ORIGINAL ARTICLE

# Randomised pragmatic comparison of UK and US treatment of acute asthma presenting to hospital

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**Background:** Systemic corticosteroids and inhaled $\beta_2$ agonists are accepted first line treatments for acute severe asthma, but there is no consensus on their optimum dosage and frequency of administration. American regimens include higher initial dosages of $\beta_2$ agonists and corticosteroids than UK regimens.

**Methods:** In a prospective, pragmatic, randomised, parallel group study, 170 patients of mean (SD) age 37 (12) years with acute asthma (peak expiratory flow (PEF) 212 (80) l/min) presenting to hospital received treatment with either high dose prednisolone and continuous nebulised salbutamol as recommended in the US or lower dose prednisolone and bolus nebulised salbutamol as recommended in the UK by the BTS.

**Results:** Outcome measures were: ΔPEF at 1 hour (BTS 89 l/min, US 106 l/min, p=0.2, CI –8 to 41) and at 2 hours (BTS 49 l/min, US 101 l/min, p<0.0001, CI 28 to 77); time to discharge if admitted (BTS 4 days, US 4 days); rates of achieving discharge PEF (>60%) at 2 hours (BTS 64%, US 78%, p=0.04); time to regain control of asthma as measured by PEF ⩾80% best with ⩽20% variability (BTS 3 days, US 4 days, p=0.6); PEF at 24 hours in patients admitted (BTS 293 l/min, US 288 l/min, p=0.8); and control of asthma in the subsequent month (no significant differences).

**Conclusions:** Treatment with higher doses of continuous nebulised salbutamol leads to a greater immediate improvement in PEF but the degree of recovery at 24 hours and speed of recovery thereafter is achieved as effectively with lower corticosteroid doses as recommended in the British guidelines.

The main therapeutic agents for the treatment of acute severe asthma are oxygen, inhaled $\beta_2$ agonists, and systemic corticosteroids. Despite their long history of use, there is a lack of worldwide consensus among physicians or specialist committees as to the optimum dose and frequency of administration of these drugs with differences in dosing being largely historical rather than based on clinical evidence.

The likelihood of admission to hospital after a presentation with acute asthma is around 25% lower in the US than in the UK.[1] Whether this is due to more intensive treatment being administered in the US than in the UK or to differences in health care organisation and provision between the two countries remains unclear.

The British and American guidelines for the management of acute severe asthma[2 3] differ most notably in the dosage and frequency of administration of both inhaled β agonists and systemic corticosteroids. With respect to β agonists, US practice is to use lower doses of salbutamol (albuterol) at a higher frequency of dosing than in the UK, with continuous nebulisation being recommended in US guidelines. Both US and UK guidelines recommend dosages that exceed the licensed level of 5 mg given 6 hourly.[4] For corticosteroid dosage, US authors recommend up to 60 mg prednisolone 4 hourly for up to 72 hours and then 60 mg/day thereafter,[5] while UK guidelines recommend 30–60 mg once daily.[2]

To date no study has directly compared US and UK guidelines in a single population to see if outcomes differ. We have therefore undertaken a prospective, randomised, parallel group study in a single centre with a high prevalence of asthma to see if these different therapeutic approaches result in different outcomes.

## METHODS

### Subjects

The local ethics committee approved the study. All patients who self-presented or presented via their general practitioner to the Norfolk and Norwich Hospital with acute asthma were considered for the study. Eligible patients were aged 18–64 years and had a peak expiratory flow (PEF) on presentation of ⩽75% of their personal best, or predicted best if a personal best in the previous 12 months was not known (hereafter referred to as percentage of best).[6] Conditions excluding entry to the study were pregnancy, pneumonia, pneumothorax, diabetes mellitus, peptic ulceration on treatment, hypertension on treatment, ischaemic heart disease and cardiac arrhythmias. Patients in extremis due to asthma, as defined by collapse, respiratory arrest, hypercapnia or the need for immediate intubation, were not eligible for the study. Patients not wishing to enter the study were treated as recommended in the British Thoracic Society guidelines for acute asthma.[2]

### Interventions

After giving informed consent, patients were randomised to receive one of two treatment protocols. Randomisation, performed on entry to the study in the emergency department or in the medical admissions unit, was by sequential opaque sealed envelopes in which treatment allocation had been predetermined using blocked randomisation by a statistician (EB) unconnected to the study.

