

The ABCs of CKD Chronic Kidney Disease



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Disclosures

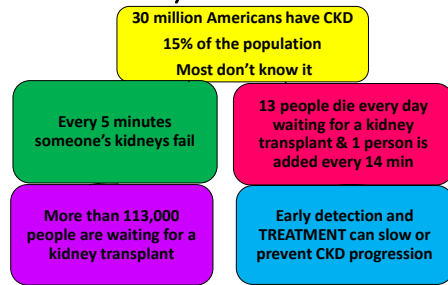
None

Objectives

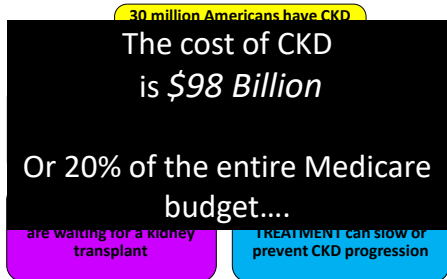
- 1) Review the pathophysiology of both the kidney and CKD to include the diagnosis of stages 1-5
- 2) Discuss both the causes and treatments of CKD
- 3) Discuss proven methods to prevent progression of CKD in patients



Kidney Disease Facts



Kidney Disease Facts



And it is growing.....

- CKD is the fastest growing chronic disease
- The rate of growth is highest in the 20-54 y/o!
- The incidence of CKD grew by 89%
- Death from CKD grew by 98%
- Disability from CKD grew 62%



Analysis of the Global Burden of Disease...1990-2016, Kidney International 2018

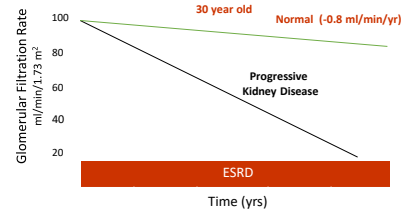
And it is changing.....
New in 2021

- In August 2020, the American Society of Nephrology and the NKF institute a Task Force to look into race-based issues in GFR
- Kidney Disease Improving Global Outcomes (KDIGO) announces no more updates to CKD management guidelines
- KDIGO announces specific updates for diagnoses that occur in CKD with a goal to keep the guidelines relevant
- In October 2020, **Diabetes Management in CKD** is published
- In February 2021, **Hypertension Management in CKD** is published
- In March 2021, NKF/ASN announce a new **GFR calculator**

KDIGO Management of Diabetes in CKD, KDIGO Management of HTN in CKD, ASN/NKF Race Task Force



Normal Age Progression of Kidney Function



Stages of CKD

Composite ranking for relative risks by GFR and albuminuria (KDIGO 2009)		Albuminuria stages, description and range (mg/g)					
		A1		A3			
		Optimal and high-normal	High	Very high and nephrotic			
		<10	10-29	30-299	≥300-1999	>2000	
GFR stages, description and range (ml/min per 1.73 m ²)	G1	High and optimal	>105	90-104			
	G2	Mid	75-89	60-74			
	G3a	Mid-moderate	45-59				
	G3b	Moderate-severe	30-44				
	G4	Severe	15-29				
G5	Kidney failure	<15					

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of CKD, *Kidney International*, Jan 2013, Vol 3, Issue 1



GFR Calculators for Kidney Function

- **1976 Cockcroft-Gault formula**
 - Compared 249 White hospitalized males with inulin vs calculator
 - Requires age, gender, SCr, weight
 - 15% less in females (never confirmed)
 - Reports as CrCl, often in FDA package inserts
- **1999 Modification of Diet in Renal Disease (MDRD) formula**
 - Compared 1585 CKD patients with iothalamate vs calculator
 - Requires age, gender, race (Black/other), SCr, BUN, Albumin
- **2000 Modification of Diet in Renal Disease (MDRD) formula**
 - Isotope evaluation decreased need for 6 variables
 - Requires age, gender, race (Black/other), SCr
- **2003 CKD-EPI formula**
 - Developed with input from large data bases at NIH (NHANES, AASK)
 - Contains 'correction' for Black race as 1.159
 - Requires age, gender, race (Black/other), SCr



Race as a 'Social, not Biological Construct'
NKF/ASN Task Force: Considerations for the Task Force

