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Asthma and Corticosteroid Responses in Childhood and Adult Asthma

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Introduction

Asthma is a chronic respiratory disease affecting about 300 million people worldwide (1). In the United States (US), an estimated 24.6 million people, including 6.2 million children, have asthma(2). Asthma is characterized by chronic inflammation and airway obstruction. Corticosteroids, inhaled or systemic, are the most effective treatment for asthma in adults and children and they are recommended by many international asthma management guidelines(1, 3). Corticosteroids have anti-inflammatory properties, which account for their effectiveness in suppressing the underlying airway inflammatory process and controlling asthma symptoms(4).

Inhaled corticosteroids (ICS) are the mainstay treatment in patients with chronic persistent asthma(4), whereas short courses of oral corticosteroids (OCSs) are effective to establish control of asthma exacerbations or during a period of gradual deterioration of asthma not responding to step-up controller therapy(5). A large number of studies investigating ICS in asthma have demonstrated improvement in symptoms, lung function, airway

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hyperresponsiveness, and exacerbation frequency (6, 7). However, the response to these medications is highly variable, particularly when administered at moderate-to-high dosages(8). The variability in response may be attributable to different mechanisms underlying the airway inflammation (9).

Inflammation in Asthma

The majority of patients with asthma have underlying immune mediated inflammation involving Type 2 helper T (TH2) cells and innate lymphoid cells of group 2(ILC2) responses which result in production of cytokines, inflammatory peptides, chemokines, and growth factors(10). This leads to production of IgE and subsequent activation of mast cells and activation and recruitment of eosinophils resulting in airway hyperresponsiveness, smooth-muscle hypertrophy, structural airway remodeling, and mucus secretion (11). This chronic inflammation underlies the typical symptoms of asthma, which include intermittent wheezing, coughing, shortness of breath, and chest tightness. However, studies of the cellular components of airway inflammation have found increasing evidence that a significant proportion of human asthma may be driven by non-TH2 inflammation (6, 12). Asthma is classically divided into three main immunopathological phenotypes, eosinophilic, neutrophilic, and paucigranulocytic.

Mechanism of action of Corticosteroids

Molecular mechanism of action

The anti-inflammatory effects of corticosteroids are mediated by both genomic and non-genomic effects (13, 14). Inhaled corticosteroids (ICS) target gene transcription through their interactions with the glucocorticoid receptor (GR) at the glucocorticoid response element (GRE) (15).

The airway inflammation in asthma is characterized by the increased expression of multiple inflammatory genes, including those encoding for cytokines, chemokines, adhesion molecules, and inflammatory enzymes and receptors. The major action of corticosteroids is to switch off these genes (16) by reversing histone acetylation of activated inflammatory genes (transrepression) (17). The anti-inflammatory effect of ICS is mediated through their binding to the corticosteroid receptor, which can subsequently reduce inflammatory gene expression. This is often attributed to a direct inhibitory effect of the GR on inflammatory gene transcription (18). This mechanism results in the suppression of proinflammatory molecules called transrepression and upregulation of many anti-inflammatory molecules called transactivation. Transrepression accounts for many of the desired GC effects (19).

Cellular effect of corticosteroids

At a cellular level, corticosteroids reduce the number of inflammatory cells in the airways, including eosinophils, T lymphocytes, mast cells, and dendritic cells(4). These effects of corticosteroids are produced through inhibiting the recruitment of inflammatory cells into the airway by suppressing the production of chemotactic mediators and adhesion molecules and by inhibiting the survival in the airways of inflammatory cells, such as eosinophils, T lymphocytes, and mast cells(20). ICS attenuate airway eosinophil numbers, reduce asthma

exacerbations and mortality and lead to improvements in lung function and health-related quality of life (21, 22) (Box 1).

Criterion for corticosteroid responsiveness

Current asthma guidelines characterize treatment response as improved lung function, symptoms, or exacerbations (1). Corticosteroid response can be assessed through normalization or improvement across multiple domains: airflow limitation measured by lung function testing, symptom scores, and airway inflammation (23).

Assessment of Steroid Responsiveness

Asthma control should aim to: achieve day-to-day (or current) asthma control, minimize activity limitation, prevent asthma exacerbations, and reduce decline in lung function over time, while minimizing the risk of side effects from medications required to achieve this control(24). The British Thoracic Society guidelines describe the goal of total (or optimal) asthma control as comprising no daytime or nighttime symptoms, normal lung function, and no exacerbations(25).

Response to ICS should be examined across the domains of symptoms, lung function, exacerbation rate(26).. Direct and indirect measures of airway inflammation may also be considered. Table 1 details subjective and objective measures of asthma control.

In children, the definition of corticosteroid responsiveness has been debated. Currently, there is no accepted definition of steroid response. A recent study in pediatric patients with severe asthma proposed definition of steroid response in children (27, 28) as 15% increase of FEV₁ percent predicted, bronchodilator reversibility (BDR) of 12% or greater (table 2). However, it is acknowledged that this might not be an appropriate definition for children because many children with a confirmed diagnosis of severe asthma have normal spirometric results, but their symptoms remain poorly controlled (29, 30).

Symptoms

Although symptoms may be of most importance to patients, symptom perception is often poor in asthmatic children(31), making this less than ideal as a measure of response.

Lung function

Although studies in adults have relied on changes in lung function as an indicator of corticosteroid responsiveness (32), children with severe asthma often have less airflow limitation than do adults (33-36) and do not always have concordance between lung function measures and symptoms (35). Furthermore, spirometry is often normal in children even with quite severe asthma (37). Lung function is only one component of asthma control and is best assessed in combination with current symptoms(1).

However studies have assessed complete corticosteroid responsiveness by selected cut-points of symptoms, FEV₁, bronchodilator reversibility, and exhaled nitric oxide (38). In

other studies, steroid sensitivity was defined by >15% improvement in pre-bronchodilator FEV1, after a short course of oral corticosteroids (39, 40).

Factors affecting corticosteroid response in asthma in both children and adults

Even though ICS have been established as first-line treatment in adults and children with persistent asthma, there is substantial heterogeneity of responses to ICS therapy (41). The change in lung function associated with asthma treatment administration follows a near-normal distribution, demonstrating substantial interindividual variability (42), with a significant proportion of both non-responders and high responders to therapy. This wide variability in interindividual response, combined with high intraindividual repeatability, suggests a genetic basis to the heterogeneity in asthma treatment response (43). This heterogeneity is also influenced by other factors including age, sex, socioeconomic status, race and/or ethnicity, and gene by environment interactions(44). The multiple factors that appear to impact the effectiveness of inhaled corticosteroid (ICS) treatment can be characterized as either modifiable or non-modifiable (Table 3)

The modifiable factors must be assessed before consideration of response to treatment, e.g., patients should be checked for adherence to treatment, coexisting conditions should be treated (11), and the diagnosis of severe asthma must be kept in mind in some cases that does not respond to corticosteroids.

1. Potential modifiable/ reversible factors are:

- **Poor treatment adherence**—Suboptimal adherence leads to poorer clinical outcomes (45). There are two forms of non-adherence; intentional and unintentional. Unintentional non-adherence can result from the complexity of the treatment regimen or understanding of the medication (46). Intentional barriers to adherence are driven by illness perceptions and medication beliefs, patients and parents deliberately choose not to follow the doctor's recommendations. Common non-intentional barriers are related to family routines, child-raising issues, and to social issues such as poverty (47). A retrospective case control survey identified poor adherence in 22% in 57 children with difficult-to-control asthma (39).
- **Pitfalls in drug delivery**—One potential explanation of poor response to corticosteroid treatment could be the suboptimal prescribed dosing of ICS, particularly in young children who may receive less of the actuated medication delivered to the distal airways than older children and adults. Furthermore, even with appropriately chosen medication and delivery device, many people with asthma do not use their inhaler correctly (48).
- **Comorbidities**—Comorbidities that have not been managed well and alternative diagnoses such as inhaled foreign body and structural abnormalities need to be addressed in order to optimize asthma management.

- **Environmental influences and Allergen exposure**—Studies have shown that partial corticosteroid response may be due to ongoing exposure to environmental triggers(29) and that persistent allergen exposure in sensitized individuals can lead to an interleukin (IL)-2 and IL-4 mediated corticosteroid resistance(49).

