Section 1: Introduction and Methodology

Kidney International Supplements (2012) **2,** 13–18; doi:10.1038/kisup.2011.31

Chapter 1.1: Introduction

The concept of acute renal failure (ARF) has undergone significant re-examination in recent years. Mounting evidence suggests that acute, relatively mild injury to the kidney or impairment of kidney function, manifest by changes in urine output and blood chemistries, portend serious clinical consequences.[1–5] Traditionally, most reviews and textbook chapters emphasize the most severe reduction in kidney function, with severe azotemia and often with oliguria or anuria. It has only been in the past few years that moderate decreases of kidney function have been recognized as potentially important, in the critically ill,[2] and in studies on contrast-induced nephropathy.[4]

Glomerular filtration rate and serum creatinine

The glomerular filtration rate (GFR) is widely accepted as the best overall index of kidney function in health and disease. However, GFR is difficult to measure and is commonly estimated from the serum level of endogenous filtration markers, such as creatinine. Recently, Chertow *et al.*[1] found that an increase of serum creatinine (SCr) of >0.3 mg/dl (>26.5 μmol/l) was independently associated with mortality. Similarly, Lassnigg *et al.*[3] saw, in a cohort of patients who underwent cardiac surgery, that either an increase of SCr $\geqslant 0.5$ mg/dl ($\geqslant 44.2$ μmol/l) or a decrease >0.3 mg/dl (>26.5 μmol/l) was associated with worse survival. The reasons why small alterations in SCr lead to increases in hospital mortality are not entirely clear. Possible explanations include the untoward effects of decreased kidney function such as volume overload, retention of uremic compounds, acidosis, electrolyte disorders, increased risk for infection, and anemia.[6] Although, these changes in SCr could simply be colinear with unmeasured variables that lead to increased mortality, multiple attempts to control for known clinical variables has led to the consistent conclusion that decreased kidney function is independently associated with outcome. Furthermore, more severe reductions in kidney function tend to be associated with even worse outcome as compared to milder reductions.

Oliguria and anuria

Although urine output is both a reasonably sensitive functional index for the kidney as well as a biomarker of tubular injury, the relationship between urine output and GFR, and tubular injury is complex. For example, oliguria may be more profound when tubular function is intact. Volume depletion and hypotension are profound stimuli for vasopressin secretion. As a consequence the distal tubules and collecting ducts become fully permeable to water. Concentrating mechanisms in the inner medulla are also aided by low flow through the loops of Henle and thus, urine volume is minimized and urine concentration maximized (>500 m Osmol/kg). Conversely, when the tubules are injured, maximal concentrating ability is impaired and urine volume may even be normal (i.e., nonoliguric renal failure). Analysis of the urine to determine tubular function has a long history in clinical medicine. Indeed, a high urine osmolality coupled with a low urine sodium in the face of oliguria and azotemia is strong evidence of intact tubular function. However, this should not be interpreted as "benign" or even prerenal azotemia. Intact tubular function, particularly early on, may be seen with various forms of renal disease (e.g., glomerulonephritis). Sepsis, the most common condition associated with ARF in the intensive-care unit (ICU)[7] may alter renal function without any characteristic changes in urine indices.[8,9] Automatically classifying these abnormalities as "prerenal" will undoubtedly lead to incorrect management decisions. Classification as "benign azotemia" or "acute renal success" is not consistent with available evidence. Finally, although severe oliguria and even anuria may result from renal tubular damage, it can also be caused by urinary tract obstruction and by total arterial or venous occlusion. These conditions will result in rapid and irreversible damage to the kidney and require prompt recognition and management.

Acute tubular necrosis (ATN)

When mammalian kidneys are subjected to prolonged warm ischemia followed by reperfusion, there is extensive necrosis destroying the proximal tubules of the outer stripe of the medulla, and the proximal convoluted tubules become necrotic as well.[10] Distal nephron involvement in these animal experiments is minimal, unless medullary oxygenation is specifically targeted.[11] Although these animals develop severe ARF, as noted by Rosen and Heyman, not much else resembles the clinical syndrome in humans.[12] Indeed these authors correctly point out that the term "acute tubular necrosis does not accurately reflect the morphological changes in this condition".[12] Instead, the term ATN is used to describe a clinical situation in which there is adequate renal perfusion to largely maintain tubular integrity, but not

to sustain glomerular filtration. Data from renal biopsies in patients with ATN dating back to the 1950s[13] confirm the limited parenchymal compromise in spite of severe organ dysfunction.[12] Thus, the syndrome of ATN has very little to do with the animal models traditionally used to study it. More recently, investigators have emphasized the role of endothelial dysfunction, coagulation abnormalities, systemic inflammation, endothelial dysfunction, and oxidative stress in causing renal injury, particularly in the setting of sepsis.[14,15] True ATN does, in fact, occur. For example, patients with arterial catastrophes (ruptured aneurysms, acute dissection) can suffer prolonged periods of warm ischemia just like animal models. However, these cases comprise only a small fraction of patients with AKI, and ironically, these patients are often excluded from studies seeking to enroll patients with the more common clinical syndrome known as ATN.

