

Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial

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Summary

Background Within the intensive-care unit, non-invasive ventilation (NIV) can prevent the need for intubation and the mortality associated with severe episodes of chronic obstructive pulmonary disease (COPD). The aim of this study was to find whether the introduction of NIV, early after the admission on a general respiratory ward, was effective at reducing the need for intubation and the mortality associated with acute exacerbations of COPD.

Methods We did a prospective multicentre randomised controlled study comparing NIV with standard therapy in patients with mild to moderate acidosis. NIV was administered on the ward with a simple non-invasive ventilator and a standardised predefined protocol. Patients were recruited from 14 UK hospitals over 22 months.

Findings 236 patients were recruited, 118 received standard therapy alone and 118 additional NIV. The two groups had similar characteristics at enrolment. The use of NIV significantly reduced the need for intubation as defined by the failure criteria. 32/118 (27%) of the standard group failed compared with 18/118 (15%) of the NIV group ($p=0.02$). In-hospital mortality was also reduced by NIV, 24/118 (20%) died in the standard group compared with 12/118 (10%) in the NIV group ($p=0.05$). In both groups pH, PaCO₂, and respiratory rate improved at 4 h ($p<0.01$). However, NIV led to a more rapid improvement in pH in the first hour ($p=0.02$) and a greater fall in respiratory rate at 4 h ($p=0.035$). The duration of breathlessness was also reduced by NIV ($p=0.025$).

Interpretation The early use of NIV for mildly and moderately acidotic patients with COPD in the general ward setting leads to more rapid improvement of physiological variables, a reduction in the need for invasive mechanical ventilation (with objective criteria), and a reduction in in-hospital mortality.

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Introduction

Prospective randomised controlled trials of non-invasive ventilation (NIV) within the intensive-care unit (ICU) have shown reductions in the need for intubation and in-hospital mortality associated with severe exacerbations of chronic obstructive pulmonary disease (COPD).^{1–3} The evidence from randomised controlled trials within the accident and emergency department and general respiratory ward is mixed.^{4–7} Bott and colleagues, using research staff to initiate ventilation on the ward, showed that NIV improved pH and PaCO₂.⁴ On an intention-to-treat analysis there was no survival benefit from NIV, until those unable to tolerate NIV were excluded. The use of research staff makes it difficult to generalise the results of this study to routine clinical practice. Angus and colleagues randomised 17 patients to either NIV ($n=9$) or conventional therapy plus doxapram ($n=8$). There was a non-significant trend to improved survival in the NIV group with three out of eight patients dying with conventional care and nine out of nine surviving with NIV.⁵ Barbe and colleagues found NIV unnecessary because none of the 24 patients in their study died or required intubation.⁶ Wood and colleagues found that NIV delayed intubation and increased in-hospital mortality.⁷ However, of the 27 patients in this study only six had COPD, the groups were not well matched, and the level of pressure support was modest.

The use of NIV in general respiratory wards could theoretically allow the earlier use of NIV during an exacerbation and widen the availability of NIV. This is particularly important in the UK where there is a shortage of ICU and high-dependency bed provision.

We therefore aimed to find out whether NIV was feasible on the ward in non-specialist units and whether it was effective at reducing the need for intubation and in-hospital mortality, compared with standard treatment, in patients admitted with mild-to-moderate acidosis due to an exacerbation of COPD. Patients with acidosis are at higher risk of subsequent intubation and death than patients with a normal pH.^{8,9} The null hypothesis was that NIV on the ward would not reduce the need for intubation in this clinical group.⁸

Methods

Patients

Between November, 1996, and September, 1998, adult patients who were in hospital because of an acute exacerbation of COPD were prospectively recruited from 14 hospitals in the UK: Airedale District Hospital, Birch Hill Hospital (Rochdale), Bradford Royal Infirmary, Castle Hill Hospital (Hull), Churchill Hospital (Oxford), Dewsbury and District Hospital, Doncaster Royal Infirmary, Halifax General Hospital,

Huddersfield Royal Infirmary, Killingbeck Hospital (Leeds), Leeds General Infirmary, Pontefract General Infirmary, St James's University Hospital (Leeds), and York District Hospital. The study protocol was approved by the local research ethics committees and South West Thames Multicentre Research ethics committee. Patients were eligible for the study if they were admitted as an emergency with an acute exacerbation of COPD (on the basis of the clinical history, physical examination, and chest radiograph), were tachypnoeic with a respiratory rate of more than 23 per min and had a pH 7.25–7.35 with a PaCO₂>6 kPa on arrival to the general respiratory ward—ie, after initial treatment within the accident and emergency department and within a maximum of 12 h of admission. Patients with a pH below 7.25 were not included since the prognosis for this group without ventilatory support is poor and it was felt unethical to randomise these patients.⁹ Exclusion criteria were: a Glasgow coma scale below 8, pneumothorax, or active treatment deemed inappropriate. Consent was obtained from the patient.

