Well, let us be honest: although Ronco et al. [1] claim that NephroCheck has been ‘validated’, in reality the test has not succeeded in making a difference as compared with good clinical judgement [2]. In the Sapphire study [3], the area under the curve for discrimination of AKI went from 0.81 for a clinical model to 0.87 when NephroCheck was added to the clinical model. Of importance, the change in serum creatinine was deliberately left out of the model, so we have no clue what the additional value of this parameter was, and oliguria, one of the diagnostic criteria of AKI, was not even mentioned. The US Food and Drug Administration specifically warns that the test should NOT be used as a stand-alone test, and certainly not in a point-of-care set-up.

Second, the flow chart urges us to do nephroprotective actions in patients at risk, as identified by NephroCheck. I beg your pardon? Should we thus not do nephroprotection in all other patients? And if we should, what is the added value of the NephroCheck?

Third, the NephroCheck RRT model starts from the premise that AKI is a single hit, a once-in-a-hospitalisation story. We all know this is not the case, as hospitalised patients continuously face multiple threats for AKI. Accordingly, there would be a continuous need for ‘NephroChecking’. Since a major part of (preventable) AKI cases are on general wards, this would pose huge problems of logistics and cost if we were to apply the proposed algorithm in all wards. If applied only to the intensive care unit, it would completely miss the target audience [4].

This brings us to the most urgent question: should we put (lots of) our health care money on a commercial test without proven additional value, or should we invest in education and awareness of AKI? The case of early electronic warning [5] has learned that prevention only works in combination with a broader program. Such programs have a proven benefit on outcome for all patients, and thus on the hard outcome of mortality.

In conclusion, there is no ‘single easy solution’ as promised by NephroCheck or other biomarkers [6]. The nephrology community will have to accept responsibility by educating the non-nephrology community and increase general awareness of AKI.

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Con: Cautionary tales and reservations about the adoption of new technologies and biomarkers for the management of acute kidney injury

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ABSTRACT

Acute kidney injury (AKI) is an important health-care problem. Over the last decades, many innovative therapies and diagnostic approaches have been tried; however, none of these has been able to confirm consistently that they lead to improved outcomes. Much focus has been placed on intensive care unit (ICU)-associated AKI, whereas the bulk of AKI still concerns patients not in the ICU. Involvement of nephrologists in the
care of AKI patients is necessary to further improve outcomes. It is unclear whether new technologies, such as biomarkers, are helpful and could replace nephrology consultation.

**Keywords:** AKI, biomarkers, dialysis, prognosis, survival analysis

The fate of the Titanic has demonstrated that overconfident trust in new technologies and neglecting established seaman skills can be deleterious. The story of Odysseus instructs us that attractive sirens along the voyage promise, with their sweet voices, a simple voyage to a safe harbour, milk and honey, but following their advice leads to shipwreck and death. The story of the Herald of Free Enterprise teaches us that neglecting tiny, simple details of well-established knowledge can result in dramatic effects. The story of the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) [1] clarifies that not applying apparently basic knowledge in the care of patients at risk for, or with, acute kidney injury (AKI) costs lives. This paper aims to defend the viewpoint that we need to invest more time, research and money to ensure that all basic interventions with established positive outcomes to prevent and manage AKI are put into practice, rather than investing in new technology with unproven additional benefit. Nephrologists should use their clinical and education skills to achieve this goal.

AKI is an important health-care problem, associated with high morbidity, mortality and health-care spending [2]. Over the last two decades, a lot of focus has been placed on AKI in the intensive care unit (ICU), mostly in severely ill and comorbid patients, creating the impression that AKI equals ICU. Unfortunately, the cost efficiency of such interventions is extremely low, not in the least due to the high mortality associated with AKI with the need for renal replacement therapy (RRT) [3]. This evolution is in sharp contrast to the epidemiology of AKI in the real world, where it is apparent that the absolute prevalence of AKI is higher in settings outside the ICU [4]. Moreover, the majority of cases are due to very simple underlying causes such as hypotension or dehydration. At the same time, there has been a creeping tendency to opt for even more technology for the diagnosis and management of AKI. Many (expensive) innovations have been promoted, mostly with hidden industry support, but have failed to demonstrate their beneficial impact in real-life conditions. One simple and effective intervention is early consultation of the nephrologist [5], and technology that delays this should be avoided.

