What's New in Medicine

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There are no relevant financial relationships with commercial interests to disclose

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Objectives

- To review recently identified maneuvers to slow progession of CKD
- To review management of bone disease in late stage CKD
- To review the work-up of nephrotic range proteinuria including new antibody testing
- To review renal manifestations of common drugs

I have no disclosures

Case

- A 49 year old diabetic man presents to your clinic after a three year hiatus from medical care. He notes recent headaches and is concerned his blood pressure may be high. Medications include insulin, atorvastatin, aspirin, and Lisinopril. He smokes 1/2PPD.
- PE: BP 152/108 P 79 afeb. Lungs clear. Cor S4S1S2. Ext trace edema.
- **DATA: Creatinine 2.8mg/dl Albumin 3.1mg/dl ACR 4,390mg/gram**

He has been offered a new 2 year position in Antarctica. He asks you:

What is the likelihood that I will need dialysis in the next two years?

The Kidney Failure Risk Equation

- A model to estimate the risk of reaching ESKD at 2 and five years
- Validated among > 700,00 patients with CKD 3-5
- Validated in more than 30 countries
- 4 Variable equation: Age, gender, GFR, albuminuria
- 8 Variable equation: Age, gender, GFR, albuminuria, albumin, calcium, phosphorous

The Kidney Failure Risk Equation

The formulas are:

$$p = 1 - S_{ave}(t = 1{,}826)^{a}$$

$$a = -0.55418 \times \left[\left(\frac{eGFR}{5}\right) - 7.22\right] + 0.26940 \times (male - 0.56) + 0.45608 \times [in(ACR) - 5.2774] - 0.21670 \times \left[\left(\frac{age}{10}\right) - 7.04\right]$$

Kidney Failure Risk Equation (4 Variable)

Estimate risk of progression to end-stage renal disease in CKD patients using age, sex, eGFR and proteinuria with KFRE

Sex?

Male
Female

Age?

49	Years

eGFR?

24	mL/min/1.73m²

Urine Albumin Creatinine Ratio? (Note units carefully)

4300	mg/mmol

Patient location?

North America
Non-North America

ESKD risk: Our patient (4 variable risk equation)

- Risk for needing dialysis at 2 years: **52.5%**
- 5 -year risk: **90.2%**

Case

- Your pt has done some reading and asks what he can do to slow decline of kidney function. Other than controlling BP < 130/80 and the use of ACE/ARB, which of the following have been shown to slow progression of CKD?

- Correcting metabolic acidosis
- Eating a vegan diet
- Stopping smoking
- Taking an SGLT-2 inhibitor
- All of the above

Acidosis in renal failure

- Early (GFR <45cc/min)
- Non GAP
- Failure to make adequate ammonium in the proximal tubule

- Late (GFR < 25cc/minute)
  - Anion GAP
  - GFR decline
  - Organic acids accumulate in the blood leading to anion gap (phosphates, sulfates, hippurate, urate)

What is bad about acidosis?

- Breaks down bones (especially bad for kids)
- Increased muscle catabolism
- Growth hormone and insulin resistance
- Inhibits Na-K ATPase
- Systemic inflammation
- Malaise, fatigue, hypotension
- **Accelerates progression of renal disease**

Kraut JA, Kurtz I
Am J Kidney Dis. 2005;45(6):978.

Human Data

- Large observational studies show that low bicarbonate is associated with more rapid decline of renal function (n > 4000)

Shah SN, Abramowitz M, Hostetter TH, Melamed ML Am J Kidney Dis. 2009 Aug;54(2):270-7.

Dobre M., Yang W., Chen J., et al. Am J Kidney Dis 2013; 62: 670-678

- Prospective randomized studies show significant slowing of CKD progression in pts receiving alkali therapy and maintaining HC03 $\geq$ 23 meq/liter

de Brito-Ashurst I, Varagunam M, Raftery MJ, Yaqoob MM J Am Soc Nephrol. 2009

Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE Kidney Int. 2010;78(3):303.

