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Hyperglycaemia as a predictor of outcome during Non Invasive Ventilation in decompensated COPD

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Running head: A study of variables predicting the outcome of Non Invasive Ventilation during acute exacerbations of COPD and the role of hyperglycaemia

Abstract:

Rationale: Hyperglycaemia predicts a poor outcome in ICU patients. Whether this is true for respiratory failure necessitating non-invasive ventilation (NIV) is not known.

Objectives: To determine whether hyperglycaemia within 24 hours of admission independently predicts outcome of NIV during acute decompensated ventilatory failure complicating COPD exacerbations.

Methods: COPD patients presenting with acute hypercapnic respiratory failure at University Hospital Aintree between June 2006 and September 2007 and receiving NIV within 24 hours of admission were prospectively studied. Random blood glucose levels were measured before NIV administration.

Measurements and Main Results: 88 patients (mean baseline pH 7.25, PaCO2 10.20 kPa, and PaO2 8.19 kPa) met inclusion criteria with NIV normalising arterial pH off therapy in 79 (90%). After multi-variate logistic regression, the following predicted outcome: baseline Respiratory Rate (OR 0.91; 95% CI 0.84-0.99), random glucose ≥ 7 mmol/l (OR 0.07; 95% CI 0.007-0.63) and admission APACHE II score (OR 0.75; 95% CI 0.62-0.90). The combination of baseline RR < 30 breaths per minute and random glucose < 7mmol/l increased prediction of NIV success to 97% whilst use of all 3 factors was 100% predictive.

Conclusions: In acute decompensated ventilatory failure complicating COPD, hyperglycaemia upon presentation was associated with a poor outcome. Baseline respiratory rate and hyperglycaemia are as good at predicting clinical outcomes as the APACHE 2 score. Combining these variables increases predictive accuracy providing a simple method of early risk stratification.

Key words: Non Invasive Ventilation, COPD, Hyperglycaemia, APACHE II, Predictors

Introduction

Non-invasive ventilation (NIV) is an effective treatment for acute hypercapnic respiratory failure (AHRF) complicating a COPD exacerbation [1]. However, some patients do not improve with NIV and in these individuals endotracheal intubation or, where appropriate,

palliation, are needed. Several factors are associated with an increased risk of NIV failure. In one randomised controlled trial survival was worse when the initial pH was below 7.3, or if $PaCO_2$ or respiratory rate failed to improve after four hours of treatment. [2] Other factors retrospectively identified as poor prognostic markers include a high APACHE II score, radiologically confirmed consolidation, haemodynamic instability, and impaired consciousness, the presence of co-morbidities, impaired functional status and metabolic dysfunction [3-5]. NIV is now offered to COPD patients presenting with more severe acidosis than in these early clinical trials and appears to be effective in improving clinical outcomes [6]. Whether the same risk factors operate and do so to the same degree is not clear.

In patients with a wide range of conditions admitted to intensive care pre-therapy hyperglycaemia is an independent predictor of a poor outcome [7-10] which may be improved by tight glycaemic control. [11-12] A retrospective case note review of patients hospitalised with COPD exacerbations but not necessarily exhibiting respiratory failure found an increased mortality and longer hospital stay in patients with random blood glucose of 7mmol/l or more. [13] Whether hyperglycaemia upon presentation influences the outcome of NIV in acidotic COPD patients is not known nor is its relationship to other identified poor prognostic factors. To investigate these relationships we prospectively collected data about the occurrence of hyperglycaemia and the risk factors identified above in an observational study of consecutive COPD patients undergoing NIV.

