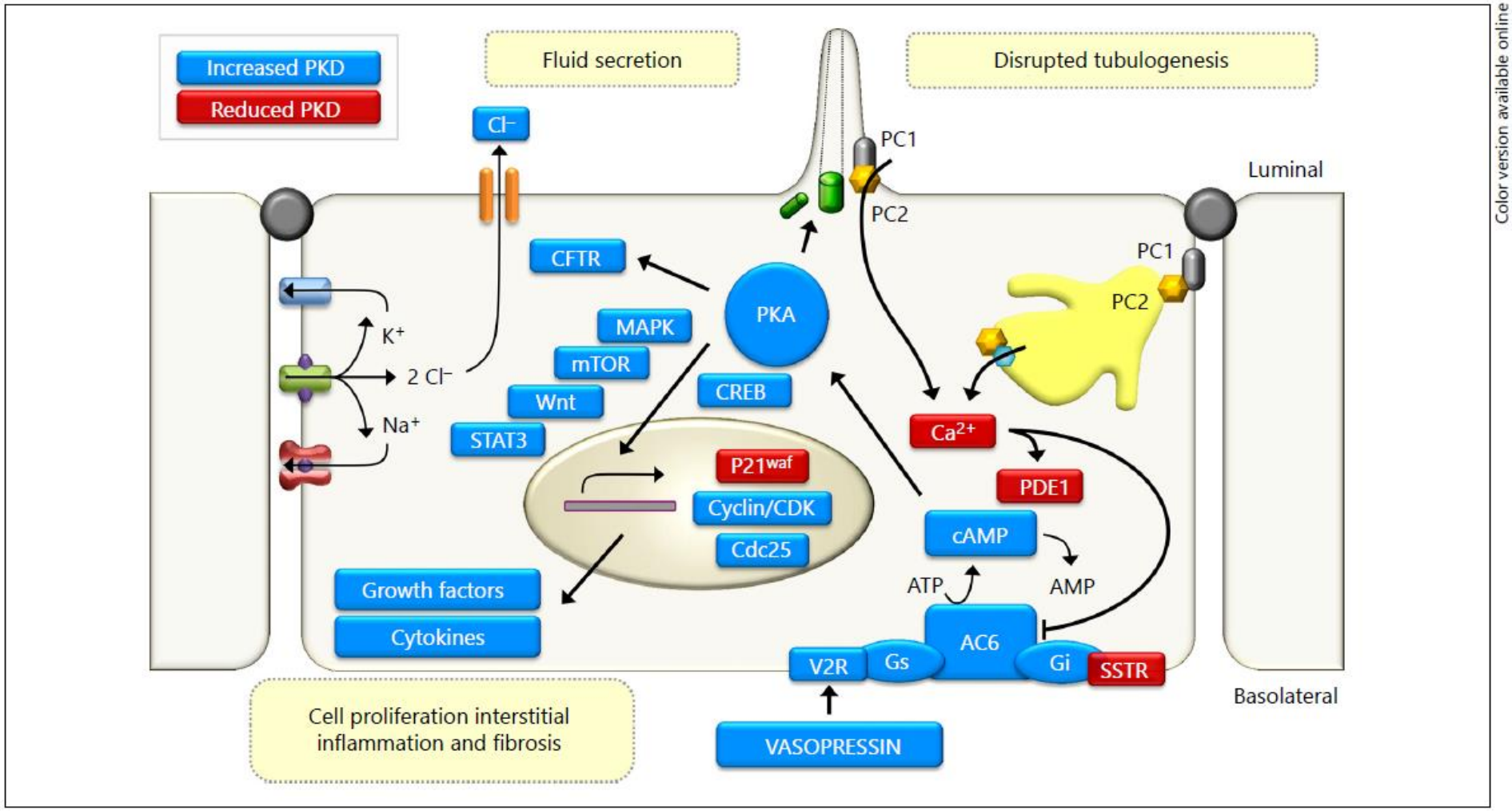


Fig. 1. Intracellular signaling in tubular cells of the collecting duct in ADPKD and the role of vasopressin.

