

Clinical Epidemiology and Health Service Evaluation Unit

**Evidence Report
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ASTHMA

Update on research conducted to produce

**“Evidence Based Guidelines: Hospital Management of Acute
Asthma”, 1999 North Western Health
&
“Asthma: Best practice guidelines”, 1999, Royal Children’s
Hospital**

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SUMMARY

Task

The Clinical Epidemiology and Health Service Evaluation Unit of Melbourne Health was asked by the Department of Human Services Victoria to review research literature, focusing primarily on clinical guidelines, relevant to diagnosis and treatment of asthma in emergency department settings, for both adult and paediatric populations.

Conclusions and recommendations

Two substantial and locally produced evidence based guidelines were identified. These guidelines are “Evidence Based Guidelines: Hospital Management of Acute Asthma”, 1999 North Western Health¹ and “Asthma: Best practice guidelines”, 1999, Royal Children’s Hospital². Both documents refer to the evidence base for recommendations, summarised in Appendix 1. As both of these documents are a number of years old now, the evidence for their recommendations needed to be revised, and modified accordingly. As such, this report updates the evidence concerning the key recommendations surrounding the Emergency Department treatment for acute asthma exacerbations.

The key recommendations that differ from these reports are:

1. Addition of inhaled ipratropium bromide 0.5mg (single dose) to coincide with initial dose of inhaled beta₂-agonist therapy for adults with mild to moderate asthma
2. Addition of inhaled ipratropium bromide 0.5mg (multiple doses) to each dose of inhaled beta₂-agonist therapy for adults with severe asthma.

Other guidelines have been obtained, and summaries of these documents have been provided in Appendix 2. However, all other guidelines have either not been produced locally, or do not have a strong link between evidence and recommendations.

Feasibility

The key recommendations from this review have implications for the Evidence Based Guidelines: Hospital Management of Acute Asthma, 1999 North Western Health (now Melbourne Health). As these guidelines were developed under the auspice of the Clinical Epidemiology and Health Service Evaluation Unit of Melbourne Health, a process of consultation with clinicians and review of these guidelines to incorporate the recommendations is a natural progression of this review.

METHODOLOGY

Search Strategy

The search strategy used was based on the methods used by the Centre for Clinical Effectiveness, Monash Medical Centre. As such, the following quote best defines the search strategy used.

“The Centre for Clinical Effectiveness defines the ‘best available evidence’ as that research we can identify that is least susceptible to bias. We determine this according to predefined NHMRC criteria (see Appendix 4).

First we search for systematic reviews, evidence-based clinical practice guidelines, or health technology assessments, and randomised controlled trials. If we identify sound, relevant material of this type, the search stops. Otherwise, our search strategy broadens to include studies that are more prone to bias, less generalizable, or have other methodological difficulties. We include case-control and longitudinal cohort studies in our critical appraisal reports. While we cite observational and case series studies, and narrative reviews and consensus statements, in our reports we do not critically appraise them. Such studies can produce accurate results but they are generally too prone to bias to allow determination of their validity beyond their immediate setting”³.

Resources Searched

We searched the following databases and Internet websites:

- Cochrane Library CD-ROM
- Medline (OVID)
- CINAHL (OVID)
- SumSearch
- National Guidelines Clearinghouse (www.guidelines.gov)
- NHS Centre for Reviews and Dissemination (NHS CRD)
http://www.nelh.nhs.uk/guidelines_database.asp
- Other known websites containing local guidelines

Refinements, Searching & Reporting Constraints

We only included articles published since 1997, and applied the following inclusion and exclusion criteria:

Inclusion Criteria

- Focus on all patients with asthma in the emergency department, but divided evidence into paediatric and adult populations
- Published primary studies;
- Published clinical practice guidelines (whether generated through evidence-based methods or through consensus)

Exclusion Criteria

- Study examined less than five patients
- Study was published in a language other than English
- Study presented data included in another published report
- Study examines long term therapy not possible to implement in ED

RESULTS

Clinical Practice Guidelines

The search identified six relevant clinical guidelines meeting the entry criteria. The descriptive characteristics of these guidelines are shown in Table 1. We include a brief summary of each guideline in the Appendices 1 and 2.

Table 1. Description of guidelines cited.

Characteristic	NWH, 1999
Developers	North Western Health, Royal Melbourne Hospital
Title	Hospital management of acute asthma: Evidence based guidelines recommended for use in the Royal Melbourne Hospital.
Target Population	Persons presenting to hospital with an exacerbation of asthma
Outcomes Considered for ED	Severity of presenting symptoms, and response to treatment (pulse rate, respiratory rate, PEFR, Speech, SaO ₂ , work of breathing)
Methods to Collect Evidence	Literature review, previous guidelines, and focus groups with staff from RMH
Methods to Analyse Evidence	Not stated
Length	18
URL	http://info.mh.org.au/default.htm
Comments	Local guideline with clear links between cited references

Characteristic	RCH, 1999
Developers	Royal Childrens Hospital
Title	Asthma best practice guidelines.
Target Population	Paediatric asthma patients
Outcomes Considered for ED	Provision of the best control of asthma by confirmation of the diagnosis using objective measures, rapid achievement and maintenance o control and regular follow up.
Methods to Collect Evidence	Search of electronic databases including Cochran, Evidenced Based Medicine databases, and OVID (Medline and others)
Methods to Analyse Evidence	Not stated
Length	61
URL	http://perseus.rch.unimelb.edu.au/intranet/genmed/newindex.htm
Comments	Good local source for treatment of peadiatric asthma. Good conection between cited evidence and recommendations.

Characteristic	NIH, 1997
Developers	National Institutes of Health
Title	Expert panel report 2: Guidelines for the diagnosis and management of asthma
Target Population	All people with asthma, with separate sections on multiple age groupings, and special situations. Includes long term management, and acute emergency department treatment of asthma exacerbations
Outcomes Considered for ED	Correction of significant hypoxemia, reversal of airflow obstruction, reduced likelihood of recurrence of severe airflow obstruction.
Methods to Collect Evidence	Medline search 91-95
Methods to Analyse Evidence	Critical review by multi-disciplinary consensus panel (clinicians and scientist with expertise in asthma), followed by voting on key recommendations of the report
Length	146
URL	http://rover2.nhlbi.nih.gov/health/prof/lung/asthma/practgde.htm
Comments	

Table 1 (cont). Description of guidelines cited.

Characteristic	SIGN, 1999
Developers	Scottish Intercollegiate Guidelines Network
Title	Emergency management of acute asthma
Target Population	Patients who present with asthma like symptoms to Accident and Emergency centres. Some reference made to paediatric patients.
Outcomes Considered for ED	Airway function
Methods to Collect Evidence	Not stated
Methods to Analyse Evidence	Not stated
Length	52
URL	http://www.icsi.org/guide/Asthma.pdf
Comments	Good referencing of evidence, but no statement on how evidence was gathered and reviewed.

Characteristic	ICSI, 2000
Developers	Institute for Clinical Systems Improvement
Title	Health care guideline: Diagnosis and management of asthma.
Target Population	Patients 5 years of age who present with asthma like symptoms and/or patients who have been diagnosed with asthma
Outcomes Considered for ED	Airway function
Methods to Collect Evidence	Not stated
Methods to Analyse Evidence	Not stated
Length	35
URL	http://www.icsi.org/guide/Asthma.pdf
Comments	Very limited referencing, and no citing of original articles

Characteristic	CMAJ, 1999
Developers	Canadian Asthma Consensus Group
Title	Canadian asthma consensus report
Target Population	Patients 5 years of age who present with asthma like symptoms and/or patients who have been diagnosed with asthma
Outcomes Considered for ED	Provision of the best control of asthma by confirmation of the diagnosis using objective measures, rapid achievement and maintenance of control and regular follow up.
Methods to Collect Evidence	Not stated
Methods to Analyse Evidence	Not stated
Length	62
URL	http://www.cma.ca/cpgs/search/english/results.asp
Comments	Good division into specialty treatment for subpopulations. Good referencing, but poor description of search strategies used.

Two other guidelines were identified but were found to be not appropriate on further examination. The producers, and location of these documents are listed in Table 2.

Table 2. Guidelines not obtained:

Guideline	Comments
Cincinnati Children's Hospital Medical Center, 1999. Evidence based clinical practice guideline for managing an acute exacerbation of asthma.	Not available in electronic format-full summary obtained from www.guidelines.gov . We have requested a hard copy, but we have not yet received a copy
University of Michigan, 2000. Asthma: Guidelines for clinical care.	Guideline not directly related to ED treatments. Chronic treatment and management http://cme.med.umich.edu/pdf/guideline/asthma.pdf

Health Technology Assessments

There were no health technology assessment reports available on the topic of acute asthma.

Citations for clinical practice guidelines and health technology assessments

North Western Health (NWH). Evidence based guidelines: hospital management of acute asthma. Melbourne: Royal Melbourne Hospital, 1999.

Royal Children's Hospital (RCH). Asthma best practice guidelines. Melbourne: Royal Children's Hospital, 1999.

National Institutes of Health (NIH). Guidelines for diagnosis and management of asthma. Bethesda, Maryland, USA: National Institutes of Health, 1997.

Scottish Intercollegiate Guidelines Network (SIGN). Emergency Management of Acute Asthma. A National Clinical Guideline. Edinburgh: Royal College of Physicians, 1999.

Institute for Clinical Systems Improvement (ICSI). Health care guideline: Diagnosis and management of asthma. Bloomington, Minnesota, USA: Institute for Clinical Systems Improvement, 2001.

Boulet L-P, Becker A, Berube D, Beveridge R, Ernst P. Canadian asthma consensus report. CMAJ 1999;161(11 Suppl):S1-S59.

Published Primary Literature

24 identified articles met the entry criteria. Critical appraisal of this literature follows. Citations and abstracts for these articles are listed in Appendix 3 arranged according to topic area.

The initial management of acute asthma for both adults and children includes the administration of oxygen, bronchodilators such as beta₂-agonists (salbutamol) and anticholinergics (ipratropium) and anti-inflammatory drugs (corticosteroids). Aminophylline, a bronchodilator, and magnesium sulphate are also drugs that have traditionally been used in the treatment of acute asthma. Both the "Evidence Based Guidelines: Hospital Management of Acute Asthma" (North Western Health) and the "Asthma Best Practice Guidelines" (Royal Children's Hospital [RCH]), make

recommendations regarding the administration of these drugs for the treatment of acute asthma^{1,2}. As both these guidelines were developed in 1999, a review of recent literature has been undertaken to identify current evidence that may lead to revision of these documents.

Beta₂ – agonists

The North Western Health guidelines, recommend the administration of high-dose inhaled bronchodilators (salbutamol 5mg via nebuliser every 15 minutes up to a maximum of 20mg) for adults in the initial management of acute asthma. The RCH guidelines also recommend the use of inhaled beta₂-agonists (salbutamol) however; they recommend the use of metered-dose inhalers (MDI) with a spacer for administration rather than nebulised delivery. The RCH guidelines refer to recent evidence demonstrating that inhaled beta₂-agonists are as effective and may have fewer side effects when delivered by MDI and spacer. “The combination of MDI/spacer is more cost effective and easier to use and also provides patients and their parents with the skills to manage an acute attack of asthma at home”².

The literature search identified a systematic review conducted by Cates and Rowe (2001) comparing the efficacy of using MDI inhalers plus spacer with wet nebulised beta₂-agonists in acute asthma for both children and adults⁴. The authors concluded that delivery of inhaled beta₂-agonists via MDI plus spacer was as effective as nebuliser administration; however, the studies excluded patients with life threatening asthma limiting generalisation of this finding to patients with mild to less severe exacerbations⁴. For adults, there were no significant differences between the two delivery methods and consequently, the choice of delivery method should reflect the patient preference. The findings were similar for children with observed other benefits (time spent in the emergency department, oxygenation and side effects) favouring the use of MDI plus spacer⁴. Review of a number of primary publications describing randomised controlled trials (RCTs) comparing the efficacy of inhaled beta₂-agonists delivered via MDI plus spacer versus nebuliser in children supports this finding⁵⁻⁷.

A systematic review conducted by Jones et al (2001) explored the effects of inhaled beta₂-agonists on asthmatic patients who require intubation and mechanical ventilation⁸. This review found there was no data from RCTs to provide evidence for or against current practices regarding the use of inhaled beta₂-agonists in asthmatic subjects who are intubated and ventilated. The authors recommended that until large RCTs are conducted, the practice should not be abandoned.

The literature search revealed one paper related to the recommended dose of inhaled beta₂-agonists⁹. This paper was a RCT comparing 2.5mg with 7.5mg nebulised albuterol (salbutamol) for adult patients with mild to moderate acute asthma and concluded that there was no advantage to the routine administration of albuterol in doses higher than 2.5mg. This recommendation differs to that of the North Western Health guidelines, however, as the recommended dose of 2.5mg is supported by only one study, it is imprudent to alter the guideline at present.

Intravenous (IV) and subcutaneous beta₂-agonists are described as second line therapy for use in patients unresponsive to inhaled bronchodilator and systemic corticosteroid therapy. A systematic review conducted by Travers et al (2001) to determine the benefit of intravenous beta₂-agonists for severe asthma in adults and children revealed

there is no evidence to support the use of IV beta₂-agonists in these patients and beta₂-agonists should be given by inhalation. IV beta₂-agonists should only be used for patients in whom inhaled therapy cannot be used¹⁰.

Recommendations: No recommended changes to the guidelines. A summary of the literature reviewed in relation to beta₂-agonists is displayed in Table 3.

Table 3. Literature re Beta₂-agonists

Author/Date	Location	Study Design/Level of Evidence	Patient Group	Authors Conclusions
Cates & Rowe, 2001 ⁴	UK	Level I - Systematic Review	Adults & Children	Metered-dose inhalers with holding chamber produced outcomes that were at least equivalent to nebuliser delivery. Holding chambers may have some advantages compared to nebulisers for children with acute asthma.
Leversha et al, 2000 ⁵	NZ	Level II – RCT	Children	In children seen in the emergency department for moderate and severe asthma, delivery of albuterol by metered-dose inhaler and spacer was a cost-effective alternative to delivery by nebulizer.
Mandelberg et al, 2000 ⁶	Israel	Level II – RCT	Children	We conclude that even in the group of unselected very young children (mean age < 2 years) with acute wheezing episode, the use of metered dose inhalers with spacer is at least as effective as the use of nebulised wet aerosol. As opposed to data from an adult population, no plateau was reached in the dose-response curve using the above doses over time.
Schuh et al, 1999 ⁷	Ontario, Canada	Level II – RCT	Children	In children with mild acute asthma, treatment with 2 puffs of albuterol by a MDI with spacer is just as clinically beneficial as treatment with higher doses delivered by an MDI or by a nebulizer.
Jones et al, 2001 ⁸	Texas, USA	Level I - Systematic Review	Adults	There are no data from randomised controlled trials to provide evidence for or against current practices regarding the use of inhaled beta ₂ -agonists in asthmatic subjects who are intubated and ventilated.
Emerman, Cydulka, McFadden, 1999 ⁹	Ohio, USA	Level I – RCT	Adults	There is no advantage to the routine administration of doses of albuterol higher than 2.5 mg every 20 minutes. It is possible that there may be an advantage in the most severely obstructed patients, although this study did not enrol enough patients with very severe asthma to evaluate this. As has been previously demonstrated, patients who subsequently require admission have a diminished response to albuterol. This decreased responsiveness is seen with the first aerosol administration and is unaffected by increasing the dose.
Travers et al, 2001 ¹⁰	Canada	Level I – Systematic Review	Adults & Children	There is no evidence to support the use of IV beta ₂ -agonists in patients with severe acute asthma. These drugs should be given by inhalation. No subgroups were identified in which the IV route should be considered.

Anticholinergics

The addition of anticholinergic agents eg ipratropium to the treatment regimen for acute asthma may be useful in aiding bronchodilatation in the early stages of treatment, particularly when asthma is severe. Previous studies have shown conflicting results. A meta-analysis conducted by Stoodley (1999) to determine whether the addition of inhaled ipratropium (0.5mg) to inhaled beta₂-agonist therapy was effective in the treatment of adults with acute asthma revealed there is a modest statistical improvement in air flow obstruction when ipratropium is used¹¹. However, the clinical significance of this improvement remains unclear and the optimal dose of ipratropium needs to be determined. The implications for practice include the recommendation of combining ipratropium/beta₂-agonist therapy in acute asthma exacerbations¹¹.

The findings of Stoodley et al are supported by another meta-analysis conducted by Rodrigo et al (1999) who explored whether there was an additive benefit using inhaled ipratropium in combination with inhaled beta₂-agonist therapy in adults with acute asthma, and the effect this had on admission rates¹². Their findings revealed the early administration of ipratropium (0.5mg) along with beta₂-agonists significantly reduces admission rates. Almost all the studies included in the meta-analysis used a single dose of ipratropium. The authors suggest there may be further benefits with multiple doses, an area that requires further examination¹².

A meta-analysis of three RCTs conducted by Lanes et al (1998) to explore the effect of adding ipratropium bromide (multi-dose) to salbutamol in the treatment of adults with acute asthma concluded that there was a small improvement in lung function and reduced risk of the need for additional treatment, subsequent asthma exacerbations, and hospitalisations¹³. The recent findings of two RCTs comparing the combination of multiple doses of inhaled anticholinergics (ipratropium bromide or oxitropium bromide) and beta₂-agonist therapy with inhaled beta₂-agonist therapy only, support a multi-dose inhaled ipratropium regimen^{14,15}. The study conducted by Rodrigo & Rodrigo (2000) compared albuterol (salbutamol) and ipratropium via MDI plus spacer at ten minute intervals for three hours (24 puffs or 2880mcg of albuterol and 504mcg of ipratropium each hour) with albuterol only¹⁵. Rodrigo & Rodrigo (2000) concluded there was a substantial therapeutic benefit from the addition of ipratropium to albuterol administered in high doses, particularly for patients with severe asthma. The improvements associated with ipratropium bromide were reflected in higher bronchodilator responses, lower rates of hospital admission, shorter time to obtain the discharge threshold and minimal side effects. The study conducted by Nankano et al (2000), whilst using a smaller sample size and an alternative to ipratropium bromide, oxitropium bromide, had similar findings¹⁴.