Cigarette smoking is also known to cause corticosteroid resistance (28, 29). In fact, tobacco smoke, even by passive exposure, leads to increased asthma symptoms and decreased response to inhaled corticosteroids. Studies found that asthmatic patients exposed to tobacco are refractory to standard controller therapies, namely inhaled corticosteroids (50). Kobayahi et al demonstrated that passive smoke exposure impaired histone deacetylase-2 function, which could contribute to steroid resistance in children with asthma (51).

- **Stress**—Recently, stress-related glucocorticoid resistance of TH2 cytokine production by T cells was described in children with asthma who reported inadequate social support(52). Although asthma exacerbation has long been thought to be affected by emotional states, evidence has only recently emerged to identify cellular and molecular mechanisms responsible for stress-induced glucocorticoid insensitivity(53).

2. Non Modifiable factors

Genetics—Genetic variation may partly explain asthma treatment response heterogeneity (54). Endogenous corticosteroid level and exogenous therapeutic response to corticosteroids are also strongly influenced by genetics (55). Previous studies have suggested that 60–80% of asthma patients have different responses to corticosteroids treatment due to genetic factors(56), highlighting the importance of gene polymorphisms for the inter-individual variability in a patient's response to medication (57). Among children participating in the CAMP study, a variation in *TBX21* coding (replacement of histidine 33 with glutamine) affected the effect of inhaled corticosteroids on airway hyperresponsiveness(58), whereas a functional variant in glucocorticoid-induced transcript 1 gene (*GLCCI1*) was associated with a decreased response to corticosteroids(59). *TBX21* encodes for the transcription factor T-bet (T-box expressed in T cells), which influences naive T lymphocyte development and has been implicated in asthma pathogenesis(58).

A review done by Duong et al., found that various potential genetic factors associated with the response to ICS, and that they could be utilized to predict the individual therapeutic response of children with asthma to ICS (57). Among the genes identified, variants in T-box 21 (*TBX21*) and Fc fragment of IgE receptor II (*FCER2*) contribute indirectly to the variability in the response to ICS by altering the inflammatory mechanisms in asthma, while other genes such as corticotropin releasing hormone receptor 1 (*CRHR1*), nuclear receptor subfamily 3 group C member 1 (*NR3C1*), stress induced phosphoprotein 1 (*STIP1*), dual specificity phosphatase 1 (*DUSP1*), glucocorticoid induced 1 (*GLCCI1*), histone deacetylase 1 (*HDAC*), *ORMDL* sphingolipid biosynthesis regulator 3 (*ORMDL3*), and vascular endothelial growth factors (*VEGF*) directly affect this variability through the anti-inflammatory mechanisms of ICS (57). The effect of genetic variants on treatment outcome might occur through differences in disease subtypes or through influences on drug level or drug target (26).

Studies have investigated the genetic influences on the ICS response in chronic treatment of asthma (23, 36). ICS response studies, such as those implicating genetic variants, are STIP1, (60)TBX21,(58, 61) and WDR21A,(62),GLCC11,(59), FBXL7,(63)9 T,10 CRHR1, and MAPT(64).

On the contrary, a recent study reported no evidence to confirm previously reported associations between candidate genetic variants and ICS response (i.e., change of FEV₁ from baseline) in patients with asthma (65).

Epigenetics—In asthmatic children, treatment response to systemic corticosteroid is heterogeneous and may be mediated by epigenetic mechanism (3).

Recently, DNA methylation has been increasingly explored due to its important role in the regulation of gene expression (66). DNA methylation (DNAm) is the modification of cytosine by adding a methyl group to the 5' position of C. DNAm mostly occurs in the context of CpG dinucleotides and represents an important epigenetic mechanism that regulates gene expression (67). Several studies have successfully identified DNAm of certain nucleotides as a biomarker for asthma (68, 69). These epigenetic biomarkers may be used to distinguish children who do not respond to steroid treatment well (66)

Patient characteristics/ phenotypes and biomarkers—Asthma encompasses a broad collection of heterogeneous disease subtypes with different underlying pathophysiological mechanisms (70). Simpson et al, described four inflammatory subtypes of asthma based on the immune cell profile of sputum taken from patients. These subtypes include eosinophilic (eosinophils >3%), neutrophilic (neutrophils >61%), mixed granulocytic (increased eosinophils and neutrophils), and paucigranulocytic asthma (normal levels of both of these specific immune cell types)(71). The neutrophilic and eosinophilic phenotype usually do not respond well to corticosteroids (72).

In clinical practice, variable responses to corticosteroid treatment have been observed. Phenotypic presentations in young children with asthma are varied and might contribute to differential responses to asthma controller medications. Treatment response to inhaled corticoids clearly dependent on certain asthma phenotypes (73, 74) Szeffler et al., found that treatment response was highly variable even in adults with mild to moderate persistent asthma and that there was some potential to relate treatment response to patient characteristics and biomarkers(75). Specifically, allergies and high levels of eNO indicated a favorable response to corticosteroids (74).

Race—Race and ethnicity may influence the response to treatment in patients with asthma(76); black patients may have a diminished response to glucocorticoids (77). Koo et al., reported that black children with severe asthma had less improvement in Feno than white children and were more likely to experience exacerbations (76). While this data suggests a differential response to therapy between asthma patients by race and ethnicity, the evidence regarding ethnic variations in response to steroid treatment is still limited. Evidence suggests that blacks have a racial predisposition to diminished glucocorticoid responsiveness, which may contribute to their heightened asthma morbidity (78). Although disparities in access to

care and quality of care, have been implicated in the racial differential outcomes(79), it is also possible that there are inherent pathophysiologic or even pharmacogenomic differences between whites and African Americans that result in these discrepancies(80).

Microbiome—Early evidence suggests that there may be a relationship between the airway microbiome and physiologic response to corticosteroids. Evidence showed that strains of *Streptococci* can influence the response of bronchial epithelial cells to corticosteroids(81) and *Haemophilus* and *parainfluenzae* species have been shown to inhibit corticosteroid response of asthmatic alveolar macrophages and peripheral blood monocytes (81, 82).

Predictors of Asthma Response to Corticosteroid

As the response to ICS is not uniform and shows variability among individuals, it would be highly desirable to identify a subgroup of patients who show a favorable (or worse) response to ICS.

In the current guidelines for asthma treatment, therapeutic strategy is adjusted on the basis of symptoms, lung function, and acute exacerbations. However, the relationship between these key components of the disease may vary among different asthmatic patients (83). Thus predictors such as baseline pulmonary function and levels of markers of allergic inflammation could be used to predict response to ICS. Lower pre-bronchodilator lung function and higher BDR of FEV1, as well as degree of airway hyperresponsiveness to methacholine is associated with more favorable response to ICS (84, 85). Further, positive ICS response has also been associated with biomarkers of TH2 inflammation, such as FeNO levels, Total eosinophil count, IgE levels, and ECP levels (74).

Biomarkers

Biomarkers known to be useful for the diagnosis of asthma as well as being relevant to the response to treatment and may be useful in personalizing care of the asthmatic patient(86). The utility of biomarkers in asthma for predicting future exacerbations, response to treatment or lung function decline is a topic of growing interest (87). Cowan et al, suggested that baseline inflammatory biomarkers enable prediction of ICS responsiveness in asthma (88).

Specific inflammatory biomarkers could potentially serve as corticosteroid response predictors (e.g. fraction of nitric oxide in exhaled breath), Eosinophilic markers (exhaled NO or sputum eosinophils) (88). Approximately 50% of asthma cases are attributable to eosinophilic airway inflammation. ICS are particularly effective in combating Th2-driven inflammation featuring mast cell and eosinophilic airway infiltration(89). Eosinophilic phenotype usually responds well to corticosteroids, except for a small subgroup of severe asthma where even in the presence of eosinophils the ICS seem to have a less responsive role(85).

1 Predictors of Response in Adults

- FeNO

- FEV1
- Smoking
- Gender

F_ENO—Over the last decade, fraction of exhaled nitric oxide (FENO) values and sputum eosinophil counts have been used as biomarkers of airway inflammation and predictors of steroid responsiveness (28, 88). FENO values are correlated with airway eosinophilia (90) and associated with airway hyperresponsiveness (91). FENO values are high in asthmatic patients (92, 93). Furthermore, studies indicate that high FENO values in asthmatic patients indicate an at-risk phenotype for exacerbation and predict clinical response to ICSs or oral corticosteroids (93). Multiple studies have found that a favorable response to fluticasone was associated with higher levels of FeNO, as well as, total eosinophil counts and levels of serum Immunoglobulin E (IgE) (84, 85, 94). Evidence indicates that F_ENO, which is a marker of T-helper cell type 2 (Th2)-mediated airway inflammation, has a high positive and negative predictive value for identifying corticosteroid-responsive airway(95). F_ENO production is very sensitive to ICS therapy because ICS therapy can directly inhibit F_ENO production by modulation of inducible nitric oxide synthase (96). In fact, studies have found that sputum eosinophils and FeNO are the best predictors of favorable response to oral prednisolone in severe asthmatics (97). High F_ENO (>50 parts per billion) strongly suggests airway eosinophilia and hence steroid responsiveness(98).

