Sick Kidneys, Safe Imaging

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Kidneys + Radiology is a Scary Combination !!

Why is it Scary?

- Radiation exposure
  - X-rays, Nuclear Medicine
- Iodinated contrast agents (ICAs)
  - Allergic reactions, nephrotoxicity
- Gadolinium-based contrast agents (GBCAs)
  - Allergic reactions, nephrotoxicity
  - Nephrogenic Systemic Fibrosis

MRI

- Residual renal function.... impact on mortality

Agenda

- Review Contrast-Induced Nephropathy (CIN)
- Describe Nephrogenic Systemic Fibrosis (NSF)
- Present an approach to safe imaging in patients with Chronic Kidney Disease

Contrast-induced Nephropathy (CIN)

Iodinated Contrast Agents (ICAs)
Gadolinium-based Contrast Agents (GBCAs)

CIN Definition

- Defined as an increase in SCr level of ≥ 25% (or 44.2 umol/L greater) than baseline within three days of receiving intravascular contrast medium, in the absence of another cause
- CIN is more likely to occur after intra-arterial use
- SCr peaks 2-3 days following exposure; returns to baseline within 14 days (usually self-limited)
- Generally non-oliguric and reversible
- Can progress to acute kidney injury …. ESRD/death

Baerlocher MO, et al. CMAJ 2010;182(13):1445 Morcos SK, et al. Eur Radiol 1999;9:1602-13

CIN-Iodinated Contrast Agents (CIN-ICA)

- Accounts for 11-14.5% of hospital-acquired AKI
- Incidence increasing
  - More ICA use, aging population, more CKD
- Most common procedures
  - Coronary angiography, contrast-enhanced CT
- CIN-ICA predicts high morbidity and mortality

Hou S, et al. Am J Med 1983;74:243-8

McCullough PA, et al. Am J Med 1997;103:368-75

Nash K, et al. AJKD 2002;39:930-6

McCullough PA, et al. Am J Cardiol 2006;98:5K-13K

CIN-ICA - Risk Factors

- Underlying renal disease or solitary kidney
- Diabetes mellitus
- Dehydration, low ECFV

} Bad combo!

- Age ≥ 70
- Cardiovascular disease (CAD, PAD, CHF, HTN)

- Concomitant use of nephrotoxic drugs
  - NSAIDs, diuretics, RAAS blockers, aminoglycosides, amphotericin B, vancomycin, chemo / immunosuppressants

Baerlocher MO, et al. CMAJ 2010;182(13):1445 Byrd LH Arch IM 1979;139(4):491

CIN-ICA
Identifying Patients at Risk

- Whose kidney function should be tested?
  - Patients with one or more risk factor(s) for renal disease
  - All patients going for angiographic procedures
- When to test?
  - Outpatients: within 1 month if stable
  - Inpatients: within 7 days (within 24 hr if unstable)

- Patients with one or more risk factors for CIN should empirically receive preventive measures

Prevention of CIN-ICA

- Avoid ICA whenever possible!
  - OR try use safer ICA's if possible
- Consider alternative safer imaging study
  - CT (-ICA), U/S, MRI (-GBCA)
- Stop nonessential nephrotoxic drugs 2-3 days prior to the procedure (ideally)
  - Diuretics stop at least 1 day prior to the day of procedure
- IV Fluid administration (avoid fluid restrictions!)
  - Use 0.9% (isotonic) NS or isotonic $NaHCO_3$

Prevention of CIN-ICA

- Iodinated contrast agents (ICA's)
  - Minimize contrast volume (<100-140 ml)
  - Avoid repeat ICA exposure within 72 hrs
- CO_2 angiography (we have it!)
  - Helps reduce volume of ICA used

Freeman R, et al. Am J Cardiol 2002;90:1068-73 Aspelin P, et al. NEJM 2003;348:491-9

Prevention of CIN-ICA

Pharmacologic Preventive Strategies

- N-acetylcysteine (oxidative stress)
  - Studies do not show consistent benefit
  - Safe, inexpensive
  - Dose: 600-1200 mg BID day before and day of procedure

Tepel M, et al. NEJM 2000;343:180-4

Nallamothu BK,et al. Am J Med 2004;117:938-947

Baker C, et al. JACC 2003;41:2114-2118

Kelly AM, et al. Ann IM 2008;148:284-294

Prevention of CIN-ICA

Role for Peri-Procedure Dialysis

- Prophylactic hemodialysis NOT helpful pre- or post-ICA administration
  - Rapid onset of ICA-induced renal injury
  - HD treatment “nephrotoxic”
    - Inflammation, oxidative stress, hypovolemia
    - ICA-induced fluid shifts between compartments
- Continuous Hemodialysis (CVVHDF)
  - ?? Helpful…… but expensive, impractical

