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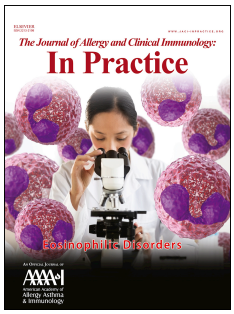

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CIGARETTE SMOKING AND ASTHMA

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Asthma; Asthma-Chronic obstructive pulmonary disease overlap; Chronic obstructive pulmonary disease; Cigarette smoking; Smokers with asthma; Smoking cessation

Word count: 4749 words

Abbreviations

ACO: asthma-COPD overlap

AHR: airway hyperreactivity

AMAZES: Asthma and Macrolides: The Azithromycin Efficacy and Safety trial

COPD: chronic obstructive pulmonary disease

FeNO: fractional concentration of exhaled nitric oxide

GINA: Global Initiative for Asthma

GOAL: Gaining Optimal Asthma Control trial

GR: glucocorticoid receptor

HDAC: histone deacetylase activity

ICS: inhaled corticosteroid

IgE: immunoglobulin E

IL: interleukin

ILC2: type 2 innate lymphoid cell

LABA: long-acting beta$_2$-agonist

LAMA: long-acting muscarinic antagonist

MART: Maintenance and Reliever Therapy

MMPs: matrix metalloproteinase

NET: neutrophil extracellular trap

NETosis: neutrophil extracellular trap formation

NK: natural killer

PDE_4: phosphodiesterase 4

PGD_2: prostaglandin D_2

PROSPERO: Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab trial

ROS: reactive oxygen species

SABA: short-acting beta$_2$-agonist

START: inhaled Steroid Treatment As Regular Therapy trial

Tc1: $CD8^+$ cytotoxic T cell

Th2: T helper 2

TNF: tumor necrosis factor

TSLP: thymic stromal lymphopoietin

T2 inflammation: type 2 inflammation

WHO: World Health Organization

ABSTRACT

Globally, around half the adult asthma population are current or former cigarette smokers. Cigarette smoking and asthma interact to induce an 'asthma-smoking phenotype(s)', which has important implications for diagnosis, pathogenic mechanisms, and management. The lack of progress in understanding the effects of smoking on adults with asthma is due in part to their exclusion from most investigative studies and large clinical trials. In this review, we summarize the adverse clinical outcomes associated with cigarette smoking in asthma, highlight challenges in diagnosing asthma among cigarette smokers with chronic respiratory symptoms, particularly in older individuals with a long-standing smoking history, and review pathogenic mechanisms involving smoking and asthma-related airway inflammation, tissue remodeling, corticosteroid insensitivity, and low-grade systemic inflammation. We discuss key components of management including the importance of smoking cessation strategies, evidence for the effectiveness of the Global Initiative for Asthma recommendations on treatment in cigarette smokers, and the role of treatable traits such as type 2 eosinophilic airway inflammation. Lastly, we provide an algorithm to aid clinicians to manage current and former smokers with asthma. In the future, controlled and pragmatic trials in real-world populations should include cigarette smokers with asthma to provide an evidence base for treatment recommendations.

Word count n=198

INTRODUCTION

Nearly 1 billion people globally are tobacco smokers.[1] Although its prevalence is projected to decrease over the next decade, the total number of smokers will remain high due to population growth. In 2020, men had a much higher prevalence of cigarette smoking than women, 26% and 5% respectively, which was particularly evident among men living in the World Health Organization (WHO) Western Pacific region of the world (42%), largely reflecting data from China, and the European region (30%).[1] A WHO survey undertaken in the early 2000s showed that the proportion of current smokers with asthma was no different from the general population.[2] Current smoking rates are higher among some asthma subgroups, such as adults attending US emergency departments with an exacerbation, where over one third were smokers.[3] International severe asthma registry data have shown a low prevalence of current smoking (<10%),[4] although higher smoking rates were found among patients with severe asthma in primary care.[5] The prevalence of former smoking in asthma ranges from around one quarter[6] to over 40%.[5, 7] Globally, cigarette smoking has an adverse impact on disability-adjusted life years of people with asthma, particularly in men and among those living in Europe, Western Pacific nations, and Southeast Asia.[8] Collectively, these findings indicate that around fifty percent of adults with asthma give a history of current or former cigarette smoking and that cigarette smoking contributes to the worldwide health burden of asthma.

Cigarette smoking and asthma interact to induce a mixed 'asthma-smoking phenotype', which has important implications for diagnosis, pathogenic mechanisms, and management.

