ACUTE SEVERE ASTHMA IN ADULTS
Supporting information

This guideline has been prepared with reference to the following:

Holguin F, Cardet JC, Chung KF et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. 2020. Eur Respir J. 2020;55

https://erj.ersjournals.com/content/55/1/1900588.long

British Thoracic Society & Scottish Intercollegiate Guidelines Network. British Guideline on the management of asthma: a national clinical guideline. 2019

https://www.brit-thoracic.org.uk/document-library/guidelines/asthma/bts-sign-guideline-for-the-management-of-asthma-2019/

Bott J, Blumenthal S, Buxton M, et al. Guidelines for the physiotherapy management of the adult, medical, spontaneously breathing patient. Thorax 2009;64(Suppl I):i1–i51

http://thorax.bmj.com/content/64/Suppl_1/i1.full

Immediate treatment

High dose oxygen verses titrated oxygen for severe exacerbations of asthma?
A 2011 RCT compared high dose oxygen with titrated oxygen in 106 patients presenting to the Emergency Department of three hospitals in New Zealand with severe exacerbations of asthma (Perrin, 2011). The transcutaneous partial pressure of carbon dioxide (PtCO2) was measured at 0, 20, 40 and 60 min. The proportion of patients with a rise in PtCO2 ≥4 mm Hg at 60 min was significantly higher in the high concentration oxygen group, 22/50 (44%) vs 10/53 (19%), RR 2.3 (95% CI 1.2 to 4.4, p<0.006). The high concentration group had a higher proportion of patients with a rise in PtCO2 ≥8 mm Hg, 11/50 (22%) vs 3/53 (6%), RR 3.9 (95% CI 1.2 to 13.1, p=0.016). All 10 patients with a final PtCO2 ≥45 mm Hg received high concentration oxygen therapy, and in five there was an increase in PtCO2 ≥10 mm Hg. The authors thus concluded that high concentration oxygen increases the risk of hypercapnia in patients with severe exacerbations of asthma and recommend a titrated regime in which oxygen is administered only to those with evidence of arterial hypoxaemia, in a dose that relieves the hypoxaemia without causing hyperoxaemia, thereby obtaining the benefits while reducing the potential for harm.

Perrin K, Wijesinghe M, Healy B et al. Randomised controlled trial of high concentration versus titrated oxygen therapy in severe exacerbations of asthma. Thorax. 2011;66:937-41
https://thorax.bmj.com/content/66/11/937.long

Evidence Level: II

Hypercapnia is not usually aggravated by oxygen therapy in asthma patients?
Patients with chronic respiratory failure have a lower than normal respiratory sensitivity to CO_2. They rely instead on a strong hypoxic drive from the peripheral chemoreceptors for their main chemical stimulus to breathing. When this is removed by oxygen administration, CO_2 retention can occur (Moloney, 2001). Oxygen therapy appears not to worsen arterial CO_2 levels in asthma but they may remain high despite oxygen, in which case intermittent positive pressure ventilation must be considered urgently (Bateman, 1998). Oxygen-induced reduction of respiratory drive may occur, however, in older patients diagnosed with asthma after a long history of chronic bronchitis (Inwald, 2001); oxygen at a lower concentration (24-28%) may be necessary to avoid this (Bateman, 1998). It has been postulated (Flenley, 1971) that a sub-group of asthmatics exists in whom carbon dioxide retention “may be aggravated by uncontrolled oxygen”. More recently it has been felt that these are the patients with pre-existing COPD mentioned above, and that 35% oxygen is both safe and adequate in these cases, before arterial blood gas measurements are available (Ford, 1989).
The first randomised controlled trial to address this question (Rodrigo, 2003) found that, of the patients given 100% oxygen (n=38), 42% had increases in $PaCO_2$ averaging 5.0 mm Hg (range 2.4-14.3 mm Hg). In the 28% oxygen group (n=36), a small mean $PaCO_2$ decrease (1.3 +/- 4.0 mm Hg) was achieved in 80.4%. The authors recommended that oxygen dose in acute severe asthma should be variable and targeted at achieving and maintaining $Sp0_2$ values with a pulse oximeter of >92%.

