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 reduce markers of chronic inflammation and reduce morbidity in patients with CF and inflammatory reaction. Systemic steroids are used to control exacerbations of respiratory infection is countered by an intense inflammatory reaction. Use of 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 Chirripin–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. 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 Dr CE Daman-Willems, Dr R Dinwiddie, Prof JF Price, Dr HA Wyatt, and Dr GJ Connell for allowing us to use their patients in this report.

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1 M BOWLER


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. 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 (interquartile range (IQR) 63 to 160).

Of six ABPA criteria investigated (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 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 antifungal agent, 17% would increase steroid dose (17% experience a 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 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,
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 130.0 (g/l).

H pylori infection is a chronic persistent infection, leading to diminished growth. Chronic gastric inflammation, dyspepsia, decreased nutritional intake, and malnutrition in childhood have been shown to diminish linear growth in H pylori positive patients.1 2 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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Detecting outbreaks of E coli O157 infection in nurseries

EDITOR,—In their report of a serious outbreak of E coli O157 in a nursery in North Wales, Al-Jader and colleagues recommend that more than one child with more than one bowel motion in a nursery should trigger action including “informing and seeking the advice of public health agencies”.1 Use of 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 children well 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.2 Well children attending nursery for six days during the period, giving an approximate total number of sessions attended of 228 (19 x 6 x 2). The probability of a well child having more than one bowel motion during any half day session was therefore about 0.026 (6/228). There are 385 nursery and playgroups in North Wales, with an average of 23 children per nursery.3 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 x 385)—that is, 230 per week. Even if the normal background rate of 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.

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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 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 care are at increased risk for infectious diseases of which gastrointestinal tract infections are among the most common.1 Numbered among these are VT+ E coli O157 infections which, as this outbreak showed, can cause severe disease. The challenge is to identify disease early.

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 toiletting record might have constituted a prompt to such 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 occur on every occasion that more than one child with more bowel motion was recorded. Most agree that faecal sampling needs, generally, to be encouraged.1 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 toiletting record constitutes a straightforward record used in a number of care settings.

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A consensus conference on iron deficiency and anaemia prevention.

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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 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 pilgrimages 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.6 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.7 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.15 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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*Total resuscitation fluid required in first 24 hours

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*Total resuscitation fluid required in first 24 hours
suppression pattern. There was biochemical evidence of multi-organ damage. He was extubated on day 5 and discharged on day 16 on phenobarbionate. He continued to have frequent myoclonic seizures. At 6 months, phenobarbionate 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. EOG showed right sided slope 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 EOG 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 transferred from all over the UK and their early epilepsy management has been undertaken at many different centres. 31 children with intractable cryptogenic epilepsies, which started before they were 3 years old, were identified (dates of birth 1979–92). 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 followed. Giving pyridoxine can be diagnostic and therapeutic—not giving a trial of pyridoxine is common and can leave a treatable cause of difficult epilepsy unrecognised and inadequately treated.

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

Editor—Zaki and colleagues compared homemade spacers with two commercially available valved holding chambers (VHCs) for the treatment of children with acute asthma.1 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 set up would not have reproduced accurately the ballistic component (polydisperse particles that is inevitably released at actuation of a pMDI). 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 disciplinary mother used to shout to her children in the next room “whatever you're doing: stop it!” This seems to have been a great incentive 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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Are sleep studies worth doing?

Editor—If sleep studies are worth doing, they are worth doing well. The study of sleep shows spike and wave activity. The signs of an emerging spastic quadraparesis remain.

Visilab 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 essential 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. In children dedicated sleep areas tolerate full polysomnography well: in the 54 full polysomnographic OSA studies performed in this unit in the past six months, 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 adult centres. UK paediatrics needs a sleep medicine wake up call, so that standards can be set from the gold standard.

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1 Shann F. Australian view of paediatric intensive care in Britain. Lancet 1995;342–68.
6 Kennedy D. Obstructive airway function in childhood obstructive sleep apnoea syndrome (OSAS). 6th World Congress on Sleep Apnoea, Sydney, Australia, March 2000.

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 percentage of energy consumed, as well as the percentage of energy from fat and, particularly, saturated fats.1 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 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 disciplinary mother used to shout to her children in the next room “whatever you're doing: stop it!” This seems to have been a great incentive 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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refreshing focus on the role of organic factors

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ISBN 1 85775 208 2

Abingdon: Radcli

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Feeding Problems in Children: a

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Those are specifically related to cultural practices

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spacers.

BOOK REVIEWS

Feeding Problems in Children: a

practical guide. Edited by Southall A,

Schwartz A. (Pp 280, paperback; £19.95.)

Abingdon: Radcliffe Medical Press, 1999,

ISBN 1 85775 208 2

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

ABC of One to Seven. Edited by Valman B.

(Pp 146, paperback; £14.95.) London:

BMJ Publishing Group, 1999. ISBN 0 7279

1232 1

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, 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 para-

graphs 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 particu-

lar 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 demys-


tify 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

J P MITCHELL

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Medical Aerosol Research Laboratory,

Trudell Medical International,

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Ontario N5V 5G4,Canada

I Zar HJ, Weinberg EG, Binns HJ, et al. Lung
deposition of aerosol: a comparison of different


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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Arch Dis Child: first published as 10.1136/adc.81.1.88 on 1 January 2001. Downloaded from http://adc.bmj.com/ on April 7, 2002 by guest. Protected by copyright.