After randomisation patients were treated by protocol according to the severity of airflow obstruction. Patients in the BTS arm received prednisolone 40 mg orally on presentation and then 40 mg once daily until asthma was controlled, and bolus nebulised salbutamol 5 mg at time 0 and 30 minutes then, if admitted, 4 hourly for at least 24 hours which was reduced to 6 hourly and subsequently changed to metered dose inhaler delivery as the patient improved. Patients in the

US arm received prednisolone 60 mg orally on presentation then, if admitted, 60 mg 6 hourly for 24 hours and subsequently 60 mg once daily until asthma was controlled, and salbutamol as a 10 mg continuous nebulisation over 1 hour which was repeated over the second hour if the PEF remained below 75% of best, followed by 2.5 mg boluses of salbutamol nebulised 4 hourly for the first 24 hours in those admitted, reducing in frequency and dose as for the BTS arm. Indications for the administration of ipratropium bromide and intravenous bronchodilators were the same for each group as recommended in the BTS guidelines.[2] Patients discharged after initial treatment who did not require admission were given prednisolone 40 mg/day in the BTS group and 60 mg/day in the US group. In both arms prednisolone was given for a minimum course of 5 days and until PEF was ⩾80% best on two consecutive days with ⩽20% variability. No attempt was made to control for treatment received before presentation.

Patients were eligible for discharge if their PEF was ⩾75% best after 1 hour or ⩾60% after 2 hours of treatment, according to the BTS guidelines,[2] and if they were improving clinically. If admitted, patients in each group were discharged when PEF was ⩾75% of best with ⩽25% variability on inhaled therapy for 24 hours before discharge. Follow up was arranged for 30 days after presentation.

### Outcome measures

PEF was recorded on presentation, at 1, 2 and 24 hours, and then at least twice daily for 30 days. Re-presentation rates, need for prednisolone because of asthma, and days when PEF was <75% best in the follow up period were recorded. For each PEF recording, when possible, the best of three efforts was recorded.

The end points were change in PEF at 1 and 2 hours after commencing treatment, rates of achieving discharge PEF (⩾60% best) at 2 hours, rate of discharge and, if admitted, time to discharge. Longer term end points were PEF at 24 hours; time to regain control of asthma (as defined by the time to reach a PEF ⩾80% best with ⩽20% variability); control of asthma in subsequent 30 days; and re-presentation rates due to unstable asthma.

### Equipment

The BTS group used a Cirrus nebuliser chamber primed with 5m l of 1 mg/ml salbutamol with a driving oxygen flow of 8 l/min, giving a particle mass median diameter (MMD) of 3.4 µm and a respirable fraction of 76%. To achieve continuous nebulisation over 1 hour in the US group a Micro-Cirrus chamber primed with 5 ml of 2 mg/ml salbutamol was driven with an oxygen flow of 5 l/min, giving an output of 0.083 g/min with a particle MMD of 2.4 µm and a respirable fraction of ⩾75% (both chambers were supplied by Intersurgical Ltd, Berkshire, UK). Nebuliser characteristics were analysed by a Malvern 2600c laser particle analyser.

PEF was measured using Mini-Wright single patient use peak flow meters (Clement Clarke International Ltd) which were retained by the patient for the duration of the study.