ARF

In a recent review, Eknoyan notes that the first description of ARF, then termed *ischuria renalis*, was by William Heberden in 1802.[16] At the beginning of the twentieth century, ARF, then named *Acute Bright's disease*, was well described in William Osler's *Textbook for Medicine* (1909), as a consequence of toxic agents, pregnancy, burns, trauma, or operations on the kidneys. During the First World War the syndrome was named "war nephritis",[17] and was reported in several publications. The syndrome was forgotten until the Second World War, when Bywaters and Beall published their classical paper on crush syndrome.[18] However, it is Homer W. Smith who is credited for the introduction of the term "acute renal failure", in a chapter on "Acute renal failure related to traumatic injuries" in his textbook *The kidney-structure and function in health and disease* (1951). Unfortunately, a precise biochemical definition of ARF was never proposed and, until recently, there was no consensus on the diagnostic criteria or clinical definition of ARF, resulting in multiple different definitions. A recent survey revealed the use of at least 35 definitions in the literature.[19] This state of confusion has given rise to wide variation in reported incidence and clinical significance of ARF. Depending on the definition used, ARF has been reported to affect from 1% to 25% of ICU patients and has lead to mortality rates from 15–60%.[7,20,21]

RIFLE criteria

The Acute Dialysis Quality Initiative (ADQI) group developed a system for diagnosis and classification of a broad range of acute impairment of kidney function through a broad consensus of experts.[22] The characteristics of this system are summarized in Figure 1. The acronym RIFLE stands for the increasing severity classes Risk, Injury, and Failure; and the two outcome classes, Loss and End-Stage Renal Disease (ESRD). The three severity grades are defined on the basis of the changes in SCr or urine output where the worst of each criterion is used. The two outcome criteria, Loss and ESRD, are defined by the duration of loss of kidney function.

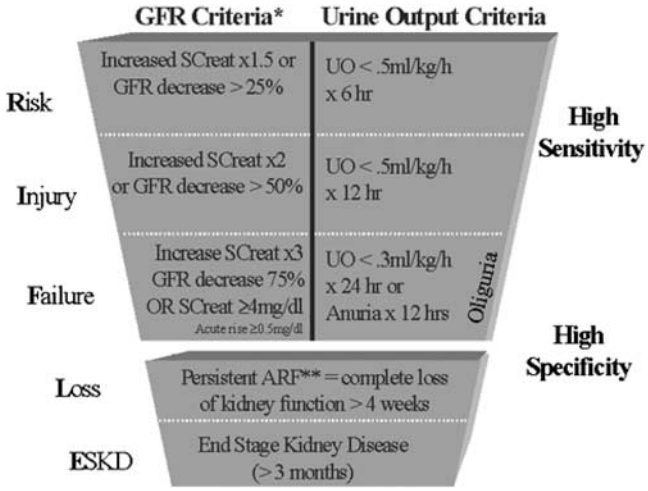

Figure 1 | The RIFLE criteria for AKI. ARF, acute renal failure; GFR, glomerular filtration rate; Screat, serum creatinine concentration; UO, urine output. Reprinted from Bellomo R, Ronco C, Kellum JA, *et al*. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004; 8: R204-212 with permission from Bellomo R *et al*.;[22] accessed http://ccforum.com/content/8/4/R204

AKI: acute kidney injury/impairment

Importantly, by defining the syndrome of acute changes in renal function more broadly, RIFLE criteria move beyond ARF. The term "acute kidney injury/impairment" has been proposed to encompass the entire spectrum of the syndrome from minor changes in markers of renal function to requirement for renal replacement therapy (RRT).[23] Thus, the concept of AKI, as defined by RIFLE creates a new paradigm. AKI is not ATN, nor is it renal failure. Instead, it encompasses both and also includes other, less severe conditions. Indeed, as a syndrome, it includes patients without actual damage to the kidney but with functional *impairment* relative to physiologic demand. Including such patients in the classification of AKI is conceptually attractive because these are precisely the patients that may benefit from early intervention. However, it means that AKI includes both *injury* and/or *impairment*. Rather than focusing exclusively on patients with renal failure or on those who receive dialysis or on those that have a clinical syndrome defined by pathology, which is usually absent (ATN), the strong association of AKI with hospital mortality demands that we change the way we think about this disorder. In a study by Hoste *et al*.,[2] only 14% of patients reaching RIFLE "F" received RRT, yet these patients experienced a hospital mortality rate more than five times that of the same ICU population without AKI. Is renal support underutilized or delayed? Are there other supportive measures that should be employed for these patients? Sustained AKI leads to profound alterations in fluid, electrolyte, acid-base and hormonal regulation. AKI results in abnormalities in the central nervous, immune, and coagulation systems. Many patients