Patients were randomly assigned to receive standard treatment or standard treatment plus pressure-support ventilation through a face or nasal mask. The randomisation schedule had a blocked design for each centre and was generated by an independent statistician who used random numbers. The individual assignments were made by the use of opaque sealed envelopes.

Standard treatment

Patients assigned to standard treatment received controlled oxygen with fixed percentage masks (or nasal cannulae if masks could not be tolerated) to maintain a target oxygen saturation (recorded by pulse oximetry) of 85–90%. The standard drug protocol consisted of nebulised salbutamol (5 mg every 4 h) or terbutaline, nebulised ipratropium bromide (500 µg every 6 h), corticosteroids (prednisolone 30 mg every day for a minimum of 5 days), and an antibiotic. Aminophylline and doxapram could be used at the discretion of the attending medical staff.

NIV

Patients assigned to the NIV group received the same medications as the patients in the standard-treatment group. NIV was initiated by the nurses in 13 centres and by physiotherapists in one, with a standard protocol. All centres used the same bilevel assist-mode ventilator (VPAP-II, ResMed, UK) and were supplied with an identical set of masks. Two facemasks (Aircraft mask [Friday Medical, UK] and a small full-face mask [Respironics, Murraysville, USA]) plus two nasal masks (small and medium Bubble Cushion Series 3 [ResMed, UK]) were supplied with the accompanying headgear. The expiratory pressure was set at 4 cm H₂O pressure. The inspiratory pressure was initially set at 10 cm H₂O and then increased in increments of 5 cm H₂O to 20 cm H₂O or the maximum tolerated over 1 h. Oxygen was entrained into the mask to maintain oxygen saturations between 85% and 90%.

Patients were encouraged to use NIV as much as possible on day 1, for 16 h on day 2, and 12 h on day 3. NIV was routinely discontinued on day 4, although an option to continue it was available if clinically indicated.

Primary outcome measure

The primary endpoint was “need for intubation”. This was defined by a set of objective criteria, avoiding the inconsistencies associated with intubation on clinical grounds. Furthermore, intubation rates are often dependent on ICU bed availability in UK studies and are therefore a potentially misleading endpoint. The criteria were derived from those used by Brochard and colleagues¹ and agreed after discussion with the participating physicians, experts in the field, and intensive-care physicians. Patients were considered to have “needed intubation” if they met any of the following criteria within 14 days of admission: pH below 7.20; pH 7.20–7.25 on two

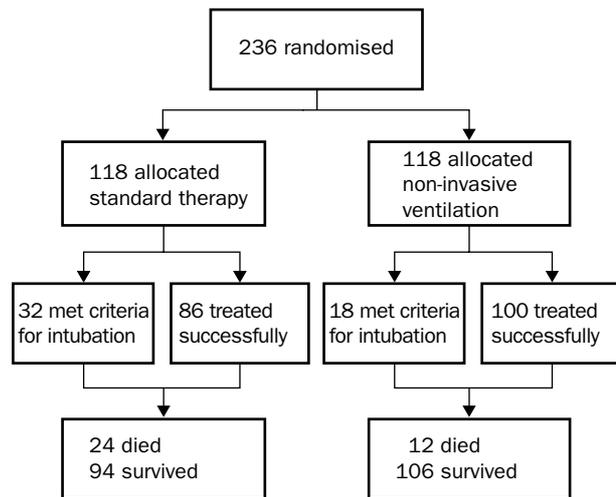


Figure 1: Trial profile

occasions 1 h apart; hypercapnic coma (Glasgow coma scale <8 and PaCO₂ >8kPa); PaO₂ below 6 kPa despite maximum tolerated FiO₂; and cardiorespiratory arrest. After meeting the criteria the attending physicians were able to offer any of the following—continued standard treatment, NIV off protocol by a more sophisticated non-invasive ventilator, or intubation and mechanical ventilation.