### Statistical analysis

Data were collected onto a computerised database (Microsoft Corporation) with statistical analysis and graphing performed using GraphPad Prism (GraphPad Software Inc) analysis software. Pre-study power calculations predicted that 160 patients would be needed to detect a difference of 30 l/min in PEF between the groups at 2 hours, with 80% power at the 5% significance level.[7] Continuous data were analysed using the Student's unpaired two tailed *t* test or the Mann-Whitney U test when not normally distributed and are expressed as mean values with 95% confidence intervals unless otherwise stated. Categorical data were analysed using the Mann-Whitney U test. The time to discharge and time to regain control of asthma were compared using Kaplan-Meier plots with log rank analysis. Discharge rates were compared by $\chi^2$ analysis. The response according to severity of presentation was analysed using two way ANOVA.

**Table 1** Mean (SD) baseline demographic data of the two treatment groups

| Variables | BTS (n=89) | US (n=81) |
|---|---|---|
| Age (years) | 34 (12) | 34 (12) |
| Female (%) | 53 | 59 |
| PEF (l/min) | 215 (72) | 206 (87) |
| PEF (% best) | 47 (13) | 45 (16) |
| Median BTS treatment step (1–5)* | 2 | 2 |
| Smoking history (pack years) | 7 | 8 |
| Oral steroid courses in last year for asthma | 1.3 | 1.8 |
| Admissions in last year | 0.4 | 0.5 |
| PEF at follow up | 424 (16) | 420 (16) |

*As assessed by BTS guidelines.[2]

**Table 2** Mean (SD) peak expiratory flow (PEF) measurements for each treatment group

| | BTS | US | p value | 95% CI |
|---|---|---|---|---|
| All patients | | | | |
| n | 89 | 81 | | |
| Initial PEF | 215 (72) | 206 (87) | 0.5 | –33 to 16 |
| PEF change at 1 hour | 89 (78) | 106 (85) | 0.2 | –8 to 41 |
| Patients with PEF ⩽75% best at 1 hour | | | | |
| n | 51 | 48 | | |
| PEF on presentation | 194 (53) | 173 (64) | 0.07 | –45 to 2 |
| PEF change at 1 hour | 42 (42) | 66 (50) | 0.01 | 6 to 43 |
| PEF change at 2 h | 49 (53) | 101 (69) | <0.0001 | 28 to 77 |

## RESULTS

Over a 16 month period 170 patients were randomised into the trial. The groups were well matched for baseline demographic characteristics (table 1).

### PEF after 1 hour

In both groups PEF increased significantly from baseline and after 1 hour of treatment a similar number of patients in each group had reached a discharge PEF of ⩾75% (n=36 (BTS), n=32 (US), p=0.9) and needed no further hospital treatment. Both groups had received 10 mg salbutamol after 1 hour although the treatments differed in modality of nebulisation. A comparison of changes in PEF at this point therefore allows assessment of the mode of nebulisation. Overall, there was no significant difference in mean PEF changes at 1 hour between the two groups (89 l/min (BTS) *v* 106 l/min (US), p=0.2). However, in those patients whose PEF remained <75% of best after 1 hour of treatment, the US continuous method of nebulisation resulted in a significantly higher PEF at this time point than the BTS bolus method (42 l/min *v* 66 l/min, p=0.01; table 2). Furthermore, unlike BTS bolus dosing, US continuous treatment in these patients was more beneficial the worse the presenting airflow obstruction (fig 1).

### PEF after 2 hours

Ninety nine patients (BTS 51, US 48) with PEF <75% best after 1 hour of treatment continued treatment over a second hour. Three patients (2 BTS, 1 US) with a PEF <75% best at 1 hour discharged themselves before further treatment. Between 1 and 2 hours the BTS group received no further β agonists and their PEF improved by only 7 l/min. In the second

