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# The Metamorphosis of Acute Renal Failure to Acute Kidney Injury

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## 1. Introduction

Successive generations of scientists and nephrologists have failed to prevent or cure Acute Kidney Injury (AKI) and thousands every year die because of this. Recent innovations in proteomics and genomics have brought hope and renewed interest in preventing this blight. Motivated by high incidence and lack of effective treatments, researchers have focussed on how to detect AKI early in the disease process so as to provide the maximum opportunity for early intervention and positive outcomes. AKI Incidence is greatest in the intensive care, at about 11-52% in larger studies (n>500) (Ahlstrom et al. (2006); Bagshaw et al. (2008); Cruz et al. (2007)). Cardiac surgery and procedures involving radiocontrast pose smaller, but significant, risk of AKI with an incidence of 3-15% depending on cohort (Harjai et al. (2008); Lassnigg et al. (2008)). From 13 studies the mortality with AKI was 31.2% and was associated with an increase in relative risk of death from 2.40 to 6.15 depending on AKI severity (Ricci et al. (2008)). Stimulating much recent research has been the discovery of new kidney injury biomarkers, some of which appear to have sufficient sensitivity and specificity to be clinically useful.

This chapter will outline the history of the development of the concepts of clearance, acute renal failure, and acute kidney injury. This history provides the context for the current clearance based AKI diagnostic paradigm. The discovery of novel kidney injury biomarkers is challenging that paradigm. We will discuss the nature of that challenge and the opportunity it provides for development of early intervention treatments. All epidemiology, biomarker studies and clinical trials rely on tools to quantify AKI and assess efficacy of diagnostic or treatment efficacy. In section 3 we will discuss those tools before moving on to considering how they may best be applied in practice (section 4).

## 2. From ARF to AKI

### 2.1 Clearance and the rise and fall of creatinine

While suppression of urine flow, ischuria renalis, was recognised as a fundamental manifestation of renal disease from the 17th Century, clear metabolic manifestations of AKI

were not documented until World War I in the German and World War II in the English literature (see Eknayan (2002); McGrath (1852)). The term “Acute Renal Failure” first appeared in the literature in 1946 (Frank et al. (1946)), although it has been attributed to Homer Smith (Eknayan (2002)). In keeping with a recent change in nomenclature we shall use the term “Acute Kidney Injury” (AKI) unless we are specifically referring to an historic use of ARF.

The historical development of clearance techniques and the relationship to glomerular filtration rate (GFR) are discussed by Berliner in his tribute to the great renal physiologist Homer Smith (Berliner (1995)). The term clearance was introduced in 1928 with reference to urea and to clearance of a defined volume of plasma in unit time (Moller et al. (1928)). The idea of creatinine clearance as a measure of glomerular filtration rate (GFR) was beautifully first demonstrated by Rehberg in experiments on himself (Rehberg (1926)). These also highlighted how variations in serum creatinine could be induced by diet: Rehberg ingested different quantities of creatinine to vary his serum creatinine. The utility of clearance as a technique was further established in the laboratory of Homer Smith, especially with para-amminohippuric acid clearance, a measure of secretion and renal blood flow (Smith et al. (1945)).

Creatinine is formed non-enzymatically from creatine in muscle, has a molecular weight of 113.12 Da, is freely filtered at the glomerulus and completely cleared by renal excretion when renal function is normal. The proximal tubules secrete creatinine, which accounts for 10 to 20% of the excreted load, and results in overestimation of GFR when measured by creatinine clearance (Perrone et al. (1992); Shemesh et al. (1985)). The contribution of tubular creatinine secretion to clearance, is increased when GFR is reduced and may reach 50%, but is highly variable amongst individuals (Perrone et al. (1992)). In contrast, the tubules reabsorb creatinine in some clinical settings such as decompensated heart failure and uncontrolled diabetes (Levinsky & Berliner (1959); Perrone et al. (1992)).

With creatinine clearance firmly established as a reasonable approximation to GFR, the next step was to estimate creatinine clearance based on the reciprocal relationship with plasma creatinine. This was popularized by the Cockcroft-Gault equation which was derived by, firstly, a regression to estimate creatinine excretion/kg body weight according to age in hospitalised male patients; then clearance was calculated by multiplying by weight and dividing by the serum creatinine (Cockcroft & Gault (1976)). An untested 15% reduction for female gender was included, based on the observation that, on average, females had less fat and muscle mass than males (Cockcroft & Gault (1976)). This formula has been widely replaced by other estimates of GFR (eGFR), most notably by the Modification of Diet in Renal Disease (MDRD) equation originally developed in a population of CKD patients (Levey et al. (1999)).

Many alternative algorithms for creatinine-based eGFR have been developed, including those regularly in use for children; these equations are more accurate and precise than estimates from measurement of creatinine alone (*KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification* (2002)). The various iterations of the MDRD equation rely on plasma creatinine plus several other variables, including gender and race, and originally albumin and urea (as blood urea nitrogen) concentrations, but excluding mass although they do incorporate body surface area via the units; the latest version is more accurate than the MDRD equation for patients with GFR > 60 ml/min (Levey et al. (2009)) but caveats remain (Rule (2010)) and drug dosing tends to be based on Cockcroft-Gault (Ryzner (2010)).

Classical measurement of clearance with timed urine collection is cumbersome, so logically, the surrogate of clearance, the serum creatinine (actually measured in plasma), is usually the sole measure used to define renal status including development of AKI. However, serum creatinine increases slowly in response to a single step alteration in GFR. Serum creatinine has a half-life of approximately 4 hours when GFR is normal and 77 hours when GFR is reduced to 5% (Chiou & Hsu (1975); see section 3.1). As 3 to 5 half-lives are required after any change in GFR to obtain a new steady-state estimate, a reliable GFR based on the serum creatinine will require at least 12 hrs after even a minimal change in GFR. The current consensus definition (RIFLE: Risk, Injury, Failure, Loss, End-stage) of AKI requires at least a 33% decline in GFR, but a 25% reduction is traditionally accepted for diagnosis of contrast-induced AKI (Bagshaw et al. (2008); Endre et al. (1989); Pickering & Endre (2009a)). Thus a new steady-state creatinine-based estimate of GFR will take from 24 to 72 hours. Obviously, the extent of increase in creatinine, which is determined by the extent of initial decrease in GFR and creatinine production, may allow diagnosis of AKI prior to the time needed to reach steady-state. However, the limited precision of creatinine measurement and the extent of intra-patient variation mean that a minimum 10% change in creatinine has traditionally been required by clinicians to demonstrate measurably significant change. An increase in serum creatinine has also been used as a major trigger for intervention (renal replacement therapy, RRT) in both AKI and chronic kidney disease (Gibney et al. (2008)). The recognised imprecision in determining change in GFR led to removal of GFR from the new Acute Kidney Injury Network (AKIN) consensus classification of AKI so that an absolute or percentage increase in creatinine alone or in combination with oliguria has become the new consensus definition of AKI (Mehta et al. (2007)). Thus, despite many limitations, such as dependence on muscle mass, diet etc (Perrone et al. (1992)), serum creatinine became the accepted shorthand for estimating GFR and significant change in creatinine became the definition of AKI and marker of AKI severity.

