

## Editorials

## Parasite infections and the risk of asthma and atopy

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Common environmental allergens stimulate IgE responses and produce allergic disease, but the allergens that produce the most potent IgE responses in nature originate from helminthic parasites.<sup>1,2</sup> Since parasitic infection is endemic in the majority of the world's population, the relationship between helminthic infection and the IgE response is highly relevant to the understanding of allergic diseases. There is a general consensus that IgE antibody is an important component of the immune resistance to helminthiasis,<sup>5-9</sup> although some conflicting results have been obtained.<sup>3,4</sup> Local IgE reactions can create unfavourable conditions in the gut for intestinal parasites, and IgE can mediate the cytotoxic activity of eosinophils against parasitic larvae. These observations have led to the concept that, from an evolutionary perspective, the primary function of the allergic response may be as part of an anti-parasitic protective mechanism, and allergic disease may be the undesirable reaction towards otherwise inoffensive environmental substances.<sup>10</sup> In developed countries the prevalence of allergic disease has increased over recent years at the same time that improved sanitary conditions have caused the virtual elimination of parasites.<sup>11-13</sup> This increase in allergic diseases has recently been attributed to a Th1/Th2 imbalance caused by diminishing exposure to common bacterial and viral infections,<sup>14,15</sup> but the decrease in helminthic infections should also be considered in this context.

Insight into this situation has come from recent immunological studies which have demonstrated that there are two different IgE responses to helminthic infections. The first of these is the host's defensive response to produce IgE specific to parasite antigens. The second response is that the host also exhibits a strong non-specific Th2/interleukin 4 dependent polyclonal synthesis of IgE<sup>16-18</sup> which results in highly elevated total serum IgE levels in parasitised populations. This polyclonal synthesis of IgE may be the helminth's defence mechanism against the effects of anti-parasite IgE. The polyclonal stimulus can suppress allergic responses by reducing the production of specific IgE antibody, resulting in an inverse relationship between total and specific serum IgE levels.<sup>18-20</sup> The polyclonal IgE also saturates the IgE receptors on mast cells and blocks access to specific IgE, which further inhibits allergic reactions.<sup>12,13,18,20,21</sup> This suppressive activity may be the reason for the diminished prevalence of allergic diseases reported in some tropical populations.<sup>22-26</sup> Of great significance is the likelihood that parasites evade the immune response by stimulating excess IgE production.<sup>27</sup> For example, in populations endemically exposed to helminths, individuals with the

highest total serum IgE levels are more quickly reinfected by the parasites after anthelmintic treatment than those with lower levels.<sup>28</sup> In addition, atopic individuals within such populations have significantly lower total IgE levels, higher specific anti-parasite IgE concentrations, and less intense helminth infections than their non-atopic counterparts.<sup>29</sup> These observations suggest that atopic hosts may have developed more effective specific responses against parasites through evolution,<sup>31</sup> and that helminths, also through evolution, have countered this by developing allergens that provoke a polyclonal IgE response. Atopic individuals mount the most effective IgE responses<sup>30</sup> and, in evolutionary terms, this might compensate for the adverse effects of allergic disease. The atopic state therefore appears to favour a specific over a polyclonal IgE response, and thus the genes that determine this may have been conserved.<sup>29</sup> However, in the absence of environmental exposure to parasites, this is more harmful than beneficial.

Molecular genetic techniques have the potential to elucidate the inherited changes underlying these evolutionary developments.<sup>32</sup> The approaches to resolving the inherited immunogenic processes are similar to those used to investigate the molecular genetics of asthma.<sup>33-36</sup> These investigations are facilitated by the work done to date on asthma genetics that concentrated on IgE responses.<sup>35,36</sup> The chance of finding DNA sequence variations that affect specific IgE responses should be much greater in parasitised than in asthmatic populations because the IgE responses to parasites are much more intense and genetic differences in the level of IgE responses should be maximised. Detecting the gene or genes involved in polyclonal production of IgE would also be of great interest. The potential benefits of this approach to understanding human responses to parasite infection are several and include: (1) basic mechanisms of the immune system may be elucidated; (2) those particularly susceptible to parasitic infection may be identified; (3) studying the IgE antibody system in its natural state may give insight into reasons why it apparently malfunctions to cause atopic disease; and (4) novel therapeutic interventions may become apparent. As an example of a possible therapy, understanding the mechanism of polyclonal IgE production might allow an artificial stimulus to be used in atopic individuals to produce polyclonal IgE to block IgE receptors and so minimise the effect of high levels of IgE specific to inhaled antigens.