with AKI already have multisystem organ failure. What is the incremental influence of AKI on remote organ function and how does it affect outcome? A recent study by Levy *et al.* examined outcomes for over 1000 patients enrolled in the control arms of two large sepsis trials.[24] Early improvement (within 24 hours) in cardiovascular ($P = 0.0010$), renal ($P < 0.0001$), or respiratory ($P = 0.0469$) function was significantly related to survival. This study suggests that outcomes for patients with severe sepsis in the ICU are closely related to early resolution of AKI. While rapid resolution of AKI may simply be a marker of a good prognosis, it may also indicate a window of therapeutic opportunity to improve outcome in such patients.

Validation studies using RIFLE

As of early 2010, over half a million patients have been studied to evaluate the RIFLE criteria as a means of classifying patients with AKI.[25–28] Large series from the USA,[28] Europe,[29,30] and Australia,[25] each including several thousand patients, have provided a consistent picture. AKI defined by RIFLE is associated with significantly decreased survival and furthermore, increasing severity of AKI defined by RIFLE stage leads to increased risk of death.

An early study from Uchino *et al.* focused on the predictive ability of the RIFLE classification in a cohort of 20 126 patients admitted to a teaching hospital for >24 hours over a 3-year period.[5] The authors used an electronic laboratory database to classify patients into RIFLE-R, I, and F and followed them to hospital discharge or death. Nearly 10% of patients achieved a maximum RIFLE-R, 5% I, and 3.5% F. There was a nearly linear increase in hospital mortality with increasing RIFLE class, with patients at R having more than three times the mortality rate of patients without AKI. Patients with I had close to twice the mortality of R and patients with F had 10 times the mortality rate of hospitalized patients without AKI. The investigators performed multivariate logistic regression analysis to test whether RIFLE classification was an independent predictor of hospital mortality. They found that class R carried an odds ratio of hospital mortality of 2.5, I of 5.4, and F of 10.1.

Ali *et al.* studied the incidence of AKI in Northern Scotland, a geographical population base of 523 390. The incidence of AKI was 2147 per million population.[31] Sepsis was a precipitating factor in 47% of patients. RIFLE classification was useful for predicting recovery of renal function ($P < 0.001$), requirement for RRT ($P < 0.001$), length of hospital stay for survivors ($P < 0.001$), and in-hospital mortality ($P = 0.035$). Although no longer statistically significant, subjects with AKI had a high mortality at 3 and 6 months as well.

More recently, the Acute Kidney Injury Network (AKIN), an international network of AKI researchers, organized a summit of nephrology and critical care societies from around the world. The group endorsed the RIFLE criteria with a small modification to include small changes in SCr ($\geqslant 0.3$ mg/dl or $\geqslant 26.5$ μmol/l) when they occur within a 48-hour period.[23] Two recent studies examining large databases in the USA[28] and Europe[29] validated these modified criteria. Thakar *et al.* found that increased severity of AKI was associated with an increased risk of death independent of comorbidity.[28] Patients with Stage 1 ($\geqslant 0.3$ mg/dl or $\geqslant 26.5$ μmol/l) increase in SCr but less than a two-fold increase had an odds ratio of 2.2; with Stage 2 (corresponding to RIFLE-I), there was an odds ratio of 6.1; and in Stage 3 (RIFLE-F), an odds ratio of 8.6 for hospital mortality was calculated. An additional modification to the RIFLE criteria has been proposed for pediatric patients in order to better classify small children with acute-on-chronic disease.[32]

Limitations to current definitions for AKI

Unfortunately, the existing criteria—while extremely useful and widely validated—are still limited. First, despite efforts to standardize the definition and classification of AKI, there is still inconsistency in application.[26,27] A minority of studies have included urinary output criteria despite its apparent ability to identify additional cases[6,29] and many studies have excluded patients whose initial SCr is already elevated. Preliminary data from a 20 000-patient database from the University of Pittsburgh suggests that roughly a third of AKI cases are community-acquired[33] and many cases may be missed by limiting analysis to documented increases in SCr. Indeed, the majority of cases of AKI in the developing world are likely to be community-acquired. Thus, few studies can provide accurate incidence data. An additional problem relates to the limitations of SCr and urine output for detecting AKI. In the future, biomarkers of renal cell injury may identify additional patients with AKI and may identify the majority of patients at an earlier stage.