Since there is an inverse relationship between serum creatinine and GFR, it is easy to forget that a small increase in serum creatinine represents a substantial decline in GFR. Consequently, prior to the now widespread reporting of eGFR estimated from creatinine, clinicians often ignored small increases in creatinine, and characterised these as “mild” or “moderate” increases. Combined with the uncertainty associated with the precision of measurement, years of ignoring such small increases in creatinine have impaired insight into how AKI is triggered. Even if an increase is observed, the delay required for diagnosis creates uncertainty regarding the timing of the renal insult leading to AKI. This represents a lost opportunity to investigate and identify the underlying pathophysiology of AKI in humans. Even mild grades of severity of AKI and transient (less than 24 hour increases in creatinine) are associated with increased hospital mortality (Chertow et al. (2005); Uchino et al. (2010; 2006)).

Inevitably, much of our interpretation of the pathophysiology of AKI is based on an animal model; the classical model utilises temporary cessation of renal blood flow to induce injury, usually through bilateral renal artery clamping. While this model may parallel human AKI after aortic surgery or renal transplantation, it greatly exaggerates the degree of tubular injury compared with that in the limited number of available human renal biopsies and is probably less relevant to AKI that does not follow hypoperfusion (Heyman et al. (2010)). Even in this model there is limited understanding of how major pathophysiological events in AKI are integrated, for example, the mechanism and timing of the switching “off” and “on” of

glomerular filtration. With few exceptions (Alejandro et al. (1995); Myers et al. (1984)), most of our experimental interventions have been validated only in this and nephrotoxic animal models (Vaidya et al. (2010)).

While there is a great deal of information about a large number of cellular (tubular and endothelial) events and the autonomic, inflammatory and renal vascular responses in experimental ischemia-reperfusion injury (Devarajan (2006); Heemskerk et al. (2009)), there is little corroborative and time-relevant clinical pathophysiological data. Usually, the clinical diagnosis of ischemic AKI is a diagnosis of exclusion. Thus, the potential delay imposed by reliance on creatinine is further delayed by investigations (eg exclusion of urinary outflow obstruction) or interventions (fluid loading to treat underlying “pre-renal” AKI) designed to exclude rather than confirm the diagnosis of ischemic AKI. Other investigations such as measurement of global or parenchymal renal blood flow, or renal biopsy, which might provide insight into human AKI, are delayed, difficult to interpret in the absence of baseline data, and usually not performed.

Since diagnosis is delayed it is not surprising, that there has been failure of pharmacological intervention in clinical trials, which are largely based on experimental interventions to prevent rather than treat AKI (Jo et al. (2007)). However, pharmacologic prevention of AKI has also largely failed, even when the apparent aetiology is known, eg parenteral administration of iodinated radiocontrast (Fishbane (2008); Nigwekar et al. (2009); Zoungas et al. (2009)). The failure to translate apparently effective pharmacologic preventive measures in animal models into clinical practice, suggests that the serum creatinine-inspired delay in diagnosis, merely complements a lack of fundamental understanding of pathophysiology in human AKI.

## 2.2 The rise and rise of injury

The change in nomenclature from acute renal failure to acute kidney injury recognised that an acute decline in renal function is usually secondary to injury (*American Society of Nephrology Renal Research Report* (2005); Mehta et al. (2007)). The need for a renal-specific biomarkers of injury akin to a troponin was presaged in the late 1990s (Star (1998)) and the discovery of such proteins was later accorded highest priority by The American Society of Nephrology (*American Society of Nephrology Renal Research Report* (2005)) with the expectation that such biomarkers would: “Diagnose AKI before the rise in serum creatinine; Stratify patients with respect to severity of injury and; Provide prognostic indicators.” The term “secondary prevention” was introduced to highlight that biomarker detection would lead to early intervention ideally prior to loss of GFR (Pickering & Endre (2009c)).

Some urinary proteins, notably  $\alpha_1$ -microglobulin,  $\beta_1$ -microglobulin, and N-acetyl- $\beta$ -D-glucosaminidase (NAG), were already known to be associated with acute tubular injury (Yu et al. (1983)), whilst others awaited discovery. In 1998 Kidney Injury Molecule-1 (KIM-1) was identified as being upregulated in the proximal tubule cells after ischemic/reperfusion (I/R) injury (Ichimura et al. (1998)) and soon discovered in the urine of patients with I/R injury (Han et al. (2002)). Around the same time a small study of ICU patients identified urinary tubular injury makers,  $\alpha$  and  $\pi$ -glutathione S-transferase ( $\alpha$  and  $\pi$ -GST), and the brush border enzymes,  $\gamma$ -glutamyl-transpeptidase (GGT) and alkaline phosphatase (AP), as diagnostic of AKI (Westhuyzen et al. (2003)). A transcriptome wide interrogation study to identify genes induced early after I/R injury identified neutrophil gelatinase-associated lipocalin (NGAL) to be upregulated in a mouse model (Mishra et al. (2003)). Plasma and urinary NGAL quickly showed spectacular success as diagnostic



markers. The first, a trial of 71 children undergoing cardiopulmonary bypass of whom 20 developed AKI showed urinary and plasma NGAL to increase 10-fold in AKI 2-h post surgery (Mishra et al. (2005)). Similarly, interleukin-18, IL-18, first identified as being released into the urine following I/R injury in mice (Melnikov et al. (2001)) was found to appear in large quantities in the urine of patients with acute tubular necrosis (Parikh et al. (2004)). Proteomic and genomic approaches continue to be a rich source of new urinary proteins which may predict AKI (Bennett & Devarajan (2011); Devarajan (2008)).

AKI Biomarker discovery has followed the well trodden path of “early promise” with some highly sensitive and specific biomarkers in demographically homogeneous populations (eg paediatric cardiopulmonary bypass surgery), followed by a more tempered response as studies evaluated candidate biomarkers in demographically heterogeneous populations with multiple causes of AKI and co-morbidities. There is no one biomarker which will successfully diagnose or predict a decline in renal function in all situations. Three factors have emerged which are likely to become determinant factors in the choice of biomarker for a particular clinical context, namely: (i) likely aetiology of AKI, (ii) pre-existing renal function, (iii) time from renal insult. IL-18 is an example of a biomarker which has been shown to be elevated following ischaemic/repurfusion injury (Hall et al. (2010); Parikh et al. (2006)), but possibly not following radiocontrast induced nephrotoxic injury (Bulent Gul et al. (2008)). Mcilroy et al demonstrated that in a cohort of 426 adult cardiac surgery patients urinary NGAL concentrations post-operatively did not differ between those who developed and those who did not develop AKI when their estimated baseline GFR (eGFR) was less than 60 ml/min, yet for those with a normal baseline eGFR (90-120 ml/min) NGAL was significantly elevated in the AKI cohort (Mcilroy et al. (2010)). In our own head to head comparison of 6 urinary biomarkers (GGT, AP, NGAL, Cystatin C, IL-18, and KIM-1) in 529 adult patients on entry to an intensive care unit, we demonstrated that the performance of biomarkers is critically dependent on both baseline renal function and time from renal insult (Endre et al. (2011)). Peak diagnostic performance at a level that may be considered clinically useful was limited to patients with eGFR 90-120 ml/min within 12-h of insult for GGT, 6-h for NGAL and from 6 to 12-h for Cystatin C, IL-18 and KIM-1, and to patients with eGFR < 60 ml/min from 12 to 36-h for GGT, Cystatin C, NGAL and IL-18.

