SHORT REPORT

Controlled study of respiratory viruses and wheezing

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Arch Dis Child 2002;**87**:221–222

Wheezing in early childhood is common, occurring in approximately 50% of children before the age of 6 years.[1] Understanding the role of respiratory viruses in triggering acute wheezing in children has been compromised by the lack of comparison groups in previous studies.[2]

The objective of this study was to investigate the association (using a control group) of two common viruses—influenza virus and respiratory syncytial virus (RSV)—with acute wheezing among children, aged 1–7 years, with a past history of wheezing.

METHODS

Children, aged 1–7 years, with two or more previous wheezing episodes, were enrolled from a paediatric community practice and an emergency department during two consecutive winters (1997/1998, 1998/1999) into this concurrent case–control study.

Cases had previous wheezing and current symptoms of an upper respiratory infection and acute wheezing (clinical score of at least 1). Controls had previous wheezing and current symptoms of an upper respiratory tract infection, without acute wheezing (clinical score of 0) at the time of enrolment or within the week following enrolment. Children were excluded if they had received immunisation for influenza in the year of enrolment. The study was approved by the Hospital for Sick Children Research Ethics Board, and informed parental consent was obtained.

Baseline characteristics were collected and wheezing severity was graded using a clinical score (minimum to maximum range: 0–10). Nasopharyngeal swab specimens were collected and examined for influenza viruses A and B and RSV by immunofluorescence microscopy (antibodies from Light Diagnostics, Temecula, CA) and cell culture (RMK cells: Viromed Diagnostics, Minniapolis, MN; and MDCK cells: American Type Culture Collection, Rockwood, MD).

The odds ratio and 95% confidence interval were determined for influenza virus and RSV in children with acute wheezing (cases) relative to children with upper respiratory symptoms alone (controls). Separate analyses were undertaken for community cases versus controls, and all cases (community and emergency cases) versus controls.

RESULTS

Table 1 shows baseline characteristics. Table 2 shows the association between acute wheezing and virus infection. For influenza virus, the odds ratio indicates that infection is not associated with acute wheezing. The adjusted odds ratio (all cases versus controls) for the risk of acute wheezing in those with influenza was 0.52 (95% confidence interval, 0.27 to 1.03). For RSV, the odds ratio indicates that infection is associated with a threefold increase in the risk of acute wheezing.

Children with influenza virus (n = 43) and RSV (n = 58) were compared. Children with influenza virus were older (median age 3.6 years *v* 2.4 years, p = 0.002), had a lower

Table 1 Baseline characteristics—community cases, emergency department cases, controls

Characteristics	Community cases (n=89)	Emergency cases (n=84)	All cases (n=173)	Controls (n=106)	p value*
Age (y), median (range)	3.1 (1.1–7.0)	3.1 (1.0–6.7)	3.1 (1.0–7.0)	3.2 (1.0–7.0)	0.11
Clinical score, median (range)	1 (1–9)	5 (1–9)	3 (1–9)	0	
Sex (% male)	61 (69)	48 (57)	109 (63)	66 (62)	0.90
Smoke exposure (% exposed)	22 (25)	20 (24)	42 (24)	18 (17)	0.15
Family history of asthma (%)	49 (55)	46 (54)	95 (55)	64 (60)	0.37
Atopy (%)	11 (12)	45 (54)	56 (32)	13 (12)	0.0002
Daycare (%)†	25 (35)	30 (43)	55 (39)	36 (44)	0.45

Values are medians or numbers (range or percentages).
*All cases *v* controls.
†Of preschool aged children.

Table 2 Association between acute episodes of wheezing and influenza virus and RSV infections

Variable	Community cases (n=89)	All cases (n=173)	Controls (n=106)	p value	Odds ratio	95% CI
Influenza (% positive)	14 (16)	20 (12)	23 (22)	0.30* 0.02†	0.67* 0.47†	0.30 to 1.49* 0.23 to 0.95†
RSV (% positive)	23 (26)	47 (27)	11 (10)	0.005* 0.0008†	3.01* 3.22†	1.29 to 7.11* 1.52 to 6.98†

Values are numbers (percentages).
*Community cases *v* controls.
†All cases *v* controls.

median clinical score (0 *v* 2, $p < 0.001$), were more likely to be recruited from the community practice (87% *v* 59%, $p = 0.003$), and were less likely to be wheezing acutely (47% *v* 81%, $p = 0.0003$), compared to children with RSV. There were no differences in sex, history of smoke exposure, family history of asthma, and history of atopy.

