

SMOKING AND ASTHMA Seminar #4822

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Introduction

Smoking prevalence in asthma is relatively close to that found in the general population. Nevertheless, relatively little is known about the relationship between active smoking and asthma owing to the exclusion of smokers from mechanistic studies and clinical trials reflecting a concern over recruiting subjects with COPD.

Smoking has been increasingly shown to elicit several negative effects in asthma and quitting may confer additional clinical benefit in individuals with asthma who smoke. Moreover, improved phenotyping of patients with asthma who smoke will become increasingly important for the design of future clinical trials and for drug development.

Smoking as a risk factor for the development of asthma

Epidemiological evidence for the association between active cigarette smoking and asthma is inconsistent due to methodological flaws. Nevertheless, the overall trends indicate a higher prevalence of asthma particularly among female smokers compared to female non-smokers (1-3) (**Table 1**).

The majority of studies that have investigated a temporal association between smoking and onset of asthma support the suggestion that smoking places an individual at a significantly increased risk of developing asthma (4-6) (**Table 1**). In an attempt to address whether smoking is a causal or a proxy risk factor, a large cohort of clinic-referred non-asthmatic adult subjects with established allergic rhinitis was investigated to determine the importance of active cigarette smoking as an additional risk factor for incident asthma at 10-yrs follow-up (7). Smoking was strongly predictive of the development of new onset asthma in allergic adults. In particular, the intensity of smoking appeared to be clearly associated given that there was a dose-response in the effect of smoking exposure with the risk of new onset asthma.

In children, the evidence for a causal relationship between (parental) smoking and the development of asthma is more convincing (8-10). A recent systematic review and meta-analysis of 76 studies examining the effect of exposure to pre- or postnatal passive smoke reported a 21% to 85% increased risk of incident asthma (10).

Clinical outcomes in smokers with asthma

Increased morbidity and mortality have been reported in asthmatic individuals who smoke (11) (**Table 1**). Compared to asthmatic non-smokers, this group of patients is at risk of developing more severe symptoms and worse asthma-specific quality of life with a huge impact on health care resources due to unscheduled doctor visits and frequent hospital admissions (12-14). Moreover, cigarette smoking in asthma is associated with higher frequency of exacerbations (15),

increased numbers of life threatening asthma attacks (16), and asthma mortality is greater among heavy smokers with asthma compared to asthmatics who do not smoke (17).

In line with these observations, asthma severity is greater in asthmatics who smoke (12-14) (**Table 1**). Using the GINA severity classification, data from a well characterized clinic cohort of allergic subjects at high risk for incident asthma followed up for 10 years shows that smoking status and smoking duration are markedly related in a dose-dependent fashion to the level of asthma severity (18). The strongest association with disease severity was observed in those who smoked more than 20 pack-years.

A strong relationship between cigarette smoking and poor asthma control has been shown in several population-based surveys (19-21) (**Table 1**). In a well characterized cohort of allergic individuals at risk for new onset asthma, smoking status and smoking duration were also related to poor asthma control in a dose-dependent fashion (18).

Effects of smoking on lung function

Smoking a cigarette can cause acute bronchoconstriction particularly in asthmatic smokers with reduced baseline lung function (22,23). The effect of smoking on the progressive decline in lung function in COPD is well established, but accelerated decline in lung function over time has been also reported in asthma (24) [45, 46]. In most longitudinal studies, the rate of decline in lung function is accelerated in smokers with asthma compared with nonsmokers with asthma (24-26) (**Table 1**). It is worth noting that lung function changes in asthma can improve after several weeks of smoking cessation (27).

Smoking and reduced corticosteroid sensitivity

Asthma patients who smoke are less sensitive to the beneficial effects of short to medium term treatment with inhaled corticosteroids (ICS) or oral corticosteroids with regard to improvements in respiratory symptoms, lung function and exacerbation rates compared to asthma patients who do not smoke (28-30) (**Table 1**). Increased ICS dosage may partially reverse unresponsiveness.