Vogt B, et al. Am J Med 2001 111:692-8 Marenzi G, et al. NEJM 2003;349:1333-40

Prevention of CIN-ICA

Patients on Dialysis

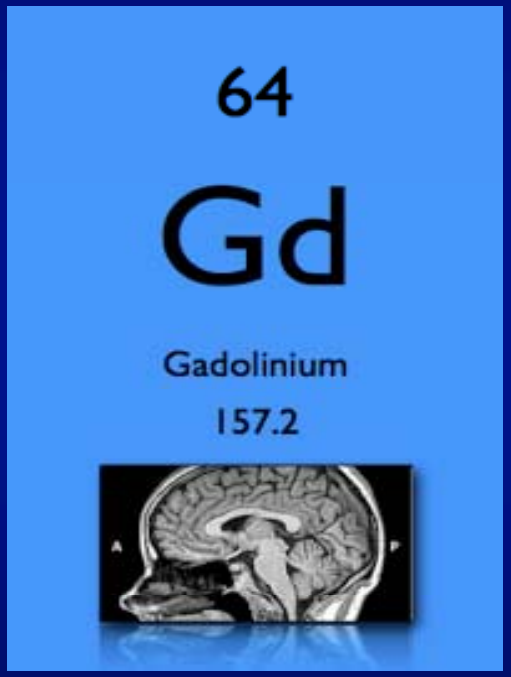
- Must try save residual renal function!
- Fluid-loading prior to ICA studies not helpful
- Coordination of contrast administration with timing of HD is unnecessary

Prevention of CIN-ICA
Follow-up

- If eGFR < 60 ml/min/1.73m^2:
  - measure serum creatinine 48-72 hrs after receiving contrast medium intravascularly
- If renal function has not returned to baseline, referral to nephrologist may be necessary

Baerlocher MO, et al. CMAJ 2010;182(13):1445

What about Gadolinium?



Is it nephrotoxic?

Benefits of Gadolinium-enhanced MRI Studies

- No ionizing radiation
- Avoid iodinated contrast agents
  - "gadolinium is a safe alternative, especially in CKD patients" (renal safe)
- Generally lower contrast dose needed for vascular studies

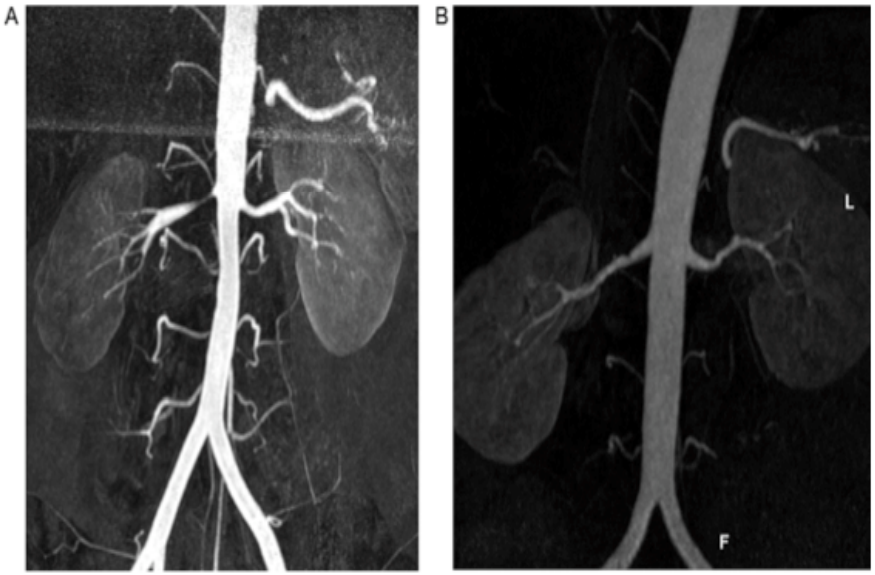


Figure 3 Normal renal function imaging of renal vasculature, (A) hypertensive patient with intimal fibroplasia tight right renal artery stenosis and (B) normotensive volunteer for potential renal donation shown to have bilateral fibromuscular hyperplasia

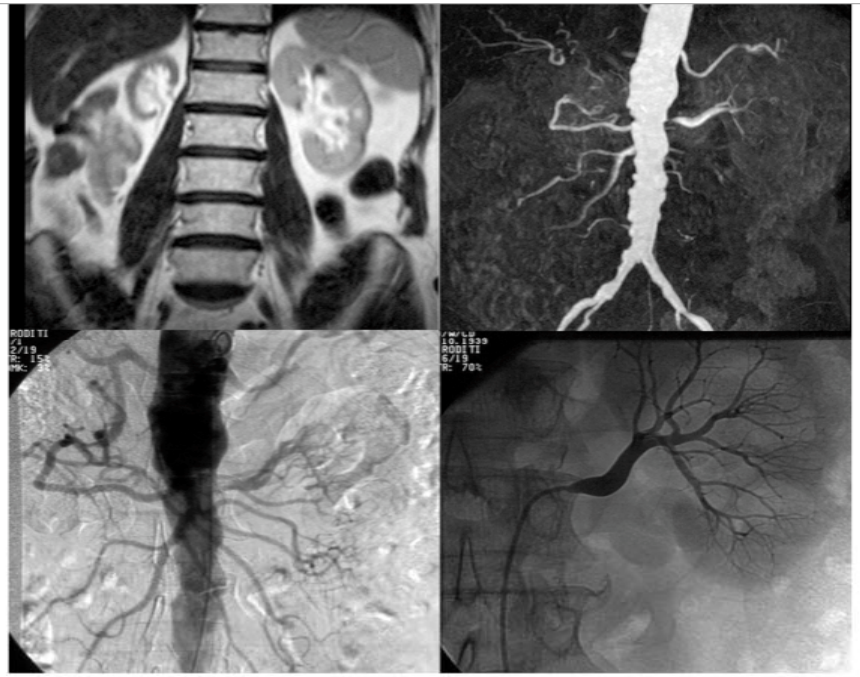


Figure 4 Patient with hypertension and impaired renal function MRI imaging (upper row) showing atrophic right kidney due to renal artery occlusion and normal left kidney supplied by tightly stenosed artery. Conventional angiography (bottom row) flush aortic and selective injections at time of revascularization confirm MRI

