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Approach to Proteinuria and Hematuria

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Overview

- Proteinuria
  - Measurement and interpretation
  - Red flag presentations
  - Diabetes vs. not diabetes
  - General management
- Hematuria
  - Measurement and interpretation
  - Urologic vs glomerular causes

How much proteinuria is normal?

	Excretion Rate (mg/day)	Percentage of Total
TOTAL	**80 (±24)**	**100**

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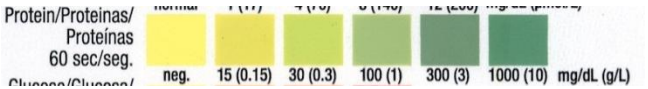
Plasma Protein (Total)	**40**	**50**
Non Plasma Proteins Total	**40**	**50**
TOTAL	**80 (±24)**	**100**

How much proteinuria is normal?

	Excretion Rate (mg/day)	Percentage of Total
Plasma Protein (Total)	40	50
Albumin	12	15
IgG	3	
IgA	1	5
IgM	0.3	
Light Chains	3.7	4.6
Kappa	2.3	
Lambda	1.4	
Beta Microglobulin	.12	<2
Other plasma proteins	20	25
Non Plasma Proteins Total	40	50
Tamm Horsfall	40	50
Other Renal Proteins	<1	<1
TOTAL	80 (±24)	100

Methods of Proteinuria Assessment



- Dipstick Urinalysis
  - Detects negatively charged proteins (albumin)
  - Semiquantitative (dependent on reader error and urine concentration)
  - Repeat dipstick under ideal conditions (no UTI, recent exercise, fevers)
- Formal quantification is needed

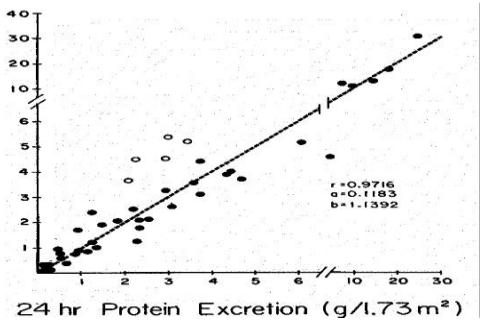
Dipstick Proteinuria Equivalent For Daily Excretion

Dipstick Reading	mg/dL	mg/day
Trace	15	100-200
1+	30	200-500
2+	100	500-1500
3+	300	2000-5000
4+	1000	>5000

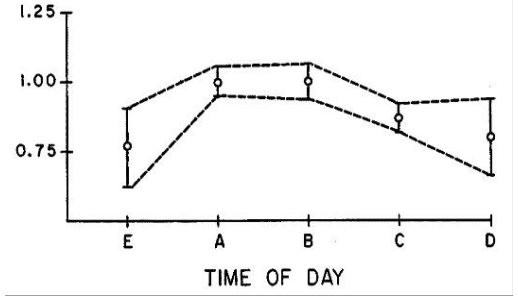
Quantification of Proteinuria

- 24 hour urine collection is gold standard
- Spot protein (or albumin)/creatinine ratio is acceptable
  - Consider timing
    - First morning void is ideal
  - Consider Body Size
    - Small size-spot measurements overestimate 24 hour urine measurements
    - Large size-spot measurements underestimate 24 hour urine measurements
- Kidney Disease Outcomes Quality Initiative (KDOQI) supports use of early morning albumin/creatinine ratio
  - Don't forget the possibility of non-albumin proteinuria (light chains)

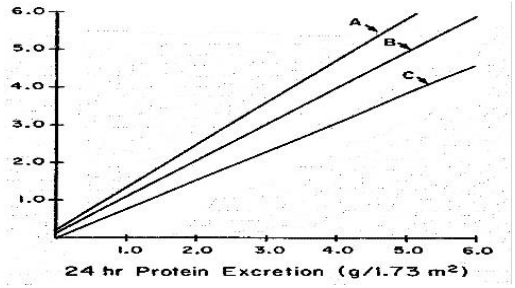
Spot urine protein/creatinine



Spot/24 hour ratio



Spot urine protein/creatinine



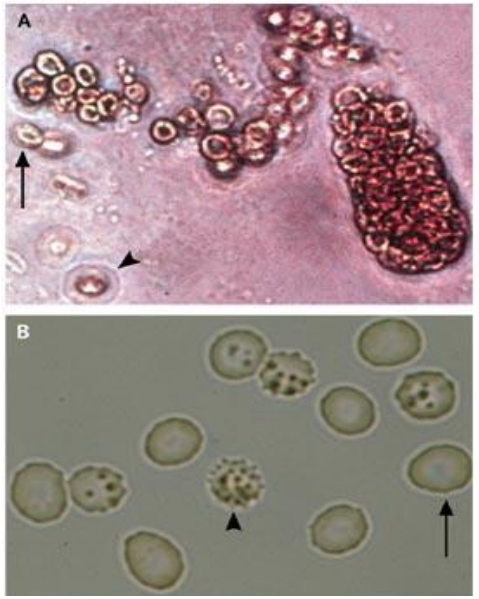
NEJM 1983; 309: 1543

What are the most urgent causes of proteinuria?

Rapidly Progressing Glomerulonephritis (RPGN)

Clinically presents with proteinuria and

- Abnormal renal function (progressing over days to weeks)
- Hematuria
- Hypertension
- Extracellular Volume Overload
- Often associated with serologic evidence of systemic disease
- Requires urgent renal evaluation (inpatient) with consideration of an urgent biopsy



If nothing urgent, does the patient have nephrotic syndrome?

- Presentation:
  - 3.5 g protein on 24 hour urine excretion
  - Hypoalbuminemia (<3 g/dL)
  - Hyperlipidemia
- Long term risk of progressive renal dysfunction
- Significant symptoms/complications related to
  - Edema
  - Infections
  - Thrombosis
  - Vitamin Deficiencies

Is there evidence of a systemic disease process?

