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Anticholinergics in the Treatment of Children and Adults with Acute Asthma: A Systematic Review with Meta-Analysis

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Running Head: **Anticholinergics in acute asthma**

ABSTRACT

Background: Current guidelines recommend the use of a combination of inhaled beta2-agonists and anticholinergics, particularly for patients with acute severe or life threatening asthma in the emergency setting. However, this statement is based on a relatively small number of randomised controlled trials and related systematic reviews. This review was undertaken to incorporate the more recent evidence available about the effectiveness of treatment with beta2-agonists and anticholinergics compared with beta2-agonists in acute asthma treatment.

Methods: A search was conducted of all randomised controlled trials published prior to April 2005.

Results: Data from 32 randomised controlled trials (n = 3611 subjects) showed significant reductions in hospital admissions in both children (RR = 0.73; 95% CI: 0.63 to 0.85, p = 0.0001) and adults (RR = 0.68; 95% CI: 0.53 to 0.86, p = 0.002) that received inhaled anticholinergics. Combined treatment also produced a significant increase on spirometric tests at 60-120 min after the last treatment in children (SMD = - 0.54; 95% CI: -0.28 to -0.81, p = 0.0001) and adults (SMD = -0.36; 95% CI: -0.23 to -0.49, p = 0.00001).

Conclusions: This review strongly suggests that the addition of multiple doses of inhaled ipratropium bromide to beta2-agonists seems indicated as the standard treatment in children, adolescent and adult patients with moderate to severe exacerbations of asthma in the emergency setting.

KEY WORDS

Anticholinergics, ipratropium bromide, oxitropium bromide, glycopyrrolate, acute asthma treatment.

INTRODUCTION

Treatment of acute asthma includes inhaled short-acting beta2-agonists, systemic corticosteroids (CCS) and supplemental oxygen.[1-2] In addition, current guidelines recommend the use of a combination of beta2-agonists and anticholinergics, particularly for patients with acute severe or life threatening asthma.[2-3] This statement is based on a relatively small number of randomised controlled trials and related systematic reviews. [4-6] However, new studies have been published after that date.[7] The aim of this systematic review was to update the evidence about the effectiveness of a combination of inhaled anticholinergics and beta2-agonists compared with beta2-agonists alone, for the emergency department (ED) treatment of children, adolescents and adults with acute asthma.

METHODS

Search strategy and selection criteria.

The search was conducted using five search strategies to identify potentially relevant trials. Firstly, we queried MEDLINE (1966 – April 2005), EMBASE (1974 – April 2005) and CINAHL (1982 – April 2005) databases using the following MeSH, full text and keyword terms: emergency OR acute asthma OR status asthmaticus OR severe asthma OR wheeze, AND anticholinergics OR ipratropium OR oxitropium, OR glycopirrolate. Secondly, an advanced search of the Cochrane Controlled Trials Register (first quarter 2005) was completed using the above search strategy to identify any additional trials. Thirdly, references from included studies, reviews and texts were searched for citations. Fourthly, a hand searching of the top 20 respiratory journals was completed. Finally, we made inquires to Boehringer Ingelheim regarding other published or unpublished trials supported by the company. Trials published solely in abstract form were excluded.

Included studies met the following criteria: 1) Target population: children (18 months to 17 years) and adults (≥18 years) with acute exacerbations of asthma presenting to an ED or equivalent care setting. 2) Intervention: single or repeated doses of inhaled anticholinergics agents given in combination with inhaled beta2-agonists compared with inhaled beta2-agonists alone. Studies involving the use of atropine were excluded. 3) Design: randomised and placebo controlled trials without language restriction. 4) Primary outcomes: admission to hospital and spirometric testing (final absolute values o change from baseline 60 to 120 min after the last combined anticholinergic and beta2-agonist inhalation). Because the peak bronchodilator effect after the administration of anticholinergics occurs within 1 to 2 h, it is reasonable to expect significant improvement during this time. Secondary outcome measures were clinical score, duration of treatment in the ED, respiratory rate, oxygen saturation, heart rate, and side effects.

Data abstraction and validity assessment.

Titles, abstracts, and citations were independently reviewed by two reviewers (GJR and JACR) to assess potential relevance for full review. From the full text, both reviewers independently assessed studies for inclusion based on the criteria for population, intervention, study design and outcomes. Data extraction included the following items: 1) Population: age, gender, number of patients studied, patient demographics, withdrawals; 2) Intervention: agent, dose, route of delivery, and duration of therapy; 3) Control: concurrent treatments; 4) Outcomes; and 5) Design: method of randomisation and allocation concealment. Any disagreement over study inclusion was resolved by

consensus. The methodological quality of each trial was evaluated using the 5-point scale (0 = worst and 5 = best) describe by Jadad et al.[8]This instrument assesses the adequacy of randomisation, blinding, and the handling of withdrawals and drop-outs.

Data analysis.

The data were combined in meta-analysis by means of random-effects models.[9] Binary outcomes were pooled using common relative risk (RR) and 95% confidence intervals (CI). The number of patients needed to treat (NNT) to prevent the adverse outcome of interest was calculated. For continuous outcomes the weighted mean difference (WMD) (for variables using the same unit of measure), or the standardised mean differences (SMD) (reported in SD units, where different units were used) and 95% CI were calculated. We tested for heterogeneity by using the DerSimonian and Laird Q statistic. We also measured heterogeneity by using the I^2 test.[10] Values of 25%, 50%, and 75% represent low, moderate and high heterogeneity respectively. Publication bias was evaluated by means of formal statistical analysis.[11] Otherwise, a p value of less than 0.05 using a two-tailed test was taken as being of significance. When heterogeneity was found, subgroup analyses were carry out in an attempt to explain the findings. Sensitivity analysis was performed to identify sources of heterogeneity. These subgroups included: intensity of anticholinergic protocol, baseline severity, co therapies, and methodological quality of the studies. The meta-analysis was performed with the Review Manager 4.2.7 software (Cochrane Review Manager, Cochrane Collaboration, Oxford, UK: 2004).

RESULTS

A total of 88 studies were examined in full text for possible inclusion; 56 studies were excluded for the following reasons: non-randomised trials (n = 4), non-acute asthma (n = 14), anticholinergics alone were studied (n = 6), hospitalised patients (n = 8), use of atropine (n = 5), chronic asthma (n = 18), and use of intravenous route (n = 1). Finally, a total of 32 randomised controlled trials (16 including children and adolescents,[12-27] and 16 including adults[28-43]) were selected (Tables 1 and 2). Five studies were supported by Boehringer Ingelheim [17-18,35-37] Data for 3611 subjects (1564 children and adolescents, and 2047 adults) were available for meta-analysis. There was a total agreement between the two independent reviewers on inclusion of studies and Jadad study quality grading. The anticholinergic agent used was ipratropium bromide in twenty-nine studies,[12-32,34-38,40,42-43] oxitropium bromide in two studies,[39,41] and glycopirrolate in one study.[33] Trials were grouped according to the intensity of the anticholinergic treatment: trials testing the addition of a single dose of anticholinergic to beta2-agonist inhalations were named single dose protocols, and trials testing more than one dose were grouped as multiple dose protocols. Thirteen studies (5 in children,[12-13,16,18,21] and 8 in adults[28-29,31-33,36,38,43]) tested a single dose protocol and the remaining 19 trials used more than one dose of anticholinergic. Of these, 18 studies tested multiple doses in a pre-determined fixed regimen (multiple dose-fixed protocol), and one study tested the addition of anticholinergics to every beta2-agonist inhalation, leaving the number of inhalations determined by the patient's needs (multiple dose flexible protocol).[20] One trial, tested the first two protocols.[18] Asthma severity was defined at baseline by spirometry (FEV_1 or PEFR 70-50% of predicted = moderate exacerbation, and FEV_1 or PEFR < 50% of predicted = severe exacerbation) or different clinical scores. Most enrolled acute asthma patients had moderate to severe exacerbations, but

several studies reported data stratified on asthma severity.[22-24,37,41-42] The most frequently reported outcomes were hospital admission (20 studies) and spirometry (26 studies); respiratory resistance measured by forced oscillation was used in one trial.[21] One study did not provide spirometry data nor admission rates.[13] Clinical scores were used only in a few studies, and the reporting of adverse effects was variable.