The combination of high F_ENO and high urinary bromotyrosine (BrTyr), which is a biochemical fingerprint of eosinophil activation, were reported in a study to predict a favorable clinical response to ICS with either improvement in ACQ, FEV₁ or airway reactivity (88).

FEV₁—Evidence concluded that short-term response to ICS with regard to FEV₁ improvement predicts long-term control from Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial (75). It is reported that favorable corticosteroid response was associated with lower levels of methacholine provocative concentration causing a 20% fall in FEV₁(74, 99). Similarly, bronchodilator reversibility was highly predictive to significant response to triamcinolone acetonide injection in the Severe Asthma Research Program (SARP III) study (100)).

Smoking—Another predictor of long-term controller response in adults was identified in the Smoking Modulates Outcomes of Glucocorticoid Therapy (SMOG) study (50), in which the response to ICS was attenuated in subjects with mild asthma who smoke, suggesting that adjustments to standard therapy may be required to attain asthma control(50, 75) in this population. Smoking is a strong predictor of poor response to ICS.

Gender—The influence of sex on ICS response has been inconsistent (83). Galant et al. found that the female sex was associated with a higher likelihood of responding to ICS therapy, defined as greater than 7.5% increase in FEV1 from baseline (101).

2 Predictors of Response in Children

- Baseline low pulmonary function
- Inflammatory markers
- Gene expression
- Aeroallergen sensitization
- Others

Baseline pulmonary function—In children, baseline parameters, favoring a greater differential response for ICS, includes decreased pulmonary function, increased FEV₁ response to a bronchodilator, airway hyperresponsiveness, and markers of allergic inflammation (eNO and ECP)(74). A recent study, SARP III cohort of adult and children with severe asthma found that baseline bronchodilator response and fractional exhaled nitric oxide had good sensitivity and specificity for predicting response in all groups except children with nonsevere asthma.(100) The Childhood Asthma Research and Education Network's Best Add-On Giving Effective Response (BADGER) study suggested that children who responded best to low-dose ICSs had worse asthma control, lower pulmonary function, and lower PC₂₀ levels, which indicate greater bronchial reactivity(102).

Inflammatory markers—Biomarkers associated with differential responses to asthma treatments have been studied in children (66). Szeftler et al. found that higher exhaled nitric oxide (eNO), blood eosinophil counts and serum immunoglobulin E (IgE) were associated with a better FEV₁ response to ICS(74).

As in adults, children with predominately allergic airways inflammation or eosinophilic phenotypes are likely to have a beneficial response to ICS (74, 75, 102) (103).

Gene expression—Transcriptional profiling of individual responses is a necessary and fundamental step to better understand the individual variation and identify biomarkers of systemic corticosteroid treatment response.(104) A recent study used genome-wide expression profiling of nasal epithelial cells to identify genes with temporal expression patterns among children with asthma before and after treatment with systemic corticosteroids, they concluded that VNN1 contributes to corticosteroid responsiveness, and that changes in vanin-1 (VNN1) nasal epithelial mRNA expression and VNN1 promoter methylation might be clinically useful biomarkers of treatment response in asthmatic children

Aeroallergen sensitization—Among other markers of allergic inflammation, children who have specific IgE or skin prick allergen sensitivity have been found to be ICS responders (74, 102). Studies suggest that children with markers of allergic asthma may experience greater benefits from inhaled corticosteroid treatment than children without such markers(75). Bacharier et al. (11) conducted secondary analysis in the CARE Network revealed that preschool children at high risk for asthma experience favorable responses to ICS therapy, particularly when indicators of greater disease severity and aeroallergen sensitization are present(105). Fitzpatrick et al., reported best response to daily ICS in

children with both aeroallergen sensitization and blood eosinophil counts of $\geq 300/\mu\text{m}^3$; they demonstrated more asthma control days and fewer exacerbations (106).

Others—Severe other clinical features have been reported to be associated with ICS sensitivity. Knuffman et al. identified that parental history of asthma strongly suggested ICS response in the asthmatic child (99). Female sex (101) and normal body weight (107) have also been shown to be associated with a favorable response to ICS. Additionally, obesity is another factor that might influence the response to ICS (108). In the TREXA trial, male sex was reported to be associated with greater duration of asthma control as a result of daily treatment with ICS (109).

Monitoring Response

Response to corticosteroids is monitored by the assessment of clinical symptoms, which only partially correlates with underlying airway inflammation (110). Several biomarkers have been assessed following treatment with corticosteroids including measures of lung function, peripheral blood and sputum indices of inflammation, exhaled gases and breath condensates (111). Some of these inflammatory biomarkers are already finding their way into clinical practice (e.g. fraction of nitric oxide in exhaled breath) (110).

Petsky et al. found that the use of FeNO to guide in asthma therapy in children might be beneficial in a subset of children. However, interpretation of low FeNO in children receiving ICS therapy may not correlate with improved inflammation or good control (102).

A recent study recommended monitoring eosinophils in the sputum of patients with severe, prednisone-dependent, asthma as a means to maintain symptom control, reduce exacerbations and preserve FEV1 in these patients (112), however this remains technically difficult in clinical practice.

Failure to respond/ non responders

Although ICS is currently recommended as the first-line therapy, the significant heterogeneity in response to asthma treatment is evident with as much as 22–60% of non-responder rate in both asthmatic children and adults treated with ICS (74, 113, 114) (115). Approximately, 5–15% of asthmatic children fail to respond to ICS and they are often treated with high doses of ICS, which then has the potential to cause significant side-effects (116, 117).

Several inflammatory phenotypes have been identified by the use of biomarkers. Most of them are based on the predominant type of cells in different biological fluids with sputum to be remained the most representative one (85). Lack of response to corticosteroids in asthma might be seen in patients who do not have a responsive endotype (Th2-low asthma), or a subset of patients who have Th2-high asthma (118). Patients with a neutrophilic phenotype, assessed by sputum cytology, frequently shows inadequate response to corticosteroid treatment (119, 120), even in mild asthma (85).

The existence of multiple mechanisms underlying glucocorticoid insensitivity raises the possibility that this might indeed reflect different diseases with a common phenotype(121). Several mechanisms have been proposed to account for a failure to respond to corticosteroids including a reduced number of GR, altered affinity of the ligand for GR, reduced ability of the GR to bind to DNA or increased activation of transcription factors, such as activator protein-1 (AP-1), that compete for DNA binding(122).

A study found that oxidation of the amino acid cysteine is associated with decreased responsiveness to systemic glucocorticoids in children with difficult-to-treat asthma (123).

Corticosteroid resistance

Corticosteroid resistant (CR) asthma was first described by Schwartz and colleagues in 1967 (124). A common definition of GC resistance is the failure of an asthmatic patient to improve FEV1 by 15% from a baseline of <75% predicted after an adequate dose (e.g. >40 mg prednisolone) for an adequate duration of time (e.g. 1-2weeks) (43).

Although the prevalence of CS resistance among children is very low, these children account for a disproportionate health care spending(125). Identification of corticosteroid resistance is important, allowing delivering alternative therapies; conversely, in the corticosteroid sensitive patient, the dose of therapy should be minimized to avoid unwanted side-effects (29).

Tobacco smoke-induced steroid resistance

Adult patients with asthma who currently smoke have relative steroid resistance (126), and require increased doses of corticosteroids for asthma control(127). The mechanisms of tobacco smoke-induced steroid resistance has been associated with a neutrophilic inflammatory phenotype(125). Neutrophilia in the airways is associated with a poor response to inhaled corticosteroids in asthma(119), and the increase in sputum neutrophils in smokers with asthma compared with nonsmokers with asthma(128) may account for the impaired response to corticosteroids.

Raised tumor necrosis factor- α levels in smokers (129) may also cause an increase in the number of glucocorticoid β receptors (130), which have been associated with corticosteroid resistance.

Even passive smoking may contribute to corticosteroid-insensitive inflammation in children with severe asthma by impairing histone deacetylase protein expression and activity (51). This stresses the need for a smoke-free environment for asthmatic children (51).

