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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).

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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.

Table 1 Statistical analysis of the case-control study

	Co-dominant				Dominant (AA/AG *v* GG)				Recessive (AA *v* AG/GG)			
	AA	AG	GG	p value	AA/AG	GG	OR (95% CI)	p value	AA	GG/AG	OR (95% CI)	p value
Controls	84 (41%)	82 (41%)	36 (18%)		166	36			84	116		
Cases	99 (47%)	93 (44%)	18 (9%)	**0.021**	192	18	**2.31 (1.27 to 4.23)**	**0.006**	99	111	1.25 (0.85 to 1.85)	0.276
Acute	30 (42%)	32 (45%)	9 (13%)	0.576	62	9	1.49 (0.68 to 3.28)	0.358	30	41	0.99 (0.57 to 1.71)	0.97
Chronic	59 (52%)	47 (41%)	8 (7%)	**0.021**	106	8	**2.87 (1.29 to 6.42)**	**0.007**	59	55	0.67 (0.43 to 1.07)	0.095

Significant associations are shown in bold.

(95% CI 1.29 to 6.42), p<0.0069; table 1) with a PAR for AA homozygotes and AG heterozygotes of 50%.

This study underlines the importance of the association of *BTNL2* rs2076530 variant with the susceptibility to develop sarcoidosis in a German population. Furthermore, our data suggest that susceptibility is preferentially towards the chronic form of the disease.

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Asthma and allergies in Germany

We read the study by Zöllner and colleagues published recently in *Thorax* about the levelling off of asthma and allergies among children in Germany between 1992 and 2001.[1] We have published a study looking at the same issue and using a similar protocol (ISAAC)[2] to assess the symptoms, diagnosis, and severity of asthma and allergies in more than 15 000 children aged 6–7 and 13–14 years between 1995 and 2000 in Münster, Germany.[3] We found a tendency towards an increase in current symptoms of asthma and allergies in both age groups, but more so among girls.[3]

Indices of diagnosis either remained the same or increased in parallel with the increase in symptoms, arguing against a change in diagnostic behaviour as an explanation for our results. Indices of severity also showed a homogenous increase in the 5 year study period, pointing towards an increase in the overall burden of asthma and allergies within the society.[3]

Regrettably, these results, coming from Germany, were not considered in either the discussion of Zöllner's report or in the affirmative title that no increase in asthma and allergies occurred in Germany in the 1990s. Even more regrettable is the fact that when our study was alluded to in the discussion and conclusion of the paper by Zöllner *et al*, it was cited—contrary to our results—as one of the studies showing a decrease or levelling off of asthma and allergies among children.[1]

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Authors' reply

Unfortunately, the paper by Maziak *et al*[1] published in *Allergy* was listed as reference number 18 instead of number 21 in the reference list of our paper.[2] We apologise for any misunderstanding which may have arisen from this error. A correction is published below.

In the paper by Maziak *et al*[1] the prevalences in 1994/5 and 1999/2000 are compared. As we know from our own studies, trend analyses based on (only) two time points may be difficult and should be interpreted with caution. Indeed, in their investigation Maziak *et al* did not find a significant increase in the lifetime prevalence of asthma and hay fever, except in one subgroup. The effect found in 13–14 year old girls could also be due to a former underdiagnosis of asthma in girls, as discussed in their paper.

Since our results are based on six cross sectional surveys, we consider the title and the conclusion—that we did not see an increase in asthma and allergies from 1992 to 2001—to be appropriate.

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CORRECTIONS

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In the paper entitled ''No increase in the prevalence of asthma, allergies, and atopic sensitisation among children in Germany: 1992–2001'' by I K Zöllner *et al* which appeared in the July 2005 issue of *Thorax* (2005;**60**:545–8), the authors apologise for a mistake which occurred in the reference list. Reference number 18 should be number 21 and references 19–21 should be listed as 18–20.

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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 (10.1136/thx.2005.040444) has been published previously on 17 June 2005 as a *Thorax* Online First article but under the incorrect DOI (10.1136/thx.2005.047803). The publishers apologise for this error. The definitive version of the article can be found at the following citation: *Thorax* 2005;**60**:740–6.

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In the paper entitled ''Hormone replacement therapy, body mass index and asthma in perimenopausal women: a cross sectional survey'' by F Gómez Real *et al* published in the January 2006 issue of *Thorax* (2006;**61**:34–40), the fourth author should be **K A Franklin**, not K Franklin.