Hospital admissions.

Ten studies accumulating 1786 children and adolescents reported hospital admissions.[14,17-19,21-24,26-27] One study tested two protocols (single and multiple fixed dose),[18] and three trials reported data stratified by asthma severity (moderate and severe patients).[22-24] At the end of treatment, patients that received inhaled beta2-agonists and anticholinergics showed a significantly lower admission rate (Figure 1). The NNT was 13 (95% CI: 9 to 28), indicating that thirteen children needed to be treated with beta2-agonists and anticholinergics to prevent one admission. There was no evidence of systematic bias identified by the measure of funnel plot asymmetry. Also, no significant heterogeneity was demonstrated, which accepts the null hypothesis of similar treatment effects. Stratification on the basis of baseline severity (moderate vs. severe) and the intensity of the anticholinergic protocol (single vs. multiple fixed dose protocol) suggested a trend towards a reduced risk of admission in children with the most severe asthma attack and treated with multiple doses of anticholinergics. The NNT to prevent one admission among severe patients was 7 (95% CI: 4 to 16). Hospital admission rate did not change when we excluded studies without explicit admission criteria (RR = 0.73; 95% CI: 0.62 to 0.85, I^2 = 0%). Finally, the use of systemic CCS did not modify this outcome (RR = 0.69; 95% CI: 0.58 to 0.81).

Nine trials totalling 1556 adults with acute asthma reported hospitalizations.[33-38,40-42] One trial reported data stratified on asthma severity (moderate and severe patients).[42] There was a significant reduction in the hospital admission rate favouring anticholinergic use (Figure 2). The NNT was 14 (95% CI: 9 to 30). There was no evidence of systematic bias identified by the measure of funnel plot asymmetry. Again, no significant heterogeneity was demonstrated. Stratification on the basis of baseline severity (moderate vs. severe) and the intensity of the anticholinergic protocol (single vs. multiple fixed dose) suggested a trend towards a reduced risk of admission in adults with the most severe asthma attack and treated with multiple doses of anticholinergics (Figure 2). Intensity of anticholinergic treatment greatly influenced the reduction in hospital admission; a greater reduction was observed with trials that use 3 or more doses of anticholinergics (RR = 0.53; 95% CI: 0.36 to 0.76, p = 0.0006, NNT = 6; 95% CI: 4 to 13). These results did not change when we only pooled studies with explicit admission criteria (RR = 0.58; 95% CI: 0.38 to 0.87, I^2 = 28%). and when systemic CCS were used (RR = 0.74; 95% CI: 0.48 to 1.14).

Spirometric testing.

Nine studies examined response to treatment in acute asthma children and adolescents using spirometry.[12,14-16,18-19,22,25,27] Five trials reported percent of change in FEV_1,[12,14-16,25] three reported percent of change in PEFR,[19,22,27] one reported change in percent of predicted FEV_1,[18] and one study reported percent of change in respiratory resistance.[21] One trial tested two protocols,[18] (single and multiple-fixed dose) and one study presented data stratified by severity of obstruction (moderate and severity).[22] Data was documented between 60 and 120 min after the

last combined treatment. When we pooled all studies, a significant improvement in spirometry favoured combination treatment (SMD = - 0.54; 95% CI: -0.28 to -0.81, p = 0.0001). However, there was significant heterogeneity (x^2 = 23.41, df = 10, I^2 = 57.3%, p = 0.009). When we pooled the seven studies that reported FEV_1 data (change in percent of predict or percent of change),[12,14-16,18,25,27] stratified by the intensity of anticholinergic treatment (one or two doses vs. more than two doses), homogeneity was achieved (Figure 3). The use of more than two doses of anticholinergics showed more benefit than the use of lower doses. There was no evidence of systematic bias. Patients treated with one or two doses of anticholinergics showed a 12.4% mean difference (95% CI: 5.4 to 19.4) of change in FEV_1 compared with patients that did not receive anticholinergics, whereas patients that received more than doses showed a 16.3% (95% CI: 8.2 to 24.5) mean difference.

Spirometry was reported by 16 studies of adult subjects.[28-43] Two trials showed data stratified by severity of obstruction (moderate and severity).[41-42] Eight trials reported FEV_1 (L),[28-29,34-37,39,42] eleven reported PEFR (L/min),[29-32,34,38-43] and one reported FEV_1 (% predicted).[33] Combined treatment produced significantly greater increase in spirometry than beta2-agonists alone (SMD = -0.36; 95% CI: -0.23 to -0.49, p = 0.00001). There was a significant heterogeneity between trials (x^2 = 25.5, df = 15, I^2 = 41.3%, p = 0.04). Homogeneity was achieved when studies that reported PEFR (L/min) were stratified by intensity of anticholinergic treatment (Figure 4).[29-32,34,38-43] Again, the use of more than two doses of anticholinergics showed higher benefit than one or two doses and there was no evidence of systematic bias. As previously observed for PEFR, patients treated with more than two doses of anticholinergics showed a 0.44 L (95% CI: 0.25 to 0.63) significant FEV_1 difference, whereas those who were treated with one or two doses experienced only a 0.15 L (95% CI: 0.05 to 0.24) difference.

Other outcomes.

Three paediatric studies [21-22,24] reported a significant reduction of clinical score after combined treatment (SMD = -0.29; 95% CI: -0.51 to -0.07, p = 0.01). No significant heterogeneity was demonstrated (x^2 = 1.33, df = 3, p = 0.72, I^2 = 0%. No apparent increase in the occurrence of side effects among subjects treated with either single or multiple dose protocols was demonstrated. Thus, there was no significant difference between groups in the five children studies that reported the presence of tremor (RR = 1.15; 95% CI: 0.79 to 1.69, p = 0.46).[13-14,17-18,27] Identical pattern was seen in three adult studies that reported the same variable (RR = 1.28; 95% CI: 0.92 – 1.78, p = 0.14).[31,35,42] Finally, six adult trials that evaluated the effect of treatment on heart rate did not find difference between groups (WMD = -2.07; 95% CI: -4.35 to 0.21, p = 0.07).[28-29,31,34-35,42] There was insufficient information to pool outcomes such as oxygen saturation due to the insufficient number of trials reporting this outcome. Analysis of the only trial which tested the administration of multiple inhalations of combined treatment until satisfactory clinical response (multiple dose-flexible protocol) showed a significant decrease of a clinical score at 30-45 min between patients treated with salbutamol and ipratropium and patients treated with salbutamol alone.[20]

