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LASTING LEGACY IN INTENSIVE CARE MEDICINE

# Acute kidney injury

Marlies Ostermann[1*], Rajit K. Basu[2] and Ravindra L. Mehta[3]



The understanding of acute kidney injury (AKI) has evolved from the perception of a single disease to a multi-factorial syndrome with a complex and varying pathophysiology and prognosis. Before 2004, more than 50 different definitions of AKI (or 'acute renal failure') were in use and the reported incidences, prevalences and outcomes were very variable. The publication of the 'Risk, Injury, Failure, Loss, and End-stage kidney disease' (RIFLE) criteria in 2004, followed by the AKI Network (AKIN) classification in 2007, and the current AKI Kidney Disease Improving Global Outcomes (KDIGO) consensus classification in 2012 [1] have facilitated epidemiological studies showing a high prevalence of AKI worldwide, a link between AKI severity and outcomes, a high risk of short- and long-term complications, including chronic kidney disease (CKD) and major economic consequences [2, 3] (Fig. 1).

AKI diagnosis and staging currently rely on a rise in serum creatinine (SCr) and/or decrease in urine output without consideration of the various aetiologies, sites and severity of injury, timing and course of disease and the response to therapy [4]. To compensate for these limitations, descriptors are often added, for instance, 'subclinical AKI' (tubular injury without a SCr rise or with a SCr rise not meeting AKI criteria), 'transient, sustained or persistent AKI' (based on the duration of SCr elevation), 'community' or 'hospital acquired' AKI, and 'recovered AKI' (SCr decrease after peak). However, there are no agreed definitions for these terms [4].

## Mechanisms contributing to AKI

Our contemporary understanding of the mechanisms involved in AKI appreciates the heterogeneity of disease. Different nephrotoxic triggers elicit divergent responses within the kidney at genetic, molecular, cellular and functional level, resulting in distinct patterns of injury [5]. For instance, volume depletion leads to activation of metabolic pathways consistent with starvation (such as gluconeogenesis, lipid metabolism) as well as anti-inflammatory molecules and predominantly affects the inner medulla. In contrast, ischaemia stimulates genes related to inflammatory, coagulation and epithelial repair pathways with most changes seen in the outer medulla. Despite a similar SCr rise, there is often little overlap of activated genes between different AKI models. The specific characteristics of different nephron segments, including heterogeneity in metabolic pathways and ability to activate cellular defence mechanisms account, at least in part, for the variable regional susceptibility of tubular cells to injurious stimuli. The patterns of injury are impacted further by associated comorbidities and components of clinical management. Research in sepsis-associated AKI presents another apt example of the evolution in knowledge [6]. Once simplified into a bipartite model of 'ischemia to the glomerulus' and 'tubular necrosis', it has expanded into a sepsis 'portfolio' of injury, inclusive of (but not limited to): (a) glomerular capillary vasomotor instability, (b) microcirculatory dysfunction, (c) mitochondrial dysregulation, (d) inflammasome perturbations from endocrine and paracrine cytokine mediators, (e) disruption in pathogen-associated molecular activity receptors, (f) tubular injury; (g) interstitial inflammation; (h) aberrant autophagy and efferocytosis of important repair molecules, and (i) impact of associated comorbidities and clinical strategies used to mitigate the insult (i.e. fluids and catecholamines). An important revelation of clinical and experimental studies is the association between AKI and new-onset CKD [3, 7]. Maladaptive repair and interactions between injured proximal tubular cells and fibroblasts appear to play a role. These insights have improved our understanding and offer targets for potential future therapies.