+ Hematuria

- Lupus Nephritis (ANA, dsDNA, C3, C4)
- Virus Associated Disease (Hep C Ab, Hep B S Ag, HIV)
  - Cryoglobulinemia (cryos, RF)
  - Membranoproliferative Disease
  - HIV Immune Complex Disease
- Monoclonal Gammopathies of *Renal* Significance (Serum and urine electropheresis and immunofixation)
  - Light/Chain Heavy Chain Deposition Disease
- Pauci Immune Glomerulonephritis (ANCA)
- IgA Nephropathy (no test)

- Hematuria

- Lupus Nephritis (Class V): ANA, dsDNA, C3, C4
- Amyloidosis (SPEP/UPEP and IFE)
- Minimal Change Disease
  - Usually a history since childhood with variable relapse frequency
- Focal Segmental Glomerulosclerosis (FSGS)
  - Usually young adults (African American)
  - Includes HIVAN (HIV) and other secondary causes
- Membranous
  - Usually older adults (Caucasian)
  - PLA2R may be a biomarker
- IgA Nephropathy (no test)

Is this just diabetic kidney disease?

- Diabetes duration?
  - How long and how severely has HgbA1c been elevated?
- Other microvascular disease (neuropathy or retinopathy)
- Gradual Progression of kidney disease
  - No proteinuria
  - Microalbuminuria (30-300 mg/g, median 19 years after diabetes diagnosis)
  - Overt Nephropathy (>300 mg/g, median 11 years after microalbuminuria)
  - Elevated Serum Creatinine/ESRD (median 10 years after overt nephropathy)
- Absence of other evidence of another systemic or primary renal disease
  - Are serologies negative?
  - Is there significant hematuria?

What other kidney diseases do patients with diabetes have?

Types of NDRD	NDRD Alone (n=220)	DN + NDRD (n=164)	P-value
ATN (109)	38 (17.3)	71 (43.3)	<0.001
FSGS (69)	48 (21.8)	21 (12.8)	0.02
Primary FSGS (6)	6 (2.7)	0	0.03
Secondary FSGS (63)			
HTN related	19 (8.6)	10 (6.1)	0.35
HTN + Obesity related	16 (7.3)	10 (6.1)	0.65`
Obesity related	4 (1.8)	1 (0.6)	0.3
Other	3 (1.4)	0	0.13
HTN nephrosclerosis (70)	39 (17.7)	31 (18.9)	0.77
IgA nephropathy (35)	23 (10.5)	12 (7.3)	0.29
Membranous (23)	18 (8.2)	5 (3.0)	
Pauci Immune GN (19)	15 (6.8)	4 (2.4)	0.05
AIN (18)	11 (5.0)	7 (4.3)	0.73
Amyloidosis (10)	10 (4.5)	0	0.01
Cast Nephropathy (10)	8 (3.6)	2 (1.2)	0.14
Postinfectious GN (6)	3 (1.4)	3 (1.8)	0.72
Atheroembolic Disease (5)	2 (0.9)	3 (1.8)	0.43

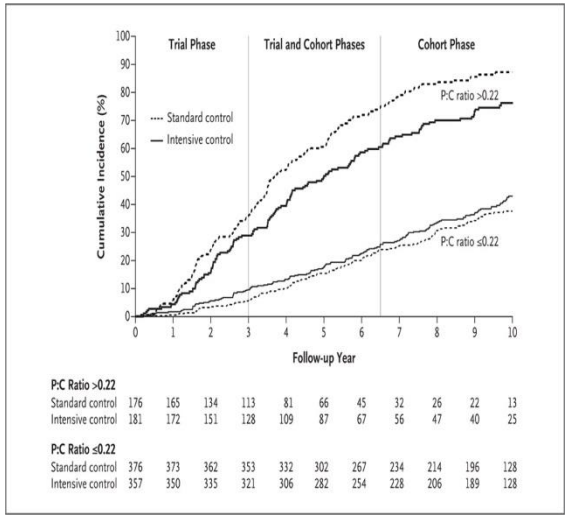
Clin J Am Soc Nephrol 2013; 8: 1718-1724

Management of Proteinuria

- Nephrology involvement if any concern this is not diabetes or if renal function is worsening
- Specific causes have specific treatments
  - Corticosteroids +/-
  - Chemotherapeutic Agents (Cytoxan)
  - Antimetabolite
  - Calcineurin Inhibitors
  - Rituximab
- General proteinuria management strategies remain

Management of Proteinuria-Stringent blood pressure control 2012 vs 2020

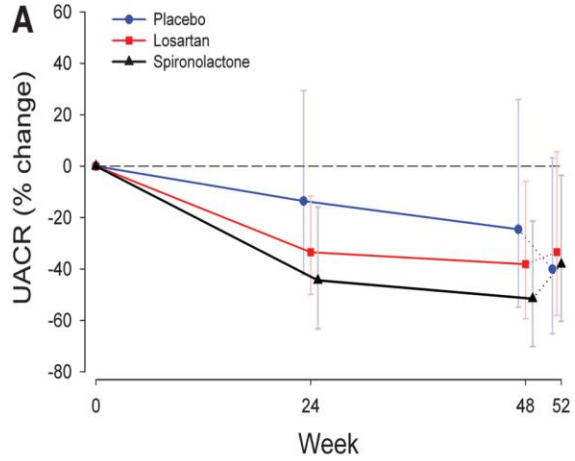
1. Advanced CKD
2. Diabetes
3. Baseline SBP 120-129 mmHg
4. Low DBP
5. Old age, Young age
6. Non standardized BP
7. “Proteinuria may no longer be an effect modifier of BP target with an SBP target <120 mmHg”