Secondary outcome measures

The respiratory rate and concentrations of arterial blood gases were measured at enrolment, 1 h and 4 h after randomisation and on day 3 in both groups. Mobility and nutritional status were assessed daily by the nursing staff with the subscale from the Braden Pressure scale.¹⁰ Mask comfort and breathlessness were also assessed by five-point verbal-rating scales—comfortable/mildly uncomfortable/moderately uncomfortable/very uncomfortable/intolerable; not breathless/mildly breathless/moderately breathless/very breathless/most breathless I have ever been. Nursing workload was recorded by an end-of-the-bed log for the first 48 h of the admission.^{11,12} Arterial blood gases on room air and spirometry were measured, when possible at discharge, or within 3 months.

Statistical analysis

The study aimed to recruit 236 patients. This sample size gave the study 80% power of detecting a clinically significant difference in the proportion of patients experiencing treatment failure at the 5% level of significance, on the assumption that 30% of the standard group would fulfil the criteria for intubation and that a reduction to 15% in the NIV group would be clinically relevant.

Results are given as means (SD) for normally distributed data and as medians with 5th and 95th centiles for non-normally distributed variables. All tests and p values are two-tailed and were analysed on an intention-to-treat basis. The group means were compared by *t*-tests and medians by the Mann-Whitney *U* test. Bonferroni's correction was applied to multiple comparisons. 2×2 tables were analysed by Fisher's exact test. Kaplan-Meier curves were generated for time data and compared by the log-rank test. Analyses were done by SPSS (version 7).

Results

Characteristics of patients

118 patients were randomly assigned to standard treatment and 118 to NIV (figure 1). The two groups had similar characteristics on admission (table 1). The use of aminophylline and doxapram was not different between the two groups.

	Standard treatment (n=118)	NIV (n=118)
Mean age (SD)	69 (8)	69 (7)
Sex (M/F)	63/55	54/64
Respiratory rate per min (range)	28 (24–40)	28 (24–36)
pH (range)	7.31 (7.26–7.35)	7.32 (7.25–7.35)
PaCO ₂ kPa (SD)	8.65 (1.70)	8.82 (1.51)
PaO ₂ kPa (range)	7.00 (4.71–12.31)	6.88 (4.50–13.8)

Ranges in parentheses are median data with 5th and 95th centiles.

Table 1: Characteristics of patients with acute exacerbations of COPD assigned to standard treatment or NIV admission

Setting

In each hospital between one and three general medical/respiratory wards were identified as sites for NIV. Of the 25 wards involved in the trial, 22 had no experience of NIV and only one was fully experienced. None had previously used the study ventilator. In none of the wards was it possible to invasively ventilate or invasively monitor patients. The median nurse:patient ratio was 1:11 (range 1:2.6 to 1:13). The mean amount of formal training given in the first 3 months of opening a ward by the research doctor and nurse was 7.6 h (SD 3.6). Thereafter each centre received 0.9 h (0.82) per month to maintain the skills.

Clinical outcomes

32 of 118 patients (27.1%) in the standard-treatment group met the primary endpoint “need for intubation” compared with 18 of 118 (15.3%) in the NIV group ($p < 0.02$; figure 2). In-hospital mortality was also reduced in the NIV group. 24/118 (20.3%) of the standard group died compared with 12/118 (10.2%, $p = 0.05$). A difference in outcome was seen between the patients with an admission pH above and below 7.30, although the results should be approached with caution, because the study was not powered for subgroup analysis (table 2).

There was no difference in the time between randomisation and meeting the failure criteria between groups ($p = 0.446$). 19/23 (59.4%) of the patients allocated