There are many excellent recent reviews of biomarkers of AKI. The pathophysiology of AKI in relation to potential biomarkers has been reviewed and discussed specifically in relation to AKI following cardiopulmonary bypass (Haase et al. (2010)), AKI with varying aetiology (Vaidya et al. (2008)), and AKI involving biomarker mediators of inflammation (Akca et al. (2009)). Reviews of biomarker performance specific to nephrotoxic injury (Bonventre et al. (2010); Ferguson et al. (2008)), septic AKI (Bagshaw et al. (2007)), ischemic injury following cardiopulmonary bypass (Haase et al. (2010)), acute allograft rejection and ischemic injury (Alachkar et al. (2010)) as well as broader reviews across aetiologies (Coca et al. (2008); Edelstein & Faubel (2010); Endre & Westhuyzen (2008); Malyszko (2010)) have been published within the last 4 years. We have published a more specialist review considering biomarkers in the early phase of injury (Pickering & Endre (2009c)) and there has been one meta-analysis of the performance of NGAL (Haase et al. (2009)).

### 2.3 Paradigm lost and paradigm found

The relationship between clearance (the function paradigm) and injury has, to date, been studied in humans primarily in sample populations of about 20 to 600 in which a biomarker's

ability to diagnose a subsequent rise in a surrogate marker of function (normally creatinine) is assessed. However, we need to explore the early stages of, and prior to, loss of renal function in order to understand the relevant pathophysiology of clinical AKI. We can conceptualise this as an evaluation of the evolution of injury phase which leads to loss of GFR and the early loss of function phase immediately following a GFR decrease (Figure 1). Detection and characterisation of this very early phase in man appears essential for progress. This highlights the need for quantifying the time course of injury biomarkers in relation to change in GFR and for real-time assessment of renal function. Two promising techniques are under development. The ambulatory renal monitor (ARM) is a shielded detector which monitors extracellular excretion of <sup>99m</sup>TcDTPA over up to 24 hours following injection and relates this to GFR (Rabito et al. (2010)). The ratiometric fluorescence approach monitors the plasma disappearance of both a rapidly filtered and a poorly filtered fluorescent marker introduced by a single bolus infusion, changes in the ratio of which enable a calculation of GFR (Wang et al. (2010)). Both techniques allow a rapid (5 to 15 min) measure of GFR. Ideally these or similar techniques would allow monitoring of kidney function from prior to the time of insult through the evolution time until change of GFR and beyond.

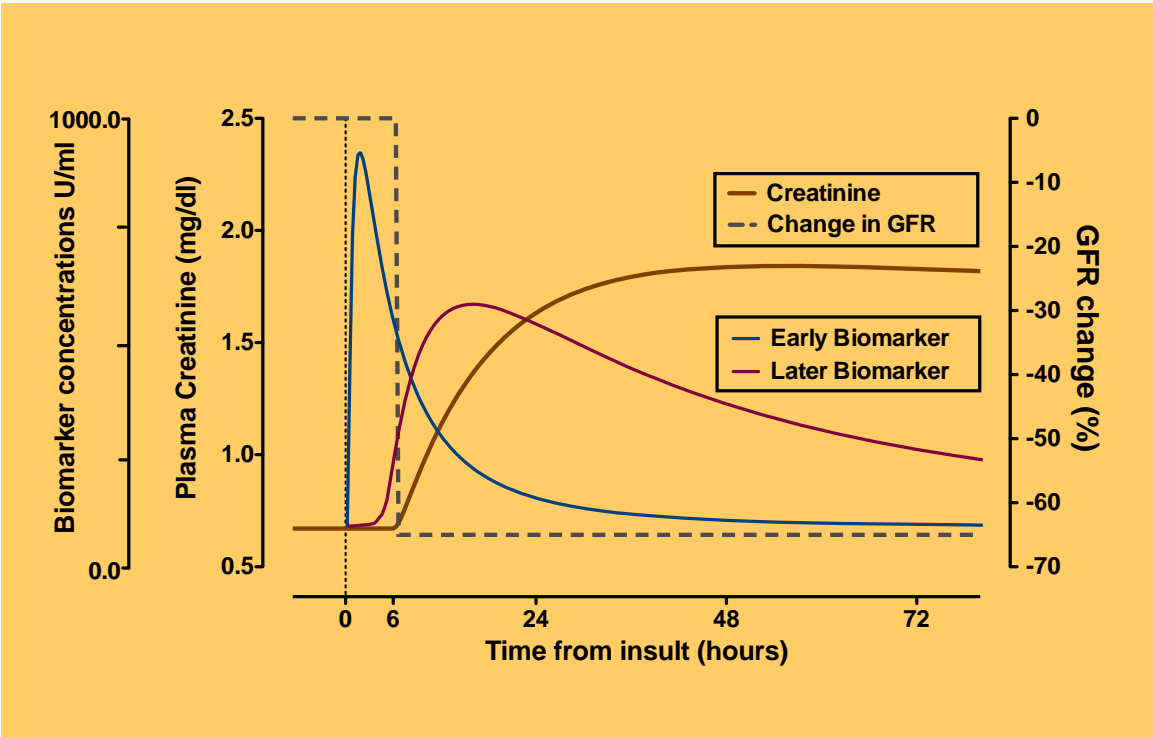


Fig. 1. The paradigm of function compared with the paradigm of injury. Following injury the early injury biomarker is elevated prior to change in function (here, a 65% loss of GFR, approximately 6 hours post-injury). The later biomarker takes takes longer to be elevated. Creatinine is only elevated following loss of GFR (following equation 6)

Much of the literature describes a biomarker as “predicting” AKI when it precedes an increase in plasma creatinine. However, a biomarker is only truly predictive if it precedes a decrease in GFR. If it is elevated shortly after such a decrease, then it should be described as *diagnostic* rather than predictive of AKI even though it may predict the latter increase in plasma creatinine.

3. Defining AKIs

In its broadest sense renal failure is simply the rapid loss of renal filtration (ie decrease in GFR). As discussed, current clinical diagnosis of AKI and evaluation of novel biomarkers of kidney injury are largely dependent on observation of changes in creatinine as a surrogate for a change in GFR. An understanding of the kinetics of the relationship between creatinine and GFR provides a basis for understanding the definitions of AKI and their limitations. Plasma cystatin C, an alternative to creatinine (Nejat et al. (2010); Westhuyzen (2006)), follows similar kinetics.

3.1 Creatinine and cystatin C kinetics

Creatinine and cystatin C are generated in tissue outside of the plasma compartment, diffuse into the plasma compartment from where they are lost by renal and non-renal excretion. Because both creatinine and cystatin C are not bound to plasma proteins the exchange between the extravascular and plasma compartments is rapid (compared with rates of production and elimination) allowing us to conflate the two compartments into one compartment with volume of distribution,  $V$  (Figure 2).

