

β lactam monotherapy versus β lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis

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Abstract

Objective To compare the effectiveness of β lactam monotherapy versus β lactam-aminoglycoside combination therapy in the treatment of patients with fever and neutropenia.

Data sources Medline, Embase, Lilacs, the Cochrane Library, and conference proceedings to 2002.

References of included studies and contact with authors. No restrictions on language, year of publication, or publication status.

Study selection All randomised trials of β lactam monotherapy compared with β lactam-aminoglycoside combination therapy as empirical treatment for patients with fever and neutropenia.

Data selection Two reviewers independently applied selection criteria, performed quality assessment, and extracted data. An intention to treat approach was used. Relative risks were pooled with the random effect model.

Main outcome measure All cause fatality.

Results Forty seven trials with 7807 patients met inclusion criteria. Nine trials compared the same β lactam. There was no significant difference in all cause fatality (relative risk 0.85, 95% confidence interval 0.72 to 1.02). For success of treatment there was a significant advantage with monotherapy (0.92, 0.85 to 0.99), though there was considerable heterogeneity among trials. There was no significant difference between monotherapy and combination treatment in trials that compared the same β lactam, whereas there was major advantage with monotherapy in trials that compared different β lactams (0.87, 0.80 to 0.93). Rates of superinfection were similar. Adverse events, including those associated with severe morbidity, were significantly more common in the combination treatment group. Detected flaws in methods did not affect results.

Conclusions For patients with fever and neutropenia there is no clinical advantage in treatment with β lactam-aminoglycoside combination therapy. Broad spectrum β lactams as monotherapy should be regarded as the standard of care for such patients.

Introduction

Patients with fever and neutropenia can be treated with a single β lactam (third or fourth generation anti-pseudomonal cephalosporins or carbapenems) or β lactam-aminoglycoside combination therapy.¹ So far studies that have compared monotherapy with combination therapy have not been large enough to compare survival. Comparative data regarding high risk subgroups are needed,^{2,3} and thus far conclusions regarding superinfections are contradictory.^{4,5}

We performed a systematic review and meta-analysis of β lactam monotherapy and β lactam-aminoglycoside combination therapy to compare all cause fatality.

Methods

We searched Medline, Embase, Lilacs, the Cochrane Library, and the Interscience Conference on Anti-microbial Agents and Chemotherapy up to the year 2002. The terms "neutropenia" and similar and "aminoglycoside" or specific aminoglycosides were crossed. References of all included trials and reviews identified were scanned for additional studies. We put no restrictions on language, year of publication, or publication status.

We included all randomised trials that compared treatment with any β lactam alone with any combination of a β lactam and an aminoglycoside for the empirical treatment of patients with fever and neutropenia. We excluded studies with a dropout rate above 30%, unless intention to treat analysis was carried out for mortality or failure outcomes. Authors of all included trials were contacted for complementary information.

Our primary outcome was all cause fatality at the end of follow up and up to 30 days after treatment was stopped. Our secondary outcomes included failure of treatment (defined as death, persistence, recurrence, or worsening of presenting infection, and any modifications to the assigned antibiotic treatment); bacterial and fungal superinfections; colonisation; and adverse events. Predefined subgroups were patients with haematological cancer, severe neutropenia ($<100/\text{mm}^3$), bacteraemia, documented infections, and *Pseudomonas aeruginosa* infections.

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A list of all identified studies can be found on bmj.com

