Tracheobronchopathy From Inhaled Corticosteroids

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Inhaled corticosteroids (ICSs) have become the mainstay of asthma control. They are also recommended as an add-on therapy to long-acting beta agonists and anticholinergics in moderate to severe COPD with recurrent exacerbations. Ultimately this clinical practice has led to the widespread use of ICSs, which are supported by a more favorable side effect profile than that of systemic steroids. CHEST 2017; 152(6):1296-1305

KEY WORDS: excessive dynamic airway collapse; inhaled corticosteroids; tracheobronchomalacia; tracheomalacia

In the 21st century, inhaled corticosteroids (ICSs) have become the mainstay of asthma control. Similarly, ICSs are recommended as an add-on therapy to long-acting beta agonists and anticholinergics in moderate to severe COPD with recurrent exacerbations. Ultimately, this clinical practice has led to the widespread use of ICSs, which are supported by a more favorable side effect profile than that of systemic steroids.

However, high doses of ICSs and the prolonged duration of the therapy may affect the airways adversely. What is considered to be a “high dose” may vary depending on the particular steroid preparation being used; therefore, defining a single dose value becomes challenging. Despite several investigations focusing on the systemic effects of this class of medications, airway complications have been underrecognized. For example, ICS therapy decreases the size

of the vascular component of the airway wall and may reduce the volume of blood distributed, potentially resulting in smooth muscle weakness. Concurrent with the increased popularity of bronchoscopy and the availability of advanced airway imaging, weakness in the walls of large airways, such as seen in tracheobronchomalacia and excessive dynamic airway collapse, is being observed with increasing frequency. The authors postulate that ICSs play a role in producing airway-specific complications, including infections and structural derangements, which may cause tracheobronchopathy. This review focuses on the adverse effects ICS therapy may have on the airway and its plausible mechanism, with specific emphasis on findings a bronchoscopist may encounter.

The use of inhaled corticosteroids (ICSs) has spared a vast number of patients with

ABBREVIATIONS: EDAC = excessive dynamic airway collapse; ICS = inhaled corticosteroid; MTB = *Mycobacterium tuberculosis*; NTM = nontuberculous mycobacteria; TBM = tracheobronchomalacia; TB-SMAS = tracheobronchial smooth muscle atrophy and separation

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bronchial asthma and COPD the unpleasant side effects of the systemic formulations. ICSs are among the top most commonly prescribed class of medications in the United States, with Medicare and Medicaid spending totaling almost \$3 billion in 2015.¹ Compared with systemic steroids, these medications have improved both the control of symptoms from bronchial asthma and COPD and the overall outcome.^{2,3}

The widespread use of ICSs warrants an increased awareness regarding their side effects. Even though the deleterious effects of ICSs occur less frequently, systemic effects can correlate with higher dosage⁴ (Table 1). The pharmacology of a specific ICS must also be examined. Some agents exhibit more bioavailability than do others. One such example is fluticasone propionate: doses > 800 µg/d have exhibited higher systemic bioavailability than other preparations, as well as more side effects.⁵ Furthermore, the penetration of ICSs into the airways may be affected by the different particulate sizes of the various compounds. Flunisolide and beclomethasone dipropionate have a smaller aerodynamic diameter than does the chlorofluorocarbon formulation.^{6,7} This property may alter a specific formulation's side effect profile on the airways, as lung deposition varies among the several formulations of ICSs. In the uncommon event of steroid resistance, the patient may inadvertently receive an unusually high dose of ICS therapy; however, its sequelae are not well defined.⁸

Systemic adverse effects from ICSs include altered bone metabolism, adrenal gland suppression, and skin and ophthalmic changes.⁹ Another well-documented complication of ICS use is colonization of the upper and lower airways with opportunistic organisms. The administration of ICSs may also produce deleterious local effects on the central airways. The authors posit that specific pathologic conditions, such as excessive

dynamic airway collapse (EDAC), tracheobronchomalacia (TBM), and tracheobronchial smooth muscle atrophy and separation (TB-SMAS), may be related to increasing overreliance on ICSs.¹⁰

This review highlights potential airway complications of the long-term use of high-dose ICS treatment, which are referred to as "steroid tracheobronchopathy." These conditions range from airway infections to direct effects on the vocal cords, airway smooth muscle, and cartilage (Table 2).¹¹

ICSs and Airway Vasculature

Corticosteroids are the most effective anti-inflammatory medications for the management of bronchial asthma and COPD.¹² Locally acting ICSs have been introduced to minimize the deleterious effects of systemic steroids.^{9,13} However, ICSs also produce adverse events. In that regard, increased understanding of the mechanism of action of ICSs may help identify potential sequelae.