The North Western Health guideline does not indicate the use of ipratropium bromide in acute asthma, however, it acknowledged there was an additional clinical benefit and the findings of a Cochrane Collaboration review were awaited before recommending the addition of ipratropium bromide to the treatment regimen¹.

The use of anticholinergics in children with asthma has also come under considerable scrutiny. A meta-analysis conducted by Plotnic and Ducharme (1997) concluded the addition of a single inhalation of anticholinergics to a beta₂-agonist regimen might improve lung function in children with acute exacerbations of asthma treated in the ED. Multiple doses of anticholinergics improve lung function and may avoid hospitalisation in severe exacerbations¹⁶. This meta-analysis was reviewed in 2001 and concluded a single dose of an anticholinergic is not effective for the treatment of mild and moderate exacerbations and is insufficient in the treatment of severe exacerbations¹⁷. The addition of multiple doses of anticholinergics to beta₂-agonist inhalations is indicated in the initial management of children with severe exacerbations of asthma. These findings are reflected in the RCH guideline².

Recommendations

1. Addition of inhaled ipratropium bromide 0.5mg (single dose) to coincide with initial dose of inhaled beta₂-agonist therapy for adults with mild to moderate asthma
2. Addition of inhaled ipratropium bromide 0.5mg (multiple doses) to each dose of inhaled beta₂-agonist therapy for adults with severe asthma.

A summary of the literature reviewed in relation to anticholinergics is displayed in Table 4.

Table 4. Literature re Anticholinergics

Author/ Date	Location	Study Design/ Level of Evidence	Patient Group	Authors Conclusions
Stoodley, Aaron & Dales, 1999 ¹¹	Canada	Level I – Systematic Review	Adults	There is modest statistical improvement in air flow obstruction when ipratropium is used as an adjunctive treatment to Beta ₂ antagonists for the treatment of acute asthma exacerbation. Although clinical significance of this improvement in airflow obstruction remains unclear, it would appear reasonable to recommend the use of combination ipratropium/beta-agonist therapy in acute asthma exacerbations since the addition of ipratropium seemed to provide physiologic evidence of benefit without risk of adverse effects.
Rodrigo, Rodrigo & Burschtin, 1999 ¹²	Uruguay	Level I – Systematic Review	Adults	The addition of ipratropium to beta-agonist therapy offers a statistically significant, albeit modest, improvement in pulmonary function, as well as a reduction in the rate of hospital admissions.
Lanes et al, 1998 ¹³	USA	Level II - RCT	Adults	Adding ipratropium bromide to salbutamol in the treatment of acute asthma produces a small improvement in lung function, and reduces the risk of the need for additional treatment, subsequent asthma exacerbations, and hospitalisations. These apparent benefits of adding ipratropium bromide were independent of the amount of beta-agonist that had been used earlier in the attack, and possibly related to a recent upper respiratory tract infection. Confirmatory studies are needed, especially for clinical outcomes.
Rodrigo & Rodrigo, 2000 ¹⁵	Uruguay	Level II - RCT	Adults	Data support a considerable therapeutic benefit from addition of ipratropium bromide to albuterol administered in high doses through MDI plus spacer, particularly in those patients in whom the FEV ₁ was less than 30% of the predicted, and had a long duration of symptoms before the ED presentation (\geq 24 hours).
Nakano et al, 2000 ¹⁴	Japan	Level II - RCT	Adults	Adding multiple doses of oxitropium bromide to salbutamol delivered by means of a metered dose inhaler with a spacer device for acute severe asthma produces a significant improvement in lung function and reduces the need for additional ED treatment.
Plotnick & Ducharme, 1997 ¹⁶	Canada	Level I – Systematic Review	Children	The addition of a single inhalation of anticholinergics to a beta ₂ -agonist regimen may improve lung function in children with acute exacerbations of asthma treated in the ED. Multiple-dose anticholinergics improve lung function and may avoid hospitalisation in severe exacerbations.
Plotnick & Ducharme, 2001 ¹⁷	Canada	Level I – Systematic Review	Children	A single dose of an anticholinergic agent is not effective for the treatment of mild and moderate exacerbations and is insufficient for the treatment of severe exacerbations. Adding multiple doses of anticholinergics to beta ₂ -agonists appears safe, improves lung function and would avoid hospital admission in 1 of 12 such treated patients. Although multiple doses should be preferred to single doses of anticholinergics, the available evidence only supports their use in school aged children with severe asthma exacerbation. There is no conclusive evidence to support the use of multiple doses of anticholinergics in children with mild or moderate exacerbations.

Corticosteroids

Systemic corticosteroids are used as first-line treatment in acute asthma to reduce airway inflammation and hasten resolution of the asthma exacerbation. There is considerable variation in the prescribing of corticosteroids relating to timing and route of administration, which ultimately affects the resolution of exacerbations.

Traditionally, systemic corticosteroids have been given either orally or intravenously, however, there is increasing support for the use of inhaled corticosteroids.

Rowe et al (2001) undertook a meta-analysis to explore the benefit of treating patients with acute asthma within an hour of presenting to the emergency department with any form of systemic corticosteroid (intravenous, intramuscular, oral)¹⁸. The authors concluded that early administration reduces the need for hospitalisation in patients with acute asthma. The benefits were greatest in patients with more severe asthma, and those not currently receiving steroids. Children appear to respond well to oral steroids, however, there are no data to provide guidance as to the efficacy of oral therapy for adults in this setting¹⁸.

Another meta-analysis conducted by Rowe et al (2001) explored the benefits of corticosteroid treatment following diagnosis, treatment and discharge from the acute care setting with the aim to determine if there is clear evidence that treatment of asthmatic exacerbations with corticosteroids is beneficial¹⁹. The findings of this review were:

- The relapse rate at 7-10 days was lower in patients who received corticosteroids (oral or intramuscular);
- Fewer patients who received corticosteroids required hospitalisation;
- Patients who received corticosteroids had less need for beta₂-agonists;
- Changes in pulmonary function tests and side effects of treatment were rarely reported¹⁹.

The authors concluded a short course of corticosteroids (oral or intramuscular) following assessment for an acute exacerbation of asthma significantly reduces the number of relapses to additional care and decreases beta-agonist use without an apparent increase in side effects. Intramuscular corticosteroids appear as effective¹⁹.

Whilst there appears to be general consensus that systemic corticosteroid therapy is beneficial in improving outcomes for patients suffering an asthma exacerbation, there is continuing debate regarding the role of inhaled corticosteroids. Edmonds et al (2001) undertook a meta-analysis to determine the benefit of inhaled corticosteroids for the treatment of patients with acute asthma managed in the emergency department and concluded that there was insufficient evidence that inhaled corticosteroid therapy results in clinically important changes in pulmonary function or clinical scores used in acute asthma²⁰. However, inhaled corticosteroids were shown to reduce admission rates in patients with acute asthma but their role in acute asthma is not clear i.e. there is insufficient evidence that inhaled corticosteroids are as effective as systemic or of their additional benefit when used in addition to systemic corticosteroids.

A further meta-analysis conducted by Edmonds et al (2001) explored the efficacy of inhaled corticosteroids alone or in addition to oral corticosteroids after discharge from the emergency department following an asthma exacerbation and concluded, in this setting, inhaled corticosteroids alone appear to be as effective as oral corticosteroids for those patients with mild exacerbations²¹. There was insufficient evidence that inhaled corticosteroid therapy provides additional benefit when used in combination with oral corticosteroid therapy.

Manser et al (2001) conducted a meta-analysis to determine whether higher doses of systemic corticosteroids (oral, intravenous, or intramuscular) are more effective than lower doses in the management of adult patients with acute severe asthma requiring hospital admission and concluded that doses of 60-80mg/day of methylprednisolone or 300-400mg/day of hydrocortisone appear to be sufficient in the initial management of adults with acute asthma requiring hospital admission. Higher doses do not appear to offer an obvious therapeutic advantage²².

Both the North Western Health and RCH guidelines advocate the administration of corticosteroids in conjunction with bronchodilators in patients with moderate to severe acute asthma upon presentation to the emergency department.

Recommendation: No change to current guidelines. A summary of the literature reviewed in relation to corticosteroids is displayed in Table 5.

Table 5. Literature re Corticosteroids

Author/ Date	Location	Study Design/ Level of Evidence	Patient Group	Authors Conclusions
Rowe et al, 2001 ¹⁸	Canada	Level I – Systematic Review	Adults & Children	Use of corticosteroids within 1 hour of presentation to an ED significantly reduces the need for hospital admission in patients with acute asthma. Benefits appear greatest in patients with more severe asthma, and those not currently receiving steroids. Children appear to respond well to oral steroids.
Rowe et al, 2001 ¹⁹	Canada	Level I – Systematic Review	Adults & Children	Corticosteroids (oral or intramuscular) reduce the relapse rate, use of beta-agonists, and hospitalisation rate at 7 to 10 days in patients who have an acute asthma exacerbation after initial assessment.
Edmonds et al, 2001 ²⁰	Canada	Level I – Systematic Review	Adults & Children	Inhaled steroids reduced admission rates in patients with acute asthma, but it is unclear if there is a benefit of inhaled corticosteroids when used in addition to systemic corticosteroids. There is insufficient evidence that inhaled corticosteroids therapy results in clinically important changes in pulmonary function or clinical scores when used in acute asthma. Similarly, there is insufficient evidence that inhaled corticosteroids alone are as effective as corticosteroids. Further research is needed to clarify if there is a benefit of inhaled corticosteroids when used in addition to corticosteroids.
Edmonds et al, 2001 ²¹	Canada	Level I – Systematic Review	Adults & Children	There is insufficient evidence that inhaled corticosteroid therapy provides additional benefit when used in combination with standard corticosteroid therapy upon ED discharge for acute asthma. There is some evidence that high-dose inhaled corticosteroid therapy alone may be as effective as corticosteroid therapy when used in mild asthmatics upon ED discharge; however, there is a significant possibility of a type II error in drawing this conclusion. Further research is needed to clarify whether inhaled corticosteroid therapy should be employed in acute asthma treatment in the ED or following ED discharge
Qureshi, Zaritsky, Poirier, 2001 ²³		Level II – RCT	Children	For the management of acute asthma, symptom improvement and the relapse rate were similar between children who received 2 doses of oral dexamethasone or 5 doses of oral prednisolone. Advantages of dexamethasone include fewer doses, reduced emesis, and a decrease in the number of school/work days missed. Patient compliance may also be improved by dispensing the second dose of medication from the ED. Dexamethasone is a practical alternative to prednisolone in the management of asthma exacerbations in children.
Manser, Reid & Abramson, 2001 ²²	Australia	Level I – Systematic Review	Adults	No differences were identified among the different doses of corticosteroids in acute asthma requiring hospital admission. Low dose corticosteroids (< or = 80 mg/day of methylprednisolone or < or = 400 mg/day hydrocortisone) appear to be adequate in the initial management of these adult patients. Higher doses do not appear to offer a therapeutic advantage.

Other Aminophylline, Magnesium Sulphate & Heliox

Aminophylline has been prescribed as a bronchodilator for many years in the treatment of asthma, however its use has declined with the introduction of more effective bronchodilators. A meta-analysis conducted by Belda, Parameswaran & Rowe (2001) to determine the magnitude of effect of the addition of IV aminophylline to beta₂-agonists in adult patients with acute asthma concluded the use of IV aminophylline did not result in any additional bronchodilation compared to standard care with beta₂-agonists²⁴. In summary:

- There is insufficient evidence to support the routine use of aminophylline in the management of acute asthma when adequate beta-agonist treatment is provided;
- The development of side effects is significantly higher with aminophylline treatment than beta₂-agonist therapy alone;
- Treatments of proven benefit should be encouraged before consideration is given to intravenous aminophylline.

Mitra et al (2001) conducted a systematic review to determine whether addition of intravenous aminophylline produces a beneficial effect in children with acute severe asthma and concluded its use should be considered early in treatment of children hospitalised with acute severe asthma with sub-optimal response to the initial inhaled bronchodilator therapy²⁵.

The North Western Health guideline does not recommend the use of IV aminophylline for the treatment of acute asthma. However, the RCH guideline recommends that for patients with critical asthma, consideration should be given to the addition of IV aminophylline to the regimen².

The use of IV magnesium sulfate in the treatment of acute asthma has been considered to provide additional bronchodilation. However, a systematic review conducted by Rowe et al (2001) concluded that current evidence does not support the use of IV magnesium sulphate in all patients with acute asthma²⁶. There is a sub-group of patients, those with severe asthma, who appear to benefit from the use of magnesium sulfate, both in terms of pulmonary function and admission rates²⁶. Neither the North Western Health nor RCH guidelines list the use of IV magnesium sulfate.

Heliox has been shown to quickly improve ventilation in nonintubated and intubated patients with acute severe asthma and respiratory acidosis and to lower airway pressures in intubated patients. It has also been shown to rapidly decrease airway resistance and dyspnea in nonintubated patients with severe asthma²⁷. Rodrigo et al (2001) conducted a meta-analysis of four randomised controlled trials to determine the effect of the addition of heliox to standard medical care on the course of acute asthma. The authors concluded the existing evidence does not provide support for the administration of helium-oxygen mixtures to patients presenting to the emergency department with moderate to severe acute asthma²⁸.

Recommendations: No change to current guidelines. A summary of the literature reviewed in relation to other medications is displayed in Table 6.

Table 6. Other medications

Author/Date	Location	Study Design/ Level of Evidence	Patient Group	Authors Conclusions
Belda, Parameswaran & Rowe, 2001 ²⁴	Canada	Level I – Systematic Review	Adults	In acute asthma, the use of intravenous aminophylline did not result in any additional bronchodilatation compared to standard care with beta-agonists. The frequency of adverse effects was higher with aminophylline. No subgroups in which aminophylline might be more effective could be identified. These results should be added to consensus statements and guidelines.
Mitra, Bassler, Ducharme, 2001 ²⁵		Level I – Systematic Review	Children	Addition of intravenous aminophylline should be considered early in the treatment of children hospitalised with acute severe asthma with sub optimal response to the initial inhaled bronchodilator therapy. Although the improvement is sustained for 24 hours, there is no apparent reduction in length of hospital stay or number of inhaled beta2-agonists nebulizations. Treatment with aminophylline is associated with an increased risk of vomiting. NB. The careful monitoring of serum theophylline in these critically ill children seemed to have prevented the occurrence of seizures associated with overdose. No firm conclusion can be drawn regarding other important side effects such as hypokalemia, hypertension, tachycardia, and diuresis.
Rowe et al, 2001 ²⁶	Canada	Level I – Systematic Review	Adults & Children	Current evidence does not support routine use of intravenous magnesium sulphate in all patients with acute asthma presenting to the emergency department. Magnesium sulfate appears to be safe and beneficial in patients who present with severe acute asthma.
Rodrigo et al, 2001 ²⁸	Uruguay	Level I – Systematic Review	Adults & Children	The existing evidence does not provide support for the administration of helium-oxygen mixtures to patients presenting to the emergency department with moderate to severe acute asthma. Heliox treatment does not have a role in the initial treatment of patients with acute asthma. These conclusions are based upon between-group comparisons and small studies. Additional research in this setting may be warranted.

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APPENDIX 1 – NWH & RCH SUMMARY OF RECOMMENDATIONS

North Western Health, 1999. Hospital management of acute asthma.

Recommendations for initial assessment to determine severity

1. **Clinical assessment:** respiratory rate; ability to speak in sentences; past history of asthma and medication taken prior to hospital, whether on corticosteroids.
(Level IV)
2. **PEF:** before (if possible) and after bronchodilator.
(Level III-2)
3. **Gas exchange:** Measurement of SaO₂ (pulse oximetry) as a routine. Arterial blood gas (ABGs) measurement should be undertaken only in patients who are assessed as severe or who fail to respond to initial treatment.
(Level III-3 and level IV)

Recommendations regarding initial treatment of an acute episode

1. Oxygen therapy at a minimum of 6 L/min via face mask to achieve arterial oxygen saturation of 95 per cent or above.
(Level 1)
2. Administration of high-dose inhaled bronchodilator (salbutamol 5mg via nebuliser, every 15 minutes up to a maximum of 20mg) using an oxygen flow rate of at least 6L/min.
(Level II)
3. Cortico-steroids should be given within one hour of presentation. For patients who are considered to be **severe**, Hydrocortisone 100mg IV (stat) and prednisolone 50mg orally should be administered in most situations but for patients on maintenance glucocorticosteroids hydrocortisone 250mg IV (stat) and 50mg prednisolone orally is recommended. All other patients should commence on 50mg prednisolone.
(Level II)
4. Antibiotics are not required unless there is radiological evidence of pneumonia or proven or suspected bacterial bronchitis.
(Level III-1)

Recommendations for monitoring response to initial treatment

1. Assess for signs of an inadequate response - respiratory rate, heart rate and oxygen saturation. ABG measurements should be initiated if not already taken.
(Level III)
2. PEF monitoring before and after bronchodilator. (Level III)
3. Indications for transfer to Intensive Care. (Level III)
4. Indications for admission. (Level III)
5. Discharge planning for patients not requiring admission.
(Level III)

Recommendations for patient education and self-management plans

**Patient education is a shared responsibility of all staff particularly medical and nursing staff.
The following should be addressed:**

1. Cause of this exacerbation. (Level 1)
2. Smoking cessation advice/counselling. (Level 1)
3. Review of inhaler (and spacer) technique. (Level 1)
4. Review of functional status and ability to manage activities of daily living.
5. Provision or review of personalised and written self-management plans to deal, in particular, with recognition of exacerbations and appropriate changes in treatment. At RMH, this plan should be written using the pre-printed form "ASTHMA ACTION PLAN" OP12/IP47 – a sample is attached as Appendix 2. (The form is available in the Emergency Department and all wards or may be obtained from Ward 6 East).
(Level 1)

Recommendations for discharge medications

1. *Adjust bronchodilator therapy. The bronchodilator regime to be followed should be established before discharge.* **(Level IV)**
2. *Review dose of oral corticosteroids in those patients on maintenance doses.* **(Level IV)**
3. *Review other medication.* **(Level IV)**

Recommendations regarding follow-up after discharge

1. *Discharge summary including details of continuing medication, best and worst PEF and asthma management plan to be faxed to the GP prior to discharge.* **(Level IV)**
2. *Patient advised to make an appointment to see GP within 7 days after discharge.* **(Level IV)**
3. *If consultant review is required appointment should be made within 4 weeks of discharge.* **(Level III)**

Royal Children's Hospital, 1999. Asthma best practice guidelines.

