Beware the dog that didn't bark: A tale of creatinine in acute kidney injury

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References

1 Rowland JP, Rigby J, Harper AC, Rowland R. Cardiovascular monitoring with acetylcholinesterase inhibitors: a clinical protocol. *Advances Psych Treatment* 2007; **13**: 178–84.

2 Isik AT, Yildiz GB, Bozoglu E, Yay A, Aydemir E. Cardiac safety of donepezil in elderly patients with Alzheimer disease. *Intern Med* 2011; **51**: 575–8.

3 Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. *Heart* 2003; **89**: 1363–72.

4 Calvo-Romero J, Ramos-Salado J. [Symptomatic sinus bradycardia associated with donepezil]. *Rev Neurol* 1998; **28**: 1070–2.

5 Bordier P, Lanusse S, Garrigue S, Reynard C, Robert F, Gencel L *et al*. Causes of syncope in patients with Alzheimer's disease treated with donepezil. *Drugs Aging* 2005; **22**: 687–94.

6 Monfredi O, Dobrzynski H, Mondal T, Boyett MR, Morris GM. The anatomy and physiology of the sinoatrial node – a contemporary review. *Pacing Clin Electrophysiol* 2010; **33**: 1392–406.

Beware the dog that didn't bark: a tale of creatinine in acute kidney injury

A rapid reduction in creatinine concentration within 24 h of cardiac arrest is reported to associate with better clinical outcomes while stable or increasing creatinines are associated with higher mortality.[1]

We reviewed the records of all adults (>17 years) suffering out of hospital cardiac arrest followed by induced hypothermia in the Christchurch Hospital intensive care unit (ICU) in 2013. Sequential plasma creatinine results for the first 36 h were grouped according to percentage change in creatinine at admission baseline, at 3–7 h, at >7–11 h and at >11–36 h. Increased creatinine ($pCr_{increase}$) was defined as a ≥20% increase from baseline, stable creatinine (pCr_{stable}) as neither an increase (<20%) nor decrease (>9%), and decreased creatinine ($pCr_{decrease}$) as a ≥10% reduction from baseline (Fig. 1). Baseline creatinine was defined as the first available creatinine after cardiac arrest. Mortality data were collected in ICU and at hospital discharge.

Of a total of 57 patients, nine were in the $pCr_{increase}$ group of whom five died (56%), 15 were pCr_{stable} of whom 10 died (67%), and 33 in the $pCr_{decrease}$ group of whom 12 died (36%) (Fig. 1). The mortality rate was greater in the pCr_{stable} group compared with the $pCr_{decreased}$ group (P = 0.018). We were unable to distinguish whether the cause of death was due to cardiogenic shock or severe hypoxic brain injury, because many individuals had both conditions, often with other pathologies, such as aspiration pneumonia.

However, these results highlight concerns with the use of plasma creatinine as a biomarker and in creatinine-based guidelines for acute kidney injury (AKI) diagnosis[2,3] as the definitions assume creatinine generation is constant. If creatinine generation is con-