- 1) Who defines Race?
- 2) With a higher incidence of African American patients on dialysis are we the problem?
- 3) Will we make health, life, and/or disability insurance harder to obtain?
- 4) Will we cause patients to have issues with medications (IE: metformin)?
- 5) Are we not referring to transplant fairly?
- 6) We have made *HUGE* strides with the labs nationwide; the enemy of good is perfect
- 7) We must all agree or there will be a patchwork of results
- 8) First Do no Harm

Race as a 'Social, not Biological Construct'
NKF/ASN Task Force

Considerations for the Task Force

- 1) Drop race out of the calculators
- 2) Change to Cystatin-C
- 3) Use a combo SCr/Cys
- 4) Use high/low rather than race-based
- 5) Use a blended formula
- 6) Use a 'low molecular weight' variable

All calculators should match nation-wide

Decisions should be made using the BEST SCIENCE

Final Task Force report at NKF annual meeting!!





National Kidney Foundation
American Society of Nephrology
Statement regarding Race

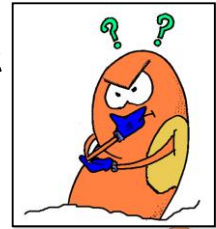


- 1) Race modifiers should **not** be included in equations to estimate kidney function
- 2) Current race-based equations should be replaced by a suitable approach that is accurate, inclusive, and standardized in every laboratory in the United States
- 3) This process is so large, detailed and the outcome so important that it will be broken down into 3 parts:

- A) Clarifying the problem and evidence
- B) Evaluating the approaches to address race in eGFR estimation
- C) Making recommendations for the best approach to replace existing equations for estimating kidney function

So now we know
how to calculate GFR
(at least in 2021!)

Who do we screen?



How do I find CKD?

Go for the obvious!

- Elderly
- Minority
- Hypertension/CVD
- Diabetes
- Family history
- Female
 - *Although less likely to go to ESRD!*
- On their medical history!

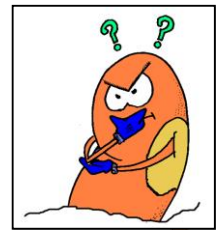
Go for the less obvious!

- Previous AKI
- Lupus, sarcoid, amyloid, gout, auto-immune...
- Previous donor/Previous transplant
- History of stones
- History of cancer
- History of oophorectomy
- History of gout
- Smoker (any type)
- Soda drinkers
- Moms who drank with pregnancy
- NAACL bingers
- Almost any medical condition



So we know who
to screen

How do we do It?



Sadie

She reports she is 85 y/o, female, has diabetes and she is black
Labs: eGFR 45ml/min

If you lose 1%/yr above the age of 30,
85-30 means 55 years of GFR loss
Or

100 (average perfect kidney function)-55 (years)
or expected eGFR is **45ml/min**
She is age appropriate....so what is her UACR?



Albuminuria As Risk Factor

The relationship between magnitude of proteinuria reduction and the risk of ESRD: Results of the AASK study of kidney disease and hypertension
Ach Intern Med 2001



The Progression of CKD: A 10-year population-based study of the effects of gender and age. KI 2006

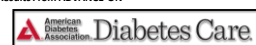


Combining GFR and albuminuria to classify CKD improves prediction of ESRD, JASN 2009

Changes in Albuminuria and the Risk of Major Clinical Outcomes in Diabetes: Results From ADVANCE-ON



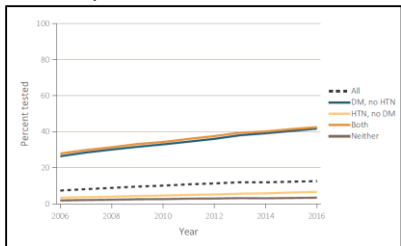
Changes in Albuminuria and subsequent risk of incident kidney disease, JASN 2017



Alberta Kidney Disease Network: Relation between kidney function, proteinuria, and adverse outcomes, JAMA 2010

19

Probability of urine albumin testing in Medicare patients at risk for CKD



Special Thanks to Scott and White of Temple TX for use of their kidney comic

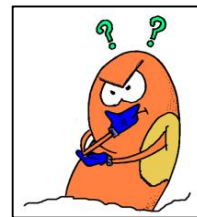


Urine Pearls

- Some labs (Quest, LabCorp) refer to a UACR as 'microalbuminuria'
- NKF has joined with Quest (Code: 39165, CPT: 82043; 82565; 82570) and LabCorp (Code: 140301, CPT: 82043; 82565; 82570) to roll out a 'Kidney Profile' that incorporates both the SCr + the UACR
- **Order a UACR at least 1x/yr to monitor kidney function**
 - For all patients with hypertension
 - For all patients with diabetes
 - For all patients with risk factors



So we know who has CKD
And we tested their urine



Now...how do we manage CKD in 2021?