KDIGO: Acidosis

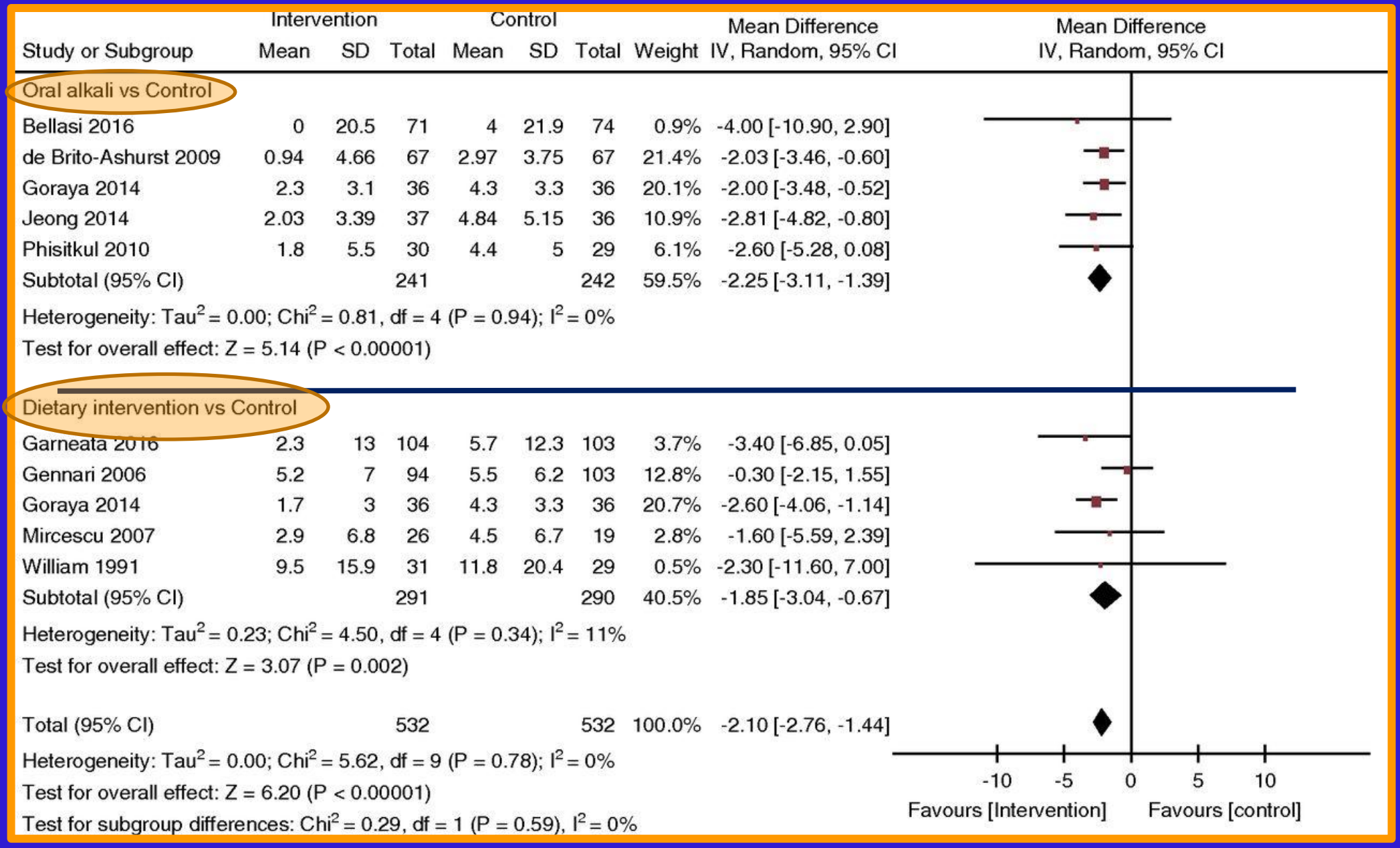
- We suggest that in people with CKD and serum bicarbonate concentrations < 22mmol/l, treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within normal range, unless contraindicated.

Two ways to improve acidosis

- Give bicarbonate
- Follow a diet that does not produce acid
  (vegetarian or vegan)

Higher BP?

Lower BP!



Navaneethan, CJASN 2019

Acidosis: Treatment

- Need to replace 0.5-1meq/kg of bicarb or about 35-70 meq daily
- Na bicarbonate tabs = 8 meq each = 4-8 tabs/day
- Na citrate (Shohl's solution) 1meq/cc = 35-70cc/day

Smoking is very bad for the kidneys

Case

- Your pt has done some reading and asks what he can do to slow decline of kidney function. Other than controlling BP < 130/80 and the use of ACE/ARB, which of the following have been shown to slow progression to CKD?

- Eating a vegan diet
- Correcting metabolic acidosis
- Stopping smoking
- **SGLT-2 inhibitors**
- All of the above

SGLT-2 inhibitors and the kidney

The Credence Study: NEJM June 2019

- 4401 diabetic CKD pts randomized to canagliflozin vs placebo
- GFR 30-90cc/min
- Albuminuria >300mg- 5,000mg/day
- All on ACE or ARB
- Primary end-points: ESKD, doubling of creatinine, death from renal or CV disease

Perkovic, NEJM June, 2019

SGLT-2 inhibitors and the kidney
Credence study results

- **Primary renal end point was reduced by 34%**
  (Hazard ratio, 0.66; 95% CI 0.53 to 0.81; P<0.001)
- Patients treated with canagliflozin also had lower rates of cardiovascular events and admissions for heart failure
- Use SGLT-2 inhibitors to slow progression of renal disease

Perkovic, NEJM June, 2019

Case

- The pt returns for a discussion of labs the following week:
- Calcium 8.3mg/dl Phosphorous 5.7mg/dl
- Vitamin D= 8ng/dl (deficient <12)
- He has heard that CKD can be “hard on the bones.” Which of the following do you advise?
- He should take Vitamin D3 (cholecalciferol)
- He should take vitamin D2 (ergocalciferol)
- He should take both
- He should avoid all vitamin D

Types of Vitamin D

- Vitamin D3 (cholecalciferol)

  sources: Milk, UV rays hitting the skin

- Vitamin D2 (ergocalciferol)

  sources: Made only in a laboratory by exposing yeast to UV rays

- 25-hydroxy vitamin D3 (calcidiol)

