Intensive Care Med (2015) 41:160–161
DOI 10.1007/s00134-014-3538-7

LETTER

John R. Prowle
Andrew Leitch
Christopher J. Kirwan
Lui G. Forni

Positive fluid balance and AKI diagnosis: assessing the extent and duration of 'creatinine dilution'

Accepted: 28 October 2014
Published online: 15 November 2014

Dear Editor,

Diagnosis of acute kidney injury (AKI) is, largely, defined by changes in plasma creatinine (pCr); however, such changes can be delayed and attenuated in critically illness [1]. Some authors have speculated that dilution of serum after volume expansion may be a primary factor in limiting the ability of pCr changes to diagnose AKI. Consequently, a pCr correction formula (Eq. 1) for relative volume expansion has been proposed, providing an estimate of pCr at a notional even fluid balance (FB) seeking to unmask hitherto 'missed' AKI [2].

$$\text{Corrected pCr} = \text{pCr} \times \frac{0.6 \times (\text{admission weight}) + \sum(\text{daily cumulative fluid balance})}{0.6 \times (\text{admission weight})} \quad (1)$$

Use of corrected pCr from diagnosis of AKI has now been employed in a number of other AKI studies [3–5]. However, this method essentially treats all cumulative volume expansion as occurring instantaneously at the point of pCr measurement, failing to account for the actual kinetics of creatinine excretion. Creatinine excretion (Cr_e) is principally excreted by unselective glomerular ultrafiltration, so $Cr_e \approx GFR \times pCr$. Thus, when volume expansion acutely reduces pCr, Cr_e will fall in parallel, and if one assumes that creatinine generation (G) remains constant, creatinine will then accumulate in the body water until pCr rises again to its baseline value, when $Cr_e = G$. The only circumstance when this will not occur will be if GFR is zero and excretion cannot be reduced further by dilution; however, in this instance, AKI diagnosis is usually unambiguous.

The effect of dilution of creatinine excretion can be appreciated by modelling pCr changes after volume expansion using the analytical solution to a single compartment, a fixed-volume model for creatinine kinetics (Eq. 2) [1].

$$Cr_t = \frac{G}{K} + \left(Cr_0 - \frac{G}{K}\right)e^{-\frac{Kt}{V}} \quad (2)$$

in which K = glomerular filtration rate (L/min), G = creatinine generation rate (μmol/min), t = time (min), Cr_0 = baseline plasma creatinine concentration (μmol/L), Cr_t = plasma creatinine concentration at time, V = total body water (L), and e = base of natural logarithmic function.

In this model, volume expansion is treated as occurring at baseline with no net gain or loss of fluid thereafter. Immediately after volume expansion, the published correction formula (Eq. 1) accurately predicts pCr prior to volume expansion; however, over time, pCr progressively rises (due to reduced excretion with unchanged generation), so that a large volume expansion (25 % of TBW) results in a 24-h pCr only 2 % below baseline, while the correction formula progressively over-estimates true creatinine prior to volume expansion (Fig. 1). Thus, unless GFR is extremely low, any dilution effect on pCr concentration is likely to be transient. As a single compartment model, the effect of the composition of the fluid administered is not assessed; however, as greater relative plasma dilution will cause greater reduction in creatinine excretion, we would predict that, over hours, the effects of colloids and crystalloids are would be similar.

Despite a lack of clear physiological basis, formula correction of pCr for cumulative FB has been applied in a number of publications over periods of 7 days or more [2–5]. The validity of this approach has been imputed by a higher mortality seen when new AKI diagnosis was made using corrected pCr [2, 4]. However, any changes in AKI classification using corrected pCr must be associated with a more positive FB, which is, in its own right, a marker of illness severity and risk factor for adverse outcomes. Similarly, reductions in creatinine generation may occur in sicker patients, potentially obscuring AKI diagnosis; however, this process is mechanistically distinct from plasma dilution and should be considered as a distinct entity not directly related to FB.

