A proposal for a practical treatment guideline designed for the initial two-hours of the management of patients with acute severe asthma and COPD using the principles of evidence-based medicine

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Abstract We have proposed a clinical treatment guideline for the management of acute, severe asthma and chronic obstructive pulmonary disease (COPD) using the principles of evidence-based medicine. The content is based upon practical clinical issues in need of consensus. A previous study has shown that this particular area is in serious need of quality control. Based on a strict 2 h time schedule with a unified treatment plan for both asthma and COPD, it is possible to secure for the patients a well-documented medical therapy promoting decision-making and clarification of the patient within this time limit. A summary of the statements is presented in a one-page, user-friendly format in order to cope with the clinician's need of having access to published evidence quickly and easily. A website (www.phanareth.dk or a website provided by Respiratory Medicine) has been established providing regular updates. A strategy for the implementation and the evaluation process has been planned after the publication of this paper. We believe this approach to be an important step towards an increase in the quality of guidelines and also a tool to make “guideline writers” aware of the responsibility of making their recommendations work.

INTRODUCTION

There is a wide range of divergent recommendations in the existing literature on the issue of treating acute exacerbations of asthma and chronic obstructive pulmonary disease (COPD). In many cases, it is not possible to get answers to practical clinical questions from commonly available guidelines, i.e. the handling of the inhalation therapy, the doses, and the frequency of medication, oxygen therapy, etc., and the recommendations may differ widely (1–3). Concerns have been raised about the efficacy and validity of guidelines and the impartiality of consensus statements has also been questioned, as has their ability to improve clinical practice. In a paper by Gibson, 21 asthma management guidelines were reviewed and major deficiencies with the assembly of evidence were found. The author concluded that recommendations should be based on unbiased methods to obtain the evidence and that a systematical evaluation and a grading of this evidence should be included in the publication (4).

The appearance of recommendations based on selected principles of evidence-based medicine (EBM), showing the grade of the strength of evidence in each statement, represents a new generation of guidelines (5–7). The approach is still at a premature stage but definitely a step in the right direction. There are, however, further issues, as pointed out in the EBM, to be taken into consideration; the process of the documentation concerning the need for a specific guideline, the formulation of clinical problems, the development of a user-friendly presentation, how to implement, and, finally, how to evaluate the impact of the guideline (8,9).
Previously, we have shown that a noticeable variation was found in the management procedures of Danish Hospitals treating patients with exacerbations of asthma and COPD, and that the treatment behavior was only moderately affected by a national publication of recommendations for the treatment (10). The knowledge we gained from these studies provided us with useful information on clinical problems making it possible to point out areas in need of quality control. As an obvious consequence, we have proposed a clinical guideline designed to cover practical issues on the initial treatment of acute severe asthma and COPD (ASAC) making use of further principles of EBM.

METHODS

We used modified components based upon the principles of EBM (8) as a template in the development process of the guideline. The components are shown below:

a. Evaluate the need for a specific guideline.
b. Formulate the problems and questions raised by clinicians encountering the patients.
c. Search the literature for clinically relevant studies/papers (the evidence).
d. Evaluate the evidence for its validity and usefulness.
e. Make a clear presentation and layout of the guideline.
f. Implement the guideline.
g. Evaluate the guideline.

Based on the experience gathered from the study of treatment behaviors in Danish Hospital settings, we documented a need for a specific clinical treatment guideline on ASAC. Furthermore, the study provided information on seven key clinical issues, which were as follows:

1. Inhalation therapy (handling, dosages, etc.).
2. Oxygen treatment (dosages and frequency).
3. Beta2-agonists (route of administration, dosages and frequency).
4. Anticholinergics (single therapy, combination therapy, dosages and frequency).
5. Corticosteroids (route of administration, dosages and frequency).
6. Methylxanthines (yes or no).
7. The strategy.

Literature search was conducted on each item for both asthma and COPD in Medline and in Cochrane reviews—no studies on infants were considered. Primarily, we searched for meta-analyses and randomized clinical trials (RCTs) but when this was not possible we searched well-designed controlled studies without randomization, descriptive studies and finally expert committee reports. Furthermore, if possible, we searched evidence-based statements in national and international guidelines.

The authors examined the evidence and the development of the recommendations was made in agreement. The levels of evidence are assigned to statements, where appropriate, using the grading criteria proposed by the NHLBI as shown in Table I. Further information are available from the NHLBI website: http://www.nhlbi.nih.gov/guidelines/obesity/ezxtbk/appndx/apndx1a1.htm.

The grading of the evidence (evidence category A, B, C or D) for each statement is marked in a bracket in the title of the items separately for asthma and COPD.