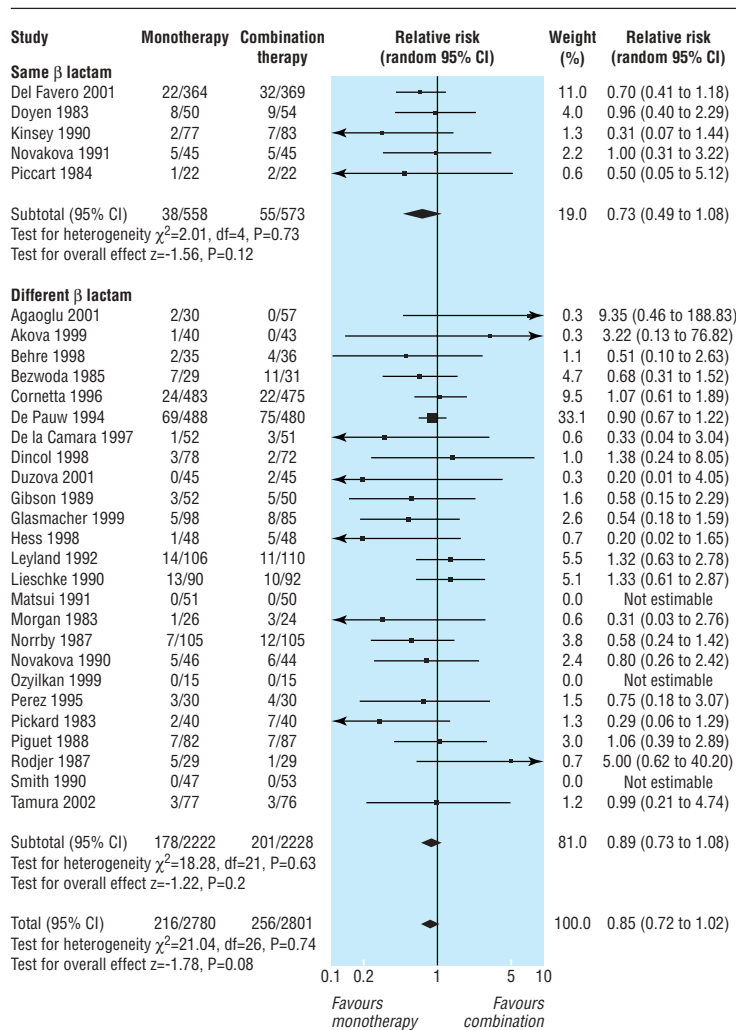


Fig 1 All cause fatality

Analyses were performed by intention to treat, unless data were given only for those patients who could be evaluated.

Results

We evaluated 72 eligible randomised trials and included 47 in the review (see bmj.com for full list of references). The trials included 7807 patients and 8803 febrile episodes (28 to 1034 patients per trial) and took place from 1981 to 2000. Nine trials compared the same β lactam, while all other trials compared one

β lactam with a different, narrower spectrum β lactam combined with an aminoglycoside.

In 21 trials (45%) randomisation procedures were adequate, and eight (17%) were blinded. Intention to treat analysis for failure was possible in 17 of the 47 trials and for fatality in 18 of 30 trials. The median dropout rate was 9%. In 31 trials febrile episodes were the unit of randomisation. The number of participating patients was given in 25 (81%) of these trials, and the episode to patient ratio varied from 1.03 to 1.63 among trials.

Many patients (89%) had haematological malignancies, and 61% had severe neutropenia (<100/mm³) on admission. Eight trials included children, five being restricted to children below 16 years. The adjusted mean percentage of documented infections was 56%, with rates varying from 24% to 94%. Bacteraemia was present in 24% of patients (4-57%). *P aeruginosa* was isolated in less than 2% (0-13%) of included patients, constituting 15% (0-44%) of all documented Gram negative isolates. Gram positive bacteria were identified more commonly than Gram negative bacteria in two third of the trials.

All cause fatality

The average all cause fatality was 6.2%, with a decline in fatality correlating with advancing year of the study ($r_s = -0.43$, $P=0.03$). Comparative fatality data were obtained for 30 trials (fig 1). When all studies were combined there was no significant difference between monotherapy and combination therapy (relative risk 0.85, 95% confidence interval 0.72 to 1.02). Five trials compared the same β lactam (0.73, 0.49 to 1.08), and 24 studies compared different β lactams (0.89, 0.73 to 1.08). No significant differences in fatality were present among all subgroups tested (table).

