Use of cyclosporin A as a steroid sparing agent in cystic fibrosis

EDITOR—In cystic fibrosis (CF) chronic respiratory infection is countered by an intense inflammatory reaction. Systemic steroids have been shown to improve lung function and reduce morbidity in patients with CF and reduce markers of chronic inflammation;1 however, there are significant side effects associated with their long term use. Low dose cyclosporin A (CyA) has been shown to be effective in the treatment of inflammatory and autoimmune diseases, corticosteroid dependent chronic severe asthma in adults, and refractory childhood asthma.2

We report six paediatric CF patients where CyA had been used as a steroid sparing agent. These patients were on treatment with high dose inhaled or nebulised steroids prior to the commencement of oral steroids, and repeated attempts at reducing the steroid dose were unsuccessful. All patients exhibited steroid related complications including Cushingoïd features, growth suppression, impaired glucose tolerance, hypertension, osteoporosis, and bone fractures. The dosage of CyA was adjusted to maintain whole blood trough levels between 100 and 150 ng/ml, using CyA doses ranging from 2 to 37 mg/kg/day.

In the four patients who benefited from CyA therapy the mean steroid dose decreased from 0.86 mg/kg/day in the one month prior to commencement of CyA to 0.30 mg/kg/day six months later and 0.25 mg/kg/day 12 months later. These patients were able to discontinue oral steroids within 18 months of commencement of CyA. Two patients did not show a reduction in mean steroid dosage, one of which underwent a successful heart-lung transplantation.

In the four patients who responded to CyA, lung function was maintained or improved, as were Chripisin-Norman chest x ray scores. Height velocity was also improved. Three patients did develop transient renal impairment, of whom only one required discontinuation of CyA. This was dose related and reversible but is infrequent with lower dose regimens used for anti-inflammatory therapy.2 Other side effects due to CyA were minimal, including mild hypertrichosis and gingival hyperplasia. There was no evidence of hypertension, hepatotoxicity, or neurotoxicity. The side effect profile of CyA is no more severe than for other immunosuppressive agents.

It is evident that CyA is a powerful but potentially toxic therapeutic agent and its use should be balanced against the risks of the disease and the long term use of steroids. These results suggest that CyA can be beneficial as a steroid sparing agent in CF patients; these data may be of help to the clinician in comparable clinical circumstances.

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S A MAGUIRE
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References

Survey of criteria used to diagnose allergic bronchopulmonary aspergillosis in cystic fibrosis

EDITOR—Allergic bronchopulmonary aspergillosis (ABPA) creates a difficult diagnostic and management problem in patients with cystic fibrosis (CF). The six major diagnostic criteria for ABPA in CF developed from asthma guidelines.3 Retrospective studies report significant variability in prevalence and the numbers of criteria for diagnosis.4 This is important as CF databases (UK CF database, European Registry, and the North American CF database) report ABPA frequency either without ascertaining the criteria used, or using limited diagnostic criteria. We have assessed consensus current practice to diagnose ABPA and how cases were treated.

This retrospective, descriptive postal questionnaire survey was addressed to senior consultants in the 58 CF specialist clinics identified by the UK CF Trust. A total of 45 replies were received (78%); three were illegible/incomplete. Results are validated by the UK CF Trust.

Table 1: Replies to questionnaire (% of all units)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Assessed yearly or more</th>
<th>Must be present</th>
<th>Prefer to be present</th>
<th>Not important</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus precipitin</td>
<td>83</td>
<td>42</td>
<td>49</td>
<td>10</td>
</tr>
<tr>
<td>Aspergillus specific IgE</td>
<td>52</td>
<td>54</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td>*CXR infiltrates</td>
<td>95</td>
<td>38</td>
<td>41</td>
<td>17</td>
</tr>
<tr>
<td>Blood eosinophilia (&gt;500/mm³)</td>
<td>83</td>
<td>24</td>
<td>56</td>
<td>20</td>
</tr>
<tr>
<td>Aspergillus fumigatus skin test</td>
<td>5</td>
<td>11</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>Total serum IgE (&gt;1000 ng/ml)</td>
<td>79</td>
<td>45</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>33</td>
<td>8</td>
<td>13</td>
<td>68</td>
</tr>
<tr>
<td>Wheeze/cough</td>
<td>—</td>
<td>46</td>
<td>39</td>
<td>15</td>
</tr>
</tbody>
</table>

*Six major criteria investigations.