There are therefore several reasons why research into the relationship between human IgE responses and parasitic disease might have more widespread relevance. This

research is unique in having the potential simultaneously to help understand two extremely common diseases, one being one of the most common diseases in developing countries and the other one of the most common diseases in developed countries.

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# Nebulised corticosteroids in the treatment of patients with asthma

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Inhaled corticosteroids are the mainstay of anti-inflammatory treatment in patients with chronic asthma, and most patients' symptoms are controlled by low or moderate doses of these agents. However, there are some patients with chronic severe asthma whose symptoms are inadequately controlled by high doses of inhaled corticosteroids and maximal bronchodilator therapy. Such patients require increasingly frequent courses of oral corticosteroids, often culminating in their long term use.

Until recently in the UK, budesonide (Pulmicort Respules, Astra Pharmaceuticals) was the only corticosteroid available for nebulisation. Fluticasone propionate (Flixotide Nebules, Glaxo Wellcome) was launched in late 1998, and is being actively marketed. The 1995 British Thoracic Society asthma guidelines state, however, that there are "... no published controlled trials of the effectiveness of nebulised budesonide in adults".<sup>1</sup> This review aims to address whether these guidelines hold true, or whether new evidence has emerged which should lead us to review this policy.

The evidence for the effectiveness of nebulised corticosteroids in the treatment of stable asthma is reviewed, together with a discussion of whether there is any evidence that their use allows a reduction in regular oral corticosteroid dose in patients with severe asthma. In considering this evidence it is important to compare the side effects of nebulised corticosteroids with those of high dose inhaled corticosteroids and with those of oral corticosteroids. Studies which compare nebulised corticosteroid with oral corticosteroid in the treatment of acute exacerbations of asthma are also reviewed. It is important to consider patient preference for nebulised, inhaled or oral therapy, which is closely linked with compliance with treatment. Finally, in such a review it is vital to consider the cost implications of any change in practice in the treatment of patients with acute and chronic asthma.

There are a large number of case reports and uncontrolled studies of the effect of nebulised corticosteroids in asthma. This review is limited to considering controlled trials where these are available but, in their absence, the evidence from uncontrolled studies is considered.

## Effectiveness of nebulised corticosteroids in stable asthma

### CHILDREN

There are few controlled trials assessing the effectiveness of nebulised corticosteroids in children with chronic asthma. In a double blind, randomised, crossover study Pedersen *et al* compared the effect of 0.5, 1.0 and 2.0 mg nebulised budesonide twice daily in 18 asthmatic children aged 6-15 years who were symptomatic despite as required  $\beta$  agonist therapy.<sup>2</sup> Comparisons at the end of four weeks showed that there was a significant dose response effect for prevention of exercise induced fall in peak flow and forced expiratory volume in one second (FEV<sub>1</sub>), such that the greatest improvement was seen in the children receiving 2.0 mg twice daily. However, this study did not include a control group. Mellon *et al* compared the effect of four doses of nebulised budesonide (0.25 mg qds, 0.5 mg bid, 0.5 mg bid, and 1 mg qds) and placebo in 481 symptomatic asth-

matic children aged six months to eight years.<sup>3</sup> They reported significant reductions in symptoms,  $\beta$  agonist use, and improvement in peak flow rates after 12 weeks of nebulised steroid treatment.

### ADULTS

The first report in adults which suggested that nebulised corticosteroids were effective and had a steroid sparing effect in patients with severe asthma came in 1992. In this open uncontrolled study Otulana *et al* studied 18 adult asthmatic patients who, despite treatment with 1200  $\mu$ g inhaled beclomethasone dipropionate or 1600  $\mu$ g inhaled budesonide per day, required at least 7.5 mg oral prednisolone per day to control their symptoms.<sup>4</sup> They received between 4 mg and 8 mg of nebulised budesonide per day for the 12-18 months of the study. Fourteen patients successfully stopped (and three patients successfully reduced) their dose of oral corticosteroid. A later similar study included 49 asthmatic patients who required more than 10 mg of oral prednisolone and 2 mg of inhaled steroid via large volume spacer per day to control their asthma symptoms.<sup>5</sup> After a four week run in period, patients received 1 mg nebulised budesonide twice daily for 12 weeks whilst attempting reduction in the dose of oral corticosteroid. Twenty two (55%) of the patients reduced their oral steroid dose by a mean of 6 mg without suffering a deterioration in asthma control. Despite the apparently positive results from both of these studies, neither of them included a control group and, since virtually all studies attempting corticosteroid reduction in the presence of placebo have reported success, these results are difficult to interpret.