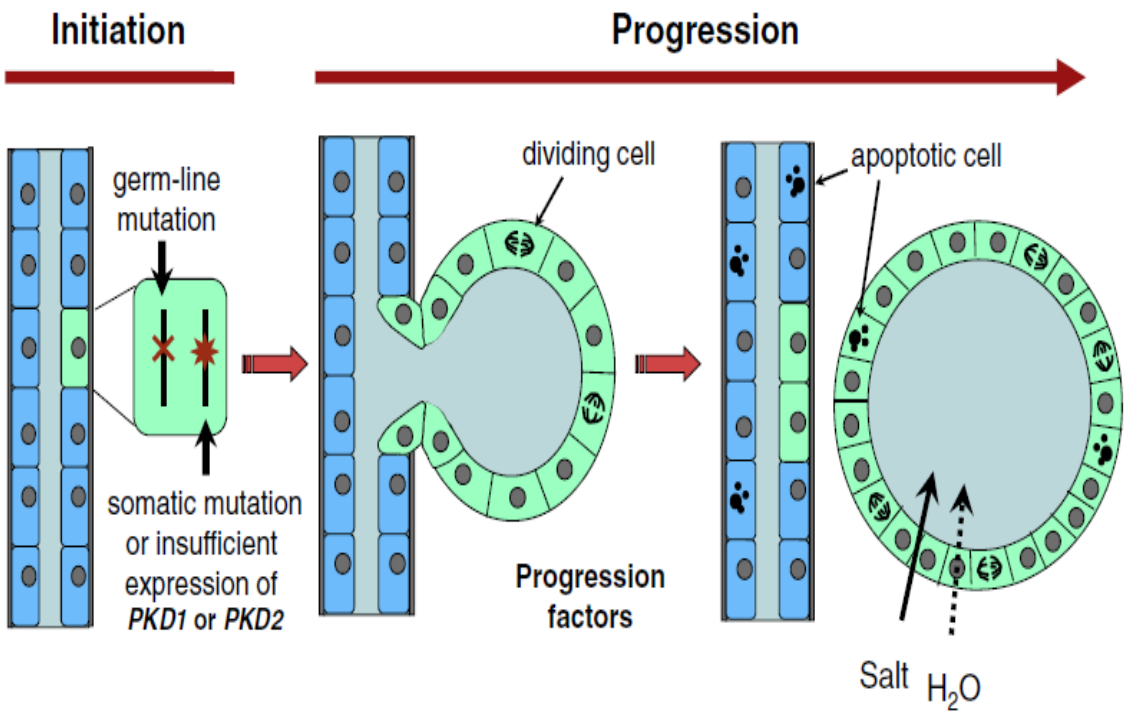


Fig. 1. Schematic diagram illustrating the initiation and progression of cyst formation. In ADPKD, all cells harbor a germ-line mutation in one allele of either *PKD1* or *PKD2*; however, a somatic mutation or insufficient expression of non-mutated allele is thought to initiate cyst formation. Progression factors, including arginine vasopressin and other cAMP agonists, stimulate cell proliferation and NaCl and water secretion causing cyst expansion [modified from Grantham et al., Kidney Int. 73: 108–116, 2007].

Clinical outcome

- **Autosomal dominant polycystic kidney disease (ADPKD) often leads to progressive renal failure due in part to continued enlargement of the cysts. Other renal manifestations include hypertension, urinary tract infection, concentrating defects, hematuria, nephrolithiasis, and acute or chronic flank and abdominal pain; protein excretion is generally not a prominent feature. All complications relate directly to the extent of renal cyst involvement, which can be assessed by total kidney volume measurements.**
- **Hematuria occurs in 35 to 50 percent of patients and may be the presenting symptom of the disease. Hematuria due to cyst rupture generally resolves with bedrest and hydration, although, with unusual and severe bleeding, percutaneous arterial embolization or even nephrectomy may become necessary. Gross hematuria is more likely among individuals with larger kidneys, hypertension, and higher plasma creatinine concentrations and is associated with more rapid progression of kidney disease.**

Clinical outcome

- **Many patients have a mild concentrating defect, which may not be clinically evident unless a history of polydipsia or polyuria is elicited. The underlying cause is not known. A central cause has been excluded since vasopressin levels are elevated in this disorder.**
- **Kidney stones occur in up to 20 percent of patients. More than one-half of stones in ADPKD are composed of uric acid, with most of the remainder being composed of calcium oxalate. Increased renal volume may be a risk factor for nephrolithiasis. Other abnormalities that predispose to stone disease include low urinary volume, low urinary citrate, and, less often, hyperuricosuria and hypercalciuria.**
- **Flank and abdominal pain is common and may be caused by cystic or parenchymal infections, nephrolithiasis, or cyst hemorrhage. Chronic kidney pain is more common in advanced disease in patients who have enlarged kidneys and may reflect either stretching of the capsule or traction on the renal pedicle. Massive polycystic liver enlargement, although uncommon, may also cause pain.**

