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Letters to the Editor

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The problems with neonatal immune system screening using glutathione levels

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Dear Editor,

We read with great interest Christopher Pavlovski's article, "Efficacy of screening immune system function in at-risk newborns", recently published in the AMJ.[1] We would like to raise a few issues about using glutathione as a neonatal screening biomarker.

Using glutathione as a surrogate marker for immune system performance is problematic since it does not appear that a decreased glutathione level (or its derivatives) or aberrant glutathione metabolism is specific to any one condition.[2] As a result, the proposed treatment options in the article do not treat the underlying problem specifically. As Pavlovski pointed out,[1] glutathione is depleted or implicated in a plethora of medical conditions, including HIV/AIDS and inflammation. Moreover, he also pointed out that external factors such as breastfeeding, diet, and supplementation can affect glutathione levels; hence, assessing it in the neonatal period may be counterproductive, particularly when enteral feeding of pre-term infants may not occur immediately following delivery.

There appears to be a role for glutathione screening for the specific metabolic disorder, reduced glutathione deficiency;[3] but this is currently not included in the list of rare metabolic disorders screened via heel-prick testing in Australia.[4]

Clinically, it is more useful to detect the precise metabolic disorder—be it a gene mutation or an abnormal level of a metabolite—rather than a surrogate, as this can dictate management and genetic counselling considerations. Newborn screening is designed to identify newborns that appear healthy but have a potentially serious underlying disease, thereby allowing early, targeted intervention as appropriate. This becomes especially important in primary immunodeficiencies (PID); yet, Pavlovski did not make adequate mention of these, which are rare but important causes of an immunologically compromised neonate/infant. One of the best-known examples of PID is severe combined immunodeficiency (SCID)—a disorder affecting T and B cells and potentially causing serious infections very early in an infant's life. However, for various reasons, screening for this condition is currently not offered in Australia.[4]

Neonatal insults, from obstetric or intrinsic pathological origins, are already well-recognised causes of secondary immunodeficiencies, for which the author was alluding to in screening. Thus, clinical acumen is still required and perhaps more valuable in determining if a neonate is likely to be immunologically compromised. Further, the proposed "treatments" of encouragement of breastfeeding, milk banks, etc., in the article are already mainstream approaches in post-natal care, and, in agreement with primary healthcare principles, are actively encouraged, assuming no contraindications. Indeed, this will be encouraged and introduced irrespective of what a biomarker, like glutathione, shows.

Perhaps the future will hold more promise for the role of glutathione testing and supplementation in established diseases. Indeed, some interest has already been shown in conditions such as HIV/AIDS.[2] As a screening test for general newborn immune status, however, currently there appears to be more problems than solutions.

Sincerely,

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Conflicts of Interest

None to declare.

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Response to "The problems with neonatal immune system screening using glutathione levels"

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Dear Editor,

In response to the letter "The problems of neonatal immune system screening using glutathione levels" by Lee et al., I would like to acknowledge the authors and thank them for their interest in the article. May I kindly note that in the original paper[1] it was observed that when GSH levels are not progressively restored from clinical interventions, then it is necessary to conduct further diagnostic evaluation to detect the underlying cause. The benefit of any new screening test—whether this be metabolic or otherwise—is difficult to assess even when using randomised controlled trials,[2] hence it is suggested that in order to evaluate such a programme more fully that a pilot could potentially be conducted to better understand and analyse any cost-benefit effect.

Sincerely,
C.J. Pavlovski

Conflicts of Interest

None to declare.

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Paracetamol-induced liver failure: Would a standard set of guidelines improve outcome?

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Dear Editor,

Paracetamol toxicity is caused by excessive use or overdose of the drug. It is the most common cause of acute liver failure (ALF) in the Western world.[1] Acute liver failure secondary to paracetamol overdose characteristically presents as an initial gastrointestinal upset shortly after ingestion, often followed 24 to 48 hours later by hepatic injury. The hepatotoxicity results not from paracetamol itself, but from one of its metabolites, N-acetyl-p-benzoquinoneimine (NAPQI), which depletes the liver's natural antioxidant glutathione and directly damages cells in the liver, leading to ALF.[2] It rapidly progresses to lactic acidosis, coma, and death in previously healthy patients with no underlying liver disease.

Acute liver failure (ALF) has a mortality of greater than 80 per cent (depending on aetiology) in the absence of liver transplantation.[1] Many patients die before a suitable organ becomes available, and morbidity and mortality after transplant is also high.

