

# Pathogenesis and Therapy Management of Steroid-Resistant Asthma

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## Educational Objectives

- To discuss the pathogenesis of steroid-resistant asthma
- To describe the management plan for patients with steroid-resistant asthma
- To explore the pharmacological treatment options for steroid-resistant asthma

## Abstract

Asthma is a disease that is characterized as a chronic respiratory disorder with reversible airflow limitation and airway hyperresponsiveness to a number of stimuli.<sup>1</sup> Chronic inflammation within the airways is thought to play a major role in the pathogenesis of asthma. The corticosteroids have potent anti-inflammatory effects and are considered the cornerstone of therapy in treating asthmatic inflammation. Most asthmatic patients respond favorably to corticosteroid therapy for treating their underlying disease; however, a small subpopulation of patients display persistent immune activation and airway inflammation, despite high doses of oral corticosteroids.<sup>1</sup> This group of patients has been classified as “steroid-resistant” because they fail to respond to aggressive courses of both inhaled and oral corticosteroid therapy to treat their asthma. It is imperative to exclude confounding factors when trying to make the diagnosis of steroid-resistant asthma in a patient. These factors include poor medication compliance, inadequate inhaled medication technique, incorrect diagnosis, unrecognized concomitant diagnoses, ongoing exposure to environmental allergens, abnormal corticosteroid pharmacokinetics, and psychosocial disturbances.

## Pathogenesis

Steroid-resistant asthma is diagnosed based on clinical and physiologic lack of responses to corticosteroids. Patients

usually have persistent asthma that is difficult to control and is characterized by nocturnal exacerbations, chronic airflow limitation ( $FEV_1 < 70\%$  of predicted), and a poor clinical response, as well as a poor spirometric response to corticosteroid therapy.<sup>1</sup> A poor response is usually defined as an inability of the patient’s lung function to improve following at least seven to 14 days of high-dose (at least 40 mg daily) oral corticosteroid therapy.<sup>1</sup> This is measured by a lack of improvement in the morning prebronchodilator  $FEV_1$  of less than 15% from baseline.

In the body, glucocorticoids passively diffuse across the cell membranes via mucociliary transport and bind with high affinity to specific cytoplasmic receptors within the cell. Once the glucocorticoid binds to its receptor, the “active” glucocorticoid–glucocorticoid receptor complex is transported into the nucleus of the cell.<sup>2</sup> Once inside the nucleus, it binds to specific DNA sites upstream from promotor regions called glucocorticoid response elements. This binding of the glucocorticoid–glucocorticoid receptor to the glucocorticoid response element results either in upregulation or downregulation of gene products.<sup>2</sup> This mechanism can be further described as glucocorticoids inhibiting the transcription of pro-inflammatory cytokines and inflammatory mediators. Glucocorticoids also act by interfering directly or indirectly with transcription factor function, which acts to suppress the inflammatory response.<sup>2</sup>

The exact mechanism of underlying steroid resistance is uncertain, but it appears that abnormalities in glucocorticoid receptor number, glucocorticoid receptor binding (ligand-binding defect), or abnormalities in the glucocorticoid–glucocorticoid receptor complex binding to DNA (DNA-binding defects) are likely to account for the poor response to corticosteroid therapy in these patients.<sup>3</sup> These binding abnormalities appear to be functional abnormalities rather than genetic ones, in that chemical mutational analyses of the glucocorticoid receptors from steroid-resistant asthmatic patients failed to reveal mutations that would explain the phenomenon.

## Identified Glucocorticoid Abnormalities

Two distinct glucocorticoid receptor abnormalities have been identified in peripheral blood mononuclear cells that were isolated from steroid-resistant asthmatic patients.<sup>4</sup> The first abnormality (type 1) involves a reduction in glucocorticoid

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receptor-binding affinity, whereas the second abnormality (type 2) manifests as a relative deficiency of the receptor sites for the glucocorticoids.<sup>4</sup> The type 1 glucocorticoid receptor defect is the most commonly identified abnormality in these patients. The binding defect is localized to the T cell, reverses when the cells are cultured in the absence of cytokines, and can be sustained by the co-culture of the cells with the combination of interleukin-2 and interleukin-4. It is important to note that T cells from normal donors, when cultured with the combination of interleukin-2 and interleukin-4, develop diminished glucocorticoid receptor binding affinity of similar magnitude to that seen in steroid-resistant asthmatic patients.<sup>5</sup> The airway cells from patients with steroid-resistant asthma demonstrate elevated levels of interleukin-2 and interleukin-4 messenger RNA compared with steroid-sensitive asthmatic patients.