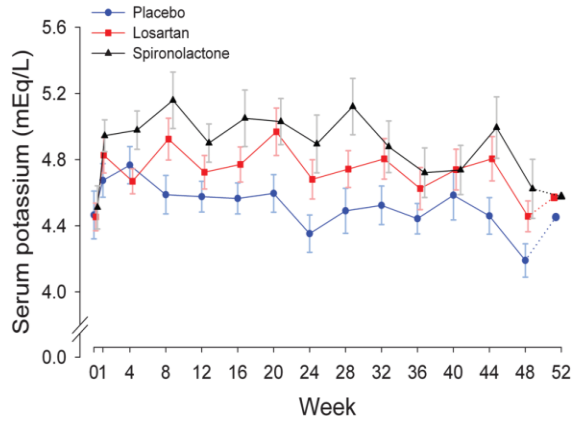


NEJM 2010; 363: 918

Single agent RAAS inhibition remains the recommended treatment for proteinuric patients

- **KDIGO guidelines recommend single agent ACEi or ARB for CKD, HTN, and albuminuria >30 mg/day with or without diabetes**
  - **Monitor Cr and K with initiation and dose titrations**
- RAAS Inhibitor + Direct Renin Inhibitor?
  - ALTITUDE trial: DM2 with microalbuminuria, macroalbuminuria, or some other CV disease
  - Aliskiren 300 mg daily vs. placebo
  - No effect on primary outcome
  - Increased risk of hyperkalemia and hypotension
- ACEi + ARB?
  - VA NEPHRON trial: DM2 + albuminuria >300 mg
  - Baseline Losartan
  - Lisinopril added
  - No effect on primary outcome
  - Increase risk of hyperkalemia and AKI
- RAAS Inhibitor + MRA
  - Dramatic Reduction in proteinuria
  - Hyperkalemia is common
  - No long term studies available on renal/CV outcomes
- Unclear if potassium binders will change attitudes or spark new trials





JASN 2009; 20: 2641

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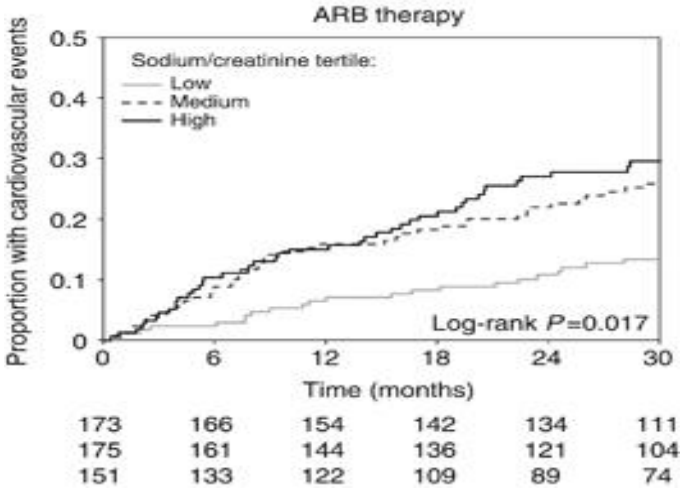
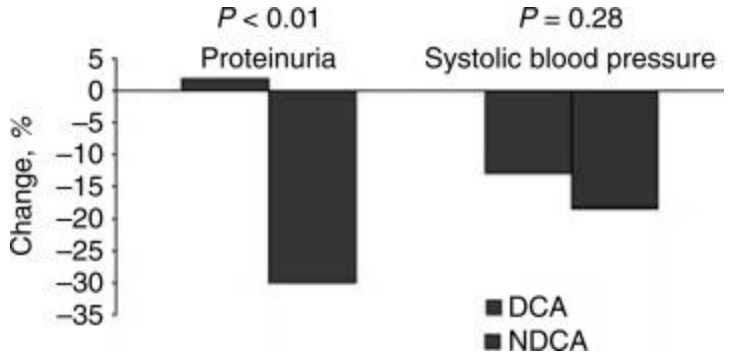
Other Considerations

- Sodium restriction (+/- diuretics) optimizes the antiproteinuric effect of RAAS inhibition (retrospective analysis of diabetic nephropathy trials
- Non-dihydropyridines offer more anti-proteinuric effects than dihydropyridines
  - Consider for patients intolerant of RAAS inhibition
  - Monitor for drug interactions
- Dihydropyridines + RAAS inhibitor are acceptable and useful if it helps control blood pressure
- Hyperlipidemia
- Thrombosis