The lack of progress in understanding the impact of smoking on adults with asthma is due in part to their exclusion from investigative studies and large clinical trials because of concerns that these patients may also have chronic obstructive pulmonary disease (COPD). The review aims to summarize the adverse clinical outcomes associated with cigarette smoking in asthma and to answer the following key questions: 1. What are the main issues that clinicians should consider when making a diagnosis of asthma in adults with chronic respiratory symptoms and a smoking history? 2. Why do patients with asthma and smoking history have worse clinical outcomes? 3. What is the best approach to managing patients with asthma and a smoking history? The article provides an update on earlier reviews of smoking and asthma.[9, 10]

ADVERSE CLINICAL OUTCOMES

Epidemiological data have demonstrated that current and former cigarette smoking[11-13] and cumulative pack-years of smoking[14] are risk factors for the development of asthma in adults. Numerous observational studies have shown that current smoking is frequently associated with worse clinical outcomes in asthma[15] (figure 1) including suboptimal asthma control,[7, 16] lower asthma or generic health-related quality of life domain scores,[17, 18] more exacerbations,[19-21] greater asthma-related health care utilization[22] and a higher proportion of individuals with chronic bronchitis.[23, 24] Likewise, greater cumulative exposure to cigarette smoke is associated with worse asthma control[25] and predicted asthma-related hospital admissions in adult-onset asthma.[26]

In asthma, current smoking status and cumulative exposure to cigarette smoke[27, 28] are associated with the development of persistent airflow obstruction over time, especially after 50 years of age, leading to asthma-COPD overlap (ACO) in some cases.[29, 30]. Several longitudinal population-based studies[31-34] reported an accelerated decline in lung function from early adulthood among current smokers with asthma compared to never smokers with asthma, which was associated with a higher pack-year history in middle-aged adults with asthma[35]. For example, data from the Busselton Health Study showed that compared to never-smokers with asthma, heavy smoking accelerated the decline by 14 ml/year in males and 7 ml/year in females[34] (figure 2). In the longitudinal population-based European Community Respiratory Health Survey, early- and late-onset asthma (defined as onset after 10 years of age) were both associated with a 10 to over 20-fold increase in the risk of adult airflow obstruction. The development of persistent airflow obstruction was independent of smoking among early-onset asthma, whereas cigarette smoking increased the risk in the late-onset asthma subgroup (25-fold increase) compared to never smoking (11-fold increase), particularly among nonatopic subjects (30-fold increase).[32] Suboptimal lung growth from early-life events may contribute to persistent airflow obstruction in adulthood among some current smokers with asthma.[36]

Several surveys of current smokers with asthma report a higher prevalence of comorbidities such as anxiety and depression,[21] osteoporosis,[37] cardiovascular diseases,[7] lung cancer,[7, 38] and pneumonia[7, 39] compared to never smokers with asthma. The cause of comorbidities in current smokers with asthma is likely to be multifactorial due to cigarette smoking, asthma, and/or oral corticosteroid burden. Current smoking is an important risk factor for increased all-cause mortality in asthma,[40] particularly in global regions with low socio-demographics.[41]

DIAGNOSIS AND DESCRIPTION

Based on symptoms of wheeze, cough, chest tightness, and/or dyspnea and objective evidence of variable expiratory airflow limitation,[42] the diagnosis of asthma in younger adults with a smoking history is often straightforward. In some cases, measuring airway hyperreactivity (AHR) to methacholine confirms the diagnosis, although even in the absence of asthma, cigarette smoking increases the occurrence of AHR by over 3-fold in heavy daily smokers (≥25 cigarettes/day).[43] Some have proposed the addition of fractional concentration of exhaled nitric oxide (FeNO) measurements for individuals whose diagnosis of asthma remains uncertain[44], but values are decreased in current smokers,[45] limiting its diagnostic value. Distinguishing asthma from symptomatic smokers without spirometry COPD (pre-COPD)[15, 46, 47] or with COPD is more problematic in older individuals with a long-standing smoking history. Data from several studies have demonstrated the poor sensitivity of bronchodilator reversibility,[48] AHR,[43] diffusing capacity of lung to carbon monoxide, computed tomography (CT) imaging of the chest, or biomarkers to differentiate asthma from smoking-related chronic airway disease.[49] Furthermore, several smoking-associated phenotypes have emerged from cluster analysis studies of asthma populations that included adults with asthma and a smoking history.[50-61] The main variables identified were smoking status, age of onset of asthma, severity of asthma, airflow obstruction, and type 2 inflammation (T2) status (figure 3). Although these clusters provide insights into the heterogeneity of asthma-smoking phenotypes, their clinical relevance is uncertain. Given the substantial risk of diagnostic misclassification of chronic airway disease in symptomatic current and former smokers,[15, 62] particularly in older age groups, we recommend an approach that involves an assessment of the probability that clinical features are suggestive

