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The acute kidney injury e-alert and clinical care bundles: the road to success is always under construction

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Numerous initiatives have focused on improving the outcomes after acute kidney injury (AKI). These vary from local-level efforts to national incentives, e.g. the National Health Service guidelines [1], and even global initiatives, e.g. the International Society of Nephrology (ISN) 0 by 25 initiative. The key hypothesis—albeit implicit—behind most of these initiatives is that early diagnosis of AKI translates into improved patient outcomes.

Front running hospitals have already developed and implemented (automated) AKI alerts into clinical care [2–5]. Clinical studies show promising results with earlier detection of AKI and suggest improvement of clinical endpoints [6]. Some argue that, since these alerts do not cause direct harm to patients, universal implementation should commence immediately. A large, adequately powered, hospital-wide study applying an automated electronic AKI alert did not confirm the high expectations. Wilson *et al.* [7] showed no benefit, and in subgroups there was even potential harm from introducing a simple AKI e-alert.

In this issue of *Nephrology Dialysis Transplantation*, Kolhe *et al.* [8] report a study exploring the effects of an AKI clinical care bundle (AKI-CB) combined with an electronic AKI alert. They found that the unadjusted case fatality rate was higher in patients for which an AKI-CB had not been completed versus those with a completed AKI-CB. In multivariable analysis, timely AKI-CB completion, i.e. within 24 h, was associated with lower odds for in-hospital death. Also, progression to higher AKI stages was less frequently observed in completed AKI-CB cases. Both studies [7, 8] made use of an electronic AKI alert and both studies aimed at improving outcomes after AKI. How can we reconcile these divergent results?

From a methodological point of view these two studies differ substantially. The study by Kolhe *et al.* [8] is a propensity score-matched cohort study. Patients who completed the AKI-CB were matched for age, gender, first AKI stage, site where AKI was diagnosed, admission method, ethnicity and a number of comorbidities. Propensity matching is an accepted statistical methodology to minimize bias for observational data. However, there are limitations to propensity matching, as it does not correct for unobserved hidden bias. Moreover, covariates that are taken into account, e.g. cancer or dementia, often are characterized by a wide range in disease severity. Both might have impacted the likelihood of AKI-CB completion. The solution to minimize unobserved bias would be to perform a randomized controlled trial, as in the study by Wilson *et al.* [7].

Second, the AKI alert was communicated to the treating team in a different way in both studies. In the current study, an 'interruptive' alert was triggered by the first attempt to order blood tests or medication for patients who had been identified as having AKI. The treating physician was able to overrule this alert by providing a reason. In all other cases, the physician had to complete the AKI-CB. This differs from the informative alert used by Wilson *et al.* [7].

A third difference between the studies is the degree of guidance offered to the treating teams after AKI was detected. The current study provided clear instructions to the treating physicians about the steps they should follow. Compliance with this clinical care bundle was the primary endpoint of this study. This is remarkably different from previous studies where no clear guidance was provided to treating teams. Of note, Wilson *et al.* also provided a link for the treating teams, referring to the Kidney Disease: Improving Global Outcomes (KDIGO) AKI guidelines [9].

Limited information is available about the actual performance of electronic AKI alert systems [10–12]. Nonetheless, several information technology and organizational aspects constitute practical challenges (Figure 1): (i) What is the acceptable delay between input of creatinine values and communication of AKI e-alerts? No clear data are available for guiding the degree of near-line versus batch processing. (ii) How to translate guidelines into a workable computer code? In the KDIGO guidelines, one of the key diagnostic criteria is 'the absolute increase of creatinine of 0.3 mg/dL or more within 48 h'. In clinical practice, creatinine is measured once daily, usually at about

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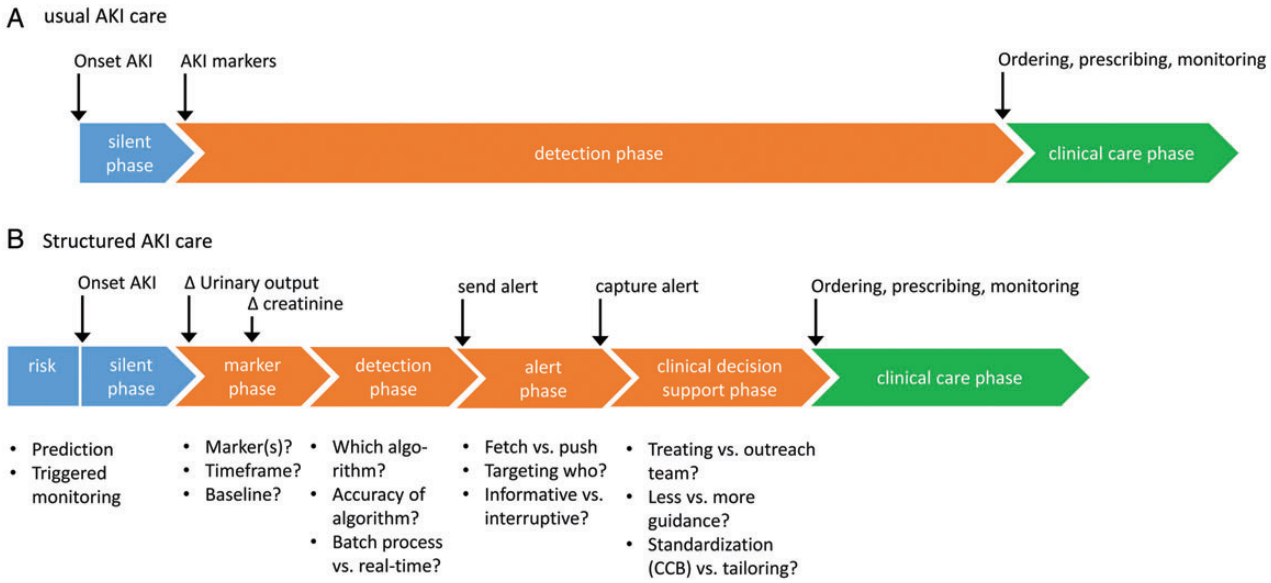