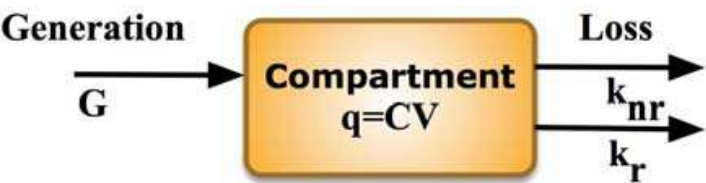


Fig. 2. One compartment pharmacokinetics model

The change in total mass ( $q$ ) of creatinine/cystatin C depends on the rate at which it is entering and the rate at which it is leaving the compartment:

$$\frac{dq}{dt} = \text{gain from generation} - (\text{renal loss} + \text{non-renal loss})$$

(1)

Under normal circumstances non-renal losses are much less than renal losses and may be ignored. The renal loss is the product of the renal elimination rate constant,  $k_r$ , and the total mass,  $q$ . As the total mass is the product of the concentration  $C$  and volume of distribution  $V$ , equation 1 becomes:

$$C \frac{dV}{dt} + \frac{dC}{dt} V = G - k_r CV$$

(2)

where  $G$  is the generation rate of creatinine/cystatin C (see Box 3.1). The volume of distribution of creatinine is equal to the total body water ( $TBW$ ) and that of cystatin C to the extracellular fluid (about one third of  $TBW$ )(see Box 3.2). If this is assumed not to change then equation 2 becomes:

$$\frac{dC}{dt} = \frac{G}{V} - k_r C$$

(3)

At equilibrium ( $dC/dt = 0$  at  $t = 0$ ), prior to any change in GFR the renal elimination rate constant may be determined from equation 3:

$$k_{r0} = \frac{G}{C_b V}$$

(4)



where  $C_b$  is the baseline concentration (at time  $t = 0$ ).  $k_{r0}$  may also be estimated from the renal clearance ( $Cl$ ) which is simply the product  $k_{r0}$  and  $V$ . For creatinine, this may be measured in critically ill patients using a short duration creatinine clearance and an estimate of an individual's volume of distribution (see below). From the EARLYARF study (Endre et al. (2010)) where 4-h creatinine clearances were measured on entry to ICU in 484 patients we were able to calculate a median (interquartile range) for  $k_{r0}$  of 0.11 (0.07-0.17)  $\text{h}^{-1}$ .

Following a loss in GFR ( $\Delta g\%$ ), the renal elimination rate constant becomes:

$$k_r = \left(1 - \frac{\Delta g}{100}\right) k_{r0} \quad (5)$$

and equation 3 may be solved numerically, or, if we assume of  $G$ ,  $V$ , or  $k_r$  are not varying, may be integrated to give the concentration as a function of time (Chiou & Hsu (1975); Chow (1985)):

$$C(t) = \frac{G}{k_r V} (1 - e^{-k_r t}) + C_b e^{-k_r t} \quad (6)$$

As  $t \rightarrow \infty$  the concentration asymptotically approaches a new steady state,  $C_{ss}$  which from equation 6 is:

$$C_{ss} = \frac{G}{k_r V} \quad (7)$$

Mathematically the concentration is within 5% of the new steady state in 4.4 half lives (Half life:  $t_{1/2} = \ln(2)/k_r$ ). In practice this is well within the uncertainty in creatinine measurements. The new steady state may also be determined by substituting equations 5 and 4 into equation 7:

$$C_{ss} = \frac{C_b}{\left(1 - \frac{\Delta g}{100}\right)} \quad (8)$$

From this equation we may determine the equivalences between a decline in GFR and a rise in creatinine used in the RIFLE definition of AKI (Table 1).

#### Box 3.1. Creatinine and Cystatin C production rates

*Creatinine production* (Bjornsson (1979)):

Male ( $r^2 = 0.919$ ):  $G_0 = (27 - 0.173 \times \text{age}) \times \text{weight}/24 \quad (\text{mg}/\text{h})$

Female ( $r^2 = 0.966$ ):  $G_0 = (25 - 0.175 \times \text{age}) \times \text{weight}/24 \quad (\text{mg}/\text{h})$

Creatinine production may decrease during critical illness (Griffiths (1996)). If the reduction is at constant rate  $m\%$ , (eg 2% per day as suggested by Griffiths) then:

$$G(t) = G_0 e^{-mt} \quad \text{and} \quad \frac{dG}{dt} = -mG$$

*Cystatin C production*

Only one study has measured the rate constant of Cystatin C (Sjostrom et al. (2005)). There was no significant difference with age, sex or lean body mass. The rate constant per  $1.73\text{m}^2$  of body surface area was:

$$G_{\text{CysC}} = 7.44 \quad (\text{mg}/\text{h}/1.73\text{m}^2)$$

Box 3.2. Estimating the volume of distribution

The volume of distribution of creatinine is equal to the total body water (*TBW*) and of cystatin C to the volume of the extracellular fluid which is about 1/3<sup>rd</sup> of the *TBW* (Hansen (2002)). *TBW* is often estimated from the body weight as:

$$TBW = 0.6 \times \text{Body weight} \quad (L)$$

More accurate formulae have been derived from population studies (Watson et al. (1980)):

Male ( $r^2 = 0.704$ ):  $TBW = 2.447 - 0.09516 \times \text{age} + 0.1074 \times \text{height} + 0.3662 \times \text{weight} \quad (L)$

Female ( $r^2 = 0.736$ ):  $TBW = 2.097 + 0.1069 \times \text{height} + 0.2466 \times \text{weight} \quad (L)$

where *height* is measured in cm, *weight* in kg, and *age* in years.

Where height is not available, the slightly less robust equations may be used:

Male ( $r^2 = 0.689$ ):  $TBW = 20.03 - 0.1183 \times \text{age} + 0.3626 \times \text{weight} \quad (L)$

Female ( $r^2 = 0.717$ ):  $TBW = 14.46 + 0.2549 \times \text{weight} \quad (L)$

3.2 Categorical consensus

In 2004 the Acute Dialysis Quality Initiative Group (ADQI) developed a consensus definition for AKI and severity staging (RIFLE: Risk, Injury, Failure, Loss, End Stage) (Bellomo et al. (2004)). The scheme involved both a creatinine based classification and a urine output based classification (Table 1). A decrease in GFR of more than 25% or increase in serum creatinine of 50% was deemed sufficient to diagnose AKI. Unfortunately, there was an error in calculating this relationship which was not identified until 2009 (Pickering & Endre (2009a)). A 50% increase in creatinine is equivalent to a one third decrease in GFR (see equation 8) not a 25% decrease. Similarly, for RIFLE stage F a 200% increase in creatinine is equivalent to a two thirds decrease in GFR not a 75% decrease. Whilst plasma creatinine rather than a GFR measure, or an estimation with creatinine clearance, is the analyte of choice in AKI studies, creatinine is but a surrogate for GFR and GFR should remain the principal diagnostic parameter of AKI (Pickering & Endre (2009b)). The ADQI group recommended AKI be defined as “sustained” (lasting at least 24hrs) and “abrupt” (1-7 days) (<http://www.ccm.upmc.edu/adqi/ADQI2/ADQI2g1.pdf>). Whilst duration did not appear in the seminal RIFLE publication it was included in later publications (Hoste et al. (2006); Lameire et al. (2006)).