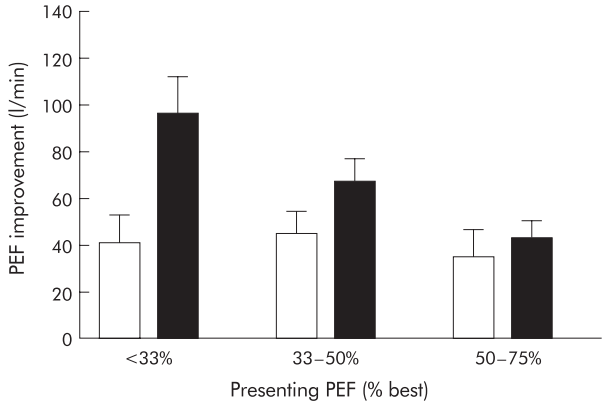


**Figure 1** Improvement in PEF after 1 hour as a function of presenting PEF severity in subjects with PEF ⩽75% best at 1 hour. Values are mean (SE). Open bars=BTS; solid bars=US. Treatment effect p=0.007 (two way ANOVA).

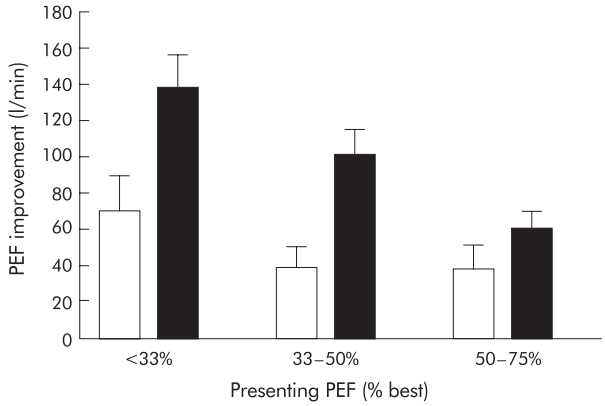


**Figure 2** Improvement in PEF after 2 hours as a function of presenting PEF. Values are mean (SE). Open bars=BTS; solid bars=US. Treatment effect p=0.0002 (two way ANOVA).

hour the US group received a further 10 mg salbutamol and their PEF improved by 35 l/min, (p<0.0001, table 2).

The mean change in PEF from baseline after 2 hours of treatment was 52 l/min greater in the US arm (p<0.0001, table 2). The significant benefit of US treatment over BTS treatment at 2 hours was maintained when the data were expressed as percentage of predicted PEF or change in percentage predicted PEF.

When responses to treatment were analysed according to severity of presenting asthma, the US treatment but not the BTS treatment was found to be increasingly beneficial with worsening airflow obstruction (fig 2).

After 2 hours of treatment 63 US patients (78%) had achieved a PEF of ⩾60% compared with 57 BTS patients (64%; p=0.04. $\chi^2$ test). This equates to a 14% higher discharge rate with the US treatment regimen than with the BTS regimen if presenting PEF is not taken into account when considering discharge.

Blood pressure and heart rate were recorded to assess the cardiovascular side effects of treatment. In both groups the heart rate fell over the 2 hour nebulisation period (BTS, time 0=114 bpm, 2 hours=98 bpm; US, time 0=109 bpm, 2 hours=98 bpm) as did mean blood pressure (BTS, time 0=104 mm Hg, 2 hours=95 mm Hg; US, time 0=98 mm Hg, 2 hours=91 mm Hg) with no significant differences between groups before or after treatment for either measurement. Serum potassium levels and cardiac rhythm were not formally monitored but no cases of hypokalaemia or arrhythmia were seen.