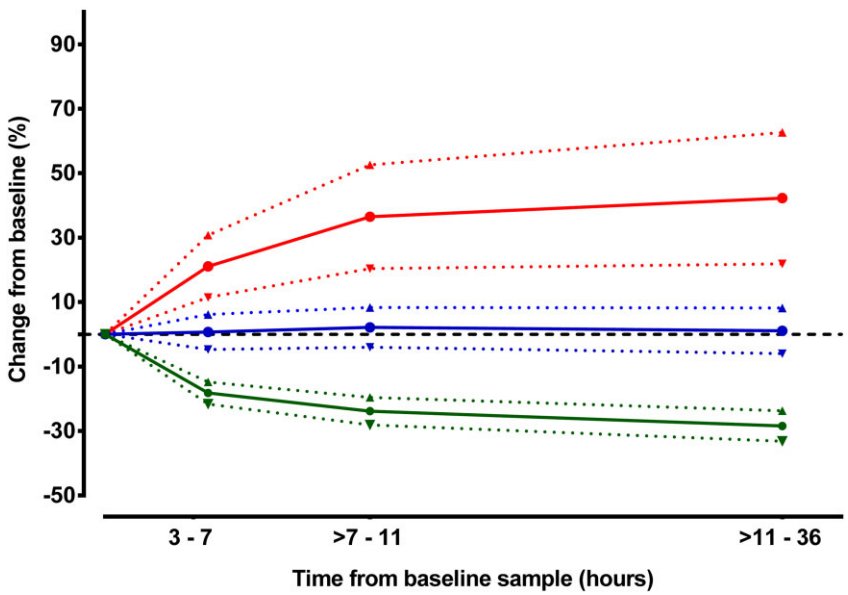

Figure 1 Changes in plasma creatinine concentration (%) relative to the first creatinine measured after cardiac arrest. Solid lines represent mean percentage change in plasma creatinine for each group; dotted lines depict 95% confidence limits. The mean baseline creatinine concentration for the $pCr_{increase}$ group was 168 μmol/L (SD: 99), for the pCr_{stable} group; 145 μmol/L (SD: 65) and for the $pCr_{decrease}$ group; 111 μmol/L (SD: 23). In the pCr_{stable} group, two patients died before the third sample (>7–11 h) was collected. In the $pCr_{increase}$ and $pCr_{decrease}$ groups, one and two patients in each group died, respectively, before 7 h post-admission to the emergency department. (—●—), Increase; (—●—), stable; (—●—), decrease.

stant, an increase in concentration is expected with reduced renal perfusion following cardiac arrest. AKI is complex and heterogenous in aetiology, with manifestations varying from minimal or no elevation in creatinine to anuric renal insufficiency with large increases in creatinine concentration. Although reduced urine output is in the consensus definitions of AKI, a decrease in urine output may follow structural or obstructive kidney disease, and recent evidence suggests the urine output criteria are too liberal.[4] Urine creatinine excretion has been shown to be decreased in those requiring longer hospital stay suggesting the presence of decreased creatinine production.[5] We hypothesise that creatinine generation decreases post-cardiac arrest. The $pCr_{decrease}$ group can then be explained by clearance with near-normal glomerular filtration rate (GFR). In this scenario, the unchanging creatinine in the pCr_{stable} group is attributable to the combination of decreased creatinine production with GFR impairment.

Prowle *et al*. recently documented a reduction in creatinine in patients who survived critical illness.[6] Like Arthur Conan Doyle's Sherlock Holmes (in *The Hound of the Baskervilles*), we caution clinicians (to 'beware') that plasma creatinine concentrations ('the dog') may not alert us to underlying AKI as is shown in the pCr_{stable} ('that didn't bark') group. Therefore, this suggests the need for intervention when creatinine does not decrease immediately after cardiac arrest. Future research could be aimed at measuring creatinine production to assess its role in patients with acute illness.

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References

1 Pickering JW, Ralib AM, Endre ZH. Combining creatinine and volume kinetics identifies missed cases of acute kidney injury following cardiac arrest. *Crit Care* 2013; **17**: R7.

2 KDIGO. Section 2: AKI Definition. Chapter 2.1: definition and classification of AKI. *Kidney Int Suppl* 2012; **2**: 19–36.

3 Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG *et al*. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11**: R31.

4 Ralib AM, Pickering JW, Shaw GM, Endre ZH. The urine output definition of acute kidney injury is too liberal. *Crit Care* 2013; **17**: R112.

5 Schetz M, Gunst J, Van den Berghe G. The impact of using estimated GFR versus creatinine clearance on the evaluation of recovery from acute kidney injury in the ICU. *Intensive Care Med* 2014; **40**: 1709–17.

6 Prowle JR, Kolic I, Purdell-Lewis J, Taylor R, Pearse RM, Kirwan CJ. Serum creatinine changes associated with critical illness and detection of persistent renal dysfunction after AKI. *Clin J Am Soc Nephrol* 2014; **9**: 1015–23.

Unusual presentation of Epstein–Barr virus encephalitis in an older patient with a dramatic clinical response to intravenous immunoglobulin

Epstein–Barr virus (EBV) usually presents non-specifically, or with infectious mononucleosis, a clinical syndrome characterised by lymphadenopathy, pharyngitis and fever, with atypical lymphocytosis.[1,2] EBV is less common in adults, as 90–95% already have antibodies.[3] Central nervous system complications, including encephalitis, are uncommon.[1,2]

A 66-year-old independent woman with no significant past history presented alert and oriented after a complex partial seizure. She experienced chills, lethargy, nausea, anorexia and a dull frontal headache 4 days prior. Physical examination was unremarkable.

Investigations are displayed in Table 1. She was commenced on oral levetiracetam 1 g t.d.s. and intravenous (IV) acyclovir 740 mg t.d.s. Two days post admission, she became acutely confused, disorientated, tachycardic, hypertensive and pyrexic.

She was found to have hospital-acquired pneumonia and mild cellulitis, so she was administered IV cefazolin 1 g daily and a single dose of gentamicin 5 mg/kg.

She was commenced on IV amoxicillin 2 g t.d.s. for queried leptospirosis or listeria and a 5-day course of intravenous immunoglobulin (IVIg) 0.4 g/kg daily for