PROTEINURIA

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BUMC INTERNAL MEDICINE ACADEMIC HALF-DAY

JANUARY 21, 2020

LEARNING OBJECTIVES

1. DIAGNOSE PROTEINURIA AND DETERMINE THE INDICATIONS FOR 24-HOUR URINE PROTEIN QUANTIFICATION, SPOT URINE SAMPLING FOR PROTEIN/CREATININE RATIO AND ALBUMIN/CREATININE RATIO, AND URINE PROTEIN ELECTROPHORESIS.
2. DISCUSS KEY STRUCTURES INVOLVED IN PROTEINURIA PATHOGENESIS.
3. DISTINGUISH GLOMERULAR FROM NON-GLOMERULAR CAUSES OF PROTEINURIA.
4. DIAGNOSE NEPHROTIC SYNDROME AND CHARACTERISTIC FINDINGS.
5. RECOGNIZE PREECLAMPSIA.
6. TREAT EDEMA ASSOCIATED WITH THE NEPHROTIC SYNDROME.

URINE COLLECTION

- 2ND URINE OF THE MORNING, MID-STREAM
- CLEANSE WITH WATER (DISINFECTANTS CAN FAVOR CELL LYSIS)
- SHOULD BE CONCENTRATED AND ACIDIC
- AVOID STRENUOUS EXERCISE 24 HOURS PRIOR
- WOMEN SHOULD NOT BE ON MENSES

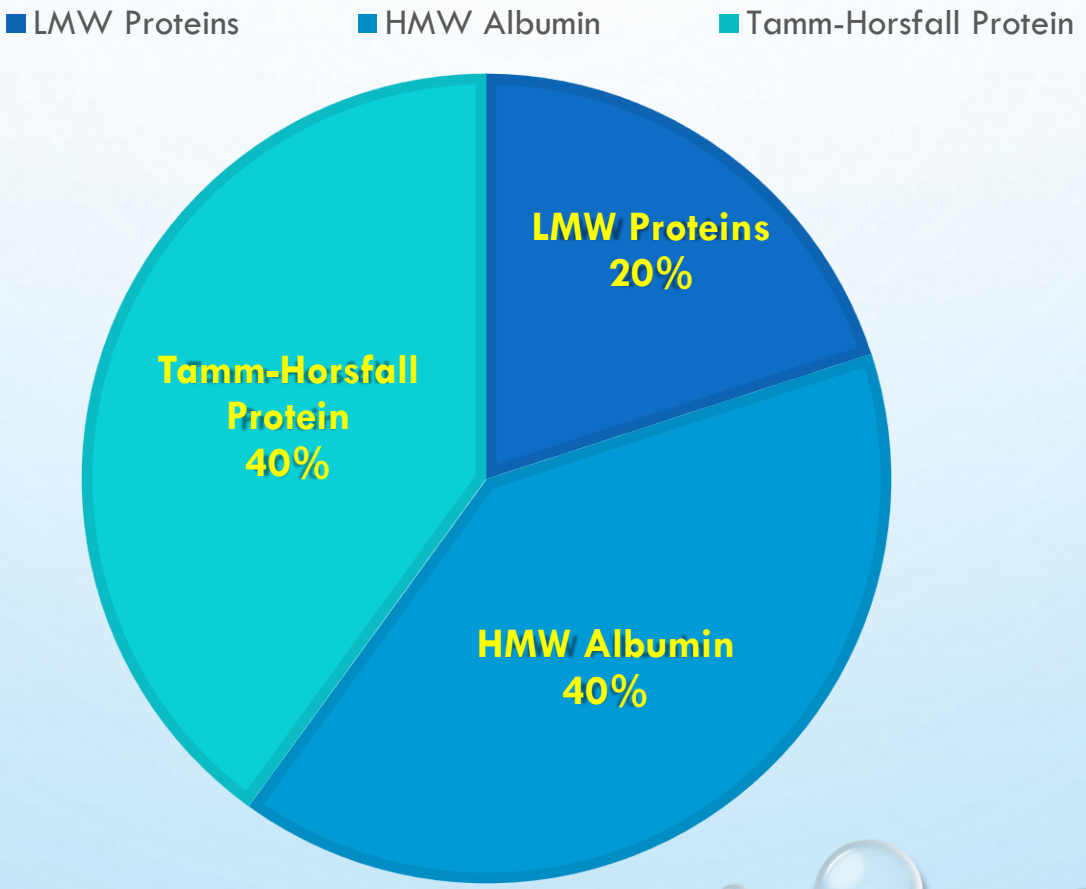
WHICH OF THE FOLLOWING IS NOT A "NORMAL" URINARY PROTEIN?

