‘Case #1—the disbelieving patient’

‘Patient with DM and difficult to control HTN followed for many years for CKD by a nephrologist finally gets up the courage to ask:’

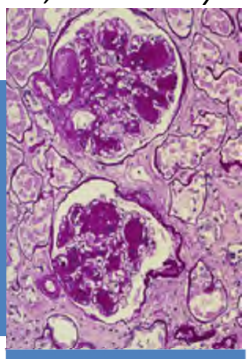
‘Doc, are <u>both</u> my kidneys really damaged?’

KP Hypertension Symposium 2018, ‘Challenging’ CKD Cases
Mark Rutkowski, MD Nephrology, CKD champion

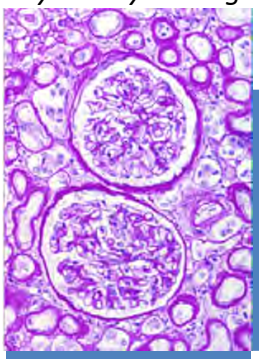
‘Case #1—the disbelieving patient’

‘Doc, are both my kidneys really damaged?’

LEFT KIDNEY feels HIGH BP



Diabetic glomerulosclerosis

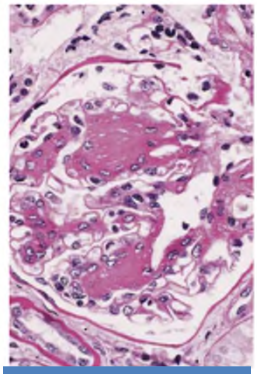


Normal Glomeruli

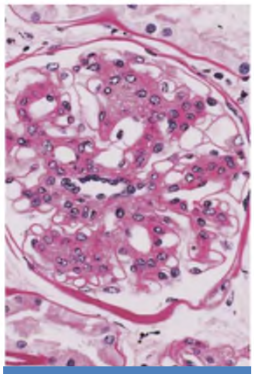
RIGHT KIDNEY feels NORMAL BP

Unilateral diabetic glomerulosclerosis Light micrographs from a postmortem examination of a diabetic patient with unilateral renal artery stenosis on the right side. Classic Kimmelstiel-Wilson nodules are seen in the glomeruli in the left kidney (left panel); in contrast, the glomeruli are normal in the "protected" right kidney (right panel). Courtesy of Helmut Rennke, MD.

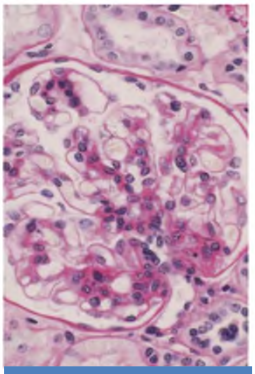
In contrast to the immediate benefit of BP control, the benefit of controlling hyperglycemia is delayed



33 year old Type 1 DM of 17 years duration at time of pancreas transplant



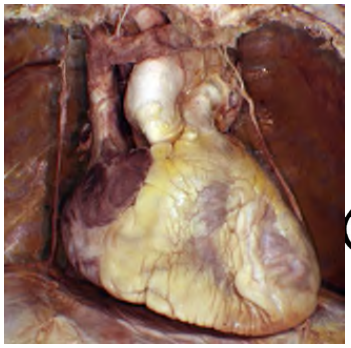
5 years of normoglycemia due to pancreas transplant

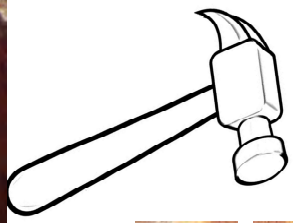


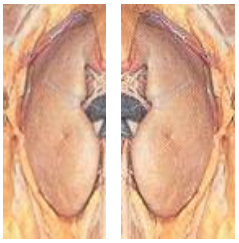
10 years of normoglycemia due to pancreas transplant

Fioretto et al, Reversal of lesions of diabetic nephropathy after pancreas transplant. NEJM 1998; 339:69-75

Kidneys are disproportionately affected by hypertension







Kidneys ~1% body weight

receive ~20% cardiac output

Case #2—the disbelieving doctor

'Is this patient's GFR really reduced?'

