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 Cushimgoid 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 Chrisepin–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.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.

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

EDITOR,—Allergic bronchopulmonary aspergillosis (ABPA) creates a 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 (53%), 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.

Table 1  Replies to questionnaire (% of all units)

<table>
<thead>
<tr>
<th>Assessed yearly or more</th>
<th>Must be present</th>
<th>Prefer to be present</th>
<th>Not important</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillus precipitin</td>
<td>83</td>
<td>42</td>
<td>49</td>
</tr>
<tr>
<td>Aspergillus specific IgE</td>
<td>52</td>
<td>54</td>
<td>31</td>
</tr>
<tr>
<td>CXR infiltrate</td>
<td>95</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>Blood eosinophilia (&gt;500/mm³)</td>
<td>83</td>
<td>24</td>
<td>56</td>
</tr>
<tr>
<td>Aspergillus fumigatus skin test</td>
<td>5</td>
<td>11</td>
<td>50</td>
</tr>
<tr>
<td>Total serum IgE (&gt;1000 ng/ml)</td>
<td>79</td>
<td>45</td>
<td>45</td>
</tr>
<tr>
<td>Bronchiectasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeze/cough</td>
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</table>

*Six major criteria investigations.

Subnormal growth in children with Helicobacter pylori infection

Editor,—We read with interest the study by Choe and colleagues3 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, 

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 gastric inflammation, dyspepsia, decreased nutritional intake, and malnutrition (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.

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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 graph. Piegas (1890–1980) considered the line graph to be one of the more difficult subjects to teach. Graphic representation of numbers is not taught in primary schools in developing countries and colleagues with knowledge of primary education suggest that primary school teachers in these countries would not be able to teach it. Experience with postgraduate doctors in the 1970s suggested that a proportion could not complete a weight chart and even fewer would have problems in interpreting it.2 A similar problem has arisen with midwives in the use and interpretation of the partograph to plot the progress of labour.

Fortunately, an alternative method of overcoming this difficulty can create their child’s growth curve. This, in turn, leads them and their relatives 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 for age was below the 25th centile. (Meegan 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 one of at least one half day sessions attended during the surveillance period.4 Well children attended on the ground floor of the nursery for two days after the outbreak. Of the 31 cases attended the nursery for two days after the outbreak, almost 100% of the total 12 outbreak cases attended the nursery for two days after the outbreak. The last two cases attended the nursery for two days after the outbreak, almost 100% of the total 12 outbreak cases attended the nursery for two days after the outbreak. The last two cases attended the nursery for two days after the outbreak, almost 100% of the total 12 outbreak cases attended the nursery for two days after the outbreak.

The outbreak needed to be reviewed. Even if the normal background rate was ten diarrhoea cases per day in 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.5 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.

1 Holmes SJ, Marrow AL, Picking LC. Childcare practices; effects on serogroups, the epidemiology of infectious diseases and antibiotic resistance. Epidemiol Rev 1996;18:10–28.

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 cases of W135 infection at our hospital. The disease is atypical 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 conjugate vaccine, and had all been...
in contact with travellers returning from Mecca. The clinical features of these cases are outlined in table 1.

The four represent 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 reported throughout Europe.1,13 Saudi Arabia has reported over 225 cases, with almost 25% mortality to the end of April 2000. It is thought that this large outbreak of an unusual strain originated in Saudi Arabia, with the pilgrimage of a record 1.3 million people to the Haj between 15–18 March 2000.1