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Bronchiectasis and non-tuberculous mycobacterial pulmonary infection

We read with great interest the paper by Wickremasinghe *et al* on the prevalence of non-tuberculous mycobacteria (NTM) in patients with bronchiectasis.[1] They showed that the prevalence of NTM was uncommon (only 2%) both in 50 newly referred patients and 50 follow up patients. However, the authors stated in the Discussion that ''it is now our practice to screen our patients routinely once a year'' because a large number of NTM isolates (28%) were detected by routine surveillance in their retrospective analysis of 71 patients with NTM sputum isolates.[1]

NTM pulmonary infection associated with bronchiectasis is increasing worldwide.[2] However, should routine periodic screening for NTM infection be necessary for all adult patients with bronchiectasis? Is sputum culture a sufficiently sensitive method to exclude active NTM infection? Are negative sputum studies sufficient to dissuade one from the diagnosis of active NTM infection?

Bronchiectasis in general can manifest in one of two forms: as a local or focal obstructive process of a lobe or segment of a lung or as a diffuse process involving most of the lungs.[3] In patients with diffuse bronchiectasis the disease is more likely to be associated with specific causes such as infection (NTM infection, *Aspergillus* infection), congenital conditions (primary ciliary dyskinesia, cystic fibrosis), or immunodeficiency.[3]

High resolution computed tomography (HRCT) has proved to be a reliable and non-invasive method for the diagnosis of bronchiectasis. The pattern and distribution of abnormalities revealed by HRCT scanning are influenced by the underlying cause of bronchiectasis. Multiple small nodules (and sometimes cavity or cavities) combined with diffuse (or widespread) bronchiectasis are reported to be the typical HRCT findings of NTM pulmonary infection associated with bronchiectasis,[4–6] which was also suggested by Wickremasinghe *et al*.[1] In patients with these characteristic HRCT findings, 34–50% of patients have active NTM pulmonary infection, especially *Mycobacterium avium* complex infection.[4 6] These abnormalities are usually confined to, or most severe in, the right middle lobe and the lingular segment of the left upper lobe in NTM pulmonary infection. This presentation is therefore now referred to as ''nodular bronchiectatic disease''.[2] Multiple small nodules around ectatic bronchi on the HRCT scan have been reported to represent peribronchial granuloma and caseous material.[4 5]

The diagnosis of this type of NTM pulmonary infection is often delayed because symptoms are mild and excretion of NTM in sputum is intermittent with few colonies retrievable in culture. Many patients therefore require bronchoscopic examination or lung biopsy for diagnosis of NTM pulmonary disease.[7] In clinical practice, HRCT scans should therefore be performed in patients with suspected bronchiectasis. NTM pulmonary infection could be suspected in selected patients who have multiple pulmonary nodules combined with diffuse bronchiectasis on the HRCT scan. Multiple sputum specimens should be examined in these patients. However, the poor sensitivity of sputum cultures suggests that, in situations where multiple sputum cultures are non-diagnostic, bronchoscopy should be performed to adequately exclude or diagnose NTM pulmonary disease.

We consider that there is no clear evidence to support the routine surveillance for NTM infection in all adult patients with bronchiectasis.

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Authors' reply

We would agree with much of the content of the interesting letter from Drs Koh and Kwon, particularly the details of *Mycobacterium avium* complex infection and the use of CT scans in making the diagnosis.[1] We have also had experience of bronchoscopy and biopsy being necessary to make the diagnosis in some cases with suggestive radiology. The one point on which we disagree is the value of routine annual screening of sputum for acid fast bacilli, and our practice of sending three samples in all patients with a deterioration in their clinical condition which is not explained or not reversed by usual treatment.

The value of this practice will require a large prospective study with cost-benefit analysis and attention paid to false negative results. However, we would argue in favour of this approach for the following reasons. Most patients have a CT scan when bronchiectasis is first suspected. Our study[2] has shown that these patients may (rarely) in the future contract NTM infection which adversely affects their condition.

As Drs Koh and Kwon state, this may be insidious and go unsuspected for long periods. In our study[2] most patients with infection (rather than colonisation) had a heavy bacterial load (smear positive) which would make it likely that routine screening would detect the patient. Repeat CT scans in all cases that might raise suspicion of NTM is impractical. Lastly, about 50% of cases with diffuse bronchiectasis remain idiopathic even after full investigation,[3] and our understanding of the pathogenesis of NTM infection is just beginning to increase. The data produced from closely studying NTM in our population of bronchiectatic patients may provide useful information in the future.

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CORRECTION

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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 (10.1136/thx.2005.040444) has been published previously on 17 June 2005 as a Thorax Online First article but under the incorrect DOI (10.1136/thx.2005.047803). The publishers apologise for this error. The definitive version of the article can be found at the following citation: *Thorax* 2005;**60**:740-6.

CORRECTION

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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 (10.1136/thx.2005.040444) has been published previously on 17 June 2005 as a *Thorax* Online First article but under the incorrect DOI (10.1136/thx.2005.047803). The publishers apologise for this error. The definitive version of the article can be found at the following citation: *Thorax* 2005;**60**: 740–6.