Clinical outcome

- **Renal cell carcinoma (RCC) is an infrequent complication of ADPKD. The diagnosis of RCC is more difficult to establish in ADPKD than in the general population since findings such as hematuria, a flank mass, or complex cysts on ultrasonography, computed tomography (CT) scanning, or magnetic resonance imaging (MRI) are common in ADPKD in the absence of malignancy. Malignancy should be suspected if the patient complains of systemic signs and symptoms that are out of proportion to the severity of the renal disease or if there is rapid growth of a complex cyst.**
- **Indications for nephrectomy include disabling symptoms due to massively enlarged kidneys and development of ventral (abdominal wall) hernias. Nephrectomy may also be considered prior to renal transplantation in the presence of recurrent infection, suspected malignancy, or extension of the native polycystic kidney into the potential pelvic surgical site.**

ADPKD is a systemic disease – with both renal- and extra-renal manifestations

Renal manifestations[1,2]

- Hypertension
- Haematuria
- Polyuria
- Nocturia
- Palpable kidneys
- Kidney stones
- Abdominal/flank pain
- Hernia
- Renal artery/vein occlusions
- Recurrent UTIs

Extra-renal manifestations[2,3,4]

- Aneurisms
- Dura and arachnoid cysts
- Vascular dissections
- Valvular heart disease
- Dilated cardiomyopathy
- Pericardial infusion
- Bile duct dilation
- Diverticulosis
- Hepatic cysts
- Pancreatic cysts
- Intraductal papillary mucinous Neoplasms
- Male infertility (seminal vesicle cysts)

