

Nephrogenic Systemic Fibrosis (NSF)

Reducing Risk in Patients with Acute Kidney Injury and Chronic Kidney Disease

What is NSF?¹⁻³

A rare disease that has occurred in people with acute kidney injury and severe chronic kidney disease and has been associated with exposure to gadolinium-based contrast agents (GBCA). There appears to be a relationship between higher and repeated dose, and NSF risk in these patient groups.

This condition can be painful, debilitating or fatal. It is characterized by pain and thickening of the skin and fibrosis of almost all organs in the body. It can involve the joints and cause significant limitation of motion within weeks to months in some cases.

Signs and symptoms include pain, burning/itching skin, red/dark areas of skin, edema, firm texture of skin, raised yellow discoloration on sclera, joint stiffness, restricted limb motion, joint pain and muscle weakness.

The precise risk of NSF to a given individual with severe kidney dysfunction is difficult to determine.

Acute Kidney Injury (AKI)⁴

Defined as a rapid (over hours to weeks) and usually reversible decrease in kidney function.

Common causes:

- Surgery
- Severe infection
- Injury
- Drug-specific kidney toxicities.

Chronic Kidney Disease (CKD)⁵

Any condition that causes slow, irreversible damage to normal kidney function.

CKD is defined by **two criteria**:

- 1) Kidney damage for ≥ 3 months defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.

or

- 2) GFR < 60 mL/min/1.73 m² for ≥ 3 months, with or without kidney damage.

Common risk factors for CKD:

- Recovery from AKI
- Diabetes
- Hypertension
- Urinary tract infection/obstruction
- Family history of CKD
- Exposure to certain drugs, and chemicals
- Older age
- U.S. ethnic/minority status.



You can reduce the risk

► IDENTIFY PATIENTS WITH AKI.

AKIN AND RIFLE STRATIFICATION OF AKI⁹

| AKI Staging Serum Creatinine | Urine Output (Common to Both) | RIFLE | |
|--|---|--------------------------|---|
| | | Class | Serum Creatinine or GFR |
| Stage 1 Increase of more than or equal to 0.3 mg/dL ($\geq 26.4 \mu\text{mol/L}$) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline | Less than 0.5 mL/kg/h for more than 6 hours | Risk | Increase in serum creatinine x 1.5 or GFR decrease >25% |
| Stage 2 Increased to more than 200% to 300% (>2- to 3-fold) from baseline | Less than 0.5 mL/kg/h for more than 12 hours | Injury | Serum creatinine x 2 or GFR decreased >50% |
| Stage 3 Increased to more than 300% (>3-fold) from baseline, or more than or equal to 4.0 mg/dL ($\geq 354 \mu\text{mol/L}$) with an acute increase of at least 0.5 mg/dL (44 $\mu\text{mol/L}$) or on RRT | Less than 0.3 mL/kg/h for 24 hours or anuria for 12 hours | Failure | Serum creatinine x 3, or serum creatinine >354 $\mu\text{mol/L}$ (4 mg/dL) with an acute rise >44 $\mu\text{mol/L}$ (0.5 mg/dL) or GFR decreased >75% |
| | | Loss | Persistent acute renal failure = complete loss of kidney function >4 weeks |
| | | End-stage kidney disease | End-stage kidney disease >3 months |

Note: For conversion of creatinine expressed in Système International d'unités units to mg/dL divide by 88.4. For both AKIN stage and RIFLE criteria, only 1 criterion (creatinine rise or urine output decline) needs to be fulfilled. Class is based on the worst of either GFR or urine output criteria. GFR decrease is calculated from the increase in serum creatinine above baseline. For AKIN, the increase in creatinine must occur <48 hours. For RIFLE, AKI should be both abrupt (within 1–7 days) and sustained (more than 24 hours). When baseline creatinine is elevated, an abrupt rise of at least 44.2 $\mu\text{mol/L}$ (0.5 mg/dL) to >0.354 $\mu\text{mol/L}$ (4 mg/dL) is sufficient for RIFLE class Failure.

