BCG vaccination by multipuncture method

I write in response to the article by Al Jarad et al on this topic. The first study to compare the efficacy of BCG vaccination and its side effects using the Bignal multipuncture device with the reusable handle and disposable heads was the pilot study of neonatal BCG vaccination carried out in 1992 for the Department of Health in our health authority.1

In previous studies in neonates and children under two, referenced in the paper by Al Jarad et al,1 an 18–20 needle percutaneous head gave approximately the same degree of tuberculin conversion as did intradermal vaccination but, to achieve this in older children and adults, 36–40 punctures were required. This would require either a 40 needle head or a double vaccination with two × 18–20 needles. This is why percutaneous BCG is currently only licensed for children aged under two years. Although in neonates2 and in Al Jarad’s study1 in older children the rate of tuberculin conversion was lower with percutaneous than with intradermal vaccination, tuberculin conversion does not necessarily equate to lower efficacy. In the early studies on BCG the protective efficacy of the vaccination was related to the presence of a scar after vaccination, but not to the tuberculin test result after vaccination. Those with a BCG scar but a negative post vaccination tuberculin test—that is, no tuberculin conversion—had the same degree of protection against tuberculosis over the 15 years following vaccination as did those with a scar and a positive post vaccination tuberculin test.3

The multipuncture method is undoubtedly easier to use in neonates because their very thin skin makes intradermal vaccination difficult, and also in nervous teenagers. Further long term studies on large numbers of subjects would be required to determine whether the technique using only 18 needles in older children is as effective as intradermal vaccination. Such studies may well prove to be unnecessary. The PHSL system for enhanced tuberculin surveillance begun this year should, with sufficient cooperation, be able to give the relevant information by the end of 2001 to show whether England and Wales meet the internationally recommended criteria for discontinuation of unselective BCG vaccination in low prevalence countries.4 BCG vaccination of selective at risk groups, however, would still be required.

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Respiratory care units for non-invasive mechanical ventilation in motor neurone disease

We read with interest the review by Polkey et al pointing out the need to use all means possible to enable patients with motor neurone disease to achieve the best quality of life.5

The authors state that, in order to maintain 24 hour ventilatory support, nasal ventilation must be complemented with alternative strategies during the day that are not suitable for widespread use in district general hospitals. We consider that it is possible to maintain 24 hour non-invasive ventilation in patients with motor neurone disease if nasal ventilation is combined with other non-invasive techniques such as mouth piece ventilation or a pneumoebol, and with manual or mechanical expiratory muscle aids to clear secretions in those patients whose weakness makes spontaneous coughing ineffective.6 It is important to provide patients with motor neurone disease with alternative strategies because they can delay tracheostomy and additional problems in most patients with motor neurone disease and are the only way for those patients who reject tracheostomy but need ventilatory support. However, we agree with Polkey et al that this treatment must be performed by trained staff in respiratory care units. Moreover, these units are the best place to prevent respiratory morbidity and mortality, to enhance cooperation between patients, relatives and caregivers, and to manage clinical and psychological problems during the terminal phase of the disease.

In our experience the care of patients with motor neurone disease outside respiratory care units needs to be improved. These patients must not be negatively discriminated against compared with other chronic patients receiving even more expensive but socially accepted treatment. We must therefore try to ensure that all patients with motor neurone disease have access to specialist expertise where this is necessary. However, we also agree that patients with motor neurone disease outside respiratory care units need to be positively discriminated against compared with other chronic patients receiving even more expensive but socially accepted treatment. We must therefore try to ensure that all patients with motor neurone disease have access to specialist expertise where this is necessary.

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AUTHORS’ REPLY
We thank Dr Servera and colleagues for their interest in our paper. We agree that patients with motor neurone disease should have access to specialist expertise where this is necessary. However, we are also conscious that travel can be difficult for some patients with advanced disease and our experience is that, in many cases, satisfactory palliation can be achieved using non-invasive positive pressure ventilation alone. This treatment could theoretically be
provided by an interested chest physician working in a district general hospital. We recognise that, in practice, it may be difficult to identify the necessary resources and that, conversely, an under-resourced service may lead to suboptimal care; however, this is true both of district hospitals and specialist centres.

Ashma deaths in Scotland and in Wales

It is surprising to say the least, that although the two inquiries into asthma deaths published recently in *Thorax*¹ made the point that most asthma deaths occurred outside hospital, the only deaths of any significance were those that occurred in hospital (the “relative rarity” of deaths in hospital), neither addressed the question as to whether more prompt admission to a hospital with respiratory intensive care facilities could have prevented some, or even many, of the domestic deaths.

