Renal and Urologic Impairments Workshop

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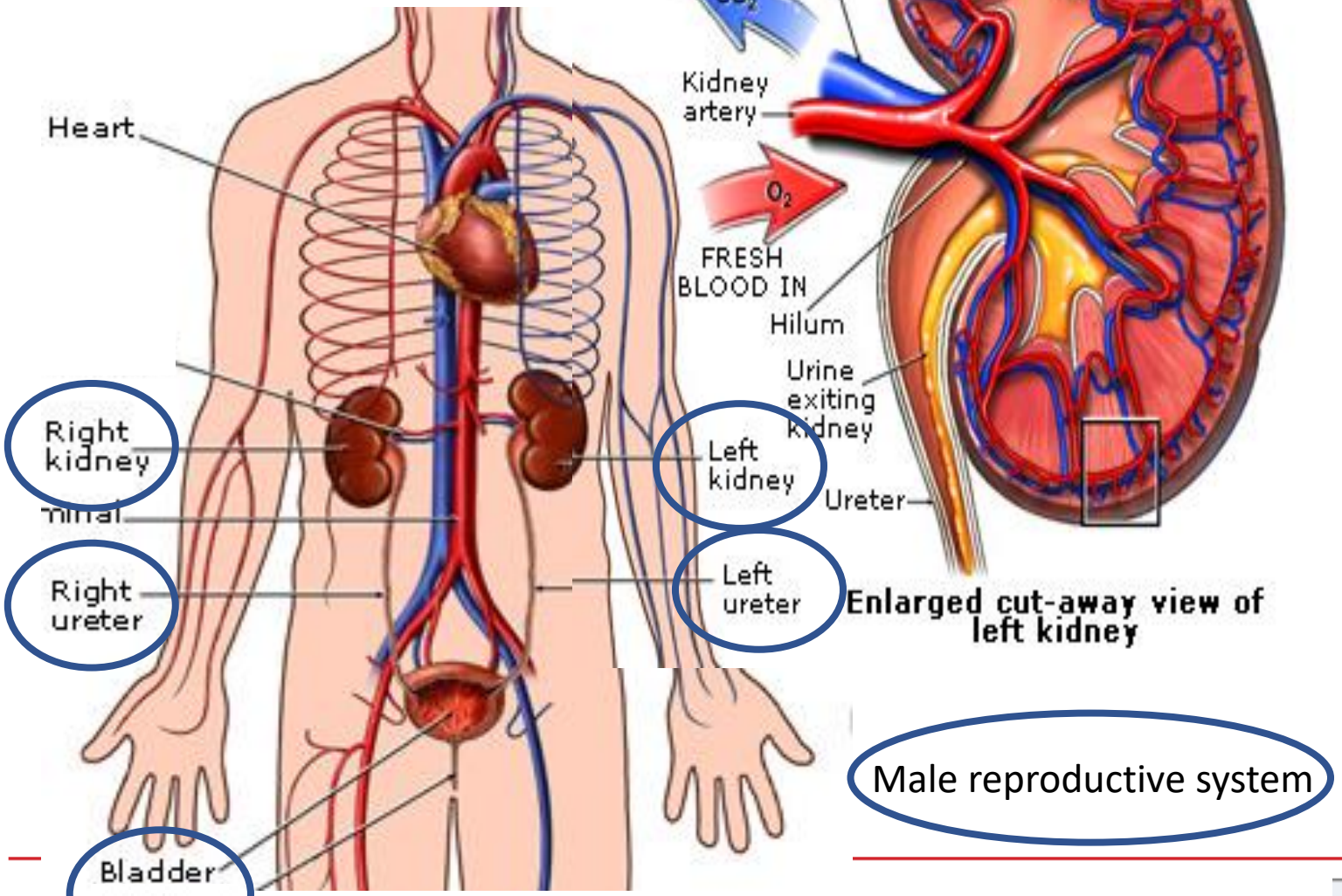
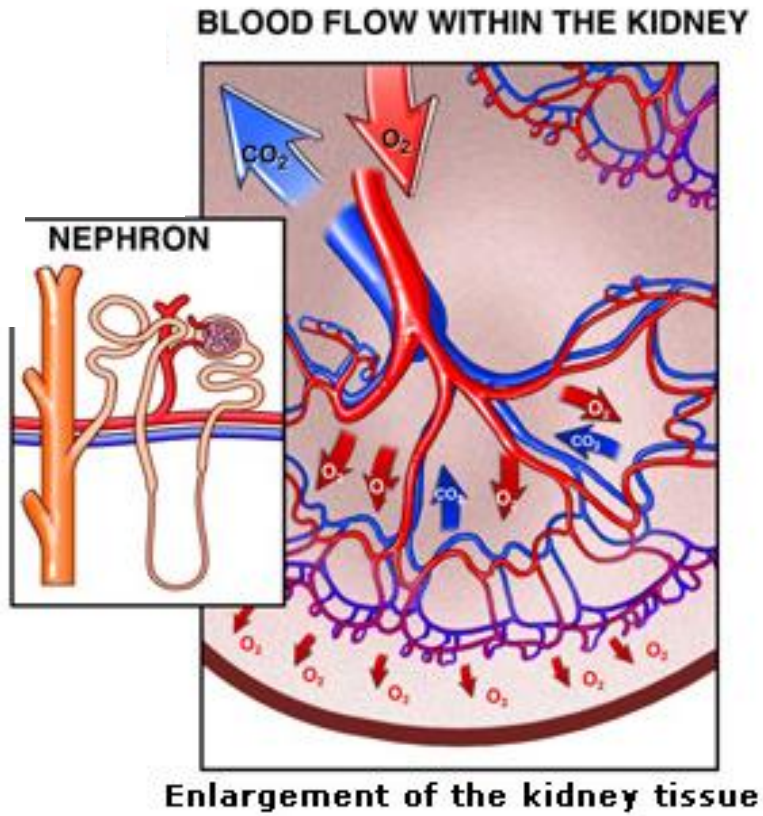
GU System

UROLOGY
NEPHROLOGY





Male reproductive system

Urine abnormalities

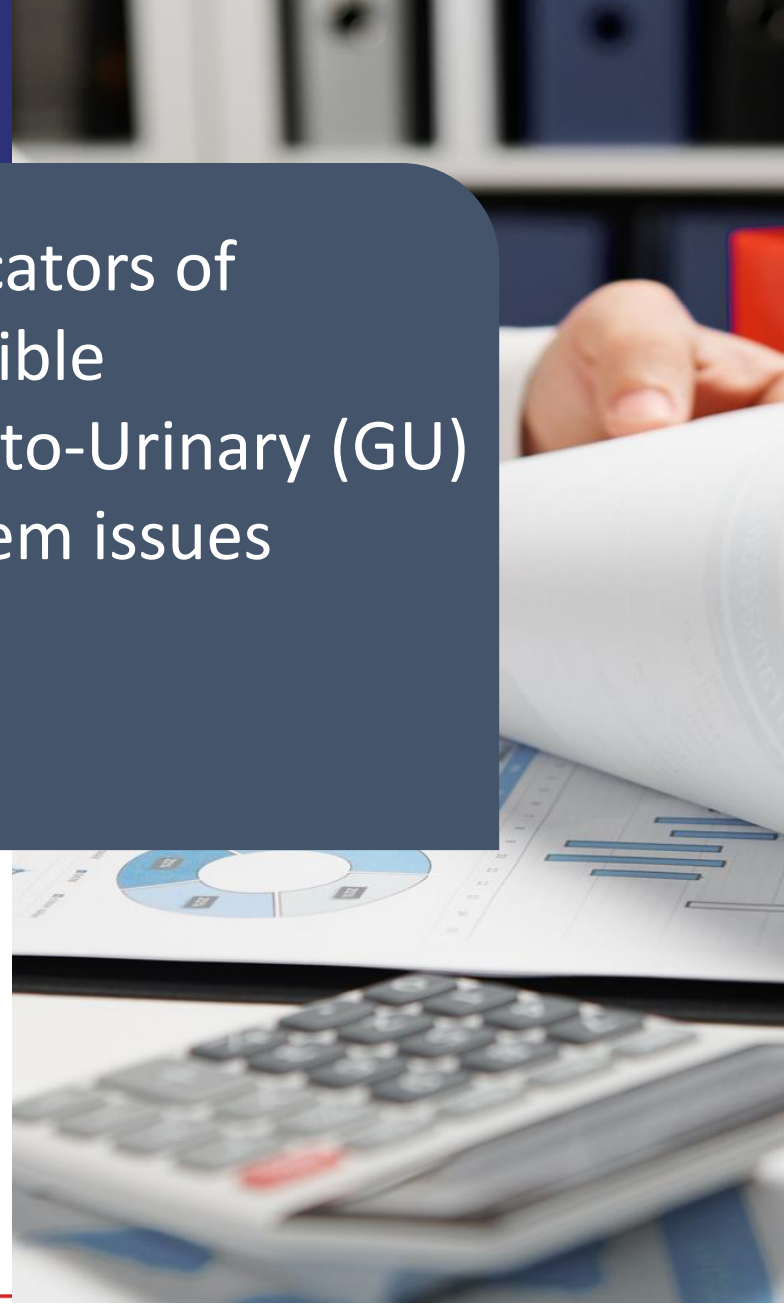
- albuminuria/proteinuria
- hematuria

Abnormal renal function tests

- Serum creatinine
- eGFR
- Cystatin C

Abnormal imaging studies

Indicators of possible Genito-Urinary (GU) System issues



Urine Abnormalities

Cases: abnormal urinalysis (UA)

Abnormality	Potential concern
Proteinuria	Early kidney disease, hypertension, diabetes, strenuous exercise
Hematuria	Urinary tract infection (UTI), kidney stones, trauma, malignancy
Glycosuria	Diabetes mellitus or renal glycosuria
Pyuria/Bacteriuria	UTI or asymptomatic bacteriuria
Crystalluria	Risk of kidney stones
Abnormal pH/Specific Gravity	Dehydration, metabolic disorders
Additional considerations	**Potential explanations, examples**
Repeat UA without abnormality, transient	exercise, dehydration, minor infections
Repeat UA with abnormality, persistent	chronic kidney disease, diabetes
Symptoms, dysuria	Infection or inflammation
Symptoms, flank pain	kidney stones, pyelonephritis, or trauma
Without symptoms	Early or subclinical disease (evaluation), transient condition, lab factors
Family history	polycystic kidney disease, glomerulonephritis

Urine testing

24-hour urine collection

Cumbersome

Unreliable

Dipstick

Chemical strips change color when dipped into urine

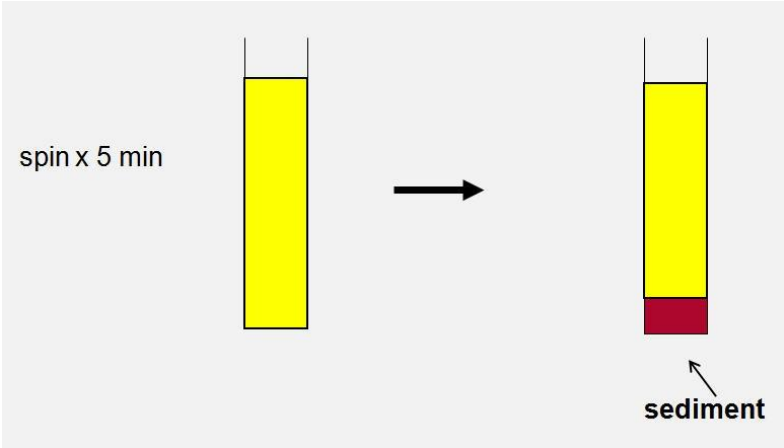
★ “Spot” urine

Measures the amount in random urine sample

Greater specificity

Urinalysis: Microscopic exam

- Microscopic exam – few drops of spun urine examined under the microscope



- WBCs (leukocytes)
- RBCs (erythrocytes)
- Epithelial cells
- Casts

Case 1: 46-year-old male, no admitted medical history, blood chemistry results normal

URINALYSIS				
GLUCOSE	NEGATIVE		0.00 - 0.24	(GM%)
PROTEIN		66 H	0 - 30	(MG%)
MICROALBUMIN		39.0 H	0 - 3	(MG/DL)
MALB/CREATININE RATIO		374.2 H	0 - 30.0	(MG/GMCR)
LEUKOCYTE SCREEN	NEGATIVE		NEGATIVE	
HEMOGLOBIN SCREEN	NEGATIVE		NEGATIVE	
WHITE BLOOD CELLS	0		0 - 9	(/HPF)
RED BLOOD CELLS	1		0 - 4	(/HPF)
GRANULAR CASTS	0		0	(/40LPF)
HYALINE CASTS	0		0 - 10	(/40LPF)
SPECIFIC GRAVITY	1.023		1.003 - 1.035	
URINE TEMPERATURE	96.0		90.5 - 99.6	(FAHR.)
CREATININE	104.2		27.0 - 260.0	(MG/DL)
PROT/CREATININE RATIO		0.63 H	0.00 - 0.20	(MG/MGCR)
ADULTERANT TESTS WITHIN NORMAL LIMITS				

Case 1: 46 yo male, critical thinking questions

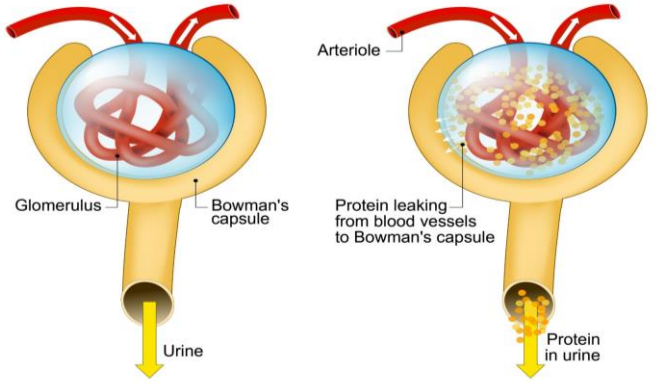
- Urinalysis (UA)
  - Protein 66 (0-30 mg/dL)
  - Albumin 39.0 (0-3 mg/dL)
  - Albumin /creatinine ratio 374.2 (0-30 mg/g Cr)
  - Protein /creatinine ratio 0.63 (0.0 – 0.20)

- What is the abnormality?
- What are the possible etiologies?
- What other information would be helpful to know?
- What is the underwriting mortality/morbidity concern?
- Would your decision change if there were other urine abnormalities also present?
- What is your recommendation?