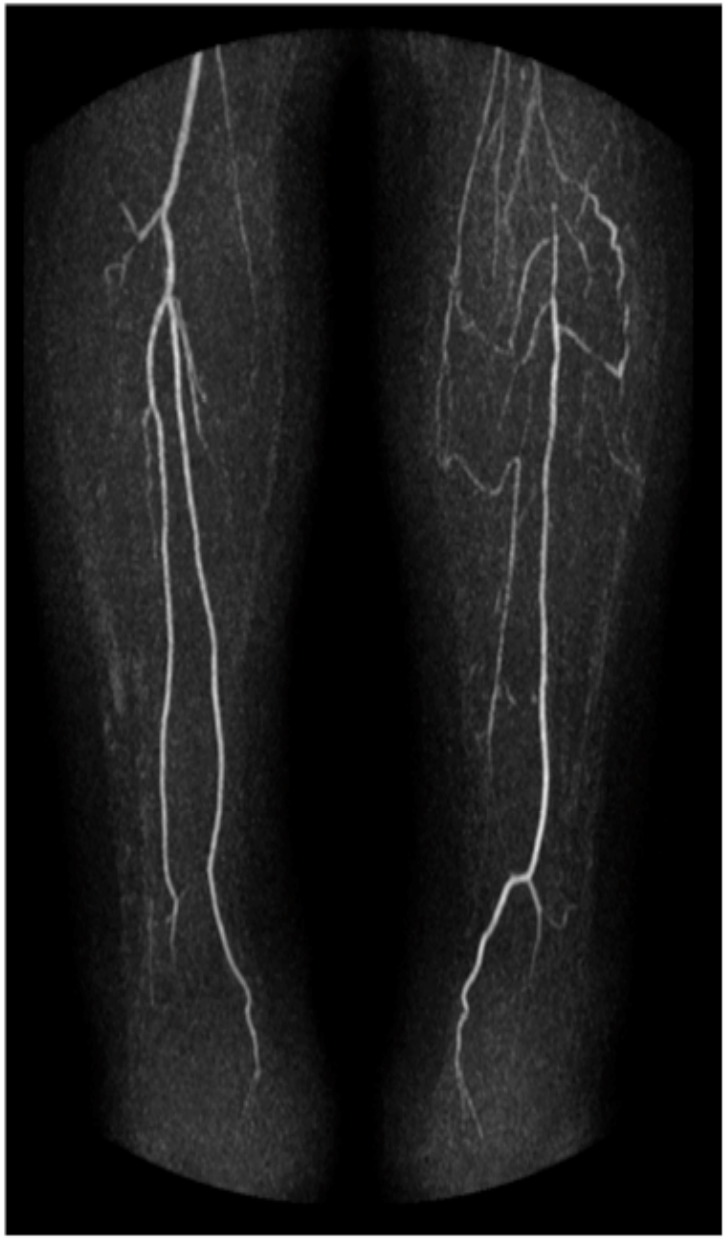


Figure 5 Lower limb contrast-enhanced MRA at calf level in patient with critical lower limb ischaemia showing occlusive tibial artery disease

Gadolinium (Gd^{3+})

- Powerful paramagnetic properties
- Free Gd^{3+} is toxic in native unbound state
  - Potent inhibitor of calcium channels
    - Cardiovascular and neurologic toxicity
- Free Gd^{3+} deposits in liver, bone and lymph nodes … slowly released from body (< 1%/yr)

Penfield JG, et al. Nat Clin Pract Neph 2007;3(12):654-668

Gadolinium (Gd^{3+})

- Gadolinium must be **chelated** for use in humans
  - Reduces toxicity of agent (prevents intracellular deposition)
  - Improves water solubility
    - Facilitates rapid and complete renal excretion
  - Controls biodistribution
  - Prevents biotransformation

Gadolinium-chelates

Gadolinium-based contrast agents (GBCA's)

- GBCA's are used in about 30-45% of MRI studies
- GBCA nephrotoxicity (CIN) is uncommon
  - Similar risk factors as for CIN related to ICAs
- Excretion half-life about 1.3-1.6 hrs in patients with normal renal function (>95% excreted by 24 hrs)
  - Prolonged in CKD - >> 30 hrs with GFR < 5ml/min!

Akgun H, et al. Arch Pathol Lab Med 2006;130(9):1354-7

Nephrogenic Systemic Fibrosis (NSF)