KI 2012; 82: 330



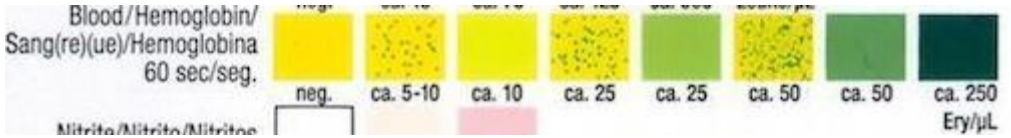
Proteinuria Summary

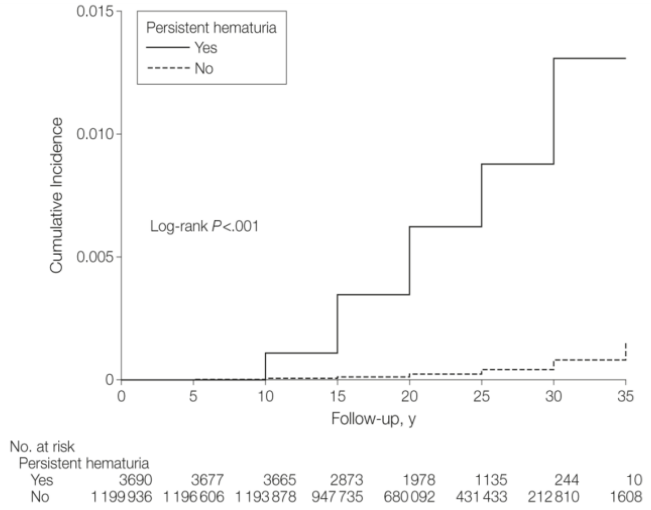
- Normal protein excretion is less than 150 mg/day with less than 20 mg/day of albuminuria
- Proteinuria requires confirmation and quantification (first morning void albumin/creatinine)
- Evaluation requires, CMP, UA, renal imaging and establishing a RPGN is not present
- An evaluation for systemic disease should be undertaken and nephrology evaluation for consideration of biopsy and evaluation for systemic disease
- Independent of the etiology, chronic proteinuria should be managed with tight blood pressure control (120-130???) using single agent RAAS inhibition if possible with other considerations for add-on therapy with diuretics and/or calcium channel blockers

Hematuria

Hematuria

- Are there red blood cells in the urine?
  - Dipstick reflects peroxidase activity as a marker of free hemoglobin
    - Sensitivity 91-100%
    - Specificity 65-99% (myoglobin, hemolyzed RBC)
  - American Urology Association defines clinical hematuria as ≥3 RBC/HPF
    - One sample is sufficient if the following are excluded
      - Vigorous Exercise
      - Trauma
      - Menstrual Bleeding
      - Urinary Tract Infection
    - Prevalence of 2.5-31%
      - Malignancy in about 1% (of all cases)
      - Glomerular hematuria is not always benign
- What is the origin of the red blood cells?





JAMA 2011; 306: 729-736

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Non Glomerular Hematuria in the Upper Tract

Age < 50 years	Age > 50 years
Nephrolithiasis	Nephrolithiasis
Pyelonephritis	Renal-cell cancer
Polycystic Kidney Disease	Polycystic Kidney Disease
Medullary Sponge Kidney	Pyelonephritis
Hypercalciuria/hyperuricosuria	Renal pelvis or ureteral transitional cell cancer
Renal trauma	Papillary necrosis
Papillary necrosis	Renal infarction
Ureteral stricture and hydronephrosis	Ureteral stricture and hydronephrosis
Sickle cell trait or disease	Renal tuberculosis
Renal infarction or AVM	

Causes of non-glomerular hematuria in the lower tract

Age < 50 years	Age > 50 years
Cystitis, prostatitis, urethritis	Cystitis, prostatitis, urethritis
Benign bladder and ureteral polyps/tumors	Bladder cancer
Bladder cancer	Prostate Cancer
Prostate cancer	Benign bladder and ureteral polyps and tumors
Urethreal and meatal strictures	

Updated Guidelines (2020) require risk stratification for imaging

Risk Factors for Urothelial Cancer	Additional Urothelial Cancer Risk Factors
Age	Irritative lower urinary tract symptoms
Male sex	Prior pelvic radiation history
Smoking use	Prior cyclophosphamide/ifosfamide chemotherapy
Degree of microhematuria	Family history of urothelial cancer or Lynch syndrome
Persistence of microhematuria	Occupational exposure to benzene chemicals or aromatic amines (rubber, petrochemicals, dyes)
History of gross hematuria	Chronic indwelling foreign body in the urinary tract

Updated Guidelines (2020) require risk stratification for imaging

Low Risk (meets all criteria)	Intermediate Risk (meets at least one)	High Risk (meets at least one)
Women age < 50 Men age <40	Women 50-59 Men 40-59	Women or men >60
Never smoker or <10 pack years	10-30 pack years	>30 pack years
3-10 RBC/HPF on a single UA	11-25 RBC/HPF on single UA Low risk patients with no prior eval and 3-10 RBC/HPF on repeat	>25 RBC/HPF on single UA
No risk factors for urothelial cancer	+ risk factors for urothelial cancer	History of gross hematuria

Updated Guidelines (2020) require risk stratification for imaging

Low Risk (meets all criteria)	Intermediate Risk (meets at least one)	High Risk (meets at least one)
Women age < 50 Men age <40	Women 50-59 Men 40-59	Women or men >60
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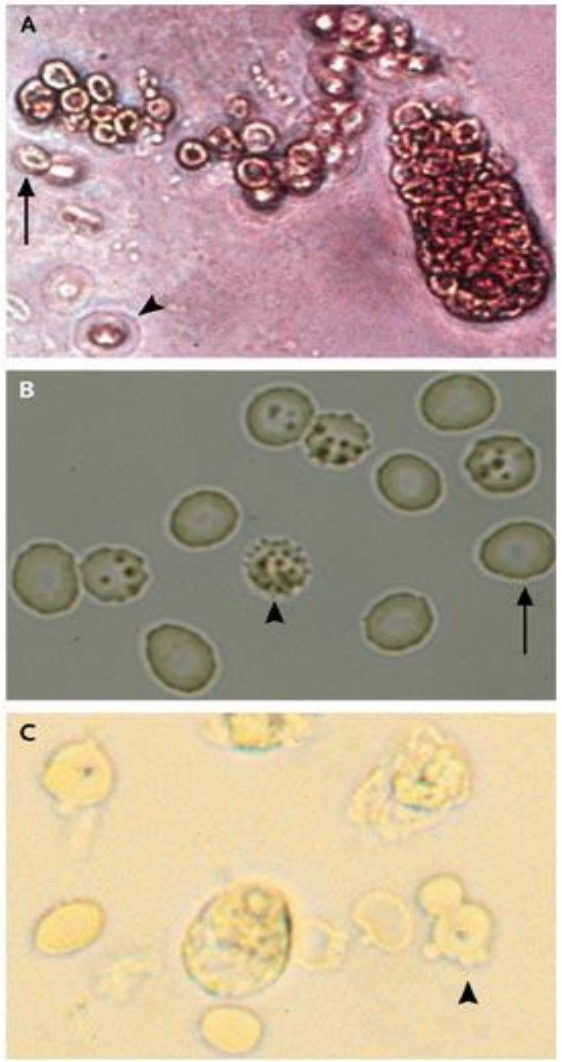
3-10 RBC/HPF on a single UA	11-25 RBC/HPF on single UA Low risk patients with no prior eval and 3-10 RBC/HPF on repeat	>25 RBC/HPF on single UA
No risk factors for urothelial cancer	+ risk factors for urothelial cancer	History of gross hematuria Family history of RCC or known genetic risk
Engage in shared decision making to repeat UA within 6 months or proceed with cystoscopy and US	Renal ultrasound and cystoscopy	Cystoscopy and axial upper tract imaging 1. Multiphase CT Urography 2. MR Urography 3. Retrograde pyelogram + non contrast imaging