ICSs suppress airway inflammation and components of airway remodeling,¹⁴ specifically affecting the tracheobronchial vasculature through both rapid and delayed mechanisms.^{15,16} Rapid actions include hypoperfusion of the airways¹⁷ and reduction in the release of inflammatory mediators.¹⁸ The delayed actions of ICSs include a decrease in both leukocyte recruitment¹⁹ and the angiogenesis of the airways.²⁰

ICSs affect the airway vasculature through both genomic and nongenomic mechanisms. The therapeutic effects of ICSs in the airways of patients with obstructive lung disease are a result of genomic modifications in transcriptional mechanisms of the proinflammatory airways.¹⁸ One effect that can arise within seconds to minutes of ICS administration is a reduction in airway

TABLE 1] Dosing Equivalency of ICSs for Adults

ICS	Low	Medium	High
Beclometasone dipropionate (HFA), µg	200-500	> 500-1,000	> 1,000
Budesonide (DPI), µg	100-200	> 200-400	> 400
Ciclesonide (HFA), µg	80-160	> 160-320	> 320
Flunisolide, µg	80-160	> 160-320	> 320
Fluticasone furoate (DPI), µg	100	NA	200
Fluticasone propionate (DPI), µg	100-250	> 250-500	> 500
Fluticasone propionate (HFA), µg	100-250	> 250-500	> 500
Mometasone furoate, µg	100-220	> 220-440	> 440
Triamcinolone acetonide, µg	400-1000	> 100-2,000	> 2,000

DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; ICS = inhaled corticosteroid; NA = not available. Adapted from the 2017 GINA report.

TABLE 2] Steroid Tracheobronchopathy

Dysphonia
Infection
Vocal cord candidiasis
Community-acquired pneumonia
<i>Mycobacterium tuberculosis</i> infection
Nontuberculous mycobacterial infection
Direct effect on the central airways
Tracheobronchomalacia
Excessive dynamic airway collapse
Tracheobronchial smooth muscle atrophy and separation

blood flow through nongenomic cellular actions,¹⁵ resulting from a modulation of the norepinephrine-mediated control of vascular tone. This reduction in blood flow to the tissues has been observed in other vascular beds, including the airway mucosa and bronchial arteries of both patients with asthma and those without.²¹

Another rapid effect of ICSs is an inhibitory effect on cellular processes or mediators of inflammation.²² The inflammatory response in asthma includes increased expression of multiple inflammatory genes that encode

for cytokines, chemokines, and adhesion molecules.²² Specifically, nuclear factor-kappa B and activator protein 1 promote inflammatory gene transcription. Corticosteroids suppress proinflammatory transcription factors by reversing histone acetylation of the activated inflammatory genes.¹⁴ Inhibiting these inflammatory reactions may reduce edema formation, microvascular hyperpermeability, and inflammatory cell recruitment. Although ICSs decrease the size of the vascular component of the airway wall and decrease airway obstruction,²³ ICSs may reduce the volume of blood to the airway wall and potentially lead to airway smooth muscle weakness (Fig 1).

Airway Remodeling and ICSs

The pathogenesis of obstructive lung disease promotes airway remodeling.²⁴ In asthma, histopathologic changes of airway remodeling include damage to or loss of the normal pseudostratified structure of the airway epithelium, loss of mucus-producing goblet cells, and fibrotic thickening of the subepithelial reticular basement membrane (lamina reticularis).²⁵ In addition, asthma promotes increased vascularity, numbers of myofibroblasts, airway smooth muscle mass, and extracellular matrix.²⁶ COPD airway remodeling is

Figure 1 – Effects of inhaled corticosteroids on airway vasculature and supporting structure.

characterized by squamous cell metaplasia without significant thickening of the basement membrane, bronchial goblet cell hyperplasia, and submucosal gland enlargement.²⁷ Unlike asthma, hypertrophy of the smooth muscles in large airways is not appreciated in COPD.²⁸ However, distal airway smooth muscle hypertrophy is noted, which correlates with the degree of obstruction.²⁹ The goals of ICS therapy include reversing such airway changes.

Interestingly, steroids cause smooth muscle atrophy by catabolic effects on muscle tissue and by decreasing protein synthesis.³⁰ Long-term use of ICSs may result in the reduction of airway smooth muscle thickness in both the trachea and mainstem bronchi by reversing hyperplasia and hypertrophy. The antiproliferative effects of corticosteroids produce reductions in cytokines and airway growth factors such as granulocyte-macrophage colony-stimulating factor.³¹ The vasoconstriction noted with the use of corticosteroids¹⁵ may lead to ischemic episodes within airway smooth muscle, impair wound healing, and potentially produce a weakened posterior membrane.