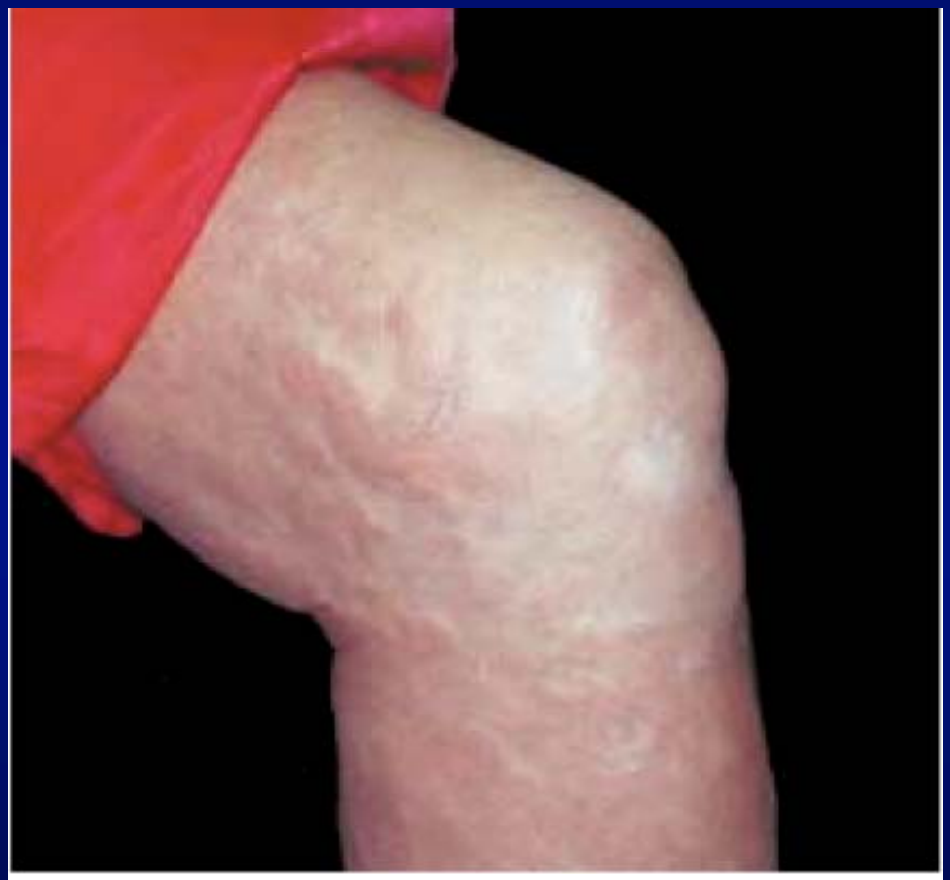


Figure 1: **A 31-year-old woman with a haemodialysis-associated cutaneous fibrosing disorder.**
Patient exhibited cutaneous thickening and hardening, chiefly on the extermities.

Entirely iatrogenic

Lots of mimics

Gadolinium-NSF Connection

Nephrol Dial Transplant (2006) 21: 1104–1108
doi:10.1093/ndt/gfk062
Advance Access publication 23 January 2006

Interesting Case

NDT
Nephrology Dialysis Transplantation

Gadolinium – a specific trigger for the development of nephrogenic fibrosing dermopathy and nephrogenic systemic fibrosis?

Thomas Grobner

Department of Nephrology, General Hospital of Wiener Neustadt, A-2700 Wiener Neustadt, Austria

- 9 HD patients underwent MR angiography over a 2 yr period
- 5 developed skin changes/biopsies c/w NSF within 2-4 weeks of MR study
- All 5 patients received Omniscan (gadodiamide) intravenously
- All 5 patients had metabolic acidosis

Grobner T. NDT 2006;21(4):1104-8

Risk Factors

- Advanced renal dysfunction
  - eGFR < 30 ml/min, dialysis (PD > HD), AKI
  - Hepatorenal syndrome, peri-op liver transplant (eGFR < 40)
- GBCA exposure
  - Contrast agent structure
  - Contrast agent dose and cumulative exposure
  - Route of excretion
    - Sole renal excretion problematic

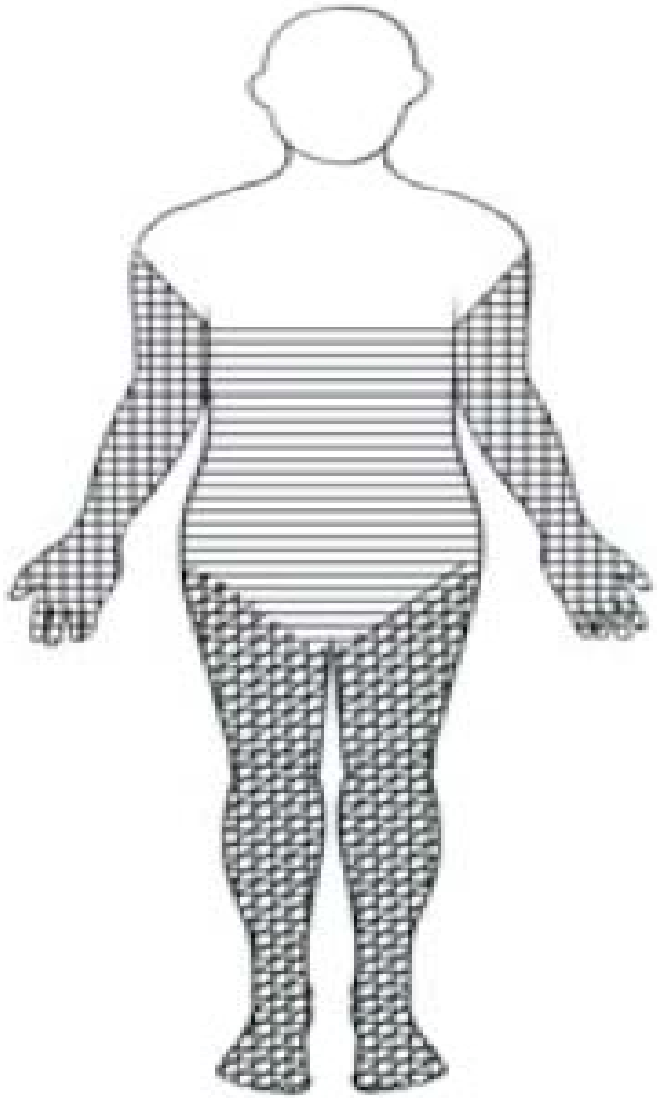


FIGURE 2. The pattern of involvement is usually symmetric. The lesions most often affect the lower extremities, followed by the upper and lower extremities and then the trunk and upper and lower extemities. The face is usually spared.