A similar outbreak occurred in 1987, due to serogroup A, subgroup III. This also followed the yearly pilgrimage to Mecca, and spread throughout Europe, USA, and Africa over the next two years.1 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.1 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 newly hyper-virulent strains of serogroups including B, W135, and Y may emerge as serogroup C disease is eliminated.1 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 sex</th>
<th>Case number</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>10/mm/F</td>
<td>Petechiae, septicemia</td>
<td>80 ml/kg fluid</td>
<td>2</td>
<td>Discharged</td>
</tr>
<tr>
<td>2</td>
<td>Father</td>
<td>27/m/M</td>
<td>Purpuria fulminans, septicemia</td>
<td>350 ml/kg fluid adrenaline 2.2 μg/kg/min</td>
<td>11</td>
<td>Peripheral gangrene</td>
</tr>
<tr>
<td>3</td>
<td>Family members</td>
<td>4/m/F</td>
<td>Meningitis, seizures, no rash</td>
<td>No fluid</td>
<td>Neurological sequelae</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2 Aunts</td>
<td>4/19/F</td>
<td>Purpuria, septicemia</td>
<td>90 ml/kg fluid dopamine 10 μg/kg/min</td>
<td>2</td>
<td>Discharged</td>
</tr>
</tbody>
</table>

*Total resuscitation fluid required in first 24 hours

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Prevention and treatment of cow’s milk allergy

EDITOR,—Divergences in existing guidelines on the prevention and treatment of cow’s milk allergy (CMA) in infants 1 seemed settled when a joint statement by the committees of ESPACI/ESPGHAN appeared in ADC.2 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.3 Though rare, this disorder should be considered in the evaluation of the risk/benefit ratio and the costs of planning a prevention strategy for which the benefits are still unclear. In this context, issues of colonic ecology and malabsorption take second place.4 The use of screening tests for errors of lactose metabolism as interpreted in the statement may also be misleading. The claim that “feeding lactose-free diets from birth . . . will cause false negative results in most neonatal screening tests for galactosesaemia” overlooks the fact that these tests do not establish blood galactose levels but the presence/deficiency of the enzymes responsible for galactosaemia.5 The assertion that “…formulas based on intact soy protein isolates are not recommended for the initial treatment of food allergy in infants, although a proportion of infants with cow’s milk protein allergy tolerate soy formula”6 is based on the ESPGAN Committee on nutrition7 and on the AAP recommendations.8 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”.9 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.9,10 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 phenobarbital, phenytoin, and clonazepam. At 48 hours, an EEG showed a burst

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References

suppression pattern. There was biochemical evidence of multi-organ damage. He was extubated on day 5 and discharged on day 16 on phenobarbtiote. He continued to have frequent myoclonic seizures. At 6 months, phenobarbtiote 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 seen since the introduction of pyridoxine. 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 Ireland 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 1987–1992). Only one of these children was presented in van Someren and colleagues against the use of full polysomnography in children and the appropriate training of both nursing and medical staff towards specific specialist training criteria; the UK sadly lacks such support. With the emergence of one paediatric unit (concentrating on sleep in rare disorders) sleep related research in the UK is linked to adult centres. UK paediatrics needs a sleep medicine ‘wake up call’, so that standards can be set from the UK.

Are sleep studies worth doing?

Editor,—If sleep studies are worth doing, they are worth doing well. The study of sleep 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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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 total energy consumed, as well as the percentage of energy from fat and calcium much higher than those for children in other developed countries. There seems little doubt that US children are growing fatter, but I am at a loss to see in what way their dietary intake explains this. Presumably the reduction in energy intake is offset by an even greater increase in activity, but the effect is that, in composition terms, the diet of today’s adolescents, though supplying more energy than required for current levels of activity, seems healthier than it has ever been.

The old fashioned disciplinary 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. Is it 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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Letters, Book reviews, Corrections

References


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

Editor,—Zin 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 hypoth- esis, 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 setup would not have reproduced accurately the ballistic component (polydispersed particles) that is inevitably released at actuation of a pMDI. It 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 (inhalational impaction of the ballistic component, turbulent deposition, etc) following actuation into the chamber would have been quite different to that observed by having patients drawing from the already formed aerosol from an anaesthetic circuit. The use of a pMDI container, and may therefore have little rel- lationship to those observed in an actual pMDI.

A well designed holding chamber (with a valve) will retain a significant portion of the coarse component of the emitted dose (parti-

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 paediatrics. Perhaps not, but for those pictures. This book isn’t cheap, but 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 appear two or three times and others are partly illustrated. Several of the pictures 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 appear two or three times and others are 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.