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DOI:
10.2147/COPD.S104238

Document Version
Peer reviewed version

Citation for published version (Harvard):
Dretzke, J, Moore, D, Dave, C, Mukherjee, R, Price, M, Bayliss, S, Jordan, R & Turner, A 2016, 'The effect of domiciliary non-invasive ventilation (NIV) on clinical outcomes in stable and recently hospitalized patients with severe obstructive pulmonary disease (COPD): a systematic review and meta-analysis', *International journal of chronic obstructive pulmonary disease*, vol. 11, no. 1, pp. 2269—2286. https://doi.org/10.2147/COPD.S104238

The effect of domiciliary non-invasive ventilation (NIV) on clinical outcomes in stable and recently hospitalized patients with severe obstructive pulmonary disease (COPD): a systematic review and meta-analysis

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Keywords: non-invasive ventilation, domiciliary, chronic obstructive pulmonary disease, hospitalization, systematic review, meta-analysis

ABSTRACT

Introduction

Non-invasive ventilation (NIV) improves survival among patients with hypercapnic respiratory failure in hospital but evidence for its use in domiciliary settings is limited. A patient's underlying risk of having an exacerbation may affect any potential benefit that can be gained from domiciliary NIV. This is the first comprehensive systematic review to stratify patients based on a proxy for exacerbation risk: patients in a stable state and those immediately post-exacerbation hospitalization.

Methods

Systematic review of randomized (RCTs) and non-randomized controlled trials comparing the relative effectiveness of different types of NIV with each other and usual care on hospital admissions, mortality and health-related quality of life (HRQoL). Standard systematic review methods were used for identifying studies (to September 2014), quality appraisal and synthesis. Data were presented in Forest plots and pooled where appropriate using random-effects meta-analysis.

Results

31 studies were included. For stable patients there was no evidence of a survival benefit from NIV (RR 0.88 (0.55, 1.43), I^2=60.4%, n=7 RCTs), but there was a possible trend towards fewer hospitalisations (WMD -0.46 (-1.02, 0.09), I^2=59.2%, n=5 RCTs) and improved HRQoL. For post-hospital patients, survival benefit could not be demonstrated within the 3 RCTs (RR 0.89 (0.53, 1.49), I^2=25.1%) although there was evidence of benefit from 4 non-RCTs (RR 0.45 (0.32, 0.65), I^2=0%). Effects on hospitalizations were inconsistent. Post-hoc analyses suggested that NIV-related improvements in hypercapnia were associated with reduced hospital admissions across both populations. Little data were available comparing different types of NIV.

Conclusion

The effectiveness of domiciliary NIV remains uncertain, however some patients may benefit. Further research is required to identify these patients and to explore the relevance of improvements in hypercapnia in influencing clinical outcomes. Optimum time-points for commencing domiciliary NIV and equipment settings need to be established.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a chronic progressive lung disease, characterized by non-reversible airflow obstruction and intermittent exacerbations.[1] Treatment for COPD is based on pharmacotherapy, pulmonary rehabilitation and, in some cases, long-term oxygen therapy (LTOT). Exacerbations are a key cause of increased morbidity, mortality and poor health status, and place a considerable burden on the healthcare system.[2] Approximately 15% of COPD patients per year have exacerbations necessitating hospital admission; [3;4] between 10-25% of patients admitted with hypercapnic respiratory failure due to COPD die in hospital.[5] Reduced exacerbation frequency is therefore an important therapeutic target.

Non-invasive ventilation (NIV) is a method of providing ventilatory support via a mask and is effective in improving survival among patients with acute or acute-on-chronic hypercapnic respiratory failure in hospital[6;7]. Evidence for domiciliary use of NIV in non-acute COPD patients is more limited despite a number of systematic reviews.[8-11] As patients immediately post-hospitalization are at greater risk of recurrence of exacerbation than those more stable[12], this difference could influence the effectiveness of NIV in preventing or reducing the impact of these events. This is the first systematic review to stratify data by these two patient groups and it is the most comprehensive review to date, including evidence from RCTs, non-randomized controlled studies and RCTs comparing different NIV settings, and considering mortality, hospitalizations and quality of life (QOL) as outcomes. Finally, this is the first systematic review to attempt an analysis, albeit exploratory, of the relationship between hypercapnia and clinical outcomes.