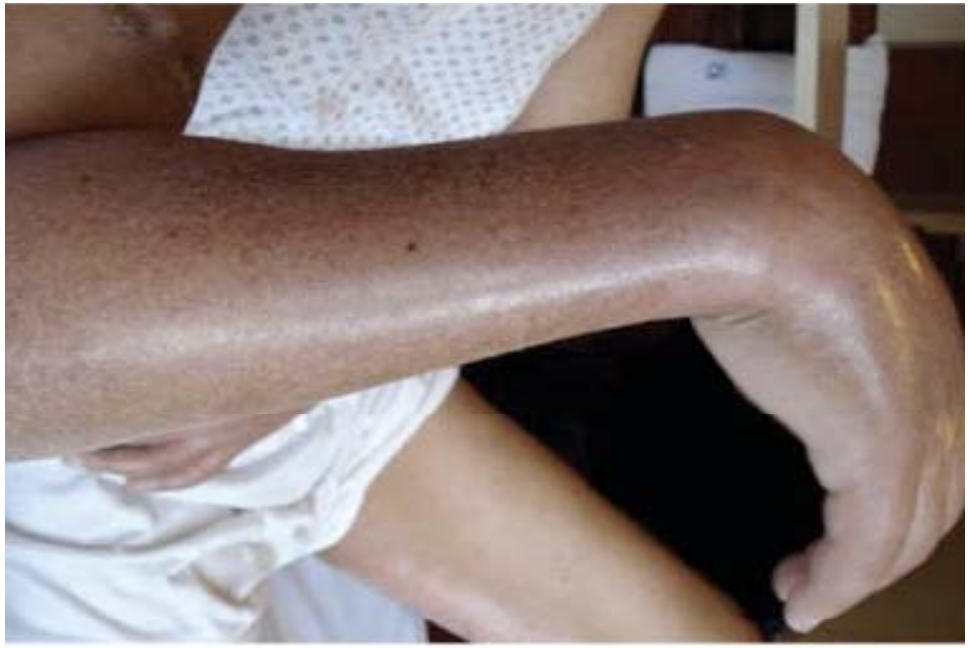


Figure 1 - Thickening and hardening of the skin of the right forearm

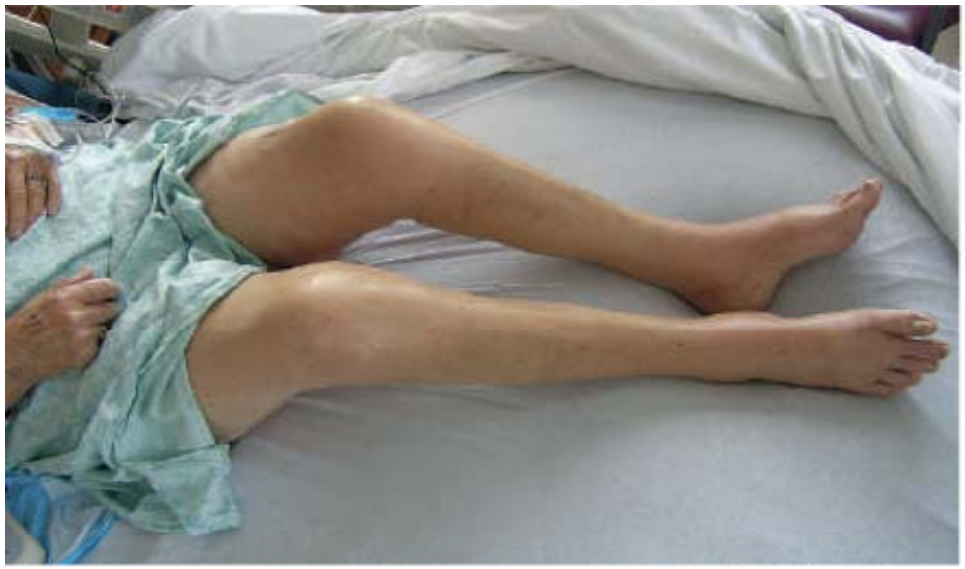
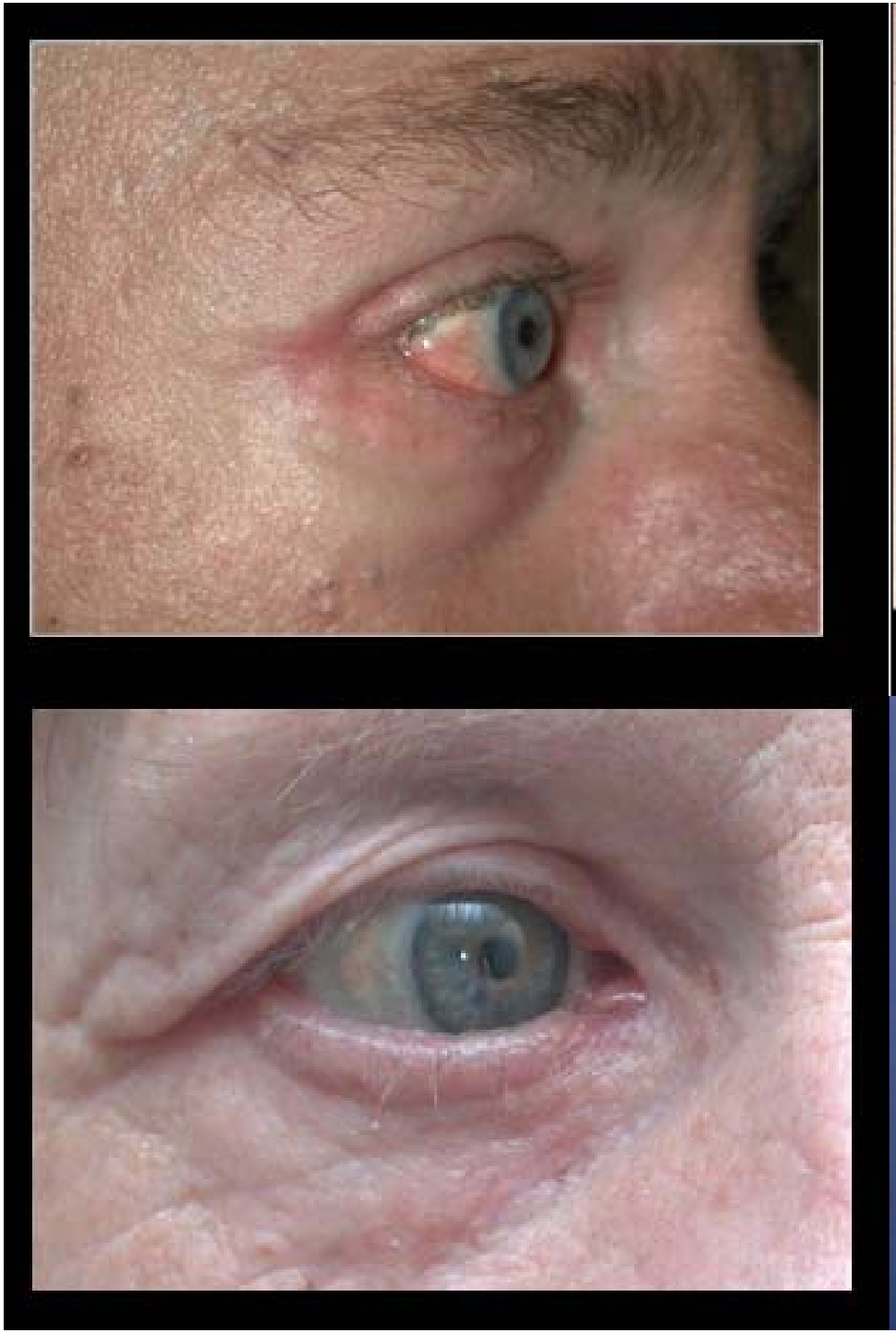


Figure 1 Skin thickening, tightness and contractures are hallmarks of the clinical findings in nephrogenic fibrosing dermopathy.



NSF Diagnosis

- Historical and Physical Examination Clues
  - New-onset pain and stiffness of the extremities
  - Cutaneous or systemic fibrosis in a patient with advanced renal dysfunction
  - Recent exposure to GBCA
- Full-thickness (deep tissue) skin biopsy at the involved site (often lower-extremity) for definitive diagnosis
  - Risk of infection (ESRD, DM, PAD)
  - Risk of nonhealing wound (in case of calciphylaxis)

Unanswered Questions

- Why don't all dialysis pts exposed to GBCA get NSF?
- How does gadolinium cause NSF?
  - Pathophysiology not completely understood
- Cases of NSF without GBCA exposure and/or normal renal function? How?
  - Wahba IM, et al. Am J Transplant 2007;7:2425-32
  - Weiss AS, et al. Nat Clin Pract Nephrol 2007;3(2):111-5
- Are there other risk factors?

Not all Dialysis Patients Develop NSF After GBCA exposure. Why?

OTHER POSSIBLE TRIGGERS

- Pro-inflammatory events (endothelial injury)
  - Sepsis, AKI, thrombotic (VTE) events, surgery (tissue or vascular injury)
  - Other hypercoagulable states, presence of APLA's
  - Recent transplantation, calciphylaxis
  - Hepatic disease (hepatorenal syndrome, hepatitis B or C)
- Degree of acidosis
- Lack of ACEi use (ACEi may block profibrotic effect of TGF-β)
- High dose of ESA's (rEPO may be fibrogenic)
  - Swaminathan S, Ahmed I, et al. Ann Intern Med 2006;145:234-5
- Iron therapy, sevelamer
- HLA type; type of renal disease; environmental toxin

NSF Treatment

- Course is variable, rarely resolves spontaneously
- Some patients have slight softening of skin and improvement over time
- No effective treatment known
- Improvement in renal function is the only modality to show effectiveness in any reproducible way
  - Recovery of AKI
  - Renal transplantation

- Otherwise: lots of case reports, series ….