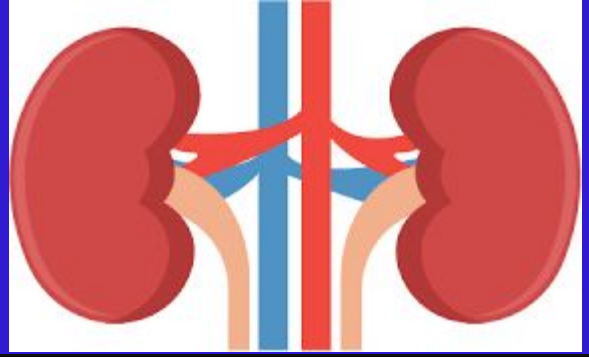
  Made primarily in the liver- major circulating form that the blood test for vitamin D detects

- 1,25 dihydroxy vitamin D3 (calcitriol)

  Made primarily in the kidney- **ACTIVE FORM!**

Case

- For CKD 3-5 patients, low vitamin D stores should be replenished with **either** ergocalciferol (D2) or cholecalciferol (D3)
- What about PTH?



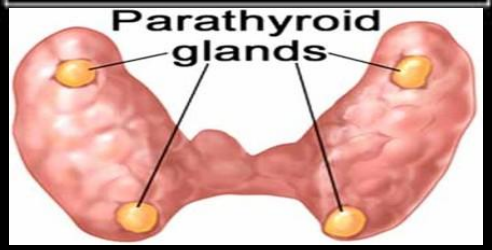
Reduced Renal Mass

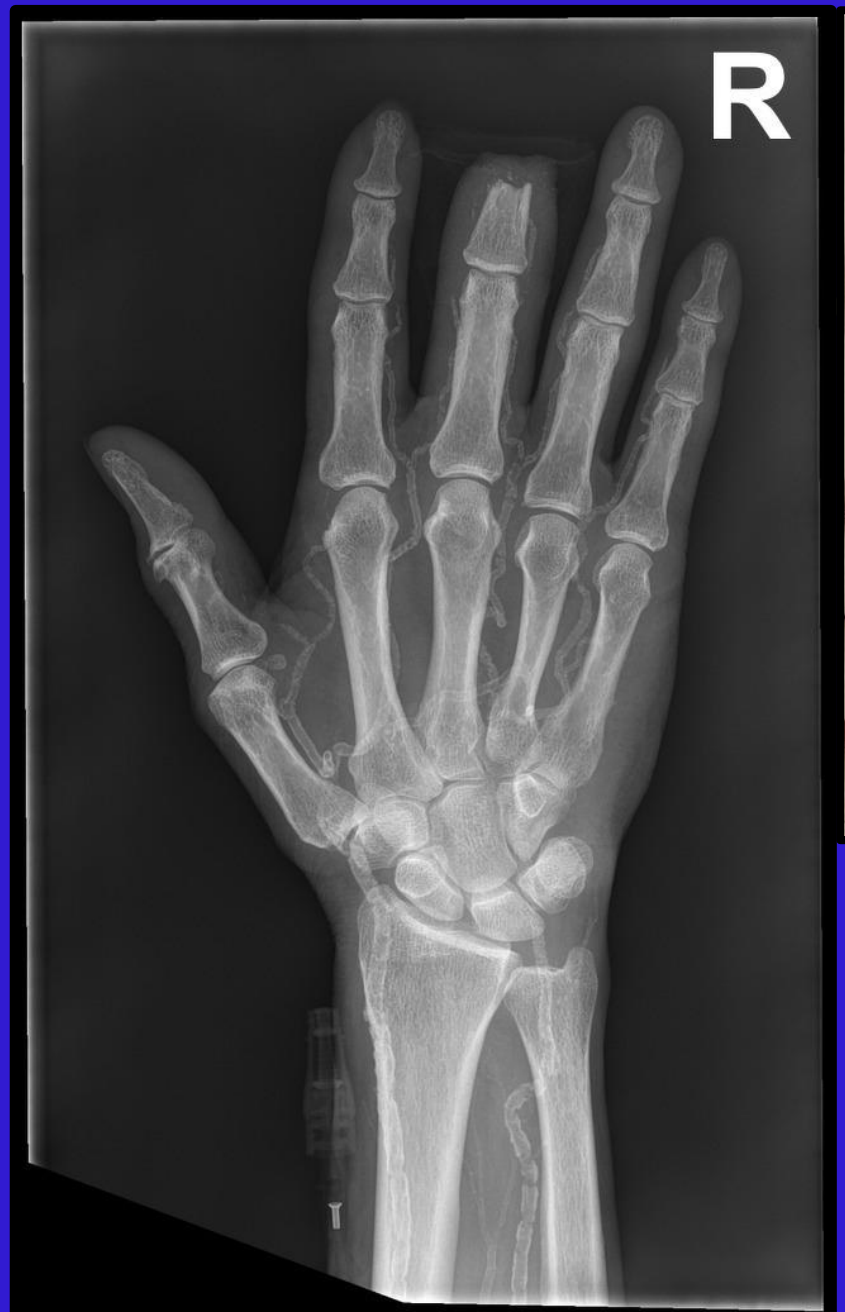
Decreased Serum $1,25\ (OH)_2\ D_3$

Increased Serum Phosphate

Hypocalcemia

Increased PTH Secretion

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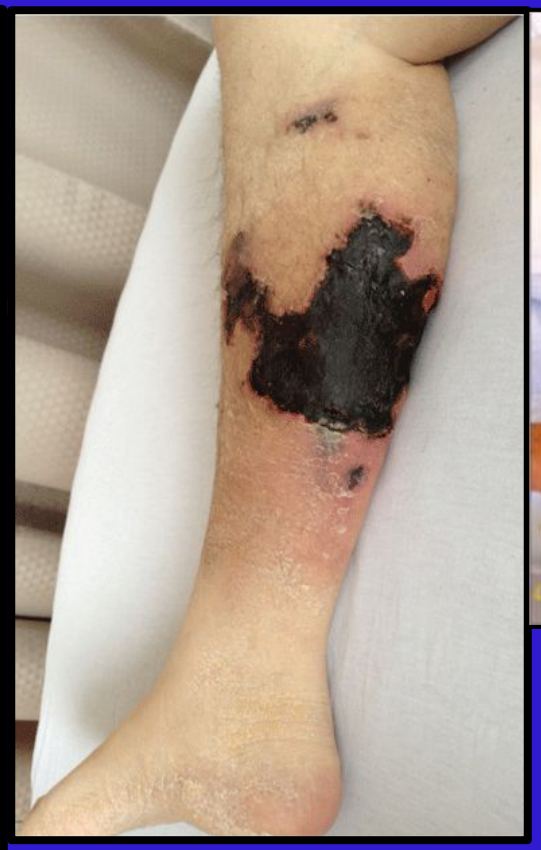
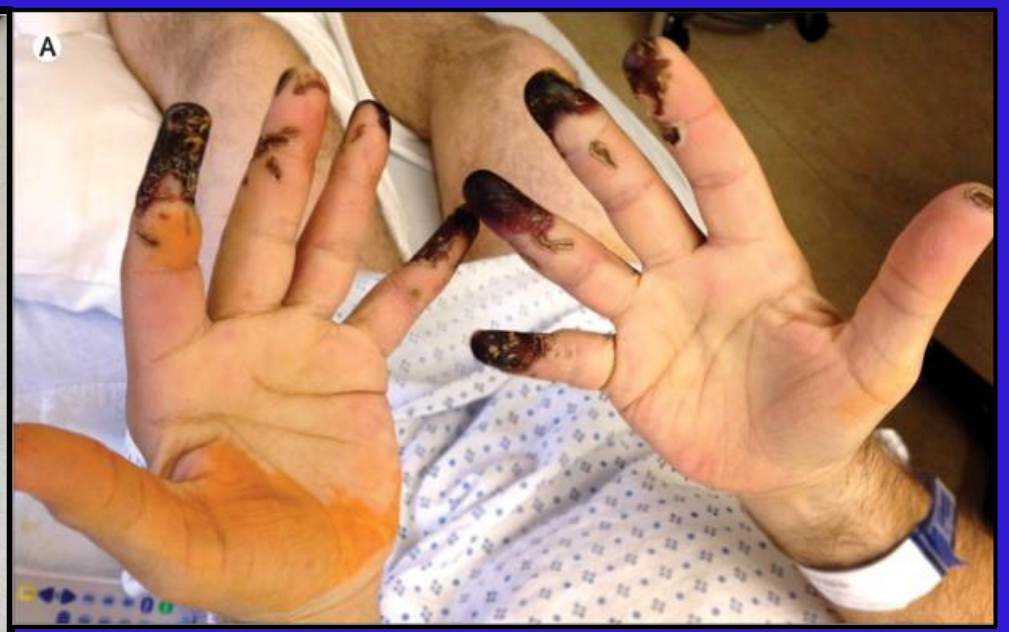



A

Recommendations for CKD3-5 patients with elevated PTH

Causes of elevated PTH

- Low calcium
- High phosphorous
- Low 25-Hydroxy D3 levels

Treatment of elevated PTH

- Give calcium, but not too much!
- Phosphorous binders
- Replete with cholecalciferol or ergocalciferol

If PTH continues to rise despite correction of these causes,
Add calcitriol at 0.25mcg qod (1,25 vitamin D)

Case

- Your patient asks you: Should I see a nephrologist?

When to refer to Nephrology

Refer early!!!!!

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90		Monitor	Refer*
	G2	Mildly decreased	60–89		Monitor	Refer*
	G3a	Mildly to moderately decreased	45–59	Monitor	Monitor	Refer
	G3b	Moderately to severely decreased	30–44	Monitor	Monitor	Refer
	G4	Severely decreased	15–29	Refer*	Refer*	Refer
	G5	Kidney failure	<15	Refer	Refer	Refer

Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1-150

Why to refer early

Early referral is good

- Informed choice of dialysis modalities (more PD)
- Early fistula placement
- Lower hospital cost
- Lower mortality
- Pre-emptive transplant
- Non-emergent start to dialysis
- Nephrologist-pt relationship

Late referral is bad

- Higher hospital costs
- No permanent access
- More likely to start HD in the hospital
- Higher dialysis mortality
- More catheters

