LETTERS TO THE EDITOR

NIV at home: resource implications

The NHS Modernisation Agency’s critical care programme report “Weaning and long term ventilation” recommends that long term non-invasive ventilation (NIV) should be available “according to need” and that this service should increase in line with demand. This need has not been well described. The Nottingham Assisted Ventilation Group (NAVG) provides home NIV for a well defined population of approximately two million. We have looked at the number of patients using NIV at the end of each year between 1991 and 2002 and compared the aetiology of respiratory failure in these patients at the beginning and end of this period.

All patients used pressure controlled ventilation with NIPPV or BREAT machines. Most patients had chronic ventilatory failure with daytime hypercapnia, but a small number of patients with neuromuscular disease had symptomatic nocturnal hypoventilation with normal daytime arterial blood gases. Patients with obstructive sleep apnoea treated with continuous positive airway pressure (CPAP) were not included in this analysis.

The mean increase in the number of patients on home NIV was 8.8 per year (fig 1). The mean (SD) age of the patients in 2002 was 54.6 (17.1) years and the male:female ratio was 1:1.7. At the end of 1991 all patients on home NIV had poliomyelitis, scoliosis, or old tuberculosis. In 2002 these diagnoses together accounted for only 26% of patients, with 28% having other neuromuscular diseases and 31% obesity/hypoventilation. Airway diseases (chronic obstructive pulmonary disease (COPD), bronchiectasis and bronchiolitis) accounted for only 13% of patients.

The number of patients requiring home NIV is rising progressively. We do not think the increase reflects a change in our indications for NIV, which are in line with published recommendations and have not changed significantly over this time period. Most of the increase is for patients with neuromuscular diseases and obesity/hypoventilation syndrome. Although evidence from randomised controlled trials is lacking, observational data strongly suggest a beneficial effect of NIV on survival in Duchenne muscular dystrophy, and in more slowly progressive neuromuscular conditions the 5 year survival on NIV is over 80%. In the absence of good epidemiological data on the prevalence of neuromuscular conditions in which NIV is likely to be indicated, it is impossible to predict the demand for this group. However, increasing awareness of the benefits of NIV by these patients and their doctors is likely to lead to more referrals for consideration of NIV. Doctors have become more aware of the obstructive sleep apnoea/hypopnoea syndrome over the last decade, and this may have resulted in more patients with obesity being referred to hospital and coming to the attention of those providing home NIV. The average weight of the UK population is increasing, and an obesity epidemic is likely to mean that patients with obesity/hypoventilation syndrome will be prominent consumers of home NIV services in the future.

In many countries patients with COPD account for a large proportion of those on home NIV. Trial data are scanty and suggest that the beneficial effects are probably small. The numbers of patients with COPD using our service remain small but, if evidence emerges of a long term survival benefit with NIV, this would have large resource implications.

We have calculated the equipment costs of the service on the assumptions that each ventilator costs £3600, has a life span of 7 years, and that every patient requires two new circuits, masks, and sets of headgear per year at a cost of £250 per patient. To start an average of 8.8 patients on home NIV, in the first year the equipment costs of setting up a home NIV service would be £26 400 for ventilators and £2200 for masks/circuits. After 5 years the new ventilator costs are unchanged, but £11 000 would be required for masks/circuits for the 44 patients at home. After 10 years the ventilator costs double because of the need to replace ventilators over 7 years old, and with 88 patients at home the total cost becomes £74 800.

The equipment costs for a home NIV service are thus substantial. We have not attempted to quantify personnel costs, which are likely to be highly variable between centres, but these will also increase if the Modernisation Agency’s recommendation that this service should be available as an outreach to all hospitals is implemented. In assessing the funding needs of a home NIV service, it should be assumed that the rate of increase in demand is likely to continue, at least in the short term.

L Turner, B Cooper, L Watson, J Britton, S Wharton, W Kin ear
Nottingham Assisted Ventilation Group, University and City Hospitals, Nottingham, UK

Correspondence to Dr W Kin ear, University Hospital, Nottingham NG7 2UH, UK;
kinear@18topgenworld.com

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Figure 1 Number of patients using non-invasive ventilation at home at the end of each year from 1991 to 2002.
GM-CSF and proteinosis

The use of recombinant GM-CSF in the treatment of pulmonary alveolar proteinosis (PAP) has been reported recently in Thorax in cases with anti-GM-CSF antibodies, which provides further evidence for considering GM-CSF as a possible keystone to the treatment of PAP.