Weight	Height	Age	S Creatinine	BUN	S Albumin
lbs	inches		mg/dL	mg/dL	g/dL
201	69	18	1.4	21	3.4

BSA Dubois	1.73/BSA
m2	
2.07	0.83

Abbreviated	Original	
MDRD GFR	MDRD GFR	Cockcrot
male	ml/min/1.73m2	ml/min
non-black	Male	Male
70	64	111

Cockcrot	CRCL—>GFR
ml/min	x0.84
LEAN Male	
86	72

Uprotein	Urine CR	Est CR Excr	CRCL	CRCL	CRCL—>GFR
mg	mg	mg	ml/min	ml/min	ml/min/1.73m2BSA
24 hours	24 hours	Male		1.73m2BSA	x0.81
6053	2600	2229	129	108	87

GFR by CKD EPI estimate **72**

Case #2—the disbelieving doctor (continued)

18 year male nephrotic albuminuria, GFR 72

'How much kidney damage could there be?'

Renal Biopsy:

Light Microscopic Findings: Multiple sections stained with H&E, PAS, Trichrome and Jones stain reveal a total of eleven glomeruli. Eight are completely fibrotic. No crescents are appreciated. The remaining glomeruli reveal a mild to moderate increase in mesangial matrix with variable increase in mesangial cellularity. The capillary walls are thin and delicate with mild ischemic wrinkling. Segmental sclerosis is seen in one glomerulus. Eosinophilic material consistent with immune complex deposition is seen in mesangium of the glomeruli. There is moderate tubular atrophy and interstitial fibrosis. Mild intimal fibrosis of large muscular arteries is seen with mild to moderate medial hypertrophy of small muscular arteries. The frozen section specimen contains a single glomerulus. All staining is limited to mesangium. There is 1-2+ IgG, 2-3+ IgA, trace IgM, 1-2+ C3, 2+ kappa and 1-2+ lambda. There is no staining with the other immunoreactants.

Comments: The findings seen in this biopsy are those of IgA nephropathy. In this biopsy, there is evidence of advanced glomerulosclerosis.

Case #2—the disbelieving doctor (continued)
'Is my treatment of BP including ACEI helping?'

Date	Creatinine	GFR
09/19/2005	2.7	31
07/11/2005	2.3	37
07/01/2004	1.5	62
01/06/2004	1.8	50
08/18/2003	1.7	54
05/14/2003	1.6	58
03/16/2003	1.7	54
08/29/2002	1.5	63
07/18/2002	1.3	74
05/16/2002	1.6	59
03/14/2002	1.5	63
01/08/2002	1.4	69
01/08/2002	1.4	69
11/26/2001	1.4	69

Lost insurance x1 year
Off all medications
Off ACEI
BP uncontrolled
Lost ~1/2 GFR

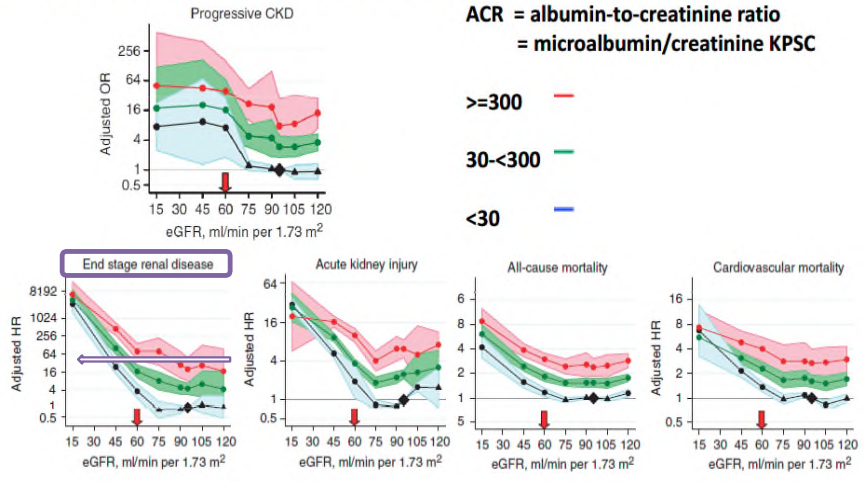
Renal biopsy

Which of the following would suggest chronic kidney damage in a patient?