Rationale for a guideline on AKI

AKI is a global problem and occurs in the community, in the hospital where it is common on medical, surgical, pediatric, and oncology wards, and in ICUs. Irrespective of its nature, AKI is a predictor of immediate and long-term adverse outcomes. AKI is more prevalent in (and a significant risk factor for) patients with chronic kidney disease (CKD). Individuals with CKD are especially susceptible to AKI which, in turn, may act as a promoter of progression of the underlying CKD. The burden of AKI may be most significant in developing countries[34,35] with limited resources for the care of these patients once the disease progresses to kidney failure necessitating RRT. Addressing the unique circumstances and needs of developing countries, especially in the detection of AKI in its early and potentially reversible stages to prevent its progression to kidney failure requiring dialysis, is of paramount importance.

Research over the past decade has identified numerous preventable risk factors for AKI and the potential of improving their management and outcomes. Unfortunately, these are not widely known and are variably practiced

worldwide, resulting in lost opportunities to improve the care and outcomes of patients with AKI. Importantly, there is no unifying approach to the diagnosis and care of these patients. There is a worldwide need to recognize, detect, and intervene to circumvent the need for dialysis and to improve outcomes of AKI. The difficulties and disadvantages associated with an increasing variation in management and treatment of diseases that were amplified in the years after the Second World War, led in 1989 to the creation in the USA of the Agency for Health Care Policy and Research (now the Agency for Healthcare Research and Quality). This agency was created to provide objective, science-based information to improve decision making in health-care delivery. A major contribution of this agency was the establishment of a systematic process for developing evidence-based guidelines. It is now well accepted that rigorously developed, evidence-based guidelines, when implemented, have improved quality, cost, variability, and outcomes.[36,37]

Realizing that there is an increasing prevalence of acute (and chronic) kidney disease worldwide and that the complications and problems of patients with kidney disease are universal, Kidney Disease: Improving Global Outcomes (KDIGO), a nonprofit foundation, was established in 2003 "to improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines".[38]

Besides developing guidelines on a number of other important areas of nephrology, the Board of Directors of KDIGO quickly realized that there is room for improving international cooperation in the development, dissemination, and implementation of clinical practice guidelines in the field of AKI. At its meeting in December of 2006, the KDIGO Board of Directors determined that the topic of AKI meets the criteria for developing clinical practice guidelines.

These criteria were formulated as follows:

- AKI is common.
- AKI imposes a heavy burden of illness (morbidity and mortality).
- The cost per person of managing AKI is high.
- AKI is amenable to early detection and potential prevention.
- There is considerable variability in practice to prevent, diagnose, treat, and achieve outcomes of AKI.
- Clinical practice guidelines in the field have the potential to reduce variations, improve outcomes, and reduce costs.
- Formal guidelines do not exist on this topic.

Summary

Small changes in kidney function in hospitalized patients are important and associated with significant changes in short- and long-term outcomes. The shift of terminology from ATN and ARF to AKI has been well received by the research and clinical communities. RIFLE/AKIN criteria provide a uniform definition of AKI, and have become the standard for diagnostic criteria. AKI severity grades represent patient groups with increasing severity of illness as illustrated by an increasing proportion of patients treated with RRT, and increasing mortality. Thus, AKI as defined by the RIFLE criteria is now recognized as an important syndrome, alongside other syndromes such as acute coronary syndrome, acute lung injury, and severe sepsis and septic shock. The RIFLE/AKIN classification for AKI is quite analogous to the Kidney Disease Outcomes Quality Initiative (KDOQI) for CKD staging, which is well known to correlate disease severity with cardiovascular complications and other morbidities.[39] As CKD stages have been linked to specific treatment recommendations, which have proved extremely useful in managing this disease,[39] we have developed recommendations for evaluation and management of patients with AKI using this stage-based approach.

Chapter 1.2: Methodology

INTRODUCTION

This chapter provides a very brief summary of the methods used to develop this guideline. Detailed methods are provided in Appendix F. The overall aim of the project was to create a clinical practice guideline with recommendations for AKI using an evidence-based approach. After topics and relevant clinical questions were identified, the pertinent scientific literature on those topics was systematically searched and summarized.