FIGURE 1: Schematic overview of AKI care. (**A**) The usual, mostly unstructured care for patients with AKI. The onset of AKI is followed by a silent phase (in blue), without any detectable changes. The duration of the silent phase is dependent on the choice of AKI markers and is followed by a period in which AKI is detectable (in orange). Actual detection of AKI is dependent on several factors and may take several days. If and when this leads to ordering of additional tests, prescription of drugs (or withholding others) and measures made to monitor patients, the clinical care phase (in green) starts. (**B**) The different phases of structured AKI care. Structuring AKI care most likely impacts the detection phase (in orange), whether other interventions are focused on shortening the silent phase (biomarker research) or by novel therapeutic interventions (in green). The silent phase may also be shortened by risk prediction algorithms, deduced from prevailing risk factors or putative renal insults. Several factors determine the total lag time between the moment at which AKI becomes detectable and the decision to take actions, e.g. ordering tests, prescribing and withholding drugs and monitoring. CCB, clinical care bundle.

the same time. Clinicians would interpret this criterion as 'a rise in creatinine of 0.3 mg/dL or more within 2 days'. However, computer code will make a strict discrimination between 47 h, 59 min and 59 s (<48 h) versus 48 h and 1 s (>48 h). Whether such differences will result in a missed diagnosis of AKI using electronic AKI alerts is not well studied. One option would be to adjust the KDIGO definition and calculate absolute rises within, for example, 56 or 60 h, but such decisions need to be supported by clinical data. (iii) Reanalysis of the Wilson study also showed that use of small changes in serum creatinine to diagnose AKI is limited by high false-positive rates caused by higher variability of serum creatinine at higher baseline values and potentially misclassifying patients with CKD in AKI studies [13]. In contrast, Cruz *et al.* [14] suggested adopting even smaller increments in creatinine to identify AKI in high-risk patients. This approach might be useful if risk prediction can be automated. Such risk assessment algorithms should rely on known risk factors (susceptibilities) and exposures (renal insults) that are retrievable from the electronic patient file. (iv) The KDIGO definition also includes 'an increase in serum creatinine to 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days'. Most AKI e-alert algorithms simplify this to 'relative increases, documented to have occurred within the preceding 7 days'. Patients lacking creatinine measurements in the 7 days preceding the occurrence of AKI will not be recognized. More elaborate systems should be able to infer the patient's baseline creatinine, thus performing more in line with the KDIGO definition. As most patients are treated in a single hospital system and/or by a single county care provider, taking into account previous creatinine values could be of help to infer baseline creatinine values. (v) Most systems rely on serum creatinine values, whereas urinary output is not taken into account in all systems to make the diagnosis of AKI. (vi) Finally, are the KDIGO criteria the best possible criteria to be used for the development of electronic AKI alert algorithms? These, as well as the preceding Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) and Acute Kidney Injury Network (AKIN) criteria, were designed as globally accepted definitions of AKI. The validity of these criteria was demonstrated looking at short- and long-term outcomes after AKI. The current use in AKI e-alert algorithms needs to be evaluated.

As pointed out by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) report [15], organizational aspects also deserve attention. As with any clinical decision support system, alerts need to reach the treating teams in order to be effective. While this seems simple in theory, AKI can occur any hour of the day, 7 days per week. In the current study, an 'interruptive' alert was used that was triggered by the first attempt to order blood tests or medication for patients who had been identified as having AKI. The likelihood for either of these attempts to occur on a weekend might be lower than during weekdays. This might be improved by sending push alerts to treating teams. Automation of such processes, however, is easier said than done [16, 17].

In conclusion, Kolhe *et al.* [8] provide ample evidence that automated AKI detection coupled to a clinical care bundle does improve outcomes in patients affected by AKI. Their findings further strengthen the case for early detection of AKI assisted by electronic alert systems. We should be cautious, however, not to oversimplify the message. Rapid detection of AKI is an

essential part of good clinical care. This does not imply, however, that early detection alone equals good clinical care and is sufficient to optimize outcomes for patients affected by AKI.

CONFLICT OF INTEREST STATEMENT

The results presented in this article have not been published previously in whole or part. The authors report no conflict of interest related to the content of this article.

(See related article by Kolhe *et al.* A simple care bundle for use in acute kidney injury: a propensity score matched cohort study. *Nephrol Dial Transplant* 2016; 31: 1846–1854)

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Dialysis and pregnancy: no longer the impossible

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Pregnancy in women with renal disease provokes anxiety in nephrologists and obstetricians alike. Chronic kidney disease (CKD) is associated with some of the highest rates of adverse maternal and neonatal outcomes compared with other pre-existing medical conditions in women of childbearing age. Women with advanced CKD also are at risk of disease progression, hastening the requirement for renal replacement therapy, shortening their life expectancy and potentially restricting their ability to care for their children, who may have complex health needs secondary to prematurity. Thus, many women with advanced CKD have been advised strongly not to conceive [1] or to wait for a kidney transplant before contemplating pregnancy.

Following the first live birth reported in a woman receiving haemodialysis in 1971 [2], the number of successful pregnancy outcomes in women with end-stage renal disease (ESRD) has been increasing, and a recent exponential rise in reported