METHODS

A protocol detailing the methodology was registered with PROSPERO (CRD42012003286).[13;14] A summary of the methods is presented here. Search strategies

incorporated a combination of text words and index terms relating to NIV and COPD. Bibliographic databases (MEDLINE, MEDLINE In Process, EMBASE, Cochrane CENTRAL, CINAHL and Science Citation Index Expanded (ISI)), the British Library's ZETOC and ISI Conference Proceedings Citation Index (CPCI) and clinical trials registers were searched from 1980 to Sept 2014. No study design or language restrictions were imposed. Citation checking of included studies was undertaken, and experts in the field consulted to identify further studies. The search strategy for MEDLINE is shown in the supplementary file.

Studies were eligible for inclusion if they met the criteria shown in Table 1.
Primary outcomes of interest were mortality, hospitalizations, exacerbations and QOL. Secondary outcomes included lung function and blood gases. Study selection was performed by two reviewers independently. Disagreements were resolved through discussion and/or referral to a third reviewer.

Risk of bias was assessed based on the Cochrane collaboration risk of bias tool (for RCTs and non-randomized controlled studies), with additional criteria considered for crossover trials (ie whether there was a carry-over effect; whether only first period data were available; whether analysis was appropriate to cross-over trials; and comparability of results with those from parallel-group trials).[15]

Data extraction was performed by one reviewer using a standardized, piloted data extraction form, with numerical data checked by a second reviewer. Study selection and data extraction of non-English language papers was performed by native speakers of the respective languages with guidance from the reviewers.

Studies were grouped according to average proximity of patients to their most recent exacerbation that required hospitalization. If patients had not been hospitalized within 4

weeks to 3 months at commencement of the study or were described as “stable”, they were classed as the stable population. Where there was clear evidence that treatment with NIV in a study commenced after an episode of hospitalization (due to an exacerbation), these patients were classed as the post-hospital population, with the assumption that on average this population were at greater risk of a subsequent exacerbation.

Separate analyses were performed for each study design (RCT, controlled studies) and primary outcome (survival and hospitalizations). Where there was clinical and methodological homogeneity between studies reporting the same outcome and using the same outcome statistic (reported or calculable), random effects meta-analysis was undertaken in STATA (Stata Statistical Software: Release 10. StataCorp LP). Results for other primary outcomes were reported narratively (exacerbations and QOL). Secondary outcome data (FEV_1, FVC, $PaCO_2$, PaO_2, 6MWD) were not pooled due to between study heterogeneity, but is presented in forest plots in order to show the overall direction of effect and uncertainty.

Exploratory post-hoc analyses of study level data were performed to determine if baseline hypercapnia could predict response to NIV, or whether change in hypercapnia correlated with any effect of NIV on mortality and hospitalizations.

PRISMA reporting guidelines are adhered to.[16]

RESULTS

Main study characteristics

Screening of the 7,405 records identified by the searches yielded 21 RCTs (18 NIV v usual care; 3 NIV vs another form of NIV) and 10 non-randomized controlled studies (5

prospective, 5 non-prospective; Figure 1). Table 2 shows the main characteristics of these studies.

All patients had GOLD stage III and/or IV COPD, or were described as 'severe' (where reported). Eighteen studies provided details on assessing patients for obstructive sleep apnea, to rule out overlap syndrome. Twenty studies were in stable populations, 9 in post-hospital populations and there were no details for two. For post-hospital populations there was clear evidence in all study reports that NIV treatment commenced after hospitalization due to an exacerbation. For both populations there was usually no information on the length of time before NIV was initiated, or previous exacerbation history. Varying proportions of patients were on LTOT. Most studies included hypercapnic patients, though the cut-off for classification varied. Two RCTs[17;18] included normocapnic patients, whilst one RCT[19] stated that the number of hypercapnic patients included was small.

NIV settings, therapeutic/tolerability targets (pressure, volume or blood gases), and reporting of these varied across studies. There was some variability in usual care, with three studies considered to have more intensive approach to usual care: a 12-week multidisciplinary rehabilitation program, followed by a long-term home-based rehabilitation program[20;21]; a pulmonary rehabilitation program for part of the RCT[18] and a "home supervision program"[22].