NSF Prevention

- Avoid use of GBCA's (use different imaging study) especially in high risk patients
- Stratify risk for NSF pre-GBCA administration
  - Risk factors, eGFR
- Use cyclic Gadolinium-chelate where possible
- Use lowest possible dose of GBCA (half usual dose)
- Avoid repeat GBCA exposure
  - Minimize cumulative dose

NSF Prevention

- Immediate post-MRI hemodialysis if a hemodialysis patient (same day, then 2 consecutive days after)
  - Hemodialysis: 99% clearance by 3rd session
  - PD: very poor clearance!
  - Start HD within 2 hrs of GBCA exposure
  - No data to support prevention of NSF
  - Need dialysis access in place prior to MRI scan

Recommendations

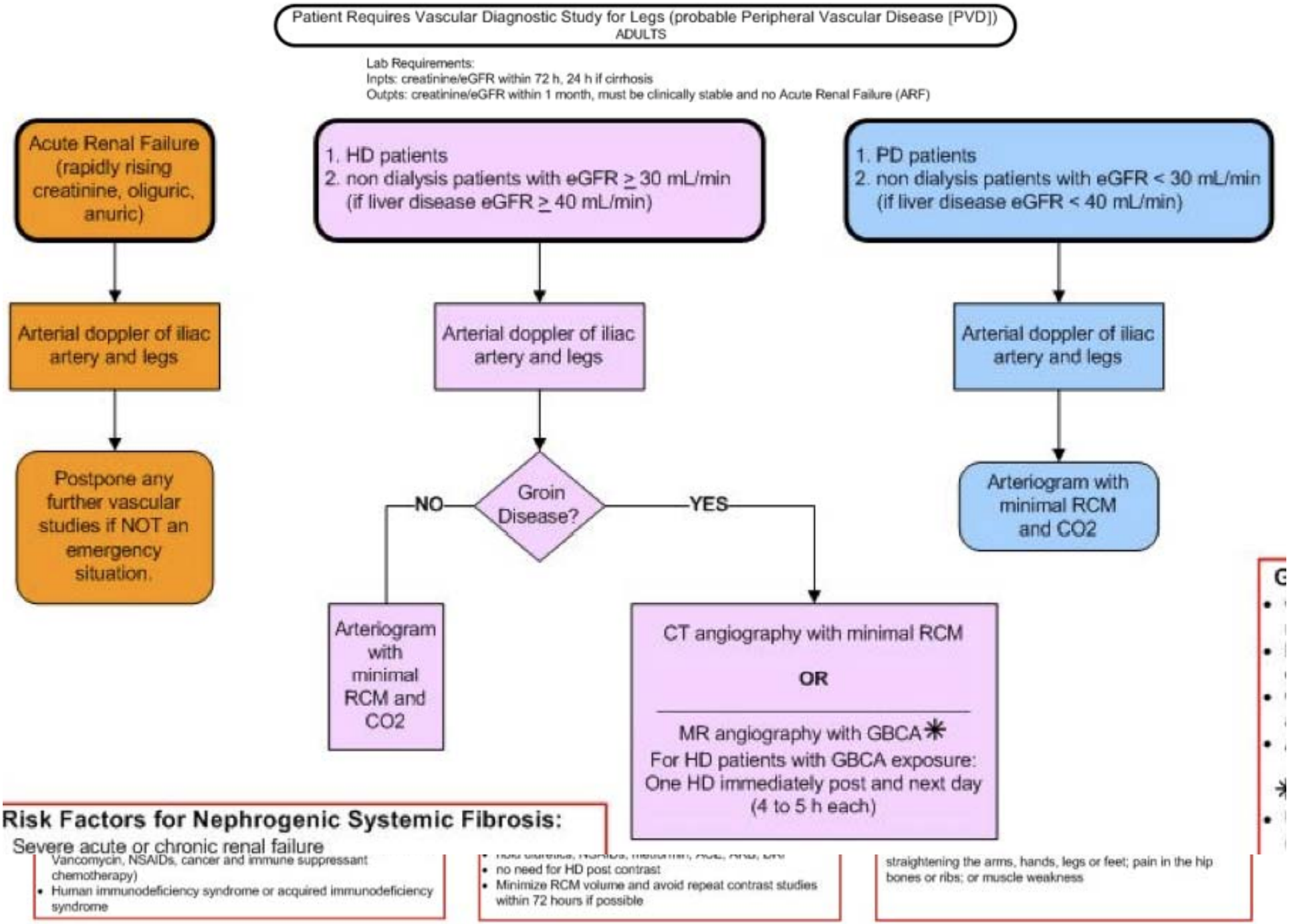
- Avoid GBCA where possible in high NSF-risk patients
- Patient should be informed about risk of NSF and provide informed consent
- Follow patient after GBCA exposure for any evidence of disease development
- In patient with established NSF, further GBCA exposure is contraindicated
- Consider HD after exposure (and next 2 d) in patients who are already on HD
  - No evidence to show NSF prevention

An Approach to Safe Imaging in CKD Patients

CIN vs. NSF (? GBCA's safer)

	CIN	NSF - lower stability agent (Gadodiamide)	NSF - higher stability agent / lower dose agents
Patients at risk	eGFR < 60 ml/min/1.73m^2	eGFR < 30 ml/min/1.73m^2 On dialysis, AKI	eGFR < 30 ml/min/1.73m^{2*} On dialysis, AKI
Incidence	9-37%	2-5% (up to 18%)	0%*
Mortality risk	> 30% at 1yr (adjusted OR of 5.5)	Rare	0%*
Other serious complications	ARF requiring dialysis	Joint contractures 0-50%	0%*