Normal urine protein

Normal urine protein:

- Plasma proteins: filtered, predominantly albumin
  - Usually 25% of total, less than 30mg/day
- Non-Plasma: Tubular, Tamm-Horsfall
  - Usually 50% - 75% of total



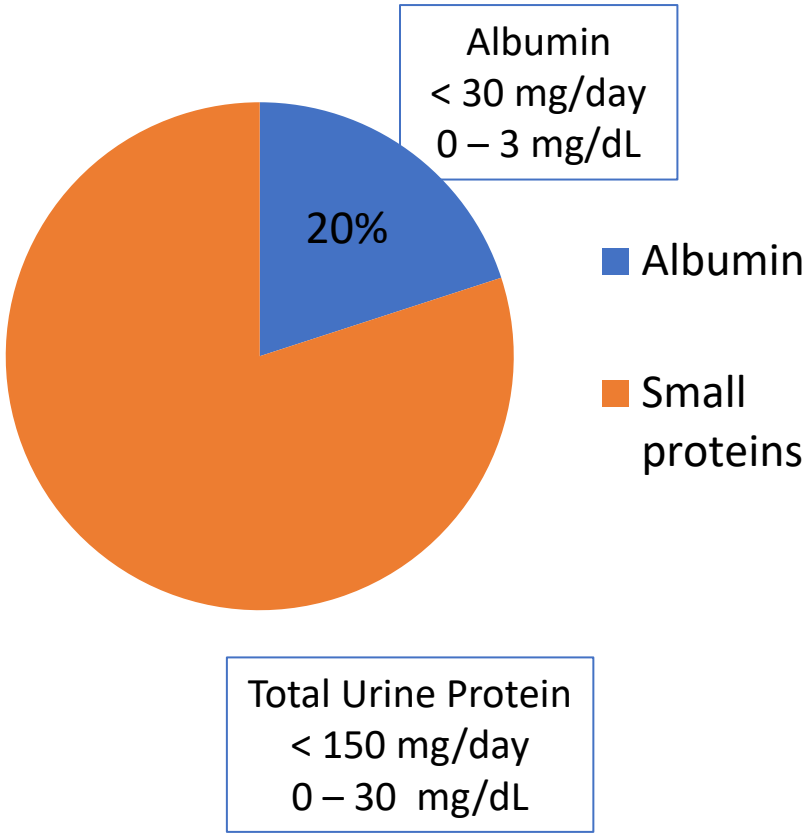
Non pathologic causes of proteinuria:

- Orthostatic: rare after age 30, 2-5% adolescents
- Exercise, fever

Proteinuria vs. Albuminuria

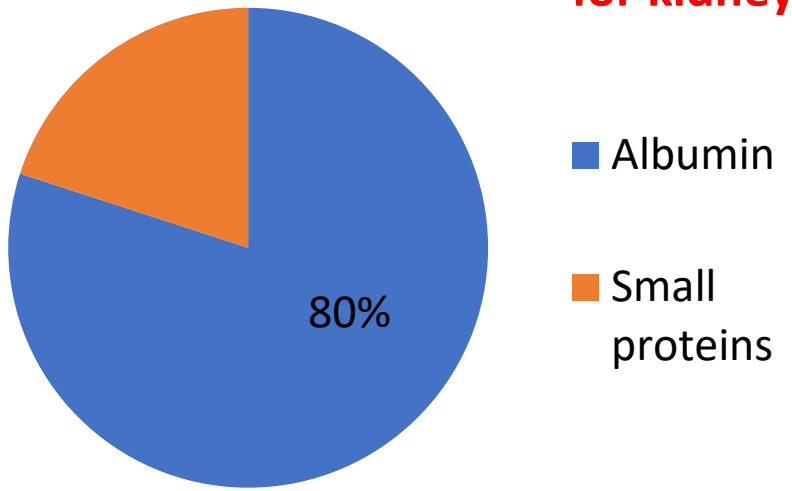
Not the same! Albumin is a type of Protein

Normal



Abnormal

*** **Albuminuria is a specific marker for kidney disease** ***



With abnormal proteinuria, albumin becomes the bulk of protein excreted abnormally in the urine

Benign Proteinurias

Often transient with lower levels of proteinuria (< 1 – 2 g/day)

- **Orthostatic** or **Postural**
  - Present when upright (after prolonged standing)
  - Absent when supine (after overnight rest)
- **Exercise-induced**
- **Fever-induced**
  - Isolated episodes after strenuous exertion or with fever
- **Contamination** of urine may occur from prostate, vaginal or seminal fluid secretion, skin, or menses

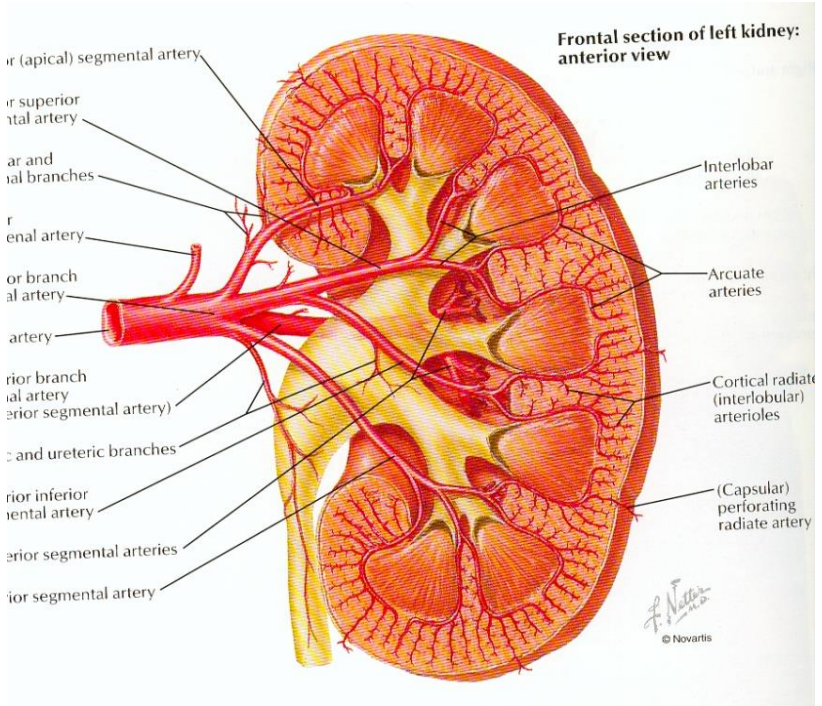
Suspect with a young person with no medical history

Generally, may be disregarded if subsequent urine is normal

Pathological Proteinurias

Often persistent

- **Glomerular**
  - Glomerulonephritis (FSGN)
  - Hypertension
  - Diabetes
- **Tubular**
  - Interstitial nephritis
  - Autoimmune nephritis
- **Overflow diseases** (e.g., multiple myeloma)
- **Urinary tract disorders** (e.g., infection, stones, tumor)



CLUES: Hypertension, Diabetes, Abnormal Serum creatinine, Abnormal urine sediment (RBC, WBCs, casts), Albuminuria

Case 1: 46 yo male, continued, “what if?

URINALYSIS				
GLUCOSE	NEGATIVE		0.00 - 0.24	(GM%)
PROTEIN		66 H	0 - 30	(MG%)
MICROALBUMIN		39.0 H	0 - 3	(MG/DL)
MALB/CREATININE RATIO		374.2 H	0 - 30.0	(MG/GMCR)
LEUKOCYTE SCREEN	NEGATIVE		NEGATIVE	
HEMOGLOBIN SCREEN	NEGATIVE		NEGATIVE	
WHITE BLOOD CELLS	0		0 - 9	(/HPF)
RED BLOOD CELLS	1		0 - 4	(/HPF)
GRANULAR CASTS	0		0	(/40LPF)
HYALINE CASTS	0		0 - 10	(/40LPF)
SPECIFIC GRAVITY	1.023		1.003 - 1.035	
URINE TEMPERATURE	96.0		90.5 - 99.6	(FAHR.)
CREATININE	104.2		27.0 - 260.0	(MG/DL)
PROT/CREATININE RATIO		0.63 H	0.00 - 0.20	(MG/MGCR)
ADULTERANT TESTS WITHIN NORMAL LIMITS				

No admitted medical history
HbA1c 8.4
Serum creatinine 1.7
Blood pressure 140/90

CLUES: Hypertension, Diabetes, Abnormal Serum creatinine, Abnormal urine sediment (RBC, WBCs, casts), Albuminuria

Case 1 46-year-old male, no admitted history, normal blood chemistry, with albuminuria	
Abnormality:	elevated urine levels of protein and microalbumin, possible kidney dysfunction
Possible etiologies:	Chronic kidney disease (CKD), especially early glomerular damage Hypertension or diabetes (including occult disease) Transient causes e.g., dehydration, fever or infection, strenuous exercise, heart failure exacerbation Glomerular diseases, e.g., IgA nephropathy, lupus nephritis, or focal segmental glomerulosclerosis
Additional information:	Repeat urinalysis to confirm persistence of proteinuria eGFR to assess kidney function Blood pressure readings Fasting glucose and HbA1c, rule out undiagnosed diabetes Medical history including family history of kidney disease Imaging or biopsy if glomerular disease is suspected
Morbidity mortality concern:	Microalbuminuria and proteinuria predictors of increased mortality, particularly CV causes; albuminuria is more predictive of mortality than total proteinuria Possibly early CKD, possible progression to renal failure or CV events
Presence of additional urine abnormalities:	Increased concern with hematuria, casts, glucose, infection markers
Recommended action	Postpone, further evaluation: repeat UA, eGFR, serum creatinine, BUN, identify comorbidities (hypertension, diabetes, coronary artery disease), possible nephrology evaluation (esp. with hematuria, RBC casts) Isolated persistent proteinuria consider moderate substandard

Case 2: 28-year-old female, no admitted medical history, normal blood pressure and serum creatinine

URINALYSIS				
GLUCOSE	NEG		NEGATIVE	(GM%)
PROTEIN		23 H	0 - 20*	(MG%)
MICROALBUMIN		3.5 H	0 - 3	(MG/DL)
MALB/CREATININE RATIO	6.0		0 - 30.0	(MG/GMCR)
LEUKOCYTE SCREEN	NEGATIVE		NEGATIVE	
HEMOGLOBIN SCREEN	NEGATIVE		NEGATIVE	
WHITE BLOOD CELLS	1		0 - 10*	(/HPF)
RED BLOOD CELLS	0		0 - 6*	(/HPF)
GRANULAR CASTS	0		0 - 5*	(/40LPF)
HYALINE CASTS	0		0 - 5*	(/40LPF)
SPECIFIC GRAVITY		> 1.035 H	1.002 - 1.035*	
URINE TEMPERATURE	96.0		90.5 - 99.6	(FAHR.)
CREATININE		578.5 H	10 - 300*	(MG/DL)
PROT/CREATININE RATIO	40		0 - 200*	(MG/GMCR)

Serum vs. Urine Creatinine

- Derived from the metabolism of creatine (skeletal muscle, dietary meat intake)
- Released into the blood circulation at constant rate
- Freely filtered in the kidney and secreted by the renal tubules
- Can be measured in both blood and urine specimens

	Serum Creatinine (blood)	**Urine Creatinine**
Traditional units	0.6 – 1.5 mg/dL	27 – 260 mg/dL
Prognostic Significance	YES	NO
Increased	Marker for reduced renal function, renal failure Inversely related to eGFR	CONCENTRATED urine specimen
Decreased	Not common; not usually a cause for concern Decreased muscle mass	DILUTE urine specimen

Merely a marker (along with Specific Gravity) for urine concentration status
No prognostic significance!