The expression of these cytokines does not fall significantly following a glucocorticoid course of therapy as it does in steroid-sensitive asthmatic patients.<sup>6</sup> Other immune cells can also display decreased glucocorticoid receptor-binding affinity after exposure to pro-inflammatory cytokines. A recently identified cytokine, interleukin-13, with properties similar to those of interleukin-4, has been shown to induce diminished glucocorticoid receptor binding affinity among monocytes, rendering these cells less sensitive to the suppressive effects of the glucocorticoids.<sup>7</sup>

The type 2 glucocorticoid receptor defect is much less frequently identified.<sup>4</sup> It displays an irreversible abnormality that affects all cell types, is associated with very low numbers of glucocorticoid receptors, and appears to be genetic.<sup>4</sup> These patients fail to derive any benefit from glucocorticoids and demonstrate few adverse effects from corticosteroids, despite long histories of chronic oral corticosteroid use. In addition to ligand-binding defects, abnormalities in DNA binding have also been described.<sup>8</sup> Adcock and colleagues evaluated the ability of dexamethasone to increase glucocorticoid receptor complex-DNA binding.<sup>8</sup> Dexamethasone failed to induce increased DNA binding among steroid-resistant asthmatic patients, whereas significant increases in DNA binding were observed among steroid-sensitive asthmatic patients and nonasthmatic controls.<sup>8</sup> Steroid-resistant asthmatic patients were found to have increased basal expression of AP-1 DNA binding in a follow-up study, which suggests that increased levels of AP-1 prevented glucocorticoid receptor-DNA binding.<sup>9</sup>

It has also been noted that there is diminished DNA binding in patients with steroid-resistant asthma. Associated with the diminished DNA binding were increases in the expression of an alternatively spliced form of the glucocorticoid receptor called glucocorticoid receptor-beta in the peripheral blood and bronchoalveolar lavage cells of steroid-resistant asthmatic patients.<sup>9</sup> The expression of the "inactive" form of the glucocorticoid receptor is upregulated after exposure to the combination of interleukin-4 and interleukin-2 *in vitro*.<sup>9</sup> This form of the receptor has both poor ligand and DNA binding, which yields the inability of the glucocorticoid-glucocorticoid receptor complex to modulate the transcription of pro-inflammatory molecules.<sup>9</sup>

### Other Identified Abnormalities

T-lymphocyte abnormalities, like the reduced ability of glucocorticoids to inhibit inactivation of T cells and increased numbers of circulating activated T cells compared with those obtained from steroid-sensitive asthmatic patients and normal controls, have also been described in steroid-resistant asthma.<sup>10</sup> Furthermore, the T cells obtained from steroid-resistant asthmatic patients are much less sensitive to the suppressive effects of glucocorticoids on cytokine production. These findings strongly suggest that T cells derived from steroid-resistant asthmatic patients are in an inactive state, which renders them less sensitive to the effects of the glucocorticoids.

Increased numbers of eosinophils have also been found within the bronchial epithelium of steroid-resistant asthmatic patients, despite the fact that most of these patients were on high-dose inhaled and oral corticosteroids.<sup>6</sup> These eosinophils are thought to mediate much of the damage to the airway that is observed in asthma, and they are very sensitive to the suppressive effects of the corticosteroids. It is unusual to observe high numbers of eosinophils in a patient on high-dose corticosteroid therapy. Using suppression of tuberculin skin test positivity following corticosteroid administration as a functional measure of monocyte response, Sousa and colleagues found that steroid-resistant asthmatic patients display much less suppression of its line following tuberculin skin testing than do individuals with steroid-sensitive asthma.<sup>11</sup> These findings suggest that in steroid-resistant asthmatic patients, multiple immune cells are insensitive to the suppressive effects of corticosteroids.