Treatment failure

When we combined all studies we found an advantage with monotherapy (0.92, 0.85 to 0.99, 47 trials), but there was significant heterogeneity among trials (χ^2 73.28, $df=46$, $P=0.0064$, fig 2). There was no significant difference between monotherapy and combination therapy in trials that compared the same β lactam in both arms (nine trials, 1.12, 0.96 to 1.29), whereas there was a significant benefit with monotherapy in trials that compared different β lactams (0.87, 0.80 to 0.93, 38 trials). Among subgroups, there was a significant advantage with monotherapy for patients with documented infections and those with haematological malignancy. No correlation was observed between

Subgroup analysis, showing number of studies and episodes included in analysis with relative risk (RR) and 95% confidence intervals

	All cause fatality			Treatment failure (same β lactam)			Treatment failure (different β lactam)		
	Studies	Episodes	RR (95% CI)	Studies	Episodes	RR (95% CI)	Studies	Episodes	RR (95% CI)
All	30	5581	0.85 (0.72 to 1.02)	9	2178	1.12 (0.96 to 1.29)	38	5920	0.87 (0.80 to 0.93)
Documented infections	12	1158	0.78 (0.52 to 1.15)	7	1006	1.05 (0.89 to 1.23)	23	2614	0.88 (0.82 to 0.96)
Bacteraemia	11	583	0.69 (0.39 to 1.22)	5	384	1.04 (0.89 to 1.21)	18	1054	0.87 (0.74 to 1.02)
Gram negative infections	13	328	0.67 (0.35 to 1.27)	7	261	1.50 (0.80 to 2.79)	21	603	0.68 (0.50 to 0.93)
<i>Pseudomonas</i> infections	7	58	0.78 (0.24 to 2.56)	3	49	1.46 (0.23 to 9.41)	12	90	0.87 (0.54 to 1.41)
Haematological cancer	13	2188	0.78 (0.58 to 1.06)	4	361	0.92 (0.76 to 1.12)	13	2287	0.83 (0.73 to 0.96)
Severe neutropenia	5	677	0.66 (0.35 to 1.26)	2*	237	1.49 (1.13 to 1.97)	6	757	0.94 (0.75 to 1.18)
Adults >16 years	21	3205	0.88 (0.72 to 1.08)	6	1173	1.21 (1.07 to 1.37)	25	3503	0.83 (0.75 to 0.92)
Children	4	327	0.75 (0.08 to 7.11)	1*	91	2.74 (1.08 to 6.98)	4	327	0.94 (0.64 to 1.39)

*Significant advantage to combination therapy.

treatment failure and fatality in the studies ($r_i=0.03$, $P=0.9$, 29 trials). Rates of treatment failures did not decline in recent years nor was the variance between studies reduced.

Superinfections and adverse events

Superinfections developed with similar frequencies after combination or monotherapy (0.97, 0.82 to 1.14, for bacterial superinfections, 24 trials; and 0.75, 0.51 to 1.10 for fungal super infections, 18 trials). Only five studies compared colonisation, and none found any differences.⁶

Adverse events were significantly more common in the combination treatment group (fig 3). The difference was most remarkable for development of renal failure (0.49, 0.36 to 0.65) and was not influenced by single daily administration of the aminoglycoside. Likewise, discontinuation of study medication due to adverse events occurred was more common in the combination group (0.57, 0.36 to 0.91).

Sensitivity analysis

Compared with smaller trials, larger trials had relative risks closer to equivalence. When we looked at treatment failure, in trials that compared different β lactams and in which the number of randomised patients was below the median, monotherapy showed a highly significant advantage (0.73, 0.64 to 0.84), while larger studies showed no such advantage (0.94, 0.89 to 1.00, $P=0.025$ for the difference). The corresponding funnel plot for treatment failure generated a nearly symmetrical "funnel distribution." Sensitivity analyses by all quality measures did not reveal any effect on our results.⁶

Discussion

Our results support the use of broad spectrum β lactam monotherapy in the empirical treatment of patients with fever and neutropenia. Most studies in our meta-analysis compared a new broad spectrum β lactam (carbapenem, ceftazidime, cefepime, piperacillin-tazobactam) with a combination of an "older" β lactam (usually an ureidopenicillin or a cephalosporin drug) and an aminoglycoside. In the comparisons the advantages of monotherapy were clear: a non-significant trend toward better survival, a significant advantage in preventing treatment failures, and fewer adverse effects. Fewer trials compared one β lactam with a combination of the same β lactam and an aminoglycoside. In these trials there were no significant benefits and more adverse effects, including severe ones, with the combination therapy. The non-significant advantage with combination therapy in these studies translates to some 20 patients who would have to be given an additional aminoglycoside to prevent one failure, which most commonly implies merely an antibiotic modification.