DISCUSSION

This systematic review constitutes an effort to incorporate the best evidence available up to April 2005 on the role of inhaled anticholinergics added to beta2-agonists in children, adolescents and adults with acute asthma in the ED setting. We found and

added new data to previous review.[3,5] Thus, ten new randomised trials (4 in children,[24-27] and 6 in adults[33-34,39,41-43) with a total of 809 patients have been detected representing an increase of 22% on the previous sample. Unlike the previous ones, this study has enabled analysis of the effect of cumulative doses, particularly in adult studies. Several important conclusions arise from this analysis. Overall, our analysis confirmed that early administration of inhaled anticholinergics with beta2-agonists lead to 30 % reduction in admission rates as much in children as in adults. Baseline severity and the intensity of anticholinergic protocol clearly influenced the magnitude of benefit. Therefore, the anticholinergic benefit is particularly important in those patients with moderate to severe obstruction (FEV_1 < 70% of predicted) and that have been treated with multiple dose fixed protocols consistent of three or more doses of an anticholinergic. These patients showed a 30 to 45% reduction in the hospital admission rate, and only 6 to 14 subjects need to be treated to prevent one hospitalisation. This is a very relevant finding since hospital admissions count for the largest part of direct health-costs for asthma in most countries, and those children or adults with more severe asthma attack are more prone to will admit to the hospital. Contrary, this review did not identify any beneficial effects of anticholinergic agents in patients with mild acute asthma. The fact that the use of systemic CCS has not shown a significant effect is concordant with the evidence that they require 6 to 12 hours to modify outcomes like hospital admission or spirometry.[44-45] The short duration of the study period in all trials was such it is improbable that these drugs could have a significant contribution.

Regarding spirometric testing, significant differences favouring the combination treatment were observed in both, children and adults trials. Again, there was a dose-response relationship; the greater benefit was obtained when patients were treated with more than two doses of anticholinergics along with a beta2-agonist. In adults, therapy with more than two doses produced clinically significant improvements in terms of FEV_1 (0.44 L) or PEFR (50.5 L/min).[46]

In our meta-analysis we also looked at secondary outcomes and side effects. However, it was difficult to analyze due to insufficient information to be pooled. A few children studies reported a significant reduction of different clinical scores after combined treatment. Finally, no apparent increase in the occurrence of side effects was observed among subjects treated with single or multiple dose protocols (tremor, heart rate).

Strengths and limitations

This study met most of the methodological criteria suggested for scientific reviews.[47] Similar to all systematic reviews, this meta-analysis is limited by the quality and quantity of existing research and how data are reported. A comprehensive search of the published literature for potentially relevant studies was conducted using a systematic strategy to avoid bias. All of the 32 trials were randomised, mostly (26 of 32) double blind. Exclusion of trials with lower methodological quality did not affect the conclusions. In addition, the assessment of the consistency of effects across studies is an essential part of the review to determine the generalisability of the findings. Thus, we obtained low values of heterogeneity (< 15%) in all group and subgroup comparisons. Finally, the generalisability of study results to different countries should be considered, particularly with regard to the hospital admission criteria. The decision to admit patients is based on many factors, including past asthma and current exacerbation histories, and

spirometric tests results, as well as clinical factors. Thus, important variations in admission criteria could influence the results. However, the results did not change when we only analyzed studies that displayed explicit criteria of hospitalization.

COMPETING INTEREST STATEMENT:

GJR: have been received from Boehringer Ingelheim several fees for speaking.

JACR: in the past five years have been received reimbursement for attending conferences from Grünenthal, Merck, GlaxoSmithKline and Andromaco, and at the present he is medical advisor for GSK. The position of this paper is a personal opinion and does not express the opinion of any pharmaceutical company.

FIGURE CAPTIONS

Figure 1. Pooled relative risk for hospital admission (with 95% confidence interval) of eligible children studies comparing addition of anticholinergics to beta2-agonists (treatment) with beta2-agonists alone (control). Trials stratified according intensity of anticholinergic treatment (single or multiple fixed dose protocols) and asthma severity (moderate or severe patients).

Figure 2. Pooled relative risk for hospital admission (with 95% confidence interval) of eligible adult studies comparing addition of anticholinergics to beta2-agonists (treatment) with beta2-agonists alone (control). Trials stratified according intensity of anticholinergic treatment (single or multiple fixed dose protocols) and asthma severity (moderate or severe patients).

Figure 3. Pooled standardised mean difference (with 95% confidence interval) in forced expiratory in 1 second (change in percent of predict or percent of change) of children studies comparing addition of anticholinergics to beta2-agonists (treatment) with beta2-agonists alone (control). Trials stratified according the intensity of anticholinergic treatment (one or two doses vs. more than two doses).

Figure 4. Pooled weighted mean difference (with 95% confidence interval) in peak expiratory flow rate (L/min) of studies in adults comparing addition of anticholinergics to beta2-agonists (treatment) with beta2-agonists alone (control). Trials stratified by intensity of anticholinergic treatment (one or two doses vs. more than two doses).

REFERENCES

1. Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults. A review. Chest 2004;125:1091-1102.
2. Global Strategy for Asthma Management and Prevention. NIH Publication 02-3659, 2004. Available on www: ginasthma.com. Accessed December 31, 2004.
3. British Thoracic Society and others. Guidelines on the management of asthma. Management of acute asthma. Thorax 2003;58:i32-50.
4. Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of ipratropium bromide in adults with acute asthma. Am J Med 1999;107-363-70.
5. 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.
6. Plotnick LH, Ducharme FM. Combined inhaled anticholinergics and beta2-agonists for initial treatment of acute asthma in children. The Cochrane Database of Systematic Reviews 2000, Issue 3. Art. No.: CD000060. DOI: 10. 1002/14651858. CD000060.
7. Rodrigo GJ, Rodrigo C. The role of anticholinergics in acute asthma treatment. An evidence-based evaluation. Chest 2002;121:1977-87.
8. Jadad AR, Moore RA, Carroll D, Jenkinson C, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. Control Clin Trials 1996;17:1-12.
9. DerSomonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.
10. Higgins JPT, Thompson SG, Deecks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.
11. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.
12. Beck R, Robertson C, Galdes-Sebaldt M, et al. Combined salbutamol and ipratropium bromide by inhalation in the treatment of severe acute asthma. J Pediatrics 1985;107:605-68.
13. Cook JJ, Fergusson DM, Dawson KP. Ipratropium and fenoterol in the treatment of acute asthma. Pharmatherapeutica 1985;4:383-86.
14. Reisman J, Galdes-Sebaldt M, Kazim F, et al. Frequent administration of inhalation of salbutamol and ipratropium bromide in the initial management of severe acute asthma children. J Allergy Clin Immunol 1988;81:16-20.
15. Watson WTA, Becker AB, Simmons FER. Comparison of ipratropium solution, fenoterol solution and their combination administered by nebulizer and face mask to children with acute asthma. J Allergy Clin Immunol 1988;82:1012-18.
16. Phanichyakam P, Kraisarin C, Sasisakulporn C. Comparison of inhaled terbutaline and inhaled terbutaline plus ipratropium bromide in acute asthmatic children. Asian Pacific J Allergy Immunol 1990;8:45-48.
17. Peterson R, Wensley D, Mitchell I, et al. Boehringer Ingelheim Trial No. 2442430, 3. 1994.
18. Schuh S, Johnson DW, Callahan S, et al. Efficacy of frequent nebulized ipratropium added to frequent high-dose albuterol therapy in severe childhood asthma. J Pediatrics 1995;126:639-45.

