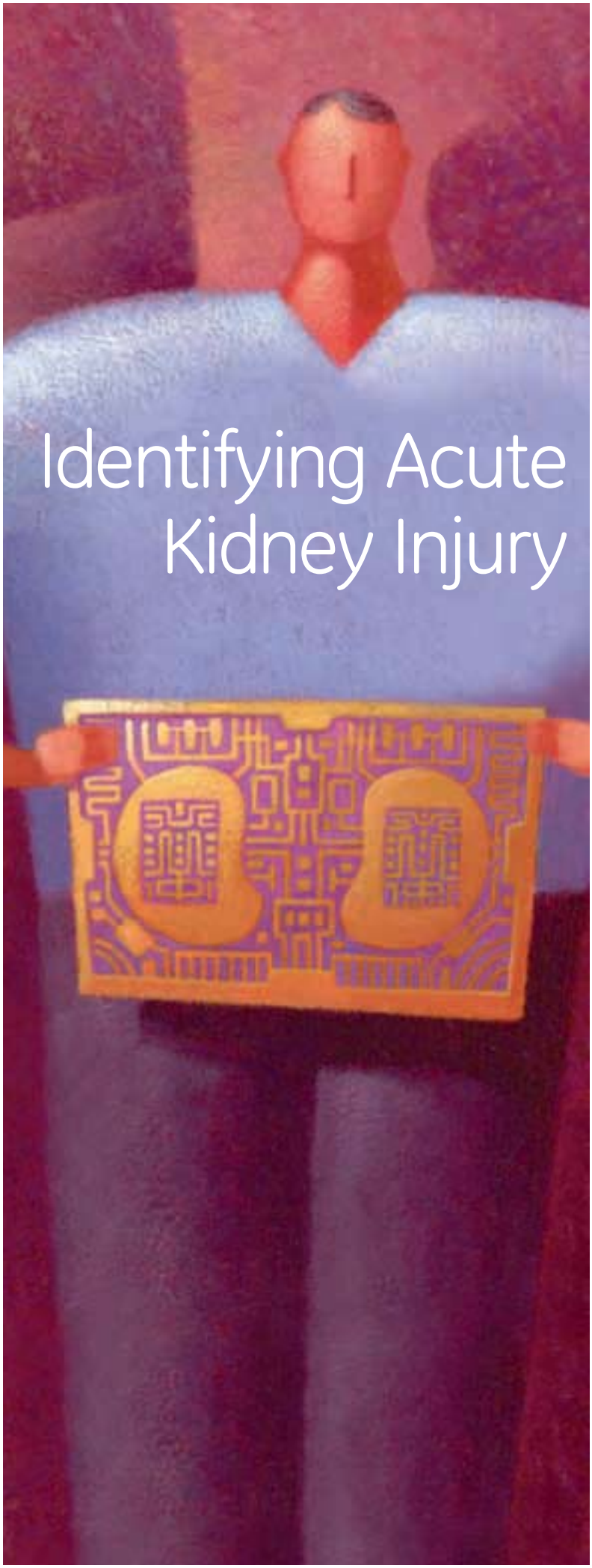

Identifying Acute Kidney Injury in High-risk Patients

By Eric Scott Cantor, MD

Radiologists across the globe began routinely screening patients for kidney disease after Nephrogenic Systemic Fibrosis (NSF) was initially associated with the use of Gadolinium Based Contrast Media (GBCM) in patients with acute or chronic severe renal insufficiency. The American College of Radiology (ACR) has since published screening guidelines to identify patients at high risk of developing NSF. These guidelines can be found at www.acr.org/SecondaryMainMenuCategories/quality_safety/contrast_manual.aspx.

One of the tools for screening patients is Glomerular Filtration Rate (GFR). GFR has historically been considered one of the primary methods used to measure renal function. Estimated GFR is a fairly rapid tool for identifying and classifying patients with Chronic Renal Failure (CRF) as defined by the National Kidney Foundation (NKF).