The Big 5

- 1) Hypertension (NEW IN 2021)
- 2) Diabetes (NEW IN 2021)
- 3) Obesity
- 4) Cardiovascular Disease
- 5) This and That (kind of defies categorization)



Hypertension (New in 2021)

If HTN doesn't cause your CKD, your CKD will cause HTN

So what is the GOAL?

KDIGO 2021 HTN Management in CKD GUIDELINES:

- Target SBP <120mm Hg
- Use an automatic office cuff measurement
- No DBP goal



Effectiveness of Lifestyle Changes

Modification	Example	Approx Reduction
Physical activity	Aerobic (brisk walking?) >30/day, most days	4-9mmHg
DASH eating plan	Low fat diet rich in fruits, vegetables	8-14mmHg
NACL restriction	Decrease to 2.4gm/day	2-8mm Hg
Moderate ETOH	1 drink/women, 2 drinks/men	2-4mmHg
Weight loss	BMI 18.5-25	5-20mmHg/10kg weight loss
Stress reduction	Practice modality	5mmHg
Quit smoking	Any which way	2-4mmHg after 1 week



NACL Restriction

Stage of Kidney Disease
= NAcl clearance

Most effective in
AA populations

Tricks:

Pork holidays

No cooking w/NAcl
'B' cooking



First Choice: ACEi/ARB

ACEi OR ARB:

First choice in Diabetes and/or CKD
Even in the AA population
Will decrease albuminuria...
Use it even if there is no albuminuria
It doesn't matter ACEi vs ARB



**One or the other
NOT BOTH!**

Only 1 or the other due to:

- inc risk of hyperkalemia
- Hypotension
- AKI/failure
- no decrease in mortality

When do I stop an ACE/ARB?

- If hyperkalemia cannot be **controlled**
 - Diet, education, medication
- What is hyperkalemia?
 - Lab dependent
 - >5.5mEq/L in CKD 4
 - >6mEq/L in CKD 5
 - >'We'll tell you in CKD 5D!!!



What do the present studies say? All observational trials

Continued use of ACEi/ARB with a GFR<30mm/min protected the heart WITHOUT an increase in ESRD*

Stopping ACEi/ARB increased mortality and MACE endpoints by 11.9-13.6% with a <8% increase in ESRD in Stage 5 patients**

*Association Between Renin-Angiotensin System Blockade Discontinuation and All-Cause Mortality Among Persons With Low Estimated Glomerular Filtration Rate, JAMA Intern Med. March 9, 2020
**Stopping Renin-Angiotensin System Inhibitors in Patients with Advanced CKD and Risk of Adverse Outcome: A Nationwide Study, JASN Feb 2021

When do I stop an ACE/ARB?

The STOP-ACEi trial

Multicenter UK randomized controlled trial of ACEi/ARB withdrawal in advanced kidney disease

Enrollment completed **June 2018**

Trial time line 3 years

Cardiac vs ESRD...

Or

Do the patients have more cardiac events or more GFR loss??

Results to be determined

Note: Trial data collection in the UK has slowed due to Covid...



Rose

74 y/o routine visit

PMH: PVD, HL, HTN.

Meds: metoprolol, HCTZ, amlodipine, ASA, atorvastatin

PE: 168/98, home 150-160s

Labs: SCr 1.2mg/dL, UACR 30mg/dL, GFR 56mm/min

Add lisinopril for BP/UACR control

F/U labs 2 weeks later, SCr 2.2mg/dL with K 5.4mEq/L

What is an acceptable rise in SCr starting an ACEi/ARB?