A. ALBUMIN
B. TAMM-HORSFALL
C. BENCE-JONES
D. LOW MOLECULAR WEIGHT PROTEINS

ANSWER

- C) BENCE JONES PROTEIN

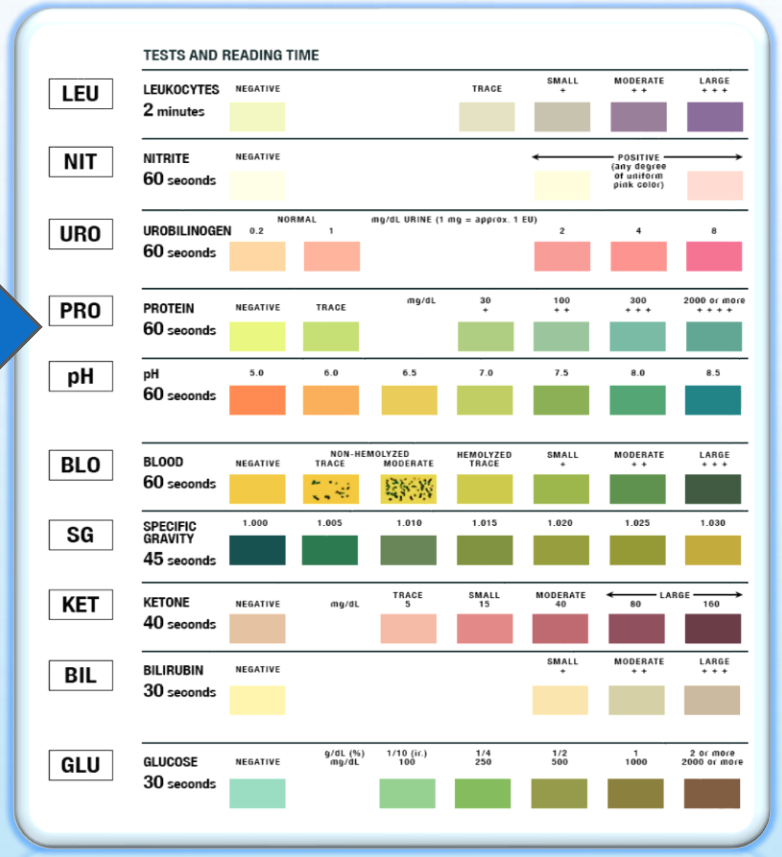
NORMAL URINARY PROTEINS



PROTEINURIA: URINE DIP

≥ 150 mg

- Urine dip detects albuminuria
  - False (-) with dilute or alkaline urine
  - False (-) with non-albumin protein
  - Threshold 150 mg protein / 24 hours
- **ALWAYS** quantify proteinuria if present
  - Urine protein/creatinine ratio (UPC)
  - 24 hour urine protein



Urine Dip

Trace = 150 mg/g

+1 = 200-500 mg/g

+2 = 0.5-1.5 gm /24 hrs

+3 = 2-5 grams / 24 hrs

+4 = ≥ 7 grams / 24 hrs

PROTEINURIA DETECTION METHODS

SPOT URINE ALBUMIN/CR RATIO
SPOT URINE PROTEIN/CR RATIO

- EASY
- LESS ACCURATE
- LOWER CREATININE IN WOMEN/ELDERLY/MALNOURISHED LEADS TO FALSELY HIGHER RATIO
- HIGHER CREATININE IN AA & PTS WITH HIGH MUSCLE MASS --> UNDERESTIMATES RATIO

24 HR URINE COLLECTION

- CUMBERSOME
- ACCURATE
- VARIATION DURING DAY
- VARIATION WITH RECUMBENCY
- ? NOCTURNAL COLLECTION AS AN ALTERNATIVE
- ALWAYS GET A URINE CREATININE TO VERIFY ACCURACY

WHICH OF THE FOLLOWING PATIENTS HAS PROTEINURIA?

A. URINE PROTEIN/CREATININE RATIO 200 MG/G

B. 24 HOUR URINE PROTEIN 120 MG

C. URINE MICROALBUMIN/CREATININE RATIO 30 MG/G

D. 24 HOUR URINE PROTEIN 300 MG

ANSWER

- D) 24 HOUR URINE PROTEIN 300 MG

DEFINITIONS

Microalbuminuria
UACR
30 – 300 mg/g

Proteinuria (sub-nephrotic)
UPC > 300 mg

Nephrotic Proteinuria
UPC > 3 grams
24hr urine > 3.5 grams

A1	A2	A3	A4
Normal to mildly Increased	Moderately Increased	Severely Increased	Nephrotic
UACR < 30 mg/g Cr	**30-300 mg/g Cr**	**> 300 mg/g Cr**	**3.5 grams/ 24 hrs**

CAUSES OF PROTEINURIA

- TRANSIENT
  - EXERCISE, FEVER, EXTREME COLD
- ORTHOSTATIC
- TUBULOINTERSTITIAL
- OVERFLOW
- GLOMERULAR

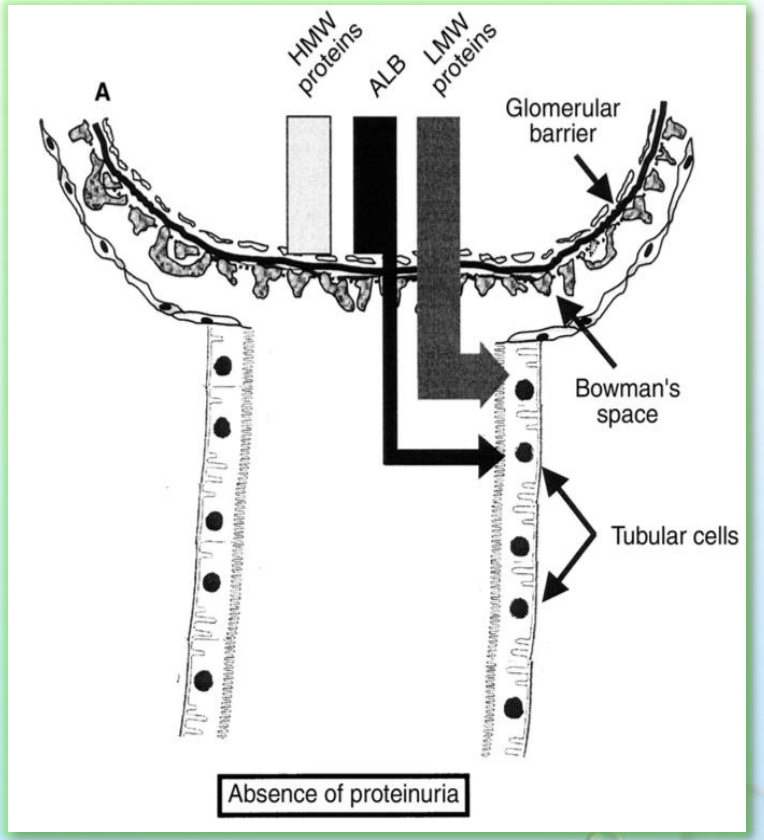
ORTHOSTATIC PROTEINURIA

- PATIENTS < 30 YEARS OLD
- BENIGN CONDITION, 3-5 % OF YOUNG ADULTS
- INCREASED URINARY PROTEIN EXCRETION IN UPRIGHT POSITION **ONLY**
- NORMAL RENAL FUNCTION, NORMAL BP, NO RISK FACTORS CKD
- **INACTIVE** SEDIMENT ON URINALYSIS
- URINE PROTEIN < 1-2 GRAMS / 24 HRS
- DX: SPLIT 24 HR URINE
  - DAY 16 HR URINE COLLECTION
  - 8 HOUR NOCTURNAL COLLECTION < 50 MG
  - ALTERNATELY CHECK 1ST AM UPC