Subnormal growth in children with Helicobacter pylori infection

Editor.—We read with interest the study by Choe and colleagues1 in which they investigated the effect of Helicobacter pylori infection and iron deficiency anaemia on growth, especially in pubescent children. In this study, height values were found to be below the 25th centile in 18 of 63 (28.6%) H pylori positive children. The prevalence rate of H pylori infection was 15.5% in children without iron deficiency anaemia and 31.3% in those with iron deficiency anaemia (p = 0.022). They also revealed that the mean height of subjects who had both H pylori infection and iron deficiency anaemia decreased significantly. They concluded that H pylori infection accompanied by iron deficiency anaemia,

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1. 10.1136/adc.84.1.89a
rather than H pylori infection alone, might delay pubertal growth.  

We investigated the frequency of diminished growth in 30 H pylori positive children (21 girls and 9 boys) diagnosed by serology and histology. The mean age was 11.5 (2.0) years (range 8–15). We found 11 (36.7%) H pylori positive patients with height values below the 25th centile. Anemia was determined in none of the patients. Mean haemoglobin concentration was 130 (9) g/l.  

H pylori infection is a chronic persistent infection, leading to diminished growth. Chronic gastric inflammation, dyspepsia, decreased nutritional intake, and malnutrition can contribute to diminished growth.  

In one study among the pastoral Maasai in Kenya, action was taken by the parents to give their children additional milk to children whose weight for age was subnormal (Megan M. Personal communication, 1999).

Growth monitoring

Editor,—Garner and colleagues recently presented a much needed review of growth monitoring. 1 This is a component of primary health care on which so much finance and health workers’ time is being expended. No doubt this review will stimulate more necessary trials.  

However, they did not touch on one important aspect of growth monitoring—that is, whether health workers using growth charts comprehend the weight for age graph. Piaget (1896–1980) considered the line graph to be one of the more difficult subjects to teach. Experience with post-primary education suggests that primary education is not taught in primary schools in developing countries. 2 Y charts comprehend the weight for age graph. 3 Using data from 19 234 children, a range of possible responses, particularly when the bowel motion is loose or offensive (inquiring about symptoms at home, suggesting a visit to the family doctor, arranging a faecal sample, and informing and seeking the advice of public health agencies). We were aware of the issue of specificity and did not suggest that all these activities should necessarily occur on every occasion that more than one child with more than one bowel motion was recorded. Most agree that faecal sampling needs, generally, to be encouraged. 4 However, to combine the activities into a workable algorithm was beyond the scope of the report. Constructing an algorithm is worth attempting, however, since, as a starting point, a recording tool constitutes a straightforward record used in a number of care settings.

Detecting outbreaks of E coli O157 infection in nurseries

Editor,—In their report of a serious outbreak of E coli O157 in a nursery in North Wales, Al-Jader and colleagues recommend that more than one child with more than one bowel motion in a nursery should trigger action including “informing and seeking the advice of public health agencies”. 1 Using data on healthy children in nurseries in the paper we have calculated the additional work that would be generated for the Public Health Department in the district in which the outbreak occurred if this policy was implemented.

Of 19 well children on the ground floor of the nursery, six had more than one bowel motion on at least one of the half day sessions attended during the surveillance period. 2 Well children attending nursery six days during the period, giving an approximate total number of sessions attended of 228 (19 × 6 × 2). The probability of a well child having more than one bowel motion during any half day session was therefore about 0.026 (6/228). There are 385 nursery and playgroups in North Wales, with an average of 23 children per nursery. 3 In an average nursery the probability that two or more well children would have more than one bowel motion in a session on any one day is 0.12, equivalent to a false alarm every eight days.

