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Individualized AKI After Care

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Abstract

Purpose of review: To summarize the current evidence around the impact of individualizing patient care following an episode of acute kidney injury (AKI) in the intensive care unit (ICU).

Recent Findings: Over the last years evidence has demonstrated that the follow-up care after episodes of AKI is lacking and standardization of this process is likely needed. While this is informed largely by large retrospective cohort studies, a few prospective observational trials have been performed. Medication reconciliation and patient/caregiver education are important tenants of follow-up care, regardless of the severity of AKI. There is evidence the initiation and/or reinstitution of renin-angiotensin-aldosterone agents may improve patient's outcomes following AKI, while they may increase the risk for adverse events, especially when reinitiated early. Additionally, 3 months after an episode of AKI, serum creatinine and proteinuria evaluation may help identify patients who are likely to develop progressive chronic kidney disease over the ensuing 5 years. Lastly, there are emerging differences between those who do and do not require renal replacement therapy (RRT) for their AKI which may require more frequent and intense follow-up in those needing RRT.

Summary: While large scale evidence-based guidelines are lacking standardization of post-ICU-AKI is needed.

Keywords

Acute Kidney Injury; long-term follow-up; chronic kidney disease; renal replacement therapy

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Introduction

Acute Kidney Injury (AKI) is a common clinical syndrome in critically ill patients and is associated with increased morbidity, mortality, and cost of care [1, 2]. While consensus guidelines for the care of AKI are mainly supportive, a tremendous variation in the care provided to those with AKI exists [3, 4]. Given this variation in inpatient care, it should not be surprising that similar differences exist in the care of survivors of AKI following discharge. Unfortunately, there are no consensus guidelines around the care of patients following an episode of intensive care unit (ICU) associated AKI. However, there is emerging data to suggest that specific post-AKI care, perhaps delivered via nephrologists can improve patient outcomes, leading some to suggest that certain standard practices should be established [5]. This review seeks to describe the data behind and best ways to implement personalized AKI aftercare.

Who needs acute kidney injury aftercare

Health services will treat an increasing number of critically ill survivors [6]. Among them, over half will experience AKI, which is associated with chronic kidney disease (CKD), end-stage kidney disease (ESKD), and death [7].

Among survivors of critical illness, who may AKI aftercare benefit? The latest systematic review showed a 3-fold increase in CKD with any AKI [8], and up to 9-fold with stage 3 AKI (a tripling of baseline serum creatinine, or 24 hours of oligo-anuria) [8]. In addition, non-recovery of kidney function has repeatedly been shown to increase the risk of subsequent CKD, worsen survival [9, 10], and better predict the risk of CKD than AKI severity itself [11, 12]. Slow recovery of kidney function after AKI may also present an additional risk factor for CKD [13]. Furthermore, proteinuria has been studied as a risk factor for CKD development after AKI and included in risk prediction models of CKD [14]. Combined, these clinical risk factors have the potential to help clinicians target AKI aftercare to the highest risk patients.

James et al developed and validated a risk prediction model for advanced CKD (estimated glomerular filtration rate (eGFR) <30ml/min/1.73m^2) after AKI [11]. Although attractive, such predictive models need to be tested prospectively. In addition, predicting advanced CKD may miss patients with smaller but still relevant declines in kidney function after AKI episodes.

There are several characteristics of ICU survivors that make stratification for inclusion for AKI aftercare challenging. Studies have relied on serum creatinine-based measurements after AKI episodes to diagnose CKD. The confounding effect of acute skeletal muscle wasting of critical illness on serum creatinine results in an overestimation of kidney function at discharge [10]. Consequently, planning of AKI aftercare based on hospital discharge values can result in a missed opportunity for many patients. Alternate functional markers such as cystatin C, correlate better with long term outcomes [15, 16]. Similarly, TIMP2•IGFBP7 improved the risk stratification of identifying ICU survivors who died or required dialysis 1 year after discharge [17].

In conclusion, follow-up care should be offered to all patients who have suffered AKI. Patients with elevated baseline creatinine, with incomplete kidney recovery or with proteinuria could be prioritized for follow-up if resources are limited.

What is acute kidney injury aftercare?