We believe that applying the correction factor for cumulative FB over periods longer than a few hours after volume expansion lacks physiological rationale or any objective evidence to support its accuracy. We suggest that investigators should discard use of the fluid correction formula in studies of AKI diagnosis.

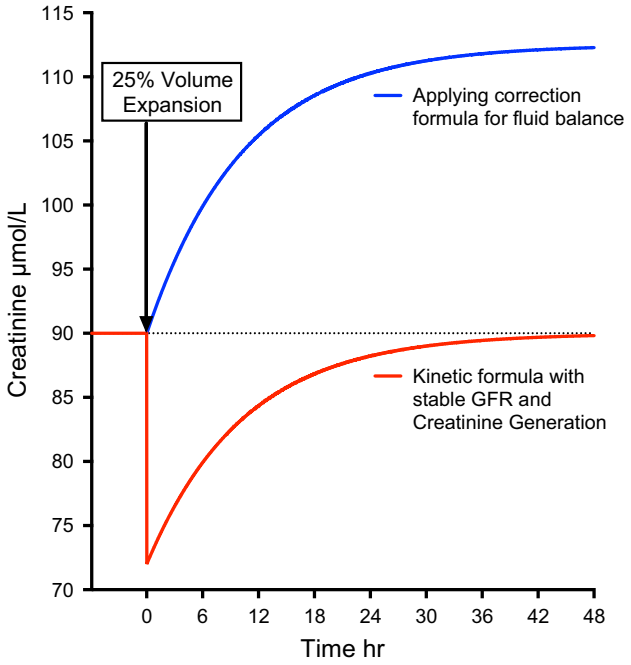

Fig. 1 Predicted plasma creatinine changes over 48 h in an 80-kg, 60-year-old man (baseline total body water 48 kg) with a baseline creatinine of 90 µmol/L. A 25 % acute volume expansion is applied at $t = 0$ (12 L) with fluid intake equal to fluid losses thereafter. GFR and creatinine generation rate are assumed to be unchanged and creatinine distributed evenly in a single compartment. A 20 % (12 µmol/L) decrease in pCr occurs acutely; however, half of this fall is recovered by 7 h and, by 24 h, pCr is 98 % of baseline despite a cumulative 12 L +ve fluid balance. Application of the correction formula [1] for fluid balance results in a 22 % over-estimation of baseline creatinine at 24 h

References

1. Waikar SS, Bonventre JV (2009) Creatinine kinetics and the definition of acute kidney injury. J Am Soc Nephrol 20(3):672–679
2. Macedo E, Bouchard J, Soroko SH et al (2010) Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. Crit Care 14(3):R82
3. Horiguchi Y, Uchiyama A, Iguchi N et al (2014) Perioperative fluid balance affects staging of acute kidney injury in postsurgical patients: a retrospective case-control study. J Intensive Care 2(1):26
4. Liu KD, Thompson BT, Ancukiewicz M et al (2011) Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. Crit Care Med 39(12):2665–2671
5. Stein A, de Souza LV, Belettini CR, Menegazzo WR, Viegas JR, Costa Pereira EM, Eick R, Araujo L, Consolim-Colombo F, Irigoyen MC (2012) Fluid overload and changes in serum creatinine after cardiac surgery: predictors of mortality and longer intensive care stay. A prospective cohort study. Crit Care 16:R99

J. R. Prowle (✉) · A. Leitch · C. J. Kirwan
Adult Critical Care Unit, The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, London E1 1BB, UK
e-mail: john.prowle@bartshealth.nhs.uk
Tel.: 020 359 40322

J. R. Prowle · C. J. Kirwan
Department of Renal Medicine and Transplantation, The Royal London Hospital, Barts Health NHS Trust, Whitechapel Road, London E1 1BB, UK

L. G. Forni
Department of Intensive Care Medicine, Surrey Peri-operative Anaesthesia Critical Care Collaborative Research Group (SPACeR), Royal Surrey County Hospital, NHS Foundation Trust, Egerton Road, Guildford GU2 7XX, UK