Not found an answer to your question? Wish to suggest an edit to this document?
Please contact the BCGP Clinical Effectiveness Librarian at bedsideclinicalguidelines@uhnm.nhs.uk

Bateman NT, Leach RM. Acute oxygen therapy. BMJ 1998;317:798-9
http://www.bmj.com/content/317/7161/798

Flenley DC. Blood gas tensions in severe asthma. Proc Roy Soc Med 1971;64:1149-51
http://europepmc.org/backend/ptpmcrender.fcgi?accid=PMC1812053&blobtype=pdf

Ford DJ, Rothwell RP. "Safe oxygen" in acute asthma: prospective trial using 35% Ventimask prior to admission. Respir Med 1989;83:189-94

Inwald D, Roland M, Kuitert L, et al. Oxygen treatment for acute severe asthma. BMJ 2001;323:98-100
http://www.bmj.com/content/323/7304/98

Moloney ED, Kiely JL, McNicholas WT. Controlled oxygen therapy and carbon dioxide retention during exacerbations of chronic obstructive pulmonary disease. Lancet 2001;357:526-8

Rodrigo GJ, Verde MR, Peregalli V, et al. Effects of short-term 28% and 100% oxygen on $PaCO_2$ and peak expiratory flow rate in acute asthma: a randomized trial. Chest 2003;124:1312-7

Evidence Level: IV

Salbutamol is effective in opening the airways?

Salbutamol is a potent bronchodilator with an action lasting 4-6 hours, and has been regarded as the treatment of choice for both chronic and acute asthma for over 30 years (Anon, 1997). Paradoxically, normal airways quickly become non-responsive to salbutamol. Although healthy subjects show a progressive reduction in the bronchodilator response over time, this is not the case in asthmatic patients (Harvey, 1982). A systematic review of 6 studies involving 393 patients (Rodrigo, 2002) has shown that the drug is equally efficacious in continuous or intermittently nebulised administration.

Anon. Using β_2-stimulants in asthma. Drug Ther Bull 1997;35:1-4

Harvey JE, Tattersfield AE. Airway response to salbutamol: effect of regular salbutamol inhalations in normal, atopic, and asthmatic subjects. Thorax 1982;37:280-7
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC459298/pdf/thorax00196-0040.pdf

Rodrigo GJ, Rodrigo C. Continuous vs intermittent beta-agonists in the treatment of acute adult asthma: a systematic review with meta-analysis. Chest 2002;122:160-5
http://journal.publications.chestnet.org/article.aspx?articleid=1080781

Evidence Level: I

Corticosteroids improve the rate of recovery of patients with acute severe asthma?

An updated Cochrane Review (Edmonds, 2012) found that the use of steroids early in the treatment of asthmatic exacerbations reduced admission in adults, particularly in those not receiving concomitant systemic steroids (OR 0.27, 95% CI 0.14-0.52). Rowe (1992) found that they were also effective in preventing relapses in the outpatient treatment of exacerbations (OR 0.15; 95% CI 0.05-0.44) and that oral and intravenous steroids had equivalent efficacy (ES –0.07; 95% CI –0.39-0.25). Intramuscular administration has also been shown to be equivalent to oral dosing (Lahn, 2004).
A Cochrane review (Manser, 2001) of 9 RCTs in a total of 344 adult patients looked at low, medium and high doses of corticosteroids in acute severe asthma. No differences were identified between the groups (a mean of 8-9% improvement in FEV1) and the reviewers concluded that low doses (e.g. </= 80mg/day of methylprednisolone) were to be preferred as higher doses gave no therapeutic advantage.
A meta-analysis of 6 RCTs in a total of 353 patients (Edmonds, 2002) found that inhaled corticosteroids used in the emergency department resulted in decreased hospital admission rates but without producing clinically significant improvements in pulmonary function. Inhaled corticosteroids have also been shown to reduce requirements for oral therapy (Ververeli, 2004).

Edmonds ML, Camargo CA, Pollack CV, et al. The effectiveness of inhaled corticosteroids in the emergency department treatment of acute asthma: a meta-analysis. Ann Emerg Med 2002;40:145-54

Edmonds ML, Milan SJ, Camargo Jr CA, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. Cochrane Database Syst Rev. 2012, Issue 12
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002308.pub2/full

Lahn M, Bijur P, Gallagher EJ. Randomized clinical trial of intramuscular vs oral methylprednisolone in the treatment of asthma exacerbations following discharge from an emergency department. Chest 2004;126:362-8 http://journal.publications.chestnet.org/article.aspx?articleid=1082734

Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. Cochrane Database Syst Rev. 2001, Issue 1 http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001740/full

Rowe BH, Keller JL, Oxman AD. Effectiveness of steroid therapy in acute exacerbations of asthma: a meta-analysis. Am J Emerg Med 1992;10:301-10

Ververeli K, Chipps B. Oral corticosteroid-sparing effects of inhaled corticosteroids in the treatment of persistent and acute asthma. Ann Allergy Asthma Immunol 2004;92:512-22

Evidence Level: I

Sedatives depress the respiratory drive, increasing the danger of death or need for endotracheal ventilation?