1. Normal GFR & Normal ACR
2. Normal GFR & Elevated ACR x2
3. Low GFR x 3 months & Normal ACR
4. Low GFR x 3 months & Elevated ACR x2
5. #3 or #4
6. #2 or #3 or #4

GFR = glomerular filtration rate
ACR = urine albumin/creatinine ratio (aka microalbumin)

Risk of renal events & mortality rises progressively for GFR <60 & albuminuria >30



Levey et al, The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference Report. Kidney International (2011) 80: 17-28. This international consensus conference included a patient-level data meta-analysis of 45 cohorts of 1.5 million individuals and to date is the most definitive statement on CKD staging.

CHRONIC KIDNEY DISEASE (CKD) CATEGORIZATION

		ALBUMINURIA LEVELS			
		Urine Albumin-Creatinine Ratio (ACR)	A1	A2	A3
		mcg/mg creatinine	<30	30-<300	300+
Chronic (>3 months) estimated Glomerular Filtration Rate (eGFR)	ml/min/1.73 m2 BSA	description	normal	moderately increased	severely increased
G1	>=90	normal or increased	***	CKD 1 (G1,A2)	CKD 1 (G1,A3)
G2	60-<90	mildly decreased	***	CKD 2 (G2,A2)	CKD 2 (G2,A3)
G3a	45-<59	mild to moderately decreased	CKD 3 (G3a,A1)	CKD 3 (G3a,A2)	CKD 3 (G3a,A3)
G3b	30-<45	moderately to severely decreased	CKD 3 (G3b,A1)	CKD 3 (G3bA2)	CKD 3 (G3bA3)
G4	15-<30	severely decreased	CKD 4 (G4,A1)	CKD 4 (G4,A2)	CKD 4 (G4,A3)
G5	<15	kidney failure	CKD 5 (G5,A1)	CKD 5 (G5,A2)	CKD 5 (G5,A3)

The Footnotes to CKD Categorization

- Diagnosis of 'CKD' requires G3,G4, or G5 persisting chronically (by definition >3 months) or A2 or A3 (confirmed >2 weeks from first and excluding results during pregnancy) or other marker of kidney damage (such as renal biopsy or imaging abnormality consistent with kidney damage).
- Use maximum ACR level in past even if later improves with treatment such as renin angiotensin blockade.
- ACR >=2200 nephrotic range.
- *** in green boxes means G1,A1 and G2,A1 could have CKD based on renal biopsy or imaging abnormality consistent with kidney damage (example: polycystic kidney disease).
- Use appropriate codes for CKD 1-5 (ICD10 N18.1-N18.5) or those linked with diabetes mellitus if appropriate.
- Add additional diagnoses on problem list for nephrotic syndrome or for specific kidney disease.
- Speckled boxes indicate possible candidate for 'CKD diagnosis' or may use non-specific code 'abnormal kidney function' (ICD10 R94.4) or 'proteinuria' (ICD10 R80.9) as appropriate to document issue was addressed and discussed with patient and keep on problem list.

CHRONIC KIDNEY DISEASE (CKD) CATEGORIZATION

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G3a	45-<59	mild to moderately decreased	CKD 3 (G3a,A1)	CKD 3 (G3a,A2)	CKD 3 (G3a,A3)
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G4	15-<30	severely decreased	CKD 4 (G4,A1)	CKD 4 (G4,A2)	CKD 4 (G4,A3)
G5	<15	kidney failure	CKD 5 (G5,A1)	CKD 5 (G5,A2)	CKD 5 (G5,A3)

Case #3--the mysterious librarian

64 year woman referred to nephrology for worsening kidney function, heart failure, hypertension