Much effort has been made to establish evidence that high-volume, early-start continuous renal replacement therapy (CRRT) using sophisticated machinery leads to improved outcomes. CRRT has been, and is still, promoted as superior to intermittent haemodialysis, although several large randomized trials failed to demonstrate any difference in outcome [6–8]. Simple hybrid solutions such as slow extended daily dialysis using simple dialysis machines reduce costs without jeopardizing outcomes [9, 10]. The use of high-volume CRRT appeared promising, as, in theory, it would lead to the removal of inflammatory cytokines. Unfortunately, in reality, protective cytokines were also removed at the same rate [11], and high-volume CRRT did not stand the test of well-performed multicentric trials. In addition, knowledge on correct dosing of antibiotics and other drugs in patients on these complex regimens was poorly documented, risking both under- and overdosing. Early start of RRT in the setting of AKI has been commended as a way to improve outcomes, based on data from observational studies [12]. Two randomized studies later, we know that starting dialysis in those who do not need it according to established criteria is as deleterious as delaying dialysis in patients who need RRT, because of therapy-resistant fluid overload, hyperkalaemia or metabolic acidosis [13, 14]. ‘Late’ and ‘early’ should thus be defined based on established criteria versus based on surrogate markers such as AKI classification or biomarkers.

In addition, there has been much effort focused on prevention to promote complex and expensive strategies over more simple and cost-effective ones. Iso-osmolar contrast media were promoted based on a presumed theoretical benefit but subsequently were shown to bring no additional benefit [15], whereas at the same time more than half of patients at risk for contrast-induced AKI (CI-AKI) do not even receive decent and highly effective pre-hydration [16]. Devices are currently being promoted in the setting of CI-AKI prevention, matching the infusion rate to the central venous pressure and diuresis. Several studies have claimed that such a strategy decreased the incidence of CI-AKI; however, closer evaluation revealed that the control group received far less fluid and that the incidence of heart failure was similar. As most studies were conducted in the setting of percutaneous coronary intervention, it is unclear whether the results are generalizable to cases of intravenous contrast administration. In addition, these studies included patients with a glomerular filtration rate of as high as 60 mL/min/1.73 m²—translating such practice to a general preventive measure would result in an unmanageable logistic nightmare.

Surprisingly, while there are numerous studies comparing different contrast media with iso-osmolar ones, preventive drugs or complicated intravenous pre-hydration regimes, the number of studies on the place of oral pre-hydration in the setting of CI-AKI is disappointingly low. Nevertheless, such a strategy would probably prevent far more CI-AKI cases in absolute numbers, as it could be applied much more broadly [15].

Over the last decade, biomarkers for early diagnosis of AKI have been brought in the arena, supported by big marketing strategies. A PubMed search restricted to the last 10 years with the keywords ‘acute kidney injury’ and ‘biomarker’ has identified 3443 papers. Of these, 663 were reviews and editorials, and only 114 true clinical trials. Various new biomarkers have been introduced, focusing on different sources of origin: enzymes released from damaged tubular cells or tubular structures (e.g. NAG, GST, AF, F actin, NHE3, etc.), proteins with decreased proximal tubular reabsorption (e.g. RBP, cystatin C, beta2MG), products of genes upregulated in response to AKI (NGAL, KIM-1) and urinary cytokines and chemokines (interleukin-18) [17]. An ideal biomarker for AKI should only increase in cases of tubular damage and should not increase in cases of failure of organs other than the kidney. However, for most biomarkers, there is ample evidence that they also increase with declining glomerular filtration rate or inflammation, or in the presence of other comorbidities without kidney
Biomarker levels should correlate with the potential lesions seen on biopsy. Whereas this can be mimicked in experimental (animal) studies, evidence to support this notion in clinical practice is lacking. Biomarker levels should have a dose response following the clinical course. The window of opportunity when these markers can potentially have a beneficial role is poorly established and mostly limited. Just as it is of no use to measure troponin in patients without chest pain, it is also of no use to measure biomarkers for an early diagnosis of AKI in all patients. In the absence of a clear timing of renal insult, it will be difficult to know which marker to use in a particular setting, unless there would be continuous sampling. A diagnostic, or even a prognostic, strategy based on biomarkers should be reliable in different settings and prove its role on top of a clinical model including standard parameters for AKI risk prediction and early diagnosis. This has so far not been proven for any biomarker [20]. In most settings, it appears that clinical appreciation by a nephrologist would be more valuable than a routinely measured biomarker. For any of the current biomarkers, no clear and non-debatable cut-off values have been established that can be applied in different settings. The threshold for release of some of these markers is very low and it is unclear how much damage is enough damage to be clinically relevant. Most biomarkers are marketed as being ‘more sensitive’, but in reality, there is a high risk that they induce plenty of false-positive results, leading to unnecessary further investigations and treatments [21, 22]. Recently, cell cycle inhibitors have been approved by the US Food and Drug Administration which, however, stated that ‘test results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including confirmation by alternative methods’. They also explicitly added that the biomarker should not be used as a standalone test. In a recent study, clinical parameters, such as response to the furosemide stress test, outperformed cell cycle inhibitors as diagnostic markers [23]. Thus, it seems that at the current time, biomarkers lack discriminatory power over what good clinical appreciation can already achieve, and their place in AKI management programmes is ill-defined because of logistical issues related to timing of sampling, lack of reference values and costs. It is therefore too early to include biomarkers in risk stratification models or use them as early diagnostic criteria for AKI.