Mechanisms for resistance—Several molecular mechanisms have been identified to account for corticosteroid resistance in asthma (125), including overexpression of proinflammatory transcription factors, phosphorylation of glucocorticoid receptors, and increases in the decoy glucocorticoid receptor- β .7 Histone deacetylase (51).

Persistent immune activation and airway inflammation, which to varying degrees is resistant to glucocorticoid therapy, appears to define the immunologic abnormality underlying steroid-resistant asthma(131).

1. Certain cytokines (particularly interleukin-2, 4, and 13, which show increased expression in bronchial biopsy samples from patients with steroid-resistant asthma) may induce a reduction in affinity of GRs in inflammatory cells, such as T-lymphocytes, resulting in local resistance to the anti-inflammatory actions of corticosteroids (132, 133).
2. Impaired nuclear localization of GRs in response to a high concentration of corticosteroids and defective acetylation of histone-4, interfering with the anti-inflammatory actions of corticosteroids (134).
3. Immunomodulation: TH2 cytokines have also been proposed to play a role in severe CR asthma. A study has shown that CD41 T cells from patients with CR asthma are less able to produce the anti-inflammatory cytokine IL-10 in response to dexamethasone than cells from patients with CS asthma (135).
4. A subset of subjects with CR asthma demonstrates airway expansion of specific gram-negative bacteria, which trigger TAK1/ mitogen-activated protein kinase (MAPK) activation and induce corticosteroid resistance (82).

Effects of Age and Disease Severity on Systemic Corticosteroid Responses in Asthma

Phipatanakul et al (100), in the SARP III cohort of adult and children with severe asthma, describe a distinction between adults and children with severe asthma in terms of their response to parenteral corticosteroids. The study reported that adults, but not children, with severe asthma remain phenotypically distinct from those with non-severe asthma. The baseline FEV1 response to bronchodilator and baseline fractional exhaled nitric oxide were good predictors of an FEV1 corticosteroid response. These findings suggest differences between children and adults in the pathobiologic underpinnings of severe asthma that require further investigation.

The difference in persistence of the phenotype after corticosteroids and BD in adults and children is interesting and suggests that as patients move to adulthood their asthma may be a less reversible disease (100).

A recent meta-analysis also showed that in mild persistent asthma response to steroids were different in adults than in children. In adult patients with mild intermittent asthma, ICS improves lung function and alleviates airway hyper-responsiveness and airway inflammation but did influence symptom scores. However, in children, the benefit of ICS in symptom control was more significant(7).

Conclusion

Corticosteroids are the most effective therapy for asthma. Corticosteroids suppress inflammation via several molecular mechanisms. Baseline features may identify ICS responsiveness and thus determine patients who would most likely to benefit from ICS treatment. Heterogeneity of the response to corticosteroids exists in adult and pediatric asthma with few biomarkers consistently indicating favorable response prior to treatment. Monitoring responses by using biomarkers as sputum eosinophils, exhaled breath condensates, and have been used as tools primarily in research studies. Using symptom assessment tools, exacerbation rate, lung function and clinically available markers of airway inflammation can help identify individual patient response in clinical practice. Asthma patients have different responses to Corticosteroids due to multiple factors. Corticosteroid resistant asthma is uncommon and presents a clinical challenges because alternative treatment choices are limited. Asthma response to steroids were found to be different in adults than in children.

Abbreviations:

GC	Glucocorticoids
ICS	Inhaled corticosteroids
OCSs	oral corticosteroids
PEF	peek expiratory flow
TH2	Type 2 helper T cell
ILC2	innate lymphoid cells of group 2
GR	Glucocorticoid receptor
GRE	Glucocorticoid response element
FEV₁	Forced expiratory volume in one second
FeNO	Fraction of exhaled nitric oxide
eNO	exhaled nitric oxide
IgE	Immunoglobulin E
BDR	Bronchodilator reversibility
ACT	Asthma Control Test
ACQ	Asthma Control Questionnaire
GINA	Global Initiative for Asthma
EPR-3	Expert Panel Report
ECP	Eosinophilic cationic protein

References

1. Global strategy for asthma management and prevention [Internet]. [Updated 2017; cited 2017 Nov Sep 1]. Available from: Available from: <http://ginasthma.org/gina-reports/>
2. CDC. NHIS Data. Table 3-1. 2015; www.cdc.gov/asthma/nhis/2015/table3-1.htm.
3. Loughheed MD, Lemiere C, Ducharme FM, Licskai C, Dell SD, Rowe BH, et al. Canadian Thoracic Society 2012 guideline update: Diagnosis and management of asthma in preschoolers, children and adults: Executive summary. *Can Respir J*. 2012;19(6):e81–8. [PubMed: 23248807]
4. Barnes PJ. Inhaled Corticosteroids. *Pharmaceuticals (Basel)*. 2010;3(3):514–40. [PubMed: 27713266]
5. Fergusson JE, Patel SS, Lockey RF. Acute asthma, prognosis, and treatment. *J Allergy Clin Immunol*. 2017;139(2):438–47. [PubMed: 27554811]
6. Haldar P, Pavord ID. Noneosinophilic asthma: a distinct clinical and pathologic phenotype. *J Allergy Clin Immunol*. 2007;119(5):1043–52; quiz 53–4. [PubMed: 17472810]
7. Du W, Zhou L, Ni Y, Yu Y, Wu F, Shi G. Inhaled corticosteroids improve lung function, airway hyper-responsiveness and airway inflammation but not symptom control in patients with mild intermittent asthma: A meta-analysis. *Exp Ther Med*. 2017;14(2):1594–608. [PubMed: 28810625]
8. Kelly HW. Inhaled corticosteroid dosing: double for nothing? *J Allergy Clin Immunol*. 2011;128(2):278–81 e2. [PubMed: 21621831]
9. Deykin A, Lazarus SC, Fahy JV, Wechsler ME, Boushey HA, Chinchilli VM, et al. Sputum eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids. *J Allergy Clin Immunol*. 2005;115(4):720–7. [PubMed: 15805990]
10. Vijverberg SJ, Hilvering B, Raaijmakers JA, Lammers JW, Maitland-van der Zee AH, Koenderman L. Clinical utility of asthma biomarkers: from bench to bedside. *Biologics*. 2013;7:199–210. [PubMed: 24009412]
11. Israel E, Reddel HK. Severe and Difficult-to-Treat Asthma in Adults. *N Engl J Med*. 2017;377(10):965–76. [PubMed: 28877019]
12. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med*. 2009;180(5):388–95. [PubMed: 19483109]
13. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med*. 2005;353(16):1711–23. [PubMed: 16236742]
14. de Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. *Am J Respir Crit Care Med*. 2012;185(1):12–23. [PubMed: 21920920]
15. Trevor JL, Deshane JS. Refractory asthma: mechanisms, targets, and therapy. *Allergy*. 2014;69(7):817–27. [PubMed: 24773466]
16. Barnes PJ. How corticosteroids control inflammation: Quintiles Prize Lecture 2005. *Br J Pharmacol*. 2006;148(3):245–54. [PubMed: 16604091]
17. Barnes PJ. Glucocorticosteroids. *Handb Exp Pharmacol*. 2017;237:93–115. [PubMed: 27796513]
18. Kelly MM, King EM, Rider CF, Gwozd C, Holden NS, Eddleston J, et al. Corticosteroid-induced gene expression in allergen-challenged asthmatic subjects taking inhaled budesonide. *Br J Pharmacol*. 2012;165(6):1737–47. [PubMed: 21827450]
19. Gensler LS. Glucocorticoids: Complications to Anticipate and Prevent. *Neurohospitalist*. 2013;3(2):92–7. [PubMed: 23983891]
20. Barnes PJ, Adcock IM. How do corticosteroids work in asthma? *Ann Intern Med*. 2003;139(5 Pt 1):359–70. [PubMed: 12965945]
21. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med*. 2000;343(5):332–6. [PubMed: 10922423]
22. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. *Lancet*. 2003;361(9363):1071–6. [PubMed: 12672309]