## Therapy Management

The steroid-resistant asthmatic patients are the most difficult and challenging for clinicians to manage. They usually display severe, debilitating asthma, and by definition, are resistant to the most effective class of medications used to treat this respiratory disorder. Before making the diagnosis of steroid-resistant asthma, a complete and comprehensive evaluation of the patient needs to be conducted to ensure that the patient has the correct diagnosis and that confounding factors have been eliminated. Sometimes, other clinical disorders like gastroesophageal



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reflux/aspiration syndromes, sinus disease, vocal cord dysfunction, environmental factors, poor compliance, or psychosocial factors can complicate the patient's asthma management.

Successful management of the steroid-resistant asthmatic patient often includes frequent clinical visits and serial objective measures of pulmonary function performed in the clinic setting as well as at home.<sup>3</sup> Peak expiratory flow monitoring performed twice daily at home can help identify worsening of the patient's asthma and assist in assessing the effect of various treatment interventions. Spirometry performed at each clinical visit is an important measure of pulmonary function in that minor deterioration or improvement in airflow can be detected and other disorders, like vocal cord dysfunction, can also be identified.<sup>3</sup> Yearly evaluation of lung volumes, performed by utilizing body box plethysmography, can provide information on the degree of hyperinflation, airtrapping, and airway resistance/conductance.<sup>3</sup> Environmental control measures are also important in the management of steroid-resistant asthmatic patients, as is a close working relationship between the patient, family, and physicians involved in the patient's care.

Pharmacologic treatment goals for steroid-resistant patients are similar to the goals for treating other asthmatic patients. They include using bronchodilators like albuterol (short-acting) and salmeterol (long-acting) as needed to relieve the airflow obstruction; protecting the airways from irritating stimuli and subsequent airway inflammation; and using anti-inflammatory medications to treat ongoing airway inflammation. These measures will assist in the reduction of airway hyperresponsiveness as well. Unlike most asthmatic patients, those with steroid-resistant asthma continue to have evidence of poor asthma control despite the use of the above measures for therapy. Therefore, the management of these steroid-resistant patients often requires optimal use of bronchodilator drug therapy as well as the use of alternative anti-inflammatory and/or immunomodulator drugs.

### **Alternative Treatment Strategies**

In patients who respond poorly to conventional doses of corticosteroids, several alternative therapeutic strategies might be beneficial. Budesonide and fluticasone, the two newer second-generation corticosteroids demonstrate a higher binding affinity and can be useful in steroid-resistant patients who display diminished glucocorticoid-glucocorticoid receptor binding affinity.<sup>3</sup> These two drugs also seem to have a greater anti-inflammatory activity and display a much greater first-pass metabolism than the other inhaled corticosteroids.<sup>3</sup> Both of these two drugs have also demonstrated steroid-sparing effects, as well as improvements in pulmonary function.<sup>12</sup> Further studies are needed to assess the efficacy of these newer inhaled second-generation corticosteroids in patients with steroid-resistant asthma.

Methotrexate in low doses has potential anti-inflammatory effects and has been used as a steroid-sparing agent in several autoimmune diseases. A number of randomized, placebo-

controlled studies have been performed to examine the role of methotrexate as an alternative asthma medication.<sup>13,14</sup> Unfortunately, these studies have yielded contrasting results, which have made it difficult to assess the drug's effectiveness. Methotrexate does appear to have the potential for modest steroid reduction, with an average reduction in corticosteroid dose of 30% to 50%.<sup>13,14</sup> A small group of patients appear to respond to methotrexate therapy, as measured by a significant reduction in their steroid doses. These reductions in steroid dosage do not seem to be sustained after therapy is discontinued. The frequency of adverse effects with methotrexate is low, but the risk of developing serious adverse effects requires careful monitoring. As with the newer inhaled corticosteroids, no specific studies evaluating methotrexate have been performed yet.<sup>3</sup>

Cyclosporine, an immunosuppressive agent, has been shown to be effective in several autoimmune diseases when used in low doses.<sup>3</sup> Alexander and colleagues evaluated low-dose cyclosporine compared to placebo over a twelve-week period in 33 patients with severe, steroid-resistant asthma.<sup>15</sup> The cyclosporine therapy resulted in significant improvements in lung function, with reductions in the frequency of asthma exacerbations that required oral corticosteroid use for treatment.<sup>15</sup> A wide variation of response to cyclosporine therapy was observed in the study. Cyclosporine therapy in asthma does not result in sustained remissions once the drug is discontinued, as has been observed in other autoimmune diseases. This means that cyclosporine would need to be given on a long-term basis for the treatment of steroid-resistant asthma. It also has many unwanted side effects, including nephrotoxicity and hypertension.