DISCUSSION

When cases and controls were analysed for the viral aetiology of their respiratory illness, cases were three times as likely to be infected with RSV, but almost half as likely to be infected with influenza virus compared with controls. This finding existed in both the community and emergency department setting.

An extensive body of literature, summarised by Pattemore and colleagues,[2] has found that influenza virus and RSV are commonly identified in wheezing illnesses and asthma exacerbations occurring in childhood. The interpretation of these studies is compromised in that control groups were not included for comparison. The unique contribution of our study was the inclusion of a control group, to allow for an estimate of the strength of the association.

Our study may be limited by the case–control study design. Although a prospective cohort study would be appropriate, this would be an intensive and invasive process, requiring participants to undergo repeated nasopharyngeal swabs, both when symptomatic (wheezing) and asymptomatic (not wheezing). Therefore, we designed a case–control study, in which controls were chosen to be free of wheezing (outcome) but comparable to cases with respect to risk of exposure. Thus, controls were selected from those individuals seeking care for broadly defined symptoms of an upper respiratory infection. A strength of the design was the inclusion of both community and emergency department controls. Furthermore, determination of outcome (wheezing) and exposure (virus infection) was conducted concurrently.

An unexpected finding was the trend of the association between influenza virus and wheezing, suggesting that infection might actually be associated with a reduced risk of wheezing (adjusted odds ratio 0.52, 95% confidence interval, 0.27 to 1.03). While this may have been a chance finding, it contrasts with previous studies, which have found a high influenza virus related morbidity in children with recurrent wheezing and asthma.[3]

New hypotheses have emerged regarding the role of viruses in promoting or preventing the development of persistent wheezing and asthma.[4] Exposure to older children at home, children at day care, and repeated viral infections (other than lower respiratory tract infections) are thought to be protective.[5 6]

Understanding the role of respiratory viruses in triggering acute wheezing, and in the long term development or prevention of recurrent wheezing, will be important when considering strategies such as immunisation and antiviral therapy. In this context, we conclude that in our study the role of influenza virus in triggering acute wheezing in young susceptible children less than 7 years of age was weak, while the role of RSV in these children was strong.

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Accepted 11 May 2002

REFERENCES

1 **Martinez FD**, Wright AL, Taussig LM, *et al*. Asthma and wheezing in the first six years of life. *N Engl J Med* 1995;**332**:133–8.
2 **Pattemore PK**, Johnston SL, Bardin PG. Viruses as precipitants of asthma symptoms. 1. Epidemiology. *Clin Exp Allergy* 1992;**22**:325–36.
3 **Neuzil KM**, Wright PF, Mitchel EF Jr, *et al*. The burden of influenza illness in children with asthma and other chronic medical conditions. *J Pediatr* 2000:**137**:856–64.
4 **Johnston SL**, Openshaw PJM. The protective effect of childhood infections. *BMJ* 2001;**322**:376–7.
5 **Ball TM**, Castro-Rodriguez JA, Griffith KA, *et al*. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000;**343**:538–43.
6 **Illi S**, von Mutius E, Lau S, *et al*. Early childhood infectious diseases and the development of asthma up to school age: a birth cohort. *BMJ* 2001;**322**:390–5.

PostScript

LETTERS

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Problems with scoring bruises

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 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 testing[2] and UTI diagnosis.[3]

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,[4] 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.

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References

1 **Dunstan FD**, Guildea ZE, Kontos K, *et al*. A scoring system for bruise patterns: a tool for identifying abuse. *Arch Dis Child* 2002;**86**:330–3.
2 **Okin PM**, Kligfield P. Gender-specific criteria and performance of the exercise electrocardiogram. *Circulation* 1995;**92**:1209–16.
3 **Lachs MS**, Nachamkin I, Edelstein PH, *et al*. Spectrum bias in the evaluation of diagnostic tests: lessons from the rapid dipstick test for urinary tract infection. *Ann Intern Med* 1992;**117**:135–40.
4 **Hlatky MA**, Pryor DB, Harrell FE Jr, *et al*. Factors affecting sensitivity and specificity of exercise electrocardiography. Multivariable analysis. *Am J Med* 1984;**77**:64–71.