19. Qureshi FA, Zaritsky A, Lakkis H. Efficacy of nebulized ipratropium in severe asthmatic children. Ann Emerg Med 1997;29:205-11.
20. Calvo GM, Calvo AM, Marin HF, et al. Is it useful to add an anticholinergic treatment to beta2-adrenergic medication in acute asthma attack? J Invest Allergy Clin Immunol 1998;8:30-34.
21. Ducharme FM, Davis GM. Randomized controlled trial of ipratropium bromide and frequent low doses of salbutamol in the treatment of mild and moderate acute asthma. J Pediatrics 1998; 133:479-85.
22. Qureshi F, Pestian J, Davis P, et al. Effect of nebulized ipratropium on the hospitalization rates of children with asthma. N Engl J Med 1998;339:1030-35.
23. Zorc JJ, Pusic MV, Ogborn CJ, et al. Ipratropium bromide added to asthma treatment in the pediatric emergency department. Pediatrics 1999;103:748-52.
24. Benito Fernández J, Maintegui Raso S, Sánchez Echanitz J, et al. Eficacia de la administración precoz de bromuro de ipratropio nebulizado en niños con crisis asmática. An Esp Pediatr 2000;53:217-22.
25. Sienra Monje JJL, Bermejo Guevara MA, del Rio Navarro BE, et al. Grado y duración de la broncodilatación mediante la administración de un agonista β2 solo vs un agonista β2 mas bromuro de ipratropio en niños con asma aguda. Rev Alergia México 2000;XLVII:26-29.
26. Timsit S, Sannier N, Bocquet N, et al. Apport du bromure d'ipratropium dans la prise en charge des crises d'asthme aux urgencies. Arch Pédiatr 2002;9:117-24.
27. Sharma A, Madaan A. Nebulized salbutamol vs salbutamol and ipratropium combination in asthma. Indian J Pediatr 2004;71:121-24.
28. Bryant DH. Nebulized ipratropium bromide in the treatment of acute asthma. Chest 1985;88:24-9.
29. Rebuck AS, Chapman KR, Abboud R, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. Am J Med 1987;82:59-64.
30. Higgins RM, Stradling JR, Lane DJ. Should ipratropium be added to beta-agonists in treatment of acute severe asthma? Chest 1988;94:718-22.
31. O'Driscoll BR, Taylor RJ, Horsley MG, et al. Nebulised salbutamol with and without ipratropium bromide in acute airflow obstruction. Lancet 1989;i:1418-20.
32. Summers QA, Tarala RA. Nebulized ipratropium in the treatment of acute asthma. Chest 1990;97:430-34.
33. Cydulka RK, Emerman CL. Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of asthma. Ann Emerg Med 1994;23:270-74.
34. Rodrigo G, Rodrigo C. Tratamiento de la crisis asmática con altas dosis de salbutamol y bromuro de ipratropio administrados mediante inhalador de dosis medida e inhalocámara. Pac Critico 1995;8:175-84.
35. Karpel JP, Schacter EN, Fanta Ch, et al. A comparison of ipratropium and albuterol vs. albuterol alone for the treatment of acute asthma. Chest 1996;110:611-16.
36. FitzGerald JM, Grunfeld A, Pare PD, et al. The clinical efficacy of combination nebulized anticholinergic and adrenergic bronchodilators vs. nebulized adrenergic bronchodilator alone in acute asthma. Chest 1997;111:311-15.

37. Garret JE, Town GI, Rodwell P, et al. Nebulized salbutamol with and without ipratropium bromide in the treatment of acute asthma. J Allergy Clin Immunol 1997;100:165-70.
38. Lin RY, Pesola GR, Bakalchuk L, et al. Superiority of ipratropium plus albuterol over albuterol alone in the emergency department management of adult asthma: a randomized clinical trial. Ann Emerg Med 1998;1998:31:208-13.
39. Kamei T, Fujita J, Okada H, et al. Comparison between fenoterol and fenoterol plus oxytropium bromide delivered by metered-dose inhaler with inspirease to relief acute asthma attack. J Asthma 1999;36:67-75.
40. Weber EJ, Levitt A, Covington JK, et al. E. Effect of continuously nebulized ipratropium bromide plus albuterol on emergency department length of stay and hospital admission rates in patients with acute bronchospasm. A randomized, controlled trial. Chest 1999;115:937-44.
41. Nakano Y, Enomoto N, Kawamoto A, et al. Efficacy of adding multiple doses of oxitropium bromide to salbutamol delivered by jeans of a metered-dose inhaler with a spacer device in adults with acute severe asthma. J Allergy Clin Immunol 2000;106:472-8.
42. 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. Am J Respir Crit Care Med 2000;161:1868-00.
43. Aggarwal P, Singh O, Wali JP, et al. Efficacy of nebulised ipratropium in acute bronchial asthma. J Indian Acad Clin Med 2002;3:353-9.
44. Rodrigo G, Rodrigo C. Corticosteroids in the emergency department therapy of acute adult asthma. An evidence-based evaluation. Chest 1999;116:285-295.
45. Rowe BH, Spooner C, Ducharme FM, et al. Early emergency department treatment of acute asthma with systemic corticosteroids. The Cochrane Database of Systematic Reviews 2001, Issue 1. Art. No.: CD002178. DOI: 10.1002/14651858.CD002178.
46. Santanello NC, Zhang J, Seidenberg B, et al. What are minimal important changes for asthma measures in clinical trial? Eur Respir J 1999;14:23-27.
47. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomized controlled trials: the QUOROM statement. Lancet 1999;354:1896-00.

Table 1.

Characteristics of children trials included in the review.

Study (year)	Design	Language & Country	Jadad Score	No Patients (age)	Mean Baseline Severity	B-Agonist Dose	Anticholinergic Dose	CCS Use
Beck et al (1985)[12]	R,DB	E, Canada	3	25 (6-17 y)	FEV_1<50 %	S 0.05 mg/kg q20 min Neb x 6	IB 0.25 mg Neb x 1	No
Cook et al. (1985)[13]	R,DB	E, Australia	4	30 (18m-12 y)	NR	F 0.125-0.5 ml Neb x 1	IB 1-2 ml Neb x 1	No
Reisman et al. 1988) [14]	R,DB	E, Canada	3	24 (5-15 y)	FEV_1<55 %	S 0.05 mg Q20 min Neb x 6	IB 0.25 mg Neb x 3	No
Watson et al. (1988) [15]	R,DB	E, Canada	3	31 (6-17 y)	FEV_1 30-70%	F 0.62 mg q60 min Neb x2	IB 0.25 mg Q60 min Neb x 2	Yes
Phanichyakam et al. (1990)[16]	R,DB	E, Thailand	1	20 (4-15 y)	NR	T 0.5 mg MDI x 1	IB 0.04 mg MDI x 1	No
Peterson et al. (1994) [17]	R,DB	E, Canada	5	163 (5-12 y)	FEV_1<70 %	S 3 mg q45 min Neb x 2	IB 0.25 mg Q45 min Neb x 2	Yes
Schuh et al. (1995)[18]	R,DB	E, Canada	5	80 (5-17 y)	FEV_1<50 %	S 0.15 mg/kg` q20 min Neb x 3	IB 0.25 mg Neb x 1 or IB 0.25 mg Neb x 3	No
Qureshi et al. (1997)[19]	R,DB	E, USA	5	90 (6-18 y)	FEV_1<50 %	S 0.15 mg/kg q30 min Neb x 3	IB 0.5 mg Neb x 2	Yes
Calvo et al. (1998)[20]	R,DB	SP, Chile	3	80 (18-55 y)	PEFR<80%	S 0.2 mg q15 min MDI x 4	IB 0.04 mg q15 min MDI x 4	Yes
Ducharme et al. (1998)[21]	R,DB	E, Canada	5	298 (2-18 y)	Mild-Moderate	S 0.07 mg/kg q30 min Neb	IB 0.25 mg Neb x 1	Yes
Qureshi et al.	R,DB	E, USA	5	434 (2-18 y)	Moderate-Severe	S 2.5-5 mg q20	IB 0.5 mg q20 min Neb x 2	Yes