TUBULOINTERSTITIAL

- PATHOGENESIS:

  TUBULOINTERSTITIAL DISEASES LEAD TO DECREASED PROXIMAL TUBULE REABSORPTION OF LOW-MOLECULAR-WEIGHT PROTEINS (PART OF NORMAL GLOMERULAR ULTRAFILTRATE)



- CHRONIC INTERSTITIAL NEPHRITIS
- FANCONI SYNDROME

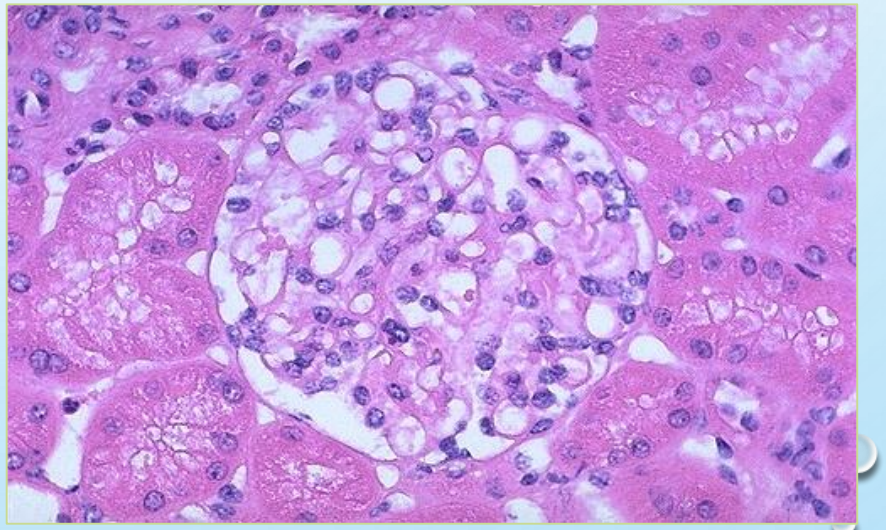
OVERFLOW

- LOW-MOLECULAR-WEIGHT PROTEINS OVERWHELM THE ABILITY OF THE PROXIMAL TUBULES TO REABSORB FILTERED PROTEINS

GLOMERULAR

- MOST COMMON & IMPORTANT CAUSE
- SUSPECT IF ACTIVE URINARY SEDIMENT
  - RBCS, CELLULAR CASTS
- SUSPECT IF > 500 MG PROTEINURIA
- SEROLOGICAL WORKUP
- RENAL BIOPSY FOR DIAGNOSIS

- PATHOPHYSIOLOGY:
  - INCREASED GLOMERULAR CAPILLARY PERMEABILITY TO PROTEIN
  - IMPAIRED PROTEIN REABSORPTION BY EPITHELIAL CELLS OF PROXIMAL TUBULES



BOARD QUESTION

A 28 YEAR-OLD WOMAN IS EVALUATED DURING A FOLLOW-UP VISIT. A RECENT LIFE INSURANCE EXAMINATION REVEALED PROTEINURIA ON DIPSTICK URINALYSIS. SHE IS OTHERWISE HEALTHY AND HAS NO PERTINENT PERSONAL OR FAMILY MEDICAL HISTORY.

ON PHYSICAL EXAMINATION, TEMPERATURE IS 36.1C, BLOOD PRESSURE IS 110/64, PULSE IS 72 AND RESPIRATION RATE IS 12. BMI IS 23. THE REMAINDER OF THE EXAM IS NORMAL.

LABORATORY STUDIES:

SERUM CREATININE:	0.8 MG/DL
ESTIMATED GFR:	> 60 ML/MIN/1.73M^2
URINALYSIS:	1+ PROTEIN, 0-2 ERYTHROCYTES/HPF, 0 LEUKOCYTES/HPF
24 HR URINE COLLECTION:	200 MG PROTEIN / 24 HOURS

BOARD QUESTION CONTINUED

WHICH OF THE FOLLOWING IS THE MOST APPROPRIATE NEXT STEP IN MANAGEMENT?

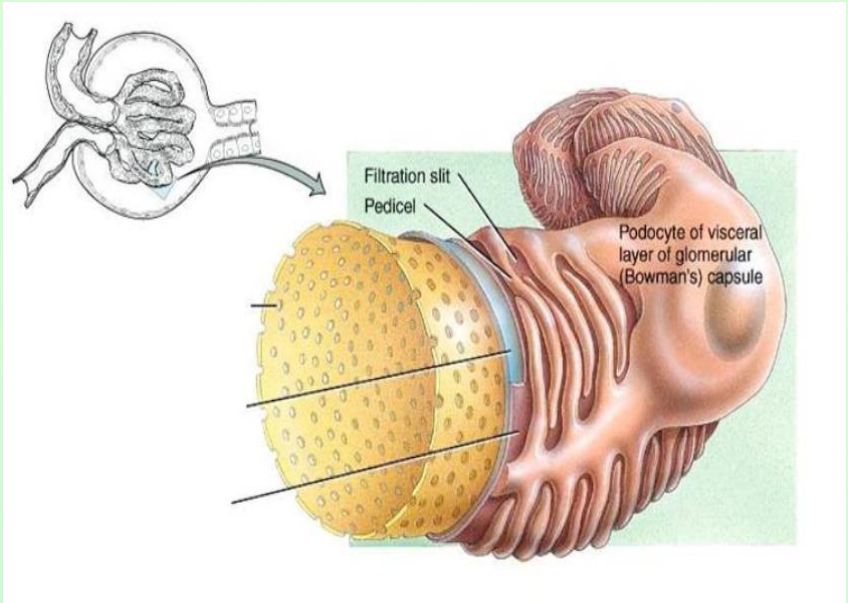
A. KIDNEY BIOPSY
B. REPEAT 24 HOUR URINE COLLECTION FOR PROTEIN
C. SPLIT URINE COLLECTION
D. SPOT URINE PROTEIN / CREATININE RATIO
E. REASSURANCE