Diagnosis of Asthma

Recommendation:

Where cough, in the absence of wheeze, is considered to be caused by asthma, consider a trial of bronchodilators and preventive medication (cromones or low dose inhaled corticosteroids), but withdraw if there is no response over 4-6 weeks (level V).

Assessment of severity of attack

Recommendation:

Mental status and accessory muscle use should be considered primary features in the assessment of acute asthma severity (level V).

Recommendation:

Initial Sa_{o2} in air, heart rate, and ability to talk should be used as additional features in the assessment of acute asthma severity (level V).

Recommendations:

- *Wheeze intensity, central cyanosis, pulsus paradoxus, and peak expiratory flow rate are not reliable for the assessment of the severity of acute asthma (level V).*
- *Chest x-ray, arterial blood gas measurements and spirometry should not be routinely used in the assessment of the severity of acute asthma (level V).*

Treatment of an acute attack

	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>	<i>Critical</i>
Oxygen	No	No	If S _a O ₂ , 92%	Yes
Inhaled β₂- agonist (salbutamol)	6 or 12 puffs, pMDI/spacer ¹ once – review after 20 minutes	6 or 12 puffs pMDI/spacer ¹ – 3 times in 1 st hr (20 minutely) – review 10 minutes after 3 rd dose	6 or 12 puffs pMDI/spacer ¹ – 3 times in 1 st hr (20 minutely) – review 10 minutes after 3 rd dose	Nebulised salbutamol continuously ²
Ipratropium	No	No	2 or 4 puffs pMDI/spacer ³ – 3 times in 1 st hr only (20 minutely)	Nebulised (250mcg) – times in 1 st hr only (20 minutely; add to salbutamol) IV methylprednisolone 1mg/kg/dose – 6 hourly on day 1
Corticosteroid	Usually no	Oral prednisolone 1mg/kg/dose – once daily for up to 3 days	Oral prednisolone 1mg/kg/dose – once daily for 3 days – if vomiting give i.v.	IV methylprednisolone 1 mg/kg/dose - 6 hourly on day 1
i.v. salbutamol	No	No	No	If poor response to nebulised therapy ⁴
Aminophylline	No	No	No	If poor response to i.v. salbutamol ⁵ (only in ICU)
Observation/admission	Observe in ED for 1 hr, then review to decide on discharge	Observe in ED for 1 hr, then review to decide on admission or discharge	Commence admission arrangements after initial assessment. - review after 1 st hr re frequency of further β ₂ – agonist therapy ⁶	Call ICU to assess patient

¹salbutamol (100 mcg/puff) delivered by pMDI and spacer – 6 puffs if < 6yo, 12 puffs if ≥ 6 yo

²salbutamol 0.5% solution delivered by nebuliser

³ipratropium (40mcg/puff) delivered by pMDI and spacer – 2 puffs if < 6 yo, 4 puffs if ≥ 6 yo

⁴salbutamol 5mcg/kg IV over 10 minutes, then infusion 1-5 mcg/kg/minute

⁵aminophylline loading dose 10mg/kg over 1 hr (if already on oral theophylline or i.v. aminophylline measure serum level to decide on requirement for and amount of loading dose); then infusion 1.1 mg/kg/hr if ≤ 9 yrs, 0.7 mg/kg/hr if > 9 years

⁶If improving, reduce frequency β₂-agonist. If no change, continue 20 minutely β₂-agonist. In deteriorating, treat as critical

Oxygen

Recommendation:

All patients with an acute exacerbation of asthma who have an SaO₂ <92% in room air should receive supplemental oxygen (level V).

β₂-agonists

Recommendations:

- Patients with mild acute exacerbations of asthma should initially receive one dose of short acting β₂-agonists via pMDI/spacer (level II).
- Patients with moderate or severe acute exacerbations of asthma should receive short acting β₂-agonists via pMDI/spacer every 20 minutes in the first hour (level II).

Recommended regimen (level II)

- a) 6 puffs via small volume spacer with mask for child <6 years
- b) 12 puffs via large volume spacer for child =6 years
- Patients with critical asthma should be given continuous nebulised salbutamol (undiluted 0.5% solution) (level II).
- Patients who deteriorate on continuous nebulised therapy should be given intravenous salbutamol (loading dose 5 mcg/kg over ten minutes; then infusion 1-5mcg/kg/min) (level II).

Ipratropium bromide

Recommendations:

- Patients with mild to moderate asthma given appropriate doses of inhaled β₂-agonists should not also be given ipratropium bromide during their acute attack (level I).
- Patients with severe exacerbations of asthma should be given inhaled ipratropium at 20 minute intervals in the first hour (level I).
- Patients with critical asthma may be given nebulised ipratropium using multiple doses in the first hour (250-500 mcg/dose) in addition to inhaled β₂-agonists (level II).

Corticosteroids

Recommendations:

- Corticosteroids should be used in conjunction with bronchodilators in patients with acute asthma of moderate, severe or critical severity. The oral route is preferred (prednisolone 1mg/kg/day, maximum 50mg), although the i.v. route (methylprednisolone 1mg/kg/dose 6 hourly) should be used if the patient is severely unwell or the oral preparation is not tolerated (level II).
- The duration of steroid treatment should be up to 3-5 days if the onset is sudden, but a weaning course over 10-14 days should be given if the attack occurs on a background of unstable asthma (level V).

Aminophylline

Recommendations:

- For patients with critical asthma, consideration should be given to the addition of i.v. aminophylline to the regimen of i.v. salbutamol, inhaled ipratropium and i.v. corticosteroids (level II).
- A loading dose of 10mg/kg (max 500mg) should be given over 1 hour, followed by a continuous infusion (1.1mg/kg/hr <9 years, 0.7mg/kg/hr =9 yrs) (level II).
- Theophylline levels should be measured if the patient is already on oral theophylline or i.v. aminophylline measure serum level to decide on requirement for and amount of loading dose (level II).
- Theophylline levels should be monitored once commenced 1 hour and 12 hours after starting (therapeutic range 60-110umol/L) (level II).

Drug Delivery in Acute Asthma

Recommendation:

- Unless extremely unwell, all patients should receive bronchodilators by pMDI and appropriate sized spacer
- Suggested regimen for pMDI and spacer during acute attacks:
children <6 years old: small volume spacer with mask
children =6 years old: large volume spacer (level I)

Admission to Royal Children's Hospital

Recommendations:

- All patients with severe or critical asthma at presentation should be admitted (level V).
- Patients with moderate asthma may require admission, depending on response to therapy, family circumstances, and the presence of high-risk factors (level V).

Transfer from the Emergency Department to the ward

Recommendations:

- Patients who require admission should be transferred to the ward as soon as ward staff are ready to continue care (level V).
- Patients with severe asthma should be transferred to the ward accompanied by ED nursing staff (level V).

Timing of discharge

Recommendation:

A patient with an acute exacerbation of asthma should be considered for discharge from the ED or the ward when they are stable and the family is able to manage the exacerbation at home (level V).

Discharge Planning

Recommendation:

Discharge should include a discharge letter and copy of Action Plan to the child's GP (level V). Correspondence to the patient's GP should include diagnosis, treatment, complications, discharge medication, follow-up arrangements and a copy of the Action Plan (level V).

Patient and Family/Education

Recommendation:

All patients discharged from the ED or the ward should have an individualised written asthma Action Plan (level V).

Discharge Medications

Recommendation:

Patients discharged from hospital or the ED following an acute exacerbation of asthma should receive: inhaled bronchodilators as required (level V). Oral prednisolone (1mg/kg) daily for up to 3 days (for those with moderate or greater severity)(level V).

Follow-up after discharge

Recommendations:

- On discharge, parents should be advised to seek further medical attention (preferably from their GP) should the patient's condition deteriorate or if there is no significant improvement within 48 hours (level V).
- Newly diagnosed patients who have presented with an acute exacerbation (ED or ward) should be referred to a paediatrician for review within 4-6 weeks (level V).
- At discharge all patients should have an outpatient appointment or appropriate follow-up arranged with a paediatrician and/or GP (level V).
- Patients presenting at RCH for acute exacerbations of asthma should be encouraged to establish/maintain a relationship with a GP (level V).

APPENDIX 2 – OTHER GUIDELINES SUMMARY OF RECOMMENDATIONS

These summaries rely heavily on the information found on the National Guideline Clearance House website, www.guidelines.gov

Expert Panel Report 2: guidelines for the diagnosis and management of asthma, 1997, National Institutes for Health.

Sources: Bethesda (MD): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung and Blood Institute; 1997 Jul. 146

Adaptation: not applicable: guideline was not adapted from another source.

Release Date: 1997 Jul (reprinted 1998 Apr, 1999 Mar)

MAJOR RECOMMENDATIONS:

Key points, classification of asthma severity, and stepwise approach to pharmacotherapy excerpted from the guideline by NGC:

Component 1: Measures of Assessment and Monitoring

Initial Assessment Diagnosis of Asthma

- To establish a diagnosis of asthma, the clinician should determine that:
Episodic symptoms of airflow obstruction are present.
Airflow obstruction is at least partially reversible.
Alternative diagnoses are excluded.
- Recommended mechanisms to establish the diagnosis are:
Detailed medical history
Physical exam focusing on the upper respiratory tract, chest, and skin
Spirometry to demonstrate reversibility
Additional studies may be considered to :
Evaluate alternative diagnoses
Identify precipitating factors
Assess severity
Investigate potential complications
- Recommendations are presented for referral for consultation or care to a specialist in asthma care.
- *The classification of asthma severity is given in the following table:*

Clinical Features Before Treatment*			
	Symptoms**	Nighttime Symptoms	Lung Function
STEP 4 Severe Persistent	Continual symptoms Limited physical activity Frequent exacerbations	Frequent	FEV ₁ or PEF ≤60% predicated PEF variability > 30%
STEP 3 Moderate Persistent	<ul style="list-style-type: none"> • Daily symptoms • Daily use of inhaled short-acting beta₂-agonist • Exacerbations affect activity • Exacerbations ≥2 times a week; may last day 	>1 time a week	<ul style="list-style-type: none"> • FEV₁ or PEF >60% - <80% predicted • PEF variability >30%
STEP 2 Mild Persistent	<ul style="list-style-type: none"> • Symptoms >2 times a week but <1 time a day • Exacerbations may affect activity 	>2 times a month	FEV ₁ or PEF ≥80% predicted PEF variability <20%
STEP 1 Mild Intermittent	Symptoms ≤ 2 times a week Asymptomatic and normal PEF between exacerbations Exacerbations brief (from a few hours to a few days); intensity may vary	≤2 times a month	FEV ₁ or PEF ≥80% predicted PEF variability

* The presence of one of the features of severity is sufficient to place a patient in that category. An individual should be assigned to the most severe grade in which any feature occurs. The characteristics noted in this figure are general and may overlap because asthma is highly variable.

** Patient at any level of severity can have mild, moderate, or severe exacerbations. Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms.

Periodic Assessment and Monitoring: Essential for Asthma Management

- The goals of therapy are to:
 - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
 - Maintain (near) "normal" pulmonary function
 - Maintain normal activity levels (including exercise and other physical activity)
 - Prevent recurrent exacerbations of asthma and minimize the need for emergency department visit or hospitalizations
 - Provide optimal pharmacotherapy with least amount of adverse effects
 - Meet patients' and families' expectations of and satisfaction with asthma care

- Periodic assessments and ongoing monitoring of asthma are recommended to determine if the goals of therapy are being met. Measurements of the following are recommended:
 - Signs and symptoms of asthma
 - Pulmonary function
 - Quality of life/functional status
 - History of asthma exacerbations
 - Pharmacotherapy

Patient-provider communication and patient satisfactions

- Clinician assessment and patient self-assessment are the primary methods for monitoring asthma. Population-based assessment is beginning to be used by managed care organizations.
- Spirometry tests are recommended (1) at the time of initial assessment, (2) after treatment is initiated and symptoms and PEF have stabilized, and (3) at least every 1 to 2 years
- Patients should be given a written action plan based on signs and symptoms and/or PEF; this is especially important for patients with moderate-to-severe persistent asthma or a history of severe exacerbations.
- Patients should be trained to recognize symptom patterns indicating inadequate asthma control and the need for additional therapy.
- Recommendations on how and when to do peak flow monitoring are presented.

Component 2: Control of Factors Contributing to Asthma Severity

- Exposure to asthma patients to irritants or allergens to which they are sensitive has been shown to increase asthma symptoms and precipitate asthma exacerbations.
- For at least those patients with persistent asthma on daily medications, the clinician should:
 - Identify allergen exposures
 - Use the patient's history to assess sensitivity to seasonal allergens
 - Use of skin testing or in vitro testing to assess sensitivity to perennial indoor allergens
 - Assess the significance of positive tests in context of the patient's
- Patients with asthma at any level of severity should avoid:
 - Exposure to allergens to which they are sensitive.
 - Exposure to environmental tobacco smoke.
 - Exertion when levels of air pollution are high.
 - Use of beta-blockers.
- Sulfite-containing and other foods to which they are sensitive.
 - Adult patients with severe persistent asthma, nasal polyps, or a history of sensitivity to aspirin or nonsteroidal anti-inflammatories should be counseled regarding the risk of severe and even fatal exacerbations from using these drugs.
 - Patients should be treated for rhinitis, sinusitis, and gastroesophageal reflux, if present.
 - Patients with persistent asthma should be given an annual influenza vaccine.

Component 3: Pharmacologic Therapy

- Underdiagnosis and inappropriate therapy are major contributors to asthma morbidity and mortality.
- Goals of asthma therapy are:
 - Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
 - Maintain (near) "normal" pulmonary function
 - Maintain normal activity levels (including exercise and other physical activity)

- Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meet patients' and families' expectations of and satisfaction with asthma care
- Persistent asthma is most effectively controlled with daily anti-inflammatory therapy.
- A stepwise approach to pharmacologic therapy is recommended:
 - The amount and frequency of medication is indicated by asthma severity and directed toward suppression of increasing airway inflammation.
 - Initiate therapy at a higher level at the onset to establish prompt control and then step down.
 - Continual monitoring is essential to ensure that asthma control is achieved.
 - Step down therapy cautiously once control is achieved and sustained.
 - Step-down therapy is necessary to identify the minimum medication necessary to maintain control.
- Regular follow-up visits (at 1- to 6- month intervals) are essential to maintain control and consider appropriate step down in therapy.
- Therapeutic strategies should be considered in concert with clinician-patient partnership strategies; education of patients is essential for achieving optimal asthma control.
- At each step, patients should be advised to avoid or control allergens, irritants or other factors that make the patient's asthma worse.
- Referral to an asthma specialist for consultation or comanagement is recommended if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care. Referral may be considered for patients who require step 3 care. For patients younger than 3 years of age, referral is *recommended* if the patient requires step 3 or 4 care and should be *considered* if the patient requires step 2 care.
- New medications are available.
 - Long-acting inhaled beta₂-agonists
 - Effective 12-hour bronchodilator
 - Adjunctive therapy to inhaled corticosteroids for maintaining control, especially helpful nighttime symptoms
 - Not to be used to treat acute symptoms or exacerbations
 - Nedocromil
 - Similar role in therapy as cromolyn sodium, with similar safety profile
 - Leukotriene modifiers

- Zafirlukast, leukotriene receptor antagonist, and zileuton 5-lipoxygenase inhibitor
- May be considered alternative daily long-term-control medication for patients with mild persistent asthma who are ≥ 12 years of age, but further clinical experience and study are needed to establish their roles in therapy
- Increased understanding of inhaled corticosteroids notes that:
 - Inhaled corticosteroids are the most potent inhaled anti-inflammatory agent currently available.
 - Early intervention with inhaled corticosteroids can improve asthma control and normalize lung function and may prevent irreversible airway injury.
 - Higher doses of inhaled corticosteroids may be associated with possible, but not predictable, growth retardation in children. The clinical significance of this potential systemic effect has yet to be determined.
 - Issues regarding clinical comparability and bioavailability of different preparations and different delivery systems indicate the need to adjust doses accordingly.
- Management of asthma exacerbations includes:
 - Inhaled beta₂-agonist to provide prompt relief of airflow obstruction
 - Systemic corticosteroid, for moderate-to-severe exacerbations, to suppress and reverse airway inflammation
 - Oxygen to relieve hypoxia for moderate-to-severe exacerbations
 - Monitoring response to therapy with serial measurement of lung function

Stepwise Approach for Managing Asthma in Adults and Children Older Than 5 Years of Age