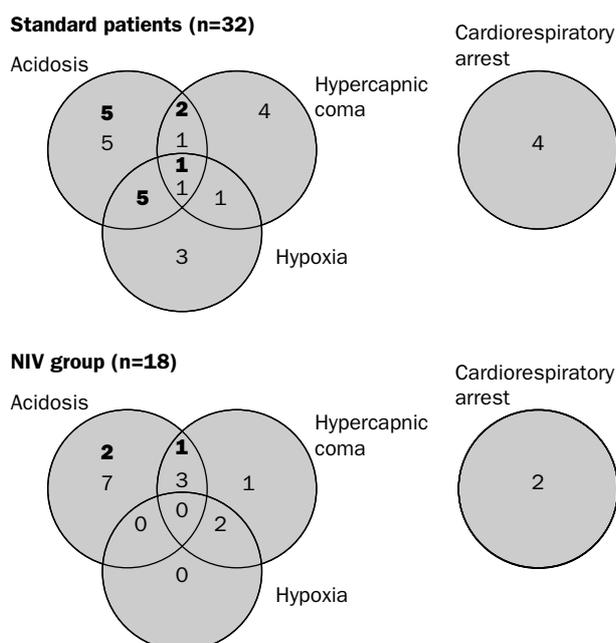


Figure 2: Cause of failure

Acidosis—roman type pH <7.2; bold type pH=7.20–7.25 on two occasions.

	Standard	NIV	p
Intention-to-treat			
Failed	32/118 (27%)	18/118 (15%)	0.02
Died	24/118 (20%)	12/118 (10%)	0.05
Subgroup analysis			
pH < 7.30			
Failed	16/38 (42%)	13/36 (36%)	0.64
Died	13/38 (34%)	8/36 (22%)	0.31
pH ≥ 7.30			
Failed	16/80 (20%)	5/82 (6%)	0.01
Died	11/80 (14%)	4/82 (5%)	0.06

Table 2: Primary outcome and in-hospital mortality

standard treatment failed on the day of admission or on the day following admission compared with 11/18 (61.1%) of those randomised to NIV. In the standard group four patients failed and died due to cardiorespiratory arrest. Of the remaining 28, 24 received some form of ventilatory support (nine invasive mechanical ventilation alone [five died], 12 non-invasive ventilation alone [seven died], and three received invasive mechanical ventilation after a trial of NIV [two died]). Three of four patients who received no ventilatory support died. In the NIV group two patients failed and died due to cardiorespiratory arrest. All 16 remaining patients received further ventilatory support. Nine continued with NIV (four died) and seven were invasively ventilated (two died).

Seven patients died without meeting the primary endpoint, which was “need for intubation in the first 14 days”. Three died in the standard group, all from respiratory failure on days 16, 64, and 69. Four died in the NIV group, two from gastrointestinal haemorrhage on day 21 and 30, one from respiratory failure on day 21, and one in association with bronchoscopy on day 22, the planned day of discharge.

The cause of death recorded on the death certificates in the standard group were as follows: respiratory failure (20); myocardial infarction (two); upper gastrointestinal haemorrhage (one); cerebrovascular accident (one). In the NIV group causes of death were: respiratory failure (nine), upper gastrointestinal haemorrhage (two), secondary to bronchoscopy (one). 8.6% of all deaths were associated with upper gastrointestinal haemorrhage.

Physiological outcomes

Table 3 shows the 1 h and 4 h values for the physiological variables. In both groups acidosis, PaCO₂, and respiratory rate improved after 4 h ($p = 0.01$ for all variables in both groups). However, NIV led to a more rapid correction of acidosis in the first hour compared with the standard group (mean difference in H⁺ concentration 1.49 nmol, 95% 0.23–2.75, $p = 0.02$) and a greater fall in respiratory rate over the first 4 h ($p = 0.035$). There was also a trend to a more rapid improvement in PaCO₂ with NIV at 1 h ($p = 0.058$). PaO₂ was similar between the two groups as expected from the protocol. Values obtained for patients after meeting criteria for intubation were not included in the analyses because additional therapy, such as invasive mechanical ventilation, would have led to marked changes and hence to difficulties with interpretation.

Mask use and tolerance

Patients assigned to the NIV group used the ventilator for a median duration of 3 days (range 0–26). The median use on day 1 was 8 h compared with 7 h on day 2 and 5 h on day 3. 7.2% of patients used the ventilator for less than 1 h on the first day of admission, rising to 23.6% on day 2

	Standard			NIV		
	0 hr (n=118)	1 hr (n=106)	4 hr (n=109)	0 hr (n=118)	1 hr (n=101)	4 hr (n=109)
pH (range)	7.310 (7.260–7.350)	7.324* (7.266–7.380)	7.350* (7.235–7.430)	7.320 (7.250–7.347)	7.342* (7.243–7.409)	7.345* (7.254–7.440)
PaCO ₂ kPa (SD)	8.65 (1.69)	8.45† (1.91)	8.09* (2.07)	8.82 (1.51)	8.18* (2.00)	8.04* (1.99)
PaO ₂ kPa (range)	7.00 (4.71–12.31)	7.50† (4.71–16.08)	8.11† (4.85–14.35)	6.88 (4.50–13.80)	7.50† (5.27–12.63)	7.48† (5.21–14.02)
Respiratory rate per min (range)	28 (24–40)	28 (19–37)	26* (19–36)	28 (24–36)	25* (15–35)	24* (13–34)

Ranges in parentheses are median data with 5th and 95th centiles. *p<0.01. †p<0.05. Comparisons are between 0 h and either 1 h or 4 h.