Methods

Patients

All patients admitted to University Hospital Aintree between June 2006 and September 2007 with an exacerbation of COPD who received NIV within 24 hours of admission to the Respiratory Failure Unit (RFU) or ICU were prospectively identified. AHRF was defined by the presence

of worsening of dyspnoea and an arterial pH<7.35 with a PaC02 >6kPa. The diagnosis of COPD was made clinically and confirmed by spirometry whenever possible. [14]Where spirometry was unavailable, a senior respiratory clinician confirmed that COPD was the most likely diagnosis based on the history, tobacco exposure, examination findings and radiology. An exacerbation of COPD was defined according to pre-existing criteria [14] while pneumonia was diagnosed when a new infiltrate on the chest radiograph occurred with one or more of the following: dyspnoea, cough, sputum production, fever greater than >38 degrees, abnormal breath sounds and rales. [15] We excluded patients with other respiratory conditions e.g. chest wall and neuromuscular disease leading to acute on chronic ventilatory failure, those presenting with acute cardiogenic pulmonary oedema, those patients where doxapram was used as an adjunct to NIV, patients commenced on NIV >24 hours following hospital admission, those with known active malignancy or a diagnosis of acute or chronic thromboembolic disease. In addition, COPD patients weaned using NIV post-extubation and those unable to tolerate the mask due to agitation or claustrophobia were excluded. Details of the local protocol in our institution for administering NIV during acute exacerbations of COPD are given in the on-line supplement.

Protocol and measurements

Before initiating NIV, the respiratory rate was measured by a physician together with the arterial blood gases which were repeated at 1 and 4 hours post-treatment. Details of the diagnosis, associated co-morbidities, usual medication including oral corticosteroids, previous lung function and the time from presentation to the initiation of NIV were recorded together with body temperature, haemodynamic status and Glasgow Coma Score (GCS) pre-NIV. Venous blood was drawn for the measurement of the blood count (Sysmex XE-2100 automated full blood count analyser; Sysmex© Milton Keynes, UK), routine biochemistry (AU 2700 automated chemistry analyser; Olympus©) and random glucose levels (Hexokinase method, AU 2700 Olympus©). In

all episodes, blood samples were taken on admission to the Emergency Department but before NIV began i.e. the first blood glucose value that was obtained on hospital arrival was used. Hyperglycaemia was defined as a random blood glucose level ≥ 7mmol/l [13]. The baseline Acute Physiology and Chronic Health Evaluation (APACHE II) score was calculated by a single investigator (B.C). [16] Pre- admission co-morbidity was assessed using the Charlson Co-morbidity index. [17] Successful NIV was defined as the resolution of respiratory acidosis leading to successful weaning from the ventilator, and no requirement for ventilatory support for at least a further 48 hours. Formal ethical approval for the study was obtained via the regional ethics committee.

Statistical analysis

Statistical analysis was performed using SPSS 15.0. Data are presented as mean and standard deviation unless otherwise stated. We used the independent sample t-test to identify significant differences in continuous variables between patients failing or succeeding with NIV and the chi-squared test for categorical variables. Statistical significance was defined as a p value <0.05. No “a priori” power calculation was performed as the relationship between blood glucose and NIV success in COPD patients was not known. The statistical significance of each variable, in predicting the outcome from NIV was initially determined using univariate logistic regression. Subsequently, baseline variables with a p value < 0.1 were included in a multivariate logistic regression model which identified the most parsimonious predictors of NIV outcome. The variables identified from the logistic regression model were used to construct receiver –operator curves (ROC) from which we determined the sensitivity, specificity, positive and negative predictive value of these factors. Candidate variables were considered in isolation and in combination to establish whether they added additional explanatory power to this analysis.

Results

Of 168 patients receiving NIV for decompensated AHRF, 109 episodes in 92 patients fulfilled the study entry criteria. 2 patients were excluded due to claustrophobia and agitation during treatment leaving 107 episodes in 90 patients (figure 1). Thirteen patients presented with more than one episode of AHRF during the study period comprising 17 such episodes in total. For those patients presenting with more than one episode of AHRF during the study period, the 1st episode was used for the purposes of the study leaving 90 episodes in 90 patients. Random blood glucose data were available in 88 of these 90 patients thus leaving 88 episodes in 88 patients for final analysis.

The ceiling of treatment was set at NIV alone in 73% (64/88) of patients. NIV failed in 16 patients (18%), one patient who received invasive ventilation surviving to discharge while the remaining 15 patients died, all of whom had NIV as their ceiling of treatment. In 11 (12%) patients, COPD exacerbation was associated with pneumonia but the mortality was not worse in this subgroup (p=0.12). NIV was administered in the RFU in 86 patients and in ICU for the remaining 2.