**Acceptable rise in SCr
is 20-30%**



Hypertension Pearls

- NACL restriction is just as effective as medications
- Always tell a patient that it will take 3-4 meds for control; If it takes fewer, they think you are brilliant
- Start with ACEi/ARB, then diuretic (if possible)
- Consider an SGLT2i early in the process; It is a diuretic
- Calcium channel blockers work **VERY** well in the AA population
- With cardiovascular disease...ACE/CCB>ACE/diuretic
- Thiazide diuretics do **NOT** work if the GFR<30ml/min
- **NOTHING works if you cannot afford it**

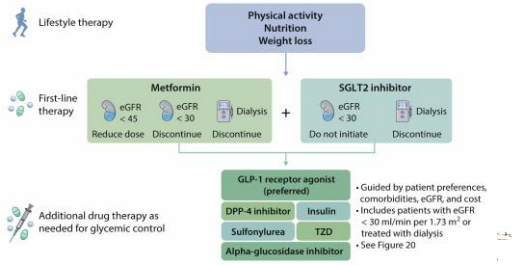


KDIGO Management of DM in CKD: 2020

- A. Use the A1C for monitoring; we know its not perfect but its our best data
 - A. Check 2-4 times/year
 - B. Check after dose change
 - C. Accuracy decreases with lower GFR
- B. Continuous glucose monitoring (CGM) data can be very useful
- C. Daily glycemic monitoring with CGM or self-monitoring of blood glucose (SMBG) will decrease hypoglycemia in those at risk
 - A. If not on a CGM or doing daily glucose checks, use medications that have a lower risk of hypoglycemia
 - B. CGM devices are rapidly evolving with multiple functionalities (e.g., real-time and intermittently scanned CGM) and may offer advantages for certain patients
- D. An individualized HbA1c target ranging from <6.5% to <8.0% in important in patients with DM and CKD



KDIGO: Update for Diabetes Treatment in CKD



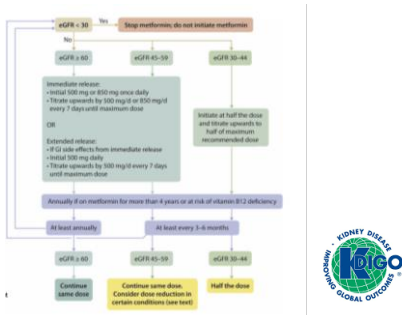
Kidney Specific Family Details: Metformin

- This should be the first medication for any DM patient
- Metformin is underutilized in DKD
- It is an older medications and therefore cheap
- **No renal dosing needed**
- Dosing is dependent of side effects (usually GI)
- Decreases CV risks which cause 70% of all CKD deaths
- Often will decrease cholesterol, triglycerides and weight

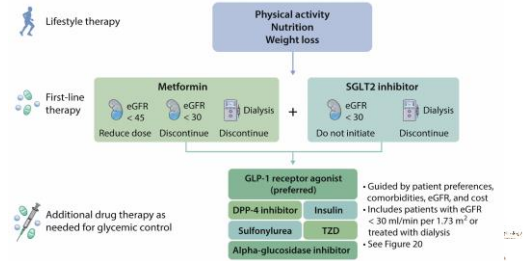


Therapeutic Considerations for Anthyperglycemic Agents in DKD CJASN May 2017

Metformin Dosing in CKD: Algorithm Format



KDIGO: Update for Diabetes Treatment in CKD



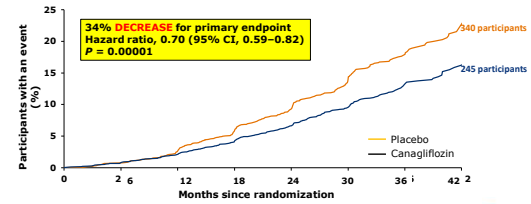
Kidney Specific Trials: SGLT2 inhibitors - CREDECE

- 4401 patients with T2DM, A1C 6.5-12%
- eGFR: 30 to <90 mL/min/1.73 m²
- **UACR: >300 to 5000 mg/g**
- Stabilized on ACEi or ARB therapy PRIOR to randomization
- Random assignment (1:1)
 - Stratified by eGFR
 - Blinded
 - Canagliflozin 100mg/d vs Placebo
- Follow-up 2.6y, stopped early due to safety committee evaluation



Perkovic V, et al. *N Engl J Med.* 2019;380:2295-2306

Primary Outcome: ESKD, Doubling of SCr, Kidney or CV death



Perkovic V, et al. *N Engl J Med.* 2019;380:2295-2306

Lessons from the CREDECE study SGLT2 inhibitors

- Initially treat with maximum dose of ACE/ARB before adding SGLT2i
SGLT2i can be used up to Stage 3a or Stage 3b for canagliflozin
- If patient on diuretic, ½ the dose....
(was researcher choice: ½ number of daily doses or ½ each dose)
- Tell patient to increase fluid (water)
- Monitor blood pressure; all SGLT2i are diuretics too!
- There will be a drop in GFR (inc in SCr) but take a deep breath, step away from EHR and ignore
- SCr bump from RAAS is 4-6w but from SGLT2i is 4-6mo
Even those with a bump in GFR had better kidney outcomes

