Today we write to draw attention to two problems with the recent study on a scoring system for bruising by Dunstan et al.1

Firstly, the authors did not publish confidence intervals for the likelihood ratios (LRs) derived from different scores threshold values (table 3), thereby not allowing readers to judge whether the LRs are statistically—let alone clinically—significant.

Secondly, the authors neglect the phenomenon of spectrum bias. This is a well described feature of many tests, whereby sensitivity and specificity (and hence derived LRs) of a test may not be clinically—significant.

Judge whether the LRs are statistically—let alone clinically—significant.

We recommend for the use of cefotaxime alone 23 per 100 live births.1 It has been reported that THI does not usually predispose to significant infection.

A male infant born at term to non-consanguineous parents presented at 3.5 months with cough, tachypnoea (70 breaths/minute), wheeze, crepitations, and hypoxia. A chest radiograph showed bilateral and patchy opacification in the hilar regions and upper lobes. Pneumocystis carinii was identified in bronchoalveolar lavage by toluidine blue staining. The immunological findings of this child were consistent with those of THI with a tG level less than the fifth centile and absent serum IgA1 which resolved with age (IgG at presentation 3.9 g/l (normal: 1.39–8.04); at 5 months 2.23 (1.39–8.04); at 10 months 1.77 (2.02–11.76); at 17 months 7.51 (2.71–13.78); IgA at 5 months <0.07 g/l (normal: 0.14–0.69); at 13 months 0.14 (0.17–1.34) and evidence of specific antibody production to tetanus, diphtheria, and Haemophilus influenzae type b following immunisation.1 Total cell numbers (total lymphocytes 6.2 x 10^9/l, CD3 68%, CD4 56%, CD8 15%) and phytohaemagglutinin induced proliferation were normal. At 3 years the child was well with normal IgG, IgA, and IgM levels. Pneumocystis carinii pneumonia presenting in the first three months of life is an infection typically seen in patients with significant T cell immunodeficiencies and X linked hyper IgM. These were excluded by normal T cell numbers and function and by normal C4D0 ligand expression and mutation analysis. There are reports of Pneumocystis carinii pneumonia in immunocompetent infants and agammaglobulinaemia. This is the first description of Pneumocystis carinii pneumonia in a patient with THI.

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References


Pneumocystis carinii pneumonia in an infant with transient hypogammaglobulinemia of infancy

Transient hypogammaglobulinemia of infancy (THI) is characterised by prolongation of the physiological decline in serum immunoglobulin concentrations seen in the first six months of life.1 The incidence reported from an Australian paediatric centre was estimated as 23 per 100 live births.1 It has been reported that THI does not usually predispose to significant infection.

A male infant born at term to non-consanguineous parents presented at 3.5 months with cough, tachypnoea (70 breaths/minute), wheeze, crepitations, and hypoxia. A chest radiograph showed bilateral and patchy opacification in the hilar regions and upper lobes. Pneumocystis carinii was identified in bronchoalveolar lavage by toluidine blue staining. The immunological findings of this child were consistent with those of THI with a tG level less than the fifth centile and absent serum IgA1 which resolved with age (IgG at presentation 3.9 g/l (normal: 1.39–8.04); at 5 months 2.23 (1.39–8.04); at 10 months 1.77 (2.02–11.76); at 17 months 7.51 (2.71–13.78); IgA at 5 months <0.07 g/l (normal: 0.14–0.69); at 13 months 0.14 (0.17–1.34) and evidence of specific antibody production to tetanus, diphtheria, and Haemophilus influenzae type b following immunisation.1 Total cell numbers (total lymphocytes 6.2 x 10^9/l, CD3 68%, CD4 56%, CD8 15%) and phytohaemagglutinin induced proliferation were normal. At 3 years the child was well with normal IgG, IgA, and IgM levels. Pneumocystis carinii pneumonia presenting in the first three months of life is an infection typically seen in patients with significant T cell immunodeficiencies and X linked hyper IgM. These were excluded by normal T cell numbers and function and by normal C4D0 ligand expression and mutation analysis. There are reports of Pneumocystis carinii pneumonia in immunocompetent infants and agammaglobulinaemia. This is the first description of Pneumocystis carinii pneumonia in a patient with THI.

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Procalcitonin as a prognostic marker in children with meningococcal septic shock

Carrol and coworkers\(^1\) confirm the findings from Karabocoglu et al\(^2\) who reported that procalcitonin (PCT) was higher in children with severe meningococcaemia (fever, petechiae, purpura, and hemodynamic instability) than in children with systemic meningococcal infection without shock (291.29 ± 167 v 19.7 ± 23 ng/ml; p < 0.001)\(^2\).