of a diagnosis of asthma or smoking-related ACO as outlined in the GINA report[42] and that describes individual clinical, physiological, pathological, biomarker variables, and treatable traits.[63, 64]

MECHANISMS OF DISEASE

Multiple risk factors contribute to the adverse health outcomes experienced by smokers with asthma. Risk factors include current or former smoking status, cumulative exposure to cigarette smoke, asthma phenotypes such as non-atopic late-onset asthma,[32] and coexistent social factors such as lower socioeconomic status, environmental exposures such as passive smoke[65] or air pollution[66] and behavioral factors. Furthermore, early life events such as maternal smoking, prematurity, early respiratory infection, and previous severe childhood-onset asthma[67] can contribute to suboptimal lung growth and submaximal lung function that impacts lung function in adulthood. The exposure to different risk factors is likely to induce heterogeneous phenotypes and endotypes.

Cellular and structural changes

Cigarette smoking can alter airway eosinophil and neutrophil numbers in asthma. Although airway eosinophils were reduced in some studies,[21, 68-70] more often eosinophil numbers were unaltered by smoking status.[71-75] A recent study of predominately former smokers with severe asthma found that a ≥10 pack-year history was associated with higher proportion of patients with eosinophilic airway inflammation, autoimmunity towards eosinophils, and reduced sputum eosinophil sensitivity to systemic corticosteroids

suggesting a phenotype of severe refractory eosinophilic asthma among former smokers with a history of a higher cumulative exposure to cigarette smoke.[76] Many studies have shown that current smoking was associated with neutrophilic airway inflammation,[68, 71, 74] whereas other data have shown that neutrophil numbers did not differ from never smokers.[21, 69, 70, 77] A cross-sectional study of over 800 adults with mild to severe asthma found similar proportions with eosinophilic, neutrophilic, and paucigranulocytic inflammation among current smokers (37%, 15%, and 45% respectively) compared with never smokers (43%, 16%, and 37% respectively).[72] Differences in risk factors may explain the variability in eosinophil and/or neutrophil numbers between studies. Overall, data from these studies have shown that over one-third of current smokers with mild to severe asthma have airway eosinophilia and over one-half have neutrophilic or paucigranulocytic airway inflammation. Additionally, exposure to cigarette smoke in adults with asthma is associated with the recruitment, activation, and/or altered function of macrophages,[78] dendritic cells,[79] mast cells,[70] natural killer cells,[80] and T and B cells[75, 79] compared to never smokers, although data are limited, and some findings are conflicting.

Structural changes to the airway epithelium associated with cigarette smoking in asthma include increased goblet cell numbers,[70, 77] epithelial cell hyperplasia,[70] and squamous metaplasia. Pathological features of epithelial remodeling may underlie respiratory symptoms since increased goblet cells numbers correlated with a self-reported history of sputum production and greater epithelial thickness correlated with self-reported breathlessness.[70] The percentage of mucus positive epithelium, epithelial thickness, and proliferating epithelial cells in former smokers was similar to never smokers with asthma,[70] suggesting reversal of epithelial cell remodeling following smoking cessation. Several studies

have found that basement membrane thickness,[70, 75, 77] histological airway smooth muscle area thickness,[75, 77] and wall thickness on CT[81] were not associated with smoking status in adults with mild to severe asthma. In contrast, data from other CT imaging studies found increased airway wall thickness in current smokers with asthma[74] and among ACO patients with a cumulative smoking history of ≥20 pack-years compared with those with <5 pack-years.[82] CT emphysema is typically absent from adults with asthma and a smoking history,[81, 82] although visual analysis showed a greater prevalence of emphysema in smoking-related ACO (≥20 pack-years) compared to those with ACO (<5 pack-years).[82] Collectively, these findings suggest remodeling of the epithelium and possibly other lung structures among current smokers with asthma.

Pathogenesis

Pathogenic mechanisms underlying airway inflammation and tissue remodeling in smokers with asthma are poorly understood but are