Table 3: **Physiological factors**

and 32.3% on day 3. This percentage incorporates those who could not tolerate the procedure, those who had failed and were invasively ventilated, and those who felt they no longer needed it (self-weaned). The median comfort score on the first 3 days of non-invasive ventilation was 2—mildly uncomfortable.

Well-being scores

NIV led to a more rapid relief of breathlessness (p=0.025). The median time to relief of breathlessness was 4 days in the non-invasive ventilation group and 7 days in the standard group. However, non-invasive ventilation neither delayed nor expedited patient mobility or nutritional intake. The median time to walking was 5 days in both groups (p=0.47). Similarly for nutrition the median time to eat an adequate diet was 4 days for the standard group and 3 days for the NIV group (p=0.17).

Nursing workload

NIV led to a modest 26 min increase in nursing workload in the first 8 h of the admission (table 4). No difference was identified after 8 h.

Length of stay and discharge data.

The median length of stay was the same for both groups at 10 days (range standard group 2–119, non-invasive ventilation group 4–137, p=0.269). Discharge blood gases on air and spirometry were available for 87 and 90 out of the standard group, respectively, and 91 and 97 out of 106 of the non-invasive ventilation group (table 5). No significant differences were identified for any of these variables at discharge.

Discussion

This study shows that the use of NIV on general respiratory wards is both feasible and clinically effective at reducing the demand for invasive ventilatory support and the in-hospital mortality associated with acute ventilatory failure in patients with a clinical diagnosis of COPD.

NIV could be established (defined as >1 h of use) in 93% of patients, similar to the 87% described by Bott and colleagues,⁴ and only consumed an additional 26 min of nursing time. In a low nurse-to-patient setting subsequent compliance could be expected to deteriorate compared with studies in intensive-care units (ICU) or with additional staff. However, the median compliance of 8 h on day 1 and 7 h on day 2 are similar to those in the

other trials. Bott and colleagues reported 7.6 h per day, Brochard and colleagues 6 h per day, and Kramer and colleagues 14.4 h over the first 2 days.^{1,2,4} The limited range of masks also appears adequate since most patients found the mask comfortable or only mildly uncomfortable.

NIV led to a fall in respiratory rate and a more rapid improvement in pH associated with a non-significant fall in PaCO₂. The fall in PaCO₂ was of the expected amplitude for the H⁺ change, indicating an improvement in respiratory acidosis.¹³ Improvements in pH within the first hour were reported in the studies by Bott and colleagues and Brochard and colleagues but only the former reported a reduction in PaCO₂.^{1,4} Falls in respiratory rate were also reported.^{1,2} These findings show that NIV increases minute ventilation by increasing tidal volume and allowing respiratory rate to fall, off-loading the respiratory muscles, which may explain the more rapid palliation of breathlessness seen in the group receiving NIV in our study and that of Bott and colleagues.⁴

The physiological changes are similar to other studies.^{1,2,4} However, the magnitude of physiological change is small compared with the change in the primary outcome, indeed by 4 h there were no physiological differences between the groups. This may reflect a systematic bias against finding large physiological changes in the study design. Once a patient met criteria for intubation, further gases were not included in the analysis, due to the confounding effects of subsequent intervention such as invasive mechanical ventilation. Hence the physiological data largely reflect the successes and exclude those that failed. Because more patients failed in the standard group there is a bias towards the minimisation of any difference in physiological change.