Goals of Asthma Treatment

- Prevent chronic and troublesome symptoms (e.g., coughing or breathlessness in the night, in the early morning, or after exertion)
- Maintain (near) "normal" pulmonary function
- Maintain normal activity levels (including exercise and other physical activity)
- Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalizations
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meet patients' and families' expectations of and satisfaction with asthma care

Stepwise Approach for managing Asthma in Adults and Children Older Than 5 Years of Age			
Treatment Preferred treatments are in bold print			
	Long-Term Control	Quick Relief	Education
STEP 4 Severe Persistent	<p>Daily medications:</p> <ul style="list-style-type: none"> • Anti-inflammatory; inhaled corticosteroid (high dose) • Long-acting bronchodilator: either long-acting inhaled beta₂-agonist, sustained-release theophylline, or long-acting beta₂-agonist tablets <p>AND</p> <ul style="list-style-type: none"> • Corticosteroid tablets or syrup long term (2mg/kg/day, generally do not exceed 60 mg per day). 	<ul style="list-style-type: none"> • Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. • Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations • Use of short-acting inhaled beta₂-agonists on a daily basis, or increasing use, indicated the need for additional long-term-control therapy. 	<p>Steps 2 and 3 action plus:</p> <ul style="list-style-type: none"> • Refer to individual education/ counseling
STEP 3 Moderate Persistent	<p>Daily medication:</p> <p>Either</p> <ul style="list-style-type: none"> • Anti-inflammatory: inhaled corticosteroid (medium dose) <p>OR</p> <ul style="list-style-type: none"> • Inhaled corticosteroid (low-medium dose) and add a long-acting bronchodilator, especially for nighttime symptoms: either long-acting inhaled beta₂-agonist, sustained release theophylline, or long-acting beta₂-agonist tablets. If needed. Anti-inflammatory: inhaled corticosteroids (medium-high dose) <p>AND</p> <ul style="list-style-type: none"> • Long-acting bronchodilator, especially for nighttime symptoms; either long-acting inhaled beta₂-agonist, sustained-release theophylline, or long-acting beta₂-agonist tablets. 	<ul style="list-style-type: none"> • Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. • Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. • Use of short-acting inhaled beta₂-agonists on a daily basis, or increasing use, indicated the need for additional long-term-control therapy. 	<p>Step 1 action plus:</p> <ul style="list-style-type: none"> • Teach self-monitoring • Refer to group education if available • Review and update self-management plan

<p>STEP 2 Mild Persistent</p>	<p>One daily medication:</p> <ul style="list-style-type: none"> • Anti-inflammatory: either inhaled corticosteroid (low doses) or cromolyn or nedocromil (children usually begin with a trial of cromolyn or nedocromil). • Sustained-release theophylline to serum concentration of 5-15 mcg/mL is an alternative, but not preferred, therapy. Zafirlukast or zileuton may also be considered for patients ≥ 12 years of age, although their position in therapy is not fully established. 	<ul style="list-style-type: none"> • Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. • Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. • Use of short-acting inhaled beta₂-agonists on a daily basis, or increasing use, indicated the need for additional long-term-control therapy. 	
<p>STEP 1 Mild Intermittent</p>	<ul style="list-style-type: none"> • No daily medication needed 	<ul style="list-style-type: none"> • Short-acting bronchodilator: inhaled beta₂-agonists as needed for symptoms. • Intensity of treatment will depend on severity of exacerbation; see component 3-Managing Exacerbations. • Use of short-acting inhaled beta₂-agonists more than 2 times a week may indicate the need to initiate long-term-control therapy. 	<ul style="list-style-type: none"> • Teach basic facts about asthma • Teach inhaler/spacer/holding chamber technique • Discuss roles of medications • Develop self-management plan • Develop action plan for when and how to take rescue actions, especially for patients with a history of severe exacerbations • Discuss appropriate environmental control measures to avoid exposure to known allergens and irritants <p>(See component 4.)</p>
<p>Step down Review treatment every 1 to 6 months; a gradual stepwise reduction in treatment may be possible</p>		<p>Step up If control is not maintained, consider step up. First, review patient medication technique or other factors that contribute to asthma severity</p>	

- The stepwise approach presents general guidelines to assist clinical decisionmaking; it is not intended to be a specific prescription. Asthma is highly variable; clinicians should tailor specific medication plans to the needs and circumstances of individual patients.

- Gain control as quickly as possible; then decrease treatment to the least medication necessary to maintain control. Gaining control may be accomplished by either starting treatment at the step most appropriate to the initial severity of the condition or starting at a higher level of therapy (e.g., a course of systemic corticosteroids or higher or dose of inhaled corticosteroids).
- A rescue course of systemic corticosteroids may be needed at any time and at any step.
- Some patients with intermittent asthma experience severe and life-threatening exacerbations separated by long periods of normal lung function and no symptoms. This may be especially common with exacerbations provoked by respiratory infections. A short course of systemic corticosteroids is recommended.
- At each step, patients should control their environment to avoid or control factors that make their asthma worse (e.g., allergens, irritants); this requires specific diagnosis and education.
- Referral to an asthma specialist for consultation or comanagement is *recommended* if there are difficulties achieving or maintaining control of asthma or if the patient requires step 4 care. Referral may be *considered* if the patient requires step 3 care (see also component 1-Initial Assessment and Diagnosis).
- *A stepwise approach for managing infants and young children (5 years of age and younger) with acute or chronic asthma symptoms is provided in the guideline document.*

Component 4: Education for a Partnership in Asthma Care

- Patient education should begin at the time of diagnosis and be integrated into *every* step of clinical asthma care.
- It is essential that education be provided by *all* members of the health care team. The principal clinician should introduce the key educational messages and negotiate agreements with patients; these messages should be reinforced and expanded by all members of the health care team.
- Teach asthma self-management, tailoring the approach to the needs of each patient. Maintain a sensitivity to cultural beliefs and practices.
- Teach and reinforce at *every* opportunity:
 - Basic facts about asthma
 - Roles of medications
 - Skills: inhaler/spacer/holding chamber use, self-monitoring
 - Environmental and control measures
 - When and how to take rescue actions
- Jointly develop treatment goals.

- To encourage an active partnership, provide all patients with a written daily self-management plan and an action plan for exacerbations. Action plans are especially important for patients with moderate-to-severe persistent asthma and patients with a history of severe exacerbations. Provide appropriate patients with a daily asthma diary.
- Encourage adherence by promoting open communication; individualizing, reviewing and adjusting plans as needed; emphasizing goals and outcomes; and encouraging family involvement

CLINICAL ALGORITHM(S): Clinical algorithms are provided for:

Management of Asthma Exacerbations: Home Treatment;

Management of Asthma Exacerbations: Emergency Department and Hospital-Based Care

DEVELOPER(S): National Heart, Lung, and Blood Institute (U.S.) (NHLBI) - Federal Government Agency (U.S.)

GUIDELINE STATUS: This is the current release of the guideline. Expert Panel Report 2 is the latest report from the National Asthma Education and Prevention Program and updates the 1991 Expert Panel Report. An update is not in progress at this time. However, a science-based committee is monitoring the scientific literature.

GUIDELINE AVAILABILITY: Electronic copies can be downloaded from the [National Heart, Lung and Blood Institute Web site](#). Print copies: Available from NHLBI Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; e-mail: nhlbiic@dgsys.com

COMPANION DOCUMENTS: The following are available:

Asthma Management Model System. Available from the: [National Heart, Lung and Blood Institute Web site](#).

Practical guide for the diagnosis and management of asthma. Available from the: [National Heart, Lung and Blood Institute Web site](#).

Print copies: Available from NHLBI Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; e-mail: nhlbiic@dgsys.com

PATIENT RESOURCES: The following is available:

Facts about controlling your asthma. Patient education brochure. Bethesda, MD: NHLBI, 1997. 8 pages. [English and Spanish language versions are available.]

Electronic copies: Available from the [National Heart, Lung and Blood Institute Web site](#).

Print copies: Available from NHLBI Information Center, P.O. Box 30105, Bethesda, MD 20824-0105; e-mail: nhlbiic@dgsys.com

Emergency Management Of Acute Asthma, 1999, Scottish Intercollegiate Guidelines Network

Key To Evidence Statements And Grades Of Recommendations

The definitions of the types of evidence and the grading of recommendations used in this guideline originate from the US Agency for Health Care Policy and Research and are set out in the following tables.

Statements of evidence
<i>Ia Evidence obtained from meta-analysis of randomised controlled trials.</i>
<i>Ib Evidence obtained from at least one randomised controlled trial.</i>
<i>Ila Evidence obtained from at least one well-designed controlled study without randomisation.</i>
<i>Ilb Evidence obtained from at least one other type of well-designed quasi-experimental study.</i>
<i>III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.</i>
<i>IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.</i>

Grades of Recommendations
A <i>Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)</i>
B <i>Requires the availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation. (Evidence levels Ila, Ilb, III)</i>
C <i>Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)</i>

Good Practice Points
<i>Recommended best practice based on the clinical experience of the guideline development group.</i>

Summary of key points from Emergency Management of Acute Asthma

Features of life threatening asthma include agitation, altered level of consciousness, fatigue, exhaustion, cyanosis, and bradycardia. Air entry is often greatly reduced, leading on occasion to a 'silent chest'.

The peak flow, if recordable, is usually less than 33% of best or predicted.

B If any one of these features is present in a patient with an acute asthma attack, the situation should be treated as life threatening.

Patient Education and Immediate Action

Patients need to know how to recognise worsening symptoms, what immediate action to take in the event of an acute asthma attack, who to contact, and what interim action to take whilst awaiting medical attention. Many patients have uncontrolled asthma for some time prior to the development of a fatal asthma attack.

◆ It is essential that time is set aside to discuss these matters at an early visit to the asthma clinic and that the message is reinforced frequently thereafter.

B The primary care team should ensure that patients and their parents, carers, or partners are aware of the need to seek urgent medical advice from a member of the team in the event of worsening asthma control.

'At Risk' Registers

C Patients who are potentially at risk of severe or life threatening asthma should be identified on an 'at risk' register drawn up in cooperation between general practices and hospital asthma clinics.

C 'At risk' registers should be accessible by the ambulance service, A&E departments, and GP out-of-hours cooperatives.

C The 'at risk' register should not be viewed as all-embracing: all cases of severe asthma should be treated on merit.

Response to Emergency Calls

The ambulance service dispatcher must afford a top priority response to 999 callers reporting breathing difficulties where the patient:

B ◆ is unable to talk in full sentences; or

B ◆ suffers from asthma and is unresponsive to medication; or

C ◆ is a child under 12 with a history of asthma or respiratory problems.

C Local guidelines should be developed in agreement with primary care teams and the ambulance service to establish procedures for achieving a dual response to acute asthma attacks.

- C Ambulance crews transporting patients with features of acute severe or life threatening asthma to A&E departments should notify the ambulance control in advance to request a medical team be mobilised to receive the patient.**

Assessment of Severity

- B The following clinical features should be observed and recorded at the earliest opportunity and reviewed at each subsequent stage:**

- ◆ pulse
- ◆ respiratory rate
- ◆ difficulty in speaking
- ◆ distress
- ◆ agitation
- ◆ level of consciousness.

- B Where possible, patients with acute asthma should have their peak expiratory flow measured prior to the commencement of therapy, but this should not delay urgent treatment in life threatening situations.**

Core Therapies

- A High dose inhaled β_2 agonists should be used as first line treatment in the management of acute asthma.**
- A High flow oxygen ($\geq 60\%$) should be given to all patients with acute severe and life threatening asthma.**
- A Systemic corticosteroids in adequate doses should be given in all cases of acute severe and life threatening asthma.**

Additional Therapies

- A In most cases, β_2 agonists should be given by inhalation. Oral β_2 agonists are not recommended in acute asthma.**
- B Nebulised ipratropium bromide alone should not be used as first line treatment for acute asthma.**
- A In life threatening and acute severe asthma resistant to standard treatment, combination therapy with nebulised ipratropium bromide and nebulised β_2 agonist should be given.**
- A Intravenous aminophylline (IV) should not be used as first line treatment in acute asthma.**
- C IV aminophylline should be used cautiously in patients with life threatening and acute severe asthma not responsive to standard therapy.**

Pre-Hospital Treatment

- ◆ In any acute asthma attack, patients should be encouraged to take 10 activations of their own bronchodilator inhaler device over 5-10 minutes whilst waiting for medical assistance or arrival of the ambulance service.
- A Nebulised β_2 agonist should be given to all patients being transported to hospital via ambulance with an acute asthma attack.**
- B Patients experiencing an acute asthma attack should be given oxygen therapy during transport to hospital.**
- A If the patient has a supply of steroid tablets or if the GP is in attendance, the appropriate dose should be started.**

Assessment and Triage on Arrival

- C The principles of triage should be employed wherever patients are admitted.**
- B All A&E departments and receiving areas should use proformas for the assessment of patients with asthma.**

Emergency Management at the Hospital

Life threatening asthma

- A Maximise inspired oxygen, using the highest available concentration of inspired oxygen via mask with reservoir bag**
- A Nebulised β_2 agonist and nebulised ipratropium bromide**
IV hydrocortisone
- B Consider parenteral β_2 agonist**
- C IV aminophylline infusion**
- C Consider intubation**
- C Refer to ITU.**

Acute severe asthma

- A Nebulised β_2 agonist**
- A High flow oxygen from a mask delivering $\geq 60\%$ inspired oxygen**
- A Oral prednisolone or IV hydrocortisone**
- A Consider nebulised ipratropium bromide if unresponsive or limited response to β_2 agonist**
- C Consider adding IV aminophylline**
- C Monitor closely**
- C Refer to medical ward.**

Moderate uncontrolled

- A β_2 agonist via spacer and mask
- A Oral prednisolone
- B Increase dose of or commence inhaled steroids
- B Assess inhaler technique
- C Monitor closely for 30 minutes:
 - ◆ If deteriorating or no improvement, admit and treat as for acute severe asthma
 - ◆ If improving, discharge home with advice to see GP within 72 hours or return if condition worsens.

Mild uncontrolled

- A Inhaled β_2 agonist
- B Increase dose of or commence inhaled steroids
- B Consider oral prednisolone
- B Assess inhaler technique
- C Observe for 30 minutes:
 - ◆ If improving, discharge home with advice to see GP within 72 hours
 - ◆ If deteriorating or no improvement, consider admission.

Monitoring and Investigation in A&E

- B Regular clinical and peak flow monitoring is essential.
- B All patients with life threatening asthma and patients with acute severe asthma not responding to treatment should have their blood gases measured.
- C Chest x-ray should not be carried out routinely in acute asthma.
 - ◆ Chest x-ray may be considered if there is doubt about the diagnosis, e.g. whether COPD or an inhaled foreign body rather than asthma, or if the patient's condition gives cause for concern.

Discharge Procedures from A&E

Indications for admission to **intensive care facilities** or a **high dependency unit** include patients requiring ventilatory support and those with acute severe or life threatening asthma who are failing to respond to therapy.

Patients with moderate uncontrolled or acute severe asthma may require **ward admission**. Oxygen saturation $\geq 92\%$ on air is an indication for admission in children.

Patients who present with mild or moderate uncontrolled asthma which responds to treatment may be suitable for **discharge from A&E** and continued treatment in the community.

C Patients with asthma should only be considered suitable for discharge if all of the following conditions are met:

- ◆ clinical signs are compatible with home management
- ◆ PEF is improving
- ◆ patients have access to continuing medical care from their general practitioner, A&E department, or a local asthma clinic.

C Prior to discharge, adequate arrangements for further treatment and follow up should be made.

Diagnosis And Management Of Asthma, 2000, Institute For Clinical Systems Improvement.

Sources: Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2000 Jun. 35 p. (29 references)

Adaptation: not applicable: guideline was not adapted from another source.

Release Date: 1998 June (revised 2000 Jun).

Major Recommendations

The recommendations for the diagnosis and management of asthma are presented in the form of an algorithm with 10 components, accompanied by detailed annotations. The major recommendations contained within this algorithm have been summarized by the National Guideline Clearinghouse (NGC). The reader is directed to the original guideline document for further discussion of each of the following topics.

Establish Diagnosis of Asthma

The diagnosis of asthma is based on the patient's medical history, physical examination, pulmonary function tests and laboratory test results. Pulmonary function tests are recommended for the diagnosis of asthma.

Asthma triggers

1. Viral respiratory infections
2. Environmental allergens
3. Exercise, temperature, humidity
4. Occupational and recreational allergens or irritants
5. Environmental irritants (perfume, tobacco smoke, wood burning stoves)
6. Drugs (aspirin, nonsteroidal anti-inflammatory drug, beta blocker) and food (sulfites)

Other historical components

1. Emergency room visits and hospitalization
2. Medication use (especially oral steroids)
3. Lung function, peak expiratory flow rate variability
4. Associated symptoms, e.g., rhinitis, sinusitis, gastroesophageal reflux (GERD)

Laboratory evaluation

1. Accurate spirometry is recommended in every patient greater than or equal to 5 years of age at the time of diagnosis.

2. Additional studies done, tailored to the specific patient

- Allergy testing (skin testing, in vitro specific IgE antibody testing)
- Chest radiography, to exclude alternative diagnosis
- Bronchial provocation testing if spirometry is normal or near normal
- Sinus x-rays or computed tomography scan
- Gastroesophageal reflux evaluation
- Complete blood count with eosinophils, total IgE, sputum exam

Spirometry is generally valuable in children greater than or equal to 5 years of age, however some children cannot conduct the manoeuvre depending on developmental ability. Spirometry measurements (FEV₁, FVC, FEV₁/FVC) before or after the patient inhales a short-acting bronchodilator should be undertaken for patients in whom the diagnosis of asthma is being considered. Airflow obstruction is indicated by reduced FEV₁ and FEV₁/FVC values relative to reference or predicted values. Significant reversibility is indicated by an increase of greater than or equal to 12 percent and 200 mL in FEV after inhaling a short-acting bronchodilator.