23. Bossley CJ, Fleming L, Ullmann N, Gupta A, Adams A, Nagakumar P, et al. Assessment of corticosteroid response in pediatric patients with severe asthma by using a multidomain approach. *J Allergy Clin Immunol*. 2016;138(2):413–20 e6. [PubMed: 27061250]
24. O'Byrne PM. Global guidelines for asthma management: summary of the current status and future challenges. *Pol Arch Med Wewn*. 2010;120(12):511–7. [PubMed: 21178908]
25. British guideline on the management of asthma. *Thorax*. 2014;69 Suppl 1:1–192.
26. Vijverberg SJH, Farzan N, Slob EMA, Neerincx AH, Maitland-van der Zee AH. Treatment response heterogeneity in asthma: the role of genetic variation. *Expert Rev Respir Med*. 2018;12(1):55–65. [PubMed: 29115880]
27. Adcock IM, Ito K. Steroid resistance in asthma: a major problem requiring novel solutions or a non-issue? *Curr Opin Pharmacol*. 2004;4(3):257–62. [PubMed: 15140417]
28. Little SA, Chalmers GW, MacLeod KJ, McSharry C, Thomson NC. Non-invasive markers of airway inflammation as predictors of oral steroid responsiveness in asthma. *Thorax*. 2000;55(3):232–4. [PubMed: 10679543]
29. Bossley CJ, Saglani S, Kavanagh C, Payne DN, Wilson N, Tsartsali L, et al. Corticosteroid responsiveness and clinical characteristics in childhood difficult asthma. *Eur Respir J*. 2009;34(5):1052–9. [PubMed: 19541710]
30. Fitzpatrick AM, Teague WG. Severe Asthma in Children: Insights from the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *Pediatr Allergy Immunol Pulmonol*. 2010;23(2):131–8. [PubMed: 21761006]
31. Rietveld S, Everaerd W. Perceptions of asthma by adolescents at home. *Chest*. 2000;117(2):434–9. [PubMed: 10669687]
32. Martin RJ, Szeffler SJ, King TS, Kraft M, Boushey HA, Chinchilli VM, et al. The Predicting Response to Inhaled Corticosteroid Efficacy (PRICE) trial. *J Allergy Clin Immunol*. 2007;119(1):73–80. [PubMed: 17208587]
33. Gupta A, Gupta LK, Rehan HS, Prakash A. Response to inhaled corticosteroids on serum CD28, quality of life, and peak expiratory flow rate in bronchial asthma. *Allergy Asthma Proc*. 2017;38(2):13–8. [PubMed: 28234041]
34. Wang G, Baines KJ, Fu JJ, Wood LG, Simpson JL, McDonald VM, et al. Sputum mast cell subtypes relate to eosinophilia and corticosteroid response in asthma. *Eur Respir J*. 2016;47(4):1123–33. [PubMed: 26699720]
35. Keskin O, Uluca U, Birben E, Coskun Y, Ozkars MY, Keskin M, et al. Genetic associations of the response to inhaled corticosteroids in children during an asthma exacerbation. *Pediatr Allergy Immunol*. 2016;27(5):507–13. [PubMed: 27003716]
36. Fitzpatrick AM, Stephenson ST, Brown MR, Nguyen K, Douglas S, Brown LA. Systemic Corticosteroid Responses in Children with Severe Asthma: Phenotypic and Endotypic Features. *J Allergy Clin Immunol Pract*. 2017;5(2):410–9 e4. [PubMed: 27665382]
37. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF, Jr., Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med*. 2004;170(4):426–32. [PubMed: 15172893]
38. Fitzpatrick AM, Stephenson ST, Brown MR, Nguyen K, Douglas S, Brown LAS. Systemic Corticosteroid Responses in Children with Severe Asthma: Phenotypic and Endotypic Features. *J Allergy Clin Immunol Pract*. 2017;5(2):410–9 e4. [PubMed: 27665382]
39. Ranganathan SC, Payne DN, Jaffe A, McKenzie SA. Difficult asthma: defining the problems. *Pediatr Pulmonol*. 2001;31(2):114–20. [PubMed: 11180686]
40. Chan MT, Leung DY, Szeffler SJ, Spahn JD. Difficult-to-control asthma: clinical characteristics of steroid-insensitive asthma. *J Allergy Clin Immunol*. 1998;101(5):594–601. [PubMed: 9600494]
41. Anderson WJ, Short PM, Williamson PA, Lipworth BJ. Inhaled corticosteroid dose response using domiciliary exhaled nitric oxide in persistent asthma: the FENotype trial. *Chest*. 2012;142(6):1553–61. [PubMed: 23364390]
42. Kainu A, Lindqvist A, Sarna S, Lundback B, Sovijarvi A. FEV1 response to bronchodilation in an adult urban population. *Chest*. 2008;134(2):387–93. [PubMed: 18403671]
43. Drazen JM, Silverman EK, Lee TH. Heterogeneity of therapeutic responses in asthma. *Br Med Bull*. 2000;56(4):1054–70. [PubMed: 11359637]

44. Lemanske RF, Jr., Busse WW. Asthma: clinical expression and molecular mechanisms. *J Allergy Clin Immunol.* 2010;125(2 Suppl 2):S95–102. [PubMed: 20176271]
45. Normansell R, Kew KM, Stovold E. Interventions to improve adherence to inhaled steroids for asthma. *Cochrane Database Syst Rev.* 2017;4:CD012226. [PubMed: 28417456]
46. Lee JX, Wojtczak HA, Wachter AM, Lee ML, Burns L, Chen D, et al. Understanding asthma medical nonadherence in an adult and pediatric population. *J Allergy Clin Immunol Pract.* 2015;3(3):436–7. [PubMed: 25609340]
47. Klok T, Kaptein AA, Brand PLP. Non-adherence in children with asthma reviewed: The need for improvement of asthma care and medical education. *Pediatr Allergy Immunol.* 2015;26(3):197–205. [PubMed: 25704083]
48. Normansell R, Kew KM, Mathioudakis AG. Interventions to improve inhaler technique for people with asthma. *Cochrane Database Syst Rev.* 2017;3:CD012286. [PubMed: 28288272]
49. Kam JC, Szeffler SJ, Surs W, Sher ER, Leung DY. Combination IL-2 and IL-4 reduces glucocorticoid receptor-binding affinity and T cell response to glucocorticoids. *J Immunol.* 1993;151(7):3460–6. [PubMed: 8376786]
50. Lazarus SC, Chinchilli VM, Rollings NJ, Boushey HA, Cherniack R, Craig TJ, et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med.* 2007;175(8):783–90. [PubMed: 17204725]
51. Kobayashi Y, Bossley C, Gupta A, Akashi K, Tsartsali L, Mercado N, et al. Passive smoking impairs histone deacetylase-2 in children with severe asthma. *Chest.* 2014;145(2):305–12. [PubMed: 24030221]
52. Miller GE, Gaudin A, Zysk E, Chen E. Parental support and cytokine activity in childhood asthma: the role of glucocorticoid sensitivity. *J Allergy Clin Immunol.* 2009;123(4):824–30. [PubMed: 19181373]
53. Haczku A, Panettieri RA. Social stress and asthma: The role of corticosteroid insensitivity. *Journal of Allergy and Clinical Immunology.* 2010;125(3):550–8. [PubMed: 20153032]
54. Leusink M, Vijverberg SJ, Koenderman L, Raaijmakers JA, de Jongste JC, Sterk PJ, et al. Genetic variation in uncontrolled childhood asthma despite ICS treatment. *Pharmacogenomics J.* 2016;16(2):158–63. [PubMed: 25963336]
55. Inglis GC, Ingram MC, Holloway CD, Swan L, Birnie D, Hillis WS, et al. Familial pattern of corticosteroids and their metabolism in adult human subjects--the Scottish Adult Twin Study. *J Clin Endocrinol Metab.* 1999;84(11):4132–7. [PubMed: 10566661]
56. Baye TM, Abebe T, Wilke RA. Genotype-environment interactions and their translational implications. *Per Med.* 2011;8(1):59–70. [PubMed: 21660115]
57. Duong-Thi-Ly H, Nguyen-Thi-Thu H, Nguyen-Hoang L, Nguyen-Thi-Bich H, Craig TJ, Duong-Quy S. Effects of genetic factors to inhaled corticosteroid response in children with asthma: a literature review. *J Int Med Res.* 2017;45(6):1818–30. [PubMed: 29251255]
58. Tantisira KG, Hwang ES, Raby BA, Silverman ES, Lake SL, Richter BG, et al. TBX21: a functional variant predicts improvement in asthma with the use of inhaled corticosteroids. *Proc Natl Acad Sci U S A.* 2004;101(52):18099–104. [PubMed: 15604153]
59. Tantisira KG, Lasky-Su J, Harada M, Murphy A, Litonjua AA, Himes BE, et al. Genomewide association between GLCCI1 and response to glucocorticoid therapy in asthma. *N Engl J Med.* 2011;365(13):1173–83. [PubMed: 21991891]
60. Hawkins GA, Lazarus R, Smith RS, Tantisira KG, Meyers DA, Peters SP, et al. The glucocorticoid receptor heterocomplex gene STIP1 is associated with improved lung function in asthmatic subjects treated with inhaled corticosteroids. *J Allergy Clin Immunol.* 2009;123(6):1376–83 e7. [PubMed: 19254810]
61. Lopert A, Rijavec M, Žavbi M, Korošec P, Fležar M. Asthma treatment outcome in adults is associated with rs9910408 in TBX21 gene. *Sci Rep.* 2013;3.
62. Cho SH, Park BL, Shin SW, Heo JS, Park JS, Park SW, et al. Association between WDR21A polymorphisms and airway responsiveness to inhaled corticosteroids in asthmatic patients. *Pharmacogenet Genomics.* 2012;22(5):327–35. [PubMed: 22366774]