- Married for 43 years,
- Works at college library for 30 years
- Hobbies: gardening and reading
- Approach to life: fastidious, careful
- Never smoked, no alcohol
- Mother died at age 70 with lung cancer, also had emphysema
- Father died at age 44 of heart attack, had diabetes
- Children age 37 & 33 healthy (no hypertension)

Case #3—the mysterious librarian (continued)

- Hypertension treated since ~age 50
- Diabetes mellitus diagnosed ~age 59
  - well controlled with glipizide, a1c 6.5, no diabetic retinopathy
- Left nephrectomy for Wilms tumor age 5
- Baseline: systolic BP 130's
  - lisinopril 20 mg qd & metoprolol 25 mg bid
- Hyperlipidemia—on statin for 10 years
  - last LDL 69 on atorvastatin 40 mg qd, TG 161
- Possible past HF preserved ejection fraction
- Baseline: renal status
  - Urine albumin/creatinine ratio (ACR) <30, maximum 65 six years ago x1
  - Creatinine 1.2 (GFR 46 persisting more than 3 months in this range)
  - Ultrasound 2 years prior: right kidney measures 11 cm length, mild increased echogenicity, absent left kidney

Which are true about the patient's kidney status?

1. CKD is not present as results are expected after nephrectomy
2. Avoid diagnosis of CKD for insurance purposes
3. CKD is present

Case #3—the mysterious librarian (continued)

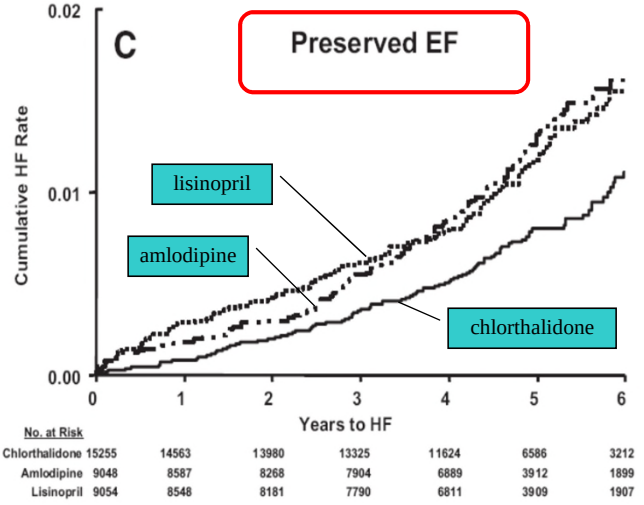
2 months prior to nephrology visit:

- Systolic BP 160-180's with dyspnea in context of URI with cough
- Chest x-ray—clear, scoliosis noted
- Echocardiogram--global hypokinesis, EF 42%, no LVH, moderate to severe mitral regurgitation, dilated inferior vena cava.
- Furosemide 20 mg every day.
- Over a month later, blood pressure remained elevated at 156/79 and 147/78 so amlodipine 2.5 mg every day was added.

Which diuretic approach is best for CKD with hypertension and heart failure?

1. Start thiazide
2. Increase thiazide
3. Stop thiazide, add furosemide once daily
4. Stop thiazide, add furosemide twice daily
5. Continue thiazide, add furosemide
6. Continue furosemide, add prn thiazide
7. It depends…

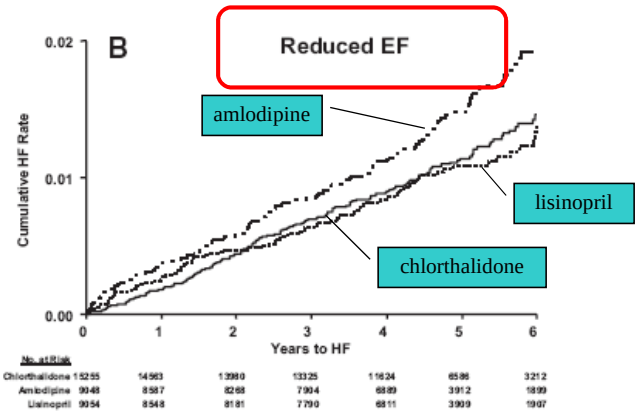
Thiazide preventing 1st admission for Heart Failure Preserved Ejection Fraction in ALLHAT