The baseline demographics of the study population are outlined in table 1. Spirometry data confirming the diagnosis of COPD were available for 82 (93%) patients, all recordings being within a year of the index admission. Details of the 6 cases where COPD was diagnosed clinically are provided in the on-line supplement. In 16 patients (18%), oral corticosteroids were taken before admission. Intravenous aminophylline was administered in 24 patients and this did not affect the outcome of NIV (3 NIV failures received aminophylline p=0.54; non significant).

Table 1: Baseline demographics of study population

Variable	**Value**
Age (years; mean & SD) *n=88*	70 (10)

Gender *n=88*	39=male (44%) 49=female (56%)
FEV1 (litres; mean & SD) *n=82*	0.68 (0.29)
FVC (litres; mean & SD) *n=82*	1.62 (0.56)
Known diagnosis of diabetes mellitus	Yes=16 (18%; 4 prescribed insulin) No=72 (82%)
Glucose level prior to NIPPV initiation *n=88*	0-6.9mmol/l=44 (50%) >7mmol/l=44 (50%)
Arterial pH prior to NIPPV initiation (mean & SD) *n=88*	7.25 (0.64)
Arterial pCO2 prior to NIPPV initiation (kPa; mean & SD) *n=88*	10.20 (2.17)
Arterial pO2 prior to NIPPV initiation (kPa; mean & SD) *n=88*	8.19 (2.65)
Calculated Bicarbonate (mmol/l; mean & SD) *n=88*	25.65 (3.60)
Respiratory Rate prior to NIPPV initiation (breaths per minute; mean & SD) *n=88*	27 (8)
APACHE II score prior to NIPPV initiation (mean & SD) *n=88*	15 (4)
Charlson co-morbidity index (mean & SD) *n=88*	1.66 (0.76)

Glycaemia and outcome of NIV

The relationship between hyperglycaemia and outcome from NIV is summarized in table 2. Hyperglycaemia was present at baseline in 50% (44/88) of patients whilst 16 (18%) had a pre-existing diagnosis of diabetes mellitus. NIV failure was seen in 34% (15/44) of patients

where random blood glucose was ≥7mmol/l compared to 2% of the group with blood glucose ≤ 6.9 mmol/l (1/44; p=0.003). The mean blood glucose level was higher in patients when NIV failed (9.03 (3.22) mmol/l v 7.01 (2.18) mmol/l; t test; p=0.003). A prior diagnosis of diabetes mellitus pre admission was not associated with failure of NIV (table 3) with the mean blood glucose in the 16 diabetic patients being 8.03 (4.02) mmol/l compared to 7.23 (2.04) mmol/l in non-diabetics (p=0.25 non significant). Of the 44 patients with hyperglycaemia, pneumonia was noted in 7 (16%) compared with 4 patients (9%) with normoglycaemia (p=0.52 non significant).

When taking only those 82 patients where the diagnosis of COPD was confirmed by spirometry, the association between hyperglycaemia and failure of NIV remained. In this sub-group, NIV was successful in 71 patients and failed in 11. Baseline hyperglycaemia was present in 41% (29/71) of NIV successes and 100% (11/11) of NIV failures (p<0.001).

In 72 patients, oral corticosteroids were not taken before hospital admission and NIV succeeded in 58. In this sub-group, baseline hyperglycaemia was present in 38% (22/58) of NIV successes and 93% (13/14) of NIV failures (p<0.001). Hyperglycaemia was not related to prior oral corticosteroid use. Of the 16 patients prescribed oral corticosteroids pre admission, 9 (56%) presented with hyperglycaemia compared to 35 of 72 (49%) not prescribed oral corticosteroids (p=0.59; non significant).