63. Park HW, Dahlin A, Tse S, Duan QL, Schuemann B, Martinez FD, et al. Genetic predictors associated with improvement of asthma symptoms in response to inhaled corticosteroids. *J Allergy Clin Immunol.* 2014;133(3):664–9 e5. [PubMed: 24486069]
64. Tantisira KG, Lazarus R, Litonjua AA, Klanderman B, Weiss ST. Chromosome 17: association of a large inversion polymorphism with corticosteroid response in asthma. *Pharmacogenet Genomics.* 2008;18(8):733–7. [PubMed: 18622266]
65. Mosteller M, Hosking L, Murphy K, Shen J, Song K, Nelson M, et al. No evidence of large genetic effects on steroid response in asthma patients. *J Allergy Clin Immunol.* 2017;139(3):797–803 e7. [PubMed: 27523435]
66. Zhang X, Biagini Myers JM, Yadagiri VK, Ulm A, Chen X, Weirauch MT, et al. Nasal DNA methylation differentiates corticosteroid treatment response in pediatric asthma: A pilot study. *PLoS One.* 2017;12(10):e0186150. [PubMed: 29028809]
67. Feinberg AP. Genome-scale approaches to the epigenetics of common human disease. *Virchows Arch.* 2010;456(1):13–21. [PubMed: 19844740]
68. Begin P, Nadeau KC. Epigenetic regulation of asthma and allergic disease. *Allergy Asthma Clin Immunol.* 2014;10(1):27. [PubMed: 24932182]
69. Yang IV, Richards A, Davidson EJ, Stevens AD, Kolakowski CA, Martin RJ, et al. The Nasal Methylome: A Key to Understanding Allergic Asthma. *Am J Respir Crit Care Med.* 2017;195(6):829–31. [PubMed: 28294656]
70. Halder P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med.* 2008;178(3):218–24. [PubMed: 18480428]
71. Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. *Respirology.* 2006;11(1):54–61. [PubMed: 16423202]
72. Alangari AA. Corticosteroids in the treatment of acute asthma. *Ann Thorac Med.* 2014;9(4):187–92. [PubMed: 25276236]
73. Zeiger RS, Szeffler SJ, Phillips BR, Schatz M, Martinez FD, Chinchilli VM, et al. Response profiles to fluticasone and montelukast in mild-to-moderate persistent childhood asthma. *J Allergy Clin Immunol.* 2006;117(1):45–52. [PubMed: 16387583]
74. Szeffler SJ, Phillips BR, Martinez FD, Chinchilli VM, Lemanske RF, Strunk RC, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol.* 2005;115(2):233–42. [PubMed: 15696076]
75. Szeffler SJ, Martin RJ. Lessons learned from variation in response to therapy in clinical trials. *J Allergy Clin Immunol.* 2010;125(2):285–92; quiz 93–4. [PubMed: 20074785]
76. Koo S, Gupta A, Fainardi V, Bossley C, Bush A, Saglani S, et al. Ethnic Variation in Response to IM Triamcinolone in Children With Severe Therapy-Resistant Asthma. *Chest.* 2016;149(1):98–105. [PubMed: 26378892]
77. Leong AB, Ramsey CD, Celedon JC. The challenge of asthma in minority populations. *Clin Rev Allergy Immunol.* 2012;43(1-2):156–83. [PubMed: 21538075]
78. Federico MJ, Covar RA, Brown EE, Leung DY, Spahn JD. Racial differences in T-lymphocyte response to glucocorticoids. *Chest.* 2005;127(2):571–8. [PubMed: 15705998]
79. Ford JG, McCaffrey L. Understanding disparities in asthma outcomes among African Americans. *Clin Chest Med.* 2006;27(3):423–30, vi. [PubMed: 16880052]
80. Wechsler ME, Castro M, Lehman E, Chinchilli VM, Sutherland ER, Denlinger L, et al. Impact of Race on Asthma Treatment Failures in the Asthma Clinical Research Network. *Am J Respir Crit Care Med.* 2011;184(11):1247–53. [PubMed: 21885625]
81. Goleva E, Harris JK, Robertson CE, Jackson LP, Martin RJ, Leung DYM. Airway microbiome and responses to corticosteroids in corticosteroid-resistant asthma patients treated with acid suppression medications. *J Allergy Clin Immunol.* 2017;140(3):860–2 e1. [PubMed: 28477847]
82. Goleva E, Jackson LP, Harris JK, Robertson CE, Sutherland ER, Hall CF, et al. The effects of airway microbiome on corticosteroid responsiveness in asthma. *Am J Respir Crit Care Med.* 2013;188(10):1193–201. [PubMed: 24024497]

83. Wu YF, Su MW, Chiang BL, Yang YH, Tsai CH, Lee YL. A simple prediction tool for inhaled corticosteroid response in asthmatic children. *BMC Pulm Med*. 2017;17(1):176. [PubMed: 29216859]
84. Carmichael J, Paterson IC, Diaz P, Crompton GK, Kay AB, Grant IW. Corticosteroid resistance in chronic asthma. *Br Med J (Clin Res Ed)*. 1981;282(6274):1419–22.
85. Perlikos F, Hillas G, Loukides S. Phenotyping and Endotyping Asthma Based on Biomarkers. *Curr Top Med Chem*. 2016;16(14):1582–6. [PubMed: 26420366]
86. Szeffler SJ, Wenzel S, Brown R, Erzurum SC, Fahy JV, Hamilton RG, et al. Asthma outcomes: Biomarkers. *Journal of Allergy and Clinical Immunology*. 2012;129(3):S9–S23. [PubMed: 22386512]
87. Buhl R, Korn S, Menzies-Gow A, Aubier M, Chapman KR, Canonica GW, et al. Assessing biomarkers in a real-world severe asthma study (ARIETTA). *Respir Med*. 2016;115:7–12. [PubMed: 27215497]
88. Cowan DC, Taylor DR, Peterson LE, Cowan JO, Palmay R, Williamson A, et al. Biomarker-based asthma phenotypes of corticosteroid response. *J Allergy Clin Immunol*. 2015;135(4):877–83 e1. [PubMed: 25488689]
89. Schleich F, Sophie D, Renaud L. Biomarkers in the Management of Difficult Asthma. *Curr Top Med Chem*. 2016;16(14):1561–73. [PubMed: 26467509]
90. Berry MA, Shaw DE, Green RH, Brightling CE, Wardlaw AJ, Pavord ID. The use of exhaled nitric oxide concentration to identify eosinophilic airway inflammation: an observational study in adults with asthma. *Clin Exp Allergy*. 2005;35(9):1175–9. [PubMed: 16164444]
91. Jatakanon A, Lim S, Kharitonov SA, Chung KF, Barnes PJ. Correlation between exhaled nitric oxide, sputum eosinophils, and methacholine responsiveness in patients with mild asthma. *Thorax*. 1998;53(2):91–5. [PubMed: 9624291]
92. Dweik RA, Comhair SA, Gaston B, Thunnissen FB, Farver C, Thomassen MJ, et al. NO chemical events in the human airway during the immediate and late antigen-induced asthmatic response. *Proc Natl Acad Sci U S A*. 2001;98(5):2622–7. [PubMed: 11226289]
93. Dweik RA, Sorkness RL, Wenzel S, Hammel J, Curran-Everett D, Comhair SA, et al. Use of exhaled nitric oxide measurement to identify a reactive, at-risk phenotype among patients with asthma. *Am J Respir Crit Care Med*. 2010;181(10):1033–41. [PubMed: 20133930]
94. Petsky HL, Kynaston JA, Turner C, Li AM, Cates CJ, Lasserson TJ, et al. Tailored interventions based on sputum eosinophils versus clinical symptoms for asthma in children and adults. *Cochrane Database Syst Rev*. 2007(2):CD005603. [PubMed: 17443604]
95. Donohue JF, Jain N. Exhaled nitric oxide to predict corticosteroid responsiveness and reduce asthma exacerbation rates. *Respir Med*. 2013;107(7):943–52. [PubMed: 23601567]
96. Radomski MW, Palmer RM, Moncada S. Glucocorticoids inhibit the expression of an inducible, but not the constitutive, nitric oxide synthase in vascular endothelial cells. *Proc Natl Acad Sci U S A*. 1990;87(24):10043–7. [PubMed: 1702214]
97. Kupczyk M, Haque S, Middelveld RJ, Dahlen B, Dahlen SE. Phenotypic predictors of response to oral glucocorticosteroids in severe asthma. *Respir Med*. 2013;107(10):1521–30. [PubMed: 23993706]
98. Wadsworth S, Sin D, Dorscheid D. Clinical update on the use of biomarkers of airway inflammation in the management of asthma. *J Asthma Allergy*. 2011;4:77–86. [PubMed: 21792321]
99. Knuffman JE, Sorkness CA, Lemanske RF, Jr., Mauger DT, Boehmer SJ, Martinez FD, et al. Phenotypic predictors of long-term response to inhaled corticosteroid and leukotriene modifier therapies in pediatric asthma. *J Allergy Clin Immunol*. 2009;123(2):411–6. [PubMed: 19121860]
100. Phipatanakul W, Mauger DT, Sorkness RL, Gaffin JM, Holguin F, Woodruff PG, et al. Effects of Age and Disease Severity on Systemic Corticosteroid Responses in Asthma. *Am J Respir Crit Care Med*. 2017;195(11):1439–48. [PubMed: 27967215]
101. Galant SP, Morphey T, Guijon O, Pham L. The bronchodilator response as a predictor of inhaled corticosteroid responsiveness in asthmatic children with normal baseline spirometry. *Pediatr Pulmonol*. 2014;49(12):1162–9. [PubMed: 24532409]