So why is it important? Need value in order to calculate the Protein/Creatinine ratio

Protein/Creatinine Ratio

(PROT/CREAT ratio, P/C ratio)

- Measured protein divided by the measured creatinine
- Represents a fair approximation of a person's 24-hr protein excretion
- **More accurate** valuation over the absolute urine protein
- **Takes into account the concentration of the urine**
- **Independent** of specific gravity or urinary volumes
- **More prognostic** than looking at individual values alone

When reviewed in underwriting, **P/C ratios take precedence over the absolute protein values**

Same goes for A/C ratios

Case 2: 28 yo female, critical thinking questions

- Urinalysis
  - Protein 23 (0-20 mg/dL%)
  - Albumin 3.5 (0-3 mg/dL)
  - Albumin/creatinine ratio 6.0 (0-30 mg/gCr)
  - Specific gravity greater than 1.035 (high)
  - Creatinine 578.5 (10-300 mg/dL)

- What is the abnormality?
- What are the possible etiologies?
- What other information would be helpful to know?
- What is the underwriting mortality/morbidity concern?
- Would your decision change if there were other urine abnormalities also present?
- What is your recommendation?

Case 2: 28-year-old female, no admitted history	
Abnormality:	Mild elevations protein, albumin, elevated creatinine, high specific gravity
Possible etiologies:	Benign/transient: dehydration (most likely given high specific gravity and creatinine), exercise-induced proteinuria, fever or stress, orthostatic proteinuria (common in young adults) Pathologic: early glomerular disease (e.g., minimal change disease, early diabetic nephropathy), tubular dysfunction, urinary tract infection (though no leukocytes or nitrites mentioned), hypertension or autoimmune disease (e.g., lupus nephritis), high muscle mass or rhabdomyolysis (for elevated creatinine)
Additional information:	If concern for pathologic: serum creatinine, eGFR; repeat UA, Urine microscopy (casts, RBCs, WBCs), Blood pressure, any history (diabetes, autoimmune disease, recent illness), any symptoms: edema, fatigue, flank pain
Morbidity mortality concern:	Transient/benign: minimal concern Persistent: possible progressive renal disease, cardiovascular risk, other systemic illness
Presence of additional urine abnormalities:	Increased concern with hematuria (glomerulonephritis or malignancy), leukocytes/nitrites (infection), casts (renal parenchymal disease), glucose/ketones (diabetes)
Recommended action	Given age, verified no medical history, normal BP and serum creatinine, consider concentrated urine and benign

Case 3: 56-year-old male, no admitted medical history

URINALYSIS				
GLUCOSE	NEGATIVE		0.00 - 0.15*	(GM%)
PROTEIN	4		0 - 20*	(MG%)
ALBUMIN	1.6		0 - 3	(MG/DL)
ALB/CREATININE RATIO		131.1 H	0 - 30.0	(MG/GMCR)
LEUKOCYTE SCREEN	NEGATIVE		NEGATIVE	
HEMOGLOBIN SCREEN	NEGATIVE		NEGATIVE	
WHITE BLOOD CELLS	0		0 - 10*	(/HPF)
RED BLOOD CELLS	1		0 - 2*	(/HPF)
GRANULAR CASTS	0		0 - 5*	(/40LPF)
HYALINE CASTS	0		0 - 5*	(/40LPF)
SPECIFIC GRAVITY	NOT PERFORMED		1.002 - 1.035*	
URINE TEMPERATURE	96.0		90.5 - 99.6	(FAHR.)
CREATININE	12.2		10 - 300*	(MG/DL)
PROT/CREATININE RATIO		330 H	0 - 200*	(MG/GMCR)

Case 3: 56 yo male, critical thinking questions

- Urinalysis
  - Protein 4 (0-20 mg/dL)
  - Albumin 1.6 (0-3 mg/dL)
  - Albumin/creatinine ratio 131.1 (0-30 mg/gCr)
  - Protein/creatinine ratio 330 (0-200 mg/gCr)

- What is the abnormality?
- What are the possible etiologies?
- What other information would be helpful to know?
- What is the underwriting mortality/morbidity concern?
- Would your decision change if there were other urine abnormalities also present?
- What is your recommendation?

Case 3: 56-year-old male, no admitted history	
Abnormality:	Albumin/Creatinine Ratio (ACR): high, macroalbuminuria Protein/Creatinine Ratio (PCR): high, proteinuria Protein: 4 mg/dL and Albumin: 1.6 mg/dL are within normal limits, but spot values can be misleading due to dilution/concentration effects. Ratios are more reliable.
Possible etiologies:	Glomerular (most likely): Diabetic nephropathy, hypertensive nephrosclerosis, glomerulonephritis (e.g., IgA nephropathy, lupus nephritis), Focal Segmental Glomerulosclerosis (FSGS) or minimal change disease Tubular or Overflow (less likely): Multiple myeloma (light chains), rhabdomyolysis (myoglobinuria), heavy exercise or fever (transient) Other: UTI or pyelonephritis
Additional information:	Serum creatinine, eGFR (assess kidney function) Blood pressure (hypertension), serum glucose (diabetes) Urine microscopy (casts, RBCs, WBCs) Repeat ACR/PCR: Confirm persistence Autoimmune markers: ANA, dsDNA, complement levels if glomerulonephritis suspected Imaging: Renal ultrasound for structural abnormalities.
Morbidity mortality concern:	Macroalbuminuria: increased risk of CKD progression, cardiovascular events, and mortality Proteinuria: Independent risk factor for renal and systemic vascular disease
Presence of additional urine abnormalities:	Increased concern with: hematuria (glomerular inflammation or malignancy); Casts (active renal parenchymal disease); Leukocytes/nitrites (infection); Glucose/ketones (diabetes)
Recommended action	Postpone for evaluation

Case 4: 43-year-old female, no admitted history, normal BP, blood chemistry, HbA1c

Urinalysis:

Protein 99 mg/dL	(< 30 mg/dL)
P/C ratio 0.55	(< 0.200)
RBC 66	

Scenarios:

1. Lab slip indicates menses
2. No indication of menses
3. History of hypertension

- What is the abnormality?
- What are the possible etiologies?
- What other information would be helpful to know?
- What is the underwriting mortality/morbidity concern?
- Would your decision change if there were other urine abnormalities also present?
- What is your recommendation?

Case 4: 43-year-old female, no admitted history, normal blood chem, BP, HbA1c	
Abnormality:	Significant proteinuria, microscopic hematuria
Possible etiologies:	Benign/Transient: menstruation (false elevation, contamination); exercise, fever, dehydration Pathologic: Glomerular: IgA nephropathy, Alport syndrome, thin basement membrane disease Tubulointerstitial disease: NSAID nephropathy, hypertensive nephrosclerosis Post-renal: UTIs, stones, tumors Systemic: Lupus, vasculitis, diabetes, hypertension
Additional information:	Confirmation of menses status Repeat urinalysis post-menses Microscopic evaluation: RBC morphology (dysmorphic RBCs suggest glomerular) Urine culture to rule out infection Serial renal function tests: eGFR, BUN Family history: Hereditary nephropathies Imaging: renal ultrasound if structural causes suspected
Morbidity mortality concern:	Persistent proteinuria and hematuria may indicate early glomerular disease, which can progress to chronic kidney disease (CKD) or end-stage renal disease (ESRD) Morbidity risk: Increased risk of hypertension, cardiovascular disease, and renal failure. Mortality risk: Elevated in cases with underlying glomerulonephritis or systemic disease
Presence of additional urine abnormalities:	Increased concern with: RBC casts or dysmorphic RBCs (glomerular pathology) White blood cells or bacteria (infection) Cylindruria or crystals: (tubular damage or stones)
Recommended action	Menses confirmed, accept or consider repeat UA after menstruation to rule out contamination Without menses or repeat confirms abnormalities, consider nephrology evaluation

34M non-smoker. No medical history.

- All labs normal. No history of proteinuria.
- Current exam shows normal BP readings
- Urinalysis
  - protein of 66 mg/dl (H)
  - P/C ratio of 0.415 (H)
- Reflex testing
  - albumin 0.6 mg/dL (normal)
  - A/C ratio normal

*** **Albuminuria is a specific marker for kidney disease** ***

Non-albuminuric proteinuria

Bence-Jones proteinuria
Light chains proteinuria
Multiple Myeloma

REMARKS: SPERM PRESENT.

Case 5: 32-year-old male, non-smoker, diabetes diagnosed last year, exam BP and renal function on blood profile are normal

Urinalysis
Protein 33 mg/dL (H) (0-30)
Protein / creatinine ratio normal
Microalbumin 6.8 mg/dL (H) (0-3)
Microalbumin/creatinine 58.8 mg/gCr (H) (0-30)

- What is the abnormality?
- What are the possible etiologies?
- What other information would be helpful to know?
- What is the underwriting mortality/morbidity concern?
- Would your decision change if there were other urine abnormalities also present?
- What is your recommendation?

Albuminuria: Underwriting Significance

Negative Prognostic Factors

- Associated with an increased risk of cardiovascular disease
- Known adverse prognostic factor in diabetics and those with HTN
- Standard of care for clinicians to routinely screen these patients with urine albumin

Positive Prognostic factors

- Can regress with treatment
  - ACE inhibitors or angiotensin II receptor blockers (ARBs)
- Can improve with better diabetic and blood pressure control
- Can improve the excess mortality risk
- Many underwriting manuals include guidance on albuminuria

Case 5: 32-year-old male, diabetes diagnosed last year, normal BP and serum creatinine	
Abnormality:	microalbuminuria, the earliest detectable sign of diabetic kidney disease
Possible etiologies:	Diabetic nephropathy: Most likely, given the recent diabetes diagnosis Transient causes: Exercise, fever, infection, hyperglycemia, or hypertension (though BP is normal here) Other renal or systemic conditions: Less likely without additional symptoms or lab abnormalities
Additional information:	Repeat microalbumin tests (persistence, 2 of 3 abnormal tests over 3–6 months confirms diagnosis) HbA1c and blood pressure trends Family history (e.g., kidney disease, cardiovascular disease) Presence of diabetic retinopathy: supports diagnosis of DKD Lifestyle factors: Diet, exercise, smoking, medication adherence
Morbidity mortality concern:	Microalbuminuria, strong predictor of progression to overt nephropathy and CKD, cardiovascular morbidity and mortality ; even in early stages, reflects endothelial dysfunction and microvascular damage, increasing long-term risk
Presence of additional urine abnormalities:	Elevated P/C ratio, hematuria or casts, elevated serum creatinine or reduced eGFR would suggest more advanced renal disease
Recommended action	Ideally serial repeat microalbumin testing over 3–6 months If persistent: more favorable with early intervention (e.g., ACE inhibitors/ARBs even with normal BP) and tight glycemic control Well managed additional minimal to mild rating; Uncontrolled or progressive: higher risk based on severity

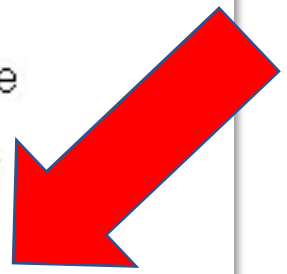
Key Points for Proteinuria/Albuminuria

- **Albuminuria** is a specific marker for kidney disease
- **Benign proteinuria** is often transient with lower levels of proteinuria (< 1 – 2 g/day)
- **Pathologic proteinuria** is often persistent
  - Suspect with comorbid medical conditions e.g., **Hypertension, Diabetes**
  - Suspect with **abnormal serum Creatinine** or **abnormal eGFR**
  - Suspect with **abnormal urine sediment** (RBCs, WBCs, casts)
  - Suspect with albuminuria
- Urine Creatinine has no prognostic significance
- P/C and A/C Ratios take precedence over absolute values
- Be aware of possible **contamination** as “proteinuria” may be due to extra-renal causes
  - Prostatitis
  - Seminal fluid
  - Vaginal secretions

Epithelial cells

- Found on skin and most inner body cavities/organs
- Having a few in urine = normal
- With larger amounts, most often represents SKIN CONTAMINATION (especially in a female)

Urine color	amber
Urine appearance	slightly cloudy
Specific gravity	1.023
pH	6.5
Urine ketone	none
Urine protein	none
Urine glucose	none
Urine nitrite	negative
Leukocyte esterase	none
RBC	32/HPF
WBC	4/HPF
Squamous epithelial	<2



WBCs in urine – Pyuria

- UTI or cystitis most common cause
- Asymptomatic bacteriuria common

WBCs	
Isolated	Often insurable without further investigation
+ Epithelial cells	Think contamination (skin, vaginal secretions)
+ protein/albumin + RBCs + casts	Think RENAL issue! Always needs investigation

CLUES for PATHOLOGICAL PROTEINURIA
Hypertension, Diabetes, ABN Serum Cr,
ABN urine sediment (RBC, WBCs, casts), albuminuria

Urinary casts

- Tiny tube-shaped particles formed in the kidney (always renal in origin)
- Molded in the shape of the tubules
- Casts often indicate pathologies: glomerular/tubular damage, inflammation, infection

Types of Casts	
Hyaline	Rarely of significance Concentrated urine Fever, exercise *Ignore
Granular	KIDNEY disease!
RBC casts	KIDNEY disease! Usually GN
WBC casts	Infection/Inflammation Sometimes kidney disease

Case 6: 55-year-old male, non-smoker, no adverse medical history

- Renal function (BUN, Creatinine) normal on blood profile
- Urinalysis
  - all normal EXCEPT
  - HEME severe positive
  - RBC 2 (within normal range)