A one-page user-friendly summary has further been developed in accordance with EBM (11).

INHALATION THERAPY

Nebulizers and metered-dose inhalers with holding chambers are equally effective for inhalation therapy (asthma; grade A, COPD; grade A)

Bronchodilatory drugs used in the treatment of severe exacerbations of asthma and COPD should be managed by inhalation according to the majority of official guidelines (6,7,12,13). However, the choice of either nebulizers or metered-dose inhalers with holding chambers (MDI/HC) for the delivery of inhaled medication is often based on tradition. In Denmark, all hospitals use a nebulizer when treating patients with ASAC although alternatives, even cheaper and easier to use, might be possible. In a Cochrane review by Cates et al. including seven studies on adults with asthma, it was concluded that MDI/HC produced outcomes that were at least equivalent to nebulizer delivery (14).

In COPD, a review on six RCTs concluded that the evidence was insufficient to determine that one method of delivery was superior to the other (7). A meta-analysis of bronchodilators delivery devices by Turner et al. has confirmed these findings in patients with acute airflow obstruction caused by asthma or COPD (15).

The MDI/HC is considered to be more efficient in comparing drug doses mg to mg, and the equivalence of doses may be from 2 to 12 times greater for the nebulized delivery to achieve the same effect as the MDI/HC (16). In the meta-analysis by Turner et al., a relative potency of 6:1 in favor of MDI/HC compared to the nebuliser was considered as equivalent (15).

Comment

We recommend the use of either nebulizers or metered-dose inhalers with holding chamber when treating patients with ASAC. To achieve equivalent bronchodilation, the ratio of the dose for a nebulizer compared to MDI/HC should be approximately 6:1.
Handling of nebulizers (both asthma and COPD; grade B)

Nebulizer performance depends on several factors and any mishandling of the device may have serious consequences for the patients. Consequently, the British Thoracic Society has published an evidence-based guideline on Nebulizer therapy with detailed information on the handling of the device (5). The statements below are based upon recommendations from the BTS guideline on Nebulizer therapy and should be taught carefully to all health-care personnel using Nebulizers.

- Use air as driving gas for the Nebulizer with a simultaneous appliance of oxygen by nasal prong or catheter. Use oxygen as driving gas if medical air is not available. Do not use small portable compressors in the emergency room. They need regular flow calibrations and the reliability is not well documented.

TABLE 1. Evidence categories

<table>
<thead>
<tr>
<th>Evidence category</th>
<th>Sources of evidence</th>
<th>Definition</th>
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<tbody>
<tr>
<td>A</td>
<td>Randomized controlled trials (rich body of data)</td>
<td>Evidence is from endpoints of well-designed RCTs (or trials that depart only minimally from randomization) that provide a consistent pattern of findings in the population for which the recommendation is made. Category A, therefore requires substantial numbers of studies involving substantial numbers of participants</td>
</tr>
<tr>
<td>B</td>
<td>Randomized controlled trials (limited body of data)</td>
<td>Evidence is from endpoints of intervention studies that include only a limited number of RCTs, post hoc or sub-group analysis of RCTs, or meta-analysis of RCTs. In general, Category B pertains when few randomized trials exist, they are small in size, and the trial results are somewhat inconsistent, or the trials were undertaken in a population that differs from the target population of the recommendation</td>
</tr>
<tr>
<td>C</td>
<td>Nonrandomized trials observational studies</td>
<td>Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies</td>
</tr>
<tr>
<td>D</td>
<td>Panel Consensus Judgment</td>
<td>Expert judgment is based on the panel's synthesis of evidence from experimental research described in the literature and/or derived from the consensus of panel members based on clinical experience or knowledge that does not meet the above-listed criteria. This category is used only in cases where the provision of some guidance was deemed valuable but an adequately compelling clinical literature addressing the subject of the recommendation was deemed insufficient to justify placement in one of the other categories (A–C)</td>
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- Use oxygen when treating acute exacerbations (asthma; grade B, COPD; grade B)

The administration of oxygen is mandatory in the treatment of patients with acute, severe asthma (12,13). The aim of the strategy is to provide a continuous arterial oxygen saturation (\(\text{SaO}_2\)) aiming at a fixed \(\text{SaO}_2 \geq 90\%\)
to prevent tissue hypoxia. There is little danger of precipitating hypercapnia when administering oxygen in acute asthma, even in high doses (13). We could not find any RCTs of oxygen in acute asthma, and recommendations are mainly based on clinical experience and pathophysiology suggesting its vital role in severe asthma.