Intravenous immunoglobulin has also been shown to be effective in treating a number of immune-mediated diseases.<sup>16</sup> The potential advantages for using intravenous immunoglobulin are its relatively low toxicity and ensured compliance (as it is only dosed on a monthly basis), along with its demonstrated efficacy in steroid-dependent asthmatic patients. Further studies are needed to support this, however. The disadvantages of using intravenous immunoglobulin include its high cost, inconvenience, and the remote potential for blood-borne infection.<sup>16</sup> Mazer and Gelfand evaluated the usefulness of monthly high-dose intravenous immunoglobulin therapy in steroid-dependent asthmatic children over a six-month time period and found the drug to result in a three-fold reduction in oral corticosteroid doses; in a reduction in symptoms; and in improved peak expiratory flow rates.<sup>16</sup> The investigators observed improvements in all study parameters within the first one to two infusions of immunoglobulin, but noted deterioration on these same parameters within eight to twelve weeks after cessation of this therapy.

The leukotriene antagonists, such as zafirlukast and montelukast, are a newer class of medications that are being used to treat asthmatic patients. Because these drugs inhibit an important step in the inflammatory cascade of the arachadonic acid pathway somewhat independent from the corticosteroids,

these medications hold promise for use in steroid-resistant asthmatic patients. The leukotriene antagonists present a potential therapy alternative and remain a viable option in the treatment of steroid-resistant asthma. Research is currently underway to determine the role of this newer class of medication in treating these steroid-resistant patients; there is some uncertainty about their role at this time. These drugs have been used in small numbers of patients and for short periods of time, and have failed to result in long-term remission.<sup>17</sup>

Nedocromil sodium has been evaluated as another therapy option for treatment of steroid-resistant asthma over the last several years. Marin et al.<sup>18</sup> were able to demonstrate that nedocromil sodium resulted in a mean increase in FEV<sub>1</sub> of 11.4% after twelve weeks of therapy and a 15% increase in morning peak expiratory flow after eight and twelve weeks of therapy, respectively. Changes in FEV<sub>1</sub> at four and eight weeks and in peak expiratory flow at four weeks of nedocromil therapy were not significant. Inhaled nedocromil sodium improved pulmonary function and decreased asthma severity in steroid-resistant asthma, but its effectiveness is not homogeneous and cannot be predicted from baseline clinical data.<sup>18</sup>

## Conclusion

Persistent immune activation and airway inflammation that is resistant to corticosteroid therapy appears to explain the immunologic abnormality that defines steroid-resistant asthma. Although much insight has been gained into the pathogenesis of steroid-resistant asthma, several issues remain unresolved. Continuous airway inflammation is thought to contribute to steroid resistance, but there needs to be a non-invasive way to determine the extent of airway inflammation. More information is needed regarding the pathology of "difficult-to-control" asthma to determine whether there are ultrastructural abnormalities present that might be reversible. Taking this into consideration, it is possible that aggressive courses of anti-inflammatory or immunomodulator therapy can suppress acute inflammation, but airway remodeling might predispose the patient to residual symptoms and the development of irreversible airway disease. Another concern is the possibility that the persistent symptoms in certain patients could be related to non-inflammatory airway hyperresponsiveness.

There is a subpopulation of asthmatic patients who continue to have persistent immune activation and airway inflammation despite high-dose oral glucocorticoid therapy. The failure of these patients to respond to aggressive courses of both inhaled and oral glucocorticoid therapy has labeled them as "steroid-resistant" asthmatic patients. Recent studies have

identified several abnormalities in either glucocorticoid receptor number, ligand and binding to the glucocorticoid receptor, or DNA-binding defects. These findings might contribute to the pathogenesis of this severe form of asthma and are thought to result from ongoing allergic inflammation. More effort must be put into understanding the pathophysiology of severe asthma to refine the pharmacotherapeutic options. With a better understanding of the mechanisms involved in the pathogenesis of steroid-resistant asthma, more specific treatment modalities can be developed for this difficult-to-treat group of severely asthmatic patients. ■

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