Pre-test probability falls, performance—that is, LR—is not independent of the likelihood ratios (LRs) derived from different score 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 vary with disease severity or prevalence. Examples of spectrum bias have been described with several tests including exercise stress testing1 and UTI diagnosis.2

The study population had a prevalence of physical abuse of 40%, much higher than the general paediatric population. Since test performance—that is, LR—is not independent of the pre-test probability, the LRs generated by a study done on this population cannot necessarily be used in a population with a much lower prevalence of abuse, as the authors have done in table 4. Since spectrum bias tends to reduce test performance as the pre-test probability falls, the LR for any given score threshold would be smaller than that quoted when applied to a population with a lower prevalence of physical abuse.

As most settings would expect to have a lower prevalence of physical abuse than the study, this reduces the value of the proposed scoring system as a clinical tool.

M Williams
Intensive Care Unit, Charing Cross Hospital, London, W6 8RF, UK

B Krishnan
Department of Paediatrics, Guy’s Hospital, London SE1 9RT, UK

Correspondence to Dr Williams; matthewwilliams.org

References

Does cefotaxime eradicate nasopharyngeal carriage of N meningitidis

We enrolled 43 children admitted with an unequivocal clinical diagnosis of meningococcal sepsis into a study to determine whether cefotaxime eradicated nasopharyngeal carriage of Neisseria meningitidis. In 28 cases (70%) the diagnosis was confirmed by positive culture from blood, nose, throat, or skin scraping, detection of meningococcal DNA in blood by polymerase chain reaction, or convalescent meningococcal serology. All children were treated with intravenous cefotaxime for seven days. Nasopharyngeal and throat swabs were obtained on the day of admission in 42 of these children, and all children had swabs repeated every day until there were at least two negative swabs.

On admission, the throat and nasopharyngeal swabs were both positive for meningococcus in two patients; in another two patients, the nasopharyngeal swab was positive while the throat swab was negative. In three patients the swabs became negative after 24 hours of treatment, and in one child it became negative after 48 hours. In these children and others in whom the swabs were negative from the day of admission, subsequent swabs remained negative.

Compared to a previous study1 that reported a nasopharyngeal carriage rate of 50% on admission and showed that the yield of meningococcus in throat swabs was unaffected by prior administration of penicillin,10 the yield from throat and nose swabs in this study (9.5%) was poor. This may reflect the fact that in practice many of these swabs were taken after the child had been given the first dose of cefotaxime. The study suggests that cefotaxime, like rifampicin,11 is effective in eradicating nasopharyngeal carriage, and in children treated with cefotaxime, additional prophylaxis with rifampicin is not necessary. However, no recommendations for the use of cefotaxime alone can emanate from these findings as the sample size was small and study design did not compare cefotaxime with gold standard treatment (either rifampicin or ceftriaxone). We are keen to coordinate a follow up multicentre study this winter involving paediatric intensive care units across the country to compare the efficacy of ceftriaxone with cefotaxime on eradication of meningococcal carriage. Interested units are kindly requested to contact us.

J Clark, R Lakshman, A Galloway, A Cant Newcastle General Hospital, UK
Correspondence to: J Clark, Department of Child Health, Newcastle General Hospital, Newcastle upon Tyne NE4 6BE, UK; julia.clark@nuth.northy.nhs.uk

References

Pneumocystis carinii pneumonia in an infant with transient hypogammaglobulinaemia of infancy

Transient hypogammaglobulinaemia 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 to be 23 per 10 000 live births.2 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 of age with cough, tachypnoea (70 breaths/minute), wheeze, crepitations, and hypoxia. A chest radiograph showed consolidation and hyperinflation, 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 an IgG level less than the fifth centile and absent serum IgA4 which resolved with age (IgA 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 influenza type b following immunisation.1 T cell numbers (total lymphocytes 6.2 × 109, 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.4 These were excluded by normal T cell numbers and function and by normal CD40 ligand expression and mutation analysis. There are reports of Pneumocystis carinii pneumonia in immunocompetent infants5 and agammaglobulinaemia.6 This is the first description of Pneumocystis carinii pneumonia in a patient with THI.

J M Smart, A S Kemp
Department of Immunology, Royal Children’s Hospital, Flemington Road, Parkville 3052, Australia; kempa@cryptic.rch.unimelb.edu.au

D S Armstrong
Department of Respiratory Medicine, Royal Children’s Hospital

References
Procalcitonin as a prognostic marker in children with meningococcal septic shock