Unfortunately, information is lacking in the report of Carrol et al\(^1\), namely: a clear definition of severe MCD (defined in their paper as a Glasgow Meningococcal Septicaemia Prognostic Score >8) and median PCT values of adult and comparison in term of prediction of outcome between PCT level and generic or specific severity scoring systems. We report that admission PCT level is an accurate predictor of mortality in the subgroup of children with meningococcal septic shock (MSS). We prospectively investigated 35 children (median age: 16 months; Q1–Q3: 4–42) with severe meningococcaemia (fever, petechiae or purpura, and hemodynamic instability) admitted to our PICU between July 1999 and May 2002. We estimated the accuracy in predicting death of PCT, C reactive protein (CRP, nephelometry)\(^4\) on admission, and the Pediatric Risk of Mortality (PRISM) score\(^5\) within 24 hrs of admission or at the time of death. Sensitivity, specificity, positive and negative predictive values, and percentage of well classified children were calculated at the following cut-off values: PCT >130 ng/ml (the best cutoff value of the PCT level was determined by \(\chi^2\) optimisation (Fisher’s test; p = 0.0004)), CRP <100 mg/l, PRISM value >20 and PRISM probability of death >50%.

Hatherill et al\(^6\) showed that the area under the ROC curve (AUC) and the standard error (SE) of the PRISM score 3\(\times\) in 35 children with MSS (PCT v PRISM value, p = 0.05; PCT v PRISM probability, p = 0.03); PCT v CRP, p = 0.06; CRP v PRISM value, p = 0.01; CRP v PRISM probability, p = 10\(^{-7}\)).

In our study, PCT on admission was as an accurate predictor of death calculated within 24 hrs of admission or at the time of death, and more accurate than the CRP level in classifying survivors and nonsurvivors of MSS. These results accord with those of Hatherill et al\(^6\) who observed, in 37 children with MSS, that admission PCT level (values not indicated) was higher in nonsurvivors (11%) than in survivors (p = 0.04) and related to the severity of organ failure (p = 0.02); however, in the whole group of children with septic shock whatever the causative organism, admission PCT functioned worse than the PRISM score (AUC 0.73 (0.59–0.88) v 0.83 (0.71–0.93); statistical comparison not performed).\(^6\)

The PRISM score is accepted in PICUs worldwide and has been reported to accurately predict outcome of meningococcal disease.\(^7\)

However, as it needs a 24 hour observation period, it cannot be used as an inclusion criterion for clinical trials. Admission PCT could represent a good alternative tool if further studies confirm its ability to predict mortality.

**Figure 1** ROC curves (AUC±SE) for PCT, CRP, and PRISM score in 35 children with MSS (PCT v PRISM value, p = 0.05; PCT v PRISM probability, p = 0.03; PCT v CRP, p = 0.06; CRP v PRISM value, p = 0.01; CRP v PRISM probability, p = 10\(^{-7}\)).

### Table 1

<table>
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<th>CRP</th>
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**References**


Incidence of severe and fatal reactions to foods

Although the article by Macdougall et al\(^3\) regarding the incidence of severe and fatal reactions to food would be seen as reassuring, we would like to express some concerns and raise some questions about the data presented. The first question is whether the ascertainment of cases is really as complete as the authors suggest. We acknowledge that the UK medical system may allow better reporting and access to mortality data than that of the US. However, the records acquired as described seem to represent the same underreporting issues as those in the US. Is it really unlikely that the BPSU misses a significant number of cases? Based upon a well characterised population in Olmstead county Minnesota and extrapolating the data to a US population of 280 million, it may be estimated that there are 200 deaths from anaphylaxis reactions to food each year.\(^3\)

A paper published in 2001, described methodology in which a National Registry had been established and was well publicised to US allergists\(^6\). Very few reports were made by allergists and none by other physicians. No cases were initially reported by physicians who conduct research in food allergy. Nearly all the cases were ascertained from the press. These news articles appeared in local newspapers and were not reported in media with a large regional or national circulation. In an earlier effort to account for all cases of food anaphylaxis, only in Colorado, a significantly

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PostScript
A second concern is the reporting of cases only up to age 15. In the paper mentioned above, of 32 fatalities 10 occurred in youngsters up to age 15. An additional 10 occurred in adolescents aged 16 to 19. Why did MacDougall et al not include all adolescents? A third question must always be raised when fatal food anaphylaxis is studied: Is it not possible that cases of fatal asthma were actually initiated by unidentified allergic reactions to food? All authors in this field are likely to agree that the ultimate cause of death may be irreversible airway obstruction, and all would agree that poorly controlled asthma increases the risk of fatal anaphylactic reactions to food, but we would suggest that the trigger responsible for individual asthma fatalities is not always determined. What about fatalities that never reach the emergency room, and are misclassified on death certificates as asthma fatalities? Individuals that die at home and are classified as asthma deaths are unlikely to be further investigated, neither in the US or the UK.

