When Creatinine Rises: Distinguishing AKI From CKD Progression

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Objectives

1. Differentiate AKI from CKD progression.
2. Apply an evidence-based diagnostic approach to evaluating rising serum creatinine in CKD.
3. Integrate risk factors and prognostic indicators to guide management, counselling, and nephrology referral.

Speaker Disclosure

Relationships with commercial interests: none
Potential for conflict(s) of interest: none
Mitigation of potential bias: nothing to mitigate

74M with CKD and type 2 diabetes seen for follow-up of diabetic kidney disease.

Cr 180 µmol/L (125 µmol/L, 2 yr earlier)

ACR 95 mg/mmol (normal <3)

Comorbidities: hypertension, hypercholesterolemia

Lifestyle: Non-smoker, no alcohol use

Current medications:

Perindopril 2 mg daily
Amlodipine 5 mg daily
Atorvastatin 40 mg daily
Metformin 500 mg bid
Dapagliflozin 10 mg daily
Semaglutide 1 mg weekly

Exam findings:

Appears well

BP 140/85 mmHg

Mild peripheral edema

How should we interpret this rise in creatinine — is this an episode of AKI or gradual CKD progression?

Why distinguish AKI from CKD

AKI = rapid decline in kidney function (days–weeks) and often reversible

CKD progression = slow, steady decline with no acute symptoms

AKI may be reversible

Interpreting the rise in Cr

Need prior Cr to distinguish AKI from CKD progression

Small increases up to 25% after starting certain medications may **not reflect true loss of function**

Consider timing, trajectory, and clinical context

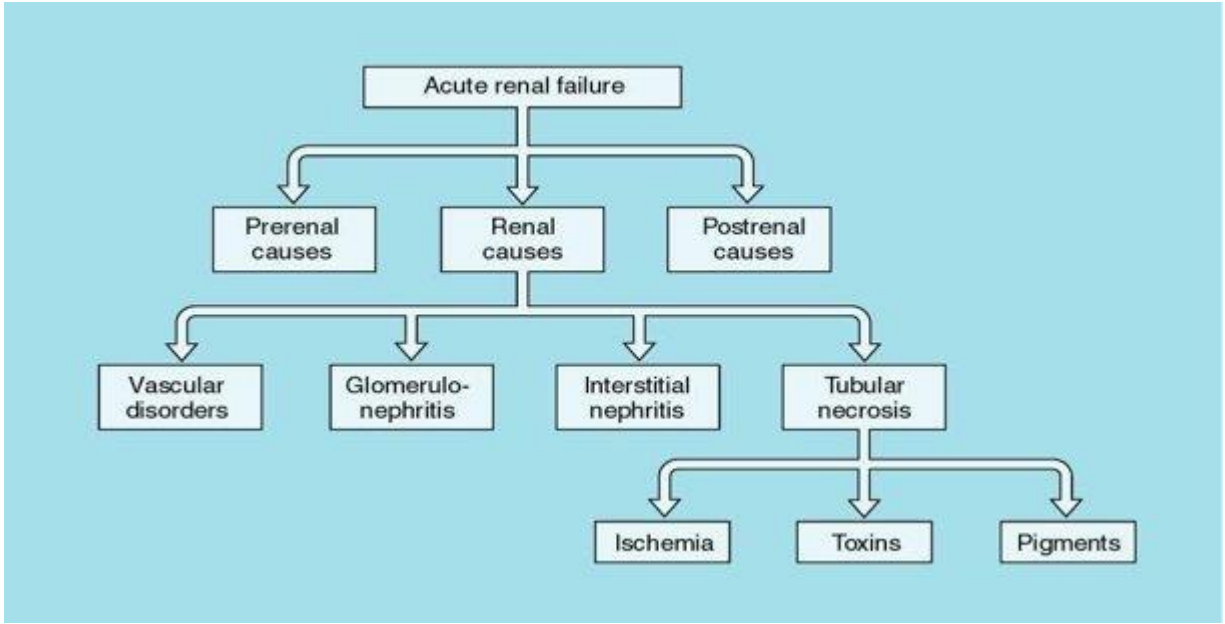
Clinical Evaluation to Differentiate

recent illness, volume depletion, infection, urinary symptoms

medications (ACEi, ARB, SGLT2i, NSAIDs)

blood pressure and volume status
hypotension or hypovolemia → suggests prerenal AKI

fluid overload



Atlas of Diseases of the Kidney, Dwinnell & Anderson

Prerenal

Decreased effective circulating volume (ECV)

Decreased cardiac output (renal venous congestion)

Excessive diuresis (e.g. due to diuretics such as furosemide or metolazone)

Cirrhosis

Renal artery stenosis

Renal

Acute tubular necrosis

- Ischemic
- Nephrotoxic (aminoglycosides, NSAIDs, cisplatin)