(1998)[22]						min Neb x 3		
Zorc et al. (1999)[23]	R,DB	E, USA	5	427 (1-17 y)	Moderate-Severe	S 2.5 mg q20 Neb x 3	IB 0.5 mg q20 min Neb x 3	Yes
Benito Fernandez et al. (2000)[24]	R,SB	SP, Spain	5	102 (5m-16 y)	Severe	S 0.2 mg/kg q30 min Neb x 2	IB 0.25 q30 min Neb x 2	Yes
SienraMonge et al. (2000)[25]	R,DB	SP, Mexico	2	30 (8-15 y)	Moderate-Severe	S 0.2`mg q10 min MDI x 3	IB 0.02 mg q10 min MDI x 3	No
Timsit et al. (2002)[26]	R	F, France	3	114 (2-15 y)	Moderate	S 0.15 mg/kg q20 min Neb x 6	IB 0.25 mg q20 min Neb x 3	Yes
Sharma et al. (2004)[27]	R	E, India	2	50 (6-14 y)	Moderate-Severe	S 0.15 mg/kg q20 min Neb x 3	IB 0.25 mg q20 min Neb x3	No

R = Randomised; SB = Single blind; DB = Double blind; E = English; SP = Spanish; F = French; FEV_1 = Forced expiratory flow in the first second; PEFR = Peak expiratory flow rate; S = salbutamol; F = Fenoterol; T = Terbutaline; IB = Ipratropium bromide; CCS= Systemic corticosteroids; NR = non reported.

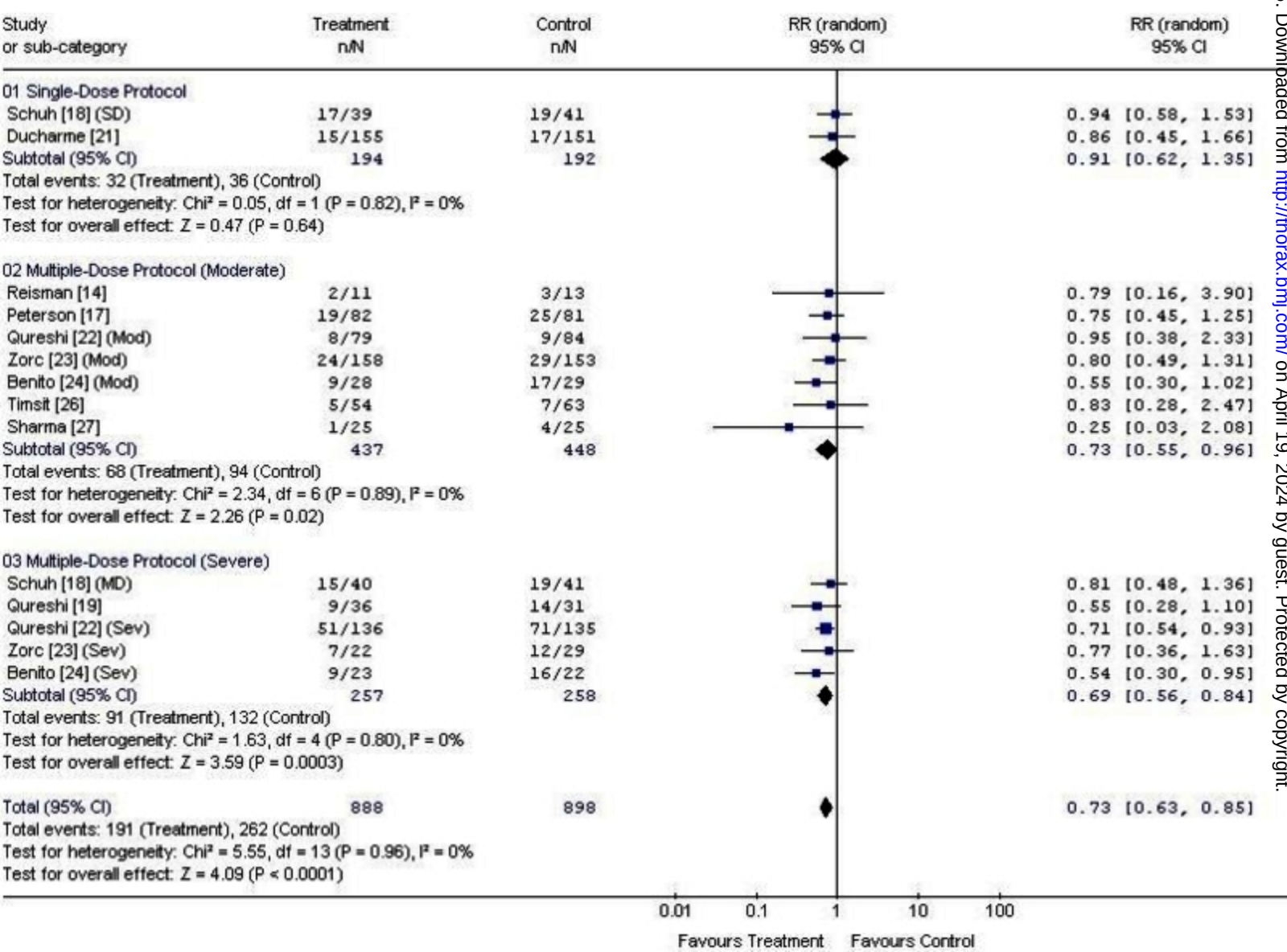
Table 2.

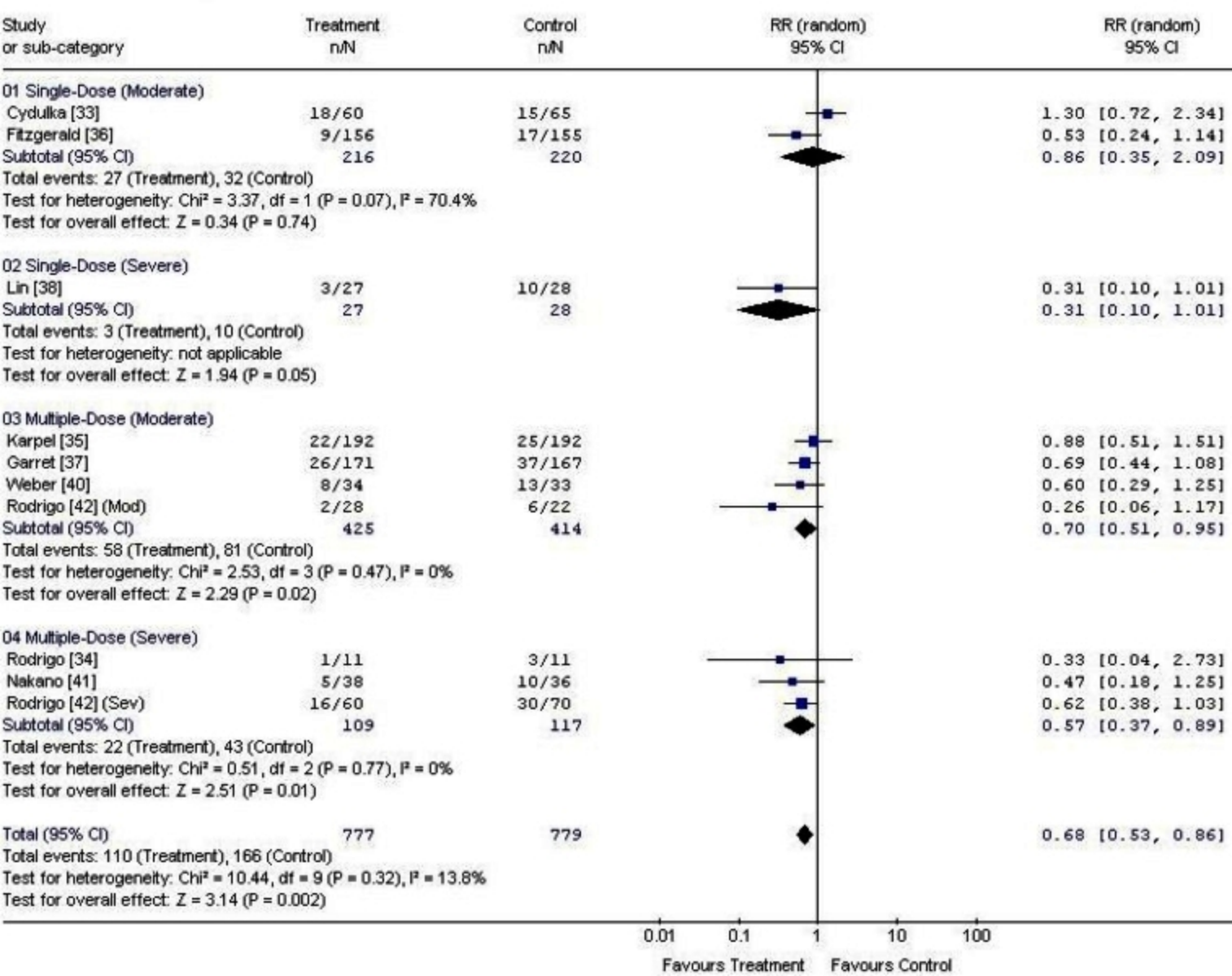
Characteristics of adult trials included in the review.