Limitations of study

We detected a sample size bias for treatment failure, with smaller studies exaggerating the beneficial effect of monotherapy. As smaller studies did not consistently differ from larger trials with respect to severity of disease, methods, or therapy, this may reflect publication bias. Most studies used febrile episodes as the unit of randomisation, allowing patients to re-enter

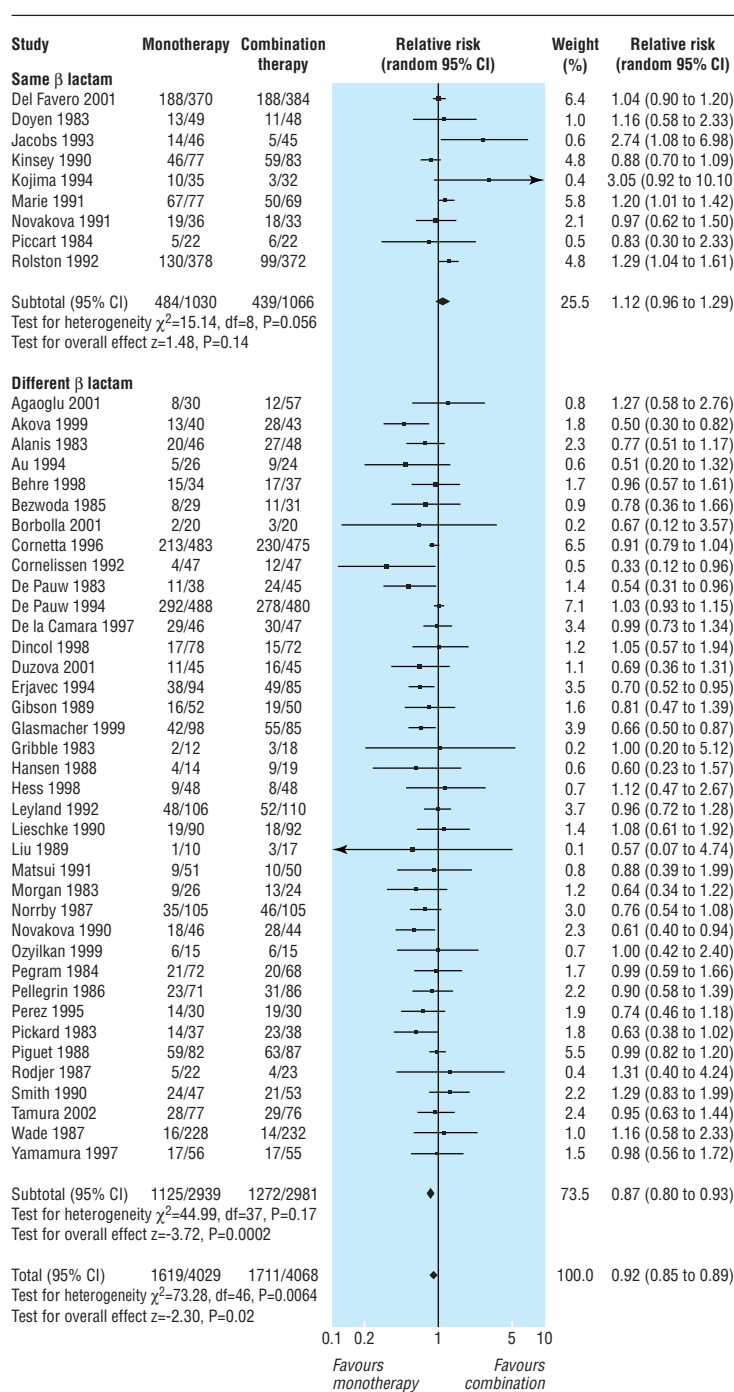


Fig 2 Treatment failure

the trial. As outcomes for re-entering patients are not independent, results may have been affected. Intention to treat analysis was possible in just over half the included trials, and adequate randomisation procedures were used in less than half of these trials. Sensitivity analyses did not detect an effect of these measures on our results.