*Correspondence: marlies.ostermann@gstt.nhs.uk
[1] Department of Critical Care, King's College London, Guy's & St Thomas' NHS Foundation Hospital, London SE1 7EH, UK
Full author information is available at the end of the article

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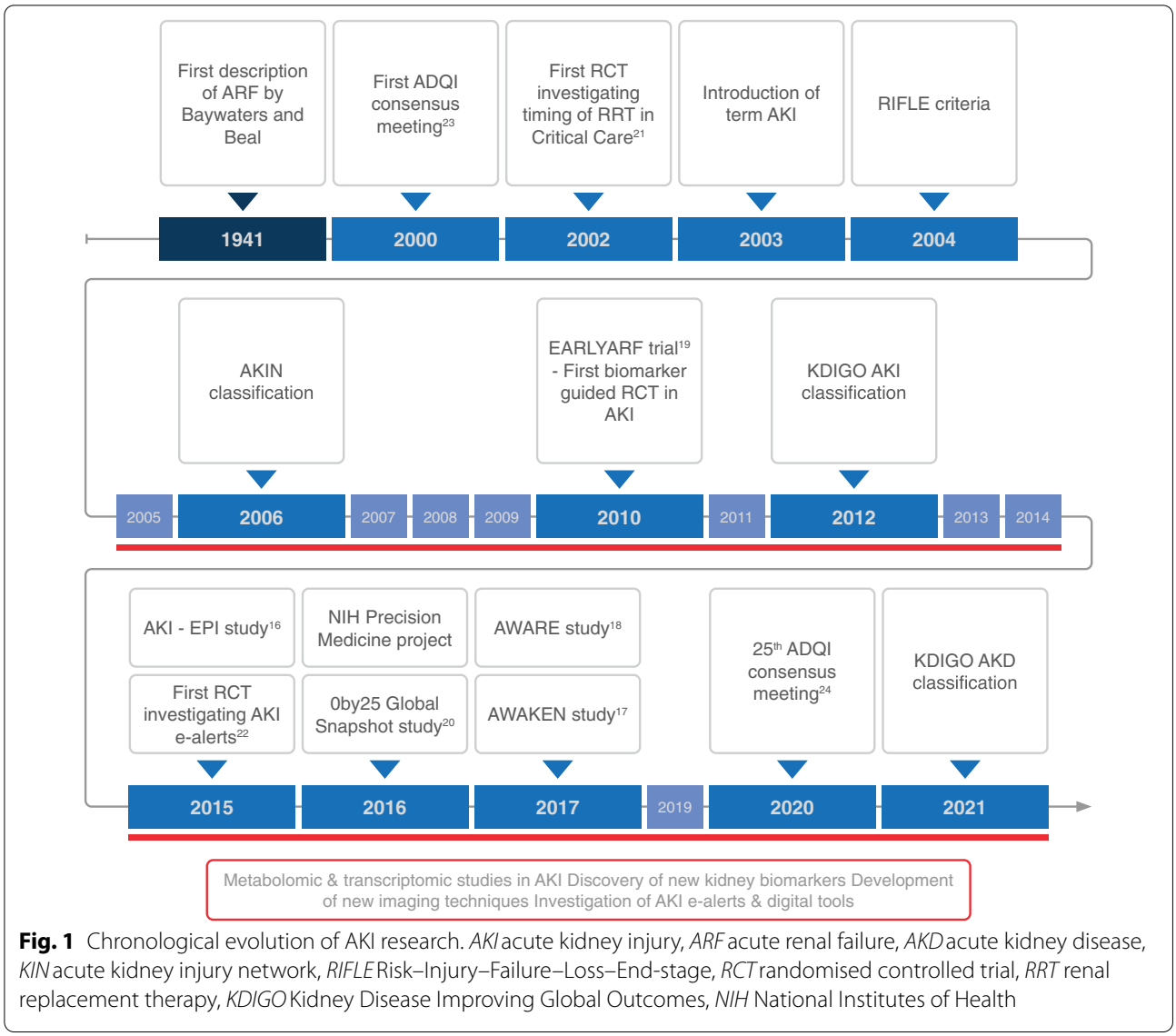


**Fig. 1** Chronological evolution of AKI research. *AKI* acute kidney injury, *ARF* acute renal failure, *AKD* acute kidney disease, *KIN* acute kidney injury network, *RIFLE* Risk–Injury–Failure–Loss–End-stage, *RCT* randomised controlled trial, *RRT* renal replacement therapy, *KDIGO* Kidney Disease Improving Global Outcomes, *NIH* National Institutes of Health

## Emerging trends

### Biomarker-based characterisation

The discovery of kidney damage biomarkers (e.g. NGAL, KIM-1, IL-18, TIMP-2, IGFBP7 and CCL14) and alternative functional markers (e.g. Cystatin C and Proenkephalin) has provided insight into the potential aetiology, pathophysiology and prognosis of AKI [8]. For instance, evidence from about 4,000 patients revealed that 15–20% had elevated NGAL levels without a SCr rise. This was associated with a two-to-threefold increased risk of death or need for renal replacement therapy (RRT) compared to patients without a SCr or NGAL rise [9].