On the back of new evidence that even minor changes in serum creatinine are associated with poor outcomes (eg Chertow et al. (2005); Lassnigg et al. (2004)), the Acute Kidney Injury Network modified the RIFLE definition to include a small absolute rise in creatinine (0.3 mg/dl or 26.4 μmol/l). Further modifications included requiring the change to occur within 48 hours for the definition of AKI, and removing RIFLE stages L and E in preference to all patients requiring renal replacement therapy to be assigned to severity stage III (Table 1). Both definitions have received broad support and there is considerable evidence for an association of increased mortality with increased RIFLE or AKIN stages (Bagshaw et al. (2008); Ricci et al. (2008)). More recently, duration of AKI (using the AKIN criteria) has been shown to be independently associated with long-term mortality (Brown et al. (2010); Coca et al. (2010); Goldberg et al. (2009)). KDIGO (Kidney Disease for Improving Global Outcomes:

www.kdigo.org ) has recently reviewed the use of the AKIN and RIFLE criteria and is shortly to release a new consensus definition which combines the two definitions.

RIFLE			AKIN		RIFLE and AKIN
Stage	Creatinine increase	GFR decrease	Stage	Creatinine increase	Urine output
Risk (R)	≥ 50%	> 33.3%*	I	≥ 0.3 mg/dl or ≥ 50%	< 0.5 mg/kg/h for 6 h
Injury (I)	≥ 100%	> 50%	II	≥ 100%	< 0.5 mg/kg/h for 12 h
Failure (F)	≥ 200% or ≥ 0.5 mg/dl and above 4.0 mg/dl	> 66.7%**	III	≥ 200% or ≥ 0.5 mg/dl and above 4.0 mg/dl	< 0.3 mg/kg/h for 24 h or anuria for 12 h

\*,\*\* corrected from 25% and 75% see Pickering & Endre (2009a)

Table 1. Severity Staging: Consensus definitions

3.3 A continuum needing continuous variables

One of the intentions of ADQI in setting up RIFLE was that it would provide common outcomes in clinical trials. During the four year period (2005-08) only 36% of published AKI (non Contrast Induced Nephropathy, CIN) trials used RIFLE or AKIN as an outcome variable, and the use was not consistent in terms of timing and duration of injury (Endre & Pickering (2010)). Amongst CIN intervention trials only 13% used RIFLE or AKIN, whereas most continued to use an increase in creatinine of ≥ 25% and/or ≥ 0.5 mg/dl (44.2 μmol/l) to diagnose CIN. This later definition is slightly anomalous as only those with pre-existing kidney disease (creatinine > 2.0 mg/dl) can have a greater than 0.5 mg/dl elevation in creatinine that is less than 25%. We have recommended that all CIN studies adopt the AKIN or RIFLE definition of AKI (Endre & Pickering (2010)).

We investigated whether a continuous variable measure of kidney function, the Relative Average Creatinine (RAVC), performed better than the RIFLE and AKIN categorical definitions as an outcome variable in AKI prevention or intervention trials. The RAVC is the integral of the area under the plasma creatinine curve above baseline creatine divided by the total time and baseline creatinine:

$$RAVC(\%) = \frac{100}{C_b t} \int_0^t (C(t) - C_b) dt$$

(9)

which in practice is calculated using the trapezoidal rule (Figure 3):

$$RAVC(\%) = \frac{100}{C_b(t_N - t_1)} \sum_{0 < n < N-1} \frac{(C_{n+1} - C_b) + (C_n - C_b)}{2} (t_{n+1} - t_n)$$

(10)

where *N* is the number of creatinine measurements.  
We created a population of 10,000 Virtual-In-Patients (VIPs) whose baseline creatinine and changes in GFR were based on real ICU populations. Placebo controlled trials were simulated by randomly assigning half the VIPs to treatments which ameliorated loss of renal

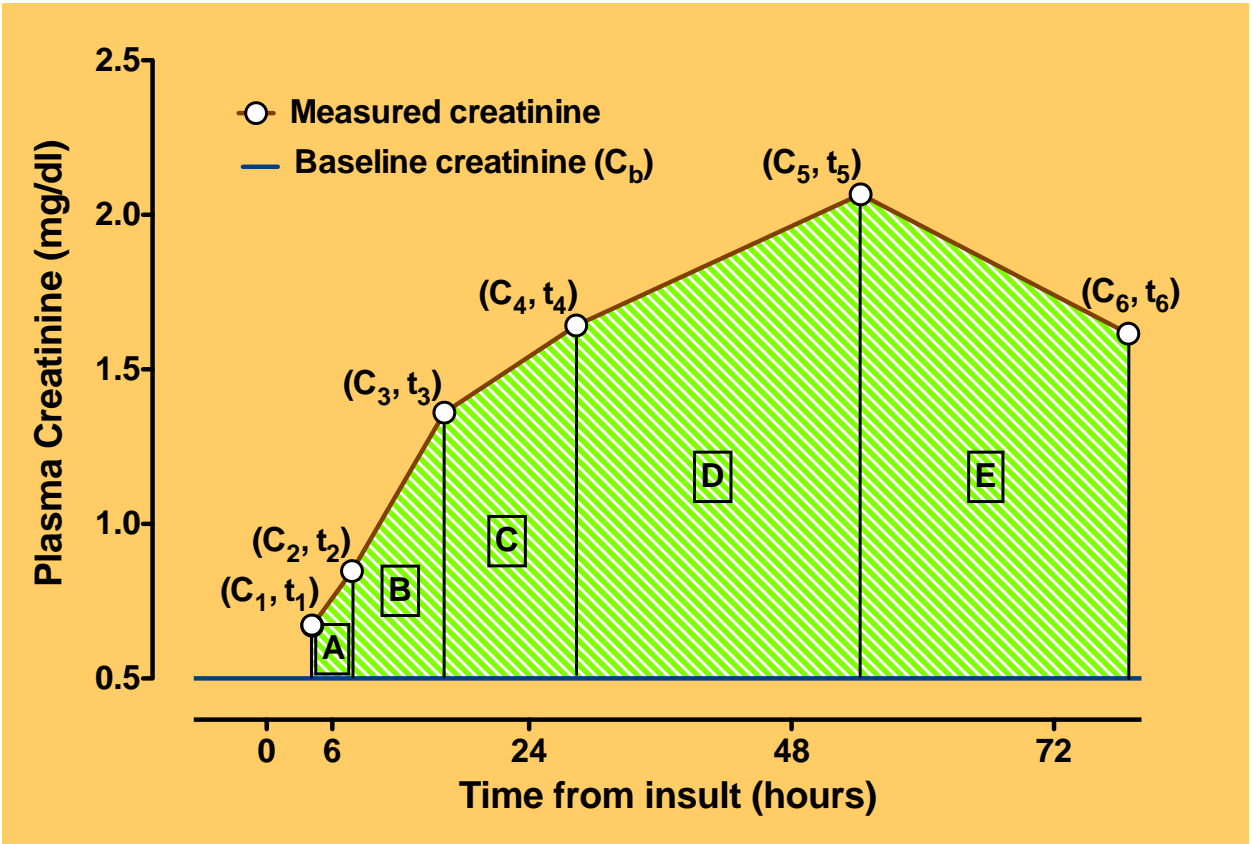


Fig. 3. The Relative Average Creatinine by the trapezoidal rule is the sum of the areas A to E divided by  $(t_6 - t_1)$ (following equation 10).

function (ie reduced the reduction in GFR). The more efficacious the treatment, the less the decrease in GFR. Creatinine profiles were calculated using equation 6 (Pickering et al. (2009)). AKIN, RIFLE and RAVC as outcome variables were compared. At low treatment efficacy, the categorical outcomes underestimated and at high treatment efficacy overestimated the effect of treatment. These effects were exaggerated when the population contained a high proportion of patients with more severe AKI. The RAVC, on the other hand, responded in an almost linear fashion across treatment efficacies. Importantly, when the efficacy was low it was best able to distinguish between placebo and treatment arms. The advantage of the RAVC over the categorical metrics is two fold, first it includes the effect of treatment on those patients who had mild kidney injury which in normal circumstances would not exceed the diagnostic threshold for AKI according to a categorical definition, but which may result in a small increase (eg 20-30%) in creatinine and, second, it measures function over a (pre-determined) time period. As discussed previously, the length of time creatinine is elevated is independently of the maximum elevation associated with mortality. The RAVC captures both severity *and* duration of injury and was used as the primary outcome in the EARLYARF trial, which was the first randomised control trial to use an injury biomarker to triage patients to placebo or high-dose erythropoietin (Endre et al. (2010)).