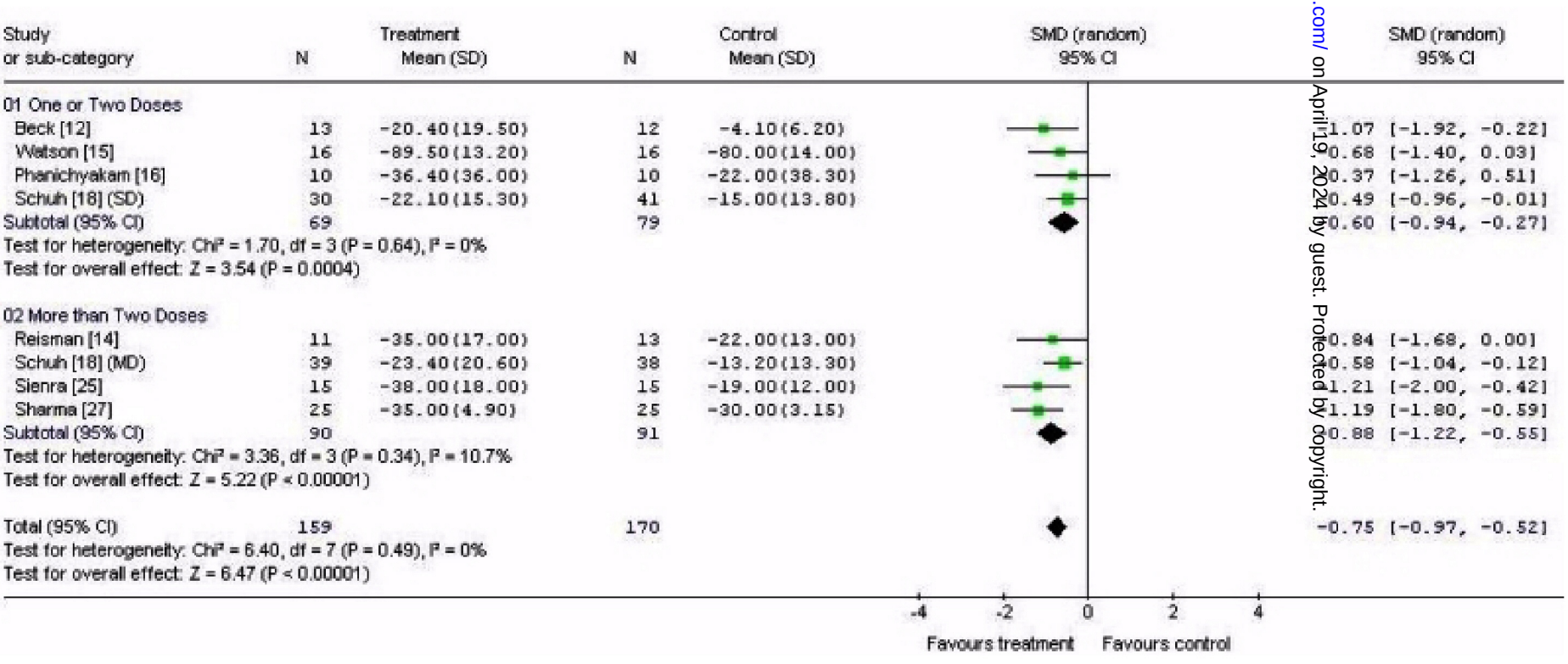
Study (year)	Design	Language & Country	Jadad Score	No Patients (age)	Mean Baseline Severity	B-Agonist Dose	Anticholinergic Dose	CCS Use
Bryant (1985)[28]	R,DB	E, Australia	2	28 (≥18 y)	FEV_1<75%	F 1 mg Neb x 1	IB 0.5 mg Neb x 1	No
Rebuck et al. (1987) [29]	MC,R, DB	E, Canada	4	148 (≥18 y)	FEV_1<70%	F 1.25mg Neb x 1	IB 0.5 mg Neb x 1	Yes
Higgins et al. (1988) [30]	R,DB	E, England	2	40 (≥18 y)	PEF<30%	S 5mg q120 min Neb x 2	IB 0.5 mg q120 min Neb x 2	Yes
O'Driscoll et al. (1989) [31]	R,DB	E, England	2	56 (≥18 y)	PEF<35%	S 10 mg Neb x 1	IB 0.5 mg Neb x 1	Yes
Summers & Tarala (1990) [32]	R,DB	E, Australia	3	76 (16-70 y)	PEF<60%	S 5 mg Neb x1	IB 0.5 mg Neb x 1	Yes
Cydulka & Emerman (1994)[33]	R,DB	E, USA	3	125 (≥18 y)	FEV_1<75%	S 2.5 mg q60 min Neb x 3	Gly 2 mg Neb x 1	Yes
Rodrigo & Rodrigo (1995)[34]	R,DB	SP, Uruguay	3	22 (18-50 y)	FEV_1<50%	S 0.4 mg q10 min MDI x 3h	IB 0.08 mg q10 min MDI x 3h	No
Karpel et al. (1996)[35]	MC,R, DB	E, USA	5	384 (18-55 y)	FEV_1<60%	S 2.5 mg q45 min Neb x 2	IB 0.5 mg Neb q45 min Neb x 2	No
FitzGerald et al. (1997) [36]	MC,R, DB	E, Canada	3	342 (18-50 y)	FEV_1<70%	S 3 mg Neb x 1	IB 0.5 mg Neb x 1	Yes
Garret et al. (1997)[37]	TC, R,DB	E, New Zealand	4	338 (18-55 y)	FEV_1<70%	S 2.5 mg q45 min Neb x 2	IB 0.5 mg q45 min Neb x 2	Yes
Lin et al. (1998)[38]	R,DB	E, USA	4	55 (≥18 y)	PEF<200 L/min	S 2.5 mg q20 min Neb x 3	IB 0.5 mg Neb x 1	No
Kamei et al. (1999)[39]	MC,R	E, Japan	3	64 (≥18 y)	FEV_1<70%	F 0.2 mg q1 min MDI x 5	OB 0.1 mg q1 min MDI x 5	Yes
Weber et al. (1999)[40]	R,DB	E, USA	5	67 (≥18 y)	PEF<70%	S 10mg q1 h Neb x 3 h	IB 1 mg q1 h Neb x 3h	No