Table 2: Relationship between glycaemia and outcome from NIV

Random blood glucose quartile (mmol/l)	NIV success (no of cases)	NIV failure (no of cases)
0-6 *(n=28)*	27 (96%)	1 (4%)
6-6.9 *(n=16)*	16 (100%)	0 (0%)
7-8.9 *(n=26)*	17 (65%)	9 (35%)

>9 (n=18)	12 (67%)	6 (33%)

Table 3: Clinical variables and outcome from NIV- univariate analysis

	NIV success (n=72)	**NIV failure (n=16)**	**Odds Ratio**	**95% CI**	**P value**
Age (mean & SD)* *n=88*	68 (10)	77 (9)	0.9	0.84-0.97	p=0.006
Gender† *n=88*	M=34 F=38	M=5 F=11	1.97	0.62-1.97	p=0.25 (NS
Smoking status† *n=88*	ex=37 current=35	ex=10 current=6	0.57	0.19-1.72	p=0.32 (NS
FEV1 (litres; mean & SD)* *n=82*	0.69 (0.30)	0.60 (0.17)	4.53	0.19- 106.4	p=0.35 (NS
FVC (litres; mean & SD) * *n=82*	1.67 (0.55)	1.35 (0.48)	3.64	0.73- 18.07	p=0.11 (NS
Diagnosis of Diabetes Mellitus† *n=16*	12	4	0.6	0.17-2.18	p=0.44 (NS
Glucose ≥ 7 mmol/l† *n=88*	Glucose≥7mmol/l=29 Glucose<7mmol/l=43	Glucose≥7mmol/l=15 Glucose<7 mmol/l=1	0.05	0.006-0.36	P=0.003
Time from admission to NIPPV administration (hours; mean & SD)* *n=88*	4.68 (4.76)	3.59 (3.85)	1.07	0.92-1.24	p=0.40 (NS
IPAP (cmH2O; mean & SD)* *n=88*	15.07 (2.17)	15.00 (3.29)	1.01	0.80-1.28	0.34 (NS)

EPAP (cmH2O; mean & SD)* *n=88*	5.24 (1.38)	5.63 (1.78)	0.84	0.58-1.2	0.16 (NS)
APACHE II (mean & SD)* *n=88*	14.63 (3.80)	19.19 (4.31)	0.76	0.65-0.89	P=0.001
Oral Corticosteroid administered prior to admission † *n=16*	14 (19%)	2 (13%)	1.69	0.34-8.31	0.52 (NS)
Charlson co-morbidity index (mean & SD)* *n=88*	1.62 (0.73)	1.88 (0.93)	0.78	0.35-1.25	0.20 (NS)
GCS (mean & SD)* *n=88*	14 (1)	13 (3)	1.21	0.93-1.45	p=0.18 (NS
Pneumonia cases† *n=11*	7	4	0.32	0.08-1.28	p=0.12 (NS
Baseline RR (bpm; mean & SD)* *n=88*	26 (6)	34 (10)	0.86	0.79-0.94	P=0.001

*T test

†Chi squared test

Arterial blood gases and outcome of NIV

The relationships between the baseline pH, subsequent change in arterial blood gases over 4 hours and outcome of NIV are shown in tables 4 and table 1 in the supplement. A baseline pH < 7.30 before

NIV did not predict NIV failure, although the relationship between outcome and presentation with a baseline pH below 7.25 approached statistical significance (p=0.09). In 84 patients,, NIV was still being used 4 hours after initiation (4 patients had died by this stage). Failure to improve arterial pH compared to baseline after 4 hours NIV treatment was not associated with treatment failure nor was the inability to normalize pH following 4 hours of NIV predictive.

Table 4: Outcome from NIV and relationship with arterial blood gas variables - univariate analysis

	NIV success (n=72)	**NIV failure (n=16)**	**Odds Ratio**	**95% CI**	**P value**
Baseline pH (mean & SD)* *n=88*	7.26 (0.06)	7.22 (0.08)	3.96	1.55-5.07	p=0.02
Baseline Pa02 (kPA; mean & SD)* *n=88*	8.15 (2.73)	8.30 (2.31)	0.98	0.80-1.20	p=0.87 (NS)
Baseline PaCO2 (kPA; mean & SD)* *n=88*	10.20 (2.19)	10.20 (2.16)	0.99	0.78-1.28	p=0.99 (NS)
Baseline calculated bicarbonate (mmol/l; mean & SD)* *n=88*	26.09 (3.44)	23.51 (3.69)	1.24	1.04-1.45	P=0.014
1 hour pH* (mean & SD) *n=88*	7.29 (0.06)	7.25 (0.09)	1.78	0.04-2.23	p=0.03

