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 by reducing 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. 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 dosages 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. Other side effects due to CyA were minimal, including mild hypertension 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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Letters to the Editor

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 are adapted from asthma guidelines. Retrospective studies report significant variability in prevalence and the numbers of criteria for diagnosis. 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 CF specialist clinics 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 centres (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, were prefered 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 treatment 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 antifungal agent, 17% would increase steroid dose (17% no experience against 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 colleagues 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, 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 antifungal agent, 17% would increase steroid dose (17% no experience against 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.
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 (9) g/l.

H pylori infection is a chronic persistent infection, leading to diminished growth. Chronic gastritis, inflammation, decreased nutritional intake, and malnutrition were determined in none of the patients. Mean haemoglobin concentration was 130 (9) g/l.

We did not detect anaemia in H pylori positive patients with diminished 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—namely, 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. Graphic representation of numbers and playgroups in North Wales, with an average of 23 children per nursery. In an average size 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 almost unworkable, and the claim that it could have prevented 10–12 of the 31 cases in the outbreak needed to be reviewed. ARCH Dis Child: first published as 10.1136/adc.84.1.89j on 1 January 2001. Downloaded from


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,1 but had not treated a single case of serogroup W135 meningococcal infection until April 2000. We would like to report four cases treated at our hospital for meningococcal infection 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
in contact with travellers returning from Mecca. The clinical features of these cases are outlined in table 1.

This recent outbreak of meningococcal serogroup C disease is considered to be a theoretical risk of other serogroups becoming more prevalent as meningococcal serogroup C disease is controlled. CMA.

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Table 1 Clinical presentation, severity and outcome

<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>No inotropes</td>
<td>Discharged</td>
</tr>
<tr>
<td>2</td>
<td>Father</td>
<td>Purpura fulminans, septicaemia</td>
<td>350 ml/kg fluid adrenaline 2.2 µcg/kg/min</td>
<td>Neurological sequelae</td>
<td>Discharged</td>
</tr>
<tr>
<td>3</td>
<td>6 family members</td>
<td>Meningitis, seizures, no rash</td>
<td>No fluid</td>
<td>No inotropes</td>
<td>Discharged</td>
</tr>
<tr>
<td>4</td>
<td>2 Aunts</td>
<td>Purpura, septicaemia</td>
<td>90 ml/kg fluid dopamine 10 µg/kg/min</td>
<td>2 Discharged</td>
<td></td>
</tr>
</tbody>
</table>

*Total resuscitation fluid required in first 24 hours

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 ESPGAN/ESPCAN appeared in 'Adult'. 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.5 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 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 nutrition6 and on the AAP recommendations.7 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.7 In the absence of prospective studies comparing the allergenicity of cow’s milk hydrolysates against soy formula 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 sustained severe 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 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...
embrace. 

In this study, sleep deprivation can be diagnosed and therapeutic—not giving a trial of pyridoxine is common and can leave a treatable cause of difficult epilepsy unrecognised and inadequately treated.

Are sleep studies worth doing?

Editor,—If sleep studies are worth doing, they are worth doing well. The study of sleep in rare paediatric centres 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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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 in the US have shown a decrease in the consumption of, 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 substantially, 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”?

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In the discussion section the authors expressed concern about low iron and fibre intakes, despite the fact that both have risen substantially, 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”?

Supporting evidence for the use of full polysomnography (PSG) may currently be limited, but in the opinion of van Someren and colleagues the advantages of PSG, which are difficult to demonstrate in most conditions, still outweigh the disadvantages. The benefits of PSG include: the ability to distinguish sleep apnoea and other sleep-related breathing disorders from other sleep disorders, the ability to assess the response to treatment, the ability to determine the impact of sleep apnoea on daily functioning, and the ability to determine the impact of sleep apnoea on daily functioning.

Full polysomnography is the current gold standard. The Vilabl has not been satisfactorily validated against full polysomnography, and the results presented in van Someren and colleague’s paper showed a discrepancy in two of 10 simultaneous recordings (a 20% error rate) with important differences in mean oxygen saturation between the two systems (93% vs 95%). It is true that full polysomnography may not be undertaken in all children for the diagnosis of OSA, but this process should be one of working down from a gold standard rather than edging up towards it. The arguments used by van Someren and colleagues against the use of full polysomnography are weak. Children in dedicated sleep areas tolerate full polysomnography well: in the 54 full polysomnographic OSA studies performed in this unit, sleep efficiency was a mean of 90% (SD 8%), which includes children with frequent wakening as a result of their OSA!

In recent years, centres in both North America and Australia have dedicated significant funding to paediatric sleep laboratories and the appropriate training of both nursing and medical staff through specific specialist training criteria; the UK sadly lacks such support. With the exception of one paediatric unit (concentrating on sleep in rare disorders) sleep related research in the UK is linked to adults centres. UK paediatrics needs a sleep medicine up wake call, so that standards can be set from a national level.

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1 Shann F. Australian view of paediatric intensive care in Britain. Lancet 1993;342:68.


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

Editor,—Zai and colleagues compared homemade spacers with two commercially available valved holding chambers (VHCs) for the treatment of children with acute asthma. 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 (polydispersed 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 (inertial deposition, etc) following actuation into the chamber would have been quite different to that observed by having patients drawing to that observed by having patients drawing into an already formed aerosol from an anaesthesia bag. Simply put, the protocol more closely simulated the release of medication from a pMDI. 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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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, allowing 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 debatable role of generated aerosol during inhalation.

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 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 and multiple feeding difficulties.

The ABC of One to Seven is worth the investment for its 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.