Does cefotaxime eradicate nasopharyngeal carriage of *N meningiditis*

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 study[1] that reported a nasopharyngeal carriage rate of 50% on admission and showed that the yield of meningococci in throat swabs was unaffected by prior administration of penicillin, 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 ceftriaxone,[2] 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.

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References

1 **Cartwright K**, Reilly S, White D, *et al*. Early treatment with parenteral penicillin in meningococcal disease. *BMJ* 1992;**305**:143–7b.
2 **Schwartz B**, Al-Tobaiqi A, Al-Ruwais A, *et al*. Comparative efficacy of ceftriaxone and rifampicin in eradicating pharyngeal carriage of group A Neisseria meningitidis. *Lancet* 1988;**1**:1239–42.

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 as 23 per 10^6 live births.[2] It has been reported that THI does not usually predispose to significant infection.[1 2]

A male infant born at term to non-consanguinous parents presented at 3.5 months with cough, tachypnoea (70 breaths/minute), wheeze, crepitations, and hypoxia. A chest radiograph showed hyperinflation and patchy opacification in the hilar regions and upper lobes. *Pneumocystis carinii* was identified in brochoalveolar 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[2] and absent serum IgA[1 2] 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 influenza type* b following immunisation.[1] T cell numbers (total lymphocytes 6.2×10^9/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 CD40 ligand expression and mutation analysis. There are reports of *Pneumocystis carinii* pneumonia in immunocompetent infants[3] and agammaglobulinaemia.[4] This is the first description of *Pneumocystis carinii* pneumonia in a patient with THI.

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References

1 **Tiller TL Jr**, Buckley RH. Transient hypogammaglobulinemia of infancy: review of the literature, clinical and immunologic features of 11 new cases, and long-term follow-up. *J Pediatr* 1978;**92**:347–53.
2 **Walker AM**, Kemp AS, Hill DJ, *et al*. Features of transient hypogammaglobulinaemia in infants screened for immunological abnormalities. *Arch Dis Child* 1994;**70**:183–6.
3 **Stagno S**, Pifer LL, Hughes WT, *et al*. Pneumocystis carinii pneumonitis in young immunocompetent infants. *Pediatrics* 1980;**66**:56–62.

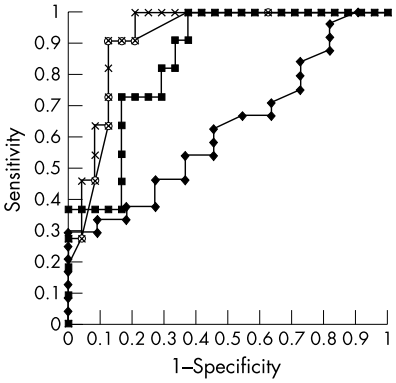
4 **Alibrahim A**, Lepore M, Lierl M, *et al*. Pneumocystis carinii pneumonia in an infant with X-linked agammaglobulinemia. *J Allergy Clin Immunol* 1998;**101**:552–3.