102. Rabinovitch N, Mauger DT, Reisdorph N, Covar R, Malka J, Lemanske RF, Jr., et al. Predictors of asthma control and lung function responsiveness to step 3 therapy in children with uncontrolled asthma. *J Allergy Clin Immunol.* 2014;133(2):350–6. [PubMed: 24084071]
103. Zacharasiewicz A, Wilson N, Lex C, Erin EM, Li AM, Hansel T, et al. Clinical use of noninvasive measurements of airway inflammation in steroid reduction in children. *Am J Respir Crit Care Med.* 2005;171(10):1077–82. [PubMed: 15709050]
104. Xiao C, Biagini Myers JM, Ji H, Metz K, Martin LJ, Lindsey M, et al. Vanin-1 expression and methylation discriminate pediatric asthma corticosteroid treatment response. *J Allergy Clin Immunol.* 2015;136(4):923–31 e3. [PubMed: 25910714]
105. Bacharier LB, Guilbert TW, Zeiger RS, Strunk RC, Morgan WJ, Lemanske RF, Jr., et al. Patient characteristics associated with improved outcomes with use of an inhaled corticosteroid in preschool children at risk for asthma. *J Allergy Clin Immunol.* 2009;123(5):1077–82, 82 e1-5. [PubMed: 19230959]
106. Fitzpatrick AM, Jackson DJ, Mauger DT, Boehmer SJ, Phipatanakul W, Sheehan WJ, et al. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol.* 2016;138(6):1608–18 e12. [PubMed: 27777180]
107. Forno E, Lescher R, Strunk R, Weiss S, Fuhlbrigge A, Celedon JC. Decreased response to inhaled steroids in overweight and obese asthmatic children. *J Allergy Clin Immunol.* 2011;127(3):741–9. [PubMed: 21377042]
108. Peters-Golden M, Swern A, Bird SS, Hustad CM, Grant E, Edelman JM. Influence of body mass index on the response to asthma controller agents. *Eur Respir J.* 2006;27(3):495–503. [PubMed: 16507848]
109. Gerald JK, Gerald LB, Vasquez MM, Morgan WJ, Boehmer SJ, Lemanske RF, Jr., et al. Markers of Differential Response to Inhaled Corticosteroid Treatment Among Children with Mild Persistent Asthma. *J Allergy Clin Immunol Pract.* 2015;3(4):540–6 e3. [PubMed: 25783161]
110. Vijverberg SJ, Koenderman L, Koster ES, van der Ent CK, Raaijmakers JA, Maitland-van der Zee AH. Biomarkers of therapy responsiveness in asthma: pitfalls and promises. *Clin Exp Allergy.* 2011;41(5):615–29. [PubMed: 21488995]
111. Brightling CE, Green RH, Pavord ID. Biomarkers predicting response to corticosteroid therapy in asthma. *Treat Respir Med.* 2005;4(5):309–16. [PubMed: 16137188]
112. Aziz-Ur-Rehman A, Dasgupta A, Kjarsgaard M, Hargreave FE, Nair P. Sputum cell counts to manage prednisone-dependent asthma: effects on FEV1 and eosinophilic exacerbations. *Allergy, Asthma & Clinical Immunology.* 2017;13(1):17.
113. Malmstrom K, Rodriguez-Gomez G, Guerra J, Villaran C, Pineiro A, Wei LX, et al. Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. Montelukast/Beclomethasone Study Group. *Ann Intern Med.* 1999;130(6):487–95. [PubMed: 10075616]
114. Szeffler SJ, Martin RJ, King TS, Boushey HA, Cherniack RM, Chinchilli VM, et al. Significant variability in response to inhaled corticosteroids for persistent asthma. *J Allergy Clin Immunol.* 2002;109(3):410–8. [PubMed: 11897984]
115. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med.* 2004;170(8):836–44. [PubMed: 15256389]
116. Adcock IM, Lane SJ. Corticosteroid-insensitive asthma: molecular mechanisms. *J Endocrinol.* 2003;178(3):347–55. [PubMed: 12967328]
117. Weiss ST, Litonjua AA, Lange C, Lazarus R, Liggett SB, Bleecker ER, et al. Overview of the pharmacogenetics of asthma treatment. *Pharmacogenomics J.* 2006;6(5):311–26. [PubMed: 16568148]
118. Dunican EM, Fahy JV. Asthma and corticosteroids: time for a more precise approach to treatment. *Eur Respir J.* 2017;49(6).
119. Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax.* 2002;57(10):875–9. [PubMed: 12324674]