Therefore, if the suggested policy was implemented, and incidents were reported to the Public Health Department, this would result in approximately 46 inappropriate calls per day (0.12 × 385)—that is, 230 per week. Even if the normal background rate was ten times lower than that seen among well children during this outbreak, this would still result in just over three calls a week to the department reporting false alarms. The proposed “early warning system” is therefore unnecessary in the community, presenting to general practice, and reported to national surveillance. 4

Meningococcal disease due to W135: fresh public health concerns

Editor,—The paediatric intensive care unit at St Mary’s Hospital in London admits more than 100 cases of meningococcal disease each year from over 50 different hospitals in the south east of England. Since 1992, the unit has treated over 650 patients with the disease, but had not treated a single case of serogroup W135 meningococcal infection until April 2000. We would like to report four children treated at our hospital for meningococcal disease caused by W135, type 2A, subtype P1.2, P1.5, which within a one month period from April 2000. They had been vaccinated recently with meningococcal serogroup C conjugated vaccine, and had all been


### Table 1 Clinical presentation, severity and outcome

<table>
<thead>
<tr>
<th>Case</th>
<th>Contact with travellers</th>
<th>Presentation/Resuscitation fluid</th>
<th>Mechanical ventilation (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grandmother</td>
<td>Petechiae, septicaemia, 80 ml/kg fluid</td>
<td>2</td>
<td>Discharged</td>
</tr>
<tr>
<td>2</td>
<td>Father</td>
<td>Purpura fulminans, septicaemia, 350 ml/kg fluid</td>
<td>11</td>
<td>Peripheral gangrene</td>
</tr>
<tr>
<td>3</td>
<td>6 family members</td>
<td>No rash or fluid, no introtropes</td>
<td>0</td>
<td>Discharged</td>
</tr>
<tr>
<td>4</td>
<td>2 Aunts</td>
<td>Purpura, septicaemia, 90 ml/kg fluid</td>
<td>2</td>
<td>Discharged</td>
</tr>
</tbody>
</table>

*Total resuscitation fluid required in first 24 hours in contact with travellers returning from Mecca. The clinical features of these cases are outlined in the table.

The data represent four out of 38 cases (with five fatalities) of serogroup W135 Neisseria meningitidis infection in England and Wales within the six week period from March to May 2000 (PHLS Meningococcal Reference Unit, personal communication), with hundreds of cases of the identical subtype being reported throughout Europe. 1,2 Saudi Arabia has reported over 225 cases, with almost 25% mortality to the end of April 2000. It is thought that this large outbreak of an unusual strain originated in Saudi Arabia, with the pilgrimage of a record 1.3 million people to the Haj between 15–18 March 2000. 1

A similar outbreak occurred in 1987, due to serogroup A, subgroup III. This also followed the yearly pilgrimage to Mecca, and to serogroup A, subgroup III. This also followed the yearly pilgrimage to Mecca. The clinical features of these cases are detailed in the statement may also be misleading. The claim that “feeding lactose-free diets in infancy . . . will cause false negative results in most neonatal screening tests for galactosemia.” In the absence of systematic studies comparing the allergenicity of cow’s milk hydrolysates with soy formulas in children with CMA, the rationale to disregard this indication appears to be lacking. E. Riva, A. Piccioni, L. Fiori, M. Giovannini. Department of Paediatrics, University of Milan Medical School, San Paolo Biomedical Institute, Via F. Sforza, 15, 20142 Milan, Italy

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### Prevention and treatment of cow’s milk allergy