Smart et al, Cochrane 2014


IF YOU TELL PEE JOKES
INSTRUCTOR
URINE FOR A BAD TIME

Case

- A 37 year old man presents to your office with a new diagnosis of primary HTN. He eats a lot of fast food and is unwilling to change his diet. You elect to start him on chlorthalidone.
- 2 weeks later, he calls complaining of great toe pain. On exam the toe is red and edematous- the pt is unable to walk on it.
- Uric acid = 8.9mg/dl.
- You stop the chlorthalidone and ponder the next medicine

Case

- Which of the following blood pressure medicines would be best to start at this time?
- Lisinopril
- Labetalol
- Losartan
- Lasix

Gout and HTN

- About 75% of patients with gout also have hypertension
- Some BP meds can help with gout and some can hurt

Losartan is associated with a lower risk for gout

- British case control study, N= 4 million patients
- 19,749 first ever diagnosis of gout *requiring treatment*
- Relative Risk for gout based on blood pressure medication:

Diuretics	β- blocker	None-losartan ARB	ACEI	Calcium channel blocker	Losartan
2.35 (2.19-2.53)	**1.49** (1.40-1.59)	**1.31**(1.17-1.47)	**1.25** (1.17-1.33)	**0.87** (0.82-0.93)	**0.78** (0.67-0.92)

Choi et al, BMJ 2012

Effects **of common meds on uric acid**

INCREASE URIC ACID

- Diuretics
- Chemotherapy
- Cyclosporine
- Salicylates
- Niacin
- Pyrazidimide
- Ethanol

DECREASE URIC ACID

- Allopurinol
- Febuxostat
- Probenecid
- Losartan
- Calcium channel blockers
- Atorvastatin
- Fenofibrate

Case

- Which of the following blood pressure medicines would be best to start at this time?
- Lisinopril
- Labetalol
- Losartan
- Lasix

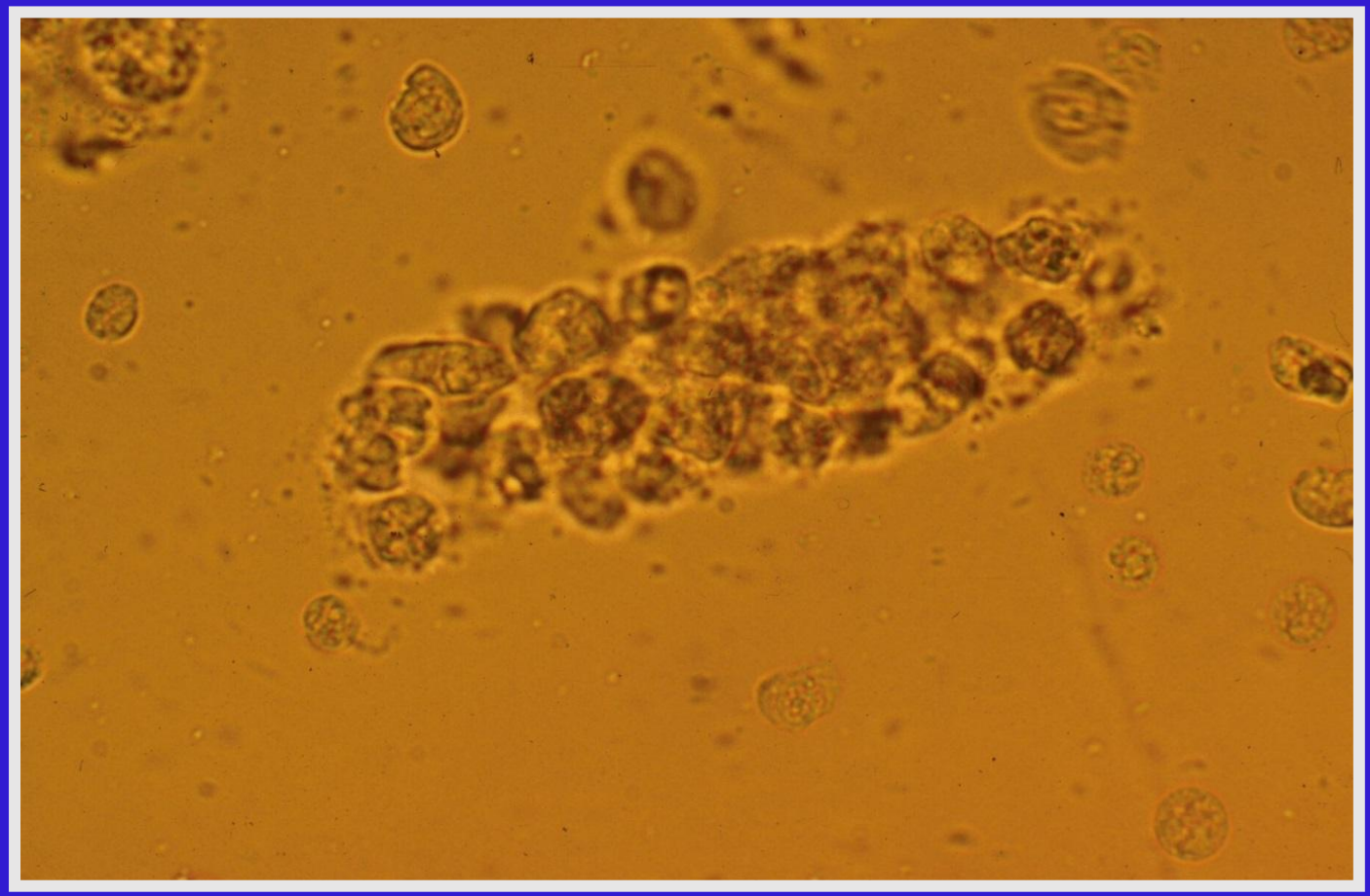
Case

- A 62 year old woman presents with sx of GERD. She is normotensive and otherwise healthy. Creat = 0.7 mg/dl.
- You prescribe omeprazole 20mg daily
- Two months later she presents with fatigue and poor appetite.