120. Moore WC, Hastie AT, Li X, Li H, Busse WW, Jarjour NN, et al. Sputum neutrophils are associated with more severe asthma phenotypes using cluster analysis. *J Allergy Clin Immunol.* 2014;133(6):1557–63 e5. [PubMed: 24332216]
121. Ito K, Chung KF, Adcock IM. Update on glucocorticoid action and resistance. *J Allergy Clin Immunol.* 2006;117(3):522–43. [PubMed: 16522450]
122. Ramamoorthy S, Cidlowski JA. Exploring the Molecular Mechanisms of Glucocorticoid Receptor Action from Sensitivity to Resistance. *Endocr Dev.* 2013;24:41–56. [PubMed: 23392094]
123. Stephenson ST, Brown LA, Helms MN, Qu H, Brown SD, Brown MR, et al. Cysteine oxidation impairs systemic glucocorticoid responsiveness in children with difficult-to-treat asthma. *J Allergy Clin Immunol.* 2015;136(2):454–61 e9. [PubMed: 25748343]
124. Schwartz HJ, Lowell FC, Melby JC. Steroid resistance in bronchial asthma. *Ann Intern Med.* 1968;69(3):493–9. [PubMed: 5673169]
125. Adcock IM, Barnes PJ. Molecular Mechanisms of Corticosteroid Resistance. *CHEST.* 2008;134(2):394–401. [PubMed: 18682458]
126. Clearie KL, McKinlay L, Williamson PA, Lipworth BJ. Fluticasone/Salmeterol combination confers benefits in people with asthma who smoke. *Chest.* 2012;141(2):330–8. [PubMed: 21636667]
127. Thomson NC, Spears M. The influence of smoking on the treatment response in patients with asthma. *Curr Opin Allergy Clin Immunol.* 2005;5(1):57–63. [PubMed: 15643345]
128. Chalmers GW, MacLeod KJ, Thomson L, Little SA, McSharry C, Thomson NC. Smoking and airway inflammation in patients with mild asthma. *Chest.* 2001;120(6):1917–22. [PubMed: 11742922]
129. Churg A, Dai J, Tai H, Xie C, Wright JL. Tumor necrosis factor- α is central to acute cigarette smoke-induced inflammation and connective tissue breakdown. *Am J Respir Crit Care Med.* 2002;166(6):849–54. [PubMed: 12231496]
130. Webster JC, Oakley RH, Jewell CM, Cidlowski JA. Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative beta isoform: a mechanism for the generation of glucocorticoid resistance. *Proc Natl Acad Sci U S A.* 2001;98(12):6865–70. [PubMed: 11381138]
131. Leung DY, Bloom JW. Update on glucocorticoid action and resistance. *J Allergy Clin Immunol.* 2003;111(1):3–22; quiz 3. [PubMed: 12532089]
132. Szeffler SJ, Leung DY. Glucocorticoid-resistant asthma: pathogenesis and clinical implications for management. *Eur Respir J.* 1997;10(7):1640–7. [PubMed: 9230260]
133. Spahn JD, Szeffler SJ, Surs W, Doherty DE, Nimmagadda SR, Leung DY. A novel action of IL-13: induction of diminished monocyte glucocorticoid receptor-binding affinity. *J Immunol.* 1996;157(6):2654–9. [PubMed: 8805670]
134. Matthews JG, Ito K, Barnes PJ, Adcock IM. Defective glucocorticoid receptor nuclear translocation and altered histone acetylation patterns in glucocorticoid-resistant patients. *J Allergy Clin Immunol.* 2004;113(6):1100–8. [PubMed: 15208591]
135. Hawrylowicz C, Richards D, Loke TK, Corrigan C, Lee T. A defect in corticosteroid-induced IL-10 production in T lymphocytes from corticosteroid-resistant asthmatic patients. *J Allergy Clin Immunol.* 2002;109(2):369–70. [PubMed: 11842311]

Key points:

- Corticosteroids are the most effective treatment for asthma; inhaled corticosteroids (ICS) are the first-line treatment for children and adults with persistent symptoms
- ICS are associated with significant improvements in lung function
- The anti-inflammatory effects of corticosteroids are mediated by both genomic and nongenomic factors
- Variation in the response to corticosteroids has been observed
- Patient characteristics, biomarkers and genetic features may be used to predict response to ICS
- Response to corticosteroids can be assessed through different measures, such as symptom free days, use of rescue therapy, FEV₁ improvement and FeNO
- The existence of multiple mechanisms underlying glucocorticoid insensitivity raises the possibility that this might indeed reflect different diseases with a common phenotype

Box 1.**Effects of Corticosteroids**

- Suppress multiple inflammatory genes that are activated in asthmatic airways by reversing histone acetylation.
- Increase mRNA degradation, thereby blocking production of pro-inflammatory cytokines
- Increase the synthesis of anti-inflammatory proteins.
- Suppress the increased microvascular permeability and plasma leakage into the airway lumen that occur in asthma which adds to the airway obstruction.
- Suppressing the production of chemotactic mediators and adhesion molecules and inhibiting its survival in the airways.
- Inhibit the remodeling process.
- Reduce the inflammatory cells in the airways, including eosinophils, T-lymphocytes, mast cells, and dendritic cells.

Table (1).**Measures of assessment of Steroid Responsiveness in adults**

Subjective measurement:
- Self-monitoring of symptoms, and activity limitations.
- Standardized asthma specific questionnaire tools (ACT, ACQ, ATAC)
- Quality of life assessments Asthma quality of life questionnaire, ped's AQLQ. (PAQLQ, AQLQ, etc)
Objective measurement
- Exacerbation rate
- Lung function Spirometry (FEV ₁)
- Peak expiratory flow (PEF)
- Bronchodilator reversibility
- Inflammatory markers:
- sputum cytology -
- Fraction of exhaled nitric oxide (FeNO) -

Table: (2)

Steroid responsiveness criteria in children with asthma (23)

Steroid response in children	
ACT score *	>19/25 or 50% increase
FeNO	normal (<24 ppb),
Bronchodilator responsiveness (FEV1)	12% increase from baseline
Morning FEV1 *	FEV1 80% of predicted value or 15% increase
Sputum eosinophil counts	(<2.5%)

* Asthma Control Test score

Adapted from Bossley CJ, Fleming L, Ullmann N, Gupta A, Adams A, Nagakumar P, et al. Assessment of corticosteroid response in pediatric patients with severe asthma by using a multidomain approach. *J Allergy Clin Immunol.* 2016;138(2):413-20 e6; with permission

Table (3)

Modifiable factors that, in patients with severe asthma, may contribute to poor symptom control and/ or exacerbations, with diagnostic investigations, and effective intervention strategies (11)

	Modifiable risk factors	Diagnosis	Intervention strategies
Medication & Delivery	Incorrect inhaler technique Poor adherence with controller therapy	Check technique against a device specific checklist	Physical demonstration and regular rechecking Identify adherence barriers including cost; simplify treatment regimen; electronic inhaler reminders for missed doses; refill reminders
Exposure	Smoking or environmental tobacco smoke; biomass fuel exposure Allergen exposure in sensitized patients (house dust mite, cat, mold, cockroach)	History, urinary cotinine Skin prick testing, history	Smoking cessation advice; alternative cooking or heating methods Selected avoidance strategies if shown to be effective
	Indoor or outdoor air pollution, extreme weather	Specific questioning, seasonal or event related	Ventilate dwelling; alternative cooking/ heating methods; avoid running during outdoor air pollution or extreme weather
	Occupational exposure to allergens or irritants	Occupational history, peak expiratory flow on work/non-work days	Early withdrawal from exposure
	Respiratory viruses including rhinovirus, respiratory syncytial virus, influenza	History, serology	Consider avoiding close contact with children when they have respiratory infections; influenza vaccination
Comorbidities	Obesity Gastro-esophageal reflux disease (GERD) Rhinosinusitis ± nasal polyposis COPD (i.e. asthma-COPD overlap) Anxiety, depression Vocal cord dysfunction Bronchiectasis Allergic bronchopulmonary aspergillosis (ABPA) Pregnancy	Body mass index Usually only relevant when symptomatic; 24-hour pH monitoring including acid and non-acid reflux ENT evaluation, nasal endoscopy and/or CT sinuses Smoking history, diffusing capacity, lung volumes, ± HRCT chest Inspiratory/expiratory flow-volume loops, functional laryngoscopy (± with exercise), HRCT larynx HRCT chest, sputum culture, investigate for immunodeficiency and ABPA Serum IgE, skin test/ specific IgE for Aspergillus, IgG Aspergillus precipitins. Pregnancy test	Diet and exercise; bariatric surgery Lifestyle changes, proton pump inhibitor, reduce medications that predispose to reflux; treatment of asymptomatic reflux may not improve asthma control Nasal corticosteroids (spray or wash), surgery if needed; consider leukotriene modifier if aspirin exacerbated respiratory disease Smoking cessation, pulmonary rehabilitation, long-acting muscarinic antagonist, check for cardiac
Social	Socioeconomic problems Illicit drug use At-risk populations (adolescents, elderly)	Empathic questioning about cost barriers to adherence; social work consultation Blood/urine testing Assess adherence, inhaler technique, comorbidities (especially in elderly), medication interactions	Community/government support; medication samples; choose lowest cost medication regimen Refer for withdrawal strategies and support

Data from From Israel E, Reddel HK. Severe and Difficult-to-Treat Asthma in Adults. N Engl J Med. 2017;377(10):965-76

Table (4)

Monitoring Corticosteroids using different measures: clinical, pulmonary function, and evidence of airway inflammation (75)

Clinical measures	Pulmonary function measures	Challenge techniques	Airway inflammation	Distal lung or small airways
Symptoms Exacerbations Asthma control and quality of life questionnaires	Change in FEV1 Change in % predicted FEV1, especially in children Post-bronchodilator FEV1	Airway hyperresponsiveness: methacholine, histamine, or cold air Exercise challenge	Induced sputum cytology Exhaled nitric oxide	Closing volume Imaging (air trapping) – high resolution CT scan Hyperpolarized helium FEF ₂₅₋₇₅

Adapted from Szeffler SJ, Martin RJ. Lessons learned from variation in response to therapy in clinical trials. *J Allergy Clin Immunol.* 2010;125(2): 285-92; quiz 93-4; with permission.