ANSWER

- C. SPLIT URINE COLLECTION
- THIS PATIENT HAS ORTHOSTATIC PROTEINURIA.

GLOMERULAR BM BARRIERS

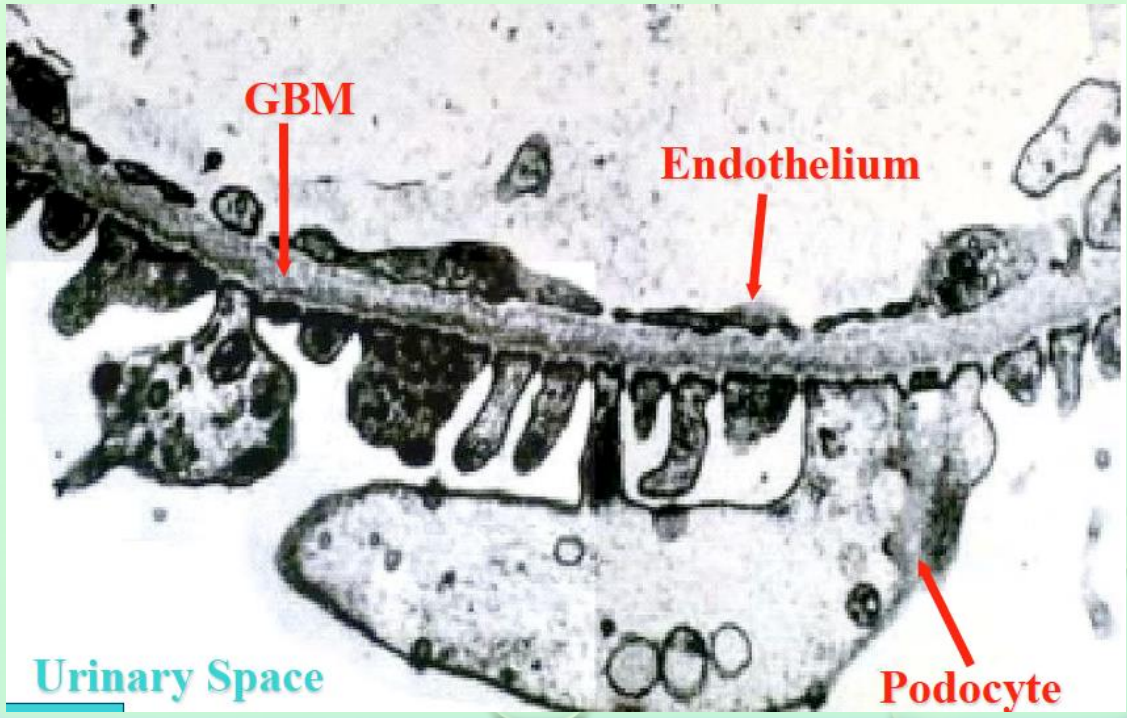
GBM Normal Barriers



The Podocyte: a key cell in the selective filtering action of the glomerular capillary wall

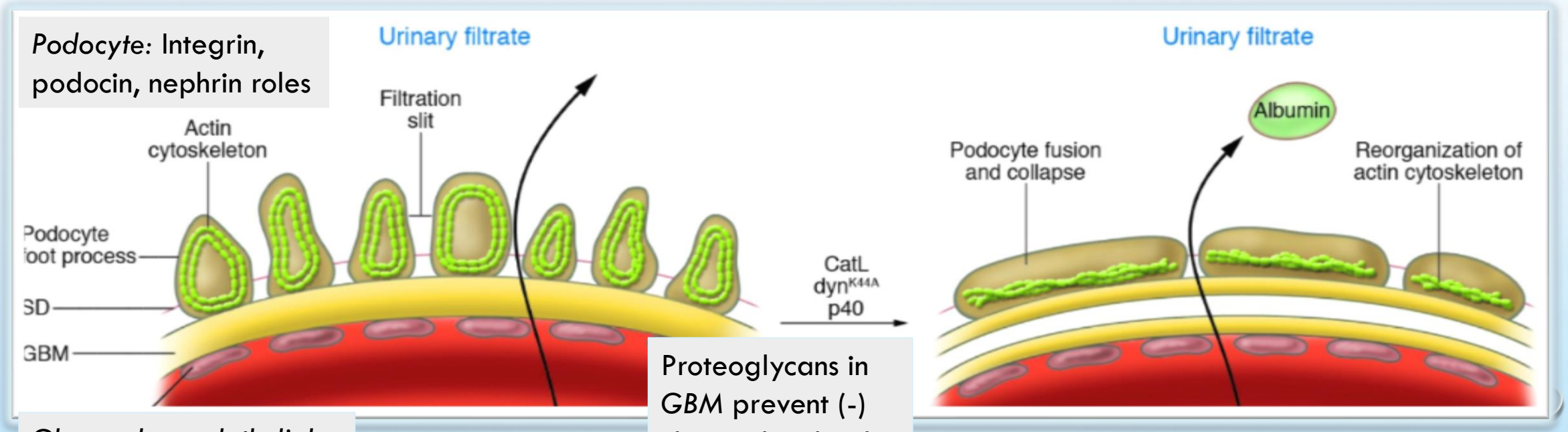
Normally the GBM restricts passage into Bowmans space by:

- Molecular size
- Electrical charge
- Sterical configuration



PROTEINURIA MECHANISMS

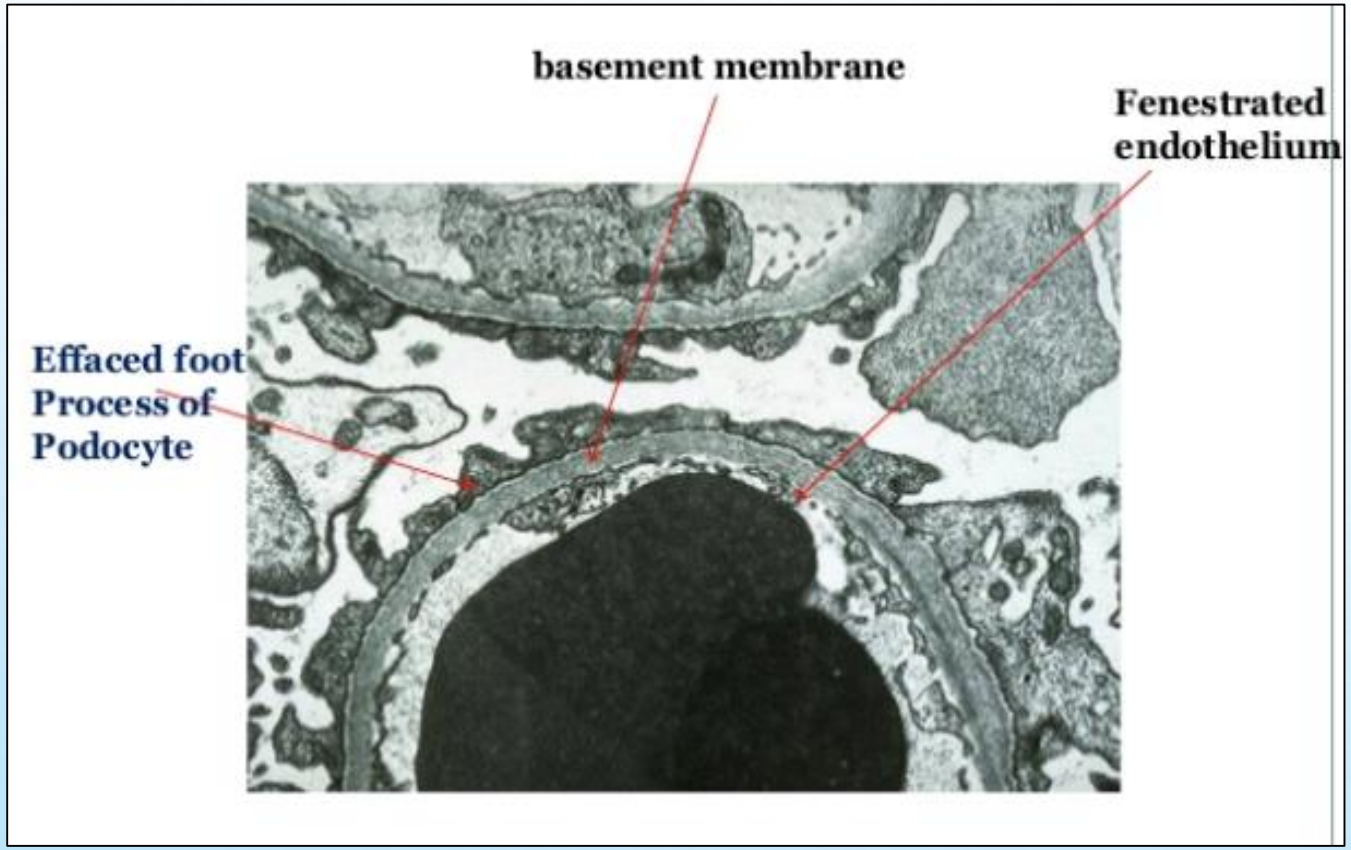
Podocyte: Integrin, podocin, nephrin roles