But what about those with Acute Renal Failure (ARF), which has also been identified as an at-risk group for those receiving gadolinium-based contrast agents? ARF can broadly be defined as an abrupt decline in renal function resulting in an inability to excrete metabolic waste and maintain proper fluid and electrolyte balance. The majority of ARF cases are secondary to acute tubular necrosis (ATN) from sepsis or nephrotoxin exposure. Most patients fully recover in a week to ten days but CRF or death is possible. Hospital length-of-stay and one-year mortality rates are significantly higher after a bout of ARF.

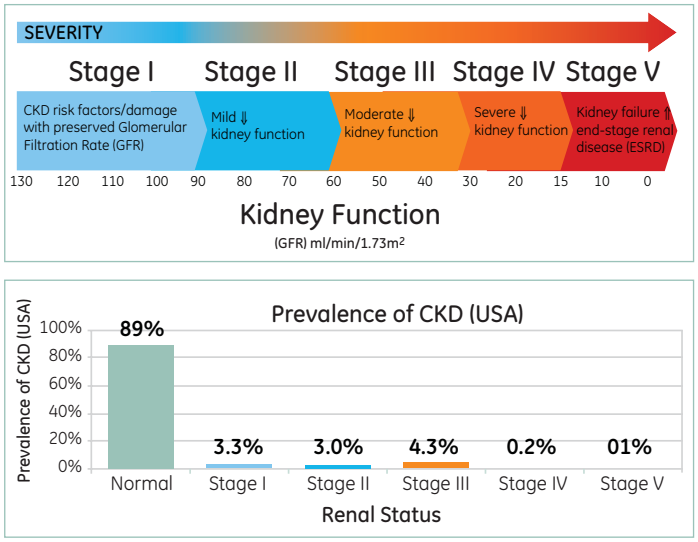

Figure 1

The incidence of ARF was reported by Ali to be 1811 cases per million in a retrospective hospital study in Scotland;[1] Liano reported 209 cases per million in 13 tertiary-care hospitals prospectively in Spain;[2] and Xue reported 23.8 cases per 1000 discharges of hospitalized US Medicare beneficiaries.[3] ARF, known to occur more frequently in older people, is rising in frequency in relationship to the changing demographics of the population, with an estimated incidence rate between 2% to 5% of hospitalized patients.

A review of the literature clearly indicates that epidemiologic studies of ARF are few in number, are all based upon sick hospitalized patients, and fraught with differences in patient populations and characteristics, and there exist differing definitions of ARF. We can, however, discern that the incidence of ARF in the outpatient setting is rare.

A practical challenge arise, since ARF has traditionally been diagnosed after the acute insult and damage occurs, because of the delay in elevation of the serum creatinine biomarker. Renal failure can be asymptomatic but is often associated with non-specific symptoms of fatigue, hematuria, flank pain, dyspnea, edema, hypertension, nausea, confusion, a decrease in urine output, or abnormal urinalysis , especially when associated with surgical or medical co-morbidities. A urinalysis examined immediately after voiding may demonstrate granular casts, renal tubular epithelial cells, proteinuria, or red blood cells. Nephrologists will likely evaluate the urine sample under the microscope; check urine specific gravity, urine electrolytes and other tests to determine the cause of the ARF or acute kidney injury (AKI).

Patients who present with AKI in the outpatient setting most commonly have AKI secondary to drug toxicity, volume depletion, or sepsis. On an in-patient basis AKI is often a result of multiple risk factors and co-morbidities.

There are three broad categories of AKI: pre-renal, renal and post-renal. Radiologists commonly administer hydration with or without bicarbonate or N-acetylcysteine to minimize renal under perfusion and risk of contrast-induced nephropathy. The most common post-renal causes of AKI are kidney stones, most commonly evaluated with renal ultrasonography. Once the clinician rules out pre-renal and post-renal cause, intrinsic renal disease is most often ascribed to ATN. ATN is most often caused by renal hypoperfusion and renal ischemia but intrinsic and extrinsic nephrotoxins should also be considered.