The Respiratory Unit at the Northern General Hospital in Edinburgh first addressed that question as long ago as 1968 when it inaugurated a self-admission scheme for patients known by the unit to be subject to life-threatening attacks of asthma, whereby the often long delays inherent in conventional admission procedures were bypassed with the willing cooperation of their general practitioners. The scheme was more fully described in 1975 and reports on 10 year and 15 year reviews of its progress were published in 1979 and 1987. These showed that the death rate in patients admitted under the scheme was only 0.3%, substantially lower than that recorded in asthmatic patients admitted to other Edinburgh hospitals which relied on the conventional admission procedures.

The asthma self-admission scheme was widely welcomed as a measure which could save lives and was copied in many other countries, including Australia. Yet in neither of the two studies reported in the November 1999 issue of *Thorax* was this important initiative even mentioned. May I ask the authors why?

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Authors’ Reply We are aware of the work to which Dr Grant refers, and agree that self-admission schemes can prevent asthma deaths by avoiding the delays that sometimes occur with conventional admission procedures. Different versions of self-admission schemes operate throughout Wales, but there is no uniform practice and it is possible that a few deaths in our series might have been prevented had such a scheme operated everywhere. However, in most cases it is unlikely that the outcome would have been different, particularly when patients failed to take their illness seriously, were not under the care of a respiratory physician, or had no prior history of severe attacks.

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Nebulised fluticasone

The place of nebulised inhaled corticosteroids in the treatment of patients with asthma is difficult to assess, but Dr J M Hill’s editorial in *Thorax* was inaccurate and below accepted standards for a major medical journal.


3 Grant IWB. Deaths from asthma. BMJ 1986; 1:575.


Nebulised fluticasone is frequently referred to, yet all the studies referenced¹ have only been published as abstracts (sponsored by the manufacturers of fluticasone) in supplements to journals. There are insufficient details for these papers to be properly scrutinised. They have not been subject to proper peer review and should have no place as the sole references for a new treatment for asthma in the editorial of a major medical journal.

Dr Hill suggests that “it may be that a general improvement in standards of asthma care, there are fewer patients with brittle disease than there were previously. Review of the cases where delays were cited as a factor showed no case where delay in reaching hospital was the only factor in patients in whom a sudden onset of symptoms was reported; poor compliance was also commented on in these few patients. A review of the cases where death occurred in A&E likewise revealed no case of sudden deterioration (within hours) definitely due to sudden onset of severe asthma; in most cases a number of other factors including aspiration of vomit and the use of non-prescribed drugs was a factor. There is therefore no evidence of deaths which would have been prevented by fast track admission and, with the more widespread administration of oxygen and nebulised bronchodilators by paramedical ambulance crews, there are other reasons for emphasising the use of normal referral services, as well as promoting patient self-management to minimise the occurrence of such episodes.

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Authors’ Reply Dr Grant’s comments are welcome and highlight the impossibility of including all the information obtained in a study such as SCIAID in a paper of suitable length for publication. The sudden deterioration of previously well patients, so called “brittle asthma”, was not a major feature of the deaths studied, raising the possibility that there may be relatively fewer such patients or that patients who die suddenly in the community, even with a history of asthma, are certain to be missed. It is noteworthy that the routine management of patients studied, including the use of inhalated steroids, was appropriate in the majority of cases, so it may be that a general improvement in standards of asthma care, there are fewer patients with brittle disease than there were previously. Review of the cases where delays were cited as a factor showed no case where delay in reaching hospital was the only factor in patients in whom a sudden onset of symptoms was reported; poor compliance was also commented on in these few patients. A review of the cases where death occurred in A&E likewise revealed no case of sudden deterioration (within hours) definitely due to sudden onset of severe asthma; in most cases a number of other factors including aspiration of vomit and the use of non-prescribed drugs was a factor. There is therefore no evidence of deaths which would have been prevented by fast track admission and, with the more widespread administration of oxygen and nebulised bronchodilators by paramedical ambulance crews, there are other reasons for emphasising the use of normal referral services, as well as promoting patient self-management to minimise the occurrence of such episodes.


3 Grant IWB. Deaths from asthma. BMJ 1986; 1:575.


6 Crompton GK, Grant IWB, Lane-Fox Unit, St Thomas’ Hospital, London SE1 7EH, UK
7 Dose of CFC-free inhaled beclomethasone (Qvar). **CMAJ** *Carr Prof* Pharmacoeconomics 1999;25:3–6.