**EDITOR.—**Divergences in existing guidelines on the prevention and treatment of cow’s milk allergy (CMA) in infants 1,2 seemed settled when a joint statement by the committees of ESPACI/ESPGHAN appeared in *ADC*. 3 However, we take exception to some of the assumptions, which have been left open to challenge from both nutritional and allergological points of view. Our concern is that lactose free diets from birth may cause neurological problems in healthy children. Galactose is a functionally important component of myelin galactolipids, but it is unclear whether a lactose free diet plays a role in the clinical neurological abnormalities of children with galactosaemia. However, lactose is essential for patients with UDP-galactose-4-epimerase deficiency. Though rare, this disorder should be considered in the evaluation of the risk:benefit ratio and the costs of planning a prevention strategy for which the benefits are still unclear. In this context, issues of colonic ecology and malabsorption take second place. 4 The use of screening tests for errors of lactose metabolism as interpreted in the statement may also be misleading. The claim that “feeding lactose-free diets from birth . . . will cause false negative results in most neonatal screening tests for galactosaemia” overlooks the fact that these tests do not establish blood galactose levels but the presence/deficiency of the enzymes responsible for galactosaemia. 5 The assertion that “. . . formulas based on intact soy protein isolates are not recommended for the initial treatment of food allergy in infants, although a proportion of infants with cow’s milk protein allergy tolerate soy formula” is based on the ESPGAN Committee on nutrition and on the AAP recommendations. While the former concerns itself with clinical gastrointestinal manifestations, the latter recommendations state in conclusion (point 8): “Most infants with documented IgE-mediated allergy to cow milk protein will do well on isolated soy protein-based formula”. Initial treatment for allergic disease is avoidance of the incriminated allergen. Soy formula has been recommended in treatment of CMA on grounds of efficacy, adequate nutrient intake, and cost. 6


### Pyridoxine-dependent and pyridoxine-responsive seizures

**EDITOR.—**Seizures in infancy and early childhood responsive to pyridoxine are well recognised but rare. Baxter has recently observed that almost a third of neonatal cases of pyridoxine dependency present with apparent birth asphyxia and/or suspected hypoxic or ischaemic encephalopathy, and recommended that, because of the high proportion of atypical cases, all children with early onset (younger than 3 years old) intractable seizures may present for evaluation even in the absence of suggestive history. 2 Following this recommendation can be of remarkable benefit.

We report a case of a caucasian boy, born at term who presented at delivery in a state of unexpected collapse requiring intubation and resuscitation. He developed tonic seizures within hours of birth and was treated with phenobarbitone, phenytoin, and clonazepam. At 48 hours, an EEG showed a burst

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suppression pattern. There was biochemical evidence of multi-organ damage. He was extubated on day 5 and discharged on day 16 on phenobarbitone. He continued to have frequent myoclonic seizures. At 6 months, phenobarbitone was replaced by sodium valproate with some initial benefit. By 7 months, he was having focal motor seizures affecting his right arm up to 40 times a day and additional atypical absences and tonic seizures. He also showed signs of an emerging spastic quadraparesis. EGG showed right sided spike and wave discharge with a frontal emphasis. At 8 months a trial of oral pyridoxine (30 mg/kg/day) was given. No seizures have been observed since pyridoxine was started. He is now 16 months old. He is maintained on pyridoxine 15 mg/kg/day; valproate has been discontinued. The EGG no longer shows spike and wave activity. The signs of spastic quadraparesis remain.

We have reviewed the notes of children attending The David Lewis Centre, a residential school for children with severe epilepsy. Children at The David Lewis Centre have been referred from all over the UK and their early epilepsy management has been undertaken at many different centres. 31 children with intractable cryptogenic epilepsies, which started before they were 3 years old, were identified (dates of birth 1979–1992). Only one of these children was recorded as having received a trial of pyridoxine early in the evolution of their epilepsies. The true prevalence of pyridoxine responsive epilepsy is difficult to assess if the recommendations of Baxter are seldom applied. Giving pyridoxine can be diagnostic particularly in those patients with atypical absences and tonic seizures. EEG showed right sided spike and wave discharge with a frontal emphasis. quadraparesis. EEG showed right sided spike and wave discharge with a frontal emphasis. At 8 months a trial of oral pyridoxine (30 mg/kg/day) was given. No seizures have been observed since pyridoxine was started. He is now 16 months old. He is maintained on pyridoxine 15 mg/kg/day; valproate has been discontinued. The EGG no longer shows spike and wave activity. The signs of spastic quadraparesis remain.