The benefit of oxygen therapy in exacerbations of COPD is definitely agreed upon official guidelines (6,7). However, concern has been raised by the fact that oxygen administration can induce hypercapria by diminishing the respiratory drive leading to CO₂-narcosis with subsequent respiratory arrest in some patients. In a study by Gunawardena et al., only a slight increase in $p$CO₂ was seen in COPD patients with “pre-treatment” hypercapnia receiving inhaled beta-agonists by a nebulizer driven by 8 l of oxygen for 15 min. The level of $p$CO₂ fell to normal values within 20 min after the termination of the nebulization (17).

Agusti et al. performed a study including 18 COPD patients with acute respiratory failure. Patients were treated with liberal doses of oxygen with the goal of maintaining a saturation $\geq 90\%$. The strategy did not worsen the respiratory acidosis significantly and none of the patients developed CO₂-narcosis (18). Similar findings have been reported in a recent published study on 24 consecutive patients admitted to hospital with acute exacerbations associated with hypercapnic respiratory failure. Oxygen was adjusted every 20 min to maintain an oxygen saturation of 91–92% in the first 2 h of admittance. It was concluded that the risk of CO₂ retention with “controlled” oxygen therapy was low (19). In a huge summary of published evidence on the exacerbations of COPD, it was concluded that oxygen administration in acute exacerbations may result in hypercapria but that the patients at highest risk for respiratory failure could be identified (7). Guided by the formula proposed by Bone et al.: $\text{pH} = 7.66 - 0.00919 (\text{PaO}_2)$, high-risk patients can be identified with a sensitivity of 77% (20). By introducing the observed $\text{PaO}_2$ into the equation, the pH calculated can be compared to the measured pH. In high-risk patients, the calculated value will be greater than the measured one indicating caution and special attention to be taken.

**Comment**

Severe hypoxemia is often seen in COPD patients with acute exacerbations and oxygen therapy may be life-saving. It seems rational trying to prevent irreversible tissue damage induced by hypoxemia by the administration of oxygen rather than treating potential reversible CO₂-narcosis by oxygen restriction. We believe, guided by careful clinical observation and by using the simple equation mentioned above to identify the risk-patients, that oxygen can be administered beneficially and relatively safely, even in high doses. If, however, the patient’s hypercapnia becomes increasingly worse under the oxygen treatment and signs of CO₂-narcosis develop, then a gradual reduction in oxygen is recommended instead of a sudden withdrawal leaving the patient in severe hypoxemia.

In the proposed guideline, it is recommended to use 3–5 l min⁻¹ oxygen during the first hours of admittance—aiming at keeping the saturation $\geq 90\%$ regardless of whether the patients suffer from asthma or COPD. It must be emphasized that oxygen administration should be continued during the nebulizer therapy if the nebulizer is driven by air.

In the second hour of the treatment, a further individualization may be possible due to the monitoring process revealing more detailed information on the patient’s status. As a consequence, we recommend the use of 1–5 l min⁻¹ oxygen during the second hour of treatment. This is, in fact, in accordance with the American Thoracic Society guideline (21).

**BETA2-AGONISTS**

**Route of administration—inhalaion equal to or better than intravenous administration (asthma; grade A, COPD; grade C)**

Inhaled beta₂-agonists is recommended as a first-line therapy by the official guidelines and is regarded as the most potent reliever of bronchospasm in acute asthma and COPD (6,7,12,13).

In a recently completed Cochrane review, 15 RCTs were included to determine the benefit of intravenous beta₂-agonists in severe acute asthma compared to other regimes (inhaled beta₂-agonists). It was concluded that the medical literature did not provide any compelling reason to favor intravenous administration to inhaled beta₂-agonist therapy (22). There are, to our knowledge, no studies of acceptable quality covering this issue in COPD.

**Comment**

We do not recommend the use of infused beta₂-agonists in acute exacerbation of asthma and COPD. Bronchodilator therapy should be given by the route of inhalation when using both beta₂-agonists and ipratropium bromide. However, the intravenous route may be considered as a supplement for patients in need of mechanical ventilation and in the case where no other treatment options have been effective.

**Potency of beta-agonists (grading; C)**

Terbutaline, salbutamol, and fenoterol are the most frequently used beta₂-agonists in ASAC. They differ in
many prospects, even in potency. The issue of potency has been investigated in several studies, mostly on stable patients, and it seems agreed upon among authors that the relation between potencies are: fenoterol/salbutamol/terbutaline:1:2:3, fenoterol being the most equally potent (23,24). This relation has been adapted in the proposed recommendation and is in accordance with several official guidelines (6,12,25–27).

Continuous nebulization equal to intermittent (asthma; grade A, COPD; grade C)

Continuous nebulization has been claimed by several specialists to be superior to intermittent nebulization. A review of eight RCTs comparing continuous vs intermittent administration of bronchodilators in acute asthma showed both regimes to be effective but with a small benefit from using continuous nebulization, especially in severe cases (28).

