LETTERS TO THE EDITOR

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 Cushingsoid 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 Chirsiprin–Norman chest x ray scores. Height velocity was also improved. Three patients did not 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.3 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.

We are grateful to Dr CE Daman-Willems, Dr R Dinwiddie, Prof JF Price, Dr HA Wyatt, and Dr GJ Connell for allowing us to use their patients in this report.

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Reference

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

EDITOR,—Allergic bronchopulmonary aspergillosis (ABPA) creates a diathesis that is often accompanied by iron deficiency anaemia,5% of patients with ABPA (IQR 1 to 8), using a median of two factors to commence treatment without clinical deterioration. Ninety percent of centres would consider starting steroid treatment in ABPA patients, with 35% of centres using a combination of oral and inhaled steroids. Of the centres that commenced CyA, 37% used plasma levels as an indication for adjustment of dosing.

The dosage of CyA was adjusted to maintain whole blood trough levels of 100 to 150 ng/ml using CyA doses ranging from 2 to 37 mg/kg/day. Thirty eight per cent of centres would commence CyA at a lower dose (17% no experience of steroid failure, 12% other, 21% no reply). Oral antifungals had been used by 69% of respondents, itraconazole in all cases. Paediatric centres were much more likely to use oral antifungals (88% vs 31%, p = 0.004, Mann–Whitney U test). Nebulised antifungals were used by 21%, amphotericin in all cases.

We also asked how many patients would currently be diagnosed as having ABPA in that unit using: (a) criteria stated as “must be present” earlier in the questionnaire; and (b) if major criteria were strictly adhered to. Clinicians considered that they had a median of 5% of patients with ABPA (IQR 1 to 8), using their own criteria, falling to a median of 0% (IQR 0 to 3) when all major criteria were strictly adhered to.

In the 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 based on 42 replies (72%) from 14 adult clinics (33%), 23 paediatric (55%) clinics, and five (12%) mixed adult/paediatric clinics. Units had a median of 100 patients (interquartile range (IQR) 63 to 160).

We have assessed consensus current practice in the diagnosis of ABPA and how cases were managed.

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

Table 1 Replies to questionnaire (% of all units)

<table>
<thead>
<tr>
<th>Criteria</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 precipitins</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/μm³)</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>10</td>
<td>56</td>
<td>56</td>
<td>30</td>
</tr>
<tr>
<td>Wheeze/cough</td>
<td>46</td>
<td>46</td>
<td>39</td>
<td>15</td>
</tr>
</tbody>
</table>

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 15.3% 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, 1 Rosenberg M, Patterson R, Mintzer R, et al. Clinical and immunological criteria for the diagnosis of allergic bronchopulmonary aspergillosis. Ann Intern Med 1977;86:405–14.

Table 1 Replies to questionnaire (% of all units)


rather than \( H \) pylori infection alone, might delay puberal 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. Anaemia was determined in none of the patients. Mean haemoglobin concentration was 130 (6.9) g/l. \( H \) pylori infection is a chronic persistent infection, leading to diminished growth. Chronic gastric inflammation, dyspepsia, decreased nutritional intake, and malnutrition in growth. We suggest that the development of short stature in \( H \) pylori positive patients may be due solely to \( H \) pylori infection itself, and is not related to iron deficiency anaemia.

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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 curve. This aspect of demonstrating the weight for age graph, comprehend the weight for age graph, can create their child’s growth curve. This, in turn, leads them and their relative to understand the weight for age curve.1 In one study among the pastoral Maasai in Kenya, action was taken by the parents to give an additional drink of milk to children whose weight for age was subnormal (Megan M. Personal communication, 1999).

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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 attending a day nursery, we have calculated the additional work that would be generated for the Public Health Department in the district where the outbreak occurred if this policy was implemented.

19 of well children on the ground floor of the nursery, six had more than one bowel motion on or about one half of the daily sessions attended during the surveillance period.1 Well children attending for 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 day nurseries and playgroups in North Wales, with an average of 23 children per nursery.1 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.