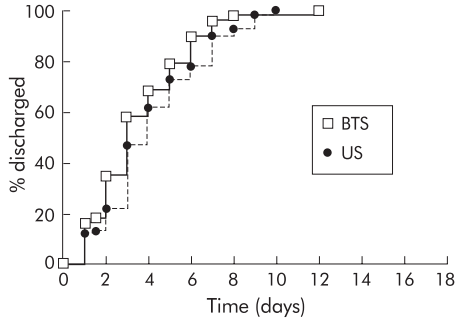


**Figure 3** Kaplan-Meier plot for the time taken to achieve discharge if admitted (n=92); p=0.14 (log rank analysis).

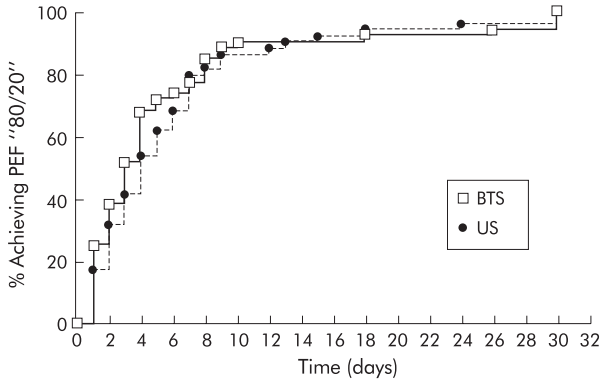


**Figure 4** Kaplan-Meier plot for time taken to achieve PEF ⩾80% best with ⩽20% variability (n=104); p=0.6 (log rank analysis).

### Recovery phase

In the 91 patients who were admitted, PEF at 24 hours showed no significant difference between the treatment groups (293 (107) l/min (BTS), 288 (126) l/min (US), p=0.8, 95% CI −55 to 44). Time to discharge from hospital in the patients admitted was compared using Kaplan-Meier plots and log rank analysis. Both groups took a median of 4 days to be discharged with no significant difference overall between the groups (fig 3). Data were available in 104 patients (54 BTS and 50 US) to assess the time to regain control of asthma, expressed as the time taken to achieve a PEF ⩾80% of best with ⩽20% variability. The BTS group took a median of 3 days and the US group 4 days to achieve control of asthma (p=0.6, fig 4).

One hundred and six patients attended follow up at 30 days. All available follow up data were analysed with no significant differences being found between the groups in days when PEF⩽75% of best, number of patients requiring further prednisolone for their asthma, or number of patients readmitted to hospital because of asthma in the 30 day follow up period. Peak flow at follow up had doubled on average from that at presentation and was similar in both groups (BTS 424 l/min, US 420 l/min, p=0.87, CI −48 to 40). No patients who entered the study required ventilation and there were no deaths.

## DISCUSSION

In this randomised study of patients presenting to hospital with acute asthma we have compared standard British and American therapeutic approaches and investigated whether outcomes differ with differing intensities of treatment.

The more intensive US protocol led to twice as much improvement in PEF at 2 hours than in the BTS group with significantly more patients achieving a PEF ⩾60% best. Despite 14% more patients in the US arm reaching discharge PEF at 2 hours, there was no difference in actual discharge rates between the groups. This is partly because the BTS

guidelines advise admission if presenting PEF is <50% best whatever the subsequent improvement. Basing discharge criteria more on PEF after treatment and ignoring the presenting PEF would have resulted in significantly more US than BTS patients being discharged. Actual admission rates in the US may be lower for several reasons. In the US emergency room treatment can continue for up to 12 hours before an admission decision is made, whereas in the UK this time is reduced to 1–2 hours. Moreover, British patients are more likely to have had treatment in the community before presentation and failed to improve, while more US patients use emergency rooms as a source of primary care and first line treatment. Also, in the US, unlike the UK, there are greater personal financial disincentives to admission.

The outcomes between 24 hours after presentation and follow up at 30 days showed no differences between the groups. The less intensive BTS treatment regimen was as efficacious in terms of speed of recovery, time to discharge if admitted, and asthma control in the following month as the US treatment regimen.

