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Mechanism and treatment strategies for steroid resistant asthma

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Abstract: *Steroid-resistant asthma (SRA) is a significant clinical challenge characterised by persistent airway inflammation and symptoms despite high-dose corticosteroid therapy. This condition is associated with increased morbidity, mortality, and healthcare costs. The underlying mechanisms of SRA are complex and multifactorial, involving genetic, inflammatory, epigenetic, and oxidative stress-related factors. Genetic factors, such as polymorphisms in the glucocorticoid receptor and other immune-related genes, play a critical role in altering corticosteroid responsiveness. Inflammatory pathways, including Th1/Th2 imbalances and the involvement of Th17 cells, as well as oxidative stress and cellular mechanisms,further contribute to resistance. Epigenetic modifications, such as DNA methylation and histone modifications, influence gene expression, potentially exacerbating inflammation and impairing steroid efficacy.*

Clinically, SRA presents with refractory symptoms, poor lung function, frequent exacerbations, and comorbid conditions. Phenotypic variations, including eosinophilic, neutrophilic, and mixed-inflammatory subtypes, offer insight into the diverse pathophysiology of SRA. Diagnosis relies on spirometric criteria and biomarkers like eosinophilic cationic protein and fractional exhaled nitric oxide.

Treatment strategies for SRA encompass both non-pharmacological interventions, such as bronchial thermoplasty, pulmonary rehabilitation, and allergen immunotherapy, and pharmacological therapies, including alternative corticosteroids, add-on therapies, biologics, and targeted therapies. While these therapies show promise in improving symptoms and lung function, ongoing research into novel therapeutic targets, epigenetic modifications, and microbiome interactions is crucial for advancing treatment. Future directions also include personalised medicine, combination therapies, and the development of predictive biomarkers, all aimed at improving outcomes for patients with steroid-resistant asthma.

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I. Introduction

Asthma is a common chronic respiratory condition characterised by inflammation and narrowing of the airways, leading to symptoms such as wheezing, shortness of breath, chest tightness, and coughing. Steroid-resistant asthma (SRA) represents a significant challenge in the management of asthma, where patients experience persistent symptoms and airway inflammation despite the use of high-dose corticosteroids, which are typically the cornerstone of asthma therapy. Corticosteroids work by reducing airway inflammation and preventing exacerbations, but in a subset of asthma patients, this treatment proves ineffective. Steroid resistance in asthma is associated with more severe disease, greater morbidity, increased healthcare utilisation, and, in some cases, higher mortality.The pathophysiology of steroid-resistant asthma is complex and involves a range of genetic, molecular, and inflammatory factors. These include alterations in glucocorticoid receptor signalling, an imbalance in the immune response (such as increased Th2/Th17 cytokine production), and abnormalities in the function of airway inflammatory cells. Environmental factors, comorbid conditions, and epigenetic changes also contribute to the development of steroid resistance, complicating its diagnosis and treatment.

Clinically, patients with steroid-resistant asthma may experience frequent exacerbations, poor lung function, and ongoing symptoms like wheezing, coughing, and shortness of breath, despite aggressive corticosteroid use. This subset of patients may require alternative treatment approaches, such as biologics, targeted therapies, and non-pharmacological interventions like bronchial thermoplasty.

Mechanisms of Steroid Resistance in Asthma

Steroid resistance in asthma is a multifactorial phenomenon that involves complex interactions between genetic, molecular, inflammatory, and environmental factors. In patients with steroid-resistant asthma (SRA), the effectiveness of corticosteroids is diminished, leading to persistent inflammation and symptoms despite standard therapy. Understanding the underlying mechanisms of steroid resistance is crucial for developing more effective treatments for these patients. Below is an overview of the key mechanisms contributing to steroid resistance in asthma:

1.Genetic Factors

Genetic variations can influence the response to corticosteroids in asthma. Certain genetic polymorphisms can impair the function of the glucocorticoid receptor (GR) or alter the immune system's response to steroid therapy.