The major caveat with respect to the interpretation of our results is the lack of data on fatality in some of the trials. All cause fatality should be the primary outcome as survival is ultimately the objective of treatment for these patients.⁷ Admittedly, only a small part of the variance in fatality is explained by infection. Appropri-

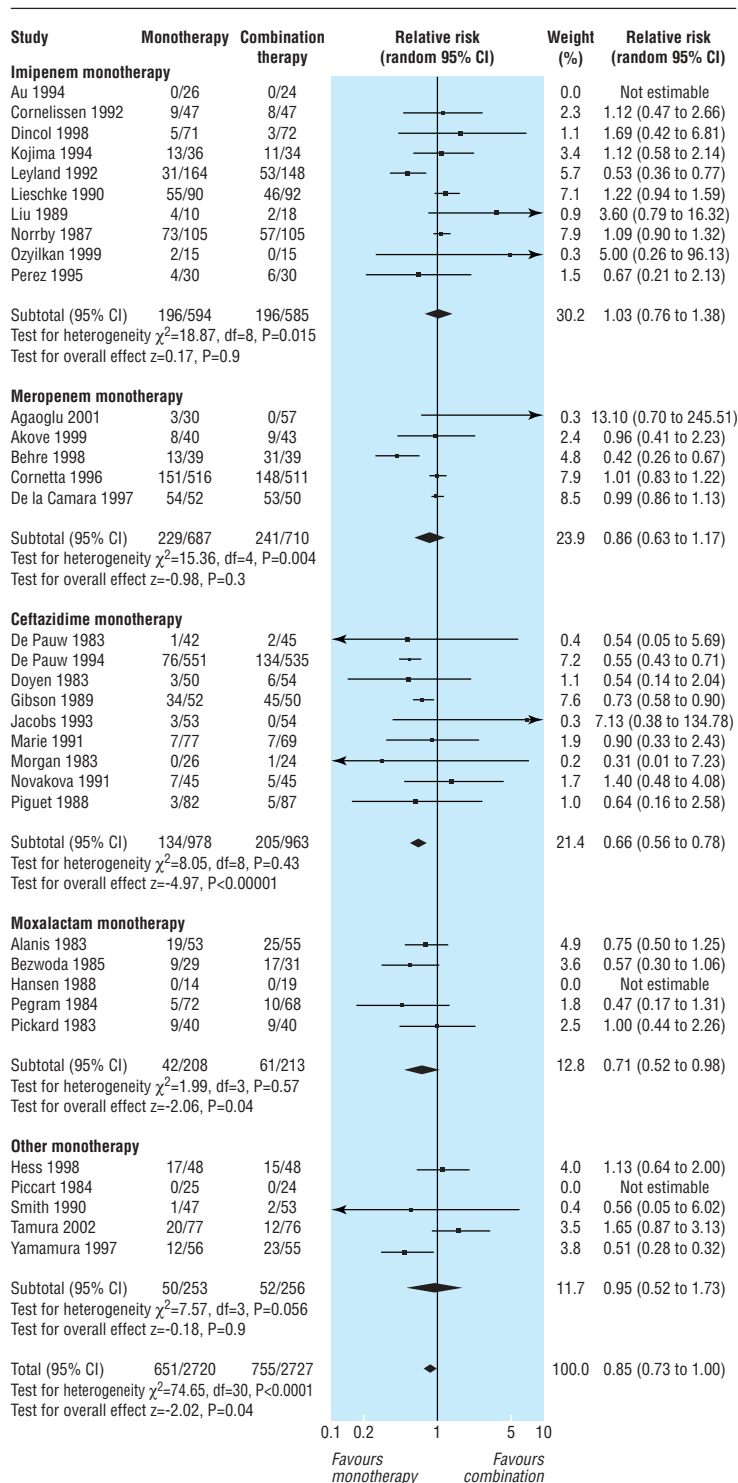


Fig 3 Any adverse event

ate randomisation, however, should ensure similar distribution of risk factors for death not related to infection between the study groups. Treatment failure, whether defined as modifications to treatment or delayed resolution of fever, is subjective and clinically less meaningful. Finally, for failure to have some prognostic importance it should correlate with fatality, and we have shown that in these studies a correlation did not exist.