Martin DR, et al. J Magn Reson Imaging 2009;30:1350-6


Patient Requires Vascular Diagnostic Study for Legs (probable Peripheral Vascular Disease [PVD])
ADULTS
Lab Requirements:
Inpts: creatinine/eGFR within 72 h, 24 h if cirrhosis
Outpts: creatinine/eGFR within 1 month, must be clinically stable and no Acute Renal Failure (ARF)
Acute Renal Failure (rapidly rising creatinine, oliguric, anuric)
Arterial doppler of iliac artery and legs
Postpone any further vascular studies if NOT an emergency situation.
1. HD patients
2. non dialysis patients with eGFR ≥ 30 mL/min (if liver disease eGFR ≥ 40 mL/min)
Arterial doppler of iliac artery and legs
Groin Disease?
NO
YES
Arteriogram with minimal RCM and CO2
CT angiography with minimal RCM
OR
MR angiography with GBCA*
For HD patients with GBCA exposure: One HD immediately post and next day (4 to 5 h each)
1. PD patients
2. non dialysis patients with eGFR < 30 mL/min (if liver disease eGFR < 40 mL/min)
Arterial doppler of iliac artery and legs
Arteriogram with minimal RCM and CO2
Risk Factors for Nephrogenic Systemic Fibrosis:
Severe acute or chronic renal failure
Vancomycin, NSAIDs, cancer and immune suppressant chemotherapy)
Human immunodeficiency syndrome or acquired immunodeficiency syndrome
no need for HD post contrast
Minimize RCM volume and avoid repeat contrast studies within 72 hours if possible
straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness

Patient Requires Contrast-Enhanced* Diagnostic Study for Suspicion of Abdominal Aortic Aneurysm (AAA) or Malignancy
ADULTS

*Lab Requirements:

Acute Renal Failure (rapidly rising creatinine, oliguric, anuric)

Postpone any contrast-enhanced study if NOT an emergency situation.

Suspicion of Abdominal Aortic Aneurysm (AAA)

Suspicion of malignancy

1 mL/

Additional Guidance:

Age less than 40 : do MRI +/- minimal GBCA (in order to minimize radiation)

If eGFR less than 30 mL/min: discuss with Radiologist re NSF risk (HD patients should have HD post GBCA exposure)

If lymphadenopathy is main concern: do CT with minimal RCM

< 30 mL/min?
sease eGFR<40
L/min?)
PD patient?

NO

abdominal ultrasound
OR
CT without contrast

CT with minimal RCM

CT OR MRI with contrast

Gadolinium Based Contrast Agent (GBCA)

- Previous chemotherapy
- Organ transplant
- Cardiovascular disease (hypertension, CHF, cardiac or peripheral vascular disease)
- Nephrotoxic drugs (loop diuretics, amphotericin B, aminoglycosides, Vancomycin, NSAIDs, cancer and immune suppressant chemotherapy)
- Human immunodeficiency syndrome or acquired immunodeficiency syndrome

Information for Patients

If you have kidney disease, contact your healthcare professional right away if you experience any of the following after receiving a GBCA: burning, itching, swelling, scaling, hardening and tightening of the skin; red or dark patches on the skin; stiffness in joints with trouble moving, bending or straightening the arms, hands, legs or feet; pain in the hip bones or ribs; or muscle weakness

consented.

- Consider acetylcysteine (Mucomyst) 600 mg po bid x 2 days
- IV hydration as per RCM guideline
- hold diuretics, NSAIDs, metformin, ACE, ARB, DRI
- no need for HD post contrast
- Minimize RCM volume and avoid repeat contrast studies within 72 hours if possible

Now for some cases…

CASE 1

- 36 yr female with suspicious 2.5cm renal mass on ultrasound exam
- SCr 120 umol/L (eGFR 44 ml/min/1.73m^2)
- Referred to Urology - “patient needs more imaging”

- **What study will you order?**
  - **CT(ICA) or MRI(GBCA)?**

CASE 2

- 57 yr male peritoneal dialysis patient in ER with new grand mal seizure
- CT Scan (-ICA): 3cm mass in right frontal lobe
- Neurosurgeon says “Get a contrast-enhanced CT or MRI” before she will see the patient
- Patient still makes 500cc urine per day

- **CT (ICA) or MRI (GBCA)?**

CASE 3

- 72yr female hemodialysis patient in ER with recurrent falls, skin tight and reduced ROM
- BP / Holter / EEG good; CT head nil new
- Good HD Rx / clearances; urine 500cc/day
- Presently being worked up for renal transplant
  - "I've had so many tests…. suspicious liver lesion"

- **What needs to be included in DDX?**

CASE 4

- 65 yr male, type 2 DM, PAD, 50 pk-yr smoker
- Known CKD, SCr 355 umol/L (eGFR 15)
- Painful wet gangrene of D2,3 of right foot
- Arterial dopplers obviously abnormal with iliac disease noted
- Vascular Surgeon vs. Interventional Rad….

- **Arteriography +ICA vs. MRI +GBCA ??**

SUMMARY THOUGHT

Safety is a relative word, especially in medicine where the risks of any therapy must be balanced against the perceived potential of benefit for the individual patient ……

Giles R. Clinical Risk 2009;00;1-7

Questions ……