Although the two protocols varied in both corticosteroid and salbutamol dosage, we are confident that the differences in early outcomes at 1 and 2 hours were due solely to the differences in β agonist. In healthy subjects prednisolone takes up to 2 hours to reach peak plasma concentrations after oral dosage and takes longer with concomitant disease.[8 9] More significantly, in contrast to the longer term effects of corticosteroids on $\beta_2$ receptor upregulation, the actions of corticosteroids in acute asthma have repeatedly been shown to have no effect on the degree of airflow obstruction before 6 hours.[10–15] A recent Cochrane collaborative meta-analysis concluded that corticosteroids have no effect on the PEF in acute asthma at 1 or 2 hours.[16] Any differences in outcome after 24 hours, however, would be likely to be due to differences in steroid dosing as the β agonist regimens of the two groups did not differ significantly after 24 hours while the US group had received six times the corticosteroid dose of the BTS group.

Fractionating doses of inhaled bronchodilators and delivering them sequentially has been shown to cause greater bronchodilation than a single bolus dose.[17–19] More recent studies have compared bolus with continuous delivery of β agonist nebulised over 2 hours or more. Two have shown at least equal efficacy,[20 21] while Shrestha *et al*[22] showed that 2.5 mg salbutamol nebulised continuously over 1 hour resulted in a higher forced expiratory volume in 1 second ($FEV_1$) than 7.5 mg nebulised as a bolus.

We have shown that patients presenting to hospital with acute asthma have significantly greater relief of their airflow obstruction in the first 2 hours if high dose continuous nebulisation of salbutamol is used as opposed to lower dose bolus nebulisation. The significant improvements in PEF at 2 hours in the US group, but not in the BTS group, suggest that the higher absolute dosage received in the US arm was partly responsible. However, in patients whose PEF did not rise above 75% best after the initial nebulisation, continuous dosing led to significantly greater bronchodilation for the same cumulative dose as given via bolus dosing. This confirms the results of previous studies[23–25] that continuous nebulisation offers the greatest benefit in the most severe airflow obstruction, an effect not seen with bolus nebulisation. This is thought to be because continuous nebulisation delivers drug sequentially to the more distal airways once the more proximal airways have bronchodilated. In bolus dosing over 5–7 minutes, distal deposition is hindered by proximal bronchospasm that is only starting to be relieved as the nebuliser is finishing. Currently in the UK, unlike in the US, there is no purpose made continuous nebuliser. To provide continuous nebulisation we altered the flow rate—and hence particle size and volume output—of a chamber normally used for alveolar drug deposition. Other authors have used syringe drivers that feed a standard chamber or have topped up a standard chamber regularly using a preprepared saline/salbutamol mixture, depending on the dose required and the output characteristics of the chamber used. However, both of these techniques are labour intensive.

While the effectiveness of corticosteroids in treating patients with acute asthma who present to hospital is universally accepted, there is no consensus as to the optimum dose and frequency of administration. Studies comparing moderate and high doses of corticosteroids have repeatedly failed to find evidence of a dose response relationship in alleviating acute asthma.[26–35] Only two studies have looked at doses similar to those recommended by the BTS. Engel and colleagues[35] found no difference between prednisolone 50 mg and methylprednisolone 1 g while Webb[36] reported a significant dose response relationship between prednisolone 0.2, 0.4 and 0.6 mg/kg, with the lower doses being significantly less effective than 0.6 mg/kg daily. A recent meta-analysis has concluded that a dose of 60–80 mg/day methylprednisolone is adequate in hospitalised patients with acute asthma.[37]

Our study is consistent with previous work showing no difference between high and moderate doses of corticosteroids, but it takes the lower limit of the dose response relationship down to prednisolone 40 mg/day which is comparable to Webb's higher dose.[36] We have considered that the lack of statistical difference in time to regain control of asthma might represent a type 2 error as this part of the study has a power to detect a difference of 1.3 days. Counter to this, however, is the lack of any difference in time to discharge between the groups and the fact that the trend in difference in time to regain control favours the lower dose BTS group. This lack of difference is also in agreement with the literature.[37]