Carrol and coworkers\(^1\) confirm the findings from Karabocuoglu et al\(^1\) who reported that procalcitonin (PCT) was higher in children with severe meningococcaemia (fever, petechial purpura, and hemodynamic instability) than in children with systemic meningococcal infection without shock (291.29 ± 117 v 19.7 ± 25 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 admission. Fisher's test (p = 0.0004), \(\chi^2\) analysis, 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 prospecitively investigated 35 children (median age: 16 months; Q1-Q3:45 with MSS (defined as ecchymotic or necrotic purpura with shock, needling fluid expansion (median for the first 24 hrs: 90 ml/kg; Q1-Q3:48–120 and catecholamine infusion) admitted to our PICU between July 1999 and May 2002. We estimated the accuracy in predicting death of PCT, C reactive protein (CRP), procalcitonin (PCT), neutrophil count, the Pediatric Risk of Mortality (PRISM) score\(^3\) and the Pediatric Risk of Mortality (PRISM) score\(^3\) 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 cutoff values: PCT >110 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%. For each severity index, we calculated the area under the ROC curve (AUC) and the standard error (SE)\(^3\) and determined the significance of comparisons.\(^4\)

Eleven of 35 children died (31%); predicted mortality with the PRISM score was 15.6 (standardised mortality ratio: 0.71; 95% confidence interval: 0.35–1.26). The median (Q1-Q3) PCT and CRP levels and PRISM value and probability of death were the following: survivors v nonsurvivors PCT 73 (15–210) v 277 (208–606) ng/ml (p = 0.001); CRP 92 (44–160) v 72 (41–109) mg/l (p = 0.23); PRISM value 17 (8–22) v 33 (26–37) (p < 0.01); PRISM probability 19 (4–42) v 88 (63–95%) (p < 0.10). Performance characteristics and AUC ± SE of PCT, CRP, and PRISM score are given in the table and the figure.

In our study, PCT on admission was as accurate as the PRISM value and probability 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\(^1\) 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).\(^5\)

The PRISM score is accepted in PICUs worldwide and has been reported to accurately predict outcome of meningococcal disease.\(^6\) 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.

### Table 1 Performance characteristics of PCT, CRP, and PRISM score in 35 children with MSS

<table>
<thead>
<tr>
<th>Severity index (%)</th>
<th>PCT</th>
<th>CRP</th>
<th>PRISM value</th>
<th>PRISM probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100</td>
<td>64</td>
<td>100</td>
<td>91</td>
</tr>
<tr>
<td>Specificity</td>
<td>63</td>
<td>46</td>
<td>63</td>
<td>83</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>50</td>
<td>35</td>
<td>50</td>
<td>100</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>100</td>
<td>46</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td>Well classified</td>
<td>74</td>
<td>51</td>
<td>74</td>
<td>86</td>
</tr>
</tbody>
</table>

### References


### Incidence of severe and fatal reactions to foods

Although the article by MacDougall et al\(^i\) regarding the incidence of severe and fatal reactions to food would be seen to be 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.\(^i\)