  BUN 79md/dl Creatinine 3.4mg/dl.

  UA: 1+ protein, Scattered WBCs and WBC casts

UA: WBC cast



Which of the following kidney problems are associated with PPI use?

- Acute Interstitial Nephritis
- CKD
- Hypomagnesemia
- All of the above

PPIs and Interstitial nephritis

- First described in 1992
- 1990s: primarily omeprazole
- To date: Many PPIs reported to cause AIN
- The most common medication to cause AIN in elderly patients
- Renal failure > > hypersensitivity symptoms and signs

Muriithi et al, AJKD 2014

The New York Times

Healthy Consumer

Heartburn Drugs Tied to Kidney Problems

By Nicholas Bakalar

January 14, 2016 12:35 pm

Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease

Benjamin Lazarus, MBBS; Yuan Chen, MS; Francis P. Wilson, MD, MS; Yingying Sang, MS; Alex R. Chang, MD, MS;
Josef Coresh, MD, PhD; Morgan E. Grams, MD, PhD

JAMA internal Medicine February 2016

Do PPIs cause CKD?: Study groups

ARIC (n= 10,482)

- PPI users = 322
- Exposure: *Self reported PPI use*
- CKD based on hospital discharge code

Geisinger (n = 248,751)

- PPI users = 16,900
- Exposure: *Based on Rx*
- CKD based on sustained drop in out-patient GFR

JAMA Int Med Lazarus et al, 2/2016

PPI use and CKD: Results

Table 2. Proton Pump Inhibitor Use and the Risk of Incident Chronic Kidney Disease[a]

	Atherosclerosis Risk in Communities Study (n = 10 482)		Geisinger Health System Replication Cohort (n = 248 751)	
Variable	No. of Events	No. of Participants	No. of Events	No. of Participants
PPI users	56	322	1921	16 900
H_2 receptor antagonist users	158	956	1022	6640
Nonusers	1224	9204	27 204	225 221
Association Between PPI Use and Incident CKD	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Unadjusted baseline PPI use vs no PPI use	1.45 (1.11-1.90)	.006	1.20 (1.15-1.26)	<.001
Baseline PPI use vs no PPI use	1.50 (1.14-1.96)	.003	1.17 (1.12-1.23)	<.001
Time-varying PPI ever use vs never PPI use	1.35 (1.17-1.55)	<.001	1.22 (1.19-1.25)	<.001
Baseline PPI use vs baseline H_2 receptor antagonist use	1.39 (1.01-1.91)	.05	1.29 (1.19-1.40)	<.001
Baseline PPI use vs propensity score-matched no PPI use	1.76 (1.13-2.74)	.01	1.16 (1.09-1.24)	<.001
Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users	NA	NA	1.24 (1.20-1.28)	<.001
Negative Control				
Baseline H_2 receptor antagonist use vs no H_2 receptor antagonist use	1.15 (0.98-1.36)	.10	0.93 (0.88-0.99)	.03