- Discrepancy in results between dipstick urinalysis and urine sediment microscopy
  - False negative microscopy could be suspected when dipstick is strongly positive for hematuria and a normal number of RBCs is found on microscopy
  - This occurs due be lysis (disintegration) of urine RBCs often encountered due to delays in processing of the urine specimen
  - Rarely, a very dilute urine produces osmotic lysis of almost all the urinary RBCs, the dipstick detects hemoglobin, but no RBCs are visible

https://www.crlcorp.com/wp-content/uploads/2016/11/OTR-Isolated-Hematuria-as-a-Mortality-Risk-Predictor.pdf

Case 6: 55-year-old male, no adverse history	
Abnormality:	Dipstick HEME: Severe positive; Microscopy RBCs: 2/hpf (normal range)
Possible etiologies:	Dipstick-positive hematuria without visible red blood cells on microscopy, most likely RBC lysis - Delayed processing: urine sample sits too long before analysis, red blood cells lyse, leaving free hemoglobin that the dipstick detects, but no intact RBCs for microscopy Less likely - dilute Urine - Low specific gravity or hypotonic urine can cause osmotic lysis of RBCs. Dipstick detects heme pigment, but microscopy sees few or no intact cells, or Myoglobinuria or Hemoglobinuria -Dipstick detects heme but can't distinguish between: Hemoglobin (from lysed RBCs) or Myoglobin (from rhabdomyolysis) - microscopy won't show RBCs in these cases.
Additional information:	Urine color: Is it red, brown, or clear? Urine specific gravity: To assess dilution. Serum creatine kinase (CK): To rule out rhabdomyolysis. Serum hemoglobin: To assess for hemolysis. Timing of sample processing: Was there a delay? Repeat urinalysis: Fresh sample, processed promptly.
Morbidity mortality concern:	Transient or due to processing artifact: minimal concern Hemoglobinuria or myoglobinuria: possible hemolysis or muscle injury Persistent unexplained hematuria: possible concern for glomerular disease, urologic malignancy, or systemic illness
Presence of additional urine abnormalities:	Increased concern with: Proteinuria (glomerular disease); casts (renal parenchymal involvement); leukocytes/nitrites (infection); crystals (stones, metabolic)
Recommended action	With no adverse history, normal other labs, consider accept as processing artifact With any red flags, repeat; if persistent, postpone for evaluation

Case #7

Negative CxTriage

A case of hematuria

Case # 7

Male age 55, applying for life and critical illness coverage

- Recent history of hematuria (30 rbcs/uL and 9 rbc/hpf on repeat)
- Seen by urologist, normal renal ultrasound, negative CxTriage which is approved in Australia
- Information on the test
  - combines genomic, phenotypic and clinical biomarkers in patients with hematuria
  - suitable for low-risk patients for whom a more extensive evaluation may not be required
  - a clinical study of 587 patients presenting with gross hematuria demonstrated that CxTriage has a sensitivity of 95% and a negative predictive value of 98.5%”

Per urologist no need for scope, do you agree?

Critical Thinking Questions

- What is the abnormality?
- What are the possible etiologies?
- What other information would be helpful to know?
- What is the underwriting mortality/morbidity concern?
- Would your decision change if there were other medical conditions present?
- What is your recommendation?

Hematuria classification

Hematuria Class	Dipstick Result	RBCs/hpf	RBCs/uL*
Trace	Trace	1-4	1-28
Small	1+	5-10	29-70
Moderate	2+	11-25	71-175
Large	3+	26-35	176-245
Macroscopic	4+	≥36	≥246

Is this

Glomerular hematuria?

Non-glomerular hematuria?

I don’t know

Per urologist no need to scope.
Do you agree?

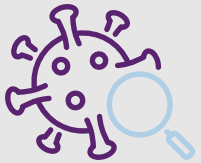
Yes

No

I don’t have enough information

Revising disease probability based on test results

What do they mean?



Is the disease present? What is the likelihood?

If we decide to rate, what rating should we apply?

RBCs (blood) in urine – Hematuria

Kidney
Renal tumor (benign/malignant)
Glomerular disease
Pyelonephritis
Renal Vein Thrombosis

Ureter
Malignancy, Stone, Stricture

Bladder
Malignancy, Cystitis

Prostate/Urethra
BPH, Cancer, Urethritis

May come from anywhere

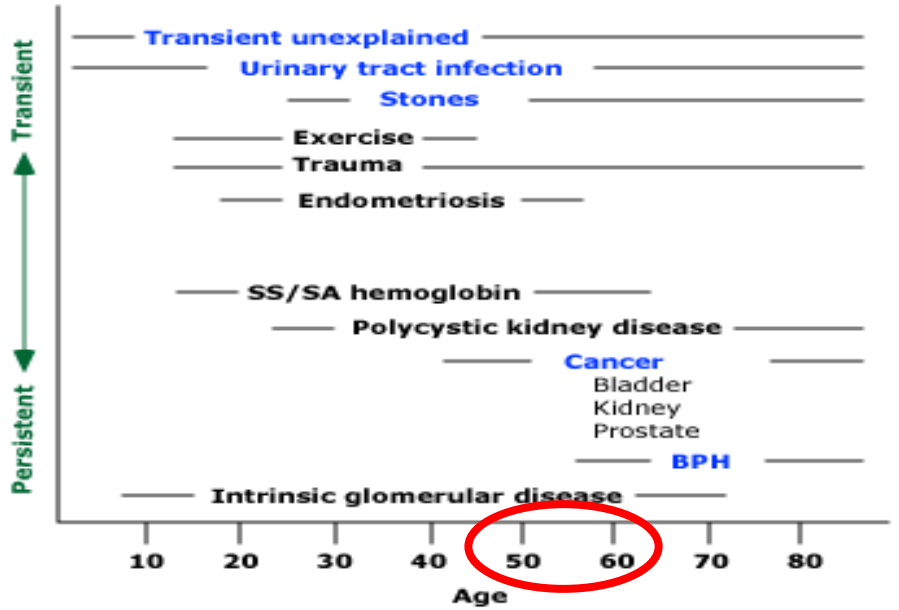
in the Urinary Tract

(kidney, ureter, bladder, prostate, urethra)

Microhematuria: ≥ 3 RBCs per HPF on microscopic evaluation

Gross Hematuria: Blood in the urine that can be seen with the naked eye

Major causes of hematuria by age and duration



Schematic representation of the major causes of hematuria in relation to the age at which they usually occur (horizontal axis), transience or persistence (vertical axis), and frequency (blue implies more frequent).
BPH: benign prostatic hyperplasia.

9-15% of normal people have "benign" transient hematuria

(J Urol 1989;141(2):350
JAMA 1986 Jul 11;256(2):224-9)

Clinical pearls

- Signs of glomerular bleeding include
  - RBC casts
  - Dysmorphic appearance of some RBCs
  - Proteinuria exceeding 500 mg/day that is temporally related to the onset of hematuria
  - One study found that a urine albumin-to-protein ratio of ≥590 mg/g had a sensitivity of 97.1 percent for glomerular hematuria
  - A rise in serum creatinine (or reduction in estimated glomerular filtration rate [eGFR]) that is temporally related to the hematuria

Is this

Glomerular hematuria?

Non-glomerular hematuria?

I don’t know

Initial microhematuria workup

- **History and Physical Exam** (assess risk factors, gyne history, etc.)
- **Blood tests** (eGFR, creatinine, BUN)
- **Urine culture** to r/o UTI (if clinically indicated)
- **Risk factor assessment** with work-up based on risk

Urothelial Cancer Risk Factors

Table 3: Urothelial Cancer Risk Factors

Risk Factors Included in AUA Microhematuria Risk Stratification System	Additional Urothelial Cancer Risk Factors[6, 14,55-59]
Age	Irritative lower urinary tract symptoms
Male sex	Prior pelvic radiation therapy
Smoking use	Prior cyclophosphamide/ifosfamide chemotherapy
Degree of microhematuria	Family history of urothelial cancer or Lynch Syndrome
Persistence of microhematuria	Occupational exposures to benzene chemicals or aromatic amines (e.g., rubber, petrochemicals, dyes)
History of gross hematuria	Chronic indwelling foreign body in the urinary tract

* The Panel recognizes that this list is not exhaustive.

Source: Barocas DA, Boorjian SA, Alvarez RD et al: Microhematuria: AUA/SUFU guideline. J Urol 2025; 204: 778

Table 4: AUA/SUFU Microhematuria Risk Stratification System 2025

Risk of malignancy*	Low/Negligible 0-0.4%[21, 22, 24]	Intermediate 0.2-3.1%[21, 22, 24]	High 1.3-6.3%[21, 22, 24]
Number of criteria patient must meet	All	One or more	One or more
Degree of hematuria on a single urinalysis	3-10 RBC/HPF⁺	11-25 RBC/HPF⁺	>25 RBC/HPF⁺
Alternative criteria for degree of hematuria		Previously low/negligible -risk patient with no prior evaluation and 3-25 RBC/HPF* on repeat urinalysis	History of gross hematuria
Age for women	<60 years	≥60 years	*Women should not be categorized as high-risk solely based on age*
Age for men	<40 years	40-59 years	≥60 years
Smoking history	Never smoker or <10 pack years	10-30 pack years	>30 pack years
Presence of additional risk factors for urothelial cancer (see Table 3)	None	Any	One or more plus any high-risk feature

*Risk of malignancy is based on the definition from the 2020 AUA/SUFU Guideline in which women being age < 50 year was a criterion for low-risk, women being age 50-59 years was a criterion for intermediate-risk, and women being age > 60 was a criterion for high-risk. Based on interval studies showing significantly lower risk of urothelial malignancy in women, women being age < 60 years is a criterion for low-risk, women being age > 60 years is a criterion for intermediate-risk, and women cannot be categorized as high-risk based on age alone in the 2025 guideline iteration.

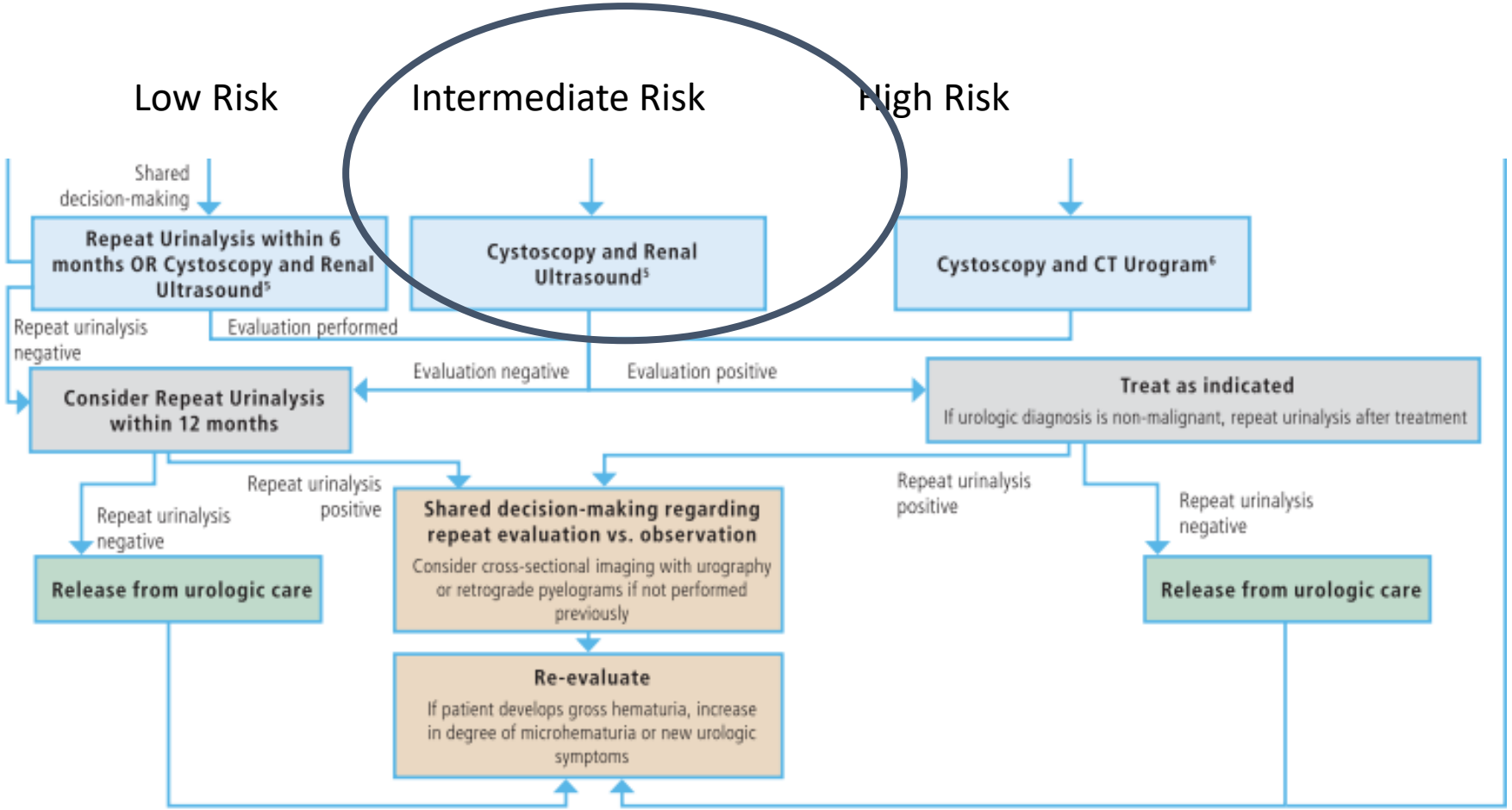
⁺HPF: High-Power Field

2025 AUA Hematuria Guidelines

Microhematuria Risk Stratification System

Microhematuria: AUA/SUFU Guideline (2025) - American Urological Association (auanet.org)