In a multicentre, randomised, double blind, parallel group study, Efthimiou *et al* compared two doses of nebulised fluticasone (0.5 and 2.0 mg twice daily) with placebo in 301 adult patients with chronic corticosteroid dependent asthma.<sup>6</sup> After 12 weeks the mean reduction in oral corticosteroid dose was significantly greater in the higher dose fluticasone group (4.44 mg/day) than in the lower dose fluticasone group (2.16 mg/day) and placebo group (1.2 mg/day). Significantly more patients in the higher dose fluticasone group than in either of the other two groups managed to stop oral corticosteroid treatment.

In practice it is the minority of patients with asthma who require regular oral corticosteroids, and most patients are treated successfully with inhaled corticosteroids. O'Reilly *et al* compared the efficacy of inhaled fluticasone propionate via metered dose inhaler and spacer with nebulised budesonide in a group of asthmatic patients.<sup>7</sup> In this multicentre, open label, crossover study 37 patients, who were usually treated with nebulised budesonide, were randomised to receive their usual dose of nebulised steroid (2 or 4 mg per day) or inhaled fluticasone propionate 1 mg twice daily for four weeks with a four week wash out period between treatments. A small number of patients were taking an oral corticosteroid on a regular basis and their steroid dose was not changed during the study. In the 24 evaluable patients at the end of the study, inhaled fluticasone was found to be more effective than nebulised budesonide at 2 mg and 4 mg in terms of its effect on morning peak flow and diurnal variability in peak flow,

although there was no difference between the two groups in the number of symptom free days. Of the patients who expressed a preference, more patients preferred the metered dose inhaler than the nebuliser, although this difference was not significant. The cost of nebulised budesonide was estimated to be 1.7–3.5 times higher than that of inhaled fluticasone administered by metered dose inhaler.

However, this study compared two different inhaled steroids and it is clear from a number of studies that fluticasone is twice as potent as budesonide at a mg for mg dose.<sup>8</sup> Therefore, a more meaningful study might compare the same corticosteroid administered by nebuliser and metered dose inhaler. Bisgaard *et al* compared the effect of budesonide administered by nebuliser and metered dose inhaler.<sup>9</sup> In this study 26 patients with moderately severe, symptomatic asthma received four weeks of treatment with budesonide 0.8 mg twice daily by metered dose inhaler and spacer or budesonide 1 mg or 4 mg twice daily by jet nebuliser activated only during inspiration. Nebulised budesonide was equally or more effective than inhaled budesonide in terms of peak flow, symptoms of asthma, and  $\beta$  agonist use. There was a trend towards greatest effect in the higher dose of nebuliser although this did not reach significance. This study suggested equipotency between budesonide administered by this nebuliser and the metered dose inhaler and spacer, suggesting that the superior efficacy of nebulised steroid in some studies may simply reflect the higher dose administered by nebuliser than metered dose inhaler. The total mass output delivered from the two devices was similar, but the fraction of small particles with the metered dose inhaler was twice that from the nebuliser.

### Side effects of nebulised corticosteroids

There is a great deal of available information about the side effects associated with the long term use of oral corticosteroid use. Less is known about the side effects associated with the use of inhaled corticosteroids. If nebulised corticosteroids are to have a place in the treatment of patients with asthma, this will surely be in patients requiring high doses of inhaled corticosteroids and/or regular oral prednisolone. It is therefore important to compare the side effects of nebulised corticosteroids with these treatments.