Fourthly, the authors’ definition of severity seems incomplete. Individuals with severe food reactions who self administer epinephrine often do not go to hospital, are less likely to have reactions that require hospitalization or cause death, and often they do not report these reactions to their physicians unless specifically queried. Some survive the reaction without treatment, become convinced that they are not allergic to a specific food, and never tell their physician. We could argue about the possible progression of these episodes to near fatal or fatal reactions, but the point here is that these deaths are under reported. The fifth issue concerns the safe administration of epinephrine. We disagree about the risk to children of the administration of a single dose of epinephrine as opposed to withholding that dose. We have no disagreement about aggressive treatment of asthma concurrently, and in fact we think that point should be emphasized. However families reading this commentary may become more fearful than they currently are, about administering epinephrine. We know that epinephrine is not always life saving even when administered in a timely fashion, however withholding it surely must increase the risk of death. Over dosage certainly may occur, but it seems more likely that an overdose would be administered by medically trained personnel than by parents. The over prescription of epinephrine is a debatable issue, however it seems a small price to pay, with a low risk, in order to save even one young life.

Finally, we are very concerned that families will interpret this paper to mean that death from food allergy is very unlikely and therefore they may relax their vigilance. If families of younger children become less concerned when their children become adolescents it may be difficult to institute a good prevention program. This is the opposite of the goal of education programs in the US (The Food Allergy and Anaphylaxis Network, www.foodallergy.org) and UK (The Anaphylaxis Campaign) aimed at making individuals with food allergy and the general population more aware of the problem and the potential for mortality. It is truly unfortunate that we cannot accurately identify all of the individuals who die during allergic reactions to food and use this information to do a better job of preventing these tragedies. We must continue our campaigns of education of medical professionals and the public, and we must be certain that emergency treatment is available when and where it is needed.


definition of severity, seems very small. Differences in protocols, there is no evidence that any immediate hypersensitivity reaction to food means their child is at high risk as well as those many parents that think any anaphylactic reaction to food or for knowing if a causal link exists”. Furthermore, such deaths will never have been reported in surveys of food allergy in other countries or in other age groups. No group has been able to address this question satisfactorily and it is a key area for further research.

We are not sure we agree that children, who have self administered epinephrine, often do not go to hospital. However we do not know the proportion and said as much, excluding this group from our definition of severity. Finally we agree that education of professionals and the public should continue based on the best data available. This include those parents whose children are truly at high risk as well as those many parents that think any anaphylactic reaction to food means their child is at high risk of an allergic death; when in reality the risk, in the absence of asthma, seems very small. Different parents will come to different views about how to proceed faced by a severe but very small risk, just as we all do in many aspects of our lives.

References

Physiologic management of DKA

Inward and Chambers provide a provocative description and discussion of the continuing confusion regarding the issues surrounding rehydration and treatment of the pediatric patient with diabetic ketoacidosis (DKA). They review some of the key issues that link fluid therapy to complications from brain swelling, and question the appropriateness of using a volume of fluid calculated by "maintenance plus deficit", calling for a second revolution in the management of DKA. In the accompanying commentary, Edge makes several statements concerning fluid therapy in DKA, including that "DKA is associated with severe fluid losses", that "any guidelines for fluid and electrolyte management must be simple to calculate", that administration of DKA is a risk for metabolic complications, and that despite published guidelines and "changes in protocols", there is no evidence that the "incidence of cerebral oedema has changed over the past 20 years". It is our opinion that the problem in the rehydration of the pediatric patient with DKA
does not lie in assigning a maintenance fluid allotment. Rather, the source of error lies largely with failure to accurately estimate the volume of deficit and the tendency to automatically assume a severe degree of dehydration from our experience with over 450 consecutive cases of moderate and severe DKA, and our weight gain data, severe DKA (ie severe ketoacidemia) does not necessarily mean severe dehydration; the converse is also true. The degree of dehydration ranges from negligible (<1%) to extreme (>20%). Severe ketoacidemia, however, does cause vasoconstriction which may be manifested peripherally by cool, mottled skin, and Kussmaul breathing which leads to very dry oral mucosa. The striking appearance of a parched mouth and the presence of cool, even mottled skin without a critical assessment of vital signs and examination of distal (foot) pulses often results in an erroneous impression of shock and “severe dehydration.” A method for estimation of the volume of deficit was described in 1990 and we continue to use this approach. Successfull therapy requires not only gradual deficit replacement (evenly over 48 hours) but an accurate estimation of the volume of deficit along with careful tracking of the clinical and biochemical response. If the deficit is assumed to be 10-15% but is actually only 3%, that patient will receive excess water independent of the more gradual timeframe and independent of the rehydration fluid given. Guidelines that have proposed “safe” limits to fluid volumes administered such as 4 litres/m²/day or 50 kg body weight/4 hours violate the concept of the individualised assessment of the degree of deficit. Inseparably, overhydration will overhydrate and severely dehydrated child; the problem is compounded when actual body weight is used instead of ideal body weight in fluid calculations for the obese patient. On the other hand, certain patients, particularly those with complicating illness—for example, septic shock, pancreatitis—may require more than 20 mld/2kg of fluid resuscitation in the first hour of resuscitation, or “pushes” of hypertonic sodium bicarbonate should not be given. On the other hand, there is no evidence that administration of physiologic concentrations of base in the rehydration fluid will prevent or treat the elevated plasma bicarbonate alkalosis which accompanies severe DKA. Whether the additional therapy minimised the risk of brain herniation during treatment.