**AUTHOR’S REPLY** The author thanks Dr Todd for his constructive comments on her review article.1

There are few published randomised controlled trials of nebulised fluticasone or budesonide in the treatment of asthma. Despite this, these agents are being actively marketed by the pharmaceutical industry so it is vital that the debate about the place of these agents in the treatment of asthma should continue. The author therefore thinks that it is justifiable to review what evidence is available, accepting its limitations in abstract form.

The author apologises for incorrectly quoting a paper comparing the potency of budesonide and fluticasone. The correct reference is cited below.2 However, the author had presumed that the readers of *Thorax* would be well aware that data comparing different inhaled corticosteroids apply only to the type of inhaler used in any comparison, and that this basic principle did not require explanation.

Dr Todd’s comments about different nebuliser systems and drug solubility are well taken. However, this was a short review of the available clinical evidence for the use of nebulised corticosteroids in the treatment of patients with asthma. It was not possible to, nor did Dr Hill, review nebuliser pharmacoconomics and, as Dr Todd states, there are no comparative studies of the potency ratio of nebulised budesonide and fluticasone.

Finally, neither Dr Hill nor her spouse has shares in any pharmaceutical company manufacturing asthma treatments. She has received payment from GlaxoWellcome, Hoechst, Boehringer, Bayer, Abbott Laboratories and Astra for presentations/lectures and for attending meetings in the last three years.

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**Pyoderma gangrenosum**

Wang et al report an interesting case of systemic pyoderma gangrenosum (PG) with associated lung injury.1 They recognise the importance of excluding Wegener’s granulomatosis (WG) in patients with respiratory symptoms and cutaneous ulceration, but in their case seem only to have done this on clinical and histopathological grounds.

A more complete assessment should include testing for cANCA and anti-protease 3 (PR3).2

We are currently treating a 54 year old ex-smoker who presented for investigation of haemoptysis and who subsequently developed episcleritis and skin lesions resembling PG. Initial investigations were Hb 11.3 g/dl, WBC 9.4 × 10^9/l, platelets 249 × 10^10/l, ESR 86 mm/h, and CRP 181 mg/l. Renal function was normal. The chest radiograph showed alveolar shadowing in the left lower zone and an HRCT scan confirmed pulmonary infiltrates.

Biopsy samples showed epithelial cell necrosis and acute inflammatory changes with no evidence of vasculitis or granulomas, consistent with PG. The ANCA assay was positive with a cytoplasmic distribution and was directed against the proteinase 3 epitope. Despite the absence of histological evidence, the clinical features and positive ANCA supported a diagnosis of PG. One month into treatment with pulsed intravenous methyl-prednisolone and cyclophosphamide the patient is clinically better with resolution of haemoptysis, healing of the pyoderma-like lesions, and a fall in the CRP (from 19 to 21 mg/l).

Patients with WG frequently present with non-specific signs and symptoms and a high index of suspicion is important.3 This case highlights the importance of testing for ANCA in patients with PG and respiratory tract symptoms as the treatment of WG requires prolonged immunosuppression for at least a year. Whilst PG itself may be associated with pANCA, the presence of ANCA directed against PR3 is highly suggestive of WG. The histological features of PG are often patchy in distribution and the absence of the characteristic findings of vasculitis, granulomas, and necrosis does not exclude the diagnosis.4

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**AUTHOR’S REPLY** I would like to thank Dr Perkins and colleagues for their interest in our article and for their suggestions. The ANCA assay was only introduced in our hospital in 1988. We are currently treating a 54 year old man who presented for investigation of haemoptysis and who subsequently developed episcleritis and skin lesions resembling PG. Initial investigations were Hb 11.3 g/dl, WBC 9.4 × 10^9/l, platelets 249 × 10^10/l, ESR 86 mm/h, and CRP 181 mg/l. Renal function was normal. The chest radiograph showed alveolar shadowing in the left lower zone and an HRCT scan confirmed pulmonary infiltrates.