Toogood *et al* in a double blind, placebo controlled, crossover study compared the potency and side effects of six weeks of oral prednisolone in a dose of 7.5–40 mg per day with six weeks of inhaled budesonide 0.4–3.2 mg per day delivered by metered dose inhaler and spacer.<sup>10</sup> Thirty four patients completed the protocol from which it was concluded that the systemic glucocorticoid activity of any particular dose of budesonide was consistently less than that of the oral dose of prednisolone. The milligram equivalent potency ratio for cortisol suppression for prednisolone versus inhaled budesonide was calculated to be 7.6:1 for steroid dependent asthmatics and 5:1 for healthy controls. In a similarly designed study Wilson *et al* compared the potency and side effects of 1 mg, 2 mg, and 4 mg nebulised budesonide twice daily with 5 mg, 10 mg, and 20 mg oral prednisolone per day.<sup>11</sup> There was significant dose-related suppression of plasma cortisol, osteocalcin, and blood eosinophils with all of the oral steroid doses, although no significant effect was seen with nebulised budesonide.

### CHILDREN

In a 12 week study 481 children aged six months to eight years received between 0.25 mg bid and 1 mg qds nebulised budesonide.<sup>12</sup> After 12 weeks the authors reported no detectable adrenal suppression (effect of ACTH stimulation on morning cortisol levels) or oropharyngeal

fungus infection. Reid *et al* gave between 1 and 4 mg/day of nebulised budesonide to 40 children with severe asthma for six months to assess its effect on growth.<sup>13</sup> In this open study they observed a statistically but not clinically significant improvement in the children's growth which they attributed to an improvement in asthma control.

Biraghi *et al* assessed the effect of nebulised flunisolide (1200  $\mu$ g daily) or sodium cromoglycate in an open, randomised, parallel group study of 29 prepubertal schoolchildren.<sup>14</sup> After four months there was no significant effect of nebulised flunisolide on any of the markers of bone formation or resorption. In another study 41 children aged 3–14 years with mild to moderate asthma were treated with albuterol, cromolyn, and nebulised budesonide<sup>8</sup> or fluticasone dipropionate.<sup>15 16</sup> Anthropometric measurements, biochemical markers of bone turnover, and DEXA scan data were not significantly different between the two groups after six months of treatment. The body mass index (BMI) fell in the corticosteroid treated group, which was attributed to an improvement in ability to exercise and quality of life.

### ADULTS

Very few studies in adults have assessed the side effects of nebulised corticosteroids and compared them with those of oral and/or inhaled corticosteroids. Wilson *et al* found no evidence of the side effects of adrenal suppression or increased osteoclastic activity after four days of treatment with nebulised budesonide in doses of 1 mg, 2 mg, or 4 mg per day.<sup>11</sup> Bisgaard *et al* reported that plasma cortisol levels were related to the dose of corticosteroid rather than the device used when they compared budesonide in a dose of 0.8 mg twice daily administered by metered dose inhaler and spacer with 1 mg and 4 mg nebulised budesonide twice daily in 26 adult asthmatic patients with moderately severe chronic asthma.<sup>9</sup> In another study serum cortisol levels were still in the normal range after 12 weeks of treatment with nebulised fluticasone in doses of 0.5 mg and 2 mg twice daily.<sup>6</sup>

### Nebulised corticosteroids in acute asthma

#### CHILDREN

Curtis *et al* randomised 19 asthmatic children aged 7–13 years with an acute exacerbation of asthma to treatment with nebulised budesonide (1 mg twice daily) or oral prednisolone (2 mg/kg/day).<sup>17</sup> There was no difference between the two groups in terms of peak flow rates or FEV<sub>1</sub> after 24 hours of treatment. In a randomised, double blind, placebo controlled study Scarfone *et al* compared the effect of 1.5 mg/kg nebulised dexamethasone with 2 mg/kg oral prednisone in 111 asthmatic children aged 1–17 years with a moderately severe acute exacerbation of asthma.<sup>16</sup> There was no difference in the rate of admissions to hospital between the two groups. Clinical improvement occurred earlier (at two hours) in the group of children who received nebulised corticosteroid.