1 hour PaCO2 (kPA; mean & SD)* *n=88*	8.84 (2.21)	9.50 (2.61)	0.88	0.68-1.15	p=0.36(NS)
1 hour PaO2 (kPA; mean & SD)* *n=88*	8.77 (2.87)	7.85 (1.64)	1.27	0.84-1.91	p=0.26 (NS)
4 hour pH* (mean & SD)* *n=84*	7.32 (0.51)	7.28 (0.90)	4.34	2.90-5.89	P=0.14 (NS)
4 hour PaO2 (kPA; mean & SD)* *n=84*	8.37 (2.39)	7.70 (1.22)	1.27	0.79-1.96	p=0.31 (NS)
4 hour PaCO2 (kPA; mean & SD)* *n=84*	8.19 (1.98)	8.47 (2.07)	0.93	0.68-1.27	p=0.66 (NS)

* T test

Logistic Regression Analysis

Of the baseline variables tested, age, blood glucose < 7mmol/l, baseline respiratory rate, APACHE II score, mean baseline arterial pH pre-NIV and calculated serum bicarbonate level were related to the outcome of NIV treatment in the uni-variate logistic regression (see tables 3&4). These variables were included in the multivariate model which identified 3 statistically significant predictors of NIV outcome: baseline Respiratory Rate (OR 0.91; 95% CI 0.84-0.99), random glucose ≥ 7 mmol/l (OR 0.07; 95% CI 0.007-0.63) and, APACHE II

score on admission (OR 0.75; 95% CI 0.62-0.90). The model correctly classified 93% of the successful outcomes in the sample.

The correlation between random blood glucose and the other statistically significant associations identifying NIV outcome in the univariate analysis are shown in supplement tables 2 & 3. Statistically significant correlations were noted between blood glucose concentration, respiratory rate and pre-NIV pH in those patients where NIV was successful and with baseline APACHE II score and pre-NIV pH where NIV failed. The correlations between baseline RR and APACHE II index and with Pre-NIV pH were 0.25 (p=0.01) and -0.16 (p=0.14 NS) respectively in the whole cohort. .

To further investigate the discriminatory power of the three variables, receiver operating curves (ROC) were constructed between RR, APACHE II index, blood glucose level and the outcome of NIV. For baseline RR and NIV outcome, the lines for sensitivity and specificity intersected at RR of 30 per minute (area under curve 0.78; 95% CI 0.62-0.94). In terms of APACHE II index, the point of intersection occurred at 16.5 (area under curve 0.79; 95% CI 0.66-0.91) and with random blood glucose level (area under curve 0.76; 95% CI 0.63-0.89) the point of intersection was at 7.3 mmol/l. The sensitivity, specificity, positive and negative predictive value of these factors in predicting a successful outcome is shown in supplement table 4. The combination of baseline RR < 30 breaths per minute and random glucose < 7mmol/l increased prediction of a successful outcome from NIV to 97% while the use of all 3 factors was 100% predictive in this population.

Discussion

NIV represents a significant advance in the management of acute respiratory failure in patients with severe COPD. The data in our observational prospective cohort study supports this with over 80% of patients recovering from an episode which a decade ago would have

required invasive ventilation. This success rate is comparable to that previously reported from ICU [18] and was not substantially different from a more mixed population of patients, many without acidosis, admitted to UK hospitals [19]. COPD patients managed with invasive ventilatory support are more likely to die from non-pulmonary causes than respiratory ones.[20] In surgical and medical intensive care practice hyperglycaemia is a known adverse prognostic marker [7,21&22]. Specific data about hyperglycaemic patients managed with non-invasive ventilation are limited. A small study suggested that 'late failure' defined by deteriorating gas exchange was more frequent in patients with an initially raised blood sugar [3]. A larger but retrospective review of a mixed population of unselected COPD patients noted longer hospital stays and greater mortality in patients presenting with hyperglycaemia. However it was not possible to adjust for the potential confounding effects of corticosteroids while many of the diagnoses based on purely clinical [13].