Mechanisms for the adverse consequences of smoking in asthma

The mechanisms accounting for the adverse consequences of smoking in asthma, including poor symptom control, accelerated decline in lung function and reduced sensitivity to corticosteroids are poorly understood, but are likely to be due to differences in airway inflammation in smokers compared to non-smokers with asthma. In allergic asthma, exposure of professional antigen-presenting cells (APCs) to allergens may lead to activation of allergen-specific T-helper cells (Th)2 and immunoglobulin (Ig)E synthesis. Later exposure to allergen then results in recruitment and activation of eosinophils, mast cells, and then mediator release, hence early and late allergic responses in the airways. Th1-cell responses may also be implicated in some pathogenesis, such as epithelial apoptosis and smooth-muscle cell activation. Regulatory T-cells (Treg) cells may suppress Th2-cell responses via cytokines including IL-10 and TGF- β . Additionally, the Th17 subset of CD4+ T-cells are associated with neutrophilic inflammation during exacerbations, and in remodelling. When cigarette smoke is added to this inflammatory milieu, activated macrophages (AMs) may contribute IL-8, LTB4, GM-CSF to induce neutrophils to survive longer and further release neutrophil elastase ROS, and tissue proteases (matrix metalloproteinases) including MMP-9 which further amplify inflammation and stimulate remodelling. AMs in smokers produce less IL-10, and thus less Th2 skewing, reduced B cell numbers and lower levels of IL-4 and IL-5. The net effect will be less active eosinophils and less IgE in the smoking vs. non-smoking asthmatic lung tissue. AMs, via Th1 and Th17 cells promote bronchial epithelial and goblet cell activation, mucus overproduction and tissue remodelling. Cigarette smoke may directly induce bronchial epithelium to release pro-inflammatory and pro-fibrotic cytokines, chemokines, growth factors, including TGF- β . This results in smooth-muscle cell and fibroblast proliferation, fibrosis and extracellular matrix deposition. TSLP may stimulate MCs to release fibrotic stimuli such as IL-13 independent of Th2 cells. MCs may also increase IL-8 production, furthering neutrophil recruitment. Thus, persistent tobacco smoke results in additive or synergistic inflammatory remodelling, and explains the reported accelerated fall in lung function in the smoking vs. non-smoking asthmatic. (Abstracted from: Polosa R, Thomson NC. ERJ 2013; 41(3):716-26.)

Asthma and smoking cessation

In spite of the reported deleterious effects of smoking on asthma symptoms, lung function and corticosteroid responsiveness, only a few studies have examined the role of smoking cessation on asthma outcomes. These studies

show improvements in symptoms and lung function in those who quit (**Table 2**). For example, in a prospective study on three groups of asthma patients of smoking reduction, complete smoking cessation or continuation of smoking (31), asthmatic smokers who quit had significant improvement in asthma-related quality of life and reduction in nocturnal and daytime rescue β 2-agonist use, inhaled corticosteroid use, daytime asthma symptoms, and airway hyperreactivity. Of note, smaller improvements occurred in smoking reducers suggesting an apparent dose-response effect. These findings are in agreement with the observed improvement in airway hyperresponsiveness one year after smoking cessation (32).

The above findings highlight the importance of smoking cessation in improving clinical and pathological outcomes of asthma. Physicians have the responsibility to alert their patients with asthma about the additional risks of smoking and to engage in smoking cessation interventions. Unfortunately, only modest cessation rates are reported in adult asthma and some studies have reported that asthmatic smokers do not believe that smoking could be a serious problem for their asthma.

Current evidence-based recommendations indicate that smoking cessation programs should combine counselling (mainly problem solving/skills training, and social support) and medications for nicotine addiction for best results (**Figure 1**). Presently, first-line medications for smoking cessation therapy include nicotine replacement therapy, bupropion and varenicline.

In practice, symptoms of asthma (primarily cough) can develop or worsen after smoking cessation (33). Thus, the asthmatic smoker who wants to quit should be advised that his/her symptoms of asthma may increase within the first couple of weeks after smoking cessation. Smokers' in this category will benefit from a temporary increase in antiasthma drugs. Moreover, given that children with asthma are extremely vulnerable to second hand smoke, their parents and other family members who smoke should be offered treatment for smoking cessation (34).

Current pharmacological treatments

Beyond smoking cessation, asthma guideline recommendations on drug treatment of asthmatics who smoke do not in general differ from non-smokers with asthma. However, this view could be challenged given that most of the recommendations on drug treatment are based on clinical studies in which patients are carefully selected to exclude current smokers or former heavy smokers. The lack of information on the best approach to manage smokers is of significant concern, given the high prevalence rates of active smoking in asthma and the poor levels of asthma control in this specific subgroup.