Various specialities are involved in the initial management of AKI and few AKI survivors receive dedicated nephrology follow-up [18, 19]. In the United States, only 9% of patients were referred to nephrology before experiencing recovery, death or dialysis [18]. Of note, 18–41% of Canadian patients who received acute dialysis for AKI were followed by nephrologists after discharge [20, 21]. The rate of nephrology follow-up has not increased since the recommendation of the KDIGO guidelines to provide follow-up 3 months after AKI [20].

These observations raise the question whether nephrologists can improve the outcomes of AKI survivors. One large retrospective study has shown that after AKI requiring acute dialysis, nephrology referral is associated with lower mortality at 2 years (8.4 vs. 10.6 per 100-patient years, HR 0.76, 95% CI: 0.62–0.93). The benefit was larger in patients with de novo kidney disease not previously managed by nephrologists [21]. In addition, a meta-analysis concluded potential long-term survival benefits with nephrology follow-up, however the evidence was of low quality. These results need to be confirmed in randomized controlled trials (RCT) [22] and a pilot RCT is under way (FUSION, ClinicalTrials.gov NCT02483039).

There are no current guidelines to determine which patients should be followed by nephrologists or primary care providers. Those at high risk of developing severe CKD could be targeted, as identified by James and colleagues [11]. Importantly, information about AKI is often not communicated at discharge, with less than half of discharge summaries document the presence of AKI [23, 24]. Communication should not only include the presence of AKI, but its cause, severity, degree of kidney recovery, changes to medications and recommended follow-up for primary care providers. Information for patients and primary care providers can be found on the “Think Kidneys” Web site (www.thinkkidneys.nhs.uk).

When should acute kidney injury aftercare be provided?

There is little new evidence to inform clinical practice guidelines on when best to review patients after AKI. Serum creatinine levels at discharge could inform the timing of future creatinine measurements. Patients with complete kidney recovery have a lower risk of CKD but should still have creatinine measurements performed since the excess risk of CKD after AKI can persist for at least 10 years [25, 26]. However, creatinine measurements may not be needed within three months in this setting. Encouragingly, ICU follow-up clinics are becoming embedded within healthcare systems. Often occurring around 3 to 6 months after ICU discharge, this timepoint could provide an appropriate juncture for clinicians to review kidney function where the impact of critical illness associated muscle wasting is less severe and therefore creatinine based eGFR assessments more reliable.

Features of acute kidney injury aftercare

The elements of care associated with improved outcomes in AKI survivors are still poorly characterized. It remains to be determined whether closer monitoring of kidney function and proteinuria, blood pressure control or other cardiovascular risk factors is beneficial.

Estimated GFR and electrolytes

The optimal frequency, duration and method of eGFR measurements after an episode of AKI is unknown (Table 1). Both baseline and discharge serum creatinine are associated with future CKD [11], and discharge creatinine best predicts the risk of subsequent CKD [11, 12]. The optimal duration of follow-up is unknown, even if there is apparent complete recovery. Some guidelines suggest a follow-up every 2–3 years [27] and potentially for at least 10 years, based on the results of Sawhney and colleagues [26]. There is very limited data on cystatin C based GFR measurements. A study in cirrhotic patients showed that in a time-varying competing risk analysis, cystatin C levels at the time of enrollment, as well as the Model for End-Stage Liver Disease (MELD) score and number of AKI episodes, independently predicted the risk of CKD over 12–18 months [28]. There is a need for future research in this field. In the meantime, the frequency and duration of follow-up could be personalized based on baseline creatinine, AKI severity and duration, the degree of kidney recovery and expected survival.

Proteinuria

Patients who suffer from AKI are more likely to develop or worsen their proteinuria [29, 30]. Unfortunately, proteinuria is unfrequently measured after AKI, with less than a third of patients being tested [14, 31]. An *a priori* planned analysis from two prospective cohort studies has shown that AKI is independently associated with an over 10% increase in urine protein-to-creatinine ratio (UPCR) [30]. Additionally, more severe AKI has been associated with greater proteinuria [29, 30].