Comments regarding the administration of base should be better defined. Rapid administra tion or “pushes” of hypertonic sodium bicarbonate should not be given. On the other hand, there is no evidence that administration of physiologic concentrations of base in the rehydration fluid will prevent or treat the elevated plasma bicarbonate alkalosis which accompanies severe DKA. Whether the additional therapy minimised the risk of brain herniation during treatment.

As ours is a referral centre, most of our patients have received initial therapy initiated in outlying hospitals, sometimes in keeping with our recommended approach, and sometimes with our recommendations instituted only after initial contact. In this setting, we have managed certain patients with severe DKA who received resuscitation fluids in excess of what their physical examination and laboratory data would dictate. It is not unusual for such patients to require as little as a typical maintenance allotment (without a deficit replacement component) for the remainder of therapy; some patients required fluid restriction to as little as two thirds the usual maintenance volume.

Our approach has been criticised because of the incidence of mannitol administration in our series. In our mannitol recipients, several of whom did not receive their initial management by us, there was no central nervous system morbidity or mortality. In another large series of patients there was a 50% failure rate of mannitol to reverse a deteriorating neurologic status, even when mannitol was given before respiratory arrest, with a near 100% failure rate when mannitol was given after respiratory arrest.1 It is possible that not all of our mannitol recipients actually had raised intracranial pressure. We believe, however, that the key to our good outcome is the fluid and electrolyte therapy on which mannitol is superimposed is relevant to its success. It is erroneous to conclude that the 100% success rate among our mannitol recipients would be reproducible in the setting of a therapy that violates the fundamental principles of rehydrating the hypertonic state DKA.

Dr Inward and Chalmers ask “do we have it right yet?” and convey concern that certain recommendations do not, as of yet, “have it right”. We agree.

Our work regarding the management of the pediatric patient in moderate to severe DKA has spanned 14 years1 and nearly 500 consecutive prospecitively managed episodes. We remain available to participate in any endeavour to continue to improve the care of the paediatric patient in DKA.

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References


The Position Statement on Injection Technique

The Position Statement on Injection Technique (March 2002, Royal College of Paediatrics and Child Health) discusses needle size and length for childhood immunisation. It concludes that there would seem to be insufficient evidence to advise any recommendation to change current practice in the use of needle size. As the authors of a research study that aimed to provide some evidence base for immunisation practice we would like to respond to this.1

Our study of 119 babies aged 4 months receiving their third dose of DPT/Hib vaccine found that significantly less redness and swelling occurred when infants were immunised using the longer 23 gauge 25mm (blue hub) needle rather than when the shorter 25 gauge 16mm (orange hub) needle was used. The magnitude of the reductions was substantial. The position statement is correct to note that in our study the difference in tenderness did not reach statistical significance. However we believe our study still
justifies a recommendation for the use of the longer needle for immunisation in 4 month old infants.

We believe the non-significant difference in tenderness with the different needles must be interpreted with caution, and should not be taken as a rationale for ignoring the significant benefits in terms of reduced redness and swelling. Tenderness was in fact reduced by the same relative amount as redness, but as tenderness occurred less frequently, the results were not formally statistically significant. We have used Bayesian analyses (using an “uninformative” prior distribution) to formally compute the chance that there is a clinically significant reduction (of at least 25% as specified in the protocol) in tenderness between the long and short needles. At six hours the probability of a clinically significant decrease in tenderness with the longer needle is 73%, whereas the chance of a clinically significant increase is only 2%. The evidence is therefore clearly in the direction of the longer needle causing less harm.

We recognise the need for further evidence on which to base immunisation practice at each of the infant immunisation ages. To this end, we are now conducting a randomised controlled trial involving over 600 infants aimed at providing a definitive answer. In the meantime, we reiterate our recommendation to practitioners to use the longer needle for immunising 4 month old infants.

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Reference