### AKI subphenotypes

Subphenotyping identifies subgroups of patients with different biological mechanisms, treatment responses or prognosis [10]. Using latent class analysis of clinical and biomarker data from the first 48 h in intensive care unit (ICU), Bhatraju et al. analysed 1800 patients of whom 794 had AKI [11]. They identified two independent populations: Subphenotype 1 was characterised by a low ratio of angiopoietin (Ang) 2/Ang1 and soluble tumour necrosis factor receptor (sTNFR) 1 and signified a hypo-inflammatory state. Mortality was lower compared to subphenotype 2 which had high Ang2/Ang1 ratios and higher sTNFR-1 and represented a hyper-inflammatory state with increased vascular permeability. These findings were replicated in 800 patients enrolled in a different

sepsis trial showing that mortality and dialysis need were higher in patients with subphenotype 2. Similarly, a post hoc analysis of the Finnish Acute Kidney Injury (FiNNAKI) study of patients with sepsis-associated AKI identified two subphenotypes with subphenotype 2 having elevated levels of inflammatory and endothelial markers, lower short-term recovery and a higher 90-day mortality [12]. The identification of these different subphenotypes underpins the change in our perception of AKI as a 'single disease' to AKI being a complex syndrome (Supplementary Fig. 1).

### AKI across the lifespan

Neonatal and paediatric AKI have emerged as important paradigms of critical care nephrology. Multi-centre studies including the AWARE and AWAKEN study have revealed unique, discernible AKI phenotypes in children different from adults [13–15] (Fig. 1). Even though AKI demonstrates a synergism with adult comorbidities on patient outcome, AKI in children with both unique comorbid conditions (e.g. inborn errors of metabolism) and in those without any medical history demonstrates the independent contribution of AKI with host outcome. Further, the effects of premature birth on kidney maturation and the impact of a single AKI episode during kidney development on short- and long-term outcomes remain incompletely understood. Finally, the influence of sex, nutrition and biological development (growth) throughout childhood and puberty on the risk and prognosis of AKI has yet to be fully characterised [14]. The kindle of injury which may start in the neonatal period of life can build on itself and manifest in a patient throughout life, being full ablaze in adulthood with higher risks of AKI related morbidities (e.g. CKD and cardiovascular events).

### Prognosis

It is now widely accepted that AKI survivors remain at risk of serious long-term renal and non-renal complications and warrant follow-up. As the data in children underscore, even following a single episode, AKI is a longitudinal, life continuum disease process. "Return of SCr to baseline" after an episode of AKI can no longer be viewed as "full renal recovery". "Acute kidney disease" has evolved as a construct, emphasising the need for follow-up [4].

## Looking to the future

AKI is a ubiquitous syndrome capable of affecting all patients regardless of age or co-morbidity profile. A deeper understanding of the complex pathophysiology of AKI, including adaptive and maladaptive repair, and identification of subphenotypes offer opportunities for new therapies and reno-protective strategies, supported by tools to measure kidney function more accurately and in real time. AKI alerts and machine learning models in electronic health records should improve earlier identification of patients while the availability of telemedicine, digital health tools and improved awareness of the disease can support follow-up of patients even in remote settings.

**Supplementary Information**
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**Author details**
[1] Department of Critical Care, King's College London, Guy's & St Thomas' NHS Foundation Hospital, London SE1 7EH, UK. [2] Ann & Robert Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL, USA. [3] University of California, San Diego Health Sciences, San Diego, CA, USA.

**Declarations**

**Conflicts of interest**
MO, RKB and RLM report no conflict of interest related to the content of the manuscript.

## Publisher's Note



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