Management of Acute Asthma

Symptoms of an acute asthma episode include progressive breathlessness, cough, wheezing or chest tightness. An acute asthma episode is characterized by a decrease in expiratory airflow that can be documented and quantified by measurement of lung function (spirometry or peak expiratory flow rate). Indications for emergency care include:

- Peak flow less than 50% predicted normal
- Failure to respond to a beta agonist
- Severe wheezing or coughing
- Extreme anxiety due to breathlessness
- Gasping for air, sweaty, or cyanotic
- Rapid deterioration over a few hours
- Severe retractions and nasal flaring
- Hunched forward

Patients presenting with acute exacerbation of their asthma should receive prompt evaluation and treatment to improve symptoms in the short term, prevent recurrence of symptoms and provide for follow-up. The following is an outline of management:

Review history and physical exam which may include:

1. History

- Severity of symptoms, limitations, and sleep disturbance
- Duration of symptoms
- Current medical treatment plan
- Rescue medication use:
 - i. Recent use of short acting beta2-agonists
 - ii. Number of bursts of oral steroids in past year
- Review Asthma Action Plan and daily charting of peak flows
- Previous emergency room (ER) visits or hospitalization
- Record triggers:
 - iii. Upper respiratory infection (URI)
 - iv. Bronchitis, pneumonia
 - v. Exposure to allergens or irritants
 - vi. Exercise

2. Physical exam

- Vital signs
- Auscultation of chest
- Peak flow rate or FEV₁
- Use of accessory muscles
- Alertness
- Color

3. Laboratory studies

Treatment with bronchodilators should not be delayed for laboratory studies. Tests which may be useful include:

- O₂ saturation (pulse oximetry)
- Arterial blood gases (ABGs)
- Chest x-ray (CXR)
- Complete blood count (CBC)

- Electrocardiogram (EKG)
- Electrolytes
- Theophylline concentration

4. Assess severity

Assessment is based on history and physical exam.

Treatment

Usual initial treatment is with short-acting nebulized beta-agonist (Albuterol, Terbutaline) 2.5-5 mg q 20 min up to 3 doses.

Alternatives:

Epinephrine

Adults: 0.3-0.5 mg subcutaneously or intramuscularly q 20 min up to 3 doses

Peds: 0.01 mg/kg up to 0.3-0.5 subcutaneously q 20 min up to 3 doses

Terbutaline

Adult: 0.25 mg subcutaneously q 20 min up to 3 doses

Peds: 0.01 mg/kg subcutaneously q 20 min up to 3 doses

Assess Response

Good response:

Peak flow or FEV₁ >70% predicted normal
No wheezing on auscultation

Incomplete response:

Peak flow or FEV₁ 50 - 70% predicted normal
Mild wheezing
Consider hospitalization, particularly for high-risk patients

- Past history of sudden severe exacerbation
- Prior intubation for asthma
- Two or more hospitalizations for asthma in the past year
- Three or more emergency care visits for asthma within the past year
- Hospitalization or an emergency care visit for asthma within the past month
- Use of >2 canisters per month of inhaled short-acting beta2-agonists
- Current use of systemic corticosteroids or recent withdrawal from systemic corticosteroids

- Difficulty perceiving airflow obstruction or its severity
- Comorbidity, as from cardiovascular disease or chronic obstructive pulmonary disease
- Serious psychiatric disease or psychosocial problems
- Low socioeconomic status and urban residence
- Illicit drug use
- Sensitivity to *Alternaria*

Poor response:

Peak flow or FEV₁ <50% predicted normal
No improvement in respiratory distress
Strongly consider hospitalization
Continue inhaled beta-agonist q 60 minutes
Start oral prednisone unless contraindicated

Adult: short course "burst" 40-60 mg/day as single or 2 divided doses for 3 to 10 days

Child: short course "burst" 1-2 mg/ kg day, maximum 60 mg/day for 3 to 10 days

Home Treatment and Revised Asthma Action Plan

Medications

- Inhaled beta-agonist every 2-6 hours
- Initiate or increase anti-inflammatory medication
 - Inhaled corticosteroids
 - Cromolyn/nedocromil
- Strongly consider systemic corticosteroids in patients with acute asthma exacerbation. Corticosteroids aid symptom resolution and prevent asthma relapse.
- Consider leukotriene modifiers
- Antibiotics are not routinely used but may be warranted if patient has signs of acute bacterial infection, fever and purulent sputum

Education

- Teach or check inhaler technique/teach nebulizer use
- Explain medications
- Review action plan
- Monitor peak flow

- Reinforce trigger control

Follow-up

- All patients need return appointment for management of asthma.
- Review and discuss signs or symptoms requiring prompt return.

Interval Evaluation should include the following:

Medical History

- Disruption of usual activities (work, school home)
- Sleep disturbance
- Level of usage of short-acting beta2-agonist
- Interval exacerbation of symptoms (either treated by self or a health care provider)
- Exposure to asthma triggers (especially inhalant allergens)
- Symptoms suggesting co-morbid conditions or alternative diagnosis
- Side effects of medications

Physical Examination

- Assess signs associated with asthma, concurrent illness or medication side effects
- Height in children
- Head, eyes, ears, nose, throat, lungs, heart, skin

Measure Pulmonary Function

It is important to measure pulmonary function at each follow-up visit. The two main methods are spirometry and peak expiratory flow rate. Spirometry recommended:

- For initial diagnosis or to reassess or confirm diagnosis
- After treatment is initiated or changed, and once symptoms and peak expiratory flow rate have stabilized to document attainment of "near normal pulmonary function"
- At least every 1 to 2 years to assess maintenance of airway function; more often as severity indicates

Peak expiratory flow rate:

- Used for follow-up, not for diagnosis

During interval assessment the clinician should question the patient and review records to evaluate the frequency, severity and causes of exacerbation. Triggers that may contribute should be reviewed. All patients on chronic maintenance medication should be questioned about exposure to inhalant allergens.

Consider Specialty Consultation:

- Adults with severe persistent asthma, consider for moderate persistent asthma
- Children with moderate to severe persistent asthma, consider for mild persistent asthma
- Poorly controlled or complex asthma including previous life-threatening asthma exacerbation, or asthma exacerbations requiring more than 2 bursts of oral corticosteroids in 1 year, or asthma complicated by other medical or psychosocial conditions
- Additional diagnostic evaluations and/or testing, e.g., allergy skin testing, bronchoprovocation
- Allergy testing is recommended for patients with persistent asthma who are exposed to perennial indoor allergens
- Evaluation and treatment of allergy, e.g., address occupation-related asthma, environmental counseling, immunotherapy
- Patients who require additional or intensive asthma education not otherwise available

Assessment of Asthma Severity

Step 1: Mild Intermittent

- Symptoms ≤ 2 times a week
- Asymptomatic and normal peak expiratory flow (PEF) between exacerbations
- Exacerbations are brief (few hours to a few days)
- Nighttime symptoms ≤ 2 times a month
- FEV₁ or peak expiratory flow ≥ 80 percent predicted and peak expiratory flow variability ≤ 20 percent

Step 2: Mild Persistent

- Symptoms ≥ 2 times a week but ≤ 1 time a day
- Exacerbations may affect activity
- Nighttime symptoms ≥ 2 times a month
- FEV₁ or peak expiratory flow ≥ 80 percent predicted and peak expiratory flow variability 20-30 percent

Step 3: Moderate Persistent

- Daily symptoms
- Daily use of inhaled short-acting beta2-agonist
- Exacerbations affect activity
- Exacerbations ≥ 2 times a week; may last days
- Nighttime symptoms ≤ 1 time a week
- FEV₁ or peak expiratory flow ≥ 60 percent - ≤ 80 percent predicted
- Peak expiratory flow variability ≥ 30 percent

Step 4: Severe Persistent

- Continual symptoms
- Limited physical activity
- Frequent exacerbations
- Frequent nighttime symptoms
- FEV₁ or peak expiratory flow ≤ 60 percent and peak expiratory flow variability ≥ 30 percent

Step Care of Pharmacologic Treatment

The aim of asthma therapy is to maintain control of asthma with the least amount of medication and hence minimize the risk for adverse effects. The stepwise approach to therapy in which the dose and number of medications and frequency of administration are increased as necessary and decreased when possible is used to achieve this control. Since asthma is a chronic inflammatory disorder of the airways with recurrent exacerbations, therapy for persistent asthma emphasizes efforts to suppress inflammation over the long-term and prevent exacerbations.

Stepwise Approach for Managing Asthma in Adults and Children Older than 5 Years of Age	
Step	Long-Term Control
<p>Step 1 - Mild Intermittent</p> <ul style="list-style-type: none"> • Symptoms ≤ 2 times a week • Asymptomatic and normal peak expiratory flow between exacerbations • Exacerbations are brief (few hours to a few days) • Nighttime symptoms ≤ 2 times a month • FEV₁ or peak expiratory flow $\geq 80\%$ predicted and peak expiratory flow variability $\leq 20\%$ 	<p><i>No daily medications needed</i></p>
<p>Step 2 - Mild Persistent</p> <ul style="list-style-type: none"> • Symptoms ≥ 2 times a week but ≤ 1 time a day • Exacerbations may affect activity • Nighttime symptoms ≥ 2 times a month • FEV₁ or peak expiratory flow ≥ 80 percent predicted and peak expiratory flow variability 20-30% 	<p>Daily medication:</p> <ul style="list-style-type: none"> • Anti-inflammatory: either inhaled corticosteroid (low dose) or cromolyn or nedocromil (children usually begin with a trial of Cromolyn or Nedocromil) • Sustained release theophylline to serum concentration of 5-15 mcg/ mL is an alternative, but not preferred therapy. • Leukotriene modifiers may be considered for persons >6 years of age.
<p>Step 3 - Moderate Persistent</p> <ul style="list-style-type: none"> • Daily symptoms • Daily use of inhaled short-acting beta2-agonists • Exacerbation affects activity • Exacerbations >2 per week, may last days • Nighttime symptoms >1 time a week • FEV₁ or peak expiratory flow $\geq 60\%$ - $\leq 80\%$ predicted • Peak expiratory flow variability $\geq 30\%$ 	<p>Daily medications:</p> <ul style="list-style-type: none"> • Either: Anti-inflammatory: inhaled corticosteroid (medium dose) OR Inhaled corticosteroid (low-medium dose) and add a long-acting bronchodilator, especially for nighttime symptoms: either long-acting inhaled beta2-agonist, sustained-released theophylline, or long-acting beta2-agonist tablets. • If needed: Anti-inflammatory: inhaled corticosteroids (medium-high dose) AND Long-acting bronchodilator, especially for nighttime symptoms; either long-acting inhaled beta2-agonist, sustained-release theophylline or long-acting beta2-agonist tablets.
<p>Step 4 - Severe Persistent</p> <ul style="list-style-type: none"> • Continual symptoms • Limited physical activity • Frequent exacerbations • Frequent nighttime symptoms • FEV₁ or peak expiratory flow $\leq 60\%$ and peak expiratory flow variability $\geq 30\%$ 	<p>Daily medications:</p> <ul style="list-style-type: none"> • Anti-inflammatory inhaled corticosteroids (high dose) AND • Long-acting bronchodilator: either long-acting inhaled beta2-agonist, sustained-release theophylline, or long-acting beta2-agonist tablets AND • Corticosteroid tablets or syrup long-term (2 mg/kg/day, generally do not exceed 60 mg/day)

<p>Step down: Review treatment every 1-6 months; a gradual stepwise reduction in treatment may be possible.</p>	<p>Step up: If control not maintained, consider step up. First review patient medication technique, adherence and environmental control (avoidance of allergens or other factors that contribute to asthma severity)</p>
<p>Quick relief:</p> <ul style="list-style-type: none"> • Short-acting bronchodilator: inhaled beta2-agonists as needed for symptoms • Intensity of treatment will depend on severity of exacerbation. • Use of short-acting inhaled beta2-agonists on a daily basis, or increasing use, indicates the need for additional long-term control therapy. 	
<p>Education:</p> <p>Step 1:</p> <ul style="list-style-type: none"> • Teach basic facts about asthma • Teach inhaler/spacer/holding chamber technique • Discuss role of medications • Develop self-management plan • Develop action plan for when and how to take rescue actions, especially for patient with a history of severe exacerbations. • Discuss appropriate environmental control measures to avoid exposure to known allergens and irritants <p>Step 2:</p> <ul style="list-style-type: none"> • Teach self-monitoring • Refer to group education if available • Review and update self-management plan <p>Step 3:</p> <ul style="list-style-type: none"> • Refer to individual education/counseling 	

Refer to Tables 8B-8D of the original guideline for a detailed discussion of usual dosages for long-term medications, estimated comparative daily dosage for inhaled corticosteroids, and usual dosages for quick-relief medications.

Asthma Education

Patient education is essential for successful management of asthma. It should begin at the time of diagnosis and be ongoing. Patient education includes basic facts about asthma, inhaler technique, written action plan including home peak flow monitoring, environmental control measures, and emphasizing need for regular follow-up visits.

Refer to the original guideline for detailed recommendations on asthma education.

Follow Up

Regularly scheduled follow-up visits are essential to ensure that control is maintained and the appropriate step down in therapy is considered. The exact frequency of clinician visits is a matter of clinical judgment.

CLINICAL ALGORITHM(S): A detailed and annotated clinical algorithm is provided for diagnosis and management of asthma.

DEVELOPER(S): Institute for Clinical Systems Improvement (ICSI) - Private Nonprofit Organization

GUIDELINE STATUS: This is the current release of the guideline. The next scheduled revision will occur within 18 months.

GUIDELINE AVAILABILITY: Electronic copies: Available from the [Institute for Clinical Systems Improvement \(ICSI\) Web site](#).

Print copies: Available from ICSI, 8009 34th Avenue South, Suite 1200, Bloomington, MN 55425; telephone, (952) 814-7060; fax, (952) 858-9675; Web site: www.icsi.org; e-mail: icsi.info@icsi.org.

COMPANION DOCUMENTS: None available

PATIENT RESOURCES: None available

Canadian Asthma Consensus Report, 1999, Canadian Asthma Consensus Group.

Louis-Philippe Boulet,* MD; Allan Becker,† MD; Denis Bérubé,‡ MD; Robert Beveridge,¶ MD; Pierre Ernst,§ MD; on behalf of the Canadian Asthma Consensus Group

Abstract

Objectives: To provide physicians with current guidelines for the diagnosis and optimal management of asthma in children and adults, including pregnant women and the elderly, in office, emergency department, hospital and clinic settings.

Options: The consensus group considered the roles of education, avoidance of provocative environmental and other factors, diverse pharmacotherapies, delivery devices and emergency and in-hospital management of asthma.

Outcomes: Provision of the best control of asthma by confirmation of the diagnosis using objective measures, rapid achievement and maintenance of control and regular follow-up.

Evidence: The key diagnostic and therapeutic recommendations are based on the 1995 Canadian guidelines and a critical review of the literature by small groups before a full meeting of the consensus group. Recommendations are graded according to 5 levels of evidence. Differences of opinion were resolved by consensus following discussion.

Values: Respiriologists, immunoallergists, pediatricians and emergency and family physicians gave prime consideration to the achievement and maintenance of optimal control of asthma through avoidance of environmental inciters, education of patients and the lowest effective regime of pharmacotherapy to reduce morbidity and mortality.

Benefits, harms and costs: Adherence to the guidelines should be accompanied by significant reduction in patients' symptoms, reduced morbidity and mortality, fewer emergency and hospital admissions, fewer adverse side-effects from medications, better quality of life for patients and reduced costs.

Recommendations: Recommendations are included in each section of the report. In summary, after a diagnosis of asthma is made based on clinical evaluation, including demonstration of variable airflow obstruction, and contributing factors are identified, a treatment plan is established to obtain and maintain optimal asthma control. The main components of treatment are patient education, environmental control, pharmacotherapy tailored to the individual and regular follow-up.

Validation: The recommendations were distributed to the members of the Canadian Thoracic Society Asthma and Standards Committees, as well as members of the board of the Canadian Thoracic Society. In addition, collaborating groups representing the Canadian Association of Emergency Physicians, the Canadian College of Family Physicians, the Canadian Paediatric Society and the Canadian Society of Allergy and Immunology were asked to validate the recommendations. The recommendations were discussed at regional meetings throughout Canada. They were also compared with the recommendations of other similar groups in other countries.

Dissemination and implementation: An implementation committee has established a strategy for disseminating these guidelines to physicians, other health professionals and patients and for developing tools and means that will help integrate the recommendations into current asthma care. The plan is outlined in this report.

Sponsors: This is a joint report of the Canadian Thoracic Society, the Canadian Paediatric Society, the Canadian Society of Allergy and Clinical Immunology, the Canadian Association of Emergency Physicians and the Family Physician Asthma Group of Canada. It is sponsored by these organizations, as well as the Lung Association and the College of Family Physicians of Canada. It was supported by 3M Pharmaceuticals, Astra Pharma Inc., Boehringer Ingelheim Canada, Ltd., Glaxo Wellcome Canada Inc., Merck Frosst Canada Inc., Novartis Pharma Canada Inc and Zeneca Pharma Inc.

APPENDIX 3 – PUBLISHED PRIMARY LITERATURE

The CE&HSEU literature review identified the following reports, which have been critically appraised as part of this review, from the primary literature. Their abstracts are copied here for information and arranged according to topic area.

Beta₂-agonists

Cates C J, Rowe BH. Holding chambers versus nebulisers for beta-agonist treatment of acute asthma. Cochrane Database of Systematic Reviews 2001:2.