We found no studies on COPD covering this issue.

Comment

In the perspective that continuous nebulization does not seem to induce increased side-effects (29), that it might have a beneficial effect on severe exacerbation, and that it reduces the amount of staff time required (30), we will recommend continuous nebulization as an alternative to intermittent nebulization (if technical equipment allows it) in the treatment of severe exacerbations of asthma and COPD.

Dose and frequency (asthma; grade A, COPD; grade B)

The optimal dose and frequency of the administration of inhaled beta2-agonists are not fully clarified. At least two well-designed studies on asthma have supported the use of small doses with a frequent interval showing that inhalations of 2.5 mg salbutamol with 20 min interval were optimal in the first hours of in-patient treatment in hospitals (31,32). The study by McFadden et al. has confirmed the benefits from this strategy (33).

Few studies cover the issue in COPD. A dosing study by Emermann and colleagues including 86 patients with COPD failed to show any difference in FEV₁ on comparing patients who received 2.5 mg nebulized albuterol every 20 min with those who received it every hour. However, it was suggested that severely obstructed patients (FEV₁ <20% predicted normal) may have benefited from the first regime (34).

Comment

Additional studies are required to determine the optimal dosing in both asthma and COPD. However, based on the above studies, we believe 2.5 mg of salbutamol (or equivalent drug) administered at 20-min intervals by nebulizer, at present, to be the best recommendation in treating acute exacerbations of both asthma and COPD. This is, in asthma, in accordance with the NHLB guideline (27) and in COPD with the BTS guidelines (26).

When using continuous nebulization, the doses of beta2-agonist must equal the recommended doses for intermittent therapy (i.e. cumulative dose of 2.5 mg salbutamol every 20 min used in intermittent nebulization equals a dose of 7.5 mg used hourly for continuous nebulization).

ANTICHOLINERGICS

Make use of combination therapy (asthma; grade A, COPD; grade B)

Combination therapy with inhaled beta-agonists and an anticholinergic agent is well documented in asthma. The rationale of adding nebulised ipratropium bromide (IPB) is the presence of increased airway vagal tone, which may not be overcome by treatment with high doses of inhaled beta2-agonists alone (35).

Two separate meta-analyses have shown significant benefits on FEV₁, peak expiratory flow (PEF) and admission rates when adding IPB to a beta-agonist in acute asthma (36,37).

In COPD, the evidence concerning the effectiveness of combination therapy is conflicting. We found four RCTs in COPD showing no difference in lung function parameters comparing combination therapy to single therapy using a beta2-agonist (38–41). In contrast, we found three RCTs which were able to show benefits from combination therapy in the lung function parameters (42–44).

Comment

In the perspective that the proposed guideline unifies the treatment of asthma and COPD and that the toxicity and the side-effects from IPB is minimal (7,30,45), combination therapy is recommended for both diseases in spite of the fact that the evidence of this strategy in COPD is rather controversial.

Dose and frequency (asthma and COPD; grade B)

From the meta-analysis by Rodrigo et al., in asthma, the average dose of IPB used in the pooled RCTs was between 0.5 and 1.5 mg during the first 2 h of the treatment
In the seven RCTs found in COPD (mentioned above) the doses of IPB ranged from 0.04 to 2 mg within the first hour of treatment. The optimal dose of IPB cannot be clarified from the existing literature neither in asthma nor in COPD.

**Comment**

The studies on asthma and COPD reviewed in this section have used additional doses of IPB ranging from 0.04 to 2.0 mg. There is no evidence in asthma to support the use of higher doses than 1.5 mg during the first 2 h of treatment in the acute settings. In COPD, though insufficiently supported by evidence, up to 2.0 mg given in the first hours may provide some additional benefit (42).

Since our proposal unifies the treatment strategy for both asthma and COPD, we find it reasonable to recommend the use of a cumulative dose of 2.0 mg IPB, well aware that the recommended dose might be slightly higher than may be supported by the evidence. However, we do not find this hazardous since the systemic side-effects of IPB are believed to be almost negligible (46) and the fact that the optimal dose yet needs to be investigated, may further justify this recommendation.

By using combination therapy with a dose of 0.5 mg IPB and 2.5 mg of salbutamol (or equivalent drug) given in 20-min intervals during the first hour (at time 0, 20, 40 and 60-min) the recommended dose is reached. Thus, if bronchodilator treatment is to be continued during the second hour, a switch to monotherapy using 2.5 mg of salbutamol (or equivalent drug) is recommended.