Although airway remodeling due to ICSs is well documented in asthma, compared with in COPD, the effects on the vascular epithelium are likely similar. Smooth muscle atrophy results from the downregulation of vascular endothelial growth factor, thereby affecting the blood supply to the airways,^{15,32} which may contribute to the weakening of the cartilaginous rings. The paucity of data examining the long-term effects of ICSs on the airways makes identification challenging, and for most patients, several years of exposure to ICS therapy will be required for those changes to be observed.

ICSs and Infections

Immunomodulation is affected by the use of either oral or inhaled corticosteroids. Corticosteroids inhibit macrophage function, induce apoptosis of dendritic cells, and suppress the activation of T cells in the airways, all of which are important defense mechanisms against bacterial, fungal, viral, and mycobacterial pathogens. ICS treatment attenuates the immune response and predisposes the host to airway infections.³³ The direct administration of steroids into the airways is likely to be detrimental to local host defense mechanisms against infection. An association between recurrent airway infection and tracheomalacia has been identified.³⁴ Patients with chronic bronchitis and cystic fibrosis are commonly found to have tracheobronchomalacia.^{35,36}

Inhaled Corticosteroids and Large Airways

Dysphonia

Dysphonia, or hoarseness, is a common local adverse effect of ICS therapy and occurs in 5% to 58% of patients.³⁷ Although the causes of dysphonia associated with ICS therapy have not been studied specifically, one theory involves the deposition of active ICSs in the oropharynx, leading to myopathy.³⁸ A mucosal effect in the laryngopharynx occurs independent of vocal cord candidiasis. Hypotonus of the vocal cords can be appreciated on endoscopic examination and has been seen in patients who use ICSs chronically and have symptoms of dysphonia.³⁷ A positive correlation between the dose of ICS and the severity of vocal cord myopathy has also been noted and appears to be reversible with cessation of the medication.³⁸ Additionally, a formulation of ICSs using hydrofluoroalkane rather than chlorofluorocarbons produces less deposition in the oropharynx.³⁹

Vocal Cord Candidiasis

Vocal cord candidiasis arises from decreased surface immunity of normal airway mucosa, which is thus predisposed to infection from *Candida* species. Oral candidiasis can be seen in ICS users and may present with dysphagia, dysphonia, stridor, or respiratory distress. The elderly and patients receiving antibiotics, oral glucocorticoids, or ICSs are particularly at risk.⁴⁰ Diagnosis is made by direct visualization of the vocal cords through endoscopy. Efforts to curb deposition of ICSs in the oropharynx include the use of a large volume spacer device and rinsing of the mouth and throat after administration of the drug (Fig 2).

In addition to this usually benign entity, evidence suggests that ICSs can also affect the upper airway microflora. Patients using ICSs are at greater risk for coagulase-negative staphylococci, viridans streptococci, and *C albicans* infections.⁴¹ The treatment required for these infections may be withdrawal of ICSs and use of a topical antifungal agent; however, many patients also need treatment with oral antifungal agents, such as fluconazole.

Lower Respiratory Tract Infections

An increased risk of pneumonia has been observed among patients with COPD receiving ICSs; however, the magnitude of this risk and its correlation with a specific steroid preparation or dose, or both, has not yet been clearly defined.⁴²⁻⁴⁴ One study performed in Canada that highlighted the increased risk of

Figure 2 – Vocal cord candidiasis in an immunocompromised patient taking inhaled corticosteroids.

pneumonia with ICS use was a nested case-control study within a cohort of patients with COPD. In the study, the adjusted rate ratio of hospitalization for pneumonia associated with current use of ICSs was 1.70 (95% CI, 1.63-1.77), and it was 1.53 (95% CI, 1.30-1.80) for hospitalization for pneumonia followed by death within 30 days. The peak rate ratio of hospitalization for pneumonia was associated with the highest doses of inhaled corticosteroids, equivalent to fluticasone at 1,000 µg/d or more (rate ratio, 2.25; 95% CI, 2.07-2.44).⁴² It is important to note, however, that despite the increased risk of pneumonia with the use of ICSs in COPD, no significant effect on overall mortality has been observed to date.⁴⁵ Empirical therapy for community-acquired pneumonia is based on the severity of illness, patient comorbidities, and the risk of drug-resistant microbes. Targeted therapy depends on the identification of a specific pathogen. Despite the frequent overlap of patients with asthma and those with COPD who acquire pneumonia and are taking ICSs, no recommendation to adjust ICSs in these situations or discontinue them altogether currently exists.