There was a lack of reporting of some details relevant to study quality, particularly regarding loss to follow-up, handling of missing data and blinding of outcome assessors. Only three RCTs included a "sham NIV" arm, lack of which may have led to performance bias and/or bias in patient reported QOL. By definition, the non-randomized studies were more prone to bias; some retrospective studies had clear evidence of baseline imbalances between NIV and comparator groups, with the consequence of this on study findings unknown.

Length of follow-up varied between 3 and 24 months (RCTs) and between 12 months and 10 years (controlled studies). The longest follow-up periods (4-10 years) were in the retrospective controlled studies.

Main findings

NIV compared with usual care only: stable population

Data from 7 RCTs[19;21;23-27] (pooled RR 0.88 (0.55, 1.43), I^2=60.4%) and 4 controlled studies[22;28-30] (pooled RR 1.19 (0.65, 2.18), I^2=0%) suggested no significant difference between domiciliary NIV and usual care alone in terms of survival up to 24 months (Figure 2). Excluding the RCT by Casanova[19], which included only few patients with hypercapnia, had little effect, changing the pooled RR to 0.85 (0.46, 1.58). Data from 5 RCTs[21;23-25;27] and 3 controlled studies[22;28;29] (Figure 3) suggested a trend towards fewer hospital admissions/days in hospital with NIV, , albeit not statistically significant. Evidence on exacerbations not leading to hospitalization based on 4 RCTs[17;19;21;24] and one controlled study[29] showed no significant effect of NIV (supplementary file). For QOL, there appeared to be a trend favoring NIV, but a consistent benefit could not be demonstrated; heterogeneity in outcomes measured and time-points hampered analyses of this measure (supplementary file). There was some evidence to suggest NIV improved blood gases (based on mainly unadjusted results; Figure 4 and 5).

NIV compared with usual care only: post-hospital population

No survival benefit was evident from three RCTs[31-33] (pooled RR 0.89 (0l.53, 1.49), I^2= 25.1%), though four non-randomized controlled studies[34-37], which are potentially more prone to bias, favored NIV (pooled RR 0.45 (0.32, 0.65), I^2=0%; Figure 2). Findings for hospital admissions were inconsistent, with one RCT[33] finding a statistically significant benefit of NIV, one[31] marginally favoring NIV and one[32] marginally favoring usual care (without NIV) (Figure 3). Quality-of-life data was reported in only one post-hospital RCT[32], and there were no

differences between NIV and usual care. Limited data from three trials[31-33] suggested a potential benefit from NIV in terms of reduction in $PaCO_2$ (Figure 5).

Study quality

None of the RCTs assessed as having a high risk of bias contributed data to meta-analyses, yet some of the non-randomized controlled studies in the meta-analyses (for both populations) did. The small number of studies precluded assessment of the potential for publication bias (eg using funnel plots) and sensitivity analyses around study quality.

Sub-group analysis

No further sub-group analysis (beyond study design and population) was possible given the small number of trials and inconsistent reporting of relevant characteristics. However, many clinicians believe the extent of hypercapnia or a change in hypercapnia status are related to the effect of NIV. In this context it is worth noting that the study by Köhnlein (2014)[23] had the highest hypercapnia threshold as an eligibility criterion ($PaCO_2$ ≥7kPa), and also showed a statistically significant survival benefit (and a non-significant trend towards fewer hospital admissions). Further, the study by Zhou (2008)[24], which along with the Köhnlein (2014)[23] study had the highest mean $PaCO_2$ found a statistically significant benefit from NIV in hospital admissions. In order to explore hypercapnia level further as a potential predictor of benefit from NIV, data on mean $PaCO_2$ levels prior to initiation of NIV and change in mean $PaCO_2$ levels due to NIV from each study (where reported) were plotted against mortality and hospitalization data in order to determine if baseline $PaCO_2$ levels could predict response to NIV, and whether the effect of NIV on $PaCO_2$ levels correlates with the effect on clinical outcomes (Figure 6 a-d). These exploratory analyses suggested a trend towards a correlation between changes in hypercapnia status and hospital admissions (based on 8 RCTs[21;23-25;27;31-33]). Such a potential correlation was not observed for mortality (based on 10 RCTs[19;21;23-27;31-33]. Baseline hypercapnia status did not appear to predict response to NIV for

mortality (based on 10 RCTs[19;21;23-27;31-33]); the data was suggestive of a possible trend towards a correlation between baseline hypercapnia and hospital admissions (based on 8 RCTs[21;23-25;27;31-33]). Formal sub-group analysis based on level of hypercapnia were however not deemed to be appropriate as this would have meant dichotomising trials based on an arbitrary CO_2 threshold. Adherence to NIV and effect of NIV settings could also not be analyzed.