Dapagliflozin: DAPA-CKD Trial

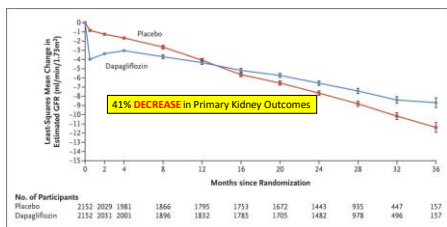
If an SGLT2i is renoprotective AND the A1C does not go down, Is an SGLT2i renoprotective for CKD WITHOUT Diabetes?

- 4425 patients, 30% without diabetes
 - eGFR: 25 to 75 mL/min/1.73 m²
 - UACR: 200 to 5000 mg/g
 - Stabilized on ACEi or ARB therapy
- Random assignment (1:1)
- Stratified by eGFR
- Blinded
- Dapagliflozin 10mg/d vs Placebo
- Follow-up 2.4y, stopped early by safety committee

Heerspink HJL, et al. *N Engl J Med.* 2020;383(15):1436-1446.



Dapagliflozin: DAPA-CKD Trial



Heerspink HJL, et al. *N Engl J Med.* 2020;383(15):1436-1446.

DAPA-CKD and SGLT2 inhibitors

- SGLT2i are reno-protective in diabetes
- SGLT2i are cardio-protective in diabetes
- SGLT2i are reno-protective in CKD
- SGLT2i are cardio-protective in CKD
- There may not be a lowering of the A1C with an SGLT2i in CKD with diabetes but it still is reno-protective
- SCr bump from RAAS is 4-6w but from SGLT2i is 4-6mo



SGLT2 inhibitors are NOT yet FDA approved for use in CKD WITHOUT DIABETES but the request is in front of the FDA

Kidney Specific Family Details: Sulfonylureas/TZDs

- Older medications and therefore cheap
- Can cause hypoglycemia
- Glyburide (*Diabeta*) metabolized in liver
 - Metabolites excreted in kidney so not good in DKD
- Glimepiride (*Amaryl*) can be used but needs renal dosing
- Glipizide (*Glucotrol*) metabolized by liver
 - Metabolites are inactive, no renal dosing
 - Can cause hypoglycemia in older, fragile patients
- TZDs cause fluid retention so not great for DKD



Therapeutic Considerations for Antihyperglycemic Agents in DKD CJASN May 2017



CKD and Insulin

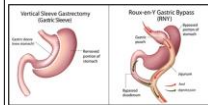


- All types are safe and effective for **All Stages of CKD**
- Basal Insulin is VERY easy to dose in CKD
- Basal Insulin with Oral Medications is fine
- CKD Patients including Dialysis may use pumps
- Dosing Requirements decrease with decreasing Kidney Function
- Decreasing Dosing Requirements are NOT logarithmic no matter what you may have read....



Bariatric Surgery

Dec 4th, 2016
Estimated GFR before and after Bariatric surgery in CKD
 Imam, et al
 Large Kaiser group (714) over 3 years
 44% minority, 58±8 (SD) y/o, 77% female
 66% w/DM, 91% w/HTN
Surgical patients had nearly 10mL/min better GFRs at 3 years than non-surgical
 RYGB had 6.6mL/min better GFR @ 3y than sleeve gastrectomy



Diabetes and Obesity Pearls

- Losing weight saves your kidneys
 - Studies show >7 year protection after bypass surgery (*JASN 2018, 2144 patients*)
- CKD diagnosis helps for Medicare coverage for Bariatric Surgery
- Some diabetic medications promote weight loss...Use them!
- If you actually followed the diabetic, kidney, hypertensive, cardiovascular diet, you would only be allowed to eat cardboard
- DASH diet is best
- High fruit and vegetables can cause hyperkalemia
 - Monitor K with any new diet changes (**and in Jan**)
- **NACL holidays help with HTN and weight loss**



Cardiovascular Disease (CVD)