- Age >=55
- HTN
- +1CHD risk
- no overt HF
- 50% DM

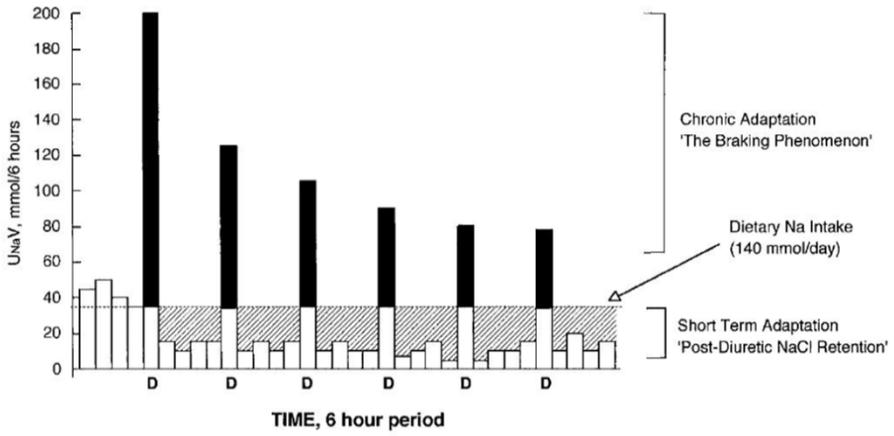
***Circulation*. 2008;118:000-000.)**

Thiazide preventing 1st admission for Heart Failure Reduced Ejection Fraction in ALLHAT



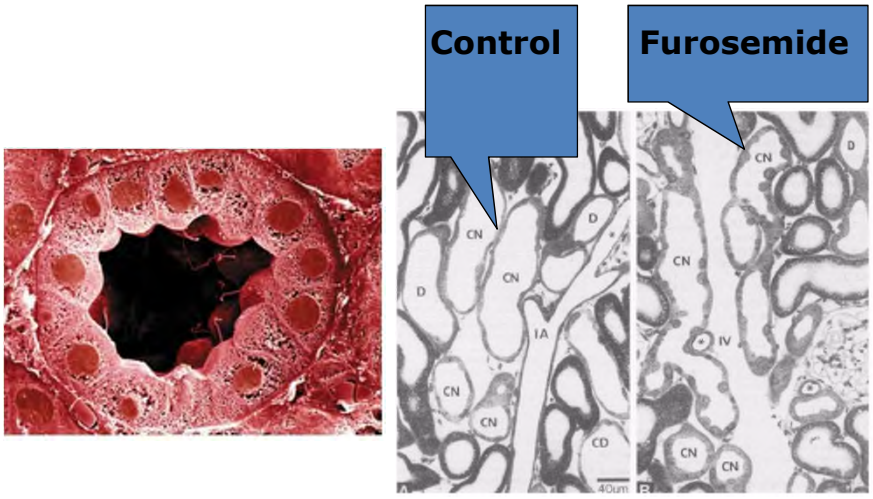
***Circulation*. 2008;118:000-000.)**

Post-diuretic sodium retention with loop diuretic



Ellison D. Diuretic therapy and resistance in congestive heart failure. Cardiology 2001;96:132-143.

Distal tubule hypertrophy on long-term loop diuretics



Thiazides to Loop for GFR <30?

- JNC7 and KDOQI—recommended to change
- JNC8– no position
- KDIGO 2012 less prescriptive about changing
- ACC AHA 2017 indicated preferable to use loop

"Thiazides appear promising for treatment of both volume overload and hypertension in patients with advanced kidney disease, either as a lone diuretic or in combination with loop diuretics, and therefore, consideration should be made for continuing thiazides even when GFR falls chronically or as add on therapy for uncontrolled hypertension or volume overload."

Sinha and Agarwal. Thiazide diuretics in Chronic Kidney Disease. Curr Hypertens Rep. 2015; 17:13

- No adequately powered trials for hard outcomes for thiazides in advanced CKD but are there any for loop diuretics?