Therefor, 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 (0.12x385)—that is, 230 per week. Even if the normal background rate were 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 almost therefore unworkable, and the claim that it could have prevented 10–12 of the 31 cases in the outbreak needs to be reviewed.

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Meningococcal disease due to \( W \) 135: 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,1 but had not treated a single case of serogroup \( W \) 135 meningococcal infection until April 2000. We would like to report four children treated at our unit for meningococcal infection due to serogroup \( W \) 135, type 2A, subtype P1.2, P1.5, within a one month period from April 2000. They had been vaccinated recently with meningococcal serogroup C conjugated vaccine, and had all been


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in contact with travellers returning from Mecca. The clinical features of these cases are outlined in Table 1.

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. A similar outbreak occurred in 1987, due to 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. A similar outbreak occurred in 1987, due to serogroup A, subgroup III. This also

*Total resuscitation fluid required in first 24 hours

![Table 1 Clinical presentation, severity and outcome](https://example.com/table1.png)

<table>
<thead>
<tr>
<th>Case</th>
<th>Contact with travellers</th>
<th>Presentation</th>
<th>Resuscitation fluid*</th>
<th>Mechanical ventilation (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Grandmother</td>
<td>Petechiae, septicaemia</td>
<td>80 ml/kg fluid</td>
<td>2</td>
<td>Discharged</td>
</tr>
<tr>
<td>2</td>
<td>Father</td>
<td>Purpura fulminans, septicaemia</td>
<td>350 ml/kg fluid</td>
<td>11</td>
<td>Peripheral gangrene</td>
</tr>
<tr>
<td>3</td>
<td>6 family members</td>
<td>Meningitis, seizures, no rash</td>
<td>saline 2.2 μg/kg/min</td>
<td>0</td>
<td>Discharged</td>
</tr>
<tr>
<td>4</td>
<td>2 Aunts</td>
<td>Purpura, septicaemia</td>
<td>90 ml/kg fluid</td>
<td>2</td>
<td>Discharged</td>
</tr>
</tbody>
</table>

**Table 1 Clinical presentation, severity and outcome**

The switch to serogroup B disease is eliminated. The clinical features of these cases are very similar to those seen in meningococcal serogroup C disease. The potential to alter its capsular polysaccharide vaccine: new opportunities and new challenges. Menin-


**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 infants3 seemed settled when a joint statement by the committees of ESPACI/ESPGHAN appeared in *ADC*. 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.1 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.2 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.2 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.1 In the absence of prospective studies comparing the allergenicity of cow’s milk hydrolysates against soy formulas in children with CMA, the rationale to alter this indication appears to be lacking.

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**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 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 or status should receive a trial of pyridoxine whatever the suspected cause.1 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. 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 EEG 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 are 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 and therapeutic—not giving a trial of pyridoxine is common and can lead to a treatable cause of difficult epilepsy unrecognised and inadequately treated.

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Are sleep studies worth doing?

Editor,—If sleep studies are worth doing, they are worth doing well. The study of sleep...
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 debate about the efficacy of homemade spacers manufactured add on delivery devices for use in pMDI based treatment.

That said, if a VHC is unavailable for whatever reason, an empty drinking bottle may be better than nothing at all.

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BOOK REVIEWS


Given the wide prevalence of feeding problems in children and their potential impact on health, it is important for all health professionals working with children to gain an understanding of feeding difficulties. In several chapters of this book there is a refreshing focus on the role of organic factors in feeding problems, which may highlight the wide range of subtle organic features that can contribute to and exacerbate feeding difficulties in children. The impact of other factors on feeding is also covered—for example, the effect of temperament, appetite, growth, developmental stage, prior experience with foods, and cognitive development, all of which are critical in understanding each child’s feeding difficulty and creating appropriate 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 with 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 diversions.

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 practices within cultures. This is critical in 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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In a recent letter by Russell and Gillett (Arch Dis Child 2000;85:436), the sentence: “The in house assays used for AGA and EmA were performed on 10–20 ml of serum or plasma; thus capillary samples were more than adequate.” should have read: “The in house assays used for AGA and EmA were performed on 10–20 microlitres of serum or plasma; thus capillary samples were more than adequate.” We apologise for this error.

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