As a result of the potentially increased risk of pneumonia with the use of ICSs in patients with COPD,

interest in elucidating an association between *Mycobacterium tuberculosis* (MTB) and ICS use has led to several investigations. One meta-analysis of randomized controlled trials comparing the use of ICSs in patients with COPD with the rate of MTB infection revealed an almost twofold increase in the rate of MTB infection among patients receiving ICSs.^{46,47} Indeed, COPD by itself is thought to be a risk factor for MTB infection. A nested case-control study within a population at intermediate risk for MTB infection identified an increased rate of TB diagnosis with an adjusted OR of 1.20 (95% CI, 1.08-1.34). The increased risk for the development of MTB infection was also found to be a dose-dependent phenomenon (P for trend < .001).⁴⁸

Several species of nontuberculous mycobacteria (NTM) can cause pulmonary infections that present with a variety of clinical symptoms: dry or productive cough, dyspnea, fatigue, and occasionally hemoptysis. Diagnostic criteria require the presence of pulmonary disease and the isolation of mycobacteria from one bronchial washing or recurrent sputum samples. With the increasing incidence of NTM disease over the past few decades,⁴⁹ the identification of risk factors has become more important. Structural lung diseases, such as COPD and bronchiectasis, have a known association with NTM infection.⁵⁰ The estimated prevalence of NTM infection in patients with asthma has been reported to be as high as 1.7%.⁵¹ A nested case-control study revealed an association between ICS therapy and NTM infection in older patients with more severe airflow limitation and taking higher doses of ICSs. Of the 464 patients who had been using ICSs for more than 1 year, the authors observed concomitant NTM infection in 14 patients. Of these 14 patients, 13 had been using ICSs for more than 5 years at the time of diagnosis. Half of the patients with NTM infection required treatment and experienced clinical improvement.⁵² These associations prompt the question as to whether or not NTM infection contributes to the difficulty in controlling asthma.

Direct Effects on the Central Airway

Obstructive lung disease is a respiratory disorder of small bronchi and larger bronchioles that may display endoscopic findings of posterior membrane collapse.⁵³ Large airway collapse due to a loss of integrity of the airway wall may develop over time with the use of ICSs.¹⁰ The physiological changes observed in the

large airways results in limited airflow and decreased flow rates.⁵⁴

Tracheobronchomalacia

TBM is defined as weakness of the tracheal and bronchial walls due to the softening of supporting airway cartilage and hypotonia of myoelastic elements.⁵⁵ These changes lead to tracheal and bronchial collapse, which can become pronounced over time. The condition is suspected on dynamic CT imaging of the chest and is diagnosed during bronchoscopy.⁵⁶⁻⁵⁸ Tracheal injury or prolonged intubation may directly damage the wall and produce a segmental defect. Additional causes of diffuse TBM include relapsing polychondritis, smoke inhalation, chronic gastroesophageal reflux disorder, and recurrent airway

infections. These mechanisms affect the integrity and structural rigidity of the airway wall. Pathologic findings in TBM include atrophy of the longitudinal elastic fibers and fragmentation of the tracheal cartilage.⁵⁹

The authors believe that the previously described mechanisms of ICS therapy contribute to airway weakening through decreased blood flow to the ICS-affected areas. Furthermore, decreased blood flow and repetitive airway infections from the use of ICSs may lead to weakened airway walls and the development of tracheobronchomalacia.⁶⁰

TBM progresses in severity over time, and data have not indicated any degree of reversal.⁶¹ Treatment of TBM is largely focused on airway stabilization with stenting vs surgery. Patients who are surgical candidates may

Figure 3 – Inspiration and expiration CT scans of the chest, revealing excessive dynamic collapse of airways. Note compromised tracheal lumen from the lax posterior wall, whereas the integrity of the cartilage is well maintained.

undergo airway stabilization with tracheobronchoplasty and placement of mesh at the posterior membrane to open the otherwise-flattened airway. Nonsurgical candidates are treated with noninvasive positive-pressure ventilation or airway stenting with silicone stents.⁵⁵ Special care should be taken to reduce factors that may potentiate airway weakness, such as antigastroesophageal reflux medication or the need for surgical treatment of the reflux.⁶² Additionally, the physician should consider whether continuing ICS therapy in these patients has any benefit, as the sequelae could be counterproductive (Figs 3, 4).