Volume overload in CKD

A Randomized Crossover Trial of Dietary Sodium Restriction in Stage 3–4 CKD

Rajiv Saran, Robin L. Padilla,† Brenda W. Gillespie,‡ Michael Heung,* Scott L. Hummel,§‖ Vimal Kumar Derebail,¶ Bertram Pitt,§ Nathan W. Levin,** Fansan Zhu,** Samer R. Abbas,** Li Liu,** Peter Kotanko,**†† and Philip Klemmer¶*

Results

whole-body extracellular volume -1.02 L

urinary sodium -57.3 mEq/24 h

weight -2.3 kg

24-hour systolic BP -10.8 mmHg

Clin J Am Soc Nephrol 12: 399–407, 2017.

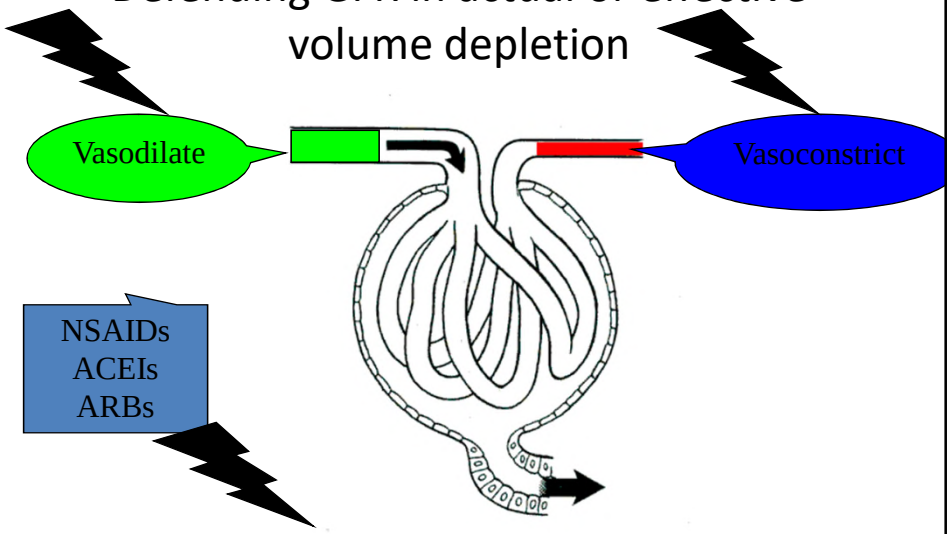
Case #3—the mysterious librarian (continued)

- ~ 6 weeks later: serum creatinine 2.5 (baseline 1.2)
  - Furosemide was stopped
  - Patient was told to drink more fluid
  - Lisinopril was not held

Which are true about diuretics and ACEI /ARB and decline in GFR?

1. Holding both diuretics and ACEI/ARB is an appropriate action when decline in kidney function is known or suspected to be acute.
2. Chronic decline in GFR to <60 always indicates that diuretics and/or ACEI/ARB are damaging the kidneys and should be stopped permanently.

Defending GFR in actual or effective volume depletion



REVERSIBLE CAUSES OF GFR DECLINE

It is crucial to evaluate reversible causes of GFR decline prior to assigning CKD diagnosis and assessing CKD risk.[1] Recheck serum creatinine/eGFR after:
a) evaluating volume and hemodynamic status (both volume depletion and volume overload via heart failure physiology may trigger decline)
b) stopping non-steroidal anti-inflammatories and other potential nephrotoxins (including fenofibrate, trimethoprim-sulfamethoxazole) if clinically appropriate,
c) TEMPORARILY holding or reducing diuretics[2] and ACE inhibitors and angiotensin receptor blockers[3] if clinically appropriate prior to recheck.

[2]Diuretics are often essential for blood pressure control especially in CKD. Initial decline in GFR with blood pressure control may be functional and associated with slower long-term decline in GFR (see Apperloo, Alfred J.; de Zeeuw, Dick; de Jong, Paul E. A short-term antihypertensive treatment-induced fall in glomerular filtration rate predicts long-term stability of renal function. Kidney International. 51(3):793-797, March 1997).