What is the most urgent cause of hematuria?

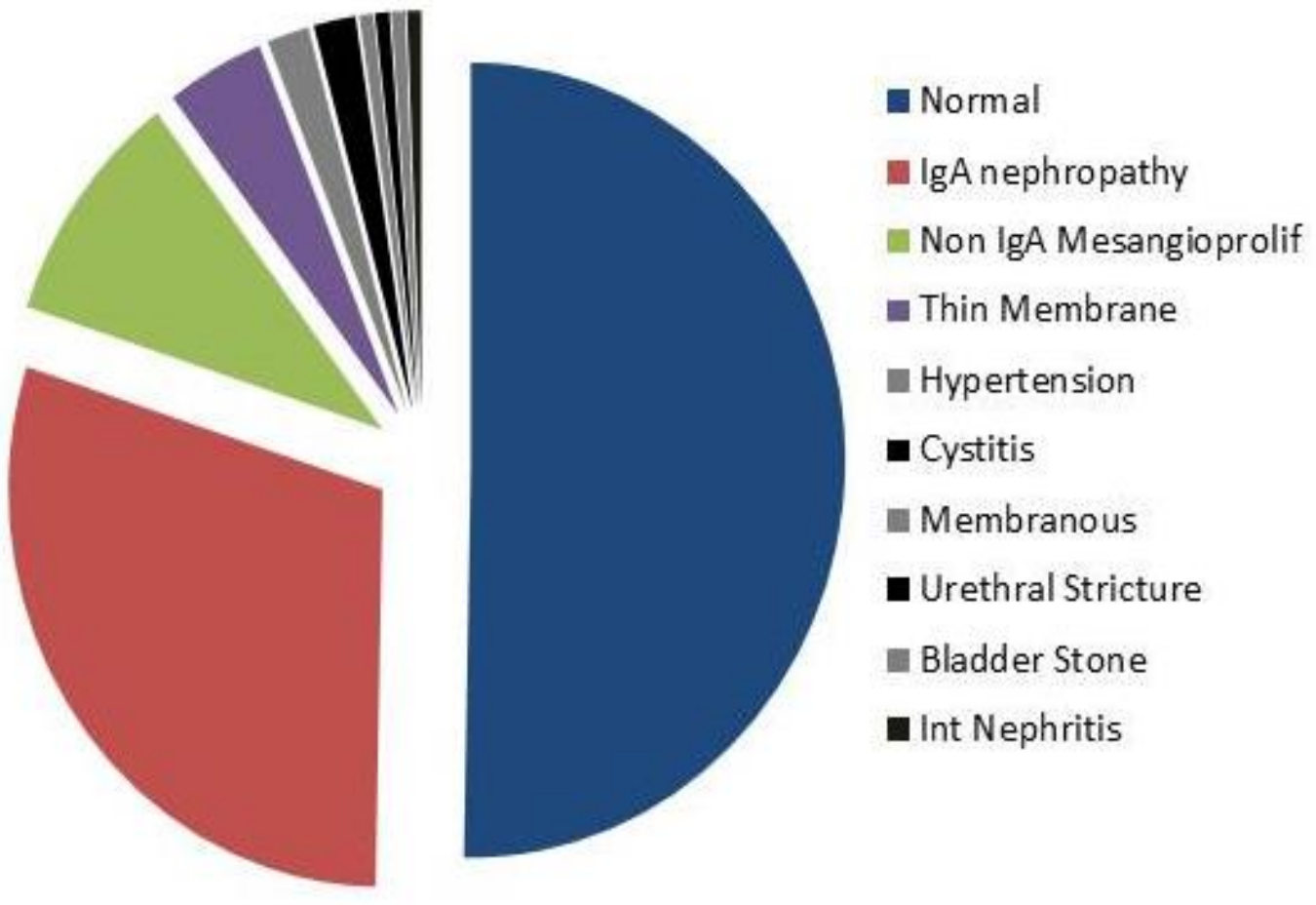
- Rapidly Progressing Glomerulonephritis (RPGN)
- Clinically presents with proteinuria and
  - Abnormal renal function (progressing over days to weeks)
  - Proteinuria
  - Hypertension
  - Extracellular Volume Overload
  - Often associated with serologic evidence of systemic disease
  - Requires urgent renal evaluation (inpatient) with consideration of an urgent biopsy



Systemic disease considerations

- Lupus Nephritis (ANA, dsDNA, C3, C4)
- Hepatitis Associated Disease (Hep C Ab, Hep B S Ag)
  - Cryoglobulinemia
  - Membranoproliferative Disease
- Deposition Diseases (Serum and urine electropheresis and immunofixation)
  - Light/Chain Heavy Chain Deposition Disease
  - Amyloidosis
- HIV nephropathy or immune complex related disease (HIV Ab)
- Pauci Immune Glomerulonephritis (ANCA)