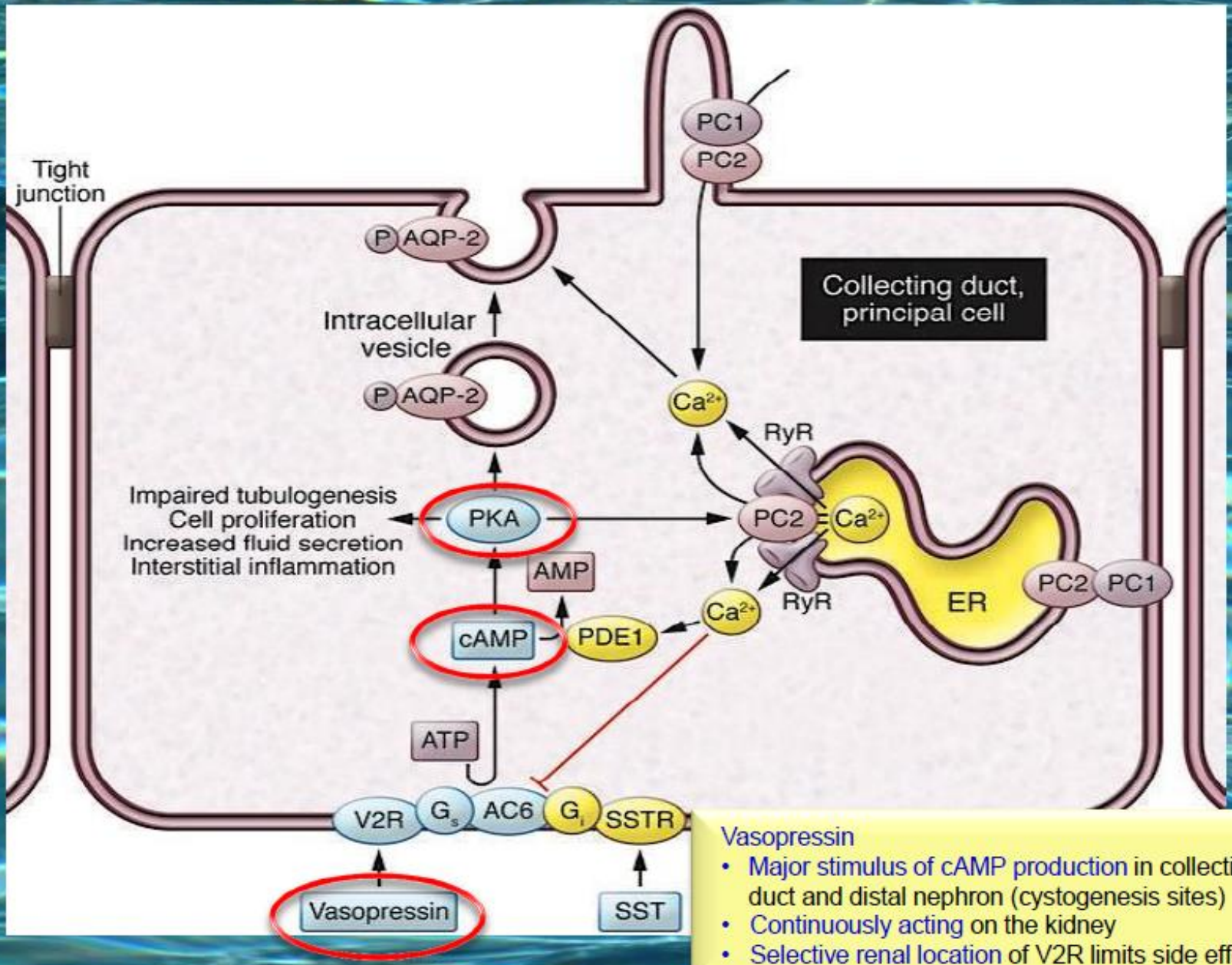
Extrarenal complications

- Cerebral aneurysms
- Hepatic and pancreatic cysts
- Cardiac valve disease
- Colonic diverticula
- Abdominal wall and inguinal hernia
- Seminal vesicle cysts

Treatment

- **Treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) may, in addition to lowering the blood pressure, slow the rate of progression of ADPKD, especially among patients with proteinuria. For patients who have no contraindications to an ACE inhibitor (such as pregnancy), we suggest using an ACE inhibitor as the initial antihypertensive agent .**
- **Promising specific therapies that are being evaluated include vasopressin receptor antagonists and increasing fluid intake to suppress plasma vasopressin levels.**
- **Patients with ADPKD and renal failure are most commonly treated with hemodialysis or undergo renal transplantation with equivalent or better overall outcomes compared with non-ADPKD patients.**

Rationale for V2R Antagonism in ADPKD[¨]



Vasopressin

- Major stimulus of cAMP production in collecting duct and distal nephron (cystogenesis sites)
- Continuously acting on the kidney
- Selective renal location of V2R limits side effects

Rationale for Water Therapy in ADPKD

- cAMP is one of the key drivers of cyst enlargement
- In animal models, ingestion of large amounts of water promotes diuresis by suppressing plasma levels of arginine vasopressin (AVP) and renal levels of cAMP, slowing cyst progression

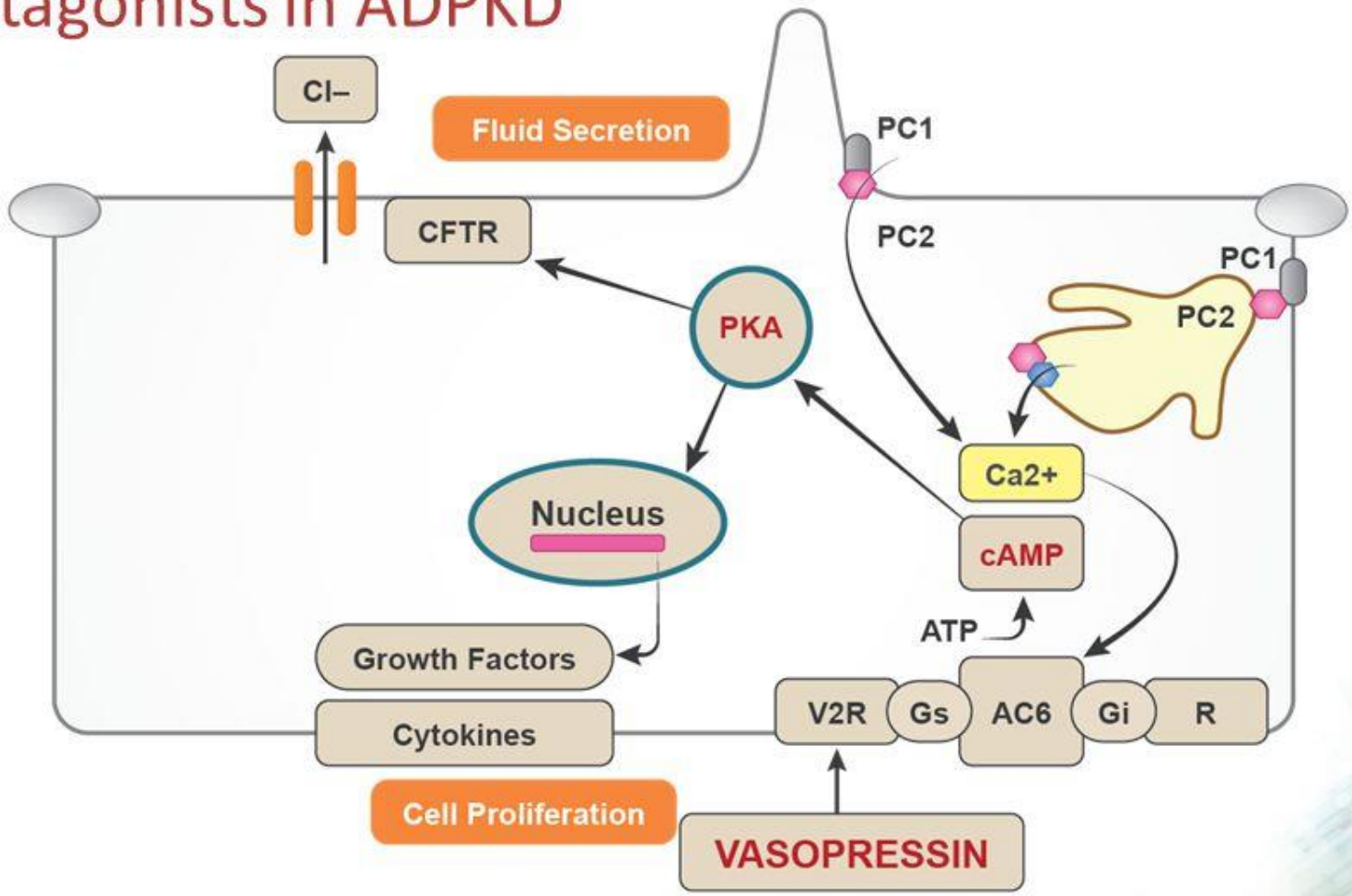
Adapted from: Wang CJ, *et al. Clin J Am Soc Nephrol* 2011; 6(1):192-7.