One multicenter prospective study showed that proteinuria, rigorously quantified 3 months after AKI, is one of the strongest risk factors for kidney function deterioration, suggesting a potential mechanism linking AKI and CKD (Table 1) [14]. After multivariate adjustment, neither the presence of AKI nor its severity was associated with kidney disease progression. Limitations include absence of data regarding proteinuria before hospitalization and serial proteinuria measurements after AKI. According to some studies, models without albuminuria could still accurately predict severe CKD at one year [11, 26]. However, in these studies, albuminuria levels were semi-quantified, often missing, or measured at inconsistent time points.

Quantification of proteinuria after hospitalized AKI should be used more frequently since it has prognostic information that is additive to serum creatinine. It may be premature to recommend routine monitoring of ACR within 3 months after discharge among all AKI survivors. Future work to characterize the mechanism of this proteinuria is needed to determine whether this represents a modifiable risk factor in the AKI to CKD pathway, and to determine whether reducing proteinuria after AKI could delay kidney disease progression.

Blood pressure

Retrospective data suggest that AKI patients are more prone to develop hypertension and that severe hypertension, defined as a systolic blood pressure higher than 180 mm Hg, could be a modifiable risk factor to reduce the risk of recurrent AKI (Table 1) [32, 33].

Cardiovascular events, stroke and atrial fibrillation

In a meta-analysis, AKI was associated with an increased risk of heart failure, acute myocardial infarction, and stroke (Table 1) [34]. Other large subsequent studies have confirmed the same association for heart failure [35, 36]. In a retrospective cohort study of patients requiring dialysis for AKI, the risk of subsequent atrial fibrillation (AF) was increased compared to a non-AKI cohort (Table 1) [37]. AKI could contribute to atrial remodeling due to increased FGF-23 levels, which would then promote AF [38]. Additional studies are needed to confirm these findings and further elucidate mechanisms of increased cardiovascular risk after episodes of AKI.

Diabetes

In the Taiwanese Registry, AKI patients who were weaned off dialysis had a higher incidence of new-onset diabetes (Table 1) [39]. These results need to be confirmed but suggest that severe AKI may affect long-term metabolic regulation.

In conclusion, eGFR at discharge and after 3 months, as well as ACR and eGFR measured 3 months after AKI can provide crucial information on the risk of subsequent deterioration of kidney function. While the occurrence of AKI and its severity are associated with progressive CKD, the strengths of associations are not as crucial after considering urine ACR, eGFR, demographics, and traditional CKD risk factors at 3 months after discharge [14]. The optimal frequency of follow-ups after AKI is currently unknown and could be tailored to the patient's risk of progressive CKD and expected survival. Lifelong cardiovascular risk factors assessment should be offered to most if not all patients.

Specific acute kidney injury aftercare interventions

Optimal care after AKI includes the identification and management of key modifiable risk factors for which there is scant data to guide evidence-based management (Table 2).

Teaching about AKI and non-pharmacological options

Patient education remains a challenge regarding AKI and its future consequences on CKD and overall health. In a survey of AKI-related awareness and knowledge, 80% of patients were unaware that they had AKI and 53% that they had a "problem with their kidneys" [40]. Communication of future risk of CKD to AKI survivors allows promotion of healthy behaviors and improved management of CKD and cardiovascular risk factors. We are unaware of any specific data on the role of exercise and nutrition after AKI. One feasibility study has shown that addressing AKI outcomes associated with obesity is possible [41].

Avoidance of nephrotoxins and medication reconciliation

Patient education after AKI should also include information regarding avoidance of NSAID use. Unfortunately, nephrotoxins are still frequently used after AKI. Among 826 AKI survivors, 19% of them were using a NSAID regularly [42]. If kidney recovery occurs, medications should be adjusted. For example, in patients with diabetes, this may include the re-initiation of metformin or sodium-glucose co-transporter 2 inhibitor which can improve long-term kidney outcomes.

Blood pressure management

There are currently no optimal target BP levels following AKI. BP levels should be tailored according to patients' age and comorbidities, including proteinuria. Additional trials are required to assess optimal target BP levels and BP medications after AKI to prevent CKD progression.