3.4 The baseline issue

All creatinine based definitions of AKI and the RAVC depend on knowing the normal, or “baseline”, plasma creatinine for each individual. For patients undergoing elective surgery

this is easily obtainable prior to surgery. However, about half of the patients entering the ICU have no previous record of plasma creatinine to serve as a baseline. For trials this requires a retrospective determination of renal function. The ADQI recommend assuming a normal (eg 75 ml/min) GFR for all these patients and “back-calculating” a plasma creatinine using the MDRD equation. Unfortunately, this has proved erroneous. We showed that in our VIP population and in an ICU population that this approach seriously overestimates the proportion of patients with AKI using either the AKIN or RIFLE definitions (Pickering & Endre (2010); Pickering et al. (2009)). Randomly assigning a baseline creatinine produced just as accurate results as back-calculation. In a population already with AKI the presence of patients with CKD was seen to be driving the overestimation (Bagshaw et al. (2009)). Using the emergency department creatinine as an alternative baseline underestimated AKI (AKIN) and lowered the sensitivity (Siew et al. (2010)).

In the EARLYARF trial we overcame this problem by using an adjudicated hierarchical approach to choose in each patient the measured plasma creatinine that best represented normal renal function. Outpatient plasma creatinine prior to admission were considered the most likely to represent true baseline function. Whilst CKD can be diagnosed over three months, up to twelve months appears to be a reasonable time period prior to admission in which to ascertain baseline creatinine as it reduces misclassification of AKI (Lafrance & Miller (2010)). Amongst patients with no pre-admission creatinine measurement, a post-discharge measurement is the next best option if it is stable. Increasing creatinine may be indicative of developing CKD. Hence, it is preferable that a post-discharge creatinine is within three months of the insult. As a last resort the lower of the first hospital or final hospital (when there is recovery) may be used. We have presented our recommended hierarchical approach in table 2. This differs from the earlier approach in that we now consider that for cardiac arrest and trauma patients where there is no baseline prior to admission available the first hospital sample is likely to be the best estimate of baseline function if it is measured close to the time of renal insult. In our experience this is less than 2-h for most cardiac arrest and trauma patients. For the creatinine to have increased considerably in this time frame the loss of GFR would have had to have been substantial.

### 3.5 Quantifying function in a dilute environment

Fluid resuscitation dilutes plasma creatinine concentrations, which in turn may lead to delayed diagnosis or severity underestimation. This may explain why the only successful AKI intervention in the ICU has been early consultation with a nephrologist (Mehta et al. (2002)). The effect of fluids may be estimated by adjusting plasma creatinine for fluid balance (Macedo et al. (2010)):

$$C_{adjusted} = C_{measured} \times \frac{\text{admission weight (kg)} \times 0.6 + \sum \text{daily cumulative fluid balance (L)}}{\text{admission weight (kg)} \times 0.6} \quad (11)$$

### 3.6 Injury meets function

Current evaluation of novel biomarkers of renal injury is largely confined to evaluation of their performance to predict increases in plasma creatinine which lead to a diagnosis of AKI according to RIFLE or AKIN. This runs the risk of missing significant injury because creatinine did not increase beyond the diagnostic threshold of 50% or 0.3 mg/dl. In a large series



Situation	Timing of baseline creatinine sample
1 Elective surgery	Prior to surgery
2 All	Pre-hospital outpatient or prior admission  Preferably this is between 7 and 90 days prior to admission. 7 days avoids a period which may reflect changing renal function. Less than 90 days is preferable because 90 days is the period usually used to diagnose CKD. Up to 365 days may be used if there is little likelihood of CKD having developed during that period.
3 Cardiac Arrest	First hospital  If a pre-hospital value is not available and the time between insult and the first measurement is short (< 2h). Within a short time frame the creatinine will not (yet) have become elevated.
4 Trauma	First hospital  If a pre-hospital value is not available and the time between insult and the first measurement is short (< 2h) and crush-injuries are not involved.
5	Post ICU discharge  Within 90 days of admission to avoid capturing the development of CKD.
6	Lowest of first hospital or final ICU

Table 2. Hierarchical determination of baseline creatinine

of experimental studies of nephrotoxic AKI biomarkers, serum creatinine and blood urea nitrogen (BUN) were the poorest predictors of histologically determined injury compared with numerous urinary biomarkers (Dieterle et al. (2010); Ozer et al. (2010); Vaidya et al. (2010); Yu et al. (2010)). In what may turn out to be a seminal publication Haase et al. (2011) demonstrated that across 10 studies patients with a positive NGAL, yet negative plasma creatinine, for AKI had worse outcomes (mortality, need for dialysis, and ICU length of stay) than those with both negative NGAL and negative creatinine.

Biomarker clinical utility is most often quantified by the area under the receiver operator characteristic curve (AUC or c-statistic, see Box 3.3). The AUC is crude estimation of the ability of the biomarker to distinguish between those with and without AKI. However, a high AUC does not necessarily imply clinical utility. Clinical utility depends on what alternative biomarkers there are, what treatments are available, and the risks and costs involved with false negatives or false positives. The calculation of the sensitivity, specificity and particularly the negative and positive predictive values at either an established cut-off from the literature, or a cut-off chosen for clinical reasons, or derived mathematically from the ROC. The latter is usually either the cut-off closest to a Sensitivity and Specificity of 1 or the Youden index.

Comparing AUCs between different studies is problematical. AUCs for AKI are highly dependent on the AKI definition. Typically a definition requiring greater injury (eg RIFLE sustained for 24-h, compared with an increase of 0.3 mg/dl within 48-h) will result in higher AUCs. Within a study when more than one biomarker is being measured they should be compared using the method of DeLong (DeLong et al. (1988)). One biomarker should not be described as “better” than another unless the difference between the two is statistically significant at  $p < 0.05$ .

Box 3.3. The Area Under the Curve (AUC)

The receiver operator characteristic curve (ROC) is a plot of sensitivity verse 1-specificity. An AUC of 1 means the biomarker always discriminates between patients with and without the disease (no false negatives and no false positives). An AUC of 0.5 is equivalent to a coin toss. Whilst an AUC of less than 0.5 means the reciprocal of the biomarker is diagnostic. Some statistics packages, however, will always express the AUC as greater than 0.5 by inverting the biomarker concentration where necessary. The AUC from a study is strictly speaking an estimate of the AUC of the population, therefore it should **always** be presented with appropriate confidence intervals (usually 95%). The 95% confidence interval is  $\pm 1.96$  times the standard error of a proportion:

$$\widehat{AUC} - 1.96\sqrt{\widehat{AUC}(1 - \widehat{AUC})/n} \text{ to } \widehat{AUC} + 1.96\sqrt{\widehat{AUC}(1 - \widehat{AUC})/n}$$

where  $n$  is the sample size and  $\widehat{AUC}$  the estimated AUC. This equation is adequate for sample sizes  $> 30$ , but for smaller sample sizes a bootstrapping should be used. Only an AUC for which the lower limit of its 95% confidence interval is greater than 0.5 may be described as diagnostic (or prognostic).