Different types of NIV

With regard to the effectiveness of different NIV settings, three small crossover trials in stable populations were identified; two[38;39] comparing higher versus lower pressure NIV, and one[40] comparing different back-up rates. All were short-term (6-8 weeks) and did not assess mortality or hospitalizations/exacerbations. Treatment compliance was similar between arms in two studies[39;40], and higher in the high pressure arm for the third[38] but drop-out rates were high in the pressure trials.[38;39] The limited QOL data precluded drawing firm conclusions. The only statistically significant result [38] was greater $PaCO_2$ reduction with higher pressure NIV (supplementary file).

DISCUSSION

This is the first systematic review of domiciliary NIV to attempt to account for differing baseline risks of exacerbation by categorising populations into stable and post-hospital based on proximity to an in-patient stay for an exacerbation; it is also the most comprehensive to date, including evidence from RCTs, non-randomized controlled studies and RCTs comparing different NIV settings, and without restriction to English language only publications. Overall, the evidence from RCTs in a stable population could not demonstrate benefit for mortality from domiciliary NIV compared to usual care alone (7 RCTs[19;21;23-27] and 4 controlled studies[22;28-30]), although there was a trend towards fewer hospital admissions (5 RCTs[21;23-25;27] and 3 controlled studies[22;28;29]) and, to a lesser extent, improved QOL (7 RCTs[17;18;21;23;26;27;41] and 1 controlled study[29]) for the stable population. A survival

benefit for the post-hospital population could not be shown based on three RCTs[31-33], though there was some evidence of benefit based on four (potentially biased) non-randomized controlled studies[34-37]. Findings for hospital admissions (3 RCTs[31-33]) were inconsistent. There was too little evidence to draw any conclusions on the potential benefits of higher pressure NIV settings.

Exacerbation risk and domiciliary NIV

It was hoped that sub-group analyses based on the frequency of exacerbations prior to NIV treatment would be possible, as frequent exacerbators (patients with ≥2 exacerbations/year) are a clinically relevant subgroup[42],with a generally stable exacerbation frequency on other existing therapies.[43] However, this was hampered by lack of reporting of this parameter.

There is evidence, however, to support the use of recent hospitalization as a proxy for a higher risk of recurring exacerbation. Prior hospital admission is recognized to be the biggest driver for a further exacerbation requiring admission[12], and NIV use in hospital has also been recognized as a predictor of overall exacerbation rate.[44] Furthermore, recurrent type 2 respiratory failure, ie respiratory failure with carbon dioxide retention, occurs in over 30%, and readmission at 1 year in 60%, of those who require NIV acutely in hospital.[45] Consequently stratification based on NIV started at recent hospitalization was thought a justifiable surrogate marker of exacerbation risk. In reality there is likely to be much more of a continuum of risk, and it is further unknown what proportion of the post-hospital populations considered in the individual studies are COPD patients at the more severe end of the disease spectrum.

Which patients may benefit from domiciliary NIV?

The results of the review show that division of data based on potential exacerbation risk did not indicate a difference between populations in terms of mortality or hospitalizations; in fact

there was no clear evidence for benefit for either population, though there was a non-significant trend towards a benefit with NIV in the stable population, for hospital admissions. The apparent similarity in hospitalization effect in our chosen subgroups is perhaps surprising given that those previously admitted are at higher risk of subsequent readmission. It is possible that the division used failed to capture other important differences within and between populations-for example the pre-treatment exacerbation rates were unknown. There was evidence of some heterogeneity between both stable and post-hospital studies, with some studies showing a significant benefit from NIV; one RCT[23] in a stable population showed a statistically significant benefit from NIV for mortality (Figure 2), and one RCT for stable[24] and two for post-hospital populations[31;33] showed significant benefit for hospital admissions (Figure 3). Two of these RCTs[23;33] used a higher hypercapnia threshold for patient inclusion (>7PaCO_2); one RCT[25] had a lower inclusion criterion (>6Pa CO_2), though means were suggestive of higher levels. There was no detail on the inclusion threshold for the third RCT.[24]

Elements such as blood gases, prior admissions and social support have been identified as drivers to clinical decision making regarding domiciliary NIV in COPD[46], all of which may impact NIV efficacy. The non-randomized post-hospital studies[22;28-30] assessing mortality (Figure 2) suggest a beneficial effect from NIV (significant pooled RR) and it is possible patient selection for NIV biased findings towards a positive response to NIV.