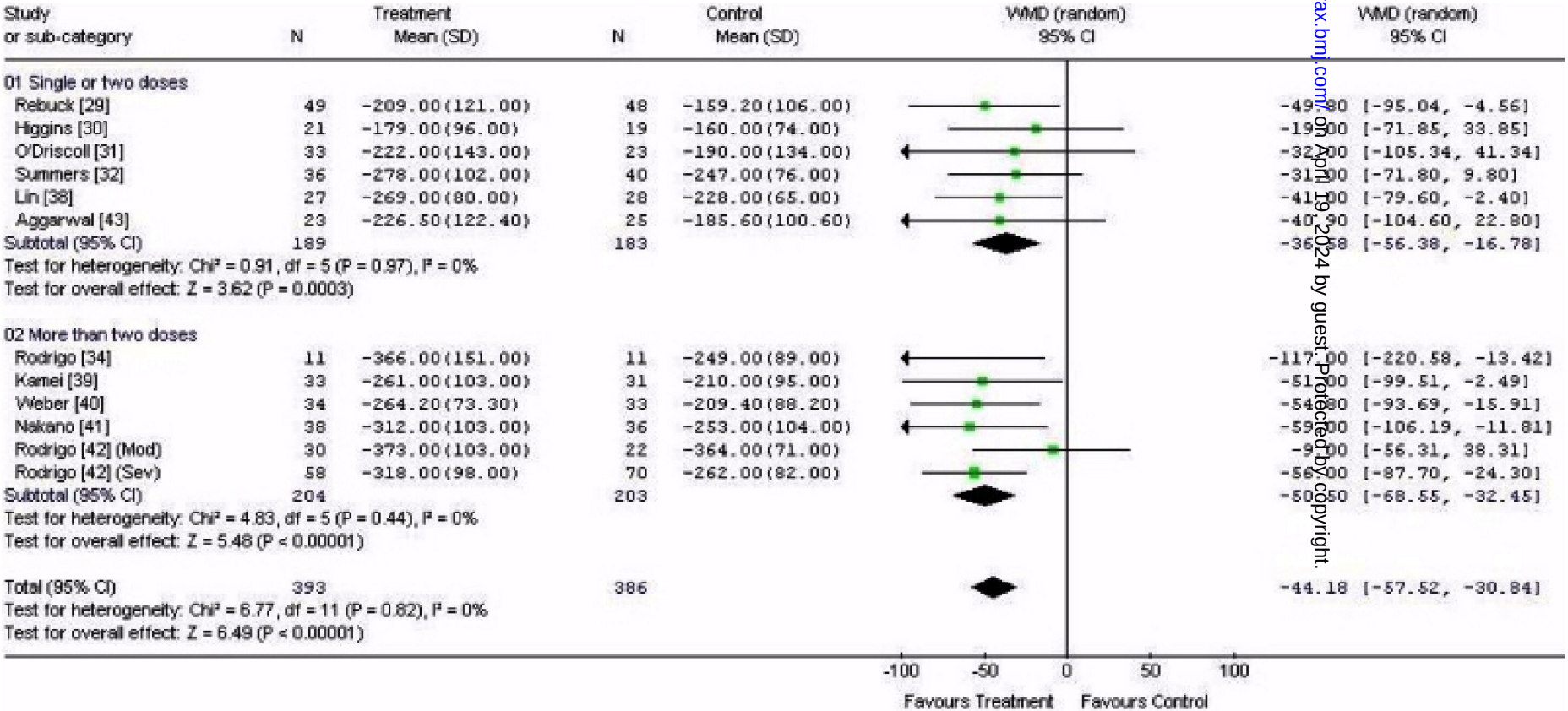
Nakano et al. (2000) [41]	R,SB	E, Japan	4	74 (≥18 y)	PEF<50%	S 0.4 mg q20 min MDI x 3	OB 0.4 mg q20 min MDI x 3	Yes
Rodrigo & Rodrigo (2000)[42]	R,DB	E, Uruguay	5	180 (18-50 y)	FEV_1<50%	S 0.4 mg q10 min MDI x 3h	IB 0.08 mg q10 min MDI x 3 h	No
Aggarwal et al. (2002) [43]	R	E, India	2	48 (13-50 y)	PEF<50%	S 5 mg q60 min Neb x 2	IB 0.5 mg Neb x 1	No

MC = Multicenter; TC = Two center; R = Randomised; SB = Single blind; DB = Double blind; E = English; SP= Spanish; FEV_1 = Forced expiratory flow in the first second; PEF = Peak expiratory flow; S = salbutamol; F = Fenoterol; IB = Ipratropium bromide; OB = Oxitropium bromide; Gly = Glycopirrolate; CCS = Systemic corticosteroids.




Study
or sub-category
Treatment
n/N
Control
n/N
RR (random)
95% CI
RR (random)
95% CI
01 Single-Dose (Moderate)
Cydulka [33] 18/60 15/65 1.30 [0.72, 2.34]
Fitzgerald [36] 9/156 17/155 0.53 [0.24, 1.14]
Subtotal (95% CI) 216 220 0.86 [0.35, 2.09]
Total events: 27 (Treatment), 32 (Control)
Test for heterogeneity: Chi² = 3.37, df = 1 (P = 0.07), I² = 70.4%
Test for overall effect: Z = 0.34 (P = 0.74)
02 Single-Dose (Severe)
Lin [38] 3/27 10/28 0.31 [0.10, 1.01]
Subtotal (95% CI) 27 28 0.31 [0.10, 1.01]
Total events: 3 (Treatment), 10 (Control)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.94 (P = 0.05)
03 Multiple-Dose (Moderate)
Karpel [35] 22/192 25/192 0.88 [0.51, 1.51]
Garret [37] 26/171 37/167 0.69 [0.44, 1.08]
Weber [40] 8/34 13/33 0.60 [0.29, 1.25]
Rodrigo [42] (Mod) 2/28 6/22 0.26 [0.06, 1.17]
Subtotal (95% CI) 425 414 0.70 [0.51, 0.95]
Total events: 58 (Treatment), 81 (Control)
Test for heterogeneity: Chi² = 2.53, df = 3 (P = 0.47), I² = 0%
Test for overall effect: Z = 2.29 (P = 0.02)
04 Multiple-Dose (Severe)
Rodrigo [34] 1/11 3/11 0.33 [0.04, 2.73]
Nakano [41] 5/38 10/36 0.47 [0.18, 1.25]
Rodrigo [42] (Sev) 16/60 30/70 0.62 [0.38, 1.03]
Subtotal (95% CI) 109 117 0.57 [0.37, 0.89]
Total events: 22 (Treatment), 43 (Control)
Test for heterogeneity: Chi² = 0.51, df = 2 (P = 0.77), I² = 0%
Test for overall effect: Z = 2.51 (P = 0.01)
Total (95% CI) 777 779 0.68 [0.53, 0.86]
Total events: 110 (Treatment), 166 (Control)
Test for heterogeneity: Chi² = 10.44, df = 9 (P = 0.32), I² = 13.8%
Test for overall effect: Z = 3.14 (P = 0.002)
0.01
0.1
1
10
100
Favours Treatment
Favours Control





had a chest CT scan on referral. They fail, however, to describe a role for chest CT, but do imply that it may be indicated for patients undergoing video-assisted thoracoscopic drainage (VATS). There is no evidence in the current literature supporting the use of CT scans before VATS. The British Thoracic Society guidelines do not recommend routine CT scans in children with empyema.[2]

In our centre all patients with empyema requiring intervention undergo VATS (approximately 40/year). We would suggest that chest CT scanning is not indicated before VATS in nearly all cases. We have found chest CT scans to be helpful, however, in situations where the patient has not responded to appropriate treatment with antibiotics and VATS. In this situation the possibilities are reaccumulation of pleural fluid, abscess formation or more extensive parenchymal involvement, differential diagnoses that are distinguished by CT scanning and information that is critical to the decision to reoperate (or not).