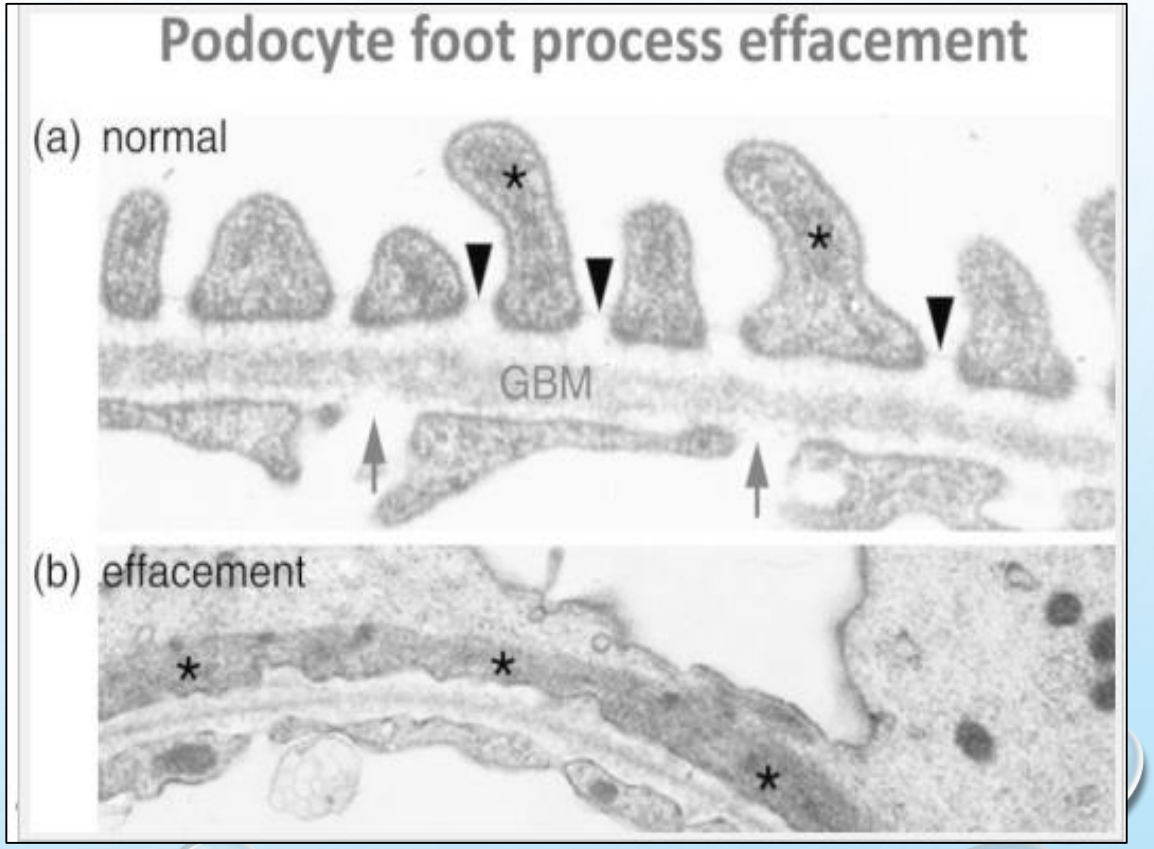


Glomerular endothelial cell: glycocalyx albumin barrier; also requires VEGF to fxn

Proteoglycans in *GBM* prevent (-) charged molecule passage

PODOCYTOPATHY: PODOCYTE EFFACEMENT





WHICH OF THE FOLLOWING IS NOT A CHARACTERISTIC FINDING OF NEPHROTIC SYNDROME?

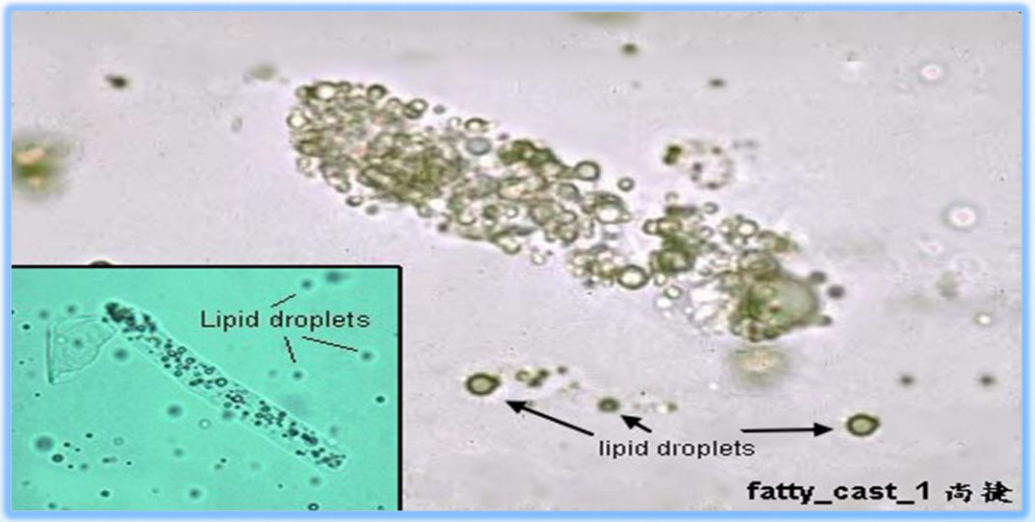
A. PROTEINURIA 3500 MG
B. WAXY CASTS ON URINE MICROSCOPY
C. EDEMA
D. HYPERCOAGUABILITY
E. HYPERLIPIDEMIA