Glucocorticoid Receptor (GR) Polymorphisms: Mutations in the glucocorticoid receptor gene (NR3C1) can lead to structural changes in the GR, impairing its ability to bind cortisol or translocate to the nucleus. This reduces the GR's capacity to regulate the expression of anti-inflammatory genes and increases resistance to corticosteroids.

Other Genetic Variants: Polymorphisms in genes such as TBX21 (which regulates Th1/Th2 balance) and STAT3 (which is involved in cytokine signalling) have been linked to altered immune responses and steroid resistance. These genetic factors may influence the differentiation of T-helper cells and the production of pro-inflammatory cytokines.

2.Inflammatory Pathways

Inflammation in asthma is primarily driven by immune cells such as T-helper cells, eosinophils, and neutrophils. In steroid-resistant asthma, dysregulation of inflammatory pathways leads to persistent airway inflammation despite corticosteroid therapy.

Th1/Th2 Imbalance: Asthma is traditionally classified based on an imbalance between Th2 and Th1 immune responses. Steroid resistance is often associated with a shift towards a Th1-dominant or mixed Th1/Th2 phenotype, which is less responsive to corticosteroids.

Neutrophilic Inflammation: Neutrophilic asthma, often observed in smokers and in certain severe forms of asthma, is characterised by airway inflammation driven by neutrophils. Neutrophils produce pro-inflammatory cytokines and enzymes that contribute to airway remodelling, and their response to corticosteroids is generally less effective compared to eosinophilic inflammation.

3.Epigenetic Modifications

Epigenetic changes—alterations in gene expression that do not involve changes to the DNA sequence—can play a significant role in steroid resistance by modifying how the immune system responds to corticosteroids.

Histone Modifications: Inflammatory genes in asthma can be regulated by histone modifications, such as acetylation and methylation. These changes can influence the activation or suppression of genes involved in inflammation. In SRA, histone modifications may promote the expression of pro-inflammatory genes while inhibiting the anti-inflammatory actions of corticosteroids.

4.Oxidative Stress

Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) and antioxidant defences, plays a significant role in inflammation and steroid resistance.

Reactive Oxygen Species (ROS): In asthma, excessive ROS production by inflammatory cells such as neutrophils, eosinophils, and macrophages leads to airway damage and inflammation. ROS can impair glucocorticoid receptor function by oxidising key signalling molecules and reducing the receptor's ability to translocate to the nucleus.

Antioxidant Depletion: In steroid-resistant asthma, there is often a depletion of antioxidants such as glutathione, which are essential for neutralising ROS. This imbalance exacerbates inflammation and impairs the corticosteroid response.

Clinical Features:

1. Refractory Symptoms: Persistent wheezing, coughing, shortness of breath, and chest tightness.
2. Poor Lung Function: Reduced forced expiratory volume (FEV1) and forced vital capacity (FVC).
3. Frequent Exacerbations: Recurrent hospitalizations, emergency department visits, and oral corticosteroid use.

Classification of SRA:

1. Mild Steroid Resistance

Asthma remains poorly controlled despite low-dose inhaled corticosteroids (ICS).
Management: Higher doses of ICS or the addition of other medications like leukotriene modifiers or long-acting beta-agonists (LABAs) may be necessary.
Key Feature: Partial response to increased corticosteroid dose.

2. Moderate Steroid Resistance

Asthma remains uncontrolled despite medium to high doses of ICS.
Management: Use of combination therapies, including ICS/LABA or adding biologics like monoclonal antibodies (e.g., omalizumab, mepolizumab) for eosinophilic asthma or severe allergic asthma.
Key Feature: Limited response to high-dose ICS, with significant symptoms and exacerbations.

3.Severe Steroid Resistance

Asthma remains uncontrolled despite very high doses of ICS and additional treatment options (e.g., systemic steroids, biologics, or other immunomodulatory treatments).
Management: Biologics (e.g., dupilumab, benralizumab) and other immune-targeted therapies are often used. Systemic corticosteroids may be required intermittently or continuously.
Key Feature: No significant improvement with high-dose steroids or adjunct therapies. Severe limitation in daily activities, frequent exacerbations, and the need for oral steroids.