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**Therapeutic equivalence of inhaled salbutamol**

The meta-analysis by Hughes et al was hindered by difficulties in comparing trials that were often flawed and of varied design.1 The authors correctly pointed out that, in most of the studies, the use of salbutamol as the null hypothesis was invalid. In addition, all but two of the studies looked at the bronchodilator effects in the presence of basal airway tone, when the top of the dose response curve for bronchodilator response occurs in mild to moderate asthma at a salbutamol dose of approximately 200 µg for chlorofluorocarbon (CFC) or hydrofluoralkane (HFA) pressurised metered dose inhalers (pMDIs).2 To construct a proper dose response curve to estimate relative bronchodilator potency would therefore necessitate the use of doses much lower than 200 µg or evaluation of patients with more severe asthma. Two of the cited studies evaluated functional antagonism against histamine induced bronchoconstriction in patients with mild to moderate asthma. However, in such patients the dose response curve for bronchoprotection is relatively shallow. For example, in a recent study of 72 patients with mild to moderate asthma a fourfold increment in the dose of formoterol Turbobaluer (from 6 µg to 24 µg) only resulted in a shift in the methacholine hyperresponsiveness of one doubling dose.3

One simple way of evaluating bioequivalent doses of inhaled salbutamol is to evaluate the relative respirable lung dose, which can be quantified as lung bioavailability (LB) with early lung absorption profile in the first 20 minutes after inhalation, expressed as the maximal plasma concentration (C max) for the same nominal dose.4

We have therefore reviewed eight studies performed in our laboratory using an identical design in which a nominal dose of 1200 µg salbutamol was administered via different devices in healthy volunteers.5 Where the same device was evaluated in two or more


**AUTHOR’S REPLY** I would like to thank Dr Perkins and colleagues for their interest in our article and for their suggestions. The ANCA assay was only introduced in our hospital in 1997 so we could not use this method to distinguish between WG and PG before that time. The diagnosis of WG in our hospital depends mainly on histopathological examination. In September 1999 the patient came for re-examination. All drugs had been stopped for more than four months, she had no symptoms, and all investigations (including chest radiograph, ESR, and CRP) were normal. Wang et al reported the treatment outcome of 158 patients with WG.6 One hundred and thirty three patients received standard treatment of daily low dose cyclophosphamide (2 mg/kg/day) plus prednisone (1 mg/kg/day). This protocol produced marked improvement or partial remission in 91% of recipients; 75% experienced complete remission with a median time of 12 months.

Less than 10% of patients so treated experienced remission as late as six years after beginning the protocol. However, 10 cases received corticosteroid only. In this group only two of six cases with limited WG (without oral injury) achieved sustained remission. The authors concluded that the course of WG had been dramatically improved by daily treatment with cyclophosphamide and corticosteroid; other treatment regimens had not achieved such high rates of remission and successful maintenance.

Compared with Hoffmann’s standard protocol, the duration of cyclophosphamide and a short duration of treatment in our patient were lower and shorter, respectively. We feel it is unlikely that the clinical picture would have improved so significantly within 10 days if the diagnosis was WG. Of course, the best way is to perform an ANCA test and we intend to do so.

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studies, the highest value for C\text{max} was used. A significant difference in lung bioavailability between Nebuhaler spacer with HFA-pMDI (C\text{max} = 2.96 ng/ml) and small volume antistatic metal spacer (Airomir CFC-free MDI plus Nebuchamber). The Sidestream nebuliser resulted in a decreased lung dose of salbutamol by dry powder inhaler (Turbuhaler) and Diskus dry powder inhaler devices. As expected, the addition of a Volumatic spacer increased the lung delivery for both CFC-pMDIs and HFA-pMDIs. When used in combination with a Volromatic spacer there was greater delivery with HFA than with CFC. The Sidestream nebuliser resulted in a lower relative lung dose than any of the other devices. However, if an adjustment is made to reflect the usual 2500 µg nominal dose administered by nebuliser (C\text{max} = 2.52 ng/ml), the lung dose is similar to the adjusted value for a 400 µg nominal dose from a Nebuhaluer spacer with HFA-pMDI (C\text{max} = 2.96 ng/ml).

Although decreased airway calibre in asthmatic patients will reduce the lung dose of salbutamol from a given device,\textsuperscript{11} the relative difference in lung bioavailability between devices will remain the same and is related to the bronchodilator response.\textsuperscript{12,13} Measurement of the lung bioavailability of salbutamol in healthy subjects may therefore represent a simple in vivo method for preliminary quantification of the relative lung dose from different inhaler devices to select rational doses for subsequent clinical equivalence studies in asthmatic patients.

NOTICE

International Pediatric Respiratory and Allergy Congress

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Respiratory care units for non-invasive mechanical ventilation in motor neurone disease

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