- More than 70% of kidney patients die of CVD
- Statins are underutilized in CKD
- CKD patients are **2-3X** more likely to have atrial fibrillation
 - Take the time to listen with that stethoscope
 - Warfarin vs DOACs is still debated but KDIGO states to use NOACs
- Smoking is an issue
 - Including vaping, marijuana and cigarette
 - No studies on chewing tobacco



KDIGO Guidelines for dosing in A Fib

CrCl (ml/min)	Apixaban* (Eliquis®)	Dabigatran (Pradaxa®)	Edoxaban** (Savaysa®, Lixiana®)	Rivaroxaban (Xarelto®)
>95	5mg bid	150mg bid	60mg qd ^{AA}	20mg qd
51-95	5mg bid	150mg bid	60mg qd	20mg qd
31-50	5mg bid (CrCl cut off 25ml/min)	150mg bid or 110mg bid ^A	30mg qd	15mg qd
15-30	2.5mg bid	Unknown	30mg qd could be considered	15mg qd could be considered
<15 not on dialysis	Unknown	Not recommended	Not recommended	Unknown
<15 on dialysis	Unknown	Not recommended	Not recommended	Unknown

Decrease Smoking Rates



PEDIATRICS

Kidney function and tobacco smoke exposure in US adolescents *Pediatrics* May 2013

For current black smokers there is an 83% ↓ kidney function
 19 cig/day = ↓ 75% kidney function
 >20 cig/day = ↓ 97% kidney function
 ...worse with menthol cigarettes!
J Am Heart Association, May 2016



SMOKING or VAPING KILLS NEPHRONS
Marijuana is safe in CKD
As long as it is not smoked or vaped



Hyperlipidemia

CKD = Heart Disease



SHARP Trial: Statins or statins + ezetimibe
 Fibrates are not recommended in CKD by KDIGO
 Debatably is effective in Stage 5/5D CKD

Uremia affects LDL levels making them unreliable
When you put a CKD patient on a Statin
FIRE AND FORGET

<http://kdigo.org/home/guidelines/lipids/>

SHARP: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with CKD (Study of Heart and Renal Protection): a randomised placebo-controlled trial, *Lancet* 2011



Hyperlipidemia: KDIGO Guidelines

Recommended doses (mg/d) of statins in adults with CKD		
Statin	eGFR G1-G2	eGFR G3a-G5, including patients on dialysis or with a kidney transplant
Lovastatin	GP (General public)	nd (not determined)
Fluvastatin	GP	80 ¹
Atorvastatin	GP	20 ²
Rosuvastatin	GP	10 ³
Simvastatin/Ezetimibe	GP	20/10 ⁴
Pravastatin	GP	40
Simvastatin	GP	40
Pitavastatin	GP	2

CVD Pearls



- A CKD patient is more likely to die of CVD than via kidney failure
- All CKD and DM patients should be on a statin
 - Add Vit D if leg cramps
 - **REAL** rhabdo from statins is <5%
- CKD patients are 2X more likely to have cardiac arrhythmias
 - Mainly a fib
- **All patients with CKD have heart disease**



This and That

- Drinking soda after exercise hurts the kidney
- Sleep (7h/night) is reno-protective
- Bilateral oophorectomy increases CKD risk
 - Increase 7.5% if premenopausal
- Increasing H2O does not help the kidneys
- Marijuana (oral) does not hurt the kidney and may be helpful in pain
 - **ETOH is reno-protective**
- PPIs **do** cause CKD but very small risk
- As you lose kidney function, you are more likely to have a serious fall
- Untreated Hepatitis C will cause loss of GFR
- Gut and Dental disease are predictive of CKD



Optimal Follow-up Guidelines for CKD
 Office visit + Labs

CKD Stage	Length of time	for next appointment
3A	6 months	
3B	3.2 months	
4		2 months
5		1.2 months

The Magic Referral

I always hear that your nephrology consultants complain about referrals...

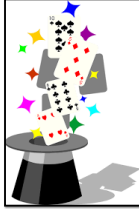
We *are* overwhelmed but...

Start your referral with:

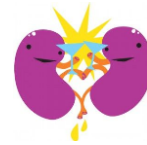
'Per KDIGO Guidelines,

I am referring this patient due to...'

- 1) Uncontrolled HTN
- 2) Stage 4 CKD
- 3) GFR dropped 25% in 6 months *or*
- 4) SCr increased 25% in 6 months
- 5) Patient request



Thank you for helping us care of
CKD Patients!



References

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