Despite smokers with asthma having reduced sensitivity to corticosteroids, it seems appropriate that these patients receive ICS given that not all smokers with asthma are insensitive to ICS. Nevertheless, many smokers with asthma will continue to be symptomatic despite ICS and in these patients a step-up in therapy will be required. There is now recent evidence that add-on long acting β 2-agonists are beneficial in smokers with asthma (35,36) and this is likely to be a preferable option to increasing the dose of ICS. An open label study of asthmatic patients with a limited smoking history showed benefits from treatment with the combination of inhaled budesonide and formoterol administered as a maintenance and reliever therapy (36). Adding leukotriene receptor antagonists may be of greater benefit in asthmatic smokers. The preliminary findings of a randomized, parallel-group 6-month study to evaluate the efficacy of oral montelukast, fluticasone propionate and placebo in 1019 patients with chronic asthma who smoke cigarettes reported that both interventions produced small improvements in the percentage of asthma-control days (primary outcome) compared to placebo (ClinicalTrials.gov Identifier: NCT00284856). The efficacy of adding anti-leukotriene drugs to combination therapy in smokers with asthma is not known. A recent 12-week study found that patients with COPD and concomitant asthma achieve improvements in lung function with the inhaled tiotropium, which suggests that inhaled tiotropium may be of benefit in smokers with particularly when associated with persistent airflow obstruction (37). A further study is underway that is examining the efficacy of inhaled tiotropium compared with an inhaled LABA in smokers with asthma (ClinicalTrials.gov Identifier: NCT00546234).

A brief clinical review of asthma and smoking summarizes recent literature and a clinical approach to the smoking asthmatic (38).

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TABLE 1: SUMMARY OF ADVERSE EFFECTS OF ACTIVE CIGARETTE SMOKING AND ASTHMA

Adverse effects of active smoking and asthma	Details of adverse effects
Increased prevalence of asthma	Higher prevalence of asthma particularly among female smokers compared to female non-smokers; the interaction between smoking and gender is particularly evident among heavier as compared to lighter smokers or non-smokers.
Incident asthma	Smoking is highly predictive of the development of new onset asthma in allergic adults with a clear dose-response effect of smoking exposure.
Increased asthma morbidity and mortality	Asthmatic smokers are at risk of developing more severe symptoms, higher frequency of exacerbations, and worse asthma-specific quality of life; cigarette smoking in asthma is also associated with increased numbers of life threatening asthma attacks and greater asthma mortality.
Greater asthma severity	Smoking status and smoking duration are strongly related in a dose-dependent fashion to the level of asthma severity. The strongest association with disease severity was observed in those who smoked more than 20 pack-years.
Uncontrolled asthma	A relationship between smoking and poor asthma control has been reported in population-based surveys and in controlled studies. Smoking status and smoking duration are also related to poor asthma control in a dose-dependent fashion.
Accelerated decline in lung function	The rate of decline in lung function is accelerated in smokers with asthma compared with non-smokers with asthma, although there are also a few negative studies.
Persistent airflow obstruction	A proportion of smokers with asthma develop persistent airflow obstruction.
Corticosteroid insensitivity	Asthma patients who smoke appear to be less sensitive to the beneficial effects of corticosteroids with regard to respiratory symptoms and lung function, irrespective of the route of administration of treatment.

Table 2: SUMMARY OF STUDIES EXAMINING THE EFFECT OF SMOKING CESSATION ON ASTHMA OUTCOMES

Citation	Participants	Findings
Tonnesen P, et al. Nicotine Tob Res 2005	220 asthmatics undergoing a smoking cessation program with NRT. At 4 months, 27 were abstainers, 33 reducers, and 50 relapsers or continuing smokers.	Improvements in the asthma-specific quality-of-life score, and reductions in self-reported day and night use of rescue beta ₂ -agonists, in doses of ICS, in daytime asthma symptoms, and in AHR were reported in the abstainers. For reducers, smaller improvements occurred for night use of rescue beta ₂ -agonists, doses of ICS, and AHR.
Piccillo G, et al. Respir Med 2008	57 smokers with seasonal allergic rhinitis ± asthma undergoing a smoking cessation program with NRT ± bupropion. At 12 months, 16/57 of the participants had quit smoking.	A significant improvement in AHR to direct and indirect bronchoprovocation was observed after cessation in the quitters but not in the smoking cessation relapsers.
Chaudhuri R, et al. Am J Respir Crit Care Med 2006	32 asthmatic smokers given the option to quit or continue smoking. Eleven opted to continue smoking, whereas 10/21 managed to quit smoking for up to 6 weeks.	After smoking cessation, quitters achieved considerable improvement in lung function and a fall in sputum neutrophil count compared with subjects who continued to smoke.