The management of patients with ALF presents complex and challenging problems to all those involved in their care. Such patients inevitably have serious derangement of function in multiple organ systems and an evidence-based, coordinated approach is necessary to optimise clinical outcomes. Frequent clinical evaluation and assessment of various biochemical and haematological parameters forms the cornerstone of clinical care. The early institution of general supportive therapies, such as control of elevated

intracranial pressure and haemofiltration for renal failure, as well as specific therapies (e.g., N-acetylcysteine for paracetamol overdose) can provide the opportunity for potential liver recovery, or allow sufficient time for graft procurement in patients requiring transplantation.[3]

We report here on a small retrospective study investigating whether the institution of a standard set of guidelines, which were based on the King's College criteria for the management of paracetamol toxicity, could have an impact on the outcomes of our patients admitted with paracetamol-induced acute liver failure. The guidelines were developed for use at a single tertiary intensive care unit.

We identified patients admitted with the coded diagnosis of liver failure or pharmaceutical overdose admitted under the toxicology or liver failure units between 1999 and 2010. The guidelines, which were introduced in 2005, were used to ask questions of the data and divided the patients into pre- and post-protocol groups.

Comparisons were made between patients treated in the pre-protocol and post-protocol groups, and patients who did and did not survive hospital admission. Continuous data were inspected for normality and compared using t-tests or Mann-Whitney U tests as appropriate. All data were represented as median and inter-quartile ranges unless otherwise stated. Categorical data were compared using Chi-squared tests or Fisher exact tests as appropriate. Exact *p* values are reported and statistical significance was defined as $p<0.05$.

Multivariable analyses examining potential predictors of ICU mortality were performed using backwards stepwise logistic regression, with the base model including all recorded patient baseline characteristics and physiological response to paracetamol ingestion in the first 24 hours of ICU admission, and $p>0.10$ used for retention in the model. The final best model was subjected to ROC analysis, and significant predictors were combined with APACHE III risk of death to investigate whether, in this subgroup of patients, the APACHE III risk model could be improved upon.

All analyses were performed using Stata 9.2 (Stata Corp, College Station, TX, USA).

Forty-one patients were studied. Nine were included in the pre-protocol group and 32 in the post-protocol group. The most substantial effects of introducing the protocol included increasing the use of 20 per cent saline to treat and prevent cerebral oedema[3] (25 per cent vs. 67.9 per cent, $p=0.046$). This was done by aiming for a mild hypernatraemia of 145–150mmol/L. The incidence of a very high INR was reduced by administering 10mg of IV vitamin K daily and FFP if required. The INR was kept within the target range of <5 (those without an ICP monitor) or <2 (those with an ICP monitor) for 11.1 per cent in the pre-protocol group vs. 46.9 per cent in the protocol group ($p=0.07$). The proportion of patients receiving an ICP monitor decreased from 33.3 per cent to 5 per cent ($p=0.08$). The frequency of use of cardiac output monitoring was increased (11.1 per cent vs. 34.4 per cent, $p=0.176$). Blood sugar was to be maintained between 6–10mmol/L with 10 per cent dextrose infusion or insulin infusion as required. The lowest recorded blood sugar level was also increased ($p=0.03$), though there was no difference in the number of patients given 10 per cent dextrose. The percentage of patients whose blood sugar was kept within the target range of 4–8mmol/L rose to 53.1 per cent after the protocol was introduced ($p=0.005$).

No significant difference was observed in the use of continuous renal replacement therapy (CRRT), though there was a substantial difference observed in continuous venous haemodiafiltration (CVVHDF) use, which increased by 40 per cent in the protocol period ($p=0.06$). The highest ammonia prior to institution of CRRT was significantly higher in the pre-protocol group ($p=0.0074$). This remained the case at 24 hours ($p=0.0008$). The guidelines did not change the duration of NAC administration relative to the proportion of ICU stay, the rate at which norethisterone was used and the use of active cooling. Patients whose lactate fell over the first four hours were less likely to have an adverse outcome. Eleven out of 12 patients whose lactate level fell initially survived compared with nine out of 16 whose lactate did not ($p=0.048$). Patients whose lactate fell initially were less likely to have a significant bleed ($p=0.048$).

There was no difference between the two groups in the percentage of patients alive at ICU discharge.

There were acknowledged limitations to this study. Since this was a non-randomised study with comparisons taken from two time periods, it is therefore possible that other changes or improvement in general critical care practice might have led to improvements over time with or without a new set of guidelines being introduced.

The number of patients within each group was unequal, with only nine patients being assessed from the pre-protocol period. This was possibly due to incomplete and/or

incorrect coding practices and had the potential to skew the results.

In summary, our small study has suggested that the institution of guidelines provide a guide as to when to initiate treatment so that injurious extremes of physiological and biochemical derangement can be prevented, thus emphasising the value of protocols for the management of specific and selected conditions.

Sincerely,

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