JAMA Int Med Lazarus et al, 2/2016

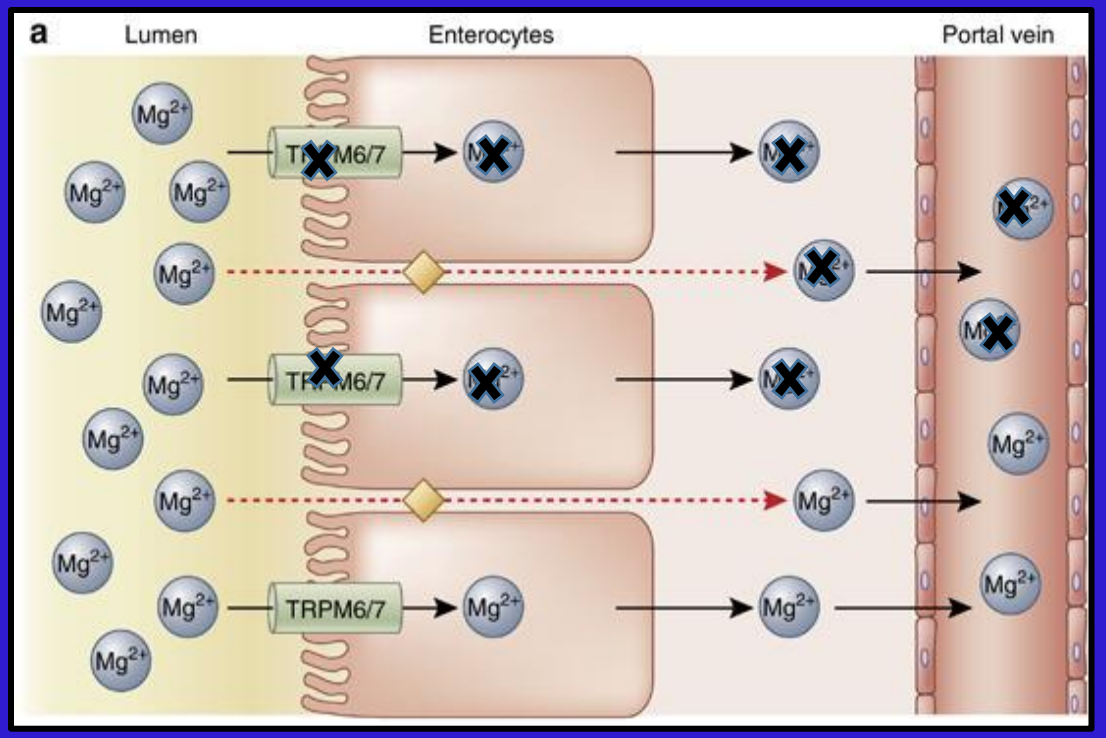
PPIs and kidney disease

- Meta-analysis of 2.4 million patients including 534,000 PPI users
- 4 cohort studies
- 5 case control studies
- NO randomized controlled trials
- “PPI usage was associated with adverse kidney outcomes; however, these findings were based on observational studies and low-quality evidence. Additional rigorous studies are needed for further clarification”.

Nochaiwong, NDT 2/2018

PPIs and hypomagnesemia

↑pH

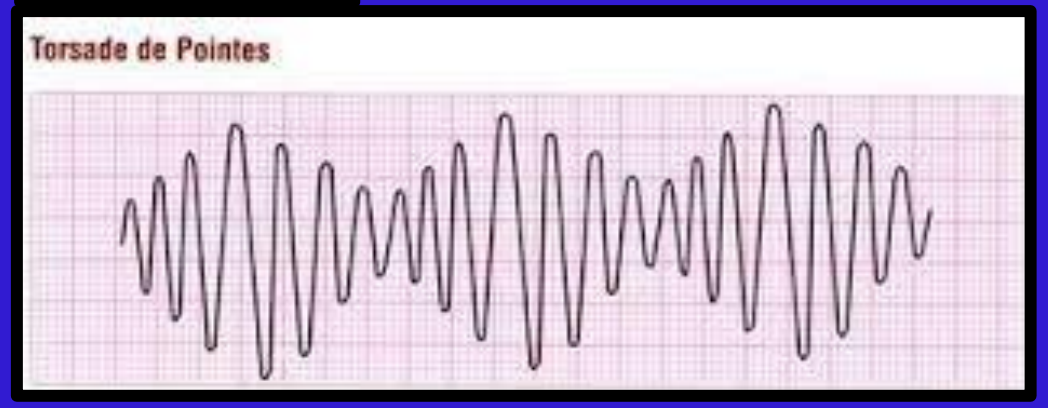


Mark A Perazella
Kidney Int 2013 83: 553-556

Complications of hypomagnesemia

- Neuromuscular

- Cardiovascular



- Electrolyte abnormalities: ↓ K, Ca

PPIs and Hypomagnesemia

- Most pts on PPI > 1 year
- Risk is not high
- Majority asymptomatic, but tetany, seizure, arrythmias described
- Loop diuretics magnify risk in several studies
- Relapse after re-challenge with another PPI

PPIs and the Kidney:Recommendations

- **Hypomagnesemia**

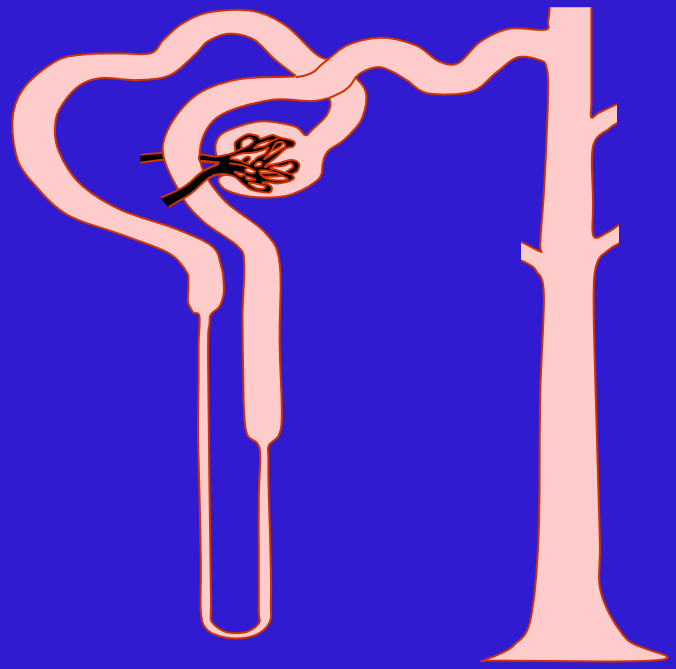
- Consider following mag levels in pts with poor intake
- Pts on diuretics
- Pt on long-term PPIs (> 6 mos)

- **AIN**

- Idiosyncratic and hard to predict
- ?Follow creatinine twice yearly in PPI users

- **CKD**

- Consider minimizing use if creatinine rises
- Ask yourself: Does this pt really need a PPI?