Abbreviations: AKIN, Acute Kidney Injury Network; RIFLE, risk, injury, failure, loss, and end stage; AKI, acute kidney injury; GFR, glomerular filtration rate; RRT, renal replacement therapy.

► IDENTIFY PATIENTS WITH RISK FACTORS FOR CKD.

► FOR PATIENTS WITH CKD (NOT ON DIALYSIS), EVALUATE KIDNEY FUNCTION BY ESTIMATING GFR PRIOR TO GBCA-ENHANCED MRI.

Estimate GFR (eGFR)⁵:

Serum creatinine alone should not be used to assess the level of kidney function.

For adults use:

Abbreviated MDRD Study equation

$$\text{GFR (mL/min/1.73 m}^2\text{)} = 186^* \times (\text{Serum Creatinine})^{-1.154} \times (\text{age})^{-0.203}$$
 x (0.742 if female) x (1.212 if African American)

For children use:

Schwartz equation

$$\text{Creatinine Clearance (mL/min)} = 0.55 \times \text{Length (cm)} / \text{Serum Creatinine}$$

Online calculators available at www.kidney.org

*Note: If laboratory creatinine method is standardized to IDMS, use 175 instead of 186.

MDRD: Modification of Diet in Renal Disease.

► **CONSIDER RISK VERSUS BENEFIT OF PERFORMING A GBCA-ENHANCED MRI.**

Risk of contrast induced nephropathy (CIN) after an iodinated enhanced study should be almost always considered greater than the risk of developing NSF after a standard dose GBCA-enhanced MR study.

► **MINIMIZE RISK FOR NSF IN AKI AND CKD.**

- In AKI, GBCAs should be avoided unless absolutely necessary, particularly in patients with:

Rising creatinine (GFR cannot be estimated in AKI given non-steady state condition)

Hepatorenal syndrome, or

Perioperative liver transplant.

- Stage CKD severity and follow appropriate intervention.⁵

| GFR (mL/min/1.73 m ²) | CKD Stage | Description | Interventions to reduce risk for NSF ^{3,7,8} |
|-----------------------------------|-----------|--|---|
| ≥90 | 1 | Kidney damage (e.g., proteinuria) with normal or ▲ GFR | The risk, if any, for developing NSF among patients with mild to moderate CKD or with normal kidney function is unknown but thought to be extremely low. |
| 60–89 | 2 | Kidney damage with mild ▼ GFR | |
| 30–59 | 3 | Moderate ▼ GFR | |
| 15–29 | 4 | Severe ▼ GFR | Avoid use of GBCA in patients with GFR <30 mL/min/1.73 m ² unless the diagnostic information is essential and unavailable with non-contrast MRI or other imaging modalities. |
| <15 (or dialysis) | 5 | Kidney Failure | |

Value of hemodialysis (HD) in lowering NSF risk^{3,6,7}

HD hastens elimination of GBCA.

The value of HD in preventing NSF after GBCA exposure is unknown; recent data suggest a benefit of HD: chronically dialyzed CKD patients had a lower incidence of NSF than patients with CKD stage 5 not yet on dialysis.

Inserting a HD catheter carries risks including infection and other complications. The risks and potential benefits of HD after GBCA should be evaluated in the clinical context of the individual patient.

Key Recommendations^{3,7}

- Weigh the risk and benefit of performing GBCA-enhanced MRI in patients with kidney disease. If possible, avoid using GBCA in patients with known NSF risk.
- Obtain a history and/or laboratory tests.
- Counsel patient and obtain informed consent.
- Identify patients undergoing chronic dialysis.
- Estimate GFR before GBCA-enhanced MRI in all patients with CKD.
- Identify AKI, especially in hospitalized patients.
- Allow sufficient time for elimination of GBCA before re-administering.
- Avoid repeated or higher doses of GBCA.
- Institute long-term monitoring for NSF after GBCA exposure in at risk patients.

FDA has requested manufacturers of all GBCAs to add a Boxed Warning about Nephrogenic Systemic Fibrosis. See: www.fda.gov/medwatch/safety

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