Renin-angiotensin-aldosterone system (RAAS) inhibitors

Several studies have suggested that the benefits of RAAS inhibition after AKI seems to outweigh their risks in terms of CKD progression [25] and mortality [43, 44] (Table 2). Before initiating a RAAS inhibitor prior to discharge after AKI, clinicians need to consider their potential benefit for cardiovascular outcomes and BP control, while balancing these against the risk of hyperkalemia and recurrent AKI.

Statins

According to retrospective data, the use of a statin did not reduce cardiovascular events [45] or the risk of CKD [25]. Further RCTs should evaluate the use of statins in AKI survivors to determine if long-term kidney function and mortality could be improved. The KDIGO guidelines recommend that adults 50 years or older with CKD (GFR <60 ml/min/1.73 m^2) should be prescribed a statin [46].

In conclusion, there is no high-quality evidence showing that interventions can lower morbidity and mortality following AKI. Communication for AKI survivors should include future risk of CKD as well as avoidance of nephrotoxins and the importance of cardiovascular risk factor management.

Specific considerations for the aftercare of patients who received renal replacement therapy

Follow-up of patients after an episode of dialysis requiring AKI (AKI-D) presents unique features and challenges. There are no wide-scale validated evidence-based care plans for AKI-D patients [5, 47]. Simply applying ESKD care plans to those with AKI-D, or worse yet labeling them as prematurely ESKD, is likely to confound care and potentially forestall any impending kidney recovery [48]. Patients with AKI-D have the most to benefit from early, specialist nephrology input. Despite the lack of evidence, the Acute Disease Quality Initiative (ADQI) has recently proposed the WATCH-ME care bundle to improve the care of outpatients with AKI-D (Table 3) [5]. This multi-pronged kidney focused care bundle

tackles a variety of topics for patients receiving dialysis some of which are specific to AKI and others of which overlap with the care of ESKD patients.

Weight Assessment -

Unlike in the setting of ESKD where attempts are made to establish the lowest tolerated dry weight, those with AKI-D patients should be allowed to be on the hypervolemic side of euvolemia. This “permissive hypervolemia” will help decrease the risk of intradialytic hypotension which has been shown to correlate with lower rates of kidney function recovery / dialysis independence [49]. Currently no specific guidelines exist about how much ultra-filtration is safe in patients with AKI-D but guidance from ESKD point to keeping rates at less than 13 ml/kg/hr [50]. While data is lacking in those patients with some urine output diuretics should be utilized to assist with negative fluid balance and limit weight gain between dialysis treatments.

Access –

Given that the majority of patients with AKI will be receiving dialysis through a central venous catheter they need to be educated about the complications of catheters. Vein preservation should be addressed given the increased risk of ESKD, but in many cases placement of arterial-venous access can be postponed until there is clarity around long-term kidney prognosis [51].

Teaching:

The importance of patient and caregiver education cannot be overstated. Patients must understand that AKI-D can be reversible, be instructed to identify themselves as AKI-D to other health-care workers and be aware of the signs and symptoms of kidney recovery [49, 52]. Since a significant percentage of AKI-D patients will have no nephrology care prior to their index hospitalization they should work with dialysis unit staff to understand the multi-disciplinary nature of kidney care.

Clearance -

Underlying kidney function assessments should be protocolized in AKI-D patients. This can be done through looking at pre-dialysis labs and include timed urine collections. While limited data exists on the utility of clearance assessments in AKI-D, care facilities should regularly assess patients for recovery. Separately, as with ESKD patients, and informed by a large multicenter RCT, patients with AKI-D should receive adequate dialysis clearance (Kt/V urea of 1.2 three times a week) [53]. As AKI-D patients recover function, they may not require the same level of clearance and some may tolerate twice or once weekly dialysis. There is limited data to support this incremental step-down of dialysis but it mirrors how ESKD care is often ramped up to three times a week [54, 55].

Hypotension –

In patients with AKI-D, intradialytic hypotension has been linked with decreased chances of recovery to dialysis independence [49]. As such patients should be instructed on minimized inter-dialytic weight gain to reduce ultrafiltration needs and mitigate the risk of hypotension.

Similarly, education around holding hypertension medications on dialysis days (or sick day protocols) may be warranted for some patients prone to hypotension.