Most populations included in studies were hypercapnic (see Table 2 for details), although the threshold used to define this varied. Post-hoc analyses undertaken across both stable and post-hospital populations suggested a trend towards a positive correlation between changes in hypercapnia and hospital admissions (but not for mortality nor correlation using pre-treatment PaCO_2 level). As these are exploratory analyses the results should be interpreted cautiously; the analysis used aggregate -study level- data both for baseline hypercapnia,

change in hypercapnia and for clinical outcomes, and a patient level association cannot be inferred even if there is clear biological plausibility. Further caveats relate to the fact that not all trials contributed data to these analyses and that $PaCO_2$ change scores were mostly not adjusted for baseline differences. Nevertheless it does suggest that there should be further investigation of the association between hypercapnia and clinical outcomes, particularly with regard to the ability of the NIV to reduce $PaCO_2$ levels. Patients hypercapnic at discharge may normalize their $PaCO_2$ levels over time, although those who remain hypercapnic have higher mortality.[47] Thus if hypercapnia (or change in hypercapnia) were a driver of NIV response and were used to select patients for treatment after an exacerbation, subsequent reassessment may be needed to determine likelihood of ongoing benefit.

The current recommendation in the UK suggest that domiciliary NIV is considered on health economic grounds if a patient has had three hospital admissions with acute hypercapnic respiratory failure.[48] There may be other, as yet unconfirmed, patient characteristics which influence its effectiveness. Uncertainty also remains regarding the length of time NIV may provide benefit for; there are at least two RCTs[49;50] looking at the effect of discontinuing NIV, but this question was beyond the scope of this systematic review.

<u>Strengths and limitations</u>

A number of RCTs of reasonably good methodological quality were available, particularly for the stable population, and a comprehensive search strategy meant that this systematic review identified more relevant studies than previous ones, even after taking into account different search periods. No language restrictions meant that 19% of the included studies were non-English, a substantial proportion of the overall evidence base omitted by prior reviews.[8-11] This is also the first systematic review to examine patient –related outcomes and incorporate data from non-randomized studies. Furthermore, by calculating summary

measures from raw data or converting data, the number of results that could be presented in forest plots was maximized. In contrast to some previous systematic reviews, secondary outcome data (lung function, blood gases and 6MWD) were not pooled due to a lack of results adjusted for baseline differences. This means that our analyses are likely to be more robust.

There were several limitations in the available data, largely due to inconsistency of reporting (particularly for hospital admissions) or measurement tools (especially for QOL). This meant that not all available evidence could contribute to the pooled estimates. Furthermore, admissions data may be skewed, thus the mean (SD) may not be an appropriate metric to use, though it was frequently reported. For primary outcomes, there was a lack of data explicitly linking the number of exacerbations to subsequent hospitalizations and survival for individual patients. This latter point has potential implications for double-counting data as these outcomes are not independent of each other. Ventilator settings may influence effectiveness, and settings have changed over time, such that earlier settings may today be considered ineffective. The small crossover trials[38;3940] in this analysis did not allow any conclusions to be drawn, and sub-group analysis based on the larger/parallel trials was not possible due to inconsistent reporting: studies variously reported mean, median or target settings, based either on pressure, blood gas or volume targets, with some stating only that levels were adjusted to patient comfort/tolerance. Reporting times also varied (eg at start of study or at discharge).