**CORTICOSTEROIDS**

Corticosteroids should be used in the treatment of acute exacerbations (asthma; grade A, COPD; grade A)

The benefit of treating patients with acute asthma with systemic corticosteroids has been documented in a Cochrane review including 12 RCTs involving 863 patients. A significant reduction in hospital admissions was achieved by the administration of corticosteroids (intravenous or orally) within an hour of the presentation to the emergency department (47).

In COPD we found five RCTs comparing the effect of corticosteroids to placebo (48–52). The study by Albert et al., including 44 in-patients showed better improvement of FEV1 in patients treated with corticosteroid compared to placebo (49). However, the statistical methods and analyses in Albert’s study have been seriously questioned leaving the evidence from this study unclear (53). Another study by Thompson et al. from 1996 showed accelerated recovery in 13 out-patients receiving oral prednisolone measured by lung function parameters, blood gases and dyspnea score compared with the 14 patients in the placebo group (48). However, taking the small sample and the patient population (out-patients) in to account, no consistent conclusions can be made. A study by Emerman et al. could not show any effect of 100 mg methylprednisolone compared to placebo in 96 patients with acute exacerbation of COPD (51). Davies and colleagues randomized 56 COPD patients admitted with severe exacerbation to receive either low-dose corticosteroid (30 mg oral prednisolone) or identical placebo for 14 days. Significant improvements in lung function and shortening of length of hospital stay were associated with the use of corticosteroids. Unfortunately, information on the acute effect (within a few hours of the presentation to the ER) cannot be clearly extrapolated since the protocol was started within 3 h of the presentation in the emergency room and because the measurement of the first treatment responses was done after 24 h (52).

The largest study has been performed by Niewoehner et al. including 271 patients with COPD admitted to hospital with acute exacerbation. Patients were randomized in three groups; two active groups initially treated with the same doses of intravenous corticosteroids (125 mg methylprednisolone every 6 h for 3 days) followed by different regimes of tapering off oral prednisolone and one placebo group. Moderate benefits were detected in the first 8 weeks in the two active groups compared to placebo but no difference was found at a follow-up after 6 months. The protocol was activated within 12 h of the presentation of the patient in the emergency room with the first measurement of response after 24 h of entering the study. Neither does this study provide any conclusive information on the acute effect of corticosteroids (50).

**Comment**

There is solid evidence to support the use of corticosteroids in acute asthma and the drug should be administered as early as possible upon the arrival of the patient.

In exacerbations of COPD, there is substantial evidence to promote the use of a short course of systemic corticosteroids. However, the effect within the first hours of treatment has not been investigated but the literature supports a beneficial effect detectable after 24 h. It is, however, not clear when to initiate the treatment with corticosteroids. Data suggest that commencement within 12 h of presentation in the emergency department to be sufficient.

Consequently, we recommend the use of systemic corticosteroids in both diseases administered upon arrival of the patient. The fast commencement directed by the evidence on asthma advocating an initiation as early as possible.
Equal benefits from intravenous and oral administration (asthma; grade A, COPD; grade A)

The equal benefit of orally and intravenously administered corticosteroids in severe conditions of asthma has been well documented (47,54,55). In a Cochrane review by Rowe et al. there was no evidence to suggest that one route improved outcomes more than the other.

In COPD, the pattern is similarly verified in a meta-analysis by Wood-Baker et al., showing no difference between the two routes of administration (56).

Comment
The evidence supports the use of both administration forms as options. However, we will recommend the use of intravenous administration of corticosteroids only to reflect the importance of having an intravenous access to the patient as a precaution.

Dose and frequency (asthma; grade A, COPD; grade A)

A Cochrane review by Manser et al. has recently been published to determine whether higher doses of oral/intravenous corticosteroids are more effective than lower doses in the management of acute asthma. Measurements of FEV1, respiratory failures, and side-effects showed no difference in a follow-up period of 24 h when comparing methylprednisolone equivalents in low ($\leq 80$ mg) vs medium ($> 80$ mg and $\leq 360$ mg) vs high dose ($> 360$ mg) (55). In a meta-analysis by Rowe et al., it was suggested that doses of $< 30$ mg in the first 24 h were sub-optimal (54).

A Cochrane review by Wood-Baker et al. based on seven RCTs on exacerbations of COPD compared doses between 25 and 160 mg of methylprednisolone in the first 24 h to placebo. No convincing effect on the measured outcomes could be detected even when using high doses (56). However, in the study by Niewoehner et al., a significant improvement in FEV1 was seen in the corticosteroid-group after 24 h using 125 mg every 6 h (50).