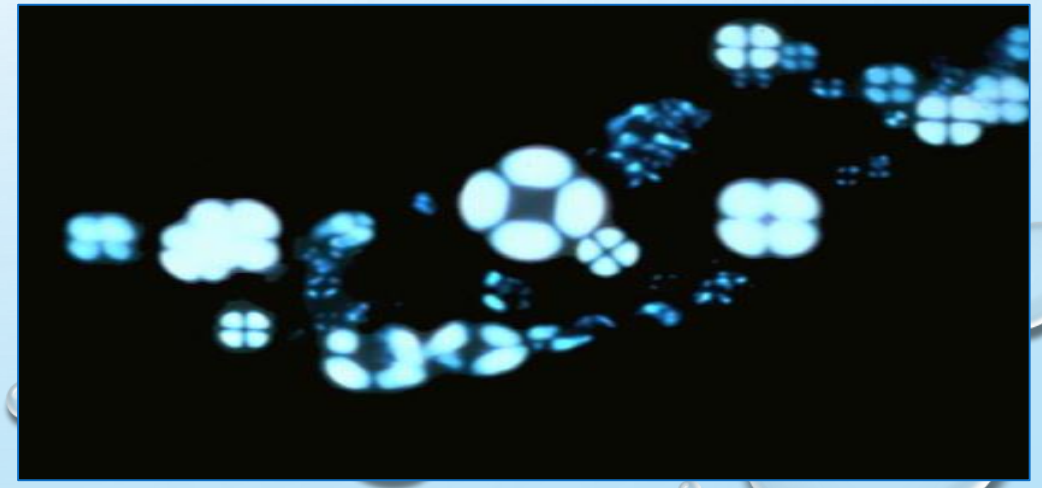
ANSWER

- B) WAXY CASTS ON URINE MICROSCOPY

NEPHROTIC SYNDROME

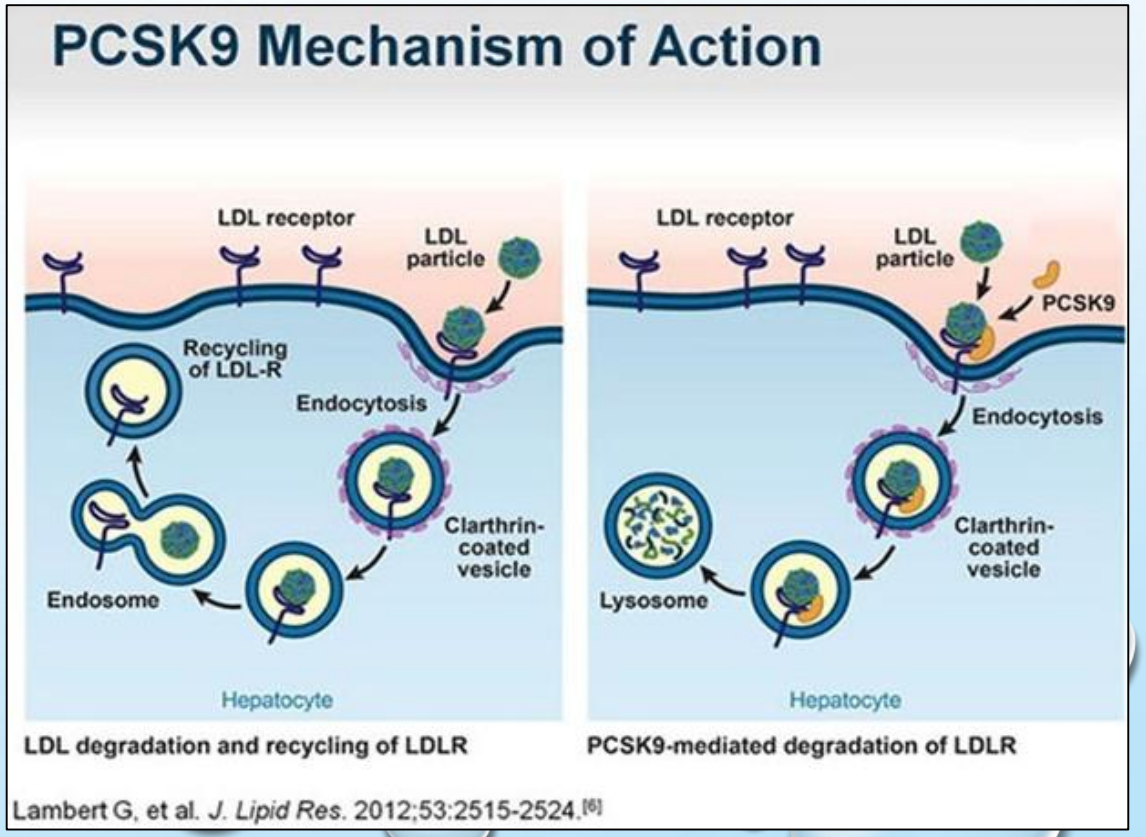
- NEPHROTIC-RANGE PROTEINURIA
  - > 3.5 GM / 24 HR URINE
  - > 3-3.5 GM ON UPC
- LIPIDURIA
  - FATTY CASTS, OVAL FAT BODIES
- HYPOALBUMINEMIA
- EDEMA
- HYPERLIPIDEMIA





PATHOGENESIS OF LIPID ABNORMALITIES IN NEPHROTIC SYNDROME

- REDUCED PLASMA ONCOTIC PRESSURE & HYPOALBUMINEMIA
- ENHANCED HEPATIC SYNTHESIS OF LIPOPROTEINS CONTAINING APOLIPOPROTEIN B AND CHOLESTEROL
- DIMINISHED LIPID CATABOLISM
- INCREASED PCSK9 FROM HEPATOCYTE AND DECREASED CLEARANCE
  - PCSK9 BINDS LDL RECEPTORS ON THE SURFACE OF THE HEPATOCYTE, CAUSING THE RECEPTOR TO BE INTERNALIZED AND DEGRADED IN THE LYSOSOME, THUS LEADING TO INCREASED LDL



BOARD Q

- A 37 YEAR-OLD WOMAN IS EVALUATED FOR A HEADACHE LASTING 1 DAY. SHE IS IN THE THIRD TRIMESTER OF HER FIRST PREGNANCY. UNTIL NOW, THE PREGNANCY HAS BEEN UNREMARKABLE, INCLUDING BLOOD PRESSURE AND URINE PROTEIN MEASUREMENTS. HER ONLY MEDICATION IS A PRENATAL VITAMIN.
- ON PHYSICAL EXAM, BLOOD PRESSURE IS 166/115 MM HG; OTHER VITAL SIGNS ARE NORMAL. THERE IS NO PAPILLEDEMA, THE PATIENT HAS A GRAVID UTERUS CONSISTENT WITH HER STAGE OF PREGNANCY, AND THERE IS NO ABDOMINAL TENDERNESS.

Lab study	Result
Hemoglobin	12.3 g/dL
Platelet count	70,000 / uL
Alanine aminotransferase	72 U/L
Aspartate aminotransferase	80 U/L
Bilirubin	Normal
Creatinine	1.4 mg/dL
Electrolytes	Normal
Peripheral blood smear	Normal
Urinalysis	2+ protein

BOARD Q CONTINUED

- WHICH OF THE FOLLOWING IS THE MOST LIKELY DIAGNOSIS?