<u>Recommendations for future research pertaining to domiciliary NIV in COPD</u>

Variable quality of data reporting, lack of exacerbation data, potential bias and heterogeneity of reported outcomes were striking features of the included studies. These features are not uncommonly encountered when conducting systematic reviews. Whilst trials of medications are often required to report certain outcomes as part of the licensing process, medical device studies, such as those included in our review, have not always had to meet such standards

despite also being subject to regulatory processes. More detailed reporting of exacerbations in particular would be valuable in this high risk population. It has been suggested that new RCTs could include a sham NIV arm in order to minimize potential bias, as well a higher and lower pressure NIV arm, to enable further exploration of the relationship between pressure and effectiveness; many of the earlier studies included used pressures which experts would now consider equivalent to a sham treatment (eg Casanova 2000[19]). However, sham NIV could lead to an overestimate of the potential benefit of NIV, due to its potential disbenefits on quality-of-life, therefore two control arms (with and without sham NIV) are more likely to be appropriate. Qualitative work in NIV users and prescribers not surprisingly suggests a focus on patient-centered measures (eg QOL, daily activity) is needed, alongside research to delineate those in whom the treatment is most effective.[46] Which instruments best capture QOL in this patient group and whether instruments are convertible is debatable.

There is at least one ongoing trial (the UK HOT-HMV trial, NCT00990132), which includes a population with an underlying risk of recurrent events similar to the post-hospital population described here. Findings from this trial will be important, but additional evidence from individual patient data (IPD) analyses of pooled studies may be required to determine whether specific patient characteristics or equipment settings predict benefit from NIV, and to establish optimum time-points for starting (and potentially discontinuing) NIV. A previous review[8;9] attempted such analyses, but based on a smaller group of studies, and without considering hospitalizations or survival.

Conclusions

The effectiveness of domiciliary NIV remains uncertain, however some patients appear to benefit. Further research is required to identify these patients and to explore the relevance of hypercapnic status or changes in hypercapnia due to NIV in influencing clinical outcomes for

patients on long-term NIV; optimum time-points for starting NIV and equipment settings also need to be established.

Contributorship

JD was the lead systematic reviewer, wrote and edited sections of the paper, undertook study selection, data extraction and analysis, and quality assessment.
DM was co-Principle Investigator and methodological lead, led all aspects of the project, contributed to all aspects of the project, undertook study selection, and wrote and edited sections of the paper.
CD advised on clinical aspects of the project, and undertook study selection.
RM advised on clinical aspects of the project and undertook study selection.
MP advised on statistical aspects, analysed data and edited statistical methodological sections of the paper.
SB devised the search strategies and ran the searches in electronic databases.
XW translated Chinese papers, undertook data extraction and data checking.
RJ undertook study selection and contributed to methodological aspects of the project.
AT was co-Principle Investigator and clinical lead, oversaw all clinical aspects of the project, undertook study selection, and wrote and commented on sections of the paper.
All authors read and approved a draft of the article.

Competing interests

AT's clinic has been loaned sleep monitors by ResMed Inc. who also produce NIV equipment. RM has received non-financial support from ResMed Inc and Breas Medical in the form of training sessions for the NIV equipment supplied to his NIV multidisciplinary team. DM and JD acted as peer reviewers for the Cochrane systematic review by Struik et al[8] which is included in this report. RJ was awarded a grant in respect of an NIHR Post-

doctoral fellowship during the conduct of the study. The fellowship relates to a different COPD project.

Acknowledgements

The authors thank the following: Simon Stevens for his invaluable administrative support and excellent organizational skills. All members of the patient group for supporting and contributing to this project: Maireade Bird, Michael Darby, Don Etheridge, Chris Huckle, Jan Turner and Anne Yeomans. Chris Cates, Peymane Adab, Brendan Cooper, Rob Stockley for contributions to wider team meetings. All the people who kindly gave their time to help translate articles.

Role of funding source

This article summarizes independent research funded by the National Institute for Health Research (NIHR) under its HTA Programme (Ref 11/27/01). The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Table legends

Table 1: Study inclusion criteria

Table 2: Main study and intervention characteristics

Figure legends

Figure 1: PRISMA flow diagram (study selection process)

Figure 2: Mortality (Relative Risk)

Figure 3: Hospital admissions per patient per year (Weighted Mean Difference)

Figure 4: PaO_2 (Mean Difference)

Figure 5: $PaCO_2$ (Mean Difference)

Figure 6 a-d: Hypercapnia and clinical outcomes

Supplementary file

Search strategy for MEDLINE; Exacerbations results; Quality- of-Life results; Results of RCTs comparing different types of NIV

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