Summary: Current Understanding of Water Therapy for ADPKD

- There is no consensus as to whether increased water can alter the natural course of disease
- The size and quality of the limited available evidence makes definitive conclusions impossible at this point
- There is no consensus or evidence on the appropriate volume of water to recommend
  - 3-4 L daily may be appropriate
  - It is unknown if goals can be achieved over the longer term
- Increased water consumption does have known benefits for prevention of nephrolithiasis[1]
- Adherence to water therapy is difficult for many patients

1. Hall PM. *Cleve Clin J Med* 2009;76(10):583-91.

Mechanism of Action of Vasopressin-2-receptor Antagonists in ADPKD



AC6: adenylate cyclase 6; Ca2+: calcium; Cl-: Chloride; CFTR: cystic fibrosis transmembrane conductance regulator; Gi & Gs: G proteins; mTOR: mammalian target of rapamycin; PC1: polycystin-1; PC2: polycystin-2; PKA: protein kinase A; R: somatostatin receptor; V2R: vasopressin 2 receptor.
Adapted from Alam A, *et al. Am J Kidney Dis* 2015; in press.

Tolvaptan for the Treatment of ADPKD: Conclusions

- In the pivotal clinical study, tolvaptan showed efficacy in:
  - Slowing progression of increase in kidney volume
  - Slowing deterioration of kidney function
  - Improving symptoms (*e.g.*, pain)

- Signal of liver toxicity in the pivotal trial led to the recommendations for monitoring at baseline and throughout treatment

Renal cysts

Renal cysts are categorized as simple or complex. Simple renal cysts are commonly observed in normal kidneys, with an increasing incidence as individuals age. They are benign, asymptomatic lesions that rarely require treatment.

Definition of Bosniak classification of cystic renal masses by CT scanning

Category I – Simple benign cyst with the following features:
Hairline thin wall.
Density less than 20 Hounsfield units (similar to water).
Does not contain septa, calcification, or solid components.
Does not enhance.
Category II – Cystic lesions with the following features:
A few hairline thin septa.
"Perceived" enhancement may be present. There is no measurable enhancement.
Uniformly high attenuation lesions <3 cm that are well marginated and do not enhance fall into this category.
Category IIF – Minimally complicated cysts that do not neatly fall into category II. These lesions are generally well marginated but have some suspicious features that require follow-up:
Multiple hairline thin septa or minimal smooth thickening of the wall or septa.
"Perceived" enhacement of septa or wall may be present.
Thick and nodular calcification of the wall or septa, but no measurable contrast enhancement is present.
Totally intrarenal, nonenhancing, high attenuation lesions >3 cm in diameter fall in this category.
Category III – True indeterminate cystic masses that typically undergo surgical evaluation, although many lesions are benign. These lesions show the following:
Thickened irregular or smooth walls or septa in which measurable enhancement is present.
Category IV – These mostly malignant lesions have the following features:
All category III criteria.
Enhancing soft-tissue components adjacent to, but independent of, the wall or septum.

Adapted from Israel GM, Bosniak MA. An update of the Bosniak Renal Cyst Classification System. Urology 2005; 66:484.