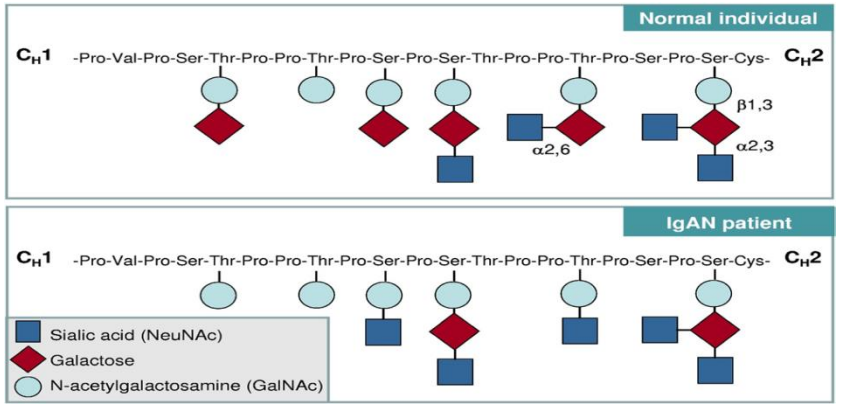
Renal biopsy findings with negative serologies



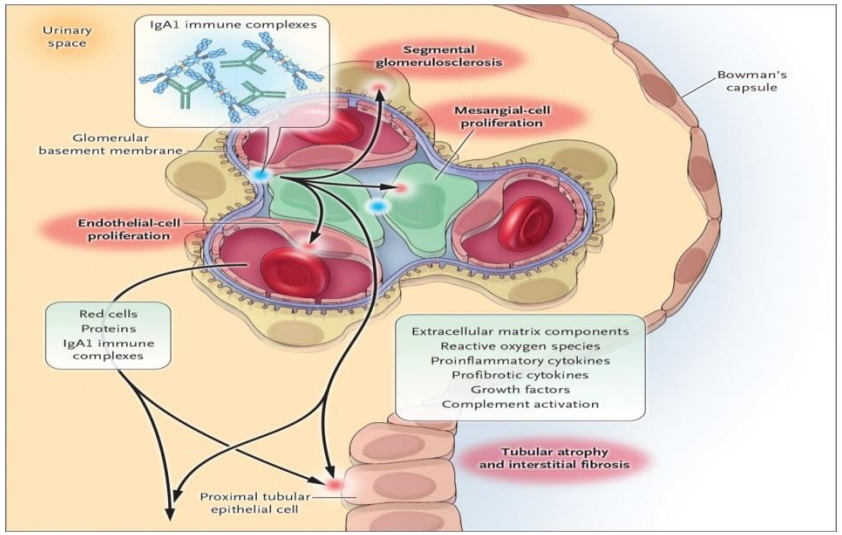
Adapted from *QJM* 1994; 87: 329

IgA Nephropathy

- The most common glomerular disease worldwide
  - Young Patients: macroscopic hematuria following URI or GI illness
  - Older patients: hypertension, proteinuria, CKD
  - AKI with macroscopic hematuria usually transient and reversible
- Secondary Causes Include
  - Dermatitis Herpetiformis
  - Seronegative Arthirtis
  - Small Cell Carcinoma
  - Lymphoma
  - Disseminated TB
  - Inflammatory Bowel Disease
  - Cirrhosis
  - Celiac Disease