Background: In acute asthma inhaled beta-agonists are often administered to relieve bronchospasm by wet nebulisation, but some have argued that metered-dose inhalers with a holding chamber (spacer) can be equally effective. In the community setting nebulisers are more expensive, require a power source and need regular maintenance. Objectives: There is controversy as to whether wet nebulisers are better than metered dose inhalers with holding chambers to deliver beta₂-agonist medications for acute asthma. Comparisons of hospital and home use are also of interest. The objective of this review was to assess the effects of holding chambers compared to nebulisers for the delivery of beta₂-agonists for acute asthma. Search strategy: We searched the Cochrane Airways Group trials register and the Cochrane Controlled Trials Register. Selection criteria: Randomised trials in adults and children (from two years of age) with asthma, where holding chamber beta₂-agonist delivery was compared with wet nebulisation. Data collection and analysis: One reviewer applied study inclusion criteria and extracted the data. Trial quality was assessed independently by two reviewers. Missing data were obtained from the authors or estimated. Main results: This review analysed 686 children and 375 adults included in 16 trials. Method of delivery of beta₂-agonist did not appear to affect hospital admission rates. In adults, the odds ratio of holding chamber versus nebuliser was 1.12, 95% confidence interval 0.45 to 2.76. The odds ratio for children was 0.91, 95% confidence interval 0.4 to 2.1. Children's length of stay in the emergency department was significantly shorter when the holding chamber was used, with a weighted mean difference of -0.62 hours, 95% confidence interval -0.84 to -0.40 hours. Adults' length of stay in the emergency department was similar for the two delivery methods. Peak flow and forced expiratory volume were also similar for the two delivery methods. Pulse rate was lower for holding chamber in children, weighted mean difference -8.3% baseline, 95% confidence interval -11.5 to -5.0. Conclusions: Metered-dose inhalers with holding chamber produced outcomes that were at least equivalent to nebuliser delivery. Holding chambers may have some advantages compared to nebulisers for children with acute asthma. (This abstract has been prepared centrally).

Leversha AM, Campanella SG, Aickin RP, Asher MI. Costs and effectiveness of spacer versus nebulizer in young children with moderate and severe acute asthma. Journal of Pediatrics 2000;136(4):497-502.

OBJECTIVE: To compare the costs and effectiveness of albuterol by metered dose inhaler (MDI) and spacer versus nebulizer in young children with moderate and severe acute asthma. **DESIGN:** Randomized, double-blind, placebo-controlled trial in an emergency department at a children's hospital. The participants were children 1 to 4 years of age with moderate to severe acute asthma. Patients assigned to the spacer group received albuterol (600 microg) by MDI by spacer (AeroChamber) followed by placebo by nebulizer (n = 30). The nebulizer group received placebo MDI by spacer followed by 2.5 mg albuterol by nebulizer (n = 30). Treatments were repeated at 20-minute intervals until the patient was judged to need no further doses of bronchodilator, or a total of 6 treatments. **RESULTS:** Clinical score, heart rate, respiratory rate, auscultatory findings, and oxygen saturation were recorded at baseline, after each treatment, and 60 minutes after the last treatment. Baseline characteristics and asthma severity were similar for the treatment groups. The spacer was as effective as the nebulizer for clinical score, respiratory rate, and oxygen saturation but produced a greater reduction in wheezing (P = .03). Heart rate increased to a greater degree in the nebulizer group (11.0/min vs 0.17/min for spacer, P < .01). Fewer children in the spacer group required admission (33% vs 60% in the nebulizer group, P = .04, adjusted for sex). No differences were seen in rates of tremor or hyperactivity. The mean cost of each emergency department presentation was NZ\$825 for the spacer group and NZ\$1282 for the nebulizer group (P = .03); 86% of children and 85% of parents preferred the spacer. **CONCLUSION:** The MDI and spacer combination was a cost-effective alternative to a nebulizer in the delivery of albuterol to young children with moderate and severe acute asthma.

Mandelberg A, Tsechori S, Houry S, Gilad E, Morag B, Priel IE. Is nebulized aerosol treatment necessary in the pediatric emergency department? [see comments]. Chest 2000;117(5):1309-13.

BACKGROUND: Infants and small children admitted to the pediatric emergency department (PED) with acute wheezing episodes (AWE) are currently treated with nebulized wet aerosol (NWA). **OBJECTIVE:** To determine the efficacy of MDI with Nebuchamber (Astra AB; Lund, Sweden), a nonelectrostatic spacer device (NESD), as compared to NWA in the treatment of an unselected population of babies and small children with AWE. **DESIGN:** Randomized, double-blind, placebo-controlled trial. Forty-two children referred to the PED (median age +/- SD, 16 +/- 15 months) with AWE received either placebo MDI through a NESD (four puffs) and salbutamol 0.5 mL (2.5 mg) as a NWA (group I, n = 19), or salbutamol MDI and 0.5 mL of saline solution administered in the same manner as above (group II, n = 23). This treatment was repeated three times every 20 min. **RESULTS:** The respiratory rates (RRs) at baseline were as follows: group I, 45 +/- 11.2 breaths/min; and group II, 52.3 +/- 11.3 breaths/min (p = not significant [NS]). After the first, second, and third interventions, the percent fall from baseline of the RR were as follows: group I, 8.9, 13.1, and 17.9%, respectively; group II, 8.6, 14.6, and 18.6%, respectively. There was no significant difference at any time in the results between the two groups. The clinical scores (CSs) at baseline were as follows: group I, 6.6 +/- 1.3; group II, 6.8 +/- 1.49 (p = NS). After the first, second, and third interventions, the percent fall from baseline of the CS were as follows: group I, 9.1, 17.9,

and 23.2%, respectively; group II, 8.6, 18.9, and 24.7%, respectively. These results, also, did not differ significantly at any time between the two groups. Hospitalization rate and side effects did not differ between the two groups. CONCLUSIONS: We conclude that even in the group of unselected very young children (mean age < 2 years) with AWE, the use of MDI with NESD is at least as effective as the use of NWA. As opposed to data from an adult population, no plateau was reached in the dose-response curve using the above doses over time.

Schuh S, Johnson DW, Stephens D, Callahan S, Winders P, Canny GJ. Comparison of albuterol delivered by a metered dose inhaler with spacer versus a nebulizer in children with mild acute asthma. Journal of Pediatrics 1999;135(1):22-7.

OBJECTIVE: In children with mild acute asthma, to compare treatment with a single dose of albuterol delivered by a metered dose inhaler (MDI) with a spacer in either a weight-adjusted high dose or a standard low-dose regimen with delivery by a nebulizer. STUDY DESIGN: In this randomized double-blind trial set in an emergency department, 90 children between 5 and 17 years of age with a baseline forced expiratory volume in 1 second (FEV₁) between 50% and 79% of predicted value were treated with a single dose of albuterol, either 6 to 10 puffs (n = 30) or 2 puffs (n = 30) with an MDI with spacer or 0.15 mg/kg with a nebulizer (n = 30). RESULTS: No significant differences were seen between treatment groups in the degree of improvement in percent predicted FEV₁ (P = .12), clinical score, respiratory rate, or O₂ saturation. However, the nebulizer group had a significantly greater change in heart rate (P = .0001). Our study had 93% power to detect a mean difference in percent predicted FEV₁ of 8 between the treatment groups. CONCLUSION: In children with mild acute asthma, treatment with 2 puffs of albuterol by an MDI with spacer is just as clinically beneficial as treatment with higher doses delivered by an MDI or by a nebulizer.

Jones A, Rowe B, Peters J, Camargo C, Hammarquist C. Inhaled beta-agonists for asthma in mechanically ventilated patients. Cochrane Database of Systematic Reviews 2001:2.

Background:, A small number of patients with acute severe asthma require intubation and positive pressure ventilation. The beneficial effects of inhaled bronchodilators on acute asthma in spontaneously breathing subjects are well established, but there remain important questions regarding inhaled beta₂-agonists, for patients who are intubated and receiving ventilation., Objectives:, To determine the effects of inhaled beta-agonists on asthmatic patients who require intubation and mechanical ventilation., Search strategy:, Randomised controlled trials were sought from the Cochrane Airways Group Asthma Register. Primary authors and content experts were contacted to identify eligible studies and bibliographies from known reviews and texts were searched., Selection criteria:, Randomised, controlled clinical trials involving adult patients with acute asthma, who were intubated and supported with positive pressure ventilation. Studies were to be included if patients were treated with beta₂-adrenergic agonist agents and there was a comparator group treated with either placebo, no medication, or 'standard' treatment.,

Data collection and analysis:, Two reviewers independently examined all identified articles. The full text of any potentially relevant article was reviewed independently by two reviewers., Main results:, The search yielded 152 abstracts. Of these, four articles were identified as potential trials. None of the four trials met the inclusion criteria for the review., Conclusions:, There are no data from randomised controlled trials to provide evidence for or against current practices regarding the use of inhaled beta2-agonists in asthmatic subjects who are intubated and ventilated.

Emerman C, Cydulka R, McFadden E. Comparison of 2.5 vs 7.5mg of inhaled albuterol in the treatment of acute asthma. Chest 1999;115(1):92-6.

STUDY OBJECTIVE: This study was conducted to determine whether the addition of inhaled ipratropium to inhaled beta-agonist therapy is effective in the treatment of adults with acute asthma exacerbation. **METHODS:** Published reports of randomized, controlled trials assessing the use of ipratropium and beta-agonists in asthma were identified by a search of the MEDLINE, EMBASE, CINAHL, Biological Abstracts on CD, the Cochrane Library, and Current Contents databases. Bibliographies from identified studies and from review articles were manually searched. Published and unpublished reports in English, French, and Italian were identified and assessed for inclusion in the metaanalysis. Randomized, double-blind, placebo-controlled trials were selected in which ipratropium was used as adjunctive therapy to beta-agonists in adult patients with acute asthma exacerbation presenting to a hospital emergency department or similar acute care setting. Data were extracted independently by 2 reviewers. For eligible trials, the mean percent change in peak expiratory flow rate (PEFR), or forced expiratory volume in one second (FEV1), and their SDs were assessed in the ipratropium-treated and control groups. The effect of ipratropium on hospitalization rates and adverse effects were also analyzed. **RESULTS:** Data from 10 studies, reporting on a total of 1,377 patients with asthma, were pooled using a weighted average method. Compared with placebo, the use of ipratropium was associated with a pooled 7.3% improvement in FEV1 (95% confidence interval [CI] 3.8% to 10.9%), corresponding to an absolute improvement in FEV1 in the ipratropium/ beta-agonist group, which was 100 mL (95% CI 50 to 149 mL) above that seen for the group that received beta-agonist without ipratropium. Similarly, the pooled estimate of treatment effect in trials that reported data as PEFR was 22.1% (95% CI 11.0% to 33.2%), corresponding to an absolute peak expiratory flow improvement of 32 L/min (95% CI 16 to 47 L/min) in favor of the ipratropium/ beta-agonist combination group. When these data were combined using effect size as a common measure, the use of ipratropium was associated with a summary effect size of .38 (95% CI .27 to .48). Effect sizes were negatively correlated with baseline mean expiratory flows, suggesting that studies enrolling patients with more severe airflow obstruction showed greater absolute benefits of combination bronchodilator therapy. For the 3 trials reporting hospital admission data (n=1,031), patients receiving ipratropium had a relative risk of hospitalization of .73 (95% CI .53 to .99). The use of ipratropium was not associated with any severe adverse effects when used in conjunction with beta2 -agonists. **CONCLUSION:** There is a modest statistical improvement in airflow obstruction when ipratropium is used as an adjunctive treatment to beta2 -agonists for the treatment of

acute asthma exacerbation. Although the clinical significance of this improvement in airflow obstruction remains unclear, it would seem reasonable to recommend the use of combination ipratropium/ beta-agonist therapy in acute adult asthmatic exacerbations, since the addition of ipratropium seemed to provide physiologic evidence of benefit without risk of adverse effects.

Travers A, Jones AP, Kelly K, Barker SJ, Camargo JCA, Rowe BH. Intravenous beta2-agonists for acute asthma in the emergency department. Cochrane Database of Systematic Reviews 2001:2.

Background:, Inhaled beta-agonist therapy is central to the management of acute asthma. The use of intravenous beta-agonist agents may also be beneficial in this setting., **Objectives:**, To determine the benefit of intravenous (IV) beta2-agonists for severe acute asthma treated in the emergency department., **Search strategy:**, Randomised controlled trials (RCT) were identified using the Cochrane Airways Group Register which is a compilation of systematic searches of MEDLINE, EMBASE, CINAHL, and CENTRAL as well as hand searching of 20 respiratory journals. Bibliographies from included studies and known reviews were also searched. Primary authors and content experts were contacted to identify eligible studies., **Selection criteria:**, Only RCTs were considered for inclusion. Studies were included if patients presented to the emergency department with acute asthma and were treated with IV selective or nonselective beta2-agonists versus placebo, inhaled beta2-agonists, or other standard of care. Pulmonary function, vital signs, arterial gasses, adverse effects, and/or clinical success could be reported as outcome measures. Two reviewers independently selected potentially relevant articles and selected articles for inclusion. Methodological quality was independently assessed using two scoring systems and two reviewers., **Data collection and analysis:**, Data were extracted independently by two reviewers, and confirmed with corresponding authors. Missing data were obtained from authors or calculated from data present in the papers. Trials were combined using a random effects model for odds ratios (OR) or weighted mean differences (WMD) and reported with 95% confidence intervals (95% CI)., **Main results:**, From 746 identified references, 55 potentially relevant articles were identified and 15 were included. The trials included 584 patients. Overall, selective IV beta2-agonist use conferred no advantage over the comparator regimes. For example, it was associated with a lower PEF after 60 mins compared to inhaled beta2-agonist, although the difference was not statistically significant (-24.7 l/min; 95%CI 2.9, -52.3). There was no difference in heart rate (4.5 bpm; 95% CI -4.9, 14.0). In the well performed blinded studies there was no difference in autonomic side effects between treatments (Odds Ratio 2.2 (95%CI 0.9, 5.7)., **Conclusions:**, There is no evidence to support the use of IV beta2-agonists in patients with severe acute asthma. These drugs should be given by inhalation. No subgroups were identified in which the IV route should be considered.

Anticholinergics

Stoodley R, Aaron S, Dales R. The role of ipratropium bromide in the emergency management of acute asthma exacerbation; a metaanalysis of randomized controlled trials. Annals of Emergency Medicine 1999;34(1):8-18.

PURPOSE: The optimal dose of albuterol to use in the treatment of acute asthma has yet to be established. The National Asthma Education and Prevention Program (NAEPP) recommends a starting dose of 2.5 to 5 mg of aerosolized albuterol every 20 min, although European authorities recommend higher doses. The purpose of this study was to compare 2.5 vs 7.5 mg of nebulized albuterol for the treatment of acute asthma.

SUBJECTS: We studied 160 patients presenting to the emergency department with acute asthma. **METHODS:** On enrollment, patients underwent baseline testing, including initial spirometry. All patients received prednisone, 60 mg, orally. Patients then received in a randomized, double-blinded fashion, nebulized albuterol either 2.5 or 7.5 mg every 20 min for a total of three doses. Spirometry was repeated after each of the first two treatments and again 40 min after completion of the three treatments. **RESULTS:** The pretreatment FEV1 was 36.9+/-16.6% of predicted normal in the low-dose group vs 41.5+/-15.4% of predicted normal in the high-dose group (not significant [NS]). The patients in the low-dose group had a 50.3+/-62.6% improvement in FEV1 pretreatment to post-treatment, whereas those in the high-dose group had a 44.6+/-48.2% improvement in FEV1 (NS). There was no difference in the admission rate in the low-dose group (43%) as compared with that of the high-dose group (39%; NS). **CONCLUSION:** We conclude that there is no advantage to the routine administration of doses of albuterol higher than 2.5 mg every 20 min. It is possible that there may be an advantage in the most severely obstructed patients, although this study did not enroll enough patients with very severe asthma to evaluate this. As has been previously demonstrated, patients who subsequently require admission have a diminished response to albuterol. This decreased responsiveness is seen with the first aerosol administration and is unaffected by increasing the dose.

Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. The American Journal of Medicine 1999;107(4):363-370.

PURPOSE: To review the literature to determine whether inhaled ipratropium bromide provides additive benefits to adults with acute asthma who are being treated with beta-agonists in an emergency department. **SUBJECTS AND METHODS:** English-language studies, both published (1978 to 1999) and unpublished, were retrieved using Medline, Science Citation Index, Current Contents, bibliographic reviews of primary research, review articles, consultation with experts, and the register of Medical Editors' Trial Amnesty. Only randomized, double-blind, controlled trials that enrolled patients having an exacerbation of asthma were included. The main outcome measure was pulmonary function; hospital admission rate was also evaluated. **RESULTS:** Ten studies including 1,483 adults with acute asthma were selected (mean age 32 +/- 13 years, 36% men). The overall effect size in SD units of pulmonary function showed a significant benefit from ipratropium (effect size 0.14, 95% confidence interval [CI]: 0.04 to 0.24, P = 0.008). Study-specific effect sizes ranged from 0.03 to 0.63. This pooled effect size was equivalent to a 10% (95% CI: 2% to 18%) increase in forced expiratory volume in 1 second (FEV1) or peak expiratory flow in the ipratropium group compared with the control group. Analysis of the four studies that included patients with extreme obstruction

(FEV1 or peak flow <35% of predicted at presentation) showed substantial improvement with ipratropium therapy (effect size 0.38, 95% CI: 0.09 to 0.67). In the five trials (1,186 patients) that studied the effect of ipratropium administration on hospital admissions, pooled results revealed that ipratropium reduced admission rates significantly (odds ratio 0.62, 95% CI: 0.44 to 0.88, P = 0.007). CONCLUSIONS: The addition of ipratropium to beta-agonist therapy offers a statistically significant, albeit modest, improvement in pulmonary function, as well as a reduction in the rate of hospital

Lanes SF, Garrett JE, Wentworth CE, 3rd, Fitzgerald JM, Karpel JP. The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: a pooled analysis of three trials. Chest 1998;114(2):365-72.