In summary, we have shown that continuous nebulisation of salbutamol for the treatment of acute asthma is readily performed, well tolerated, and leads to significantly greater bronchodilation than bolus nebulisation for patients whose attack does not resolve rapidly after initial treatment. We have shown that there is greater benefit from continuous nebulisation in patients with worse airflow obstruction, and that in those with persistent airflow obstruction additional bronchodilation can be achieved by repeat dosing above salbutamol 10 mg. We have also shown that prednisolone 40 mg/day as a single daily dose is as effective as prednisolone 60 mg 6 hourly for 24 hours followed by 60 mg/day thereafter. We recommend that continuous nebulisation of $\beta_2$ agonists be considered in patients with acute asthma that is poorly responsive to initial bronchodilator therapy, and that daily doses of prednisolone higher than 40 mg, with their greater risk of side effects, are unnecessary.

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## REFERENCES

1 **McFadden ER Jr**, Elsanadi N, Dixon L, *et al*. Protocol therapy for acute asthma: therapeutic benefits and cost savings. *Am J Med* 1995;**99**:651–61.

2 **British Thoracic Society**, *et al*. The British guidelines on asthma management: 1995 review and position statement. *Thorax* 1997;**52**(Suppl 1):S1–20.
3 **National Heart**, Lung and Blood Institute. *Guidelines for the diagnosis and treatment of asthma*. Publication no 97-4051. Bethesda, MD: National Institutes of Health, 1997.
4 **British Medical Association**. *British national formulary*. 43rd ed. London: British Medical Association, 2002.
5 **McFadden ER Jr**. Doses of corticosteroids in asthma. *Am Rev Respir Dis* 1993;**147**:1306–10.
6 **Quanjer Ph**, ed. Standardisation of lung function tests: 1993 update. Report of the working party for the European Community for Steel and Coal. *Eur Respir J* 1993;**6**:Suppl.16.
7 **Altman D**. Statistics and ethics in medical research. III. How large a sample? *BMJ* 1980;**281**:1336–8.
8 **Davis M**, Williams R, Chakraborty J, *et al*. Prednisone or prednisolone for the treatment of chronic active hepatitis? A comparison of plasma availability. *Br J Clin Pharmacol* 1978;**5**:501–5.
9 **Pharmaceutical Society**. *Martindale: the complete drug reference*. 32nd ed. London: Pharmaceutical Press, 1999: 1048–9.
10 **Stein LM**, Cole RP. Early administration of corticosteroids in the emergency room treatment of acute asthma. *Ann Intern Med* 1990;**112**:822–7.
11 **Fanta CH**, Rossing TH, McFadden ER Jr. Glucocorticoids in acute asthma: a critical controlled trial. *Am J Med* 1983;**74**:845–51.
12 **Littenberg B**, Gluck EH. A controlled trial of methylprednisolone in the emergency treatment of acute asthma. *N Engl J Med* 1986;**314**:150–2.
13 **Morell F**, Orris R, de Gracia J, *et al*. Controlled trial of intravenous corticosteroids in severe acute asthma. *Thorax* 1992;**47**:588–91.
14 **Rodrigo C**, Rodrigo G. Early administration of hydrocortisone in emergency room treatment of acute asthma: a controlled clinical trial. *Respir Med* 1994;**88**:755–61.
15 **Lin RY**, Persola GR, Westfal RE, *et al*. Early parenteral corticosteroid administration in acute asthma. *Am J Emerg Med* 1998;**15**:621–5.
16 **Rowe BH**, Spooner C, Ducharme FM, *et al*. Early emergency department treatment of acute asthma with systemic corticosteroids (Cochrane Review). In: *The Cochrane Library*. Issue 2. Oxford: Update Software, 2000.