Hematuria Urologic work-up 2020

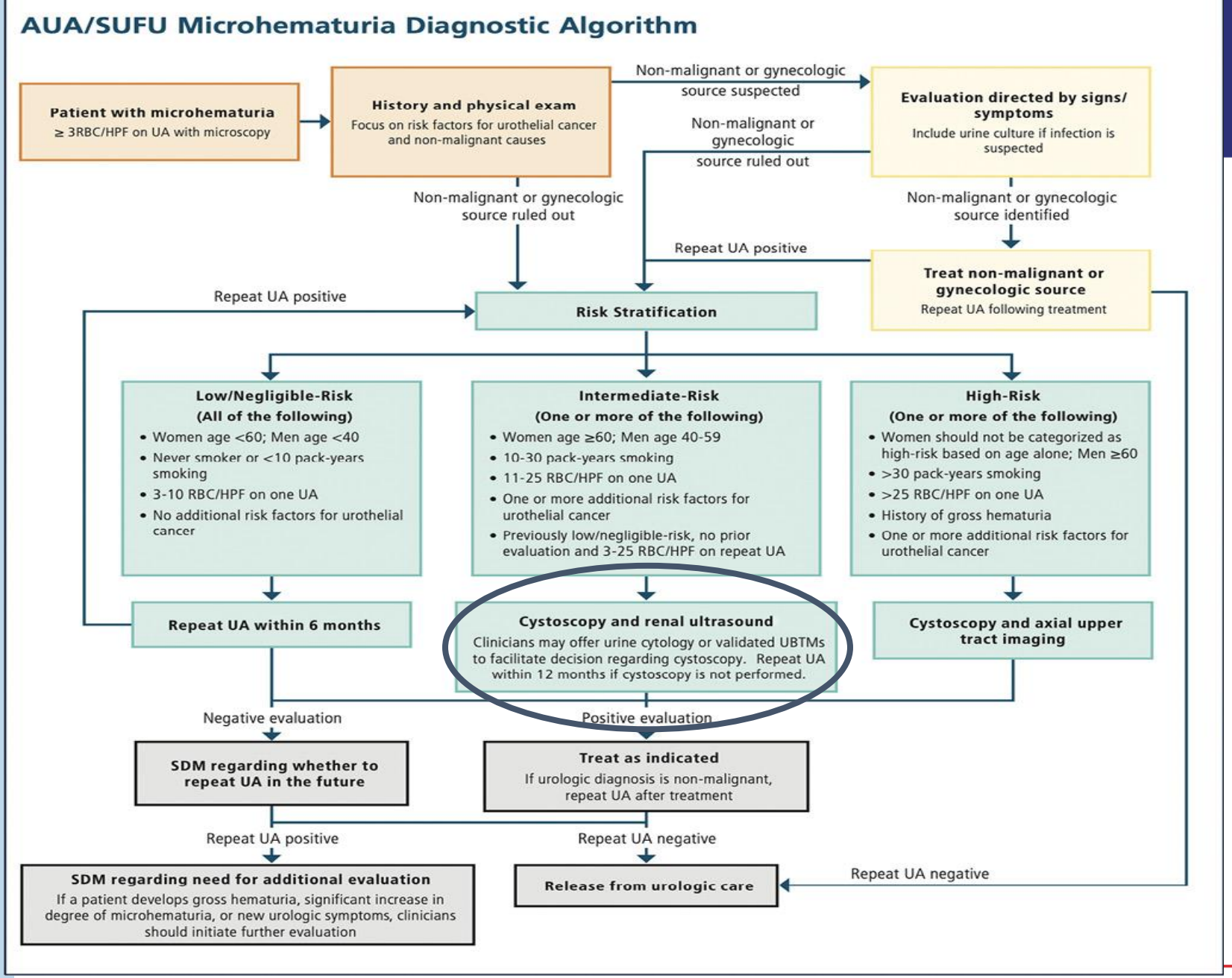


Microhematuria: AUA/SUFU Guideline (2020) - American Urological Association (auanet.org)

Source: Barocas DA, Boorjian SA, Alvarez RD et al: Microhematuria: AUA/SUFU guideline. J Urol 2020; 204: 778

AUA 2025 Hematuria Guidelines

Refined Risk Stratification and Introduction of Urinary Biomarkers



Barocas DA et al, J Urol. 2025;213(5):547-557.

October 18-23, 2025

2025 Updated guidance on the use of urine-based tumor markers (UBTM) and cytology

"Some appropriately counseled intermediate-risk patients may wish to avoid cystoscopy"

Cytology or validated UBTM assist in decisions regarding the utility of cystoscopy

Negative testing- low likelihood of having bladder cancer

No cystoscopy- kidney and bladder ultrasound and urinalysis within 12 months

Repeat urinalysis shows persistent hematuria, cystoscopy recommended

Refined Risk Stratification 2025-Urine cytology and biomarkers

- Low-risk group, minimal risk of malignancy, repeat UA rather than immediate evaluation
- In the absence of high-risk features, women should not be categorized as high risk based on age alone
- UBTMs or cytology may be utilized for further risk stratification of **intermediate-risk patients** who wish to avoid cystoscopy
- UBTMs/cytology should not be used in low-/negligible- or high-risk patients to inform decision for cystoscopy

What is your decision?

Standard

Substandard

Postpone for complete workup

Specifics of the CxTriage test

- Information on the test
  - "combines genomic, phenotypic and clinical biomarkers in patients with hematuria
  - suitable for low-risk patients for whom a more extensive evaluation may not be required
  - a clinical study of 587 patients presenting with gross hematuria demonstrated that …. has a sensitivity of 95% and a negative predictive value of 98.5%"

AUA Microhematuria Risk Stratification System

Low (patient meets all criteria)	Intermediate (patients meets any one of these criteria)	High (patients meets any one of these criteria)
• Women age <50 years; Men age <40 years • Never smoker or <10 pack years • 3-10 RBC/HPF on a single urinalysis • No risk factors for urothelial cancer (see Table 3)	• Women age 50-59 years; Men age 40-59 years • 10-30 pack years • 11-25 RBC/HPF on a single urinalysis • Low-risk patient with no prior evaluation and 3-10 RBC/HPF on repeat urinalysis • Additional Risk factors for urothelial cancer (Table 3)	• Women or Men age >60 years • >30 pack years • >25 RBC/HPF on a single urinalysis • History of gross hematuria

Source: Barocas DA, Boorjian SA, Alvarez RD et al: Microhematuria: AUA/SUFU guideline. J Urol 2020; 204: 778

Urinary molecular markers for the detection of bladder cancer (Jan. 2025)

Bladder tumor antigen	50 to 90	90	Urinary tract infection, hematuria, calculi, BPH, prior intravesical treatment
NMP 22	42 to 100	70 to 91	Inflammation
NMP 52	97	94	
BLCA-4	89 to 96	95 to 100	
BLCA-1	80	87	
Survivin	64 to 100	93 to 100	
CK 8 and CK 18	35 to 79	68	
CK 19	43 to 96	70	Urinary tract infection, calculi, post-BCG
FDP	70	68 to 86	
Hyaluronic acid, hyaluronidase	82 to 100	81 to 90	
mRNA markers			
▪ Cxbladder*	74 to 95	45 to 81	
▪ Xpert Bladder Cancer Monitor¶	46 to 84	77 to 95	
▪ Bladder EpiCheck	62 to 68	82 to 88	

BPH: benign prostatic hyperplasia; NMP: nuclear matrix protein; BLCA-4: bladder cancer-associated NMP 4; CK: cytokeratin; BCG: Bacillus Calmette-Guerin; FDP: fibrin degradation products.

* Cxbladder test: *IGFBP5*, *HOXA13*, *MDK*, *CDK1*, *CXCR2*.

¶ Xpert Bladder Cancer Monitor test: *IGF2*, *ANXA10*, *ABL1*, *UPK1B*, *CRH*.

UpToDate®

Performance metrics of a test

Sensitivity:
minimizes **false –**

Specificity:
minimizes **false+**

PPV and NPV

- Allow you to *clinically* say how likely it is that a patient has a specific disease
- Directly relate to **prevalence** (number of cases in a defined population at a single point in time, usually expressed as a %)

Clinical Calculator: Predictive value of a test

Positive Predictive value

Prevalence	30	%
Sensitivity	50	%
Specificity	70	%

Result

PPV	41.67	%

Negative Predictive Value

Prevalence	30	%
Sensitivity	50	%
Specificity	70	%

Result

NPV	76.56	%

Mortality risk calculation based on post-test probability of disease

- If we know what the mortality risk of the disease we are testing for, we can convert post-test disease probability to relative mortality risk
  - Assume the disease that we are testing for has a relative mortality risk of 300%.
  - The pretest probability of disease is 30% and the **post-test probability of disease is 20%.**
  - The relative mortality risk (MR) can be computed as:
  - **Mortality Risk given Test + = (p[D] | Test + x MR Disease) + (1 - p[D] | Test + x MR STD**
- **Calculate the risk**
  - 0.2*300%+0.8*100%= 60%+80%=**140%**

Case #8

Why search for zebras?

Another case of proteinuria

Case #8

56-year-old male

- Clean application, no medical history
- Urinalysis: PCR 1500 mg/g (200 mg/g), ACR 300 mg/g (30 mg/g), normal KFTs, normal BP readings

Should we be concerned?

Why search for zebras when underwriting kidney disease?

Discussion questions

What investigations, if any, would you like to see?

What is the morbidity and mortality risk?

Discussion Questions

#1

List lab abnormalities: high grade proteinuria and moderately increased albuminuria

#2

Is this isolated proteinuria?

#3

What if his blood work shows elevated globulin and a monoclonal spike is detected on protein electrophoresis?

#4

What kind of proteinuria do you suspect?

What kind of proteinuria did he have?

Mainly glomerular?

Mainly non-glomerular?

I don’t have enough information

Discussion questions?

- Is this benign proteinuria (e.g., transient, orthostatic)?
- Is this isolated proteinuria?
- Does he have history of renal disease or systemic disease such as dm, SLE?
- Does he have any symptoms or signs such as fever, fatigue, weight loss, joint pain, rash, bone pain, signs of edema?
- Does he have normal RFTs and bp readings?

Definitions of Proteinuria and Albuminuria

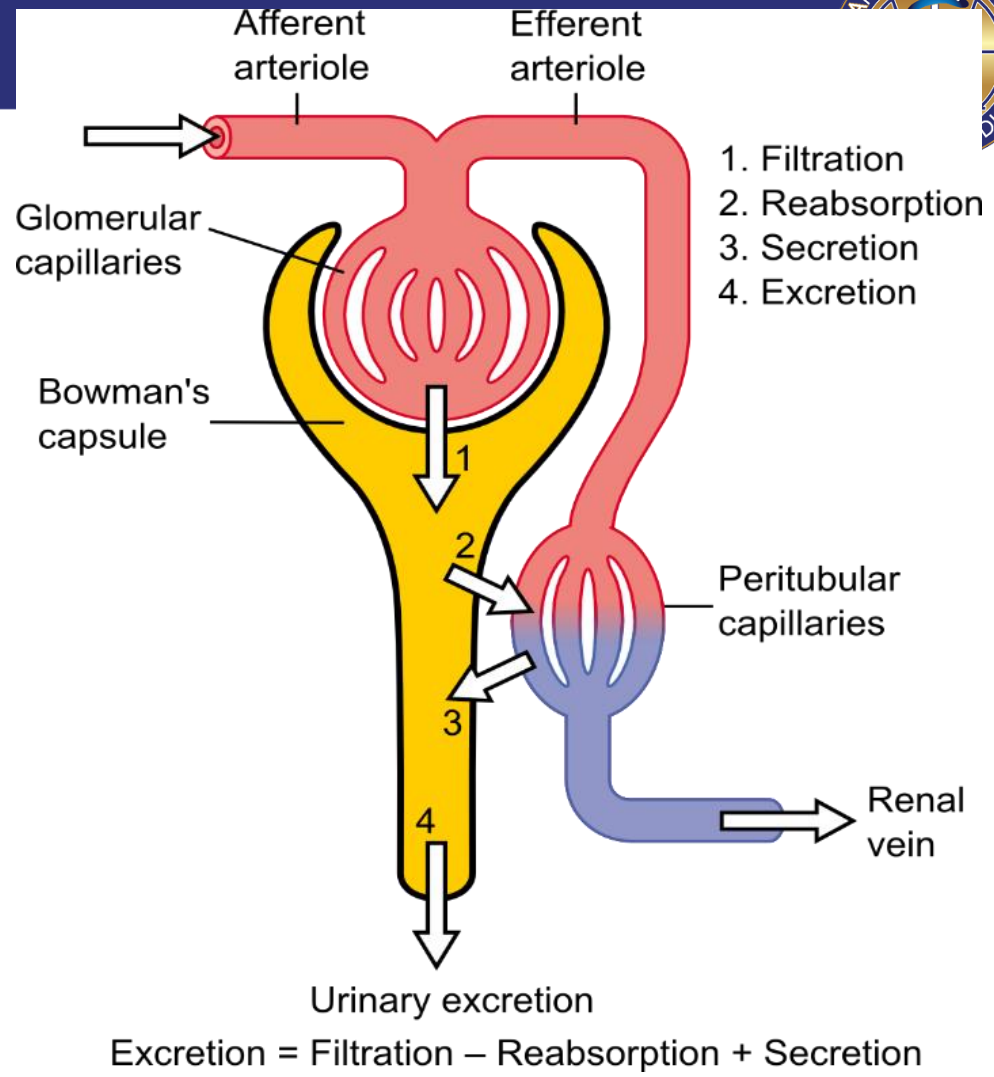
Urine Collection Method	Normal	Microalbuminuria	Macroalbuminuria or Clinical Proteinuria
Total Protein			
24-hour excretion (varies with method)	<300 mg/d	NA	>300 mg/d
Spot urine dipstick	<30 mg/dL	NA	>30 mg/dL
Spot urine protein-creatinine ratio (varies with method)	<200 mg/g	NA	>200 mg/g
Albumin			
24-hour excretion	<30 mg/d	30-300 mg/d	>300 mg/d
Spot urine albumin-specific dipstick	<3 mg/dL	>3 mg/dL	NA
Spot urine albumin-creatinine ratio (varies by sex*)	<17 mg/g (men) <25 mg/g (women)	17-250 mg/g (men) 25-355 mg/g (women)	>250 mg/g (men) >355 mg/g (women)