Are sleep studies worth doing?

Editor,—If sleep studies are worth doing, the study of sleep related research in the UK is now accumulating that even mild OSA may be associated with significant neurocognitive deficits in the already formed aerosol from an anaesthetic agent. The practice of using empty drink bottles was evaluated, acknowledge that the procedure was not done in a double-blind fashion. The authors told us that during the past thirty years the youth of today are decadent and unhealthy. Could the authors not have had the imagination to explore the meaning of these results and even suggest that some things might be improving instead of getting worse?

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Data presented do not justify pessimistic conclusions

Editor,—In a recent article, Cavadini and colleagues told us that during the past thirty years the youth of the US have shown a decrease in the amount of milk consumed, as well as the percentage of energy from fat and, particularly, saturated fats. What are the conclusions of the article? That “these trends... may compromise the health of future US populations.” In the discussion section the authors expressed concern about low iron and fibre intakes, despite the fact that both have risen steadily in the past 30 years. Concern is also expressed about falling calcium intake, due to a decrease in consumption of dairy products. US milk intake has always been exceptionally high and, being rich in saturated fat, a reduction is probably desirable. However, the current lower intake still supplies levels of calcium much higher than those for children in other developed countries.

There seems little doubt that US children are growing fatter, but I am at a loss to see in what way their dietary intake explains this. Presumably the reduction in energy intake is offset by an even greater increase in activity, but the effect is that, in composition terms, the diet of today’s adolescents, though supplying more energy than required for current levels of activity, seems healthier than it has ever been.

The old fashioned disciplinarian mother used to shout to her children in the next room “whatever you’re doing: stop it!”. This seems to be our attitude towards young people as a group. It is sad to see a scientific article falling back onto the accepted paradigm that the youth of today are decadent and unhealthy. Could the authors not have had the imagination to explore the meaning of these results and even suggest that some things might be improving instead of getting worse?

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Spacers and holding chambers: Not the last word, we hope

Editor,—Zei and colleagues compared homemade spacers with two commercially available valved holding chambers (VHCs) for the treatment of children with acute asthma.1,2 We, as the manufacturer of one of the VHCs that was evaluated, acknowledge that the practice of using empty drink bottles is common in some countries (either by necessity or choice), but we are highly concerned about the support to the hypothesis, given by implication in this paper, that coffee cup or drink bottle spacers are as effective as properly designed add on devices. In this paper, the production technique did not simulate the release of medication from a pressurised metered dose inhaler (pMDI). Instead, the technique created a radio labelled aerosol by pneumatic nebulisation into a bag (which would have acted as a particle pre-selector). This set up would not have reproduced accurately the ballistic component (polydisperse particles) that is inevitably released at actuation of a pMDI. This has already been shown that these particles are more effectively separated by a VHC than a spacer (with no valve). Had a pMDI containing the radio-labelled aerosol been used (as is the normal practice in gamma scintigraphic studies evaluating pMDI systems), we believe that the dynamic aerosol behaviour (incidental impact of the ballistic component, turbulent deposition, etc) following actuation into the chamber would have been quite different to that observed by having patients drawing in the already formed aerosol. This was analogous to what occurs inside a VHC used with a pMDI. A well designed holding chamber (with a valve) will retain a significant portion of the coarse component of the emitted dose (parti-
circles greater than about five microns aerodynamic diameter) from the pMDI. A spacer (homemade or otherwise) will not perform this function effectively. Rather, it will momentarily contain the aerosol and then deliver particles of all sizes to the well coordinated patient who is able to time inhalation with actuation of the pMDI. In the case of corticosteroids, the emitted coarser particles can promote local topical infections—such as, oral candidiasis, as well as increases in overall systemic absorption.

