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; 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.1

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 Cushinoid 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 dosing 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 developed 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.

We are grateful to DrCE Daman-Williams, Dr R Dunwiddie, Prof JP Price, Dr HA Wyatt, and Dr GJ Connell for allowing us to use their patients in this report.

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**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 were adapted 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 of criteria used by UK clinicians to support a diagnosis of 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 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).

Of six ABPA major criteria investigations (table 1), centres routinely tested (at least yearly) a median of four (mode five).

Clinicians were also asked how many of eight factors (table 1) associated with ABPA diagnosis must be present, or were not considered important. It was considered that a median of two factors (IQR 1 to 4) must be present, three preferred to be present (IQR 2 to 5), and one factor was not considered important (IQR 1 to 2.3). Forty per cent of centres considered one or more further factors in addition to those provided.

Thirty eight per cent of centres would begin treatment without clinical deterioration (62% treat on deterioration). Initial treatment in all centres (100%) was prednisolone: in paediatric patients 1 mg/kg/21% and 2 mg/kg in 76%; in adults 30 mg/day in 50% (range 20–60 mg/day). In response to failure of steroid treatment 33% would add an anti-fungal agent, 17% would increase steroid 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% ± 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.

This questionnaire shows considerable variability in the criteria used to diagnose ABPA in CF. Prospective reporting of cases with defined criteria will be the only way to reliably identify the true prevalence of ABPA. Database surveys may overestimate the true prevalence.

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**Subnormal growth in children with Helicobacter pylori infection**

**EDITOR,**—We read with interest the study by Choe and colleagues5 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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**Table 1 Replies to questionnaire (% of all units)**

<table>
<thead>
<tr>
<th>Test Condition</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><em>Aspergillus precipitans</em></td>
<td>83</td>
<td>42</td>
<td>49</td>
<td>10</td>
</tr>
<tr>
<td><em>Aspergillus specific IgE</em></td>
<td>52</td>
<td>54</td>
<td>31</td>
<td>15</td>
</tr>
<tr>
<td><em>CRX infiltrate</em></td>
<td>95</td>
<td>38</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td><em>Blood eosinophilia (&gt;500/mm³)</em></td>
<td>83</td>
<td>24</td>
<td>56</td>
<td>20</td>
</tr>
<tr>
<td><em>Aspergillus fumigatus skin test</em></td>
<td>5</td>
<td>11</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td><em>Total serum IgE (&gt;1000 ng/ml)</em></td>
<td>79</td>
<td>45</td>
<td>45</td>
<td>10</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td>51</td>
<td>35</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>Wheezing/ cough</td>
<td>46</td>
<td>39</td>
<td>15</td>
<td>20</td>
</tr>
</tbody>
</table>

*Six major criteria investigations.*
rather than H pylori infection alone, might delay puberty 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 130.0 (g/l). H pylori infection is a chronic persistent infection, leading to diminished growth. Chronic gastric inflammation, dyspepsia, decreased nutritional intake, and malnutrition patients. Growth monitoring. Growth monitoring is not taught in primary schools in developing countries. A systematic review of trials. Arch Dis Child 2000;82:197–201.

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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 diarrhoea be taken as an early warning sign and that appropriate measures are taken to prevent outbreaks. We agree that diarrhoea is an early warning sign of E coli O157 infection in nurseries. We also agree with Al-Jader and colleagues that diarrhoea is too subjective an indication for the parents to use. We believe that the only reliable and very early warning sign is the presence of at least 10 bloody bowel motions during 1 day.

In one nursery with 23 children per nursery, diarrhoea was recorded in a single session on any one day. Diarrhoea is not as precise an indication as the presence of at least 10 bloody bowel motions. Nevertheless, Al-Jader and colleagues’ report shows clearly what happens when diarrhoea is not taken as an early warning sign. Therefore, it is clear that diarrhoea should be taken as an early warning sign and appropriate measures should be taken to prevent outbreaks.

Growth monitoring

EDITOR,—Garner and colleagues recently reported 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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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 due to serogroup W135, type 2A, subtype P1.2, P1.5, within a one month period from April 2000. They had been vaccinated recently with meningococcal serogroup C conjugate vaccine, and had all been
Table 1  Clinical presentation, severity and outcome

<table>
<thead>
<tr>
<th>Case (months)/Sex</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>10m/F Grandmother</td>
<td>Petechiae, septicaemia</td>
<td>80 ml/kg fluid</td>
<td>No inotropes</td>
<td>2</td>
<td>Discharged</td>
</tr>
<tr>
<td>27m/M Father</td>
<td>Purpura fulminans, septicaemia</td>
<td>350 ml/kg fluid adrenaline 2.2 mcg/kg/min</td>
<td>Neurological sequelae</td>
<td>11</td>
<td>Peripheral gangrene</td>
</tr>
<tr>
<td>4m/F 6 family members</td>
<td>Meningitis, seizures, no rash</td>
<td>No fluid</td>
<td>No inotropes</td>
<td>0</td>
<td>Discharged</td>
</tr>
<tr>
<td>19m/F 2 Aunts</td>
<td>Purpura, septicaemia</td>
<td>90 ml/kg fluid dopamine 10 µg/kg/min</td>
<td></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 table 1.

The children 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.

A similar outbreak occurred in 1987, due to serogroup A, subgroup III. This also followed the yearly pilgrimage to Mecca, and spread throughout Europe, USA, and Africa over the next two years.3 Requirement for pilgrims entering Saudi Arabia now includes documented vaccination with meningococcal A and C polysaccharide preparation. This public health measure has been effective in irradiating serogroup A disease in these travellers.4 A quadrivalent vaccine is available for serogroup W135 as well as serogroups A, C, and Y. This vaccine, however, is not licenced in the UK, and is only available on a named patient basis. This raises public health issues, including whether people returning from Mecca to the UK should be screened or given prophylaxis.

Even with the anticipated beneficial effects of the meningococcal C vaccination programme in England and Wales, it is important to remember that other serogroups of meningococci will continue to cause significant disease in the UK.

Until 1950, England was predominantly affected by epidemics of serogroup A meningococcal disease. The switch to serogroup B and C disease occurred after the second world war, and serogroup A disease is now rarely seen in the UK. Neisseria meningitidis has the potential to alter its capsular polysaccharide antigen through recombinational exchanges at the capsular locus. In his commentary in the Lancet in 1999, Martin Maiden expressed concern that new hyper-virulent strains of serogroups including B, W135, and Y may emerge as serogroup C disease is eliminated.5 This recent outbreak of serogroup W135 infection does not seem to represent such selection pressure. However, it highlights the need for continued clinical, laboratory, and epidemiological vigilance for meningococcal infection, particularly now that there may be a theoretical risk of other serogroups becoming more prevalent as meningococcal serogroup C disease is controlled.

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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 infants6 seemed settled when a joint statement by the committees of ESPACI/ESPAGAN appeared in ADC.7 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.8 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.9 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.10 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”11 is based on the ESPGAN Committee on nutrition12 and on the AAP recommendations.13 While the former concerns itself with clinical gastrointestinal manifestations, the latter recommends ample schedules in conclusion (point 8): “Most infants with documented IgE-mediated allergy to cow milk protein will do well on isolated soy protein-based formula”.11 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.14 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 clonazepamep. At 48 hours, an EEG showed a burst

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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 and its correlates has expanded exponentially, with many questions remaining unanswered. 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-ons.

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 (polydispersed particles) that is inevitably released at actuation of a pMDI. 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-ons.

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cicles 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 coordi
dated 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, particu
larly 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 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 prob
lems in children and their potential impact on health, it is important for all health profes
sionals 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


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

CORRECTION

In a recent letter by Russell and Gillett (Arch Dis Child 2000;85:456), 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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Data presented do not justify pessimistic conclusions

C M WRIGHT

Arch Dis Child 2001 84: 89
doi: 10.1136/adc.84.1.89i

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