A 35 year old man with a past history of idiopathic narrow alveolus treated with antilymphocytic serum in 1983 and Mycobacterium avium systemic infection presented in February 1999 with a 4 month history of dyspnoea. A diagnosis of PAP was suspected from the HRCT scan which showed fine or coarse irregular lines of attenuation (reticular pattern) involving predominantly the subpleural lung regions and ground glass opacities, honeckombing, and crazy paving in the lower lung zones. Pao, on room air was 6.9 kPa at rest. An open lung biopsy performed in May 1999 confirmed PAP. Between June 1999 and May 2001 the disease worsened, despite four whole lung lavages. At this time spirometric improvement was seen in the monocytopenia, thrombopenia, and anaemia. Indeed, this may indirectly have revealed a defect within the monocite lineage through deficient GM-CSF secretion by T cells. Based on this hypothesis, daily treatment with subcutaneous recombinant GM-CSF (Leucomax) in a dose of 5 μg/kg/day was started in September 2001. After 3 months of treatment the oxygen could be stopped; Pao, on room air was 8.6 kPa at rest. An exercise test showed oxygen saturation of 92% (compared with 86% before treatment). The HRCT scan showed a decrease in ground glass opacities and persistence of the fixed crazy paving lesions; the HRCT severity score was 4. No improvement was seen in the monocypenia or lymphopenia after treatment. The patient remains stable after more than 1 year of follow up since stopping GM-CSF treatment.

Improvement in pulmonary symptoms with GM-CSF treatment, as occurred in our patient, reinforces the hypothesis of a defect in GM-CSF production in the pathogenesis of PAP. The progenitor cells of our patient did respond normally to GM-CSF in vitro and no anti-GM-CSF antibodies were detected. Later lesions, shown by radiological imaging not to have improved with this treatment, suggest that GM-CSF has to be introduced earlier in PAP to achieve definitive remission.

F Khanjari, H Watier, J Domenech, E Asquier, P Diot
Services de Pneumologie, Hémato, Immunologie, Radiologie, CHU Bretonneau, 37044 Tours Cedex, France

K Nakata
Department of Respiratory Diseases, International Medical Center of Japan, Tokyo, Japan

Correspondence to: Professor P Diot, Services de Pneumologie, Hémato, Immunologie, Radiologie, IFR 120, CHU Bretonneau, 2 Boulevard Tonnelle, 37044 Tours Cedex, France; diot@med.univ-tours.fr

Progressive encephalomyelitis with rigidity as refractory asthma

Refactory asthma may include diseases other than bronchial asthma. We report a 19 year old woman with stridor who developed progressive encephalomyelititis with rigidity (PER).

The patient had been undergoing treatment with prednisolone for a diagnosis of refractory asthma but stopped taking steroids in March 1999 due to avascular necrosis of the femoral heads. She was admitted to hospital in January 2001 because the persistent dyspnoea and paroxysmal board-like rigidity of the extremities became exacerbated after steroid cessation. On admission she was bedridden in a dystonic position. She had miosis, stridor, urinary retention, dysaesthesia below the Th6 level, and tremor and rigidity of the masseter muscle and extremities, but she did not have opisthotonus. She was diagnosed with PER because the continuous motor unit discharges were seen on the surface electromyogram to decrease after dazepam infusion. While observing the larynx, persistent glottal closure was observed (fig 1A) and the glottis opened normally only for brief moments (fig 1B). She recovered from the dyspnoea and stridor after a tracheostomy. Her antilgutamic acid decarboxylase antibody was negative, and spinal fluid examination showed an increased protein level of 41 mg/dl which decreased to 17 mg/dl with steroid treatment. Her symptoms partially improved with steroid pulse therapy.

PER, first reported as a variant of stiff person syndrome by Kasperek and Zebrowski in 1971, is characterised by muscle pain in the extremities, the trunk, or the face due to progressive rigidity. It was unlikely that this case had asthma because the tracheostomy improved her stridor and dyspnoea. The abducting muscle was thought to work normally, indicating that hypertonia of the adducting muscles might have caused the severe stenosis of the glottic space. We conclude that PER should also be considered in cases of refractory asthma.

N Kikuchi, A Nomura, Y Ishii, K Sekizawa
Department of Pulmonary Medicine, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Ibaraki 305-8575, Japan

H Harada, K Ishii
Department of Neurology, Institute of Clinical Medicine, University of Tsukuba

T Wada
Department of Otolaryngology, Institute of Clinical Medicine, University of Tsukuba

Correspondence to: Dr K Sekizawa, Department of Pulmonary Medicine, Institute of Clinical Medicine, University of Tsukuba, 1-11 Tennoudai Tsukuba, Ibaraki 305-8575 Japan; kiko-nor@md.tsukuba.ac.jp

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Impaired cough reflex in patients with recurrent pneumonia

We read with interest the paper by Niimi et al published in February’s edition of Thorax in which the authors identified a small number of patients with unexplained recurrent pneumonias and reduced cough reflex sensitivity to capsaicin compared with an age and sex matched control group. It does seem intuitively reasonable that the risk of aspiration pneumonia might be greater in those with diminished cough responses, and this has already been demonstrated in post-stroke patients.