The inhalation valve, which distinguishes a VHC from a spacer, needs to be a carefully designed component whose function is to retain the aerosol once created, following actuation of the pMDI, then release it during the inspiratory cycle. Many children, particularly those with an acute exacerbation of asthmatic symptoms, have poor coordination, and are therefore likely to mistime inhalation with pMDI actuation. These patients, who are at greatest risk, are thus likely to derive least benefit from the use of homemade spacers.

Although we have other observations of a technical nature, the information given here should be sufficient to provide the message that this study should not be taken as the final word but rather as a finding concerning the deleterious effect of cultural practices on feeding difficulties in children, and is also essential to facilitate culturally sensitive intervention strategies. The various theories of feeding difficulties from physiological (oral motor, regulatory, neurological), psychological (behavioural, cognitive behavioural, and psychoanalytical) and cultural perspectives are covered. These are discussed in reference to multidisciplinary teamwork and the development of both hospital and community feeding services. The chapter covering the psychoanalytical perspective sits somewhat oddly within the context of the book. Less helpful advice and practical intervention techniques stem from this chapter than the others, but perhaps those with an interest in psychoanalysis will find it an appealing diversion.

It is vital that health professionals in this field develop an understanding of the impact of cultural factors, from the effect of cultural feeding practices on feeding difficulties, to the perception and importance of food and feeding within cultures. This is critical to understanding the factors that contribute to the development and maintenance of feeding problems in children, and is also essential to facilitate culturally sensitive intervention strategies. The perspectives of Indian culture are discussed and whilst one text alone cannot cover the breadth of multicultural issues that are relevant to the UK population, there is useful information on issues which are specifically related to cultural practices and those which are related to social disadvantage and poverty in general.

Whilst some chapters focus on clinical practice and opinion that may not appeal to an academic audience, practical advice, such as special issues in tube feeding, neurological impairment, and chronic illness, combined with generally sound theoretical discussion, makes this text a useful resource for health professionals involved in the assessment or treatment of feeding difficulties.

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Share prices of dot.com companies have plummeted because, we are told, there are too many players in the market place for them all to be viable. The dot.com bubble has burst. This may also be true of paediatric textbooks. Such thoughts might trouble the authors and publisher of the fourth edition of the ABC of One to Seven, were it not for the pictures it contains. Is there really demand for another general paperback text covering well trodden ground, with predictable text and liberal use of blue boxes to convey the impression that there is a lot more colour than is really the case? Perhaps not, but for those pictures. This book isn’t cheap, maybe that’s because of the pictures. In short, this book is worth the investment for the pictures alone.

Medical students like to console themselves with thick books because many of us still hold fast to the well known belief that you can learn a lot about a subject by buying a “good book”, even without opening it. Perhaps the same is true of GPs; fat books with hardback covers are much more impressive shelf-fillers than paperbacks with pictures.

But what about when the time comes to learn paediatrics? We need something on which to hang the facts of any textbook, and we all know the daunting effect of long paragraphs of plain text on page after page. This is where pictures and diagrams come into their own, and the ABC of One to Seven has them in spades. They are almost always helpful and relevant—if not adding to the explanation, then proving the useful peg on which to hang a particular fact. Captions though, are few and far between. The reader can sometimes be left confused as to the purpose of a particular illustration. Several of the pictures appear two or three times and others are decidedly outdated. Ambulances and toys seem to be used as space fillers, but others, particularly the dermatological pictures, are excellent.

This is no reference bible, and the text is simple and narrative. Facts are not flung at the reader, and the practical is emphasised over the theoretical. This is a book to demystify infancy and early childhood—the fear of the unknown can quickly be replaced with enthusiasm for such a fun subject area. The Colour Atlas of Kids: this bubble definitely remains intact.

NICK JENKINS