Acute interstitial nephritis

- Medications

Glomerulonephritis

- hematuria and/or proteinuria, +/-systemic symptoms

Postrenal

Any impediment to urine flow due to structural or functional change occurring anywhere from the renal pelvis to the tip of the urethra

What investigations to order

Repeat Bloodwork

sCr to assess trajectory

electrolytes, incl Ca

Urine Studies

Urinalysis

ACR to assess albuminuria for possible glomerular injury

Imaging

Ultrasound if kidney function decline is persistent or unexplained; esp w/ urologic history

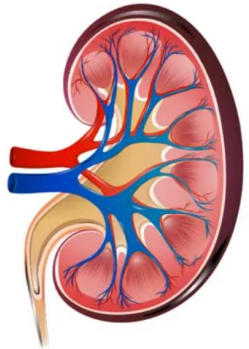
Impact of AKI on CKD Progression

AKI accelerates CKD progression

one episode ↑ risk of **kidney failure or death by ~30%**

Mechanisms include:

- Residual nephron damage
- Inflammation and fibrosis
- Loss of kidney reserve



Impact of AKI on CKD Progression

Recurrent AKI further amplifies long-term decline.

CKD increases susceptibility to AKI

A history of AKI may be identified by asking about:

- Hospitalizations
- Severe infections or illness
- Medication interruptions
- Temporary dialysis

Impact of Albuminuria

Strongly predicts **CKD progression** and **cardiovascular risk**

CKD staging incorporates both **eGFR** and **ACR**

Impact of Albuminuria

Rising proteinuria → possible glomerular disease

Stable proteinuria + rising sCr → consider hemodynamic or prerenal causes

Variability in sCr and ACR

Up to **25% variation**

ACR fluctuates due to hydration, activity, and sample conditions

Factors Affecting sCr

Volume status
Muscle mass (higher mass → higher sCr)
Supplements
Medications (e.g., trimethoprim)

Variability - Implications

Isolated elevations may not represent true decline.

Repeat testing is appropriate—two-thirds of AKI episodes resolve within 1 week.

When to refer to a Nephrologist

Standard:

eGFR < 30 mL/min/1.73 m²

ACR > 60 mg/mmol

Earlier Referral

Young patient (<40 yr)

Genetic disease (e.g., PKD)

Glomerulonephritis concern

Structural abnormalities (e.g., VUR)

Diabetes, autoimmune disease, family history, hematuria

Pregnancy

Why Early Referral Matters

Diagnosis and management of complications

Planning for potential dialysis or transplant

Why Early Referral Matters

Kidney Failure Risk Equation

uses **eGFR + ACR** to estimate 2- and 5-year kidney failure risk

Ontario Renal Network:

- 5-year KFRE risk ≥ **5%**
- Rapid decline in eGFR
- eGFR < 30 or ACR > 60

Target ACR

< 60 mg/mmol

Goal directed medical therapy

- RAAS blockade
- SGLT-2 inhibitors
- GLP-1 receptor agonists
- Non-steroidal MRAs

SGLT-2i for everyone with CKD

Trial/Analysis	Population
SGLT2 Inhibitors	
Pooled analysis (Ferreira et al.)	Patients across CKM spectrum
JAMA meta-analysis (Staplin et al.)	Patients with CKD ± diabetes
DECLARE-TIMI 58 (Mosenzon et al.)	Type 2 diabetes, CrCl >60 mL/min, with or without CVD
CANVAS Program	Type 2 diabetes with CVD or CV risk factors
EMPA-REG OUTCOME	Type 2 diabetes with established CVD
SMART-C meta-analysis	Diabetes at high ASCVD risk, HF, or CKD

Trial	Drug	Population	eGFR Range	Primary Kidney Outcome	Renal Benefit	NNT
DAPA-CKD	Dapagliflozin	CKD ± diabetes	25–75	≥50% eGFR ↓, ESKD, renal/CV death	**39% RRR**	**~19 over 2.4 yrs**
CREDENCE	Canagliflozin	T2DM + CKD	30–90	ESKD, doubling Cr, renal/CV death	**30% RRR**	**~22 over 2.6 yrs**
EMPA-KIDNEY	Empagliflozin	CKD ± diabetes	20–45 or ≥45 w/ UACR ≥200	Kidney progression or CV death	**28% RRR**	**~27 over 2 yrs**