Case

You are seeing a 64 year old caucasian man in follow-up for obesity and back pain. He complains of foamy urine. You dip it in your labs and find 3+ protein and no RBCs or WBCs. The pt denies history of diabetes.

PE: 152/80 P82

Lungs: clear

Cor: RRR no m/g/r

Ext: no edema

Labs: Creatinine of 1.4mg/dl Albumin 4.2g/dl

How would you evaluate this patient?

Three clinical types of proteinuria

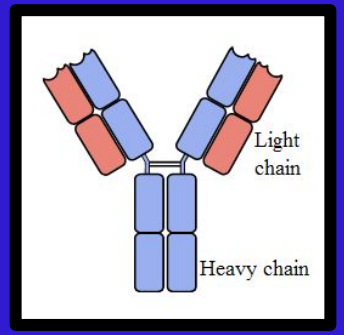
- Transient proteinuria
  - Fever, exercise, UTI, acute illness, CHF
- Orthostatic proteinuria
  - Young adults spill small amount of daytime proteinuria that disappears at night (< 1 gram/24 hours)
- Persistent proteinuria

  > 2-3 grams usually means glomerular disease

Three pathologic types of proteinuria

- Glomerular proteinuria = albuminuria
  * The only protein detected on dipstick

- Tubular proteinuria= low molecular weight proteins (Fanconi Syndrome)
- Overflow proteinuria. Bence Jones or lights chains (multiple myeloma)

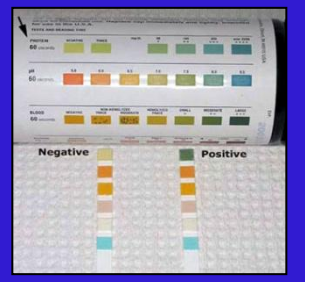


Quantifying proteinuria: Methods

- Dipstick
- 24 hour urine protein
- Spot prot/creat ratio

Limitations of testing

- Dipstick: Only senses albumin and cannot detect albuminuria until it is 8-10x normal excretion rate
- Spot prot/creat ratio: unreliable at extremes of body weight.
- 24 hour urine: vulnerable to collection errors. Inconvenient.



Case

- You obtain a 24 hour urine showing:
- Total creatinine 1600mg (patient is 80kg, so this is about 20mg/kg)
- Total protein 4.7 grams
- Serum albumin 4.1g/dl
- Creatinine 1.4mg/dl
- What further testing is indicated?

Nephrotic syndrome

- Proteinuria >3.5 g/24hr
- Hypoalbuminemia < 3g/d
- Edema
- Hyperlipidemia
- Lipiduria

Nephrotic range proteinuria

- Proteinuria > 3-3.5 grams
- Normal serum albumin
- Often no edema or other features of nephrotic syndrome
- Usually due to diabetes or “secondary FSGS”

Classification of FSGS

Primary FSGS

- Autoimmune due to a "circulating permeability factor"

Secondary FSGS

- Due to nephron loss from any renal disease
- Obesity
- HTN
- Genetic causes
- Meds, viruses
- Reflux nephropathy

Causes of Nephrotic Syndrome

Primary renal disease

- Minimal change
- FSGS
- Membranous nephropathy
- Membranoproliferative GN

Systemic disease

- Diabetes
- SLE
- Amyloidosis/myeloma

Nephrotic syndrome by pathology

- Minimal change disease

  Hodgkin's lymphoma, lithium, NSAIDs

- Membranous

  Hepatitis B, *Solid tumors*, Gold, penicillamine, NSAIDs, SLE

- Membranoproliferative

  Hepatitis C, cryos, complement abnormalities

- FSGS

  HIV, parvovirus, heroin, pamidronate

What's new in medicine:
Anti-PLA2R in primary membranous nephropathy

- Anti-PLA2R are present in 70% of patients
- *These antibodies are not found in any other glomerular disease pattern*
- Titers of anti-PLA2R track well with disease activity and are used to gauge response to treatment
- Still need to rule out secondary causes of membranous (cancers, lupus, meds, HepB)

Nephrotic syndrome/nephrotic range proteinuria work-up

- Infections: Hep B, Hep C, HIV, RPR
- Auto-immune: ANA, C3, C4
- Malignancy: SPEP, Free light chain, age appropriate cancer screening
- Anti-PLA2R
- Renal Ultrasound

Nephrotic Syndrome
Complications

- Renal vein thrombosis, DVT

  Urinary Loss of AT-III, protein C and S
- Hyperlipidemia

  Liver makes more in response to low oncotic pressure
- Infection with encapsulated organisms

  Urinary loss of IgG and complements

Nephrotic syndrome or Nephrotic range proteinuria

Management

- Quantify proteinuria: 24 hour urine or protein/creatinine ratio
- Send serologic work-up and obtain ultrasound
- Start ACE/ARB to reduce proteinuria (spironolactone another option)
- Blood pressure goal generally < 130/80
- Manage complications: clot prevention, immunizations, treat hyperlipidemia
- Nephrotic syndrome: Always refer to nephrologist: Biopsy is often indicated
- Nephrotic range proteinuria:

- If diabetic or morbidly obese, reasonable to treat with ACE/ARB if BP controlled and renal function normal

- Otherwise, refer to nephrology

THANK YOU!!!