Medication –

Medication reconciliation is a necessary component of all healthcare transitions and outpatient AKI-D is no different [56, 57]. This reconciliation process is not a one-time event as it should be repeated (perhaps weekly) especially if kidney function improves. As part of patient education, patients and their caregivers should be made aware of the kidney's role in drug metabolism and clearance. Additionally, patients should be repeatedly advised on nephrotoxin avoidance as further exposure may forestall kidney recovery [58, 59].

Conclusions

Currently there are no standards with regards to who receives follow-up care after an episode of AKI in the ICU. Given the mounting evidence of the long-term impact of AKI on survivors of critical illness, clinicians should begin to incorporate AKI follow-up care as much as possible, with every post-AKI patient getting at least some sort of follow-up. Future efforts should focus on determining which subsets of critical illness-AKI survivors are most likely to benefit from follow-up care over pre-specified time-periods. Care-bundles (e.g. WATCH-ME for AKI-D patients) represent a unique opportunity to investigate the optimal care plans for patients after an episode of AKI.

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Key points

1. All patients with a history of AKI should receive some form of AKI follow up; priority should be given to those with prior CKD, those with persistent proteinuria and those with incomplete recovery to their pre-AKI baseline.
2. Three months following an episode of AKI, patients should have their GFR and proteinuria checked in order to assess their risk of subsequent deterioration of kidney function.
3. There is limited high-quality evidence showing that interventions can lower morbidity and mortality following AKI; however, patient and caregiver education should be a mainstay of post AKI care.
4. The WATCH-ME bundle provides structure for the care of patients with a recent history of AKI-D

Table 1.

Proposed tests and outcomes after AKI

Proposed tests after AKI	Time point of measurement	Type of study	Population	Timepoint of follow-up and outcomes
Creatinine/estimated glomerular filtration rate (eGFR) and electrolytes	After AKI	Retrospective population-based cohort	14,651 hospital survivors	Associated with an excess risk of 30% renal decline and de novo CKD stage 4 over 10 years, and the risk decreased over time [26]
	eGRF at discharge after AKI	Retrospective multicenter cohort	9,973 hospitalized patients	Associated with CKD stage 4 or higher at 1 year [11]
	eGFR at 3 months after AKI	Multicenter prospective cohort	1,538 participants, of whom 50% developed AKI	Associated with future deterioration in kidney function (halving of eGFR or end-stage kidney disease (ESKD)) at 4.7 years (HR 1.50 for each 10 mL/min/1.73 m^2 decrease; 95% CI, 1.36–1.66) [14]
	eGFR normal (>60 ml/min/1.73 m^2) at 1 year after AKI requiring temporary dialysis	Single center retrospective	396 patients	8.8% developed CKD after a median of 5.3 years [60]
Albuminuria (urine albumin-to-creatinine ratio) and proteinuria (urine protein-to-creatinine ratio)	Albuminuria at 3 months after AKI	Multicenter prospective study	1,538 participants, of whom 50% developed AKI	Associated with future deterioration in kidney function (halving of eGFR or ESKD) at 4.7 years (HR 1.53 for each doubling; 95% CI, 1.45–1.62) [14] Urine ACR better predicted kidney deterioration than eGFR, and UPCR had a stronger association than ACR (HR 1.98 vs 1.53) [14]
Blood pressure	After AKI	Multicenter retrospective cohort	2,451 previously normotensive adults	Increased risk of hypertension within 2 years (22% increase (95% CI, 12–33%) after multivariable adjustment, and the risk was higher with increased AKI severity [32]
Screening for cardiovascular events (HF, MI, stroke, AF)	After AKI	Meta-analysis	254,408 adults	Increased risk of HF up to three years (RR 1.58, 95%CI 1.46–1.72) Increased risk of MI up to three years (RR 1.40, 95%CI 1.23–1.59) [34]
	After AKI	Retrospective multicenter cohort	146,941 adults	Increased risk of HF at one year (HR 1.44, 95%CI 1.33–1.56) [35]
	After AKI	Meta-analysis	254,408 adults	Increased risk of stroke at three years (RR 1.15, 95%CI 1.03–1.28) [34]
	After AKI	Retrospective population-based cohort	21,556 critically ill survivors	Increased risk of HF (HR 1.33, 95%CI 106–1.66 for stage 1 and HR 1.45, 95%CI 1.14–1.84 for stages 2–3) and MI (HR 1.51, 95%CI 1.05–2.18 for stages 2–3) up to three years [61]
	After AKI requiring dialysis	Retrospective cohort	41,463 patients	Increased risk of subsequent atrial fibrillation (AF) after 6.9 years (HR 1.30; 95% CI, 1.07–1.58) compared to non-AKI [37].
Serum glucose	After AKI requiring temporary dialysis	Retrospective population-based cohort	13,228 adults	Increased risk of diabetes within 6 years with mortality as a competing risk factor (HR 1.18, 95%CI 1.07–1.30) [39]
Serum lipids				