Our study in a well defined patient population found that hyperglycaemia, even when defined at only one time point, related to the final outcome irrespective of the diagnosis of diabetes, use of insulin or prior oral corticosteroid use, In general the degree of hyperglycaemia observed was modest but it may still reflect the significant physiological stress associated with deteriorating gas exchange and worsening lung mechanics, often accompanied by pulmonary infection. Some patients had radiological evidence of pneumonia but this did not explain the occurrence of hyperglycaemia in most patients nor did it predict NIV failure. Thus, in our data initial hyperglycaemia had independent prognostic value.

Initial observational data suggested a relationship between the severity of acidosis and the outcome of AHRF in COPD, a finding supported by subsequent randomised studies. [2&23] Our mean baseline pH was <7.25 in 42% of patients but, unlike the earlier studies, treatment succeeded in over 70% of cases. This may explain why baseline pH was a poorer discriminant in the patient population now referred for NIV. In contrast the initial respiratory rate was a good measure of treatment response as has been seen elsewhere [1, 2, 5, 24&25]. A higher respiratory rate may reflect asynchrony of the patient and the ventilator but it may also be a marker of a greater intrinsic respiratory load promoting a shortened inspiratory time and more hypercapnia. [26&27] As the respiratory muscles are unloaded by the effects of NIV, respiratory rate can fall, the associated pulmonary hyperinflation lessens along with the work of breathing and dyspnoea improves [27]. We observed a relationship between the APACHE II score and clinical outcomes, which was unsurprising as this index incorporates several variables which independently predicted outcome. However, APACHE II score was no better in predicting outcome in our data than simpler measures such as the initial respiratory rate.

Multivariate logistic regression analysis identified three factors which explained almost all the variance in outcome in our patient group and which were largely independent of each other. Receiver-operator curve analysis defined threshold values in this population, which agreed with the conventional level of elevated blood glucose in the case of hyperglycaemia and which independently identified a respiratory rate of 30, the same value used in the highly discriminant CURB65 score for pneumonia severity [28]. The relative simplicity with which these variables can be measured suggests that a simple prognostic index can be developed based on these factors if our findings are validated in other trials. The presence of RR< 30 combined with normoglycaemia prior to the initiation of NIV carried a specificity of 92% in predicting success from NIV with a sensitivity of 79%. When baseline RR <30 was combined with normoglycaemia and APACHE II index ≤16, the specificity increased to 100%. In essence, the combination of these "favourable" criteria in a COPD patient with decompensated ventilatory failure prior to initiation of NIV predicts a successful outcome. On the other hand, in terms of predicting failure of NIV, the presence of a RR≥ 30 coupled with hyperglycaemia carried a negative predictive value of 97% and a sensitivity of 92% (the failure rate was 55% in this sub-group). We therefore conclude that the presence of these "unfavourable" criteria in a patient at baseline does not imply NIV will definitely fail but such patients may require more intensive and aggressive monitoring as there is a significantly higher risk of treatment failure in such circumstances. Validation of this model in terms of predicting outcome from NIV in acute decompensated ventilatory failure is required in a second cohort of patients.

Our study has some limitations. Although a prospective study we recorded only one blood glucose value and this may vary during an acute illness. However, the use of a threshold value close to the upper limit of normal had significant discriminatory power when used as a binary outcome for NIV success. Furthermore, the timing of the

measurement was similar in all cases i.e. upon presentation to hospital but prior to NIV initiation. In addition, the overall sample size of the study was small but did comprise a relatively homogenous population. We had limited information about the role of infection in these patients but again the predictive variables selected are indirectly linked to the consequences of infection. In our cohort, acute NIV carried a relatively low failure rate of 18%. This may reflect the patient selection criteria used i.e. only COPD patients receiving NIV within 24 hours of hospital admission were included. Patients developing decompensated ventilatory failure after a longer hospitalisation or when complicated by a hospital acquired infection likely represent a sicker group carrying a higher failure rate. Our failure to identify an association with baseline pH may reflect this focused entry criteria, although the absolute values are rather lower than in several other series. The high mortality in patients who failed NIV may reflect both the severity of the initial presentation and also current UK practice towards additional supportive ventilation which continues to be a topic for debate [29]. Our data relate to the first episode on an admission when the patient was ventilated and to the outcome of that episode. One individual who recovered from such an episode subsequently died before discharge but overall our mortality is in keeping with other recent reports in the literature [6, 30]. Although not all patients had spirometrically confirmed COPD the predictive value of hyperglycaemia remained even after excluding those cases where spirometry was not performed. Certain factors known to affect tolerance to NIV were not measured such as the degree of mask leak, the presence of secretions and the ability to remove them. Further research in these important areas is needed.