Narcotics and sedatives are absolutely contraindicated in asthma because of their depressive effect on respiration (Middleton, 1980). It is likely that “there is no drug with sedative, hypnotic, or tranquillising properties which cannot cause respiratory depression” (Clark, 1971). Even sedatives considered to be “mild” e.g. nitrazepam 10mg are capable of inducing severe respiratory depression in patients with asthma or respiratory failure (Hilton, 1971).

A single-blind placebo-controlled study (Delpierre, 1981) in 40 patients with lung disease (including 26 with asthma and/or chronic bronchitis) found that oral diazepam induced a significant decrease in $P_{0.1}$ (occlusion pressure at o.1s) in 10 of 12 patients compared with placebo (2.25 +/- 1.39 vs 3.23 +/- 2.02).

Clark TJ, Collins JV, Tong D. Respiratory depression caused by nitrazepam in patients with respiratory failure. Lancet 1971;ii:737-8

Delpierre S, Jammes Y, Grimaud C, et al. Influence of anxiolytic drugs (Prazepam and Diazepam) on respiratory center output and CO_2 chemosensitivity in patients with lung diseases. Respiration 1981;42:15-20

Hilton AM. Sedative drugs in respiratory failure. Lancet 1971;ii:922

Middleton E. A rational approach to asthma therapy. Postgrad Med 1980;67:107-16, 120-2

Evidence Level: III

Chest physiotherapy is not indicated?

A retrospective study of 317 patients examined the effectiveness of a multidisciplinary 3 week rehabilitation program which included endurance training, educational meetings, chest physiotherapy, breathing exercises, and psychological support (Zampogna, 2019). The program significantly improved Six Minute Walking Test distance, Borg dyspnea and muscle fatigue (p value < 0.0001 for all outcomes) and mean SpO2 recorded during 6MWT (p value < 0.0001). Median (IQR) delta 6 minute walking distance was 33 (14-60) m. 6MWT distance ($p < 0.0001$) and the oxygen saturation ($p < 0.01$) also significantly improved.

No controlled studies were identified in adults. A randomised, placebo-controlled trial of chest physiotherapy in 38 children (Asher, 1990) found similar lung function after 4 treatments in both groups of 19.

Lung inflation techniques such as incentive spirometry, voluntary deep breathing, intermittent positive pressure breathing and continuous positive airway pressure have all been used during acute attacks, but no evidence for their efficacy has been produced (Ambrosino, 1993).

Postural drainage and chest vibration increase sputum mobilisation and expectoration, but may induce or worsen bronchoconstriction (Ambrosino, 1993).

Ambrosino N, Meriggi A. Chest physiotherapy in asthma. Eur Resp Rev 1993;3:353-5

Asher MI, Douglas C, Airy M, et al. Effects of chest physical therapy on lung function in children recovering from acute severe asthma. Pediatr Pulmonol 1990;9:146-51 http://www.cebp.nl/vault_public/filesystem/?ID=1153

Zampogna E, Centis R, Negri S et al. Effectiveness of pulmonary rehabilitation in severe asthma: a retrospective data analysis. J Asthma. 2019 [Epub ahead of print]

Not found an answer to your question? Wish to suggest an edit to this document?
Please contact the BCGP Clinical Effectiveness Librarian at bedsideclinicalguidelines@uhnm.nhs.uk

Evidence Level: IV

Addition of ipratropium to salbutamol via nebuliser enhances the bronchodilator effect?
A pooled analysis of 3 randomised controlled trials involving 1,064 patients (Lanes, 1998) compared treatment with salbutamol 2.5mg alone to treatment with salbutamol 2.5 mg combined with 0.5mg ipratropium. Patients in the combination group had lower risk for each of 3 clinical outcomes: need for additional treatment (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 hospitalisation (RR 0.80, 95% CI 0.61-1.06). Patients in this group also had improved FEV1 after 45 minutes of treatment (mean 43mL, 95% CI 20-107).
Similar results were achieved in the pooled results of an evidence-based literature review (Rodrigo, 2002), in a meta-analysis of 10 RCTs involving 1,377 patients (Stoodley, 1999), and a systematic review of 32 RCTs in 3611 patients (Rodrigo, 2005).
Despite the cumulative effect of these treatments, up to one-third of patients may remain unresponsive to a combination of inhaled β-agonists, anticholinergics and systemic corticosteroids (Nakano, 2003).