Diagnostic criteria for acute kidney injury

The formation of the Acute Kidney Injury Network (AKIN) has resulted in a new consensus definition of AKI. Likewise, nomenclature has changed to clarify the range of renal dysfunction associated with renal injury, not all of which results in kidney failure. Therefore, the preferred terminology is now Acute Kidney Injury (AKI) with ARF indicative of severe renal dysfunction that may lead to renal replacement therapy or result in end stage renal disease.

The new diagnostic criteria for AKI based upon AKIN is characterized by an abrupt (within 48 hours) reduction in kidney function defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 µmol/l),

a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours).[4] A new grading system based upon the acronym RIFLE (Risk, Injury, Failure, Loss, and End stage) has been defined by changes in serum creatinine and urine output, which divides AKI into three levels of severity. Staging can be assessed over one week as any abnormalities are typically sustained for more than 24 hours.

Challenges to rapid diagnosis remain as serum creatinine is a biomarker of renal function not injury. Estimation of CRF assumes a steady or equilibrium state, which is inconsistent with the rapid changes in renal function that occur in AKI. Creatinine increases slowly relative to the change in renal function. It may take 48 to 72 hours to observe an elevation in serum creatinine after an acute insult to the kidney. Serum creatinine level is based upon production, which varies with muscle mass, volume of distribution, and tubular secretion, which can in turn vary based upon age, sex, race, weight, diet, drugs, and muscle metabolism.

Looking ahead

A number of new biomarkers under investigation show promise in their ability to increase sensitivity, specificity, and clarification of etiology, prognosis, and time sensitivity for detection of AKI as compared to the historical use of serum creatinine. Many of these new biomarkers are released in response to tubular injury, a measure of anatomic pathology rather than function. These include urinary gamma gutamyl transpeptidase (GGT); N-acetyl glucosamindase (NAG); alpha and omega glutathione S-transferase; netrophil gelatinase associated lipcalin (NGAL); kidney injury molecule 1 (KIM-1); and cystatin C. In some circumstances, these urinary enzymes can detect AKI from 12 hours to four days earlier than a rise in serum creatinine. Although these markers are currently being used on an experimental basis, they are expected to impact the practice of clinical medicine in the not too distant future.

Until these new biomarkers are clinically available, radiologists can be reassured by the knowledge that the incidence of AKI on an outpatient basis is rare. AKI is commonly but not always associated with symptoms or change in urine output, an abnormal urinalysis and serum creatinine. Conversely, in-patients should be considered at higher risk for AKI and concomitantly NSF. They should routinely have their blood tested for serum creatinine, with a comparison made to their baseline, before administration of any GBCM. For those on chronic hemodialysis, it is recommended that they receive hemodialysis as soon as possible after administration of a GBCM and certainly within 24 hours. Gadolinium is dialysable but has not been proven to decrease the incidence or severity of NSF.

Prince et al in the September 2008 edition of Radiology study found no cases of NSF after 74,124 patient exposures to GBCM, when receiving standard dose, even without pre-screening of patients.[5] Reasonable screening and identification of patients at highest risk for NSF, based upon FDA class labeling and ACR recommendations, should minimize the risk of NSF moving forward. ■

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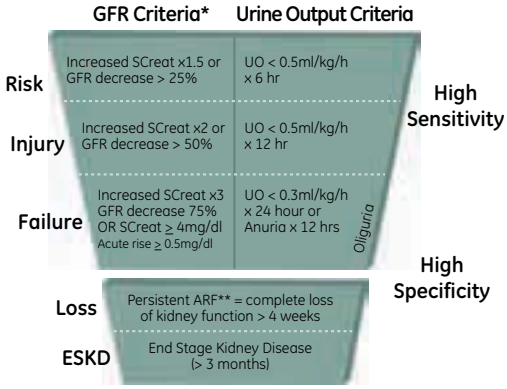

Figure 2

*GFR = Glomerular Filtration Rate

**ARF = Acute Renal Failure

Source: Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, ADQI workgroup. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Critical Care 2004, 8:R-04-R212. Available at http://ccforum.com/content/8/4/R204

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