Comment
The optimal dose of corticosteroid used in treating exacerbations is still unclear in both asthma and COPD. However, there is evidence to support that a dose ranging from 30 to – 400 mg of methylprednisolone should be used initially in asthma with no concern of side-effects. In COPD, the strongest evidence is found in Niewoehner’s study suggesting 125 mg to be the initial dose. As our proposed guideline covers both diseases, we have, in this case, chosen COPD as the determinant and recommend a dose of 120 mg of methylprednisolone to be used—well aware that this dose might be supra-optimal for asthma.

Inhaled corticosteroids (no grading)

The use of inhaled corticosteroids in acute exacerbations of asthma and COPD are controversial. However, Edmons et al. have published a Cochrane review on the subject in asthma (57). The authors could not find a clear benefit of inhaled corticosteroids (ICS) in addition to systemic corticosteroids neither could they show ICS alone as effective as intravenous administration. There are no studies, to our knowledge, covering this aspect in COPD.

The proposed guideline does not recommend the use of inhaled corticosteroids.

METHYLXANTHINES

Do not use methylxanthines in acute exacerbations (asthma; grade A, COPD; grade C)

There are conflicting messages concerning the use of methylxanthines in acute asthma when looking at recommendations from guidelines (1,3,13,27). However, the evidence is quite clear on this matter. A meta-analysis by Littenberg could not detect any benefits from adding methylxanthines to beta-agonists in acute asthma (58). This has recently been supported in a published Cochrane review by Parameswaran et al., where no additional effect to standard care with beta-agonists was found. In fact, the frequency of adverse effects was higher with aminophylline (59).

In exacerbations of COPD the evidence is still unclear. In a summary of the evidence on acute management of COPD, three RCTs were found comparing methylxanthines as add-on therapy to ”standard therapy” (including short-acting beta2-agonists). No difference between lung function parameters could be found though one study could report a trend towards lower admission rates in the aminophylline group. However, the frequency of adverse events was higher with theophylline (7).

Comment
There is no evidence to support additional benefit from the use of methylxanthines. Combined with the fact that the drug has substantial side-effects and a narrow therapeutic index, the use of methylxanthines is not recommended in the proposed guideline, neither in COPD nor in asthma.
THE STRATEGY

Use a pre-determined treatment schedule (asthma; grade B, COPD; grade C)

The treatment of acute exacerbations in an emergency setting is a multi-disciplinary task and the potential life-threatening situation demands immediate handling with prompt initiation of a multiple drug therapy. Consequently, it seems reasonable to adapt a certain treatment strategy and to have predetermined schedules for both nursing staff and physicians.

In a well-designed, controlled study by McFadden and co-workers, it was shown that a pre-determined management plan in asthma had a significant impact on the length of the stay in the emergency room, admissions, re-admissions and financial savings compared to “usual care” (33). Schnider et al. have confirmed similar findings (60). We could not find any studies in COPD covering the issue.

Comment

We have adapted the strategy used by McFadden and colleagues in the proposed guideline primarily based on an aggressive use of sympathomimetics, oxygen and corticosteroids in association with serial monitoring of key indices of improvement needed for a rational decision-making. The guideline is based on a strict management plan covering the initial 2 h of the treatment in the emergency room making no distinction between asthma and COPD (Fig.1). We believe a prompt commencement of therapy to be better than delaying the treatment due to differential diagnostic considerations. Upon arrival, the patient is immediately supplied with oxygen by a nasal catheter or a nasal prong (3–5 l/min) continuously throughout the first hour. All patients undergo an initial monitoring of the parameters listed in Fig.1 (key indices). These parameters constitute the foundation for a later “decisions making”.

Simultaneously, the patient receives intravenous corticosteroids and nebulized beta2-agonist in combination with ipratropium bromide as described in Fig.1. (t = 0 min). The inhalation therapy is repeated every 20 min and the oxygen supply should be continued during the process.

The first evaluation of “treatment response (1)” is performed after 60 min by repeating the measurements of the “key indices” done initially. Hereby, a comparison can be performed serving as a foundation for the first “decisions making”:

1. Has the patient’s condition worsened and is the patient in need of intensive care?
2. Has the patient’s monitoring parameters improved to such a degree that discharge is possible?
3. Is the condition of the patient unchanged or is it difficult to make a decision at this moment? If so, the patient is treated and observed for another hour in the emergency department.

If the patient’s condition remains unchanged or showing small progress, the treatment continues in the ER following the same strategy as in the first hour. However, combination therapy using IPB in combination with a beta2-agonist is switched to monotherapy using a beta2-agonist alone in the next hour and the oxygen therapy might be further individualized.

The second treatment response (“treatment response 2”) is performed after 2 h to enhance the final decision-making whether the patient should be discharged, admitted or referred to intensive care. As a consequence, patients are clarified within 2 h. In severe cases, it will be necessary to monitor treatment response more frequently (i.e. every 30 min) but as a standard, an hourly monitoring seems appropriate.