In summary when COPD patients develop decompensated ventilatory failure, baseline hyperglycaemia identifies patients with the greatest risk of failure with non-invasive ventilation as does an elevated respiratory rate and increased APACHE II index on admission. Combining these approaches should provide a relatively simple way of

stratifying risk and adjusting management accordingly. Respiratory rate remains an underused measurement which tracks the patient's progress. Whether change in blood glucose during therapy are as helpful remains to be studied. Tight glycaemic control has its advocates [11, 12] but careful prospective studies will be needed before this approach can be recommended in the care of patients with primary respiratory problems treated with NIV.

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Abbreviations

RR: Respiratory Rate
AHRF: acute hypercapnic respiratory failure
COPD: Chronic Obstructive Pulmonary Disease
ICU: Intensive Care Unit
IPAP: Inspiratory Positive Airways Pressure
EPAP: Expiratory Positive Airways Pressure
NIV: Non Invasive Ventilaton
kPA: kilopascal
mmol/l: millimoles per litre
NS: Non significant

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ON-LINE SUPPLEMENT

Protocol for administration of NIV complicating acute hypercapnic respiratory failure

In our institution, emergency admissions presenting with acute exacerbations of COPD and community acquired pneumonia are managed based on national guidelines [1-3] Hypercapnic respiratory failure complicating acute exacerbations of COPD is managed with a regimen of controlled oxygen, nebulised bronchodilators, corticosteroids with antibiotics and diuretics if indicated whilst the decision to administer intravenous theophyllines is left to the judgement of the admitting clinician. Arterial blood gas (ABG) analysis is performed immediately on admission with the presence of persisting/worsening respiratory acidosis (defined as pH>7.35 and PaCO2>6 kPa) following 1 hour of “medical management” and controlled oxygenation being an indication to administer assisted ventilation. However, NIV may also be administered earlier at the discretion of the admitting team should the clinical circumstances dictate e.g. hypercapnic coma in a patient where IPPV is deemed inappropriate etc. All patients admitted to our hospital with acute respiratory failure requiring Non Invasive ventilatory support are managed either in a specialised Respiratory Support Unit (RSU) under the direct supervision of a Consultant Respiratory physician or in a 12 bed Intensive Care Unit (ICU). The RSU consists of a 4 bed unit with a dedicated nurse trained in the administration of respiratory support including application of NIV and tracheostomy care. The decision to administer NIV is discussed with a Consultant Respiratory physician in all cases prior to administration. For those patients requiring assisted

ventilation in A&E, NIV is administered by means of a BiPAP Synchrony© ventilator by a trained physiotherapist whilst awaiting transfer to the RSU or ICU. Upon transfer to the RSU, a BiPAP Vision© ventilator device is used. The respiratory rate is recorded by a physician prior to initiation of NIV. Ventilator settings are adjusted according to patient comfort, oximetry and arterial blood gas values whilst ABGs performed at 1 hour and 4 hours post NIV initiation in all patients according to local protocol. At initiation of NIV, starting pressures of 10 cm H20 (Inspiratory) and 4 cm H20 (expiratory) are used and subsequently titrated upwards according to clinical response. Regarding the ventilator-patient interface, a full face mask is used both in the RSU and in ICU. Patients were encouraged to use NIV for as much as possible during the first 24-48 hours subsequent to initiation and period of use thereafter at the judgement of a Consultant Respiratory physician based on clinical circumstances. All patients are monitored continuously in terms of pulse oximetry and cardiac rhythm during the period of assisted ventilation. In all cases a ceiling of treatment based on the patients' clinical condition, their wishes and those of their carers was agreed with the physicians and intensivists responsible for their care at the time treatment began. Prior to commencement of NIV, informed verbal consent is obtained in conscious patients displaying no impairment of cognition.