Figure 4 is an example of a ROC from the EARLYARF trial (Endre et al. (2011)). It shows the ability of NGAL to diagnose AKI when the sample was taken between 12 and 36 hours following renal insult. The AUC lower limit of the 95% confidence interval, 0.62, is greater than 0.5, therefore it is diagnostic.

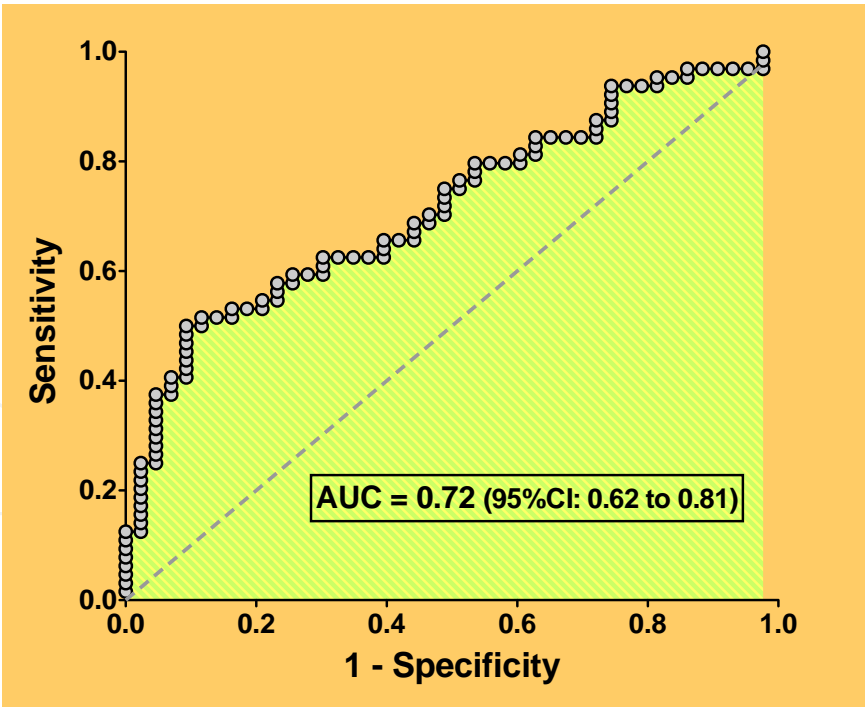


Fig. 4. An example of a receiver operator characteristic curve

It is anticipated that panels of biomarkers will be needed to diagnose AKI in heterogeneous populations with multiple AKI aetiologies. Attempts to assess a panel of biomarkers usually involve logistic regression models with two or more biomarkers measured at the same time point. The EARLYARF trial has demonstrated that the efficacy of any one particular biomarker is very much time dependent, and that each biomarker has its own “window of opportunity” during which it has diagnostic utility (Endre et al. (2011)). Logistic regression models are not a suitable approach for assessment of biomarker panels because of this. Until we know the time courses of biomarkers much better, an “either and/or” approach is likely to yield greater results. For example, in an ICU population either an elevated GGT and/or an elevated NGAL may be considered diagnostic.

There is a need to move away from assessing injury biomarkers only in relation to function. All trials should report mortality data, even if the incidence is too low for statistical analysis. This will facilitate later meta-analysis of the relationship between a biomarker and mortality. The EARLYARF trial paved the way for future trials of early intervention based on an elevated biomarker. Since the inception of that trial new biomarkers with rapid assay turn-around (necessary in an early intervention trial) have become available. Plasma and urinary NGAL, and KIM-1 head the list along with urinary Cystatin C and GGT which are already routinely available in many hospital laboratories. It is anticipated that the next early intervention trial will use one or more of these biomarkers.

### **3.7 Quantifying injury in a dilute environment**

Changes in GFR and water handling will change urinary biomarker concentrations independent of injury. Normalising biomarkers to urinary creatinine has been proposed to account for these effects. This process also amplifies the signal soon after a decline in function (Waikar et al. (2010)). This may be advantageous in an early intervention trial if the threshold for intervention is set high enough, but it may distort the analysis of biomarker performance in a biomarker performance study. Whilst there is no consensus on whether biomarkers should or should not be normalised to urinary creatinine we recommend reporting both normalised and non-normalised results.

## **4. Practical considerations**

Table 3 presents a summary of practical measures to take into account when planning AKI epidemiology, biomarker efficacy studies or prevention or intervention trials.

### **4.1 Epidemiology**

Most epidemiological studies are retrospective and face the difficulty of missing data, particularly baseline creatinine data. This was discussed in section 3.4. It is important to quantify the severity of AKI, as more severe AKI is likely to have greater long term impact on health resources. Where possible, data on the duration of AKI as well as severity should be captured as this is an independent predictor of outcome. Three areas of epidemiology lack data. First, there are comparatively few good epidemiology studies in countries other than in Europe, North America or Australasia (Cerdeira et al. (2008)). The incidence of AKI in countries with large populations such as China, India, Indonesia, Nigeria has significance beyond their own borders. Some countries have numbers of particular AKI aetiologies which, if well studied, could provide useful data world-wide. For example, with anti-retroviral therapy

reducing mortality in HIV patients, the incidence of AKI in this population may be increasing (Lopes et al. (2011)). In South-East Asia, AKI is a prominent complication of paraquat (a contact herbicide) self-poisoning (Roberts et al. (2011)). In both these cases epidemiology in countries with relevant populations would help identify the extent of risk in other countries where incidence of HIV or paraquat poisoning is relatively low. Second, there are few studies that have investigated AKI on CKD (Ali et al. (2007)). The growing world wide epidemic of CKD demands epidemiology that quantifies the additional risk CKD has for AKI and the effects of AKI on the progression of CKD. Third, there are few studies on CKD induced by AKI that have comparable control groups of hospitalised non-AKI patients (Coca et al. (2009)).

#### 4.2 Biomarker studies

It is important to report the timing of sampling for biomarker measurements in relation to putative onset of injury. As we have seen, different biomarkers are likely to have different time profiles. A weakness of many studies is that samples are taken only at one or two time points, and even then they may be outside the temporal “window of opportunity” of the biomarker, possibly rendering the study results misleading. Temporal profiles are available for many biomarkers following the time of injury which can be used to plan sampling (eg Endre et al. (2011)). For novel biomarkers, frequent sampling will be necessary to establish their time course. The first 12 hours following injury are crucial as this is the window for early intervention. There is also a need to discover and assess injury biomarkers with slightly longer (~24 to 36-h) time courses as samples may not be able to be taken earlier in many critically ill patients. Very few studies have measured biomarker profiles beyond a two or three days, yet there is tantalising evidence that some biomarkers (eg KIM-1) may become elevated during a repair phase which in some patients may not begin until several days following injury.

