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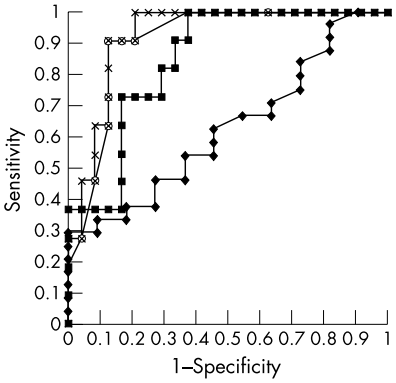
Procalcitonin as a prognostic marker in children with meningococcal septic shock

Carrol and coworkers[1] confirm the findings from Karabocuoglu *et al* who reported that procalcitonin (PCT) was higher in children with severe meningococcaemia (fever, petechia or 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 survivors and non-survivors 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; Q1:9–Q3:45) with MSS (defined as ecchymotic or necrotic purpura with shock, needing 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: nephelometry)[3] on admission, and the Pediatric Risk of Mortality (PRISM) score[4] 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 >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 3, PRISM value >20 and PRISM probability of death >50 %.[5] For each severity index, we calculated the area under the ROC curve (AUC) and the standard error (SE)[6] and determined the significance of comparisons.[7]

Eleven of 35 children died (31%); predicted mortality with the PRISM score was 15.6 (standardised mortality ration: 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=0.25); PRISM value 17 (8–22) *v* 33 (26–37) ($p < 10^{-3}$); PRISM probability 19 (4–42) *v* 88 (63–95) % ($p < 10^{-3}$). Performance characteristics and AUC ± SE of PCT, CRP, and PRISM score are given in the table and the figure.



	AUC	SE
CRP	0.63	0.10
PCT	0.85	0.06
PRISM value	0.91	0.05
PRISM probability	0.92	0.04

Figure 1 ROC curves (AUC±SE) for PCT, CRP, and PRISM score in 35 children with MSS (PCT *v* PRISM value, p=0.45; PCT *v* PRISM probability, p=0.31; PCT *v* CRP, p=0.06; CRP *v* PRISM value, $p<10^{-2}$; CRP *v* PRISM probability, $p<10^{-2}$).

In our study, PCT on admission was as accurate as the PRISM value and PRISM 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* 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).[8]

The PRISM score is accepted in PICUs worldwide and has been reported to accurately predict outcome of meningococcal disease.[9 10] 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.

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

Severity index (%)	PCT	CRP	PRISM value	PRISM probability
Sensitivity	100	64	100	91
Specificity	63	46	63	83
Positive predictive value	55	35	55	71
Negative predictive value	100	46	100	95
Well classified	74	51	74	86

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Incidence of severe and fatal reactions to foods

Although the article by Macdougall *et al*[1] regarding the incidence of severe and fatal reactions to food would be seem 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.[2]

A paper published in 2001, described methodology in which a National Registry had been established and was well publicised to US allergists [3] 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

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 emergency department log of busy hospitals.[4]

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.[3] 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 department 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.

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 hospitalisation 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 know to avoid 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 to be made is that they are frequently 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 emphasised. 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,[5] however withholding it surely must increase the risk of calamity. 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 to difficult to institute a good prevention education program. This is exactly 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.

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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 comments on the accuracy and valididity 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 interested 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[1] 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 allergy is an important question which we addressed "If a child's symptoms are only asthmatic and no allergen 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 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 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. 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.

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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 "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 base is a risk factor for intracranial complications, and that despite published data and "changes in protocols", there is no evidence that the "incidence of cerebral oedema has changed over the past 20 years".[1]

It is our opinion that the problem in the rehydration of the pediatric patient with DKA