The failure criterion in this study was a surrogate endpoint for “need for intubation”. Objective criteria were used to ensure consistency across the study and to avoid the potentially confounding effects of ICU bed availability and individual physicians’ assessment of the appropriateness for endotracheal intubation and mechanical ventilation. With these criteria the “need for intubation” fell from 27.1% to 15.3%, a reduction of 44%. That these criteria were reasonable was confirmed by a 50% reduction in mortality from 20.3% to 10.2% and a 42% reduction in actual intubation rates from 10% to 6%. This confirms the study of Brochard and colleagues in which mortality fell from 29% to 9% with

Period (range)	Standard	NIV	p
0–1 h	25 (5–84)	35 (7–95)	0.001
1–8 h	54 (11–130)	70 (19–179)	0.004
8–24 h	84 (21–262)	103 (32–228)	0.164
24–48 h	106 (34–385)	127 (30–251)	NS*

Ranges in parentheses are median data with 5th and 95th centiles. NS=not significant. *p>0.05 pre-Bonferroni correction.

Table 4: **Median nursing workload by group and time period**

	Standard	NIV
pH (SD)	7.41 (0.036)	7.41 (0.042)
PaCO ₂ kPa (SD)	6.53 (0.93)	6.67 (1.20)
PaO ₂ kPa (SD)	8.28 (2.00)	8.13 (1.73)
FEV ₁ (range)	0.68 (0.37–2.00)	0.71 (0.28–1.47)

Ranges in parentheses indicate median data with 5th and 95th centiles. FEV₁=forced expiratory volume in 1 s.

Table 5: **Characteristics at discharge**

NIV and underscores the suggestion by Bott and colleagues that mortality could be reduced in the ward setting.^{1,4} There was no difference between drug therapy received in the two groups and the additional half-hour of nursing time is unlikely to have confounded these findings. However, these results were only obtained by ensuring that the staff within these wards were trained to provide NIV and that these skills were maintained over time. Maintenance of skills was achieved by formal training, the selection of a simple ventilator with a standardised protocol, and by ensuring that the NIV was located in as few wards as possible to maximise throughput.

The failure rates are low compared with the ICU studies in which 73–74% of the patients treated conventionally needed intubation but considerably higher than the zero rate reported by Barbe and colleagues in the emergency room.^{1,2,6} This probably reflects differences in exacerbation severity, because the patients in the ICU studies were more acidotic (mean pH 7.28) than our patients (mean pH 7.31) or those in the study by Barbe and colleagues (mean pH 7.33).⁶ In addition, the amount of treatment received before enrolment is likely to differ between the studies. Failure of conventional therapy is less likely in patients enrolled shortly after pharmacological therapy is started (ie, accident and emergency department and ward studies) and more likely in patients in ICU who have failed to improve despite aggressive drug therapy. It is therefore not surprising that our failure rate in patients enrolled on arrival at the ward, after initial drug therapy, was greater than that in the study of Barbe and colleagues, but less than that in the ICU studies.^{1,2,6} An alternative explanation proposed by Schneerson is that the ICU studies tried to maintain excessively high oxygen saturations and in so doing precipitated intubation.¹⁴ To avoid that criticism, controlled oxygen was given to maintain a target oxygen saturation of 85% to 90%.

It is salient to point out that even with NIV, 15% of patients in our study met criteria for “intubation”. Hence it is important that rapid access to invasive ventilation, when considered appropriate, be available wherever NIV is done if the trend to increased mortality due to delays in invasive ventilation suggested by Wood and colleagues is to be avoided.⁷

This observation is emphasised by the subgroup analysis, which showed that patients with a pH below 7.30 on enrolment had a significantly higher failure rate and in-hospital mortality than those with an initial pH over 7.30 whether they received NIV or not. 22% of those with an entry pH below 7.30 who received NIV died. This is high compared with 9% in the study by Brochard and colleagues.¹ This suggests that this group might benefit more from NIV within a higher dependency setting or with a more sophisticated ventilator and individualised settings.

This study must, however, be put into an international perspective. In North America and in many European countries, NIV would not be considered an appropriate

treatment on the ward. However, in the UK, ICU beds are in such short supply that if COPD patients are to receive NIV it must be on the ward, where nurses provide all-round care and can adopt some of the roles of the respiratory therapist. ICU bed availability also explains the low intubation rates and higher mortality found in this and other UK studies.⁴ These features of the UK setting may reduce the generalisability of the mortality data to countries with good ICU provision. However, the prevention of intubation is generally applicable.

Contributors

P K Plant and M W Elliott were responsible for the study design, analysis, and writing of the paper. P K Plant and J L Owen were responsible for the education of staff and conduct of the trial. P K Plant was responsible for statistical analysis.

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