The choice of outcome variable is particularly important. Despite the caveats discussed with respect to using creatinine changes as a surrogate for change in GFR and the issue of comparing injury to function, we are still in a period where a functional definition of AKI is likely to be the outcome of choice for biomarker studies. Use of non-standard AKI definitions are unhelpful and should be avoided in preference to the AKIN, RIFLE and, potentially, new KDIGO AKI definitions. The duration as well as severity of creatinine increase is also of importance. The AKIN definition requires only one time point at which plasma creatinine may be elevated. This allows for mild and transient changes in function to equally be recorded as AKI. We have shown that transient increases in creatinine are associated with injury biomarkers (Nejat et al (2011b)), although not to the extent of more sustained increases. We recommend evaluating biomarkers in relation to duration of increase of creatinine as well as the increase itself.

Most biomarker studies are underpowered. The number of participants are rarely calculated *a priori*. Typically we want to ascertain if a biomarker is clinically useful. At a minimum we would want an AUC of 0.7, more likely 0.85 or greater. Given an expected incidence (proportion),  $I$ , in the population, how many participants ( $N$ ) will we need in the study? Hanley and McNeil provide a general equation which we may adapt as we are interested in the difference between the true AUC and 0.5 (Hanley & McNeil (1982)):

$$N = \frac{1}{I} \left[ \frac{0.5773Z_{\alpha} + Z_{\beta} \sqrt{0.1667 + \frac{AUC}{2-AUC} + \frac{2AUC^2}{1+AUC} - 2AUC^2}}{AUC - 0.5} \right]^2 \quad (12)$$

where  $Z_\alpha$  is the Z coefficient for a Type I error and  $Z_\beta$  for a Type II error. In order to detect a true AUC of 0.7 with  $p < 0.05$  ( $Z_\alpha = 1.96$  (two sided)) and at 80% power ( $Z_\beta = 0.84$ ) in a population with a 30% incidence 212 participants would be needed. A population with a much lower incidence, say 5%, would need a much greater sample ( $N = 1269$ ). If we were comparing a known biomarker with an AUC of 0.7 and wanting to know if another biomarker was better (AUC of 0.8 or more), then at  $p < 0.05$ , 80% power and 30% incidence we would need 676 participants. This highlights the importance of knowing *a priori* the AKI incidence, what a clinically relevant AUC would be, and choosing a sample size appropriately.

In larger studies it is possible to assess the biomarker's ability to predict premature death or need for renal replacement therapy. In both cases, it is important to assess the risk relative to known risk factors. A useful technique is to use logistic regression models and compare a model of known risk factors with one with the same risk factors plus the biomarker. The integrated discrimination improvement (IDI) is a useful technique which, along with the AUC, allows for analysis of biomarker performance across the whole range of biomarker concentrations (Pencina et al. (2008)).

Studies in heterogeneous populations with multiple aetiologies and timing of injury are particularly difficult. Given the recent findings with respect to biomarker dependency on pre-existing renal function it is important that study size is sufficient to allow for cohort analysis, in particular cohorts of CKD and sepsis. In studies with CKD patients it is important to measure urinary albumin. Albumin is a possible AKI biomarker in its own right, but also competes for reabsorption in the proximal tubules with cystatin C and NGAL, IL-18 and possibly other markers (Nejat et al (2011a)).

The quality of reporting of biomarker studies varies widely. The Standards of Reporting of Diagnostic Accuracy (STARD) statement provides minimum standards and is worth referring to in the planning of the study (Bossuyt et al. (2003)). Biomarker concentrations should almost always be presented as median with inter-quartile range as they are usually non-normal distributions. With the jury still out on "normalising" urinary biomarkers to urinary creatinine we have recommended that both normalised and non-normalised results be presented.

#### 4.3 Clinical trials

Clinical trial design follows one of three paradigms: (i) Prevention, namely treatment prior to a procedure which may cause injury; (ii) Early intervention following a raised biomarker, but prior to observation of functional change (eg Endre et al. (2010)); (iii) Late intervention following an elevation of creatinine (Pickering & Endre (2009c); Pickering et al. (2011)). Whilst it may be anticipated that if successful prevention or early intervention treatments are developed there will be less need for late intervention treatments, late intervention treatments will still be needed either where prevention or early intervention fails, or where it is not possible to administer it. Injury biomarkers will play a role in all three paradigms. Some are being identified as risk factors, prior to a procedure (Bennett et al. (2008)), whilst others will be elevated early enough after injury to allow early intervention, finally others will serve as outcome variables. As with plasma creatinine as an outcome variable, analogous to the RAVC, it is likely that a continuous measurement of the biomarker over a pre-specified duration will serve best as an outcome variable.



	Epidemiology	Biomarker Studies	Clinical Trials
1 Use a continuous outcome variable (eg RAVC)	n/a	possibly	✓
2 Use RIFLE, AKIN or KDIGO definition as outcome variables (including for CIN trials)	✓	✓	✓
3 Use a hierarchical-adjudicated approach to determine baseline creatinine	✓	✓	✓
4 Include hard outcomes (RRT, Death)	✓	✓	✓
5 Include plasma cystatin C as an outcome	n/a	✓	✓
6 For subcohort analysis use KDIGO guidelines for CKD staging (Levey et al. (2003))	✓	✓	✓
7 Measure 2 to 4-h creatinine clearance	n/a	✓	✓
8 Use corrected $\Delta GFR(\%)$ for RIFLE classes R or F (Pickering & Endre (2009a))	n/a	✓	✓
8 Apply treatment within the time window following insult determined by experimental &/or pilot data	n/a	n/a	✓
9 Measure biomarkers within the time window following insult determined by experimental &/or pilot data	n/a	✓	n/a
10 Report urinary biomarker concentrations & concentrations normalised to urinary creatinine	n/a	✓	n/a
11 Report median and inter-quartile range for biomarker concentrations	n/a	✓	n/a
12 Report times and duration for which plasma outcomes were determined	✓	✓	✓

Table 3. Practical considerations

5. Conclusion

The discovery of many early biomarkers of kidney injury has begun to shift the paradigm from assessment of change in filtration function to measurement of direct injury. Lest we throw the baby out with the bathwater we must recognise the complementary role of assessing both renal injury and renal function. Our techniques for assessing injury are still in their infancy, but show much promise. Our techniques for assessing function have a long history, yet, as we have shown, have room for improvement. In particular, we are learning to use appropriate surrogates of function, categorical or continuous, depending on the type of study we are conducting. We await the development of rapid, near “real-time” measures of function which are the missing link in enabling us to understand the temporal profile of injury in relation to functional change. We also look forward to an era of clinical trials which utilise the injury biomarkers discovered to date so as to properly test of drugs found to be effective soon after injury in experimental models.

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## **Basic Nephrology and Acute Kidney Injury**

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The first section of the book covers the basics of nephrology and second section focuses on acute kidney injury. This easy to reference text examines the physiological and biochemical aspects of renal diseases - all in one convenient resource. Experts in the field discuss topics of increasing concern in nephrology including newer methods of assessing renal function. The field of acute kidney injury in nephrology is a rapidly evolving one with research translating into clinical guidelines and standards. This text brings together experts to provide an authoritative reference for management of AKI in various clinical settings. Pregnancy related AKI is an important entity which has also been discussed in detail. The recent advances in the field of critical care AKI have been incorporated as well and help the reader to update their knowledge.

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