All these new interventions and approaches can be a matter of debate between (optimistic) believers and (realistic) sceptics on whether or not they contribute to better outcomes; the real discussion should be, however, on the opportunity cost of introducing these new techniques in the clinical domain—how many opportunities to prevent or improve the outcome of AKI would be missed by having a myopic focus on this technique, rather than applying sufficient attention to established beneficial (admittedly less exotic and more simplistic) strategies? NCEPOD [1, 24] informs us that substantial improvements in the outcome of AKI could be achieved if basic evaluations, such as appreciation of volume status, urinary output, administration of nephrotoxic drugs and episodes of hypotension, are performed and acted upon in a systematic manner. Of note, the majority of these avoidable insults occur on a general ward, not in the ICU or emergency department. Starting from this observation, many initiatives have been taken to increase early awareness for AKI, based on combinations of simple and available tools such as urinary output, serum creatinine or medication lists [25]. Initial studies indicated that monitoring of urinary output in particular can assist in early detection of AKI [26, 27]. Existing AKI classifications express the urinary output in mL/min/kg and thus presume the presence of indwelling bladder catheters. However, urinary output measured in 8-h blocks is also predictive and diagnostic, and thus allows translation of the high-tech environment of the ICU to the general ward [28]. Although early warning systems need to be based on cleverly engineered information technology to assemble all the different types of necessary information from diverse sources, it is the ‘human factor’ in particular that will determine whether the device will have a positive impact or not. Recently, a text message-based warning system did not result in improved outcomes, simply because it failed to change the behaviour of end-users [29]. The underlying reasons for this failure include a very low-threshold alarm setting, causing ‘alarm fatigue’ because of many false-negative alarms. Moreover, the system generated only one message per patient, neglecting the multi-hit aspect of AKI. Last, there was no education or awareness programme coupled with implementation of the device. This lack of bringing in the human factor was most likely the essential missing link in creating a successful tool. In a large propensity-matched cohort study [30], completion of an AKI care bundle in response to an electronic alert on enhanced AKI risk was associated with an improvement of in-hospital death and a lower progression to higher AKI stages. The care bundle guides the user through basic, but essential, steps to improve the care for those at risk for, or with, AKI. Introduction of the early warning system was also accompanied by education and awareness programmes, thus increasing the general knowledge on, and attention for, the risk factors for AKI within the wider medical team.

All these examples teach us that we should construct a balanced introduction strategy of new technologies in the management of AKI. First, we need to ensure that all knowledge on what effective treatments are has already been implemented in practice. Most of these might be rather simple things from a technical perspective such as awareness for AKI, assessment of volume status, avoidance of nephrotoxic medications, observation and reporting of urinary output and avoidance of hypotension during renal replacement. To achieve this, we will need to invest in education, and the nephrology community has a huge responsibility in this. Second, every new technique needs to build sufficient evidence on the effectiveness of treatment above what is already established practice. Third, it needs to be assessed whether broad implementation of those techniques with proven superior outcomes is also cost-effective. Cost-effectiveness should also include evaluation of the impact of introducing the new technology on other aspects of AKI in terms of resources, staff, time and logistics. Only if these have all been established should the new technology be
recommended for introduction in clinical practice. Such a policy will result in sustainable, robust care programmes, rather than flashlight, ever-changing, short-lived hype-of-the-day campaigns.

Nephrologists have a big responsibility in maintaining this rigorous approach to implementing new technology and in ensuring their specific skills are broadly available.

CONFLICT OF INTEREST STATEMENT

None declared.


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