Relevant signs of deterioration have been listed in the guideline specified for asthma and COPD as proposed by the GINA-guidelines (12) and the GOLD-guidelines (6) and should be monitored regularly to assess the severity and to act upon if deterioration occurs. Further, the discharge criteria from the same guidelines have been listed. There is no available grading of the evidence on these statements.

By means of this strategy, we believe patients are secured a sufficient baseline treatment satisfying the quality demands of a modern acute setting. Regular training of doctors and nurses and a close teamwork between the emergency staff are mandatory adapting this management strategy. However, the results could be a rational and effective course giving patients a treatment which is unified, sufficient and well documented.

Other treatments and diagnostics

Antibiotics

The use of antibiotics in acute exacerbations is controversial in both asthma and COPD. A Cochrane review by Graham et al. found two RCTs including 97 patients with acute asthma but could not find any substantial benefits comparing the use of antibiotics to placebo (61).

In COPD, a review on the basis of 11 RCTs concluded that antibiotics are effective in the treatment of patients with acute exacerbations of COPD. However, many of the studies were performed before the emergence of pathogens that are resistant to multiple antibiotics (7). The GOLD-guideline claims antibiotics to be effective only in patients with worsening dyspnea and cough also having increased sputum volume and purulence (6).

We do not find the evidence of the use of antibiotics neither in asthma nor in COPD and, therefore, do not
A practical clinical treatment guideline for acute severe asthma and COPD - an evidence-based management plan covering the first two hours of treatment in the ER

**INITIAL - MONITORING**
- Blood gases or pulse oximetry (+/- oxygen)
- Peak flow (best of three), pulse, blood pressure, resp. frequency. Clinical judgement (classify yes/no):
  - Cyanosis, use of accessory muscles, ronchi, stridor, diaphoresis and anxiety.

**Assessment**
- 0 min

**OXYGEN - THERAPY**
- 3 - 5 l/min. through nasal catheter also during the nebuliser therapy - aiming at a fixed saturation of ≥ 90%.

**Assessment**
- 0 min

**CORTICOSTEROIDS** + **INHALATION THERAPY**
- 120 mg methyl-prednisolone Intravenous or 150 mg prednisolone orally
- Nebuliser: 5 mg terbutaline or 2.5 mg salbutamol in combination with 0.5 mg ipratropium bromide.
  - Flow: 6-8 l x min-1, driving gas: air, nebulisation time: < 10 minutes, fill-volume: 4 ml
  - pMDI + spacer: Use same drug as for nebulisers but in a 6-fold decreased dose

**Assessment**
- 20 min

**INHALATION THERAPY**
- Repeat combination therapy as above

**Assessment**
- 20 min

**INHALATION THERAPY**
- Repeat combination therapy as above

**Assessment**
- 40 min

**TREATMENT RESPONSE (1)**
- Repeat initial monitoring parameters and assess the treatment response. Decide whether the patient should be discharged, transferred to IC-unit or continue treatment in the emergency room.
- 1 - 5 l/min. through nasal catheter between and under nebuliser therapy aiming at a fixed saturation of ≥ 90%.

**Assessment**
- 60 min

**DISCHARGE**
- Discharge with course of oral prednisolone 30-40 mg daily for 10 days and a raised dose of inhaled steroid and bronchodilator. Control after one week in a pulmonary outpatient setting

**Assessment**
- 80 min

**INHALATION THERAPY**
- Mono therapy with 5 mg terbutaline or 2.5 mg salbutamol

**Assessment**
- 100 min

**INHALATION THERAPY**
- Mono therapy with 5 mg terbutaline or 2.5 mg salbutamol

**Assessment**
- 120 min

**INHALATION THERAPY**
- Mono therapy with 5 mg terbutaline or 2.5 mg salbutamol

**Assessment**
- 120 min

**TREATMENT RESPONSE (2)**
- Repeat initial monitoring parameters and assess the treatment response. Decide whether the patient should be discharged, transferred to IC-unit or admission.

**INTENSIVE CARE UNIT**
- Judged by the clinical and paraclinical signs listed.

**Discharge criteria in asthma**
- PEF > 70% pred.
- Physical examination: normal
- No distress
- Saturation > 90%
- Sustained response > 60 minutes

**Discharge criteria in COPD**
- Beta2-agonist required no more frequently than every 4 hrs
- The patient is able to walk across the room
- Clinically stable for 12 – 24 hrs
- Arterial blood gases stable for 12 – 24 hrs
- Practical arrangement solved (medication, family home care arrangements)

**ADMITTANCE**

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**Fig. 1.** Summary of treatment guideline (full-size format).
recommend it as a routine. However, if patients exhibit the symptoms mentioned above confirmed by (or suspected because of) infiltrates on the chest X-ray, a treatment with antibiotics should be established. The choice of agents should, of course, be in accordance with local patterns of antibiotic sensitivity among pathogens.