Am J Kidney Disease 2011; 58: 992



NEJM 2013; 368: 2402-2414

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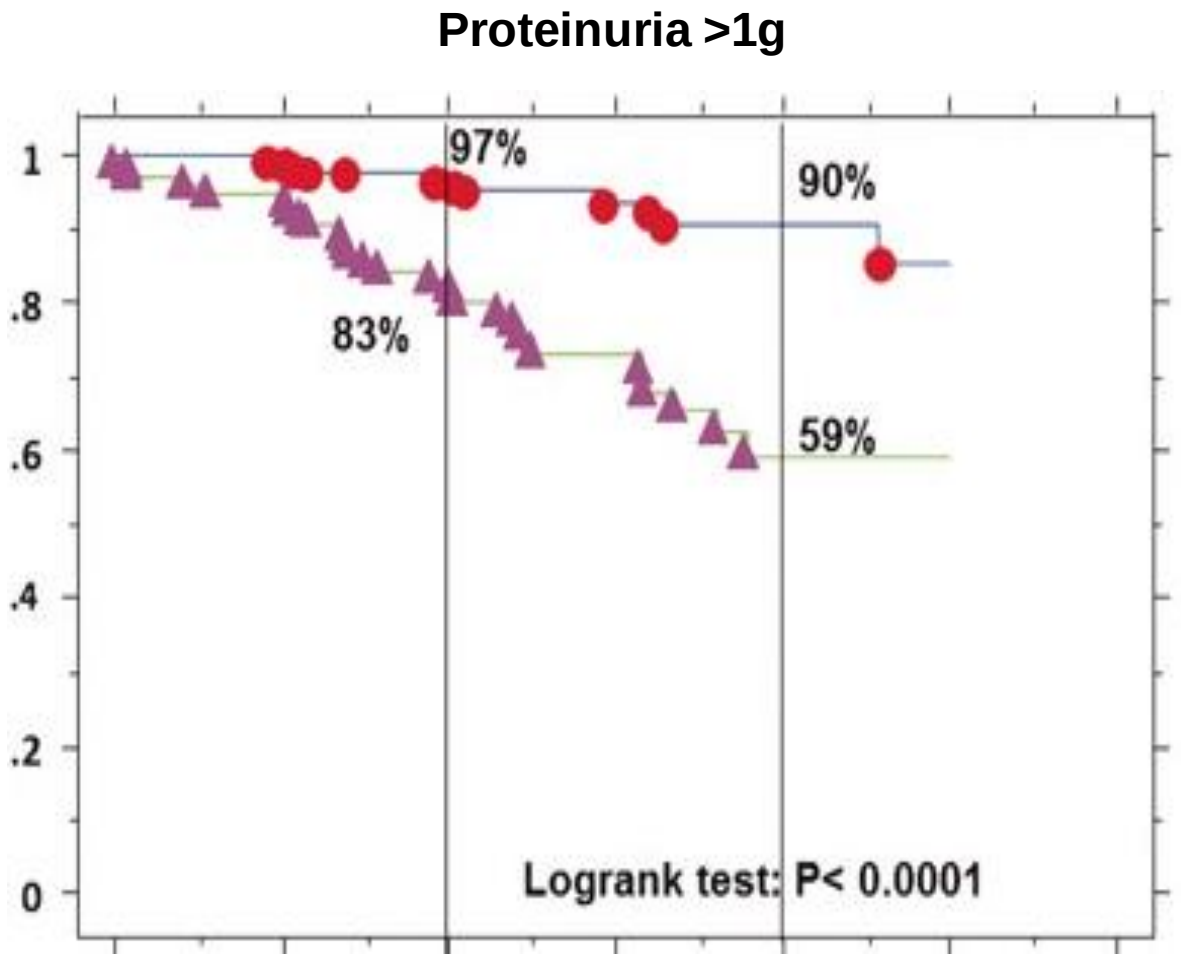
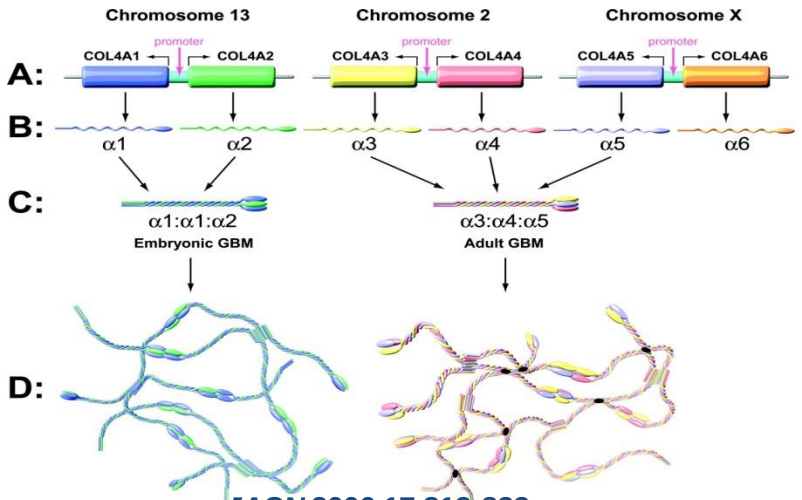
Proteinuria predicts worse outcomes in IgA nephropathy

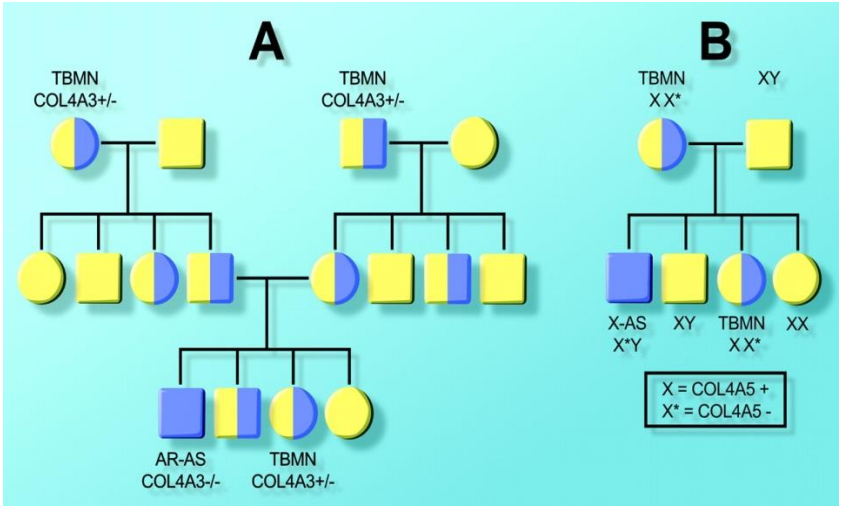


Alport syndrome and thin basement membrane disease

- Abnormal production of basement membrane collagen chains
- COL4A5 (X-linked)
  - Mutations in males cause Alports (85% of cases)
  - Females are carriers (previously referred to as TMBD)
- COL4A3 or COL4A4 (Autosomal Recessive)
  - Homozygous Mutations cause Alports (15% of cases)
  - Compound Heterozygous are affected with Alports
  - Heterozygous Mutations has TBMD and is Alports carrier
- **Alports**
  - Abnormal matrix deposition, inflammation and fibrosis
  - **Early onset of hematuria and CKD**
  - **ESRD by early adulthood is likely**
  - **X-linked Female Carriers have hematuria and 15% risk for ESRD**
- Extrarenal Manifestations
  - **Bilateral high tone sensineuronal hearing loss**
  - **Lenticonus (cataracts) and fleck retinopathy**