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Table 2.

Potential interventions after AKI

Interventions	Additional information	Outcome	Level of evidence
Teaching	Education around AKI and risk of future HTN, CKD, ESKD, cardiovascular outcomes (HF, MI) and stroke	Association between AKI and these outcomes – no data on education and outcomes	Meta-analysis [7, 8, 34], retrospective studies [32]
	Promote healthy behaviors (diet, exercise, weight)		No evidence
Medications	Avoidance of NSAID use, medication reconciliation (re-initiation of metformin or sodium-glucose co-transporter 2 inhibitor)		No evidence
Blood pressure level	Tailor according to patients' age and comorbidities		No evidence
Renin-angiotensin-aldosterone system (RAAS) inhibitors	587 patients - initiation of RAAS inhibitor after renal recovery following cardiac surgery-associated AKI	Lower risk of CKD progression (HR 0.46, 95%CI 0.30–0.70)	Retrospective analysis of a prospective cohort [25]
	1551 patients, RAAS inhibitor after renal recovery	Lower risk of mortality at one year (HR 0.48, 95%CI 0.27–0.85)	Retrospective cohort [44]
	10,242 adults matched for drug use, new use of RAAS inhibitors	Not associated with increased AKI requiring hospitalization over 3 years - this latest model accounted for baseline, time-updated, and potential time-dependent confounders	Retrospective cohort [62]
	46,253 adults matched for drug use • New and continued RAAS inhibitors use within 6 months after AKI * • Stopping a RAAS inhibitor prescribed before admission	• Reduced mortality at 2 years (HR 0.85; 95% CI, 0.78–0.93 and HR 0.77; 95% CI, 0.73–0.80, respectively) • No association with ESKD (limited data) • Increased risk of hospitalization for AKI and/or hyperkalemia (HR 1.28; 95%CI, 1.12–1.46) • Increased mortality at 2 years	Retrospective cohort [43]
Statins	AKI developing CKD – missing data on some important covariates	Lower risk of mortality after 2 years (HR 0.74; 95%CI 0.69–0.79) No reduction in cardiovascular events	Retrospective cohort [45]
		No effect on CKD (HR 0.94, 95% CI 0.70–1.25)	Retrospective analysis of a prospective cohort [25]

* Starting a RAAS inhibitor within 90 days compared to after 90 days following discharge was associated with increased mortality

Table 3.

The WATCH-ME Bundle for Patients with AKI-D

WATCH-ME Bundle	
Weight Assessment	• Education around the concept of Dry Weight • Optimizing diuretic regimens and volumes status • Permissive hypervolemia to avoid intradialytic hypotension
Access for Dialysis	• Education around the care of central venous catheters • Vein preservation awareness • If appropriate education and preparation for arteriovenous accesses
Teaching (Patient and Caregiver)	• Education around AKI-D and short- and longer-term sequelae of this clinical syndrome • Education with other care providers (primary care, dieticians, nurses, social workers, pharmacists) around the patient's new clinical needs
Clearance	• Clinical assessment of underlying kidney function with timed urinary clearances • Clinical assessments of the quality of the dialysis clearance (Kt/V or urea reduction ratio)
Hypotension (Blood Pressure Management)	• Patient and caregiver education around the avoidance of intradialytic hypotension • Education around blood pressure administration on dialysis and non-dialysis days
Medications	• Frequent medication reconciliation, review, and management • Discuss the risks and benefits for renin-angiotensin-aldosterone agents • Review all over the counter medications • Education the patient and caregivers about nephrotoxins and the role of kidneys in medication dosing