Details of patients identified by a clinical diagnosis of COPD
Diagnosis of COPD made in primary care, patient established on inhaled bronchodilators, presentation with AHRF resulting in death in 4 cases; diagnosis of COPD made in secondary care, patient established on inhaled bronchodilators, unable to perform valid spirometry due to severe dementia in 2 cases of which 1 survived to discharge; 2 of the 6 cases presented with pneumonia.

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Table 1 (supplement): Outcome from NIPPV and relationship with arterial blood gas threshold values

	NIPPV success n=74	NIPPV failure n=16	Odds Ratio	95% CI	P value
Baseline pH ≥ 7.30†	19/74	3/16	1.49	0.38-5.83	0.56 (NS)
Baseline pH< 7.30 *n=90*	55/74	13/16			
Baseline pH ≥ 7.25†	47/74	6/16	2.90	0.95-8.87	0.06 (NS)
Baseline pH < 7.25 *n=90*	27/74	10/16			
Presence of any improvement in pH by 4 hours* *n=86*	70/74	9/12	0.15	0.03-0.81	0.16 (NS)

pH ≥ 7.35 by 4 hours pH < 7.35 by 4 hours *n=86* †	33/74 41/74	4/12 8/12	0.62	0.17-2.25	0.47 (NS)

† Chi squared test

* T test

Table 2 (supplement): Correlation of random blood glucose with significant variables following univariate analysis in NIV successful outcomes (n=72)

Variable	Correlation coefficient*	P value
Age (years)	-0.04	0.71 (NS)
Respiratory Rate (breaths per minute)	0.29	0.01
APACHE II index	0.04	0.73 (NS)
Pre-NIV pH	-0.21	0.07
Serum Bicarbonate (mmol/l)	-0.16	0.18 (NS)

*Spearmans Rank Correlation

Table 3 (supplement): Correlation of random blood glucose with significant variables - univariate analysis in NIV failures (n=16)

Variable	Correlation coefficient*	P value
Age (years)	0.36	0.17 (NS)

Respiratory Rate (breaths per minute)	0.27	0.32 (NS)
APACHE II index	0.53	0.04
Pre-NIV pH	-0.67	0.006
Serum Bicarbonate (mmol/l)	-0.41	0.12 (NS)

*Spearmans Rank Correlation

Table 4 (Supplement): Sensitivity, specificity, positive and negative predictive value of RR, glycaemia and APACHE 2 index in predicting outcome of NIV

	Sensitivity	Specificity	Positive predictive value	Negative predictive value
RR<30/minute n=65; success=61 (94%)	82%*	75%*	94%*	48%*
APACHE II ≤16 n=56; success=51 (91%)	69%*	69%*	91%*	32%*
RBG<7mmol/l n=44; success=43 (98%)	60%*	94%*	98%*	34%*
APACHE II ≤16 RBG<7mmol/l	76%*	100%*	100%*	47%*

N=29; success=29 (100%)				
RR<30/minute APACHE II ≤16 N=42; success=41 (98%)	89%*	89%*	98%*	62%*
RR<30/minute RBG<7mmol/l *n=39; success=38(97%)*	79%*	92%*	97%*	55%*
RR<30/minute RBG<7mmol/l APACHE II ≤16 *n=25;success=25(100%)*	86%*	100%*	100%*	66%*
RR≥30/minute n=25; failure=12(48%)	75%†	82%†	48%†	94%†
APACHE II >16 n=34; failure=11 (32%)	69%†	69%†	32%†	91%†
RBG≥7mmol/l n=44; failure=15 (34%)	94%†	60%†	34%†	98%†
APACHE II >16 RBG≥7mmol/l n=19; failure=10 (53%)	100%†	76%†	53%†	100%†
RR≥30/minute APACHE II >16 n=13; failure=8 (62%)	89%†	89%†	62%†	98%†

RR≥30/minute RBG≥7mmol/l *n=22;failure=12(55%)*	92%†	79%†	92%†	97%†
RR≥30/minute RBG≥7mmol/l APACHE ❙❙ >16 *n=12; failure=8(67%)*	100%†	86%†	67%†	100%†

*denotes success of NIV; †denotes failure of NIV