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

References

1 **Carrol ED**, Newland P, Riordan FAI, *et al*. Procalcitonin as a diagnostic marker of meningococcal disease in children presenting with fever and a rash. *Arch Dis Child* 2002;**86**: 282–5.
2 **Karabocuoglu M**, Kaya O. Plasma procalcitonin levels correlated with the severity of systemic meningococcal disease in children. *Crit Care Med* 2000;**28**(Suppl):A170.
3 **Leclerc F**, Chenaud M, Delepoulle F, *et al*. Prognostic value of C-reactive protein level in severe infectious purpura: a comparison with eight other scores. *Crit Care Med* 1991;**19**:430–2.
4 **Pollack MM**, Ruttimann UE, Getson PR. Pediatric risk of mortality (PRISM) score. *Crit Care Med* 1988;**16**:1110–6.
5 **Mok Q**, Butt W. The outcome of children admitted to intensive care with meningococcal septicaemia. *Intensive Care Med* 1996;**22**:259–63.
6 **Hanley JA**, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;**143**:29–36.
7 **Hanley JA**, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;**148**:839–43.
8 **Hatherill M**, Tibby SM, Turner C, *et al*. Procalcitonin and cytokine levels: relationship to organ failure and mortality in paediatric septic shock. *Crit Care Med* 2000;**28**:2591–4.
9 **Castellanos-Ortega A**, Delgado-Rodriguez M. Comparison of the performance of two general and three specific scoring systems for meningococcal septic shock in children. *Crit Care Med* 2000;**28**:2967–73.
10 **Leteurtre S**, Leclerc F, Martinot A, *et al*. Can generic scores (Pediatric Risk of Mortality and Pediatric Index of Mortality) replace specific scores in predicting the outcome of presumed meningococcal septic shock in children? *Crit Care Med* 2001;**29**:1239–46.

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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References

1 **Macdougall CF**, Cant AJ, Colver AF. How dangerous is food allergy in childhood? The incidence of severe and fatal allergic reactions across the UK and Ireland. *Arch Dis Child* 2002;**86**:2236–9.
2 **Yocum MW**, Butterfield JH, Klein JS, *et al*. Epidemiology of anaphylaxis in Olmstead County: A population-based study. *J Allergy Clin Immunol* 1999;**104**:452–6.
3 **Bock SA**, Munoz-Furlong A, Sampson HA. Fatalities due to anaphylactic reactions to foods. *J Allergy Clin Immunol* 2001;**107**:101–3.
4 **Bock SA**. The incidence of severe adverse reactions to food in Colorado. *J Allergy Clin Immunol* 1992;**90**:683–5.
5 **Sampson HA**. Peanut allergy. *N Engl J Med* 2002;**346**:1294–8.

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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Reference

1 **Yocum MW**, Butterfield JH, Klein JS, *et al*. Epidemiology of anaphylaxis in Olmsted County: a population based study. *J Allergy Clin Immunol* 1999:**104**:452–6.

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

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, and our weight gain data,[2] severe DKA (ie severe ketoacidemia) does not necessarily mean severe dehydration; the converse is also true.[2 3] The degree of dehydration ranges from negligible (<1 %) to extreme (>20 %).[3] 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":[3] A method for estimation of the volume of deficit was described in 1990[2] and we continue to use this approach successfully. Successful therapy requires not only gradual deficit replacement (evenly over 48 hours) but an accurate estimation of the volume of deficit along with critical monitoring of the clinical and biochemical response.[3] 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 type of fluid given. Guidelines that have proposed "safe" limits to fluid volumes administered such as 4 litres/m^2/day[4] or 50 ml/kg body weight/4 hours[5] violate the concept of the individualised assessment of the degree of dehydration and will invariably overhydrate the mild to moderately 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 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 hypotonic 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 required to inhibit the hepatic fatty acyl carnitine cycle leading to ketoacid formation.[6] A delay in insulin administration only serves to enhance and prolong ketoacidemia, thereby extending the period of time during which the patient remains vulnerable to central nervous system and other complications.

Our proposed management strategy may not satisfy the call for simplicity but it is an easily learned approach. It requires an understanding of relevant, known pathophysiology, the monitoring of serial physical examinations and laboratory studies with special attention to correction of acidemia and osmolality, and the anticipatory care that is inherent in the care of the critically ill.[2 3 6–10 12] Physiologic management was first described between 1988[10] and 1990,[2] and set forth with additional detail and data in 1994.[3] It is rarely described in its complete form when referenced in texts; mere portions of our recommendations do not constitute what we have called physiologic management. Not only is it unlikely that large numbers of patients outside our own institution have been managed using our guidelines in their entirety, but the recommendations simply are not old enough to be reflected in data over the past 20 years. We suspect that physiologic management is significantly underrepresented in the multicentre studies conducted thus far, all of which compare variations of traditional therapy (empiric volume resuscitation whether or not shock is present, assumption of a large volume of deficit, planned rehydration in less than 48 hours with either 0.45% or 0.9% NaCl, with or without urinary output replacement). In a retrospective portion of our study in 1990[2] we compared these same therapies and also found that no form of traditional therapy minimised the risk of brain herniation during treatment.