Excessive Dynamic Airway Collapse

EDAC has historically been characterized by excessive posterior membrane collapse due to atrophy of the longitudinal elastic fibers. In contrast to TBM, the supporting airway cartilage is not affected in EDAC. Despite this difference, the evaluation and management of EDAC share some similarities with those of TBM. The EDAC diagnosis is made through a dynamic CT scan of the chest or video bronchoscopy, with particular focus on observing that the tracheal cartilage is spared from any dynamic deformity.⁵⁹ Atrophy of airway smooth muscle from ICS therapy may promote the development of EDAC. The vasoconstriction of blood vessels supplying the posterior membrane may

propagate the weakness of the posterior membrane as well.

As in TBM, treatment for EDAC involves airway stenting and tracheobronchoplasty.⁵⁹ In a single case report of a patient with EDAC, lung transplantation improved symptoms, flow-volume loop curves, and observed airway collapse.⁶³ Once again, the question of continuing or ceasing ICS therapy in the patient with EDAC must be addressed in published guidelines. If ICS therapy is found not to be beneficial, it should be withheld (Figs 5, 6).

Tracheobronchial Smooth Muscle Atrophy and Separation

Atrophy of the smooth muscles in the airways has been associated with separation of the posterior tracheal wall from the ends of adjacent cartilage rings. During this process, the pars membranacea of the trachea is detached from the ends of the C-shaped cartilage rings, producing a nearly complete airway collapse (Fig 7). TB-SMAS involves the proximal large airways, sparing the distal airways. Histopathologic evidence of posterior membrane separation from the cartilage rings has been noted in an explanted lung of a patient with TB-SMAS (Fig 8). The cause is speculated to be multifactorial, but the sequelae of ICS therapy are proposed to be a significant contributing factor.⁶³ Published case reports

Figure 4 – Flexible bronchoscopy revealing excessive dynamic collapse of airways. Note compromised tracheal lumen from the lax posterior wall, whereas the integrity of the cartilage is well maintained. Courtesy of Dr Tim Murgu.

Figure 5 – Tracheomalacia. Note the loss of integrity of the tracheal wall cartilages. Courtesy of Dr Tim Murgu.

reveal that a number of patients with TB-SMAS had been exposed to several years of ICS therapy. To prevent excessive collapse of the airways, management of TB-SMAS ranges from airway stenting with silicon stents to T tubes. More invasive treatment includes tracheobronchoplasty.¹⁰

The causes of EDAC and TB-SMAS have been focused on small airway diseases leading to high transthoracic

Figure 6 – CT scan of the chest revealing tracheomalacia. Note loss of integrity of the tracheal wall cartilage. Courtesy of Dr Tim Murgu.

Figure 7 – Tracheobronchial smooth muscle atrophy and separation. Note separation of the medial end of the cartilages of the right main bronchus (arrow) from the posterior wall.¹⁰

Figure 8 – Histologic examination of the airway wall from the explanted lung, revealing total absence of airway smooth muscle in a patient with tracheobronchial smooth muscle atrophy and separation (H&E). C = cartilage; CT = connective tissue; G = mucosal glands).¹⁰

pressures. The value of lung transplantation in patients with recalcitrant collapse of the large airways remains to be studied (Fig 6, Video 1).^{10,63}

Conclusions

The benefits of ICS therapy in patients with asthma and COPD are well recognized. The authors concur that ICSs should be used in concordance with published national and international guidelines. Indeed, one practical suggestion is to use dual therapy without ICSs in patients with mild COPD who are not experiencing frequent exacerbations.

However, an important purpose of this review is to heighten clinician awareness of airway-related sequelae and complications associated with ICSs. The increasing incidence of EDAC and TBM and the development of conditions such as TB-SMAS concomitant with the increased use of ICSs strongly suggest deleterious effects of the drug on the airway smooth muscle and cartilage. The use of ICSs may increase the incidence of bacterial and fungal infections of the airways, bacterial pneumonia, and tuberculous and nontuberculous mycobacterial infections. In patients with more severe obstructive lung disease who warrant higher ICS doses, the decision to continue high-dose ICSs must be carefully considered. These patients may acquire NTM infections due to the severity of underlying lung disease, or an underlying NTM infection may cause more severe obstructive lung disease.

When confronted with any of these complications, the interventional pulmonologist should be cognizant of the potential role of ICSs in their causation. Amidst the growing body of evidence that documents the sequelae of ICSs, it has become imperative that clinicians pause and reassess, initially and periodically, the optimal dose of inhaled steroids that achieves desired therapeutic effects and minimizes harm.

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