Bingham *et al* compared the effect of 1 mg twice daily nebulised fluticasone dipropionate with 2 mg/kg/day oral prednisolone in 321 asthmatic children aged 4–16 years.<sup>18</sup> Morning peak flow was significantly higher in the nebulised corticosteroid group, but there was no significant difference in symptoms,  $\beta$  agonist use, sleep disturbance, or symptom free days between the two groups. In a multicentre, randomised, double dummy, parallel group study of 1 mg twice daily nebulised fluticasone propionate or oral prednisolone in 56 preschool children aged 48 months or less with an acute exacerbation of asthma, Francis *et al* demonstrated equal efficacy and safety in both treatment groups.<sup>19</sup>



## ADULTS

There are few data addressing the efficacy of nebulised corticosteroids in the treatment of acute exacerbations of asthma in adults. Winter *et al* reported the results of a randomised, double blind, parallel group study of the effect of substitution of 50 mg per day oral prednisolone for 2 mg twice daily nebulised fluticasone in 20 patients in the early stages of recovery from an acute exacerbation of asthma.<sup>20</sup> After 10 days of treatment there were no significant differences between the groups in terms of improvement in peak flow, asthma symptoms, or requirement for bronchodilator therapy. The authors concluded that nebulised fluticasone is an effective alternative to oral prednisolone in adults in the early stages of recovery from an acute exacerbation of asthma.

## Conclusions

The most likely group of patients to be prescribed nebulised corticosteroids are those who have severe symptomatic asthma requiring high doses of inhaled corticosteroids and/or regular oral corticosteroids. There is very little evidence that nebulised corticosteroids are more effective than high dose inhaled corticosteroids in this patient group, although one placebo controlled study reported significant reductions in the regular oral corticosteroid dose with the addition of nebulised fluticasone.<sup>6</sup> Although there are few data comparing the side effects of inhaled and nebulised corticosteroids with those of oral corticosteroids, the evidence would seem to suggest that the side effects are less for the same therapeutic benefit with high doses of inhaled and nebulised steroids.<sup>10-11</sup> More studies are required to address this question.

At least one study suggests that the superior efficacy of nebulised corticosteroid over corticosteroid delivered by metered dose inhaler relates simply to the delivery of a higher dose of corticosteroid, rather than because the nebulised preparation is more effective.<sup>9</sup> A randomised study to compare the efficacy and side effects of nebulised fluticasone (or budesonide) with the same dose of fluticasone (or budesonide) delivered by metered dose inhaler and spacer, dry powder device, or the newer, smaller particle, CFC-free inhaler is needed.

The only study which has attempted to assess patient preference suggested that nebulised budesonide was less popular than corticosteroid administered by metered dose inhaler and spacer, presumably because of the time required for nebulisation.<sup>7</sup> This also requires further study.

Although only a few asthmatic patients have severe asthma requiring high dose inhaled and/or regular oral corticosteroids, there would be significant cost implications if all patients requiring regular oral corticosteroid were to commence treatment with a regular nebulised corticosteroid. One recent community based study estimated this group at step 5 of the BTS asthma guidelines to be 1% of all asthma patients.<sup>21</sup> At present one month of treatment with oral prednisolone in a dose of 10 mg/day costs 86 pence per month, while 1 mg nebulised budesonide twice daily costs £132.92 and 0.5 mg nebulised fluticasone twice daily costs £60.24.

So what should be the present recommendation for the use of nebulised budesonide and fluticasone in the treatment of asthma? A few patients with apparently severe asthma have another cause for their symptoms and it is important to exclude vocal cord dysfunction, gastro-oesophageal reflux, or psychological disease which may be exacerbating their symptoms.<sup>22</sup> However, a minority of patients with asthma have troublesome symptoms despite high doses of inhaled corticosteroids and maximal bronchodilator therapy and require frequent doses of oral

prednisolone and/or regular oral prednisolone. In conjunction with rigorous attempts to reduce the oral steroid dose, an "n-of-1" trial of higher doses of inhaled steroids is probably justifiable in these patients but, to date, there is no evidence that delivering the same dose of corticosteroid by inhaler rather than by nebuliser would be any less effective. There would be significant cost implications of changing from corticosteroid delivered by inhaler to corticosteroid delivered by nebuliser. More work is required in this area.

There are a small number of studies suggesting that nebulised corticosteroids may be as effective as oral corticosteroids in the treatment of acute severe exacerbations of asthma. The cost implications of a change in treatment practice for these patients would be huge and perhaps, at present, nebulised corticosteroids should be restricted to patients who are not keen or are unable to take oral corticosteroids because of side effects. Further research will no doubt clarify many of these issues in the near future.

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