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Title

The challenge of infrequency

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We thank Drs Perry and Singh for their comments on our article titled 'Febrile children in the Emergency Department: frequency and predictors of poor outcome'(1). Drs Perry and Singh raise several issues about the clinical scores that were chosen and the outcomes that were included in the study.

The scores that were chosen for evaluation in our study reflect existing severity scores which are widely used to assess organ dysfunction in patients evaluated for sepsis. In contrast, warning tools such as the paediatric early warning score (PEWS) used in the United Kingdom exist in multiple forms (>18) and serve to identify children at risk of deterioration in a general ED or ward population.

The study inclusion criteria were designed to capture the broad range of children presenting to the ED with febrile illness reflecting a real-world cohort. It is in these un-differentiated children that the clinical scores evaluated in our study would be applied in clinical practice. As such, it was expected that the vast majority would have an infective cause for fever, consistent with the epidemiology of paediatric ED presentations. Non-infective / auto-immune febrile syndromes, such as Systemic Lupus Erythematosus or Crohn Disease are rare in this population and hence unlikely to have a significant impact on the study findings.

The majority of the paediatric literature on severe infection in the ED has focussed on the utility of clinical signs for *diagnosing* sepsis. The inclusion of organ dysfunction criteria in this study was intended to investigate their utility for *risk stratification*. New organ dysfunction is used in the adult Sepsis-3 criteria and by the Paediatric Sepsis Definition Taskforce(2). We concur that

mental health outcomes and long-term disability are without doubt important, though were necessarily beyond the scope of a retrospective study.

Poor outcomes in febrile children presenting to the ED are very uncommon in industrialised countries. Only 4/6217 (<0.1%) of febrile patients required inotropic support in our dataset, and only one patient died. In the United Kingdom, of a cohort of 5156 children, 1 patient required inotropic support and 1 patient died(3). Predicting which patients will require inotropic support or die is therefore very difficult, the pre-test likelihood is inherently very low. Complicating matters further, most children with febrile illness have abnormal vital signs, which represents a normal, adaptive response to infection in the majority of cases. Currently used clinical scores and biomarkers perform poorly, as shown in our study, indicating the need for new approaches. In the ED setting, the initial *diagnosis* of sepsis remains a clinical one. Applying predictive tests to this select patient group, with a higher pre-test likelihood of poor outcome, may yield better test characteristics for clinical scores and biomarkers and improve their clinical utility for *risk stratification*.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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