Figure 1 Laryngoscopy showing [A] glottal stenosis due to spastic adducting muscles while breathing and [B] the absence of paralysis of the abducting muscle.
Our concerns with this study are twofold. The first is the finding that unexplained recurrent pneumonia is uncommon (seven cases over a 5 year period) whereas insensitivity to tussive stimuli is relatively common in normal healthy volunteers. Indeed, it has been a sufficiently regular occurrence that the majority of cough challenges developed have had to incorporate an in-built method of assigning a theoretical cough threshold to non-coughers. This is usually taken as either the greatest concentration inhaled or the next incremental concentration which would have been inhaled if the test had continued. The proportion of subjects who do not cough will obviously vary between different cough challenge methodologies. In a recent as yet unpublished study the proportion of non-coughing healthy volunteers in our laboratory was approximately 10% with a Mefar dosimeter based protocol and a maximum inhaled concentration of 3 M citric acid. Pounsford and Saunders' found that over one quarter of women tested did not cough during their citric acid cough challenge and that these subjects had the ability to smoke cigarettes pleasurably on an intermittent occasional basis. In more recently published studies over half of the large control group of healthy individuals did not achieve C5 thresholds to their maximum challenge of 500 µM capsaicin. The discrepancy between the relative prevalence of the two findings raises concerns that recurrent pneumonias can be purely attributed to low cough reflex sensitivity per se.

This brings us to our second area of concern and offers a possible alternative explanation for their cases. Niimi et al state that they excluded patients in an immunocompromised state (diabetes mellitus, corticosteroid therapy, active malignancy, AIDS) and found that immunoglobulin levels including IgG subclasses were normal. They do not, however, seem to have excluded functional immunoglobulin deficiencies which may be diagnosed by measuring patients’ immune responses to tetanus toxoid and pneumococcal vaccination. This well recognised condition is a cause of recurrent bronchial sepsis which is associated with normal immunoglobulin/complement levels, as well as normal neutrophil/lymphocyte counts. It is possible that the patients described may have been suffering from undiagnosed immunodeficiency as an alternative cause for their recurrent pneumonias, and we believe that functional immunoglobulin deficiency should be looked for in all such patients.

C M Barber, A D Curran, D Fishwick
Royal Hallamshire Hospital, Sheffield S10 2JF, UK; chris@chrisandrachael.freeserve.co.uk

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Authors’ reply
We thank Barber et al for their comments on our paper and agree that unexplained recurrent pneumonia is not a very common condition. In fact, we could recruit only seven cases over a 5 year period at a university hospital department which specialises in respiratory infection.

They claim that insensitivity to tussive stimuli is a relatively common finding in normal healthy volunteers on the basis of a number of previous publications and their own experience, and suggest that the recurrent pneumonias may not be entirely the result of a low cough sensitivity per se. This argument against the conclusion of our study does not, however, seem to be relevant. We used a 15 second tidal breathing method to test capsaicin cough sensitivity which, although it has been used at only a few institutions, has established reproducibility. In our study the capsaicin cough threshold that caused five or more coughs (C5) in 21 healthy controls (18 men, mean (SD) age 61 (15) years) ranged from 2.44 to 156.3 µM with a median of 19.5 µM. The highest concentration of capsaicin prepared was 625 µM. In another group of 57 younger healthy volunteers from our laboratory (50 men, mean (SD) age 28 (6) years) C5 titres ranged from 0.61 to 156.3 µM with a median of 19.5 µM. Only two subjects had a C5 titre of 156.3 µM (unpublished data). Similarly, in 160 normal volunteers investigated by Fujimura et al using the first 5 second tidal breathing method of capsaicin sensitivity testing, C5 titres ranged from 0.49 to 1000 µM (the highest dose) with a median of 15.6 µM. Only one subject had a C5 titre of 1000 µM. We are therefore convinced that, when the 15 second tidal breathing method is used, “healthy” subjects rarely fail to respond to the highest concentrations of capsaicin. The different prevalence of non-responders in our laboratory from that of Doherty et al, who also used capsaicin, may be because they adopted a single breath method using a dosimeter. However, a study in 100 healthy volunteers using capsaicin and a dosimeter showed a distribution of C5 similar to ours. We would like to emphasise that, when the results of cough sensitivity tests are analysed, they should be cautiously compared with the results from appropriate controls obtained using exactly the same method, preferably in the same laboratory.

We did not exclude functional immunoglobulin deficiencies which might have been present in our patients. If this had been the case, however, impairment of the cough reflex might have played an additional role in the development of recurrent pneumonia.

A Niimi, M Mishima
Department of Respiratory Medicine, Graduate School of Medicine, Kyoto University, Sakyo-ku, Kyoto 606–8507, Japan; niimi@kuhp.kyoto-u.ac.jp

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F Khanjari, H Watier, J Domenech, E Asquier, P Diot and K Nakata

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