A paper published in 2001, described methodology in which a National Registry had been established and was well publicised to US allergists.\(^i\) 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 national or regional circulation. In an earlier effort to account for all cases of food anaphylaxis, only in Colorado, a significantly
higher number of cases were reported from
rural regions as compared to metropolitan
areas strongly suggesting either misdiagnosis
or inaccurate recording of cases in the emer-
gency department log of busy hospitals.
A second concern is the reporting of cases
only up to the age of 15. In the paper mentioned
above, of 32 fatalities 10 occurred in young-
sters 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 reac-
tions to food, but we would suggest that the
target responsible for individual asthma
fatalities is not always determined. What
about fatalities that never reach the emer-
gency department and are misclassified on
death certificates as asthma fatalities? Indi-
viduals that die at home and are classified as
asthma deaths are unlikely to be further
investigated in either the US or the UK.
Fourthly, the authors’ definition of severity
seems incomplete. Individuals with severe
food reactions who self administer epi-
phrine often do not go to hospital, are less
likely to have reactions that require hotali-
sation 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 have an allergy 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 in either the US or the UK.
Finally, we are very concerned that families
will interpret this paper to mean that death
from anaphylaxis is very unlikely and therefore
they may relax their vigilance. If families of
younger children become less con-
cerned when their children become adoles-
cents it may be difficult to institute a good
prevention program. This is directly
opposed to 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
data more aware of the problem and the
potential for mortality. It is truly unfortu-
nate that we cannot accurately identify all of
the individuals who die during allergic reac-
tions 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.
References
1 Macdougall CF, Cant AJ, Colver AF. How
dangerous is food allergy in childhood? The
incidence of severe and fatal allergic
reactions in England and Ireland. Arch Dis
2 Yocum MW, Butterfield JH, Klein JS, et al.
Epidemiology of anaphylaxis in Olmsted
County: A population based study. J Allergy
3 Bock SA, Munoz-Furlong A, Sampson HA.
Fatalities due to anaphylactic reactions to
4 Bock SA. The incidence of severe adverse
reactions to food in Colorado. J Allergy Clin
Authors’ reply
We thank Bock et al for their interest in our
article. We respect their views on the
interpretation of the data but it is of course
for each reader to come to their own opinion
on these. We would like to respond to their com-
ments on the accuracy and validity of our
data.
Did our paper under ascertain deaths? Bock
et al base their concerns on our methods of
case ascertainment and on comparison with
another study. We cannot be certain about this
but as the text indicated we used many
sources and spoke to many experts in the
field. We agree we did not search local
newspapers but this would have been almost
impossible as few were on CD-ROM in the
1990s. As mentioned, we did search national
newspapers and all cases we came across were
already known through one of our other
sources. Finally, since publication, no-one
has told us of a case we appear to have missed.
We specifically studied children up to 15 years
because this is the group we were inter-
ested in. Many recommendations on risks to
children are based on inferences from data
covering all ages and we wanted to bring a
proper paediatric perspective. Indeed the
interpretation Bock et al give to the paper they
cite is grossly misleading. They suggest
extrapolation to a US population would lead to
200 deaths from food each year yet the
paper, in which there is only one death
(occurring during exercise), covers all ages
and reactions to all allergens, not just food.
The issue of whether asthma deaths may
have been precipitated by food must be an
important question which we addressed “If a
child’s symptoms are only asthmatic and no
allergy is suspected, then there is no means
for attributing such reactions 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
d 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 profes-
sionals and the public should continue based
on the best data available. This must include
those parents whose children are truly at high
risk as well as those many parents that think
any immediate hypersensitivity 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. Differ-
ent 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.
A Colver
Northumbria Health Care Trust and University
of Newcastle upon Tyne, Donald Coursier House,
Walker Terrace, Gateshead NE8 1EB, UK
C Macdougall
Newcastle General Hospital, Westgate Road,
Newcastle upon Tyne NE4 6BE, UK
A Cant
Paediatric Immunology and Infectious Diseases Unit,
Newcastle General Hospital, UK
Correspondence to D Bock; Bockdoc@aol.com
Correspondence to Dr Colver; alan.colver@ncl.ac.uk
Reference
1 Yocum MW, Butterfield JH, Klein JS, et al.
Epidemiology of anaphylaxis in Olmsted
County: a population based study. J Allergy
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).1
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 “mainte-
nance plus deficit”, calling for a second
revolution in the management of DKA. In the
accompanying commentary, Edge makes sev-
eral 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
fluid is a risk factor for mortality, that
changes in protocols, and that despite published
literature and “changes in protocols”, there is no
evidence that the “incidence of cerebral oedema has
changed over the past 20 years”.5
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 episodes of moderate and severe DKA, we found that our weight gain data, severe DKA (ile 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 vascular constriction which may be manifested peripherally by cool, mottled skin, and Kussmaul breathing which leads to peri-orbital edema and mucusa. 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 analysis successfully. Successful therapy requires not only gradual deficit replacement (evenly over 48 hours) but an accurate estimation of the volume of deficit along with careful timing 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 deficit actually given. Guidelines that have proposed “safe” limits to fluid volumes administered such as 4 litres/m2/day or 50 ml/kg body weight/4 hours violate the concept of the individualised assessment of the degree of deficit which will invariably overweight the mild to moderately dehydrated child; the problem is compounded when actual body weight is used instead of ideal body weight in fluid replacement 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 ml/kg of fluid resuscitation in the first treatment hour and more than 50 ml/kg in the first four hours. Setting arbitrary fluid volume limits per hour or per day endanger particularly those patients at the mild and severe ends of the dehydration spectrum. Although the insult would be greater with hypertonic fluid, overhydration occurs readily with isotonic fluid as well when water requirements are overestimated.

DKA represents the effects of a complex disruption of normal metabolism, which leads to metabolic death if left untreated. Shock (decreased peripheral pulses, with or without hypotension), if present, should be corrected rapidly. Insulin should be given preferably by continuous, low dose, intravenous infusion, as soon as possible to begin correction of ketoacidemia/ketoacidosis. Regardless of the serum concentration of glucose, insulin is recommended in order to protect the hepatic fat-carnitine cycle leading to ketoadipation. A delay in insulin administration only serves to enhance and prolong ketoadipsia, thereby extending the period of time, in which the patient is at risk. Successful therapy minimised the risk of brain herniation during treatment.

Comments regarding the administration of mannitol for intracranial hypertension 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 result in either harmful or desirable. In our experience, this practice mitigates the development of hyperchloremic acidosis during treatment.

As ours is a referral centre, most of our patients have a history of therapy initiated in outlying hospitals, sometimes in keeping with our recommended approach, and sometimes with our recommendations instituted only after intracranial pressure 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. 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 that the fluid and electrolyte therapy on which mannitol is superimposed is relevant to its success. It is erroneous to misinterpret a 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).

The 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 reimmunisation to change current practice in the use of 25 gauge needles. As the authors of a research study that aimed to provide some evidence base for immunisation practice we would like to respond to this.

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 18mm (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.

L Diggle
Oxford Vaccine Group, Department of Paediatrics, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU, UK

J Deeks
Centre for Statistics in Medicine, Institute of Health Sciences, University of Oxford, Oxford OX3 7LF, UK

Correspondence to: L Diggle; linda.diggle@paediatrics.ox.ac.uk

Reference