Lanes SF, Garrett JE, Wentworth CE, et al. The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: a pooled analysis of three trials. Chest 1998;114:365-72
http://journal.publications.chestnet.org/data/Journals/CHEST/21811/365.pdf

Nakano Y, Morita S, Kawamoto A, et al. Efficacy of a consensus protocol therapy in adults with acute, severe asthma. Ann Allergy Asthma Immunol 2003;90:331-7

Rodrigo GJ, Rodrigo C. The role of anticholinergics in acute asthma treatment: an evidence-based evaluation. Chest 2002;121:1977-87
http://journal.publications.chestnet.org/article.aspx?articleid=1080662

Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. Thorax 2005;60:740-6
http://thorax.bmj.com/content/65/12/1118.long

Stoodley RG, Aaron SD, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: a metaanalysis of randomized clinical trials. Ann Emerg Med 1999;34:8-18

Evidence Level: I

In patients with life threatening features, IV magnesium sulphate improves the outcome?
A 2017 review concluded that “Based on the current evidence, nebulized magnesium should not be routinely used in acute asthma. There is evidence that the use of intravenous magnesium sulfate is favored in selected cases. In patients with a severe asthma exacerbation with a poor initial response to inhaled 2 agonists, an infusion of 2g of magnesium sulfate delivered over 20 min may be considered” (Maselli, 2017).
A retrospective study of 619 Japanese patients with severe acute asthma who were treated with IV magnesium sulphate were paired with controls (Hirashima, 2015). No statistical difference was found in terms of 28-day mortality (1.3% vs 1.8%, P = 0.488) or median length of stay (16 days vs 13 days, P = 0.640).
A multicentre, placebo-controlled, double-blind, randomised clinical trial in 248 patients with acute severe asthma (Silverman, 2002) found that mean FEV_1 on arrival in the emergency department increased from 22.9% predicted to 48.2% predicted in the treatment group, vs 43.5% predicted in the placebo group (mean difference 4.7%; 95% CI 0.29-9.3%; p=0.045). All patients received nebulised β-agonists and IV corticosteroids; the treatment group received in addition 2g IV magnesium sulphate. This standard treatment in addition to magnesium may represent a critical limitation in this study, in that the addition of, say, ipratropium could alter the response to magnesium (Rodrigo, 2004).

Maselli DJ, Peters JI. Medication Regimens for Managing Acute Asthma. Respir Care. 2018;63:783-796

Hirashima J, Yamana H, Matsui H et al. Effect of intravenous magnesium sulfate on mortality in patients with severe acute asthma. Respirology. 2016;21:668-73

Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. Chest 2004;125:1081-1102
http://journal.publications.chestnet.org/article.aspx?articleid=1082263&resultClick=3

Silverman RA, Osborn H, Runge J, et al. IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. Chest 2002;122:489-97
http://journal.publications.chestnet.org/article.aspx?articleid=1080856

Evidence Level: I

Subsequent management

For how long should prednisolone be continued in patients recovering from acute severe asthma?

A randomised controlled trial in 35 patients (O'Driscoll, 1993) concluded that tapering was unnecessary provided that patients were adequately treated initially and that protection was provided by medium to high doses (400-2000 mcg) of inhaled steroids after withdrawal of the oral dose.
A double-blind placebo controlled study in 35 patients discharged home after severe acute asthma (Hatton, 1995) gave one group (n=19) oral prednisolone 40 mg/d for 14 days and the other (n=16) placebo. There was no difference between the two groups in the median values of the forced expiratory volume in 1 second, forced vital capacity, total lung capacity or diurnal variation in PEF either at the time of discharge or at 14 and 28 days afterwards, again suggesting that tapering was unnecessary.
A prospective, placebo-controlled trial of 5 vs 10 days of oral prednisolone in 44 patients (Jones, 2002) found no difference in symptoms between the two groups.
A Cochrane review of 6 trials involving 374 children and adults (Rowe, 2007) found that a short course of corticosteroids (varying between 3 and 10 days) significantly reduced the number of relapses without any apparent increase in side effects. Results in the first week after discharge were RR 0.38; 95% CI 0.2 – 0.74. This effect was maintained over the first 21 days following discharge (RR 0.47; 95% CI 0.25 – 0.89; NNT = 10).