Group member selection and meeting process

The KDIGO Co-Chairs appointed the Co-Chairs of the Work Group, who then assembled the Work Group to be responsible for the development of the guideline. The Work Group consisted of domain experts, including individuals with expertise in nephrology, critical care medicine, internal medicine, pediatrics, cardiology, radiology, infectious diseases and epidemiology. For support in evidence review, expertise in methods, and guideline development, the NKF contracted with the Evidence Review Team (ERT) based primarily at the Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, Massachusetts, USA. The ERT consisted of physician-methodologists with expertise in nephrology and internal medicine, and research associates and assistants. The ERT instructed and advised Work Group members in all steps of literature review, critical literature appraisal, and guideline development. The Work Group and the ERT collaborated closely throughout the project. The Work Group, KDIGO Co-Chairs, ERT, liaisons, and NKF support staff met for four 2-day meetings for training in the guideline development process, topic discussion, and consensus development.

Evidence selection, appraisal, and presentation

We first defined the topics and goals for the guideline and identified key clinical questions for review. The ERT performed literature searches, organized abstract and article screening, coordinated methodological and analytic processes of the report, defined and standardized the search methodology, performed data extraction, and summarized the evidence. The Work Group members reviewed all included articles, data extraction forms, summary tables, and evidence profiles for accuracy and completeness. The four major topic areas of interest for AKI included: i) definition and classification; ii) prevention; iii) pharmacologic treatment; and iv) RRT. Populations of interest were those at risk for AKI (including those after intravascular contrast-media exposure, aminoglycosides, and amphotericin) and those with or at risk for AKI with a focus on patients with sepsis or trauma, receiving critical care, or undergoing cardiothoracic surgery. We excluded studies on AKI from rhabdomyolysis, specific infections, and poisoning or drug overdose. Overall, we screened 18 385 citations.

Outcome selection judgments, values, and preferences

We limited outcomes to those important for decision making, including development of AKI, need for or dependence on RRT, and all-cause mortality. When weighting the evidence across different outcomes, we selected as the "crucial" outcome that which weighed most heavily in the assessment of the overall quality of evidence. Values and preferences articulated by the Work Group included: i) a desire to be inclusive in terms of meeting criteria for AKI; ii) a progressive approach to risk and cost such that, as severity increased, the group put greater value on possible effectiveness of strategies, but maintained high value for avoidance of harm; iii) intent to guide practice but not limit future research.

Grading the quality of evidence and the strength of recommendations

The grading approach followed in this guideline is adopted from the GRADE system.[40,41] The strength of each recommendation is rated as level 1 which means "strong" or level 2 which means "weak" or discretionary. The wording corresponding to a level 1 recommendation is "We recommend … should" and implies that most patients should receive the course of action. The wording for a level 2 recommendation is "We suggest … might" which implies that different choices will be appropriate for different patients, with the suggested course of action being a reasonable choice in many patients. In addition, each statement is assigned a grade for the quality of the supporting evidence, A (high), B (moderate), C (low), or D (very low). Table 1 shows the implications of the guideline grades and describes how the strength of the recommendations should be interpreted by guideline users.

Furthermore, on topics that cannot be subjected to systematic evidence review, the Work Group could issue statements that are not graded. Typically, these provide guidance that is based on common sense, e.g., reminders of the obvious and/or recommendations that are not sufficiently specific enough to allow the application of evidence. The GRADE system is best suited to evaluate evidence on comparative effectiveness. Some of our most important guideline topics involve diagnosis and staging or AKI, and here the Work Group chose to provide ungraded statements. These statements are indirectly supported by evidence on risk relationships and resulted from unanimous consensus of the Work Group. Thus, the Work Group feels they should not be viewed as weaker than graded recommendations.

Table 1 | Implications of the strength of a recommendation

	Implications		
Grade*	Patients	Clinicians	Policy
Level 1 "We recommend"	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 "We suggest"	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

SPONSORSHIP

KDIGO gratefully acknowledges the following sponsors that make our initiatives possible: Abbott, Amgen, Belo Foundation, Coca-Cola Company, Dole Food Company, Genzyme, Hoffmann-LaRoche, JC Penney, NATCO—The Organization for Transplant Professionals, NKF—Board of Directors, Novartis, Robert and Jane Cizik Foundation, Shire, Transwestern Commercial Services, and Wyeth. KDIGO is supported by a consortium of sponsors and no funding is accepted for the development of specific guidelines.

SUPPLEMENTARY MATERIAL

Appendix F: Detailed Methods for Guideline Development.

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/AKI.php