Comments regarding the administration of base should be better defined. Rapid administration 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 solution are either harmful or undesirable. In our experience, this practice mitigates the development of hyperchloremic acidosis during treatment.

As ours is a referral centre, most of our patients have some form of therapy initiated in outlying hospitals, sometimes in keeping with our recommended approach, and sometimes with our recommendations instituted only after initial telephone 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.[1] 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.[11] 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 assume 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 of DKA.

Drs Inward and Chambers 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 years[1 12] and nearly 500 consecutive prospectively 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

1 **Inward CD**, TL Chambers, Edge J. Fluid management in diabetic ketoacidosis. *Arch Dis Child* 2002;**86**:443–5.
2 **Harris GD**, Fiordalisi I, Harris WL, *et al*. Minimizing the risk of brain herniation during treatment of diabetic ketoacidemia: a retrospective and prospective study. *J Pediatr* 1990;**117**:22–4.
3 **Harris GD**, Fiordalisi I. Physiologic management of diabetic ketoacidemia. A 5 year prospective pediatric experience in 231 episodes. *Arch Pediatr Adolesc Med* 1994;**148**:1046–52.
4 **Duck SC**, Wyatt DT. Factors associated with brain herniation in the treatment of diabetic ketoacidosis. *J Pediatr* 1988;**113**:10–4.
5 **Mahoney CP**, Vleck BW, DelAguila M. Risk factors for developing brain herniation during diabetic ketoacidosis. *Pediatr Neurol* 1999;**21**:721–7.
6 **Fiordalisi I**, Harris GD. Diabetic Ketoacidemia. In: Finberg L, Kleinman RE, eds. *Saunders Manual of Pediatric Practice, 2nd edn*. Philadelphia: WB Saunders Co, 2002: 938–46.
7 **Harris GD**, Fiordalisi I, Yu C. Maintaining normal intracranial pressure in a rabbit model during treatment of severe diabetic ketoacidemia. *Life Sci* 1996;**59**:1695–702.
8 **Harris GD**, Lohr JW, Fiordalisi I, *et al*. Brain osmoregulation during extreme and moderate dehydration in a rat model of severe DKA. *Life Sci* 1993;**53**:185–91.
9 **Bohn D**, Daneman D. Diabetic ketoacidosis and cerebral edema. *Curr Opin Pediatr* 2002;**14**:287–91.
10 **Harris GD**, Fiordalisi I, Finberg L. Safe management of diabetic ketoacidemia. *J Pediatr* 1988;**13**:65–7.
11 **Rosenbloom A**. Intracranial crises during treatment of diabetic ketoacidosis. *Diabetes Care* 1990;**13**:22–33.
12 **Fiordalisi I**, Harris GD, Gilliland MGF. Prehospital cardiac arrest in diabetic ketoacidemia. Why brain swelling may lead to death before treatment. *J Diabet Compl* 2002;**16**:214–9.

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

1 **Diggle L**, Deeks J. Effect of needle length on incidence of local reactions to routine immunisation in infants aged 4 months: randomized controlled trial. *BMJ* 2000;321:931–3.

CORRECTION

The paper by Parkin *et al* in the September issue of Archives (*Arch Dis Child* 2002;**87**:221–2) was missing acknowledgements. The following paragraph should have been included:

Rita Arseneault, Audrey Bell-Peter, Diana Cohen, Pauline Matthews, Suzanne Stewart, and Olwen Tennis participated in patient enrollment and data collection. Derek Stephens assisted in statistical consultation. Rose Cheung and Carol Collins did the immunofluorescence microscopy and virus isolation tests. Dr Raymond Tellier oversaw virus testing for part of the time while he was on service.

Funding: This work was supported in part by grants from the Hospital for Sick Children Research Institute and the American Academy of Pediatrics. The Paediatric Outcomes Research Team is supported by a grant from the Hospital for Sick Children Foundation.