OBJECTIVE: To assess the effect on FEV1 and clinical outcomes of adding ipratropium bromide to salbutamol in the treatment of acute asthma. **METHODS:** We conducted a pooled analysis of three randomized double-blinded clinical trials conducted in the United States, Canada, and New Zealand. The studies enrolled 1,064 patients aged 18 to 55 years who presented at the emergency department with acute asthma. Patients were randomized to treatment with a combination of nebulized 2.5 mg salbutamol plus 0.5 mg ipratropium bromide, or 2.5 mg salbutamol alone. Medications were administered at baseline and, in the US study, at 45 min. FEV1 was measured at baseline, 45 min, and 90 min. Patients were followed up for 48 h after hospital discharge for occurrence of asthma exacerbation and hospitalization. **RESULTS:** Treatment groups were comparable at baseline. Of the 1,064 patients randomized, 1,015 patients (95%) remained in the study for measurement at 45 min, and 961 patients (90%) completed the final measurement at 90 min.

Comparison of overall improvement in FEV1 at 45 min indicated a better response for patients receiving combination therapy (mean difference=43 mL, 95% confidence interval [CI]=-20, 107). The distribution of change in FEV1 was skewed by a small number of patients with extreme values (38 of 1,064=3.6%) that may have been due to unreliable lung function testing. Removing these outliers produced a larger and more precise estimate of effect (mean difference=55 mL, 95% CI=2,107). Because the distribution was skewed, we performed nonparametric analyses that showed evidence of a beneficial effect of combination therapy. The difference between median values at 45 min is 40 mL (Wilcoxon p value=0.03). In addition, 4.9% (95% CI=-1%, 11%) more patients in the combination group achieved at least 20% of their potential improvement, as measured by the difference between their baseline FEV1 and their predicted FEV1. Patients receiving combination therapy had lower risk for each of three clinical outcomes: the need for additional treatment (relative risk [RR]=0.92, 95% CI=0.84, 1.0), risk of asthma exacerbation (RR=0.84, 95% CI=0.67, 1.04), and risk of hospitalization (RR=0.80, 95% CI=0.61, 1.06). **CONCLUSION:** Adding ipratropium bromide to salbutamol in the treatment of acute asthma produces a small improvement in lung function, and reduces the risk of the need for additional treatment, subsequent asthma exacerbations, and hospitalizations. These apparent benefits of adding ipratropium bromide were independent of the amount of beta-agonist that had been used earlier in the attack, and possibly related to a recent upper respiratory tract infection. Confirmatory studies are needed, especially for clinical outcomes.

Rodrigo GJ, Rodrigo C. First-line therapy for adult patients with acute asthma receiving a multiple-dose protocol of ipratropium bromide plus albuterol in the emergency department. *American Journal of Respiratory & Critical Care Medicine* 2000;161(6):1862-8.

We designed a larger, double-blind, randomized, prospective trial to test our hypothesis that patients with acute asthma given combination high dose therapy with ipratropium bromide (IB) and beta(2)-agonists will have greater improvement in pulmonary function and fewer hospital admissions than those given beta(2)-agonists alone. One hundred eighty patients (mean age +/- SD, 34.3 +/- 10.5 yr) who presented to an emergency department (ED) for treatment of an exacerbation of asthma (baseline FEV(1) < 50% of predicted) were assigned in a randomized, double-blind fashion to receive albuterol and placebo (n = 92) or albuterol and IB (n = 88). Both drugs were administered through a metered-dose inhaler and spacer at 10-min intervals for 3 h (24 puffs or 2,880 microg of albuterol and 504 microg of IB each hour). Primary outcome measures were improvement in pulmonary function (FEV(1) or peak expiratory flow [PEF]), and hospital admission rates. In both groups, pulmonary function improved significantly over baseline values (p < 0.01). Subjects who received IB had an overall 20.5% (95% CI: 2.6 to 38.4%) (p = 0.02) greater improvement in PEF and a 48.1% (95% CI: 19.8 to 76.4%) (p = 0.001) greater improvement in FEV(1) from the control group. At the end of protocol (3 h), 39% (n = 36) of patients in the control group and 20% (n = 18) in the IB group were admitted (p = 0.01). The use of high doses of IB reduced the risk of hospital admission 49% (relative risk = 0.51, 95% CI: 0.31 to 0.83). Five (95% CI: 3 to 17) patients would need to be treated with high doses of IB to prevent a single admission. Kaplan-Meier-estimated curves of the proportion of patients who reached the discharge threshold during the 3 h of treatment, showed a significant difference in favor of the IB group (log-rank test = 0.005). A subgroup analysis showed that patients most likely to benefit from the addition of high doses of IB were those with more severe obstruction (FEV(1) <= 30% of predicted) and long duration of symptoms before the ED presentation (>= 24 h). On the contrary, previous use of inhaled beta(2)-agonists did not modify the admission rate and the pulmonary function response to IB. In conclusion, our data support a substantial therapeutic benefit from the addition of IB to albuterol administered in high doses through MDI plus spacer, particularly in patients with FEV(1) less than 30%, and with long duration of symptoms before the ED presentation (>= 24 h).

Nakano Y, Enomoto N, Kawamoto A, Hirai R, Chida K. Efficacy of adding multiple doses of oxitropium bromide to salbutamol delivered by means of a metered-dose inhaler with a spacer device in adults with acute severe asthma. *Journal of Allergy & Clinical Immunology* 2000;106(3):472-8.

BACKGROUND: The efficacy of combination therapy adding multiple doses of anticholinergics to beta(2)-agonists to improve outcome has not been established in adults with acute severe asthma. **OBJECTIVE:** This study was undertaken to compare the outcome of adults with acute severe asthma treated with 4 puffs of salbutamol (100

microg/actuation) every 20 minutes for 3 doses plus 4 puffs of oxitropium bromide (100 microg/actuation) with each of the 3 salbutamol doses versus salbutamol alone administered by means of a metered-dose inhaler with a spacer device. METHODS: A randomized, single-blind, placebo-controlled study was performed in 74 patients between 18 and 55 years old presenting to the emergency department (ED) for treatment of acute asthma with a peak expiratory flow (PEF) of 50% or less than the normal predicted value. The primary endpoint was improvement in PEF over the course. The secondary endpoint was the need for additional ED treatment at 120 minutes. RESULTS: The increase in PEF over the course was significantly greater in the oxitropium plus salbutamol treatment group ($P < .0001$). The mean absolute difference in PEF at 120 minutes for combination therapy compared with salbutamol alone was 37.8 L/min ($P = .001$). In addition, the proportion of need for additional ED treatment was less in the combination group than the group receiving salbutamol alone (odds ratio, 0.32; 95% confidence interval, 0.11-0.90). CONCLUSION: Adding multiple doses of oxitropium bromide to salbutamol delivered by means of a metered-dose inhaler with a spacer device for acute severe asthma produces a significant improvement in lung function and reduces the need for additional ED treatment.

Plotnick L, Ducharme F. Efficacy and safety of combined inhaled anticholinergics and beta-2-agonists in the initial management of acute paediatric asthma. Evidence-Based Medicine 1997;November/December:176. (Abstract unavailable)

Plotnick LH, Ducharme FM. Combined inhaled anticholinergics and beta2-agonists for initial treatment of acute asthma in children. Cochrane Database of Systematic Reviews 2001:2.

Background:, Several randomized controlled trials have examined, with conflicting results, the efficacy of the addition of anticholinergics to beta2 agonists in acute pediatric asthma. The pooling for a larger number of randomized controlled trials may provide not only greater power for detecting group differences and also provide better insight into the influence of patients' characteristics and treatment modalities on efficacy., Objectives:, The aims of this study were to estimate the therapeutic and adverse effects attributable to the addition of inhaled anticholinergics to beta2 agonists in acute pediatric asthma., Search strategy:, We searched Medline (1966 to April 2000), Embase (1980 to April 2000), Cinahl (1982 to April 2000) and reference lists of studies. We also contacted drug manufacturers and trialists., Selection criteria:, Randomised trials comparing the combination of inhaled anticholinergics and beta2 agonists with beta2 agonists alone in children aged 18 months to 17 years with acute asthma., Data collection and analysis:, Assessments of trial quality and data extraction were done by two reviewers independently., Main results:, Of the 40 identified trials, 13 were relevant and eight of these were of high quality. The addition of a single dose of anticholinergic to beta2 agonists did not reduce hospital admission [RR=0.93 (95% CI: 0.65, 1.32)]. However, significant group differences in lung function supporting the combination of anticholinergics and beta2-agonists were observed 60 minutes [SMD=0.57 (95% CI:0.21,

0.93)] and 120 minutes [SMD=0.53 (95% CI: 0.17, 0.90)] after the dose of anticholinergic. In contrast, the addition of multiple doses of anticholinergics to beta2 agonists reduced the risk of hospital admission by 25% [RR=0.75 (95% CI: 0.62,0.89)] in children with predominantly moderate and severe exacerbations. Twelve (95% CI: 8, 32) children would need to be treated to avoid one admission. When restricting this strategy to children with severe exacerbations, seven (95% CI: 5, 20) children need to be treated to avoid an admission. At 60 minutes after the last anticholinergic inhalation, a weighted mean group difference of 9.68 in change in % predicted FEV1 [95% CI:5.70, 13.68] favored anticholinergic use. In the two studies where anticholinergics were systematically added to every beta2 agonist inhalation, irrespective of asthma severity, no group differences were observed for the few available outcomes. There was no increase in the amount of nausea, vomiting or tremor in patients treated with anticholinergics.,
Conclusions:, A single dose of an anticholinergic agent is not effective for the treatment of mild and moderate exacerbations and is insufficient for the treatment of severe exacerbations. Adding multiple doses of anticholinergics to beta2 agonists appears safe, improves lung function and would avoid hospital admission in 1 of 12 such treated patients. Although multiple doses should be preferred to single doses of anticholinergics, the available evidence only supports their use in school-aged children with severe asthma exacerbation. There is no conclusive evidence for using multiple doses of anticholinergics in children with mild or moderate exacerbations.

Corticosteroids

Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database of Systematic Reviews 2001:2.

Background:, The airway edema and secretions associated with acute asthma are most effectively treated with anti-inflammatories such as corticosteroids delivered by inhaled, oral, intravenous or intra-muscular routes. There is an unresolved debate about the use of systemic corticosteroids in the early treatment of acute asthma for emergency department patients., Objectives:, To determine the benefit of treating patients with acute asthma with systemic corticosteroids within an hour of presenting to the emergency department (ED)., Search strategy:, Randomised controlled trials were identified from the Cochrane Airways Group Asthma Register. Primary authors and content experts were contacted to identify eligible studies. Bibliographies from included studies and known reviews were searched., Selection criteria:, Only randomised controlled trials (RCTs) or quasi-randomised trials were eligible for inclusion. Studies were included if patients presenting to the ED with acute asthma were treated with IV/IM or oral corticosteroids (CS) vs. placebo within 1 hour of arrival and either admission rate or pulmonary function results were reported., Data collection and analysis:, Trial selection, data extraction and quality assessment were carried out independently by two reviewers, and confirmed with corresponding authors., Main results:, Twelve studies involving 863 patients (435 corticosteroids; 428 placebo) were included. Early use of CS for acute asthma in the ED significantly reduced admission rates (N = 11; pooled OR: 0.40, 95% CI: 0.21 to 0.78). This would correspond

with a number needed to treat of 8 (95% CI: 5 to 21). This benefit was more pronounced for those not receiving systemic CS prior to ED presentation (N = 7; OR: 0.37, 95% CI: 0.19 to 0.70) and those with more severe asthma (N = 7; OR: 0.35, 95% CI: 0.21 to 0.59). Oral CS therapy in children was particularly effective (N = 3; OR: 0.24, 95% CI: 0.11 to 0.53); no trials in adults used the oral route. Side effects were not significantly different between corticosteroid treatments and placebo. A further search was conducted in September 2000 which did not yield any further trials. Conclusions: Use of corticosteroids within 1 hour of presentation to an ED significantly reduces the need for hospital admission in patients with acute asthma. Benefits appear greatest in patients with more severe asthma, and those not currently receiving steroids. Children appear to respond well to oral steroids.

Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database of Systematic Reviews 2001:2.

Background: Acute asthma is responsible for many emergency department visits annually. Between 12-16% will relapse to require additional interventions within two weeks of ED discharge. Treatment of acute asthma is based on rapid reversal of bronchospasm and reducing airway inflammation and this review examines the evidence for using systemic corticosteroids to improve outcomes after discharge from the ED. Objectives: To determine the benefit of corticosteroids (oral, intramuscular, or intravenous) for the treatment of asthmatic patients discharged from an acute care setting (i.e. usually the emergency department) after assessment and treatment of an acute asthmatic exacerbation. Search strategy: The Cochrane Airways Group "Asthma and Wheez* RCT" register was searched using the terms: a) Asthma OR Wheez* b) Glucocorticoid OR Steroid* AND c) Exacerbat* OR Relapse* OR Emerg*. In addition, authors of all included studies were contacted to determine if unpublished studies which met the inclusion criteria were available. Bibliographies from included studies, known reviews and texts were also searched for additional citations. Selection criteria: Only randomized controlled trials were eligible for selection. Studies were included in this review if they dealt with the outpatient treatment of asthmatic exacerbations using glucocorticoids at discharge and reported either relapse rate or PFTs. Two independent reviewers first identified potentially relevant studies and then selected articles for inclusion. Methodological quality was assessed independently by two reviewers. Agreement was assessed using kappa (k) statistics. Data collection and analysis: Data were extracted independently by two reviewers; authors were contacted to verify the extracted data and clarify missing information. When author contact was unsuccessful, missing data were estimated from graphs where possible. Sensitivity, sub-group and overall analyses were performed using the Cochrane Review Manager. Main results: A search that yielded 229 references identified 169 (73%) original publications. Reviewers identified 8 studies for potential inclusion (k =0.76); 18 references were added by searching publication reference lists and contact with authors. Of these 26 articles, a total of 7 were included in the overview. Two studies used intramuscular corticosteroids, five studies used oral corticosteroids. Significantly fewer patients in the corticosteroid group

relapsed to receive additional care in the first week (odds ratio (OR) 0.35; 95% confidence interval (CI): 0.17, 0.73). This favourable effect was maintained over the first 21 days (OR 0.33; 95% CI: 0.13, 0.82). Patients receiving corticosteroids had less need for beta-agonists (weighted mean difference (WMD) -3.3 activations/day; 95% CI: -5.5, -1.0). Changes in pulmonary function tests (SMD 0.045; 95% CI: -0.47, 0.56) and side effects (SMD 0.03; 95% CI: -0.38, 0.44) in the first 7-10 days, while rarely reported, showed no differences between the treatment groups. Statistically significant heterogeneity was identified for the side effect results; all other outcomes were homogeneous. It appears that IM corticosteroids are similarly efficacious to a 7-10 day tapering course of oral agents. From these results, as few as 13 patients need to be treated to prevent relapse to additional care after an exacerbation of asthma. Conclusions: A short course of corticosteroids following assessment for an acute exacerbation of asthma significantly reduces the number of relapses to additional care and decreases beta-agonist use without an apparent increase in side effects. Intramuscular corticosteroids appear as effective as oral agents.

Edmonds ML, Camargo JCA, Pollack Cv, Jr., Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. Cochrane Database of Systematic Reviews 2001:2.

Background: Systemic corticosteroid therapy is central to the management of acute asthma. The use of ICS may also be beneficial in this setting. Objectives: To determine the benefit of ICS for the treatment of patients with acute asthma managed in the emergency department (ED). Search strategy: Randomised controlled trials (RCTs) were identified from the Cochrane Airways Review Group register. Bibliographies from included studies, known reviews, and texts also were searched. Selection criteria: Only RCTs or quasi-randomised trials were eligible for inclusion. Studies were included if patients presented with acute asthma to the ED or its equivalent, and were treated with ICS or placebo, in addition to standard therapy. Two reviewers independently selected potentially relevant articles, and then independently selected articles for inclusion. Methodological quality was independently assessed by two reviewers. Data collection and analysis: Data were extracted independently by two reviewers if the authors were unable to verify the validity of extracted information. Missing data were obtained from the authors or calculated from other data presented in the paper. Main results: Seven trials were selected for inclusion, but data were not available for one of them. In the six usable trials, (4 adult, 2 paediatric), a total of 352 patients were studied (179 ICS, 173 non-ICS treated). Patients treated with ICS were less likely to be admitted to hospital (OR: 0.33; 95% CI: 0.17, 0.64). This benefit was confined to patients not receiving concomitant systemic steroids (CS). Patients receiving concomitant CS showed a similar, but non-significant, trend towards reduced admissions compared to placebo treatment (OR 0.45; 95% CI: 0.18, 1.14). Patients receiving ICS also demonstrated small, significant improvements in peak expiratory flows (PEFR WMD: 8%; 95% CI: 3, 13 %) and forced expiratory volumes (FEV1 WMD: 5%; 95% CI: 0.4, 10 %). The treatment was well tolerated, with few reported adverse side effects. A secondary analysis compared ICS alone vs CS alone; in the four trials included, there was significant heterogeneity between

the study results for admission rates which precluded meaningful pooling of the study results., Conclusions:, Inhaled steroids reduced admission rates in patients with acute asthma, but it is unclear if there is a benefit of ICS when used in addition to systemic corticosteroids. There is insufficient evidence that ICS therapy results in clinically important changes in pulmonary function or clinical scores when used in acute asthma. Similarly, there is insufficient evidence that ICS alone is as effective as CS. Further research is needed to clarify if there is a benefit of ICS when used in addition to CS.

Edmonds M, Carmargo CJ, Saunders L, Brenner B, Rowe B. Inhaled steroids in acute asthma following emergency department discharge. The Cochrane Library 2000(3):CD002316.