Method	Normoalbuminuria	Microalbuminuria	Clinical Proteinuria
Spot Urine for Albumin:Creatinine Ratio	< 30 mg/g	≥ 30 mg/g <300 mg/g	≥ 300 mg/g

negative	0 mg/dL
trace	15-30 mg/dL
1+	30-100 mg/dL
2+	100-300 mg/dL
3+	300-1000 mg/dL
4+	>1000 mg/dL

What kind of proteinuria do you suspect?

- Continuous filtration and cleansing of the blood, removes waste, impurities
- Filtrate: first urine which leaks out of the blood vessels into the Bowman capsule and into tubules
  - What can be in the filtrate?
    - Glucose
    - AA
    - Na
  - What doesn't get filtered?
    - RBCs (small amounts only)
    - **Larger proteins, e.g., albumin (small amounts only)**



Source: https://courses.lumenlearning.com/suny-dutchess-ap1/chapter/physiology-of-urine-formation-in-the-nephrons/

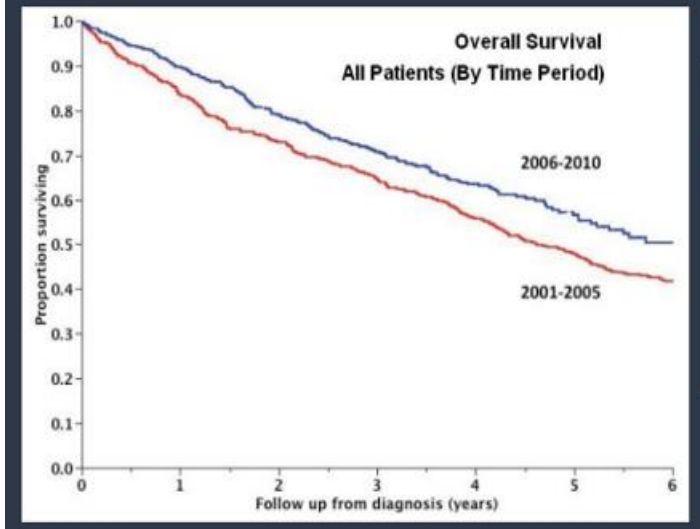
MGUS basics

- People with MGUS have the following features
  - The M-protein level in the blood is less than 30 g/L and often stays at the same level for many years
  - Plasma cells make up less than 10% of the blood cells in the bone marrow
  - **No M-protein or only small amounts of monoclonal light chain in urine**
  - There is no tumour and there are no **CRAB** features (signs) of multiple myeloma (high **c**alcium level, **r**enal insufficiency, **a**nemia or **b**one disease)

People with MGUS do not have any signs or symptoms

Why worry about MGUS?

MULTIPLE MYELOMA: PROGNOSIS



BETTER THAN IT WAS

...BUT STILL BAD

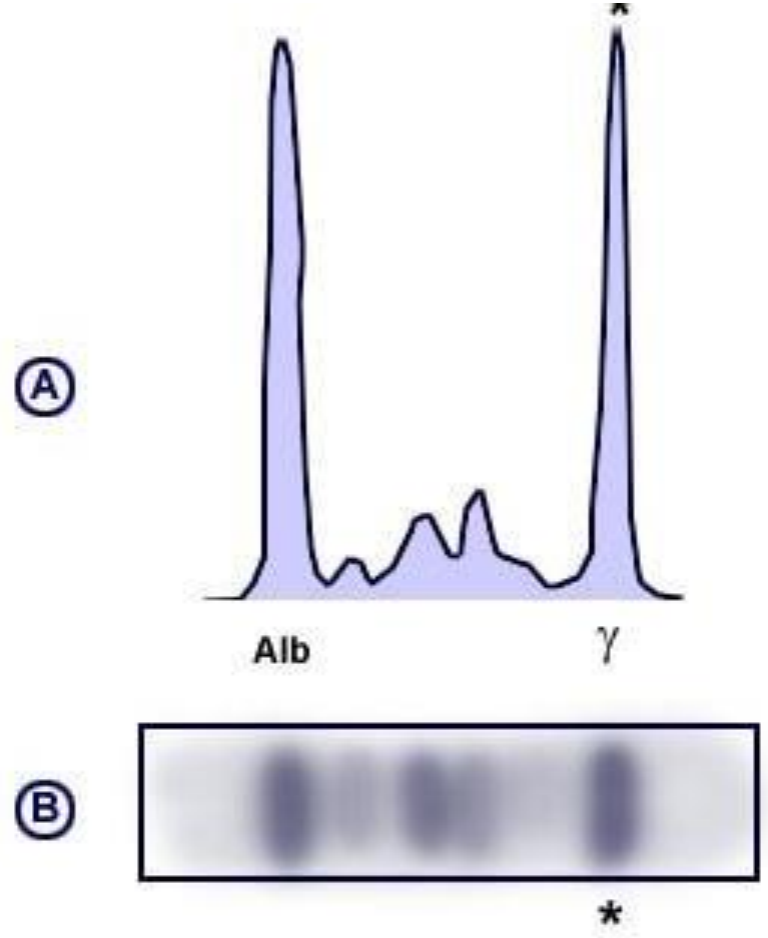
Better than it was…

but still bad.

Not every MGUS becomes myeloma, but all myelomas come from MGUS

M protein (monoclonal protein or paraprotein)

- Monoclonal **immunoglobulin** present in an amount that can be detected by immunofixation of serum or urine, or by a serum free light chain (FLC) assay
- Can be an intact immunoglobulin (i.e., containing both heavy and light chains) or can be composed of only light chains or only heavy chains
- The presence of an M protein indicates an underlying clonal plasma cell or lymphoproliferative disorder



Source: https://www.uptodate.com/contents/laboratory-methods-for-analyzing-monoclonal-proteins/abstract/1

Serum and urine protein electrophoresis and immunofixation

SERUM ELECTROPHORESIS *Amended*

		Flags	RefInterval	Units
Total Protein	71.0		62.0 - 77.0	g/L
Albumin	41.0		36.0 - 48.0	g/L
Globulin	30.0		20.0 - 42.0	g/L

Remarks
(1)MONOCLONAL BAND DETECTED IN MID GAMMA REGION.(2)PARAPROTEIN LEVEL 15 g/L.

IMMUNOFIXATION
Immunofixation
IgG KAPPA MONOCLONAL BAND.

CALCIUM *Amended*

		Flags	RefInterval	Units
Calcium (Corrected for Alb)	2.27		2.16 - 2.52	mmol/L

URINE ELECTROPHORESIS *Amended*

		Flags	RefInterval	Units
U-BJP	Negative			
Urine Protein	53.00		0.00 - 150.00	mg/L

Remarks
NO MONOCLONAL BAND DETECTED.

IMMUNOFIXATION URINE
Immunofixation
NEGATIVE FOR MONOCLONAL BAND.

- **S and Urine PEP**: electrophoresis for the **detection** and **quantification** of a monoclonal protein in the blood
- **Serum immunofixation**: confirms the presence of a monoclonal protein and identifies **the type** (e.g., IgG Kappa); it **does not quantify** the M-protein

Dipstick method does not detect Bence-Jones protein (free light chain protein)

What is your decision?

Rated?

Postpone?

I don’t have enough information

Why search for zebras?

Monoclonal gammopathy of renal significance

*"Although Monoclonal gammopathy of renal significance is considered a non-malignant or premalignant hematologic condition, its effects on the kidney are **not** benign, and patients frequently develop progressive kidney disease and end-stage kidney disease"*

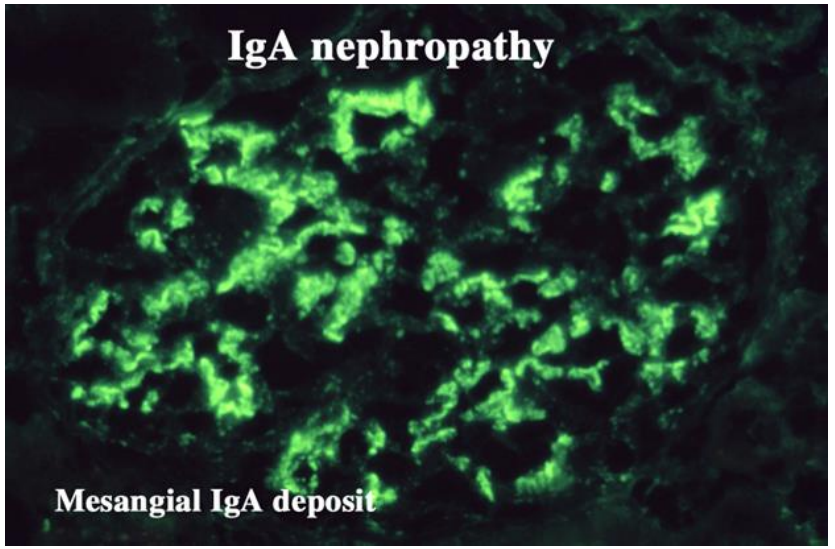
KIDNEY FUNCTION TESTS
CHRONIC KIDNEY DISEASE

Case #9

- 56-year-old female, build 151cm/52.3 kg (5 feet and 115 lbs)
- History of IgA nephropathy and “renal disease” due to analgesic abuse
- Nephrology report indicates no serial renal function tests (RFTS)
- Current labs protein creatinine ratio of 0.98 mg/mg creatinine (0.2), serum creatinine **115 µmol/l** (90 µmol/l) (1.3 mg/dl)
- BP is 120/80
- **Anemia** secondary to thalassemia trait & IgA nephropathy; on iron supplement, Hb 9.5 g/L

IgA Nephropathy

- Most common type of glomerulonephritis
  - Occurs with greatest frequency in Asians and Caucasians
    - 200k in US, 200K in Europe, 800k in China, 130k in Japan
- Peak incidence in the second and third decades of life
- Progression to ESKD if higher proteinuria levels and/or an elevated serum creatinine level
  - 20-30% at 20 years



http://www.uptodate.com

Clinical presentation of IgAN

I. 40% present with one or recurrent episodes of visible hematuria, usually following an upper respiratory infection

II. 40% have microscopic hematuria and usually mild proteinuria, incidentally, detected on a routine examination

III. <10% present with either nephrotic syndrome or acute rapidly progressive glomerulonephritis picture characterized by edema, hypertension, and renal insufficiency as well as hematuria

Additional Information

- Renal biopsy
  - Ig A nephropathy with high grade chronicity, at least 35% cortical scarring, interstitial nephritis is suggested (“no cellular crescents but 3 glomeruli with fibrous crescent, patchy areas of tubular atrophy, diffuse moderate interstitial inflammatory infiltrates”)
- Initial disease presentation
  - Nephrotic syndrome; history of NSAIDS use