Sedatives

The use of sedatives in the treatment of acute exacerbations of asthma and COPD is controversial and is not recommended in our treatment schedule. If, however, anxiolytics are to be used, drugs producing a minimum of respiratory depression are recommended (i.e. levomepromazine).

Chest X-rays and others

Chest radiography is a useful test in identifying alternative diagnosis and possible infections (6,7,13) and should be performed within the first hours without delaying or interfering with the treatment schedule.

The collection of blood samples with the measurement of plasma electrolyte, blood count, C-reactive protein and urea concentrations should be regarded as a standard procedure in the acute settings.

DISCUSSION

We have proposed a guideline focusing on practical clinical issues treating patients with acute, severe asthma and COPD in an emergency setting. The presented recommendation is designed to cover the initial 2 h of a treatment strategy securing a well-documented, standardized treatment and promoting decision-making and clarification of the patient within this time limit. Since the treatment of acute exacerbations for asthma and COPD is based on the same therapeutic principles, we have proposed a unified medical treatment in the recommendation. Consequently, some minor compromises have been necessary resulting in a tendency towards an “over-use” of medication in accordance with the evidence. However, we are dealing with a potential life-threatening disease justifying “over-treatment” rather than “under-treatment”.

Though many clinical signs are similar in asthma and COPD upon presentation in the emergency settings, there are differences in the para-clinical findings and in the signs used to evaluate deteriorations and improvements. Therefore, it has been necessary to discriminate between these indicators using different criteria for asthma and COPD as illustrated in the scattered blocks on both sides of the recommendation (Figs. 1 and 2). There are disadvantages using a pre-determined treatment plan with a rigid therapeutic regime and precautions are needed: extremely ill patients with severe respiratory failure should be transferred immediately without delay to the intensive care unit and on the other hand, milder cases may be dragged through unnecessary medical approaches. It must be emphasized that this recommendation does not deprive the respiratory staff of their usual responsibility and care for the patients nor does it exempt doctors from using their clinical skills and “common sense”. However, we believe this recommendation to be useful as a tool in managing the vast majority of patients presenting with severe exacerbations and should be regarded as a support for a rational therapeutic approach giving strength to the diagnostics, the quality of the treatment, and the decision-making.

Essential parts of the EBM have been used creating this guideline. We have documented a need for quality control and a need for a specific clinical recommendation treating acute, severe exacerbations in Danish acute settings (10). As pointed out in the EBM, we have formulated problems and targeted several key clinical issues to be investigated (62). The evidence was appraised by a group of four clinicians and recommendations were made in agreement. We are well aware that this is not fully in accordance with the EBM calling on multi-disciplinary expert panels as a correct methodologic approach (9). This may have introduced certain subjective biases into the process, but even so some advantages may have been gained. As no political issue had to be considered, we were not forced into compromised solutions weakening the statements and we were not biased by any financial influence. In fact, this might even have strengthened the recommendation from a clinical point of view. We believe EBM to be a tool not only justified in the hands of expert panels and specialists but also a tool to be used by any clinician in doubt of possible aspects of management, diagnosis and prognosis (11).

The ambitious task unifying recommendations for both asthma and COPD has called upon a major review of published literature in search of evidence and some studies may have been overlooked. However, the statements (and the grading of statements) are in most cases based on Cochrane reviews, meta-analysis and well-designed RCTs making us believe our appraisal to be reliable. It is, though, important to emphasize that the guideline should be updated regularly. This should be a continuous process with updates as new trial data emerge if the recommendation is to continue to be useful in clinical practice (63). As a consequence, we have established a web address (www.phanareth.dk) in which regular updates of the proposed guideline will be available.

It is crucial for clinical teams, especially the emergency teams with little time and much information to absorb, to be capable of accessing published evidence quickly.
Assessment

THERAPY

Summary of the treatment guideline in pocket size format.

At this moment, the process of distribution and implementation is in progress. The summary of the guideline is available in different formats, including口袋 size format.

We have planned to evaluate the impact of the guideline on clinical practice. We will report the results of this evaluation in our next publication.
Conclusion
We have used the principles of EBM in the development of a practical treatment guideline targeting clinicians working in the emergency ward treating patients with acute severe exacerbations of asthma and COPD. We believe this approach to be an important step towards an increase in the quality of guidelines and also a tool to make "guideline writers" aware of the responsibility of making their recommendations work.

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