4.Corticosteroid-Insensitive Asthma (True Steroid Resistance)

This is a rare and extreme form of steroid resistance where asthma does not improve or even worsens with corticosteroids.
Management: Requires novel or experimental therapies, such as biologic agents targeting specific immune pathways (e.g., T2 inflammation, IL-5, IL-13, or IgE-mediated pathways). Management may also involve a more personalised approach to address specific pathophysiological mechanisms (e.g., airway remodelling).

Biomarkers: In steroid-resistant asthma, biomarkers like eosinophil count, FeNO (fractional exhaled nitric oxide), and IgE levels can help guide treatment, especially for identifying which biologic therapies may be effective.

Pharmacological Interventions:

Inhaled Corticosteroids (ICS) – High Doses:

Use: For mild-to-moderate steroid resistance; increasing ICS dose may improve control.
Examples: Fluticasone, Budesonide.
Combination Therapy (ICS/LABA):

Use: For moderate steroid resistance, combination therapy often helps in better symptom control.
Examples: Fluticasone/Salmeterol, Budesonide/Formoterol.

Biologics (Targeted Immunotherapy):

Use: For severe steroid resistance; targets specific immune pathways involved in asthma.
Examples:
Omalizumab: Anti-IgE therapy for allergic asthma.
Mepolizumab, Benralizumab: Anti-IL-5 therapy for eosinophilic asthma.
Dupilumab: Anti-IL-4/IL-13 therapy for T2 inflammation.
Tezepelumab: Targets thymic stromal lymphopoietin (TSLP) for severe asthma.

Systemic Corticosteroids (Oral or IV):

Use: For exacerbations or in cases where inhaled therapies are insufficient. However, prolonged use should be minimised due to side effects.
Examples: Prednisolone, Methylprednisolone.

Non-Pharmacological Interventions:
Asthma Education:

Educating patients on proper inhaler technique, adherence to medications, and recognizing early signs of asthma exacerbation.
Goal: Improve medication efficacy and reduce avoidable exacerbations.

Lifestyle Modifications:

Weight Management: Obesity can worsen asthma control, and weight reduction may improve symptoms.
Physical Activity: Regular, moderate exercise can improve lung function and reduce symptoms.
Avoidance of Triggers: Identifying and avoiding allergens (e.g., dust, pet dander) or irritants (e.g., smoke, pollution).

Allergen Immunotherapy (Allergy Shots):

For patients with allergic asthma, desensitisation to specific allergens through immunotherapy can reduce asthma symptoms.
Use: Best for patients with identified environmental allergies.

Breathing Exercises :
Techniques aimed at improving oxygen intake and reducing hyperventilation during asthma attacks.
Goal: Reduce the frequency of asthma exacerbations and improve control.

Airway Clearance Techniques:

Techniques like chest physiotherapy, postural drainage, and the use of devices like oscillatory positive expiratory pressure (OPEP) may help clear mucus from the airways, especially in those with chronic mucus production.

II. Conclusion:

Steroid-resistant asthma (SRA) is a challenging condition where asthma symptoms persist despite high doses of corticosteroids, requiring a comprehensive and individualised treatment approach. Management includes optimising pharmacological therapy, such as biologics targeting specific immune pathways (e.g., IL-5, IgE), and using add-on treatments like long-acting bronchodilators or leukotriene modifiers. For severe cases, systemic steroids may be necessary for short-term control, though their long-term use should be avoided due to side effects.

Non-pharmacological interventions play a crucial role in managing SRA, including patient education, lifestyle modifications, allergen avoidance, and techniques like breathing exercises. Identifying and avoiding asthma triggers, improving medication adherence, and optimising environmental control are key to reducing exacerbations and improving quality of life.