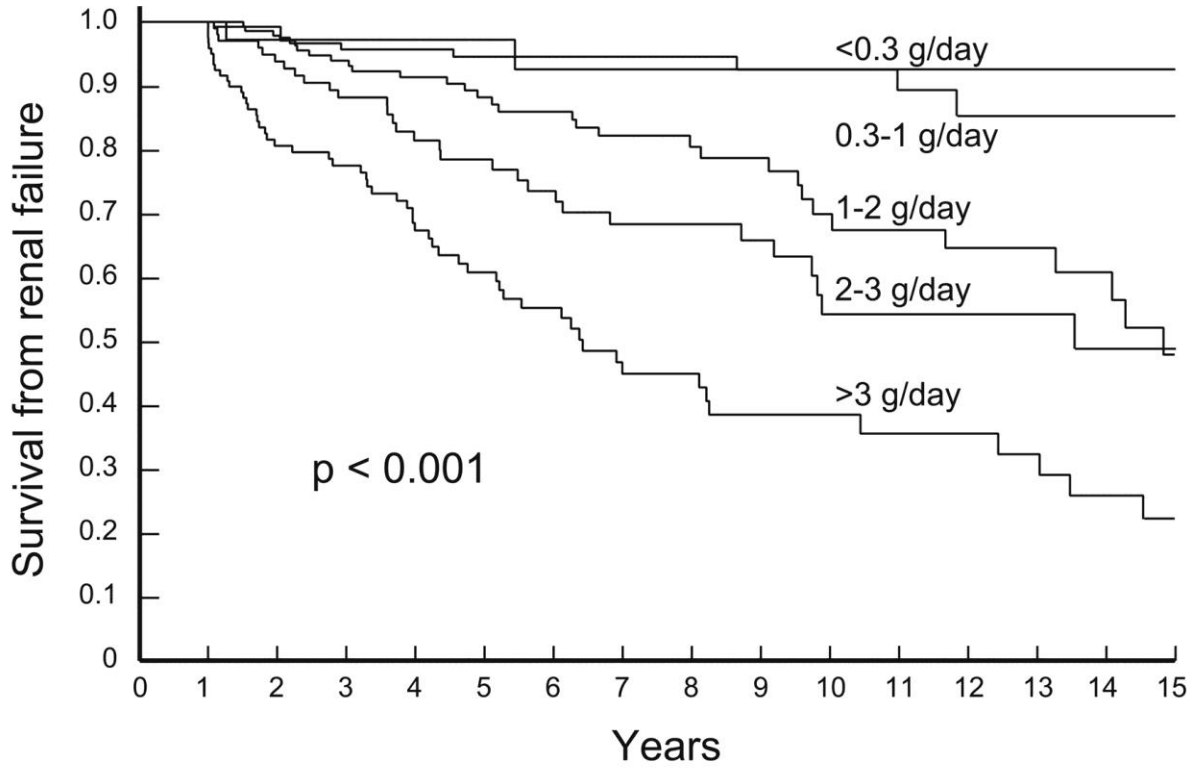
Risk Stratification in IgAN

- Clinical predictors of progression of IgA nephropathy include
  - elevated serum creatinine
  - hypertension
  - persistent protein excretion above 1000 mg/day

Initial disease presentation

- Nephrotic syndrome; history of NSAIDS use

Renal survival by category of proteinuria in 542 patients with biopsy proven IgA Nephropathy



<0.3 g/day	37	22	8	1
0.3-1 g/day	134	79	35	11
1-2 g/day	145	79	28	10
2-3 g/day	105	50	18	4
>3 g/day	120	44	13	6

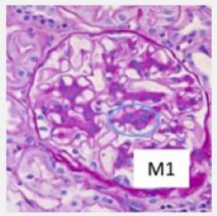
Nephrotic syndrome at diagnosis

Heather N. Reich et al. JASN 2007;18:3177-3183

Oxford classification
(MEST-C score)

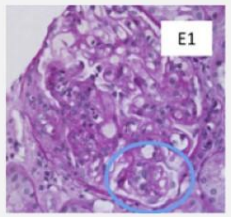
Histologic risk factors for progressive disease

Using MEST-C Scores for Dynamic Patient Stratification



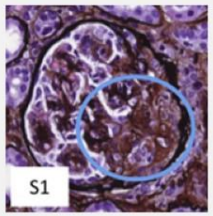
Mesangial hypercellularity

≥ 4 mesangial cells in any mesangial area of a glomerulus



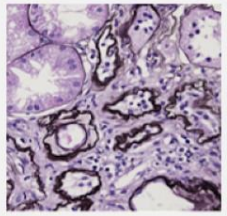
Endocapillary hypercellularity

Increased number of cells in glomerular capillary lumen



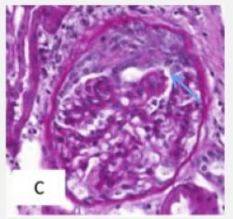
Segmental glomerulosclerosis

Adhesion or sclerosis not involving the entire glomerulus



Tubular atrophy/ interstitial fibrosis

Percentage of tubular atrophy/interstitial fibrosis of cortical area



Cellular/fibrocellular crescents

Extra capillary cell proliferation > 2 cell layers thick and < 50% matrix

M	E	S	T	C
M0 ≤ 50% of glomeruli	E0 Absence	S0 Absence	T0 0% to 25%	C0 Absence
M1 > 50% of glomeruli	E1 Any presence	S1 Any presence	T1 26% to 50%	C1 < 25% of glomeruli
			T2 > 50%	C2 ≥ 25% of glomeruli

Pattrapornpisut P, et al. Am J Kidney Dis. 2021;78:429-441; Lusco MA, et al. Am J Kidney Dis. 2016;68:e33-e34.

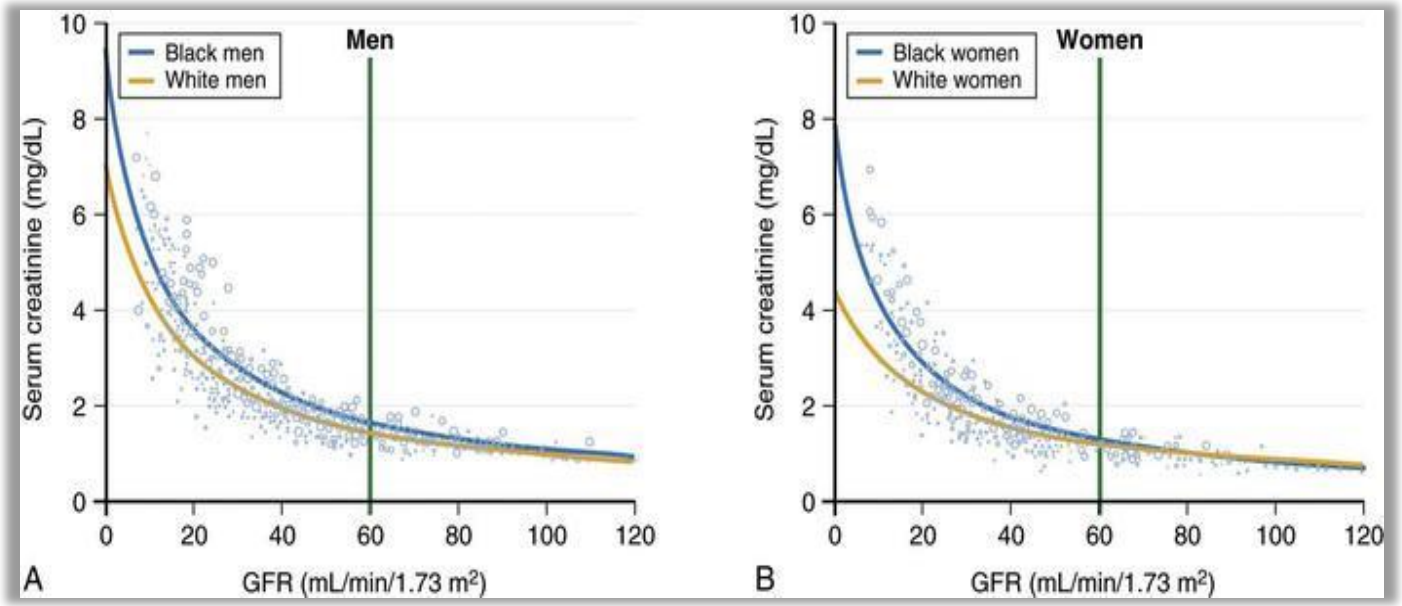
Key Questions

1. What do you think of her serum creatinine level, and does it correlate well with her GFR/renal function?
2. Does she have CKD? What stage?
3. What else would you like to know?

Renal Function Tests and Estimation of GFR

- Serum creatinine and Blood Urea Nitrogen
- Serum Cystatin C
- Creatinine Clearance measurement and estimation
- eGFR

Serum Creatinine



Relation between serum creatinine levels and measured glomerular filtration rate (GFR) by 125I-iothalamate GFR among black and white men and women.
Note how a significant decrease in GFR can occur, despite normal or near-normal serum creatinine values.

Levey AS, Bosch JP, Lewis JP, et al: A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461-470.

Key limitations in using creatinine to estimate GFR

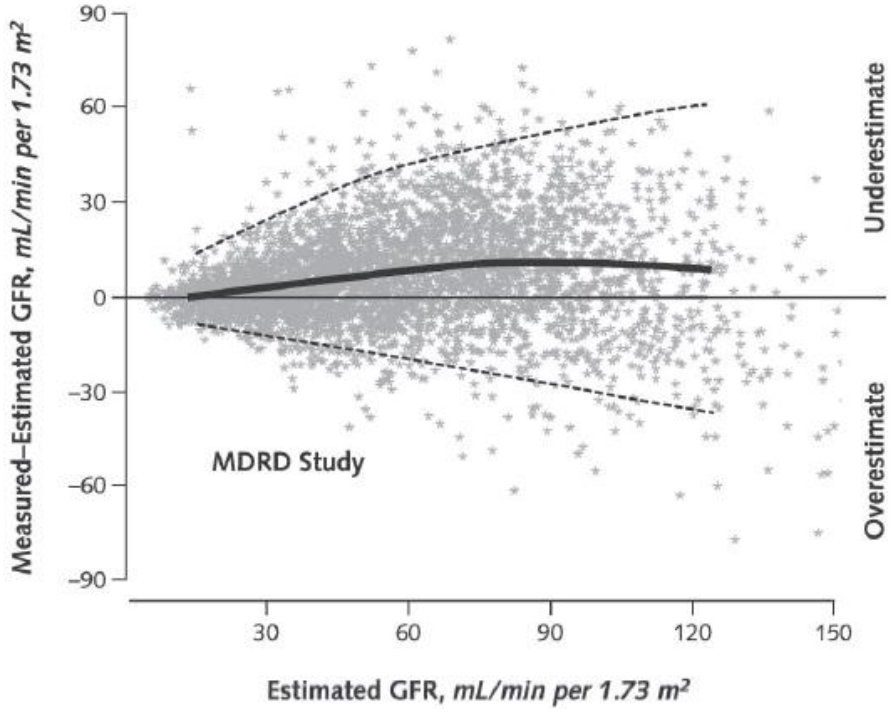
- Issues associated with **creatinine measurement**

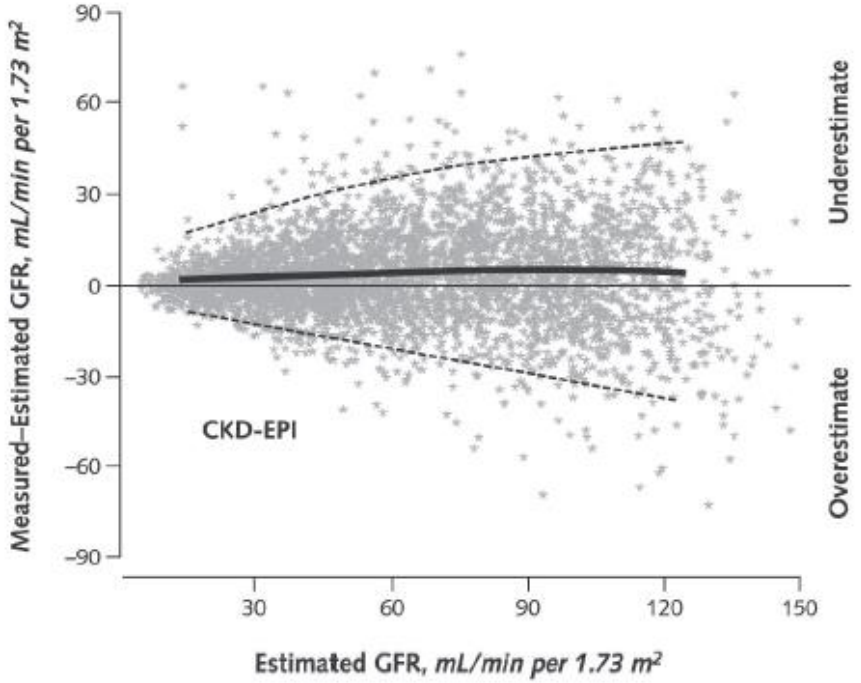
  (^ temperature, hemolysis, transportation)
- Variations in **creatinine production** (diet, gender, ethnicity?, creatine supplements)
- Variations in **creatinine secretion** (drugs)
- Certain substances may interfere with **the assay** (Cefoxitin)

FACTOR	MECHANISM
Age, sex, ethnicity, body habitus, malnutrition, deconditioning, exercise, amputation, paralysis.	Lower muscle mass generates less creatinine and hence has lower serum creatinine levels.
Pregnancy	Decreases S.Cr due to increase in plasma volume (dilutional) and increase in GFR.
Extrarenal creatinine excretion	Intestinal creatinine degradation and creatinine excretion in other bodily fluids increases in advanced CKD.
Dietary protein intake	Diets heavy in meats can increase creatinine level. Vegetarians have lower S.Cr.
Cimetidine, trimethoprim	Blocks tubular Cr secretion raising S.Cr values.
Fibrates	May increase Cr production by muscles. (?)
Flucytosine, hemoglobin	Falsely increases S.Cr values by interfering with enzymatic assay.
Metamizole, methyldopa, ethamsylate	Falsely decreases S.Cr values by interfering with enzymatic assay.