In addition, Jaffe *et al* do not take the opportunity to critically examine the role of chest ultrasound scans in patients with empyema. In our experience, clinical examination and chest radiography can determine the presence of pleural fluid. If the purpose of the ultrasound scan is to determine whether the fluid is simple (a parapneumonic effusion) or organised (empyema), this can be achieved more simply with a lateral decubitus or erect chest radiograph. The decision to undertake definitive management with urokinase or VATS is determined by the presence of unremitting infection and/or fluid volume in the pleural space. It is an outdated paradigm that the distinction between simple and organised pleural fluid makes any difference to subsequent treatment or outcome. The main use for ultrasound scanning should be for those children who are found to have a unilateral whiteout on the chest radiograph at presentation and for whom the distinction between pleural space and parenchymal disease is difficult to make.

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REFERENCES

1. **Jaffe A,** Calder AD, Owens CM, *et al*. The role of routine computed tomography in paediatric pleural empyema. *Thorax*. Published Online First 20 May 2008. doi: 10.1136/thx.2007.094250.
2. **Balfour-Lynn IM,** Abrahamson GC, Cohen G, *et al*. BTS guidelines for the management of pleural infection in children. *Thorax* 2005;**60**(Suppl 1):i1–21.

Author's response

We thank Massie *et al* for correctly questioning the clinical need for routine chest CT scanning before performing video-assisted thoracoscopic surgery (VATS). Our study was pragmatically designed to reflect clinical practice in our institute, where thoracic surgeons routinely request a pre-operative CT scan for use as a "road map" when performing minimally invasive endoscopic surgery where direct visual access is limited. This helps to plan and assist in placement of the ports and instruments in order to decrease risk and avoid potential complications such as bronchopleural fistula which would result as a consequence of puncturing the lung parenchyma in close proximity to the pleura. We agree with them that there is no evidence base to support this practice in terms of risk, and our study was not designed to answer this question.

The principle of providing surgical "road maps" (which cross-sectional imaging now provides) is prevalent in many areas of cardiothoracic imaging where CT and MRI are added as an adjunct to echocardiography and ultrasound scans in order to enhance anatomical (and, indeed, sometimes functional) information to enhance quality and provide a safer more informed patient journey.

We are surprised that Massie *et al* advocate the use of a lateral decubitus chest radiograph in place of an ultrasound scan which is not, in fact, a recommendation of the BTS guidelines. Indeed, this would be a retrograde step in terms of the quality of information and the radiation burden, and should only be advocated where there is no access to ultrasound.

As discussed in our paper, ultrasound is an invaluable tool as it is cheap, mobile, easy to use, can differentiate transonic from purulent fluid, solid lung from fluid and enables the radiologist to mark the spot for chest drain insertion. Although it has been used to stage the disease, we agree that it is not useful in predicting the clinical outcome as was evident in our study. Importantly, ultrasound does not carry a radiation burden.

One of the key messages we had hoped to emphasise in our study is the critical need to reduce exposure of children to unnecessary radiation. With this in mind, we disagree with Massie *et al* and continue to advocate the use of ultrasound as the most important imaging modality in managing children with empyema. The BTS guidelines also support this view.

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CORRECTIONS

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A U Wells, N Hirani, and on behalf of the British Thoracic Society Interstitial Lung Disease Guideline Group, a subgroup of the British Thoracic Society Standards of Care Committee, in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Soc. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. *Thorax* 2008;**63**(Suppl V):v1–v58.

The correct list of authors for these guidelines is: B Bradley, H M Branley, J J Egan (Irish Thoracic Society), M S Greaves, D M Hansell, N K Harrison, N Hirani, R Hubbard, F Lake (TSANZ), A B Millar, W A H Wallace, A U Wells, M K Whyte, M L Wilsher (TSANZ), The British Thoracic Society Standards of Care Committee, in collaboration with the Thoracic Society of Australia and New Zealand, and the Irish Thoracic Society.

doi:10.1136/thx.2005.047803corr1

G J Rodrigo, J A Castro-Rodriguez. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis (*Thorax* 2005;**60**:740–6). This article was originally published with an incorrect digital object identifier (doi). It has been updated with the correct doi: 10:1136/thx.2005.047803. We apologise for any inconvenience caused.

doi:10.1136/thx.2005.058156corr1

T Hirano, T Yamagata, M Gohda, *et al*. Inhibition of reactive nitrogen species production in COPD airways: comparison of inhaled corticosteroid and oral theophylline (*Thorax* 2006;**61**:761–6). This article was originally published with an incorrect digital object identifier (doi). It has been updated with the correct doi: 10.1136/thx.2005.058156. We apologise for any inconvenience caused.

doi:10.1136/thx.2005.057935corr1

J Batra, T P Singh, U Mabalirajan, *et al*. Association of inducible nitric oxide synthase with asthma severity, total serum immunoglobulin E and blood eosinophil levels (*Thorax* 2007;**62**:16–22). This article was originally published with an incorrect digital object identifier (doi). It has been updated with the correct doi: 10.1136/thx.2005.057935. We apologise for any inconvenience caused.

the UK may not see a single case of tuberculosis in several years.

Nevertheless, given the consequence of pulmonary tuberculosis to the individual and society, it is appropriate for clinicians and general practitioners to ensure that tuberculosis is among the differential diagnoses in patients with relevant symptoms and signs and to investigate for tuberculosis fairly promptly. Every attempt should be made to obtain a microbiological diagnosis. As Jolobe points out, it is also true that patients with smear-negative culture-positive tuberculosis can transmit infection, although less so than those who have a positive smear from direct sputum examination.[4] Exclusive extrapulmonary tuberculosis is, however, not infectious and the suggestion to the contrary is erroneous.

In view of the current rise in the incidence of tuberculosis, without high case detection and the adequate treatment of cases, tuberculosis may not remain an uncommon illness in the UK. Vigilance for both pulmonary and extrapulmonary tuberculosis is required.

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REFERENCES

1. **Kruijshaar ME,** Abubakar I. Increase in extrapulmonary tuberculosis in England and Wales 1999–2006. *Thorax* 2009;**64**:1090–5.
2. **French CE,** Kruijshaar ME, Jones JA, *et al*. The influence of socio-economic deprivation on tuberculosis treatment delays in England, 2000–2005. *Epidemiol Infect* 2009;**137**:591–6.
3. **Abubakar I,** Crofts JP, Gelb D, *et al*. Investigating urban-rural disparities in tuberculosis treatment outcome in England and Wales. *Epidemiol Infect* 2008;**136**:122–7.
4. **Behr MA,** Warren SA, Salamon H, *et al*. Transmission of Mycobacterium tuberculosis from patients smear-negative for acid-fast bacilli. *Lancet* 1999;**353**:444–9.

CORRECTION

doi:10.1136/thx.2005.040444

The paper entitled "Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis" by G J Rodrigo and J A Castro-Rodriguez (Thorax 2005;**60**:740–746. doi:10.1136/thx.2005.047803) was published twice online first, on one of those occasions with an incorrect DOI (doi:10.1136/thx.2005.040444).