GLP-1 RAs for CKD

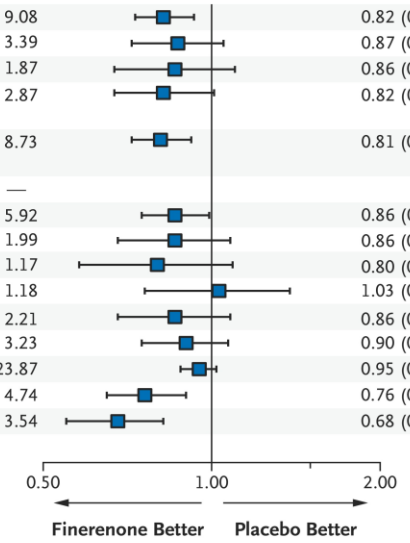
Trial	Drug	Population	Kidney Outcome (as reported)	Renal Effect	NNT (time)
FLOW	Semaglutide	T2DM + CKD	Kidney failure, ≥50% eGFR ↓, or kidney/CV death	**HR 0.76**	**~23 (3.4 yrs)**
LEADER	Liraglutide	T2DM (high CV risk)	New or worsening nephropathy	**HR 0.78**	**~67 (3.8 yrs)**
REWIND	Dulaglutide	T2DM (broad risk)	Macroalbuminuria, ≥30% eGFR ↓, or RRT	**HR 0.85**	**~40 (5.4 yrs)**
SUSTAIN-6	Semaglutide	T2DM (high CV risk)	New or worsening nephropathy	**HR 0.64**	**~44 (2.1 yrs)**
AMPLITUDE-O	Efpeglenatide	T2DM + CVD and/or CKD	Renal composite (function decline ± macroalbuminuria)	**HR 0.68**	**~19 (1.8 yrs)**

GLP-1 RAs for CKD

AJKD Meta-Analysis (Chen et al., 2025)	Patients with baseline eGFR <60 mL/min/1.73 m²	eGFR <60 mL/min/1.73 m²	17,996 (12 trials)	**15% reduction in composite kidney outcome** (OR 0.85, 95% CI 0.77-0.94). **22% reduction in >30% eGFR decline** (OR 0.78). **24% reduction in >40% eGFR decline** (OR 0.76).	**23% reduction in all-cause mortality** (OR 0.77, 95% CI 0.60-0.98). **14% reduction in composite CV outcomes** (OR 0.86, 95% CI 0.74-0.99).

Finerenone – DM & CKD

Outcome	Finerenone (N=2833)	Placebo (N=2841)	Finerenone (N=2833)	Placebo (N=2841)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)		*no. of patients with event per 100 patient-yr*			
Primary composite outcome	504 (17.8)	600 (21.1)	7.59	9.08	0.82 (0.73–0.93)	0.001
Kidney failure	208 (7.3)	235 (8.3)	2.99	3.39	0.87 (0.72–1.05)	—
End-stage kidney disease	119 (4.2)	139 (4.9)	1.60	1.87	0.86 (0.67–1.10)	—
Sustained decrease in eGFR to <15 ml/min/1.73 m^2	167 (5.9)	199 (7.0)	2.40	2.87	0.82 (0.67–1.01)	—
Sustained decrease of ≥40% in eGFR from baseline	479 (16.9)	577 (20.3)	7.21	8.73	0.81 (0.72–0.92)	—
Death from renal causes	2 (<0.1)	2 (<0.1)	—	—	—	—
Key secondary composite outcome	367 (13.0)	420 (14.8)	5.11	5.92	0.86 (0.75–0.99)	0.03
Death from cardiovascular causes	128 (4.5)	150 (5.3)	1.69	1.99	0.86 (0.68–1.08)	—
Nonfatal myocardial infarction	70 (2.5)	87 (3.1)	0.94	1.17	0.80 (0.58–1.09)	—
Nonfatal stroke	90 (3.2)	87 (3.1)	1.21	1.18	1.03 (0.76–1.38)	—
Hospitalization for heart failure	139 (4.9)	162 (5.7)	1.89	2.21	0.86 (0.68–1.08)	—
Death from any cause	219 (7.7)	244 (8.6)	2.90	3.23	0.90 (0.75–1.07)	—
Hospitalization for any cause	1263 (44.6)	1321 (46.5)	22.56	23.87	0.95 (0.88–1.02)	—
Secondary composite kidney outcome	252 (8.9)	326 (11.5)	3.64	4.74	0.76 (0.65–0.90)	—
Sustained decrease of ≥57% in eGFR from baseline	167 (5.9)	245 (8.6)	2.41	3.54	0.68 (0.55–0.82)	—



eGFR restrictions

eGFR 20 for SGLT-2i

None for GLP-1 RAs

None for RAAS and ns-MRAs

Case

No recent illness, stable intake, no medication changes

Mild edema → likely due to CCB, not proteinuria

A1c at target (6.9%)

1 Week Later:

sCr: 178 µmol/L, ACR: 100 mg/mmol

Consistent with **CKD progression**, not AKI

Case

Sodium restriction 2 g/day

Perindopril increased to 4 mg daily for BP & proteinuria

CCB continued (edema mild)

2 weeks: sCr 200 µmol/L (hemodynamic ACEi effect)

4 months: BP 129/77, sCr 190, ACR 55 mg/mmol