Performance of the CKD-EPI and MDRD Study Equations

CKD-EPI equation should be used for general population as it performs better than MDRD





Andrew S. Levey, et al; A New Equation to Estimate Glomerular Filtration Rate, Ann Intern Med 2009

Cystatin C

- Protein that is produced by all nucleated cells and found in bodily fluids
- Cystatin C-based estimates for GFR are believed to be less influenced by muscle mass or diet than creatinine-based estimates
- Some studies showed that correlates better with gfr than serum creatinine especially at higher levels of GFR
- Higher cystatin C levels are associated with
  - male sex, greater height and weight, higher lean body mass, higher fat mass
  - diabetes
  - higher levels of inflammatory markers
  - hyper- and hypothyroidism, and glucocorticoid use

Inker, Lesley et all, Assessment of Kidney Function, June 12 2018; https://www.uptodate.com

Understanding the limitations of eGFR equations

- Creatinine clearance consistently overestimates GFR by at least 10-20 %
- The MDRD study and the Cockcroft-Gault equations are less accurate in populations with normal or near-normal GFR and are not longer recommended
- CKD EPI and MDRD equations **overestimate** GFR in Asian populations possibly related to differences in body mass and diet
- KDIGO 2021 guidelines on CKD recommend using the creatinine-based CKD-EPI equation as an initial test
- **Cystatin C and creatinine equation** is more accurate for the assessment of GFR than serum creatinine in certain populations and can be used as a confirmatory test for diagnosis of CKD

Staging of CKD since 2012

CKD Classification and Staging

- Green: Low risk (LR)
- Yellow: Moderate risk (MR)
- Orange: High risk (HR)
- Red: Very high risk (VHR)

Kidney function stage GFR (ml/min/1.73m²) Description and range				Kidney damage stage Urine albumin/creatinine ratio Description and range		
				A1	A2	A3
				Normal to mild increase <30mg/g	Moderate increase 30-300 mg/g	Severe increase >300mg/g
	G1	Normal or high	≥90	LR	MR	HR
	G2	Mild decrease	60-89	LR	MR	HR
	G3a	Mild to moderate decrease	45-59	MR	HR	VHR
	G3b	Moderate to severe decrease	30-44	HR	VHR	VHR
	G4	Severe decrease	15-29	VHR	VHR	VHR
	G5	Kidney failure	<15	VHR	VHR	VHR

Egfr 48 ml/min
G3a/A3

KDIGO CKD Work Group Kidney Int Suppls 2013;3:1-150

CKD Patient Approach

1. Does she have CKD?
2. Stage: assess GFR, albuminuria
3. Determine etiology
4. Assess for evidence of progression
5. Assess for associated complications
6. Assess life expectancy and future treatment

CGA staging
C=cause
G=GFR
A=albuminuria

Causes of CKD

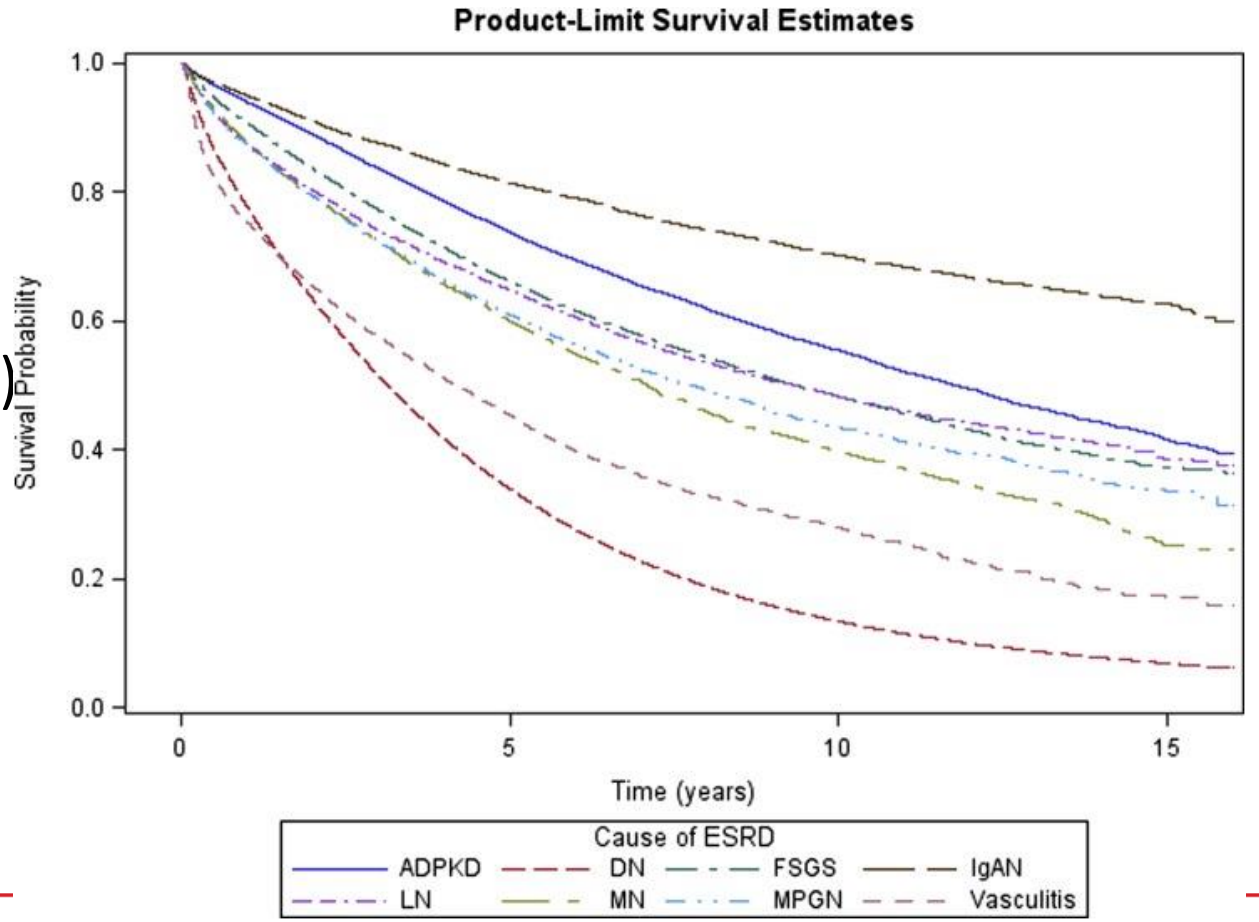
	Systemic diseases	Primary kidney diseases
Glomerular diseases	Diabetes, systemic autoimmune diseases, systemic infections, drugs, neoplasia (including amyloidosis)	Diffuse, focal or crescentic proliferative glomerulonephritis; focal and segmental glomerulosclerosis; membranous nephropathy, minimal change disease
Tubulointerstitial diseases	Systemic infections, autoimmune, sarcoidosis, drugs, urate, environmental toxins (e.g. lead), neoplasia (myeloma)	Urinary tract infections, stones, obstruction
Vascular diseases	Atherosclerosis, hypertension, ischemia, cholesterol emboli, systemic vasculitis	ANCA-associated renal limited vasculitis, fibromuscular dysplasia
Cystic and congenital diseases	Polycystic kidney disease, Alport's syndrome, Fabry's disease	Renal dysplasia, medullary cystic disease

Fatehi, Pedram et. All, Diagnostic approach to the patient with newly identified chronic kidney disease; Aug. 2018: https://www.uptodate.com

ESRD Outcomes in GN patients

O'Shaughnessy et al. 2015, 84,301 patients with ESRD attributed to GN , median follow up 2 years

- **IgAN patients**
  - **Fewest** comorbidities and lowest use of hemodialysis (70.1%)
  - Lowest crude mortality
- **Adjusted mortality highest in LN** (AHR=1.75)
- Other GN subtypes
  - Membranous nephropathy: AHR=1.23;
  - FSGS: AHR=1.37;
  - Membranoproliferative GN: AHR=1.38;
  - Vasculitis: AHR=1.51



Outcomes – Patient and Graft Survival

- Life expectancy after renal transplantation depends on
  - Patient age
  - The source of the graft
  - The primary kidney disease
  - The presence and degree of comorbidities

Graft and Patient Survival by Source

- In 2015, the five-year survival for patients who received a deceased-donor kidney in 2010 was 86.8% and for living-donor recipients was 93.5% (Scientific Registry of Transplant Recipients)
- Survival was lower in recipients age 65 years and older and in recipients with diabetes as cause of kidney failure
- Fifteen-year graft failure among adult living donor transplant recipients was 37.3% (1990-2005) and 52.8% for adult deceased donor transplant recipients

11. Hart A, Smith JM, Skeans MA, et al. OPTN/SRTR 2015 Annual Data Report: Kidney. Am J Transplant. 2017 Jan; 17(Suppl 1): 21-116. https://www.ncbi.nlm.nih.gov/pubmed/28052609

Patient and Graft Survival by Diagnosis

- The presence of systemic disorders, particularly vascular disease, is associated with poorer long-term patient survival after renal transplantation
- The survival of diabetic patients after renal transplantation is lower than that reported for nondiabetic patients due to the prevalence of extrarenal vascular disease.
- Diabetic recipients five-year graft and patient survival
  - Living donor kidney recipients : 83% graft survival and 86.6% patient survival
  - Deceased donor kidney recipient: 72% graft survival and 82.5% patient survival

Patient and Graft Survival by Diagnosis

- Diseases that primarily affect the kidneys (e.g. ADPKD and GN): better post-transplant long-term survival rates than those with systemic disorders
- Donor kidney recipients with history of glomerular disease:
  - 87% graft survival and 97% patient survival for living donor kidney recipients
  - 79% and 92.5% for deceased donor recipients
  - Superior patient and graft survival is seen Alport Syndrome (the lack of additional organ system involvement and non-recurrent nature of the disease)
- HTN as primary cause of the ESKD:
  - 84% and 91.6% graft and overall survival

Long Term Mortality and Morbidity

- Mortality:
  - Coronary artery disease (30.4%)
  - sepsis (27.1%),
  - neoplasm (13%)
  - stroke (8%)
- Morbidities for transplant patients: hypertension, hyperlipidemia, cardiovascular disease (a 10-fold increase over the general population), diabetes, osteoporosis and malignant neoplasms

Long Term Mortality and Morbidity

- Renal function parameters one year post transplantation: the most important predictors of graft survival
- Infections are the leading cause of recipient death during the first year
- Patient survival at 10 and 20 years has improved (75.9% and 64.8%, respectively)
- Ultra-long graft survival (20 years and up) is not uncommon (~ 25% of kidney transplant patients)
- Death with a functioning graft occurs in about 25% of transplant recipients

QUESTIONS?
THANK YOU!

Reported NPV for the detection of bladder cancer using UBTM

Table 5: Reported Negative Predictive Values for the Detection of Bladder Cancer Using the Available Urine Cytology and Urine-Based Biomarkers

Assay[A]	Hematuria Population	Total Patients (n)	Reported Negative Predictive Value	AUA Strength of Evidence[B]
CxBladder Resolve	MH and GH	Total n=548; MH n=289	99.8%[98]	B
CxBladder Triage	MH[C]	n=390	99%;[97] 95%CI: 95 to 100%[D]	A
	MH and GH	Total n=571; MH n=185	100%;[99] 95%CI: 94 to 100%[E]	C
NMP22 BladderChek (qualitative)	MH	n=876	95% - 100%[100-102]	C
Urine cytology	MH	n=513	95.0% - 98.7%[100, 103, 104]	C
	MH and GH	Total n=4,497; MH n=1,743	89.5%[F] - 96.0%[77, 105-107]	C
UroVysion	MH and GH	Total n=828; MH n=384	97%[105]	C
Xpert	MH and GH	Total n=1,152; MH n=597	98.0% - 99.6%[105, 106]	C

Footnotes

A. To be included in the table, NPV for the assay was reported in a purely MH population or MH patients comprised ≥25% of total hematuria population. All studies included ≥100 microhematuria patients.
B. Strength of evidence in relation to reported NPV. Refer to Table 1 for strength of evidence definition and methodology.
C. The RCT[97] is the only identified study designed to evaluate use of a urine-based biomarker to guide evaluation.
D. NPV for detection of high-grade disease[97], 100%; 95%CI: 97 to 100%. NPV for lower risk patients, 100%; 95%CI: 94 to 100%.
E. NPV reported for MH subgroup.[99]
F. NPV of 89.5%[107] reported for detection of bladder cancer and UTUC.

How is proteinuria measured

Semiquantitative methods

Chemical

- Reagent area impregnated with pH indicator (tetrabromophenol blue) and a buffer (detects Albumin)
- Dipstick is relatively insensitive to non-albumin protein
- “Microalbuminuria" will not usually be identified by this method

Turbidimetric

- Measures all urinary proteins
- Sulfosalicylic/Trichloroacetic acid
- Denatures protein