A. CHRONIC HYPERTENSION

B. ECLAMPSIA

C. GESTATIONAL HYPERTENSION

D. HELLP SYNDROME

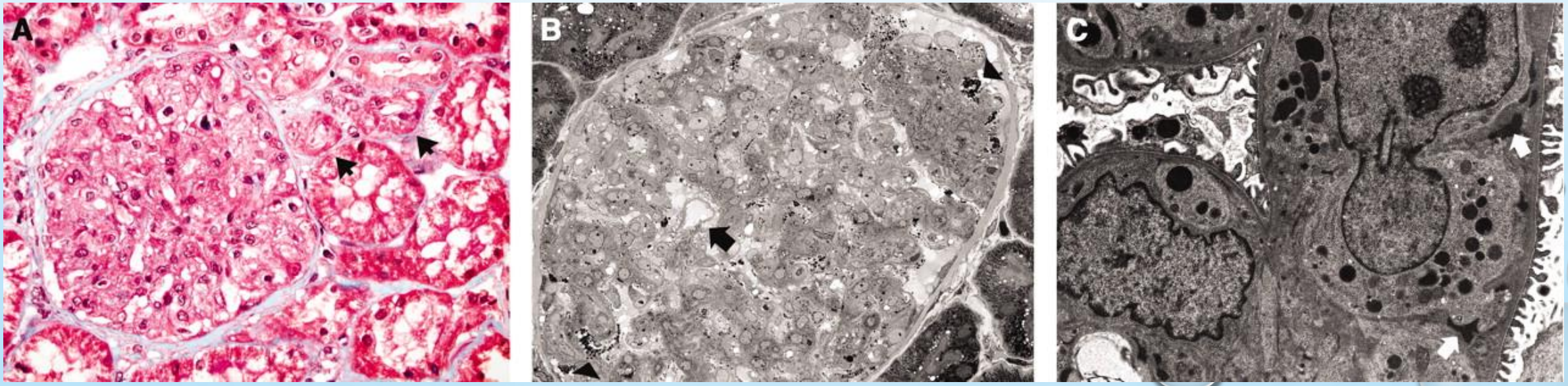
E. PREECLAMPSIA

ANSWER

- E. PREECLAMPSIA

PREECLAMPSIA

- NEW ONSET HYPERTENSION AND PROTEINURIA > 20 WEEKS GESTATION
- RENAL PATH: GLOMERULAR ENDOTHELIOSIS (SWELLING OF ENDOCAPILLARY CELLS & CAPILLARY OCCLUSION) AND THROMBOTIC MICROANGIOPATHY (TMA)



PROTEINURIA SCREENING & TREATMENT

SCREENING

- NOT COST-EFFECTIVE NOR RECOMMENDED IN GENERAL POPULATION
- DO ANNUALLY IN ALL DIABETICS
- CONSIDER IN HIGH-RISK PATIENTS (HTN, SMOKING, OBESITY, OLDER AGE)
- URINE ALBUMIN/CREATININE IS THE SCREENING TEST OF CHOICE

TREATMENT

- TREAT THE UNDERLYING PATHOLOGY
- SALT RESTRICTION
- DIURETICS
  - LOOPS ARE FIRST LINE
  - ALDACTONE RECEPTOR ANTAGONISTS
  - THIAZIDES
- RAAS INHIBITORS
- STATINS

BOARD Q

- A 45 YEAR-OLD MAN IS EVALUATED DURING A FOLLOW UP VISIT FOR MEMBRANOUS GLOMERULOPATHY DIAGNOSED 3 WEEKS AGO. HE REPORTS PERSISTENT LOWER EXTREMITY EDEMA AND NO WEIGHT LOSS DESPITE ADHERING TO A LOW SALT DIET AND TAKING MAXIMAL-DOSE FUROSEMIDE. HE DOES NOT HAVE SHORTNESS OF BREATH OR ABDOMINAL DISCOMFORT. OTHER MEDICATIONS ARE ENALAPRIL AND SIMVASTATIN.
- ON PHYSICAL EXAM, VITAL SIGNS ARE NORMAL. THE PATIENT WEIGHS 80 KG WITH A BASELINE WEIGHT OF 75 KG. THERE IS NO RASH. CARDIAC EXAMINATION IS NORMAL, AND THERE IS NO EVIDENCE OF JVD. THE LUNGS ARE CLEAR. THERE IS PITTING EDEMA IN THE LEGS BILATERALLY TO JUST BELOW THE PATELLAE.
- DOPPLER ULTRASOUND OF THE LOWER EXTREMITIES PERFORMED 3 WEEKS AGO SHOWED NO EVIDENCE OF DVT.

Lab study	Result
Albumin	2.9 g/dL
Blood urea nitrogen	20
Creatinine	1.0 mg/dL
Electrolytes	Normal
Urinalysis	NO blood; 4+ protein
Urine protein-creatinine ratio	6100 mg/g

BOARD Q CONTINUED

- WHICH OF THE FOLLOWING IS THE MOST APPROPRIATE MANAGEMENT?

A. ADD METOLAZONE

B. CHANGE FUROSEMIDE TO BUMETANIDE

C. HOSPITALIZE FOR INTRAVENOUS DIURESIS

D. REPEAT LOWER EXTREMITY DOPPLER ULTRASONOGRAPHY

ANSWER

- A) ADD METOLAZONE
- EDEMA MANAGEMENT IN A PATIENT WITH NEWLY DIAGNOSED NEPHROTIC SYNDROME STARTS WITH A SALT-RESTRICTED DIET AND AN ORAL LOOP DIURETIC; WHEN LOOP DIURETICS HAVE BEEN MAXIMALLY UPTITRATED AND WEIGHT LOSS/EDEMA CONTROL IS INSUFFICIENT, IT IS OFTEN NECESSARY TO ADD A SECOND DIURETIC THAT WORKS DISTAL TO THE LOOP OF HENLE, IE THIAZIDE OR POTASSIUM-SPARING DIURETIC.

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QUESTIONS?