17 **Heimer D**, Shim C, Williams MH. The effect of sequential inhalations of metaproterenol aerosol in asthma. *J Allergy Clin Immunol* 1980;**66**:75–7.
18 **Britton J**. Tattersfield A. Comparison of cumulative and non-cumulative techniques to measure dose-response curves for beta agonists in patients with asthma. *Thorax* 1984;**39**:597–9.
19 **Robertson CF**, Smith F, Beck R, *et al*. Response to frequent low doses of nebulized salbutamol in acute asthma. *J Pediatr* 1985;**106**:672–4.
20 **Colacone A**, Wolkove N, Stern E, *et al*. Continuous nebulization of albuterol (salbutamol) in acute asthma. *Chest* 1990;**97**:693–7.
21 **Reisner C**. Kotch A. Dworkin G. Continuous versus frequent intermittent nebulization of albuterol in acute asthma: a randomized, prospective study. *Ann Allergy Asthma Immunol* 1995;**75**:41–7.
22 **Shrestha M**, Bidadi K, Gourlay S, *et al*. Continuous vs intermittent albuterol, at high and low doses, in the treatment of severe acute asthma in adults. *Chest* 1996;**110**:42–7.
23 **Papo MC**, Frank J, Thompson AE. A prospective, randomized study of continuous versus intermittent nebulized albuterol for severe status asthmaticus in children. *Crit Care Med* 1993;**21**:1479–86.
24 **Rudnitsky GS**, Eberlein RS, Schoffstall JM, *et al*. Comparison of intermittent and continuously nebulized albuterol for treatment of asthma in an urban emergency department. *Ann Emerg Med* 993;**22**:1842–6.
25 **Lin RY**, Sauter D, Newman T, *et al*. Continuous versus intermittent albuterol nebulization in the treatment of acute asthma. *Ann Emerg Med* 1993;**22**:1847–53.
26 **McFadden ER Jr**, Kiser R, DeGroot WJ, *et al*. A controlled study of the effects of single doses of hydrocortisone on the resolution of acute attacks of asthma. *Am J Med* 1976;**60**:52–9.
27 **Britton MG**, Collins JV, Brown D, *et al*. High dose corticosteroids in severe acute asthma. *BMJ* 1976;2:73–4.
28 **Harfi H**, Hannisian AS, Crawford LV. Treatment of status asthmaticus in children with high doses and conventional doses of methylprednisolone. *Pediatrics* 1978;**61**:829–31.
29 **Luska AR**. Acute severe asthma treated without steroids. *Br J Dis Chest* 1982;**76**:15–19.
30 **Tanaka RM**, Santiago SM, Kuhn GJ, *et al*. Intravenous methylprednisolone in adults in status asthmaticus. Comparison of two dosages. *Chest* 1982;**82**:438–40.
31 **Harrison BDW**, Stokes TC, Hart GJ, *et al*. Need for intravenous hydrocortisone in addition to oral prednisolone in patients admitted to hospital with severe asthma without ventilatory failure. *Lancet* 1986;i:181–4.
32 **Raimondi AC**, Figueroa-Casas JC, Roncoroni AJ. Comparison between high and moderate doses of hydrocortisone in the treatment of status asthmaticus. *Chest* 1986;**89**:832–5.
33 **Bowler SD**, Mitchell CA, Armstrong JG. Corticosteroids in acute severe asthma: effectiveness of low doses. *Thorax* 1992;**47**:584–7.
34 **Ratto D**, Alfaro C, Sipsey J, *et al*. Are intravenous corticosteroids required in status asthmaticus? *JAMA* 1988;**260**:527–9.
35 **Engel T**, Dirksen A, Frølund L, *et al*. Methylprednisolone pulse therapy in acute severe asthma. A randomized, double blind study. *Allergy* 1990;**45**:224–30.
36 **Webb JR**. Dose response of patients to oral corticosteroid treatment during exacerbations of asthma. *BMJ* 1986;**292**:1045–7.
37 **Manser R**, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients (Cochrane Review). In: *The Cochrane Library*. Issue 2. Oxford: Update Software, 2000.