Hatton MQ, Vathenen AS, Allen MJ, et al. A comparison of "abruptly stopping" with "tailing off" oral corticosteroids in acute asthma. Respir Med 1995;89:101-4

Jones AM, Munavvar M, Vail A, et al. Prospective, placebo-controlled trial of 5 vs 10 days of oral prednisolone in acute adult asthma. Respir Med 2002;96:950-4

O'Driscoll BR, Kalra S, Wilson M, et al. Double-blind trial of steroid tapering in acute asthma. Lancet 1993;341:324-7

Rowe BH, Spooner CH, Ducharme FM, et al. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database Syst Rev. 2007, Issue 3
http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD000195.pub2/full

Evidence Level: I

If patients are likely to deteriorate when switched from nebuliser to inhaler therapy, this will happen within 24 hours?

A prospective, randomised trial in 27 patients (Raimondi, 1997) demonstrated that wet nebuliser, valved aerosol holding chamber, and dry powder inhaler methods achieved similar improvements in FEV1, despite delivering variable amounts of the drug. Similar results were achieved in another study (Robertson, 1994). This suggests that, given adequate inhaler technique, most patients should not experience deterioration in their condition due to the switch from nebuliser to inhaler.

Raimondi AC, Schottlender J, Lombardi D, et al. Treatment of acute severe asthma with inhaled albuterol delivered via jet nebulizer, metered dose inhaler with spacer, or dry powder. Chest 1997;112:24-8
http://journal.publications.chestnet.org/data/Journals/CHEST/21748/24.pdf

Robertson D. Dose-response study of albuterol by inhaler or nebulizer for acute asthma. Drug Ther 1994;24:40

Evidence Level: V

Is increasing the inhaled steroid dose effective at reducing further exacerbations?

A 2018 RCT involving 1871 UK adults and adolescents with asthma who were receiving inhaled glucocorticoids and who had had at least one exacerbation in the previous 12 months (McKeever, 2018). A self-management plan that included an increase in the dose of inhaled glucocorticoids by a factor of 4 (quadrupling group) was compared with the same plan without such an increase (non-quadrupling group), over a period of 12 months. The primary outcome was the time to a first severe

asthma exacerbation. The number of participants who had a severe asthma exacerbation in the year after randomization was 420 (45%) in the quadrupling group compared with 484 (52%) in the non-quadrupling group, with an adjusted hazard ratio for the time to a first severe exacerbation of 0.81 (95% confidence interval, 0.71 to 0.92; P=0.002). The authors therefore concluded that a temporary quadrupling of the dose of inhaled glucocorticoids when asthma control started to deteriorate resulted in fewer severe asthma exacerbations than a plan in which the dose was not increased.
A 2019 systematic review of RCTs (8 trials totalling 3866 patients) found that an increased dose of inhaled corticosteroids was associated with a significantly reduced risk of treatment failure compared with stable dose (OR 0.82, 95% CI 0.70 to 0.97) [Zhang, 2019]. There was no significant difference in unscheduled physician visits or hospital admission between increased or stable dose of inhaled corticosteroids. However, increased dose of inhaled corticosteroids increased the risk of non-serious adverse events (OR 3.50, 95% CI 1.93 to 6.35) but not serious adverse events. The authors concluded that current evidence of moderate quality supports increasing the dose of inhaled corticosteroids as part of a self-initiated action plan to reduce risk of requiring a course of systemic corticosteroids in people with an asthma exacerbation.

McKeever T, Mortimer K, Wilson A et al. Quadrupling Inhaled Glucocorticoid Dose to Abort Asthma Exacerbations. N Engl J Med. 2018;378:902-910

Zhang Y, He J, Yuan Y et al. Increased Versus Stable Dose of Inhaled Corticosteroids for Asthma Exacerbations: A Systematic Review and Meta-Analysis. Clin Exp Allergy 2019;49:1283-90
https://onlinelibrary.wiley.com/doi/full/10.1111/cea.13450

Evidence Level: I

Last amended November 2021
Last reviewed October 2023