JASN 2006;17:813-822

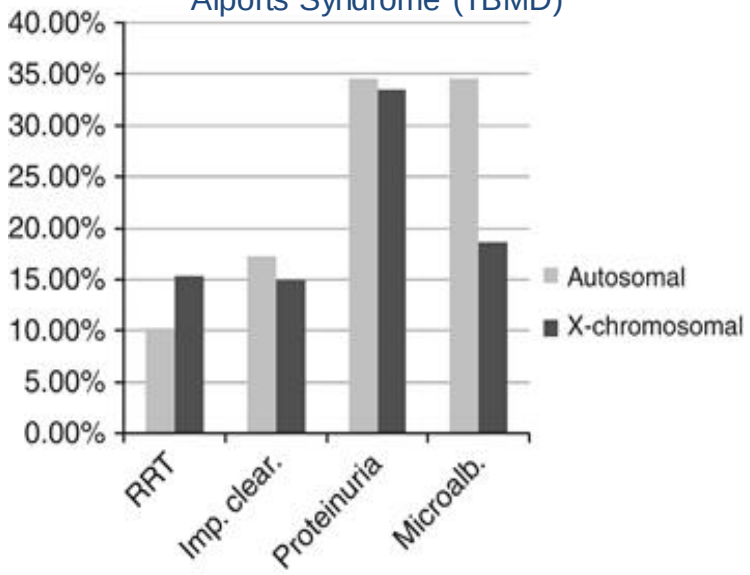


JASN 2013; 24: 364-375

Thin Basement Membrane Disease

- **Most common cause of persistent hematuria in children and adults (1%)**
- Microscopic Hematuria and diffuse thinning of the glomerular basement membrane (<250 nm)
- **Typically family association of hematuria but not of renal failure**
  - 2/3 with affected family members
  - 1/3 with de novo mutations or nonpenetrant phenotypes in family members
- Clinical course is <u>usually</u> benign ("benign familial hematuria")
  - Renal Impairment may be due to secondary FSGS or misdiagnosis of IgA or Alports
  - Increased risk of HTN or proteinuria
  - RAAS Inhibition Appropriate

Comparison of clinical outcomes in X-linked or Autosomal Recessive carriers of Alports Syndrome (TBMD)

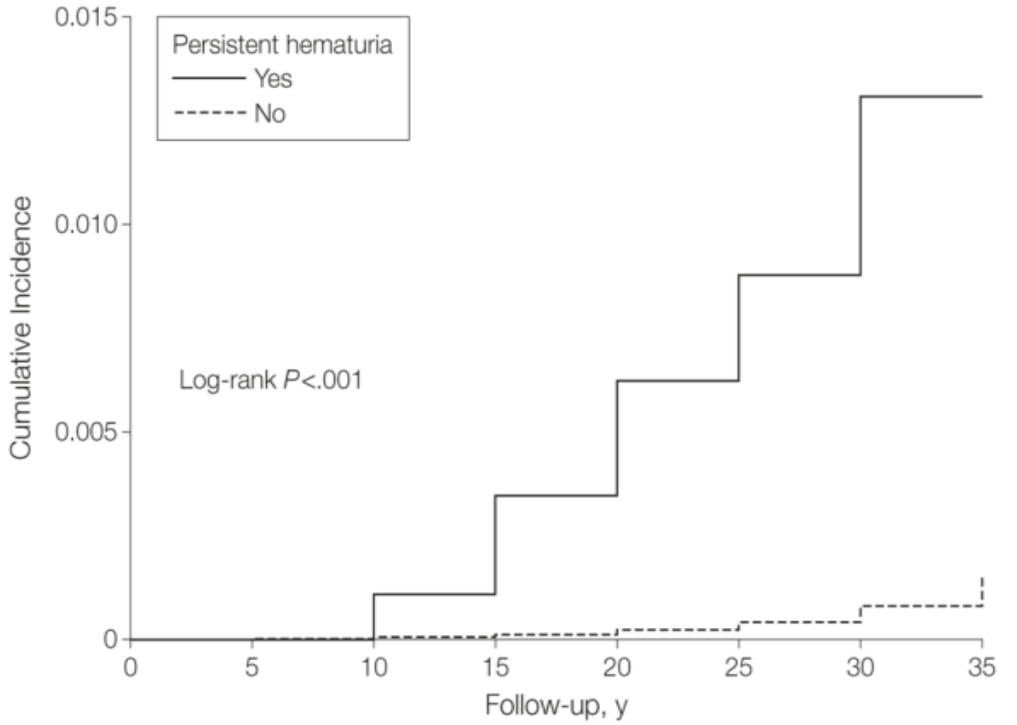


Kidney International 2012; 81: 779

Others

- Loin Pain Hematuria Syndrome
  - Loin Pain/Flank Pain Associated with Hematuria
  - Kidney Biopsies Only Revealing For Abnormal GBM width and Tubular RBC
  - High Coincidence with Subclinical Urolithiasis
  - *Am J Kidney Diseases* 2006; 47: (419-427)
- Hypercalciuria/Hyperuricosuria
  - 37 Patients With Microscopic Hematuria (normal GFR, no proteinuria) and hypercalciuria or hyperuricosuria
    - Urine calcium and uric acid levels decreased in all patients after starting HCTZ or Allopurinol
    - 22 Had Cessation of Hematuria
    - 15 Had Persistent Hematuria
      - 6 Biopsies Revealed IgA, TBMD, or Mesangioproliferative
  - **(*Kidney International* 1989; 36: 96-99)**

Long Term Outcomes with Microscopic Hematuria



No. at risk

Persistent hematuria								
Yes	3690	3677	3665	2873	1978	1135	244	10
No	1 199 936	1 196 606	1 193 878	947 735	680 092	431 433	212 810	1608

JAMA 2011; 306: 729-736

Hematuria Summary

- Establish there are persistently erythrocytes in the urine in the appropriate context
- Frequently warrants urologic evaluation
  - Risk based evaluation drives workup
    - Low risk- can repeat
    - Intermediate risk-cystoscopy and renal sonogram
    - High risk-cystoscopy and multiphase CT urogram (unless contraindicated)
- Consider glomerular disease
  - Proteinuria, renal dysfunction, hypertension, serologies
    - Serologies won't diagnose IgA nephropathy
  - Obtain a family history!
  - Continue to monitor regularly

Thank you