What is already known on this topic

Cancer patients with neutropenia and fever can be treated with a single broad spectrum β lactam antibiotic or with a combination of a β lactam and an aminoglycoside

Many randomised trials have compared monotherapy with combination therapy for these patients, but no consensus has been reached regarding the superiority of one regimen over the other

What this study adds

There is no survival advantage with combination therapy

Broad spectrum β lactam monotherapy is more successful than a narrower spectrum β lactam agent combined with an aminoglycoside

Combination therapy is associated with a significantly higher rate of adverse events, mainly nephrotoxicity

Clinical implications

From our results we consider that broad spectrum monotherapy should be the standard treatment for patients with fever and neutropenia.

Implications for clinical research

Studies of antibiotic treatment in these patients should adhere to better standards of methods and reporting. Specifically, the unit of randomisation should be the patient not the episode. Future trials of combination treatment should be performed only to address issues where doubt still exists. Synergism should be specifically assessed by comparing the same β lactam in both arms of the study. Studies should use all cause fatality as the primary outcome. The low fatality (lower in recent years) translates into a large sample size. Survival of patients, however, is the underlying reason for empirical treatment with antibiotics for fever with neutropenia.

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Competing interests: None declared.

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Stepping down inhaled corticosteroids in asthma: randomised controlled trial

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Abstract

Objectives To determine whether the dose of inhaled corticosteroids can be stepped down in patients with chronic stable asthma while maintaining control.

Design One year, randomised controlled, double blind, parallel group trial.

Setting General practices throughout western and central Scotland.

Participants 259 adult patients with asthma receiving regular treatment with inhaled corticosteroids at high dose (mean dose 1430 µg beclomethasone dipropionate).

Interventions Participants were allocated to receive either no alteration to their dose of inhaled corticosteroid (control) or a 50% reduction in their dose if they met criteria for stable asthma (stepdown).

Main outcome measures Comparison of asthma exacerbation rates, asthma related visits to general practice and hospital, health status measures, and corticosteroid dosage between the two groups.

Results The proportions of subjects with asthma exacerbations were not significantly different (stepdown 31%, control 26%, $P=0.354$). Similarly, the numbers of visits to general practice or hospital and the disease specific and generic measures of health status over the one year period were not significantly different. On average the stepdown group received 348 µg (95% confidence interval 202 µg to 494 µg) of beclomethasone dipropionate less per day than the controls (a difference of 25%), with no difference in the annual dose of oral corticosteroids between the two treatment regimens.

Conclusions By adopting a stepdown approach to the use of inhaled steroids at high doses in asthma a reduction in the dose can be achieved without compromising asthma control.

Introduction

Inhaled corticosteroids are highly effective in the treatment of asthma.¹⁻³ Their potential for causing dose related side effects has, however, led to asthma management guidelines recommending a reduction in their dose once asthma control is established.²⁻⁴ Research evidence shows that a reduction can be

achieved in the short term, in mild disease, or with the addition of other antiasthma treatments.⁵⁻⁸ The clinical implications of this approach to treatment have not, however, been tested by means of a randomised controlled trial over the longer term or for patients with moderate to severe disease. We therefore tested the hypothesis that a stepdown approach to the use of inhaled corticosteroids at high dosage can be adopted safely in adults with chronic stable asthma.

Methods

Participants

We recruited 259 participants from general practices throughout western and central Scotland. Participants were aged 18 years and older, had a diagnosis of asthma⁹ for at least one year, and were being treated with at least 800 µg inhaled beclomethasone dipropionate daily (or budesonide or fluticasone propionate at equivalent dosage). We excluded patients if they had required oral corticosteroids or visited general practice or hospital for asthma in the preceding two months.

Study design

We conducted a multicentre, randomised, double blind, parallel group trial over a period of one year.

Protocol, assignment, and masking

Run-in—We collected baseline data and use of inhaled corticosteroids before the study during a one month run-in period.

Randomisation visit—After run-in, we randomised participants to either a reduction in their dose of inhaled corticosteroid (stepdown) or a sham reduction (control). Treatment allocation was withheld from the investigators until completion of the study.

Study inhalers—A central pharmacy produced two packs of inhaled corticosteroid for each participant according to the randomisation code. The packs were identical in appearance and labelled either “usual dose” or “reduced dose” (see bmj.com).

Study visits—At randomisation, participants received a pack containing inhaled corticosteroids at usual dosage. Subsequent study visits took place at three, six, nine, and 12 months, when asthma control

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