BACKGROUND: Patients with acute asthma treated in the emergency department are frequently treated with inhaled beta-agonists and corticosteroids (CS) after discharge. The use of inhaled CS (ICS) following discharge may also be beneficial in acute asthma. **OBJECTIVES:** To determine the effect of inhaled corticosteroids (ICS) on outcomes in the treatment of acute asthma following discharge from the emergency department (ED). **SEARCH STRATEGY:** Randomised controlled trials (RCTs) were identified from the Cochrane Airways Review Group register which consists of systematic searches of EMBASE, MEDLINE and CINAHL databases supplemented by hand searching of 20 respiratory journals. In addition, abstracts from conferences were searched; primary authors and pharmaceutical companies were contacted to identify eligible studies. Bibliographies from included studies, known reviews, and texts also were searched. **SELECTION CRITERIA:** Only RCTs or quasi RCTs were eligible for inclusion. Studies were included if patients were treated for acute asthma in the ED or its equivalent, and following ED discharge were treated with ICS therapy either in addition to, or as a substitute for, oral corticosteroids (CS). Two reviewers independently assessed articles for potential relevance, final inclusion, and methodological quality - to "expand" the search. We didn't include any in the end) **DATA COLLECTION AND ANALYSIS:** Data were extracted independently by two reviewers if the authors were unable to verify the validity of information. Several authors and pharmaceutical companies provided unpublished data. The data were analysed using the Cochrane Review Manager 4.0.4. **MAIN RESULTS:** Ten trials were selected for inclusion. Three of these trials, involving a total of 909 patients, compared ICS plus CS Vs CS therapy alone. There was no demonstrated benefit of ICS therapy when used in addition to CS therapy in the trials. Relapses were reduced, but not significantly, with the addition of ICS therapy (OR: 0.68; 95% CI: 0.46 to 1.02). As well, no differences were demonstrated between the two groups for relapses requiring admission, quality of life, symptom scores, or adverse effects. Seven trials, involving a total of 1204 patients, compared high-dose ICS therapy alone Vs CS therapy alone after ED discharge. There were no significant differences demonstrated between ICS therapy alone and CS therapy alone for relapse rates (OR: 1.00; 95% CI: 0.66 to 1.52) or in the secondary outcomes of beta-agonist use, symptoms, or adverse events. However, the sample size was not adequate to confidently exclude the possibility of either treatment being significantly inferior, and severe asthmatics were excluded from these trials. **REVIEWER'S CONCLUSIONS:** There is insufficient evidence that ICS

therapy provides additional benefit when used in combination with standard CS therapy upon ED discharge for acute asthma. There is some evidence that high-dose ICS therapy alone may be as effective as CS therapy when used in mild asthmatics upon ED discharge; however, there is a significant possibility of a type II error in drawing this conclusion. Further research is needed to clarify whether ICS therapy should be employed in acute asthma treatment in the ED or following ED discharge. [References: 54]

Qureshi F, Zaritsky A, Poirier M. Comparative efficacy of oral dexamethasone versus oral prednisone in acute pediatric asthma. Journal of Pediatrics 2001;139(1):20-26.

OBJECTIVE: The objective was to determine whether 2 days of oral dexamethasone (DEX) is more effective than 5 days of oral prednisone/prednisolone (PRED) in improving symptoms and preventing relapse in children with acute asthma. **STUDY DESIGN:** This was a prospective randomized trial of children (2 to 18 years old) who presented to the emergency department with acute asthma. PRED 2 mg/kg, maximum 60 mg (odd days) or DEX 0.6 mg/kg, maximum 16 mg (even days) was used. At discharge children in the PRED group were prescribed 4 daily doses (1 mg/kg/d, maximum 60 mg); children in the DEX group received a prepackaged dose (0.6 mg/kg, maximum 16 mg) to take the next day. The primary outcome was relapse within 10 days. **RESULTS:** When DEX was compared with PRED, relapse rates (7.4% of 272 vs 6.9% of 261), hospitalization rates from the emergency department (11% vs 12%) or after relapse (20% vs 17%), and symptom persistence at 10 days (22% vs 21%) were similar. In the PRED group more children were excluded for vomiting in the emergency department (3% vs 0.3%; $P = .008$), more parents were noncompliant (4% vs. 0.4%; $P = .004$), and more children missed \geq 2 days of school (19.5% vs. 13.2%; $P = .05$). **CONCLUSION:** In children with acute asthma, 2 doses of dexamethasone provide similar efficacy with improved compliance and fewer side effects than 5 doses of prednisone.

Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. Cochrane Database of Systematic Reviews 2001:2.

Background: Corticosteroids are currently used routinely in the management of acute severe asthma. The optimal dose and route of administration continues to be debated. Some investigators have reported a greater benefit of higher doses of corticosteroids in the management of severe asthma, while others have not. **Objectives:** To determine whether higher doses of systemic corticosteroids (oral, intravenous or intramuscular) are more effective than lower doses in the management of patients with acute severe asthma requiring hospital admission. **Search strategy:** Randomised controlled trials were identified from the Cochrane Airways Group Asthma Register. In addition, primary authors and content experts were contacted to identify eligible studies. **Bibliographies** from included studies, known reviews and texts were also searched. **Selection criteria:** Studies were selected for inclusion in the review if they met the following broad inclusion criteria: described as randomised controlled trials, included patients with acute severe asthma, compared different doses of corticosteroids (any route) in 2 or more treatment arms, and had a minimum period of follow up of 24 hours. Two reviewers independently

assessed the studies for inclusion and disagreement was resolved by third party adjudication., Data collection and analysis:, Data were extracted independently by two reviewers if the authors were unable to verify the validity of information. Missing data were obtained from authors or calculated from other data presented in the paper. The data were analysed as weighted mean differences (WMD) for primary pulmonary function outcomes using a fixed effects model. For the purposes of the review, three broad categories of corticosteroid dose (equivalent dose of methylprednisolone in 24 hours) were defined in advance: low dose (≤ 80 mg), medium dose (> 80 mg and ≤ 360 mg) and high dose (> 360 mg). There were thus 3 main comparison groups: low versus medium dose, medium versus high dose and low versus high dose., Main results:, Nine trials were included; a total of 344 adult patients have been studied (96 with low dose, 85 with medium dose and 163 with high dose corticosteroids). Only 6 trials provided sufficient data for the meta-analysis. There were no clinically or statistically significant differences detected in % predicted FEV1 among comparison groups after 24, 48 or 72 hours. At 48 hours, the weighted mean difference was -3.3% predicted (95% confidence interval -12.4 to + 5.8) for the low vs medium dose comparison, -1.9% predicted (95% CI -8.1 to + 4.3) for the medium vs high dose comparison and + 0.5% predicted (95% CI -7.8 to + 8.8) for the low vs high dose comparison. There appeared to be no significant differences in side effects or rates of respiratory failure among the varying doses of corticosteroids., A further search was conducted on 3rd August 2000. No new trials were identified., Conclusions:, No differences were identified among the different doses of corticosteroids in acute asthma requiring hospital admission. Low dose corticosteroids (≤ 80 mg/day of methylprednisolone or ≤ 400 mg/day of hydrocortisone) appear to be adequate in the initial management of these adult patients. Higher doses do not appear to offer a therapeutic advantage.

Other medications

Belda J, Parameswaran K, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Cochrane Database of Systematic Reviews 2001:2.

Background:, Aminophylline has been used extensively in acute asthma, but its role is unclear especially with respect to any additional benefit when added to beta2-agonists., Objectives:, To determine the magnitude of effect of the addition of intravenous aminophylline to beta2-agonists in adult patients with acute asthma treated in the emergency setting., Search strategy:, Studies were identified from the following sources: The Cochrane Airways Group register (derived from MEDLINE, EMBASE, CINAHL standardised searches), hand searched respiratory journals and meeting abstracts. Potentially relevant articles were obtained, and their bibliographic lists were hand searched for additional articles. The search included searches of the database up to 1999., Selection criteria:, Randomised controlled trials comparing intravenous aminophylline versus placebo in adults with acute asthma and treated with beta-adrenergic agonists. Patients could be treated with or without corticosteroids or other bronchodilators., Data collection and analysis:, A total of 210 abstracts were identified. Two independent reviewers selected a total of 27 eligible studies for possible inclusion, in which quality

assessment was performed and a third reviewer was used to adjudicate disagreements. Peak expiratory flow (PEFR) and forced expiratory volume in the first second (FEV1) data were extracted and entered in Review Manager from these studies. Information not obtained from the authors was estimated from graphs. All data were entered and double checked by two reviewers. Results are reported as weighted mean differences (WMD) or odds ratio (OR), both with 95% confidential intervals (CI)., Main results:., Fifteen studies were included. Overall, the quality of the studies was only moderate; concealment of allocation was assessed as clearly adequate in only seven (45%) of the trials. The doses of aminophylline and other medications and the severity of asthma varied between studies., There was no statistically significant effect of aminophylline on airflow outcomes at any time period. The aminophylline treated group had higher values of PEFR at 12 (PEFR 8 L/min or 2.3%) and 24 hours (PEFR 22 L/min or 6.4%), but these were not significant ($p>0.05$). Two subgroup analyses were performed by grouping studies according to mean baseline airflow limitation ($n = 11$ studies) and the use of any steroids ($n = 9$ studies). There was no relationship between baseline airflow limitation nor the use of steroids on the effect of aminophylline. Aminophylline treated patients reported more palpitations/arrhythmias (OR: 2.9; 95% CI: 1.5 to 5.7) and vomiting (OR: 4.2; 95% CI 2.4 to 7.4), but no difference was found in tremor or hospital admissions., Conclusions:., In acute asthma, the use of intravenous aminophylline did not result in any additional bronchodilation compared to standard care with beta-agonists. The frequency of adverse effects was higher with aminophylline. No subgroups in which aminophylline might be more effective could be identified. These results should be added to consensus statements and guidelines.

Mitra A, Bassler D. Intravenous aminophylline for acute severe asthma in children over 2 years using inhaled bronchodilators. Cochrane Database of Systematic Reviews 2001(4).

BACKGROUND: Intravenous aminophylline was the bronchodilator of choice for many years until supplanted by more effective bronchodilators in the treatment of acute paediatric asthma. Recently there has been renewed interest in this therapy for children with acute severe asthma. **OBJECTIVES:** To determine whether addition of intravenous aminophylline produces a beneficial effect in children with acute severe asthma receiving oxygen, maximised inhaled bronchodilators and oral/intravenous glucocorticoids. **SEARCH STRATEGY:** The Cochrane Airways Group register of trials (based on MEDLINE, EMBASE, CINAHL and hand searched respiratory journals) and reference lists of relevant articles were used to identify relevant studies. The latest search was carried out in October 2000. **SELECTION CRITERIA:** Only randomised-controlled trials comparing intravenous aminophylline with placebo in children treated with inhaled bronchodilators and systemic glucocorticoids for acute asthma were considered for this review. **DATA COLLECTION AND ANALYSIS:** Full text of 35 trials were anonymized for author, date and publication and two blinded independent reviewers selected eligible studies for inclusion. Disagreement was resolved through consensus. Seven trials met the inclusion criteria. Attempts were made to contact authors to verify accuracy. Results were reported as weighted mean differences (WMD) or relative risk (RR) with 95% confidential intervals (CI). **MAIN RESULTS:** Patients in these trials were predominantly

school-aged children hospitalised for acute severe asthma with a baseline FEV1 at 35-40% of predicted and/or a baseline Pulmonary Index of 6-7. Aminophylline significantly improved percentage predicted FEV1 by 6 - 8 hours (WMD 8.4%; 95% CI: 0.82, 15.92%). The effect was maintained for 24 hours. Improvements were also seen in symptom scores at 6-8 hours (WMD= -0.71; 95% CI: -0.82,-0.60). There was no reduction in hospital stay or in number of nebulisers required. Vomiting was more likely with aminophylline therapy (Relative Risk = 3.69; 95% CI: 2.15, 6.33). REVIEWER'S CONCLUSIONS: Addition of intravenous aminophylline should be considered early in the treatment of children hospitalised with acute severe asthma with sub optimal response to the initial inhaled bronchodilator therapy. Although the improvement is sustained for 24 hours, there is no apparent reduction in length of hospital stay or number of inhaled beta2-agonists nebulisations. Treatment with aminophylline is associated with an increased risk of vomiting.

Rowe B, Bretzlaff J, Bourdon C, Bota G, Camargo CJ. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. The Cochrane Library 2001(2):14.

Background:, Treatment of acute asthma is based on rapid reversal of bronchospasm and arresting airway inflammation. There is some evidence that intravenous magnesium can provide additional bronchodilation when given in conjunction with standard bronchodilating agents and corticosteroids. No systematic review of this literature has been completed on this topic., Objectives:, To examine the effect of additional intravenous magnesium sulfate in patients with acute asthma managed in the emergency department., Search strategy:, Randomised controlled trials were identified from the Cochrane Airways Review Group register. Bibliographies from included studies, known reviews and texts were searched. Primary authors and content experts were contacted., Selection criteria:, Randomised controlled trials or quasi-randomised trials were eligible for inclusion. Studies were included if patients presented with acute asthma and were treated with IV magnesium sulfate vs placebo., Data collection and analysis:, Data were extracted and methodological quality was assessed independently by two reviewers. Missing data were obtained from authors., Main results:, Seven trials were included (5 adult, 2 pediatric). A total of 665 patients were involved. Patients receiving magnesium sulfate demonstrated non-significant improvements in peak expiratory flow rates when all studies were pooled (weighted mean difference: 29.4 L/min; 95% confidence interval: -3.4 to 62). In studies of people with severe acute asthma, peak expiratory flow rate improved by 52.3 L/min (95% confidence interval: 27 to 77.5). The forced expiratory volume in one second also improved by 9.8 % predicted (95% confidence interval: 3.8 to 15.8). Overall, admission to hospital was not reduced, odds ratio: 0.31 (95% confidence interval: 0.09 to 1.02). In the severe subgroup, admissions were reduced in those receiving magnesium sulfate (odds ratio: 0.10, 95% confidence interval: 0.04 to 0.27). No clinically important changes in vital signs or adverse side effects were reported., Conclusions:, Current evidence does not support routine use of intravenous magnesium sulfate in all patients with acute asthma presenting to the emergency department.

Magnesium sulfate appears to be safe and beneficial in patients who present with severe acute asthma.

Rodrigo G, Rodrigo C, Pollack CJ, Travers A. Helium oxygen mixture for nonintubated acute asthma patients. The Cochrane Library 2001(Issue 1).

BACKGROUND: Helium and oxygen mixtures (heliox), have been used sporadically in respiratory medicine for decades. Their use in acute respiratory emergencies such as asthma has been the subject of considerable debate. Despite the lapse of more than 60 years since it was first proposed, the role of heliox in treating patients with acute severe asthma is unclear. **OBJECTIVES:** To determine the effect of the addition of heliox to standard medical care on the course of acute asthma, as measured by pulmonary function testing and clinical endpoints. **SEARCH STRATEGY:** Randomized controlled trials were identified from the Cochrane Airways Group Asthma Register which is a compilation of systematic searches of CINAHL, EMBASE, MEDLINE, and CENTRAL and hand searching of the 20 most productive respiratory care journals. In addition, primary authors and experts were contacted to identify eligible studies. References from included studies, known reviews and texts were also searched. **SELECTION CRITERIA:** Inclusion criteria were: 1) randomized, single or double blind, controlled trials; 2) children or adults with a clinical diagnosis of acute asthma seen in emergency departments or equivalent acute care settings; 3) compared treatment with inhaled heliox compared with a control (oxygen or air). Two reviewers independently assessed the studies for inclusion and quality assessment; disagreement was resolved by a third reviewer and consensus. **DATA COLLECTION AND ANALYSIS:** Data from all included trials were combined using weighted mean differences (WMD), with 95% confidence intervals (95% CI) in a random effects model. Homogeneity of effect sizes were tested with the Dersimonian and Laird method with $p < 0.1$ as the cut point for significance. Sensitivity analyses were performed on age (adults vs. children), different helium-oxygen mixtures and methodological quality. **MAIN RESULTS:** A total of 4 randomized controlled trials were selected for inclusion with a total of 288 acute asthma patients. Three studies involved adults and one study dealt solely with children. Two were of low quality. The main outcome variable was spirometric measurements (PFT % predicted) in all trials. Pooling the four trials showed no significant differences (WMD = -1.61; 95% CI: -6.64 to 3.41). All pulmonary function tests were recorded during heliox administration (15 to 60 min). There was no evidence of heterogeneity between studies. There were no significant differences between groups when adults vs. children, high vs. low quality, and high vs. low heliox dose studies were compared. The findings were the with a fixed effects model. **REVIEWER'S CONCLUSIONS:** The existing evidence does not provide support for the administration of helium-oxygen mixtures to patients presenting to the emergency department with moderate to severe acute asthma. Heliox treatment does not have a role in the initial treatment of patients with acute asthma. These conclusions are based upon between-group comparisons and small studies. Additional research in this setting may be warranted. [References: 15]

APPENDIX 4

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Levels of evidence used by the CE&HSE Unit search

As defined by "How to use the evidence: assessment and application of scientific evidence" (National Health & Medical Research Council, Canberra, 2000):

- | | |
|-----------|--|
| Level I | Evidence obtained from a systematic review (or meta-analysis) of all relevant randomised controlled trials. |
| Level II | Evidence obtained from at least one randomised controlled trial. |
| Level III | <ol style="list-style-type: none"> 1 Evidence obtained from pseudorandomised controlled trials (alternate allocation or some other method). 2 Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case control studies or interrupted time series with a control group. 3 Evidence obtained from comparative studies with historical control, two or more single-arm studies or interrupted time series without a parallel control group. |
| Level IV | Evidence obtained from case series, either post-test or pretest/post-test. |