AHR – airway hyperresponsiveness
 NRT – nicotine replacement therapy
 ICS – inhaled corticosteroids

Figure 1 – Taken from Polosa R, Caponnetto P, Sands MF. JACI 2012

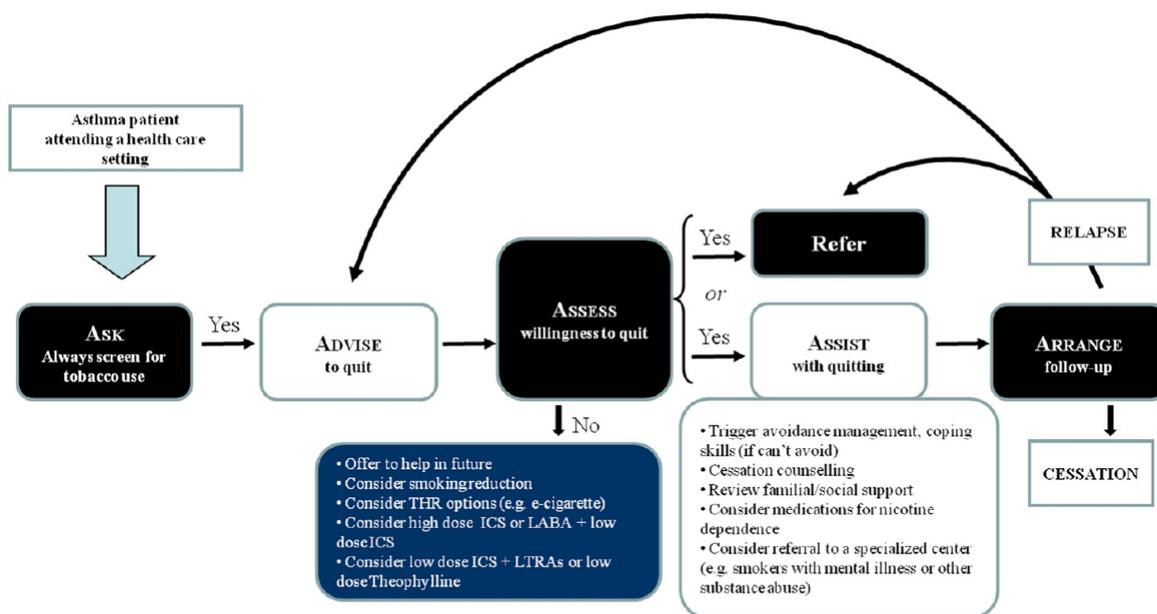


FIG 1. An algorithm for assisting the asthmatic smoker. The first step in treating tobacco use and dependence is to identify tobacco users. Asking systematically whether your asthmatic patients smoke at every visit is imperative (ASK). All smokers with asthma should be advised to quit. This advice should be clearly stated and specifically adapted in relation to the patient's asthma problems: "Did you know that by quitting you will not only improve your general health status but also your asthma symptoms?" (ADVISE). The willingness of smokers with asthma to make a quit attempt at this time should be assessed (ASSESS). If the patient is ready to quit, health care providers should be prepared to offer assistance. This entails working together with the patient to set a sensible plan with a commitment to a quit date and to frequent follow-up visits. Alternatively, referring the patient to a tobacco intervention resource (eg, a smoking cessation quit line or health educator) that would deliver additional treatment to the patient might be contemplated (ASSIST). All patients who receive a tobacco dependence intervention should be regularly assessed for abstinence, beginning within the first week after the quit date. Abstinent patients should have their quitting success acknowledged. Patients who have relapsed should be assessed to determine whether they are ready to repeat another quit attempt (ARRANGE). Modified from Fiore et al.¹⁴ LABA, Long-acting β_2 -agonist; LTRA, leukotriene receptor antagonist.