[3]While predisposing to acute kidney injury during volume depletion, ACE inhibitors and angiotensin receptor blockers have long-term benefit of slowing even G3 and G4 CKD. Strongest evidence is for A2 albuminuria or higher for hypertensive diabetics and A3 for hypertensive non-diabetics.

Case #3—the mysterious librarian (continued)

- 2 weeks later: presented in pulmonary edema requiring BIPAP with BP 184/94 and serum creatinine 2.4, BNP 482
  - Metoprolol was increased to 75 mg twice daily and lisinopril held. She was given furosemide (Lasix) 40 mg intravenous x 2 and diuresis of 1.9 liters
  - Discharged the next day without furosemide

- 1 week later: presented in pulmonary edema, BNP 775
  - Metoprolol changed to carvedilol, nuclear stress test negative for ischemia.
  - Discharged on amlodipine 5 mg qd, carvedilol 25 mg bid, furosemide 40 mg qd, isosorbide 10 mg ½ bid, KCL 8 meq qd, glipizide, aspirin
  - Creatinine 2.0 on discharge

Case #3—the mysterious librarian (continued)

- Seen by nephrology day after discharge
  - Patient felt back to her usual self, BP 128/55,
  - No evidence of pulmonary congestion or JVD
  - No carotid, femoral, or abdominal bruits
  - Dorsalis pedis pulses 3+
  - Creatinine 2.0 (GFR 25) with no improvement off lisinopril
  - Na 134, K 4.8, CO2 24,
  - U/A negative, ACR <30

What would you do next?

1. Decrease furosemide
2. Add back low dose ACEI for systolic heart failure
3. Consider low dose spironolactone
4. Cardiology evaluation for mitral regurgitation
5. Renal artery imaging

Case #3—the mysterious librarian (continued)

- Seen by nephrology day after discharge
  - Considerations: ?ATN due to cardiorenal syndrome superimposed on CKD, ?intermittent ischemia to mitral valve as cause of pulmonary edema, ?renovascular disease (less likely given no other significant atherosclerotic disease and no smoking hx)
  - Furosemide decreased to 20 mg qd, lisinopril 2.5 mg qd started, potassium stopped
  - Cardiology evaluation (patient missed previously)

Case #3—the mysterious librarian (continued)

- ~1 week later: repeat creatinine 3.5
  - asymptomatic, lisinopril stopped, furosemide held for 2 days
- Renal duplex
  - no renal artery stenosis seen but pulsus tardus and parvus of intra-renal arteries
- ~2 weeks later: readmitted with heart failure, creatinine 1.7
  - Renal MRA: severe narrowing of right renal artery
  - Renal angiogram: unsuccessful angioplasty due to severe scoliosis compromising approach
- ~2 weeks later
  - Renal angiogram: successful right renal artery stent placement

Case #3—the mysterious librarian (continued)

- 1 week after right renal artery stent: creatinine 1.4, BP 137/62, exercise tolerance improved
  - Lisinopril/HCTZ 10/12.5 mg ½ qd started, furosemide 20 mg qd changed to prn
- 1.35 (GFR 39), BP 117/61
  - on lisinopril/HCTZ 10/12.5 mg ½ qd, amlodipine 2.5 mg qd, carvedilol 25 mg bid, no prn furosemide needed
- 1.5 years later: creatinine 1.29 (GFR 43), ACR 18, BP 115/53
  - on same regimen

How do I estimate patient's future risk of progressive renal failure ?

1. Guess
2. Go to QXMD
3. Go to Aura

Aura model in KPHC for
5-year risk progression to kidney failure for GFR <60

CKD TIPS hyperlink

CKD TIPS

Details about CKD classification, referral, monitoring

Smartlink for usage in note documentation

.ckdrisk5year

Pearls

- Hypertension control remains one of the most important modifiable risk factors for the progression of CKD.
- Renal artery stenosis (unilateral in solitary kidney or severe bilateral) with flash pulmonary edema and hypertension remains an indication for renal artery intervention.