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 Cushionoid 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 Chirsipin–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.

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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.1 Retrospective studies report significant variability in prevalence and the numbers of criteria for diagnosis.2 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 (inter-quartile 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, were preferred to 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 treat-

ment in all centres (100%) was prednisolone: in paediatric patients 1 mg/kg in 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 at 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.

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 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 15.9% 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. Coren ME, Rosenthal M, Bush A. The use of cyclosporin in corticosteroid dependent asthma. Arch Dis Child 1997;77:522–3.

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 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>48</td>
<td>17</td>
</tr>
<tr>
<td>Blood eosinophils (&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></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheezes/choke</td>
<td>—</td>
<td>46</td>
<td>39</td>
<td>15</td>
</tr>
</tbody>
</table>

*Six major criteria investigations.

www.archdischild.com
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 (9) g/l.

H pylori infection is a chronic persistent infection, leading to diminished growth. Chronic gastric inflammation, dyspepsia, decreased nutritional intake, and malnutrition may influence growth. The mean age was 11.5 (2.0) years (21 girls and 9 boys) diagnosed by serology and histology. The mean height was 152 (19) cm (20th centile). Mean haemoglobin concentration was 130 (9) g/l.

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 can make the child’s growth curve. This, in time, leads them and their relative to understand the weight for age curve. 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 fell for age (Meehan M. Personal communication, 1999).

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”. Using data on healthy children reported in the paper 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.

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. Well children attending nursery for six days during the period, giving an approximate total number of sessions attended of 228 (19/256). 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 days and playgroups in North Wales, with an average of 23 children per nursery. 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 almost unworkable, and the claim that it could have prevented 10–12 of the 31 cases in the outbreak needs to be reviewed.

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 unit 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 conjugated vaccine, and had all been

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Dr Salmon comments:

Children who attend out of home child care are at increased risk for infectious diseases of which gastrointestinal tract infection is among the most common. Numbered among these are VTE E coli O157 infections which, as this outbreak showed, can cause severe disease. The challenge is to identify disease activity.

In this outbreak, given that the first two cases attended the nursery for two days after the onset of their disease on 21 August and the first case from the nursery was not reported until 1 September by which time 13 further symptomatic cases had occurred, our claim that 10–12 cases could have been prevented by taking further action, at this point, is straightforward. The toileting record might have constituted the clue to such an action. We list 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 be done 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. 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 toileting record constitutes a straightforward record used in a number of case settings.

R L SALMON
Consultant Epidemiologist


The clinical features of these cases are outlined in table 1. These cases represent four out of 38 cases (with five fatalities) of serogroup W135 Neisseria meningitidis infection in England and Wales within six weeks from March to May 2000 (PHLS Meningococcal Reference Unit, personal communication), with hundreds of cases of the identical subtype being reported throughout Europe. A 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. Requirements for pilgrims entering Saudi Arabia now include documented vaccination with meningococcal A and C polysaccharide preparation. This public health measure has been effective in irradiating serogroup A disease in these travellers. 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 meningococcal disease are not uncommon in the UK. Neisseria meningitidis has the potential to alter its capsular polysaccharide antigen through recombinational changes at the capsular locus. In his commentary in the Lancet in 1999, Mark Maiden expressed concern that new hyper-virulent strains of serogroups including B, W135, and Y may emerge as serogroup C disease is eliminated. 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.

## Table 1 Clinical presentation, severity and outcome

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (months)/ Contact</th>
<th>Presentation</th>
<th>Mechanical ventilation</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10m/F Grandmother</td>
<td>Petechiae, septicemia 80 ml/kg fluid</td>
<td>2</td>
<td>Discharged</td>
</tr>
<tr>
<td>2</td>
<td>27m/M Father</td>
<td>Purpura fulminans, septicemia 350 ml/kg fluid adrenaline 2.2 μg/kg/min Meningitis, seizures, no rash</td>
<td>11</td>
<td>Peripheral gangrene</td>
</tr>
<tr>
<td>3</td>
<td>4m/F 6 family members</td>
<td>Purpura, septicemia 90 ml/kg fluid dopamine 10 μg/kg/min Neurological sequelae</td>
<td>0</td>
<td>Discharged</td>
</tr>
<tr>
<td>4</td>
<td>19m/F 2 Aunts</td>
<td>Purpura, septicemia</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.

Serogroup W135 meningococcal disease is not uncommon in the UK. Neisseria meningitidis has the potential to alter its capsular polysaccharide antigen through recombinational changes at the capsular locus. In his commentary in the Lancet in 1999, Mark Maiden expressed concern that new hyper-virulent strains of serogroups including B, W135, and Y may emerge as serogroup C disease is eliminated. 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 infants" seemed settled when a joint statement by the committees of ESPACI/ESPGAN 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. 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 galactos-
suppression pattern. There was biochemical evidence of multi-organ damage. He was extubated on day 5 and discharged on day 16 on phenobarb frontline. 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 quadriparesis. 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 quadriparesis 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 come 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 1983–1992). 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 leave a treatable cause of difficult epilepsy unreconnised 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 is diadrics many questions remain unanswered. A well designed holding chamber (with a coarse component of the emitted dose (particulate) 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 reduction 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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M HARRIS
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1 Shann F. Australian view of paediatric intensive care in Britain. Lancet 1993;342:68.

Data presented do not justifi pessimistic conclusions

Editor,—In a recent article, Cavadini and colleagues told us that during the past thirty years the youth in the US have shown a decrease in total energy 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.
ABC of One to Seven

Feeding Problems in Children: a practical guide

BOOK REVIEWS

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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 GP’s; 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 are much more impressive shelf-fillers than those pictures. This book isn’t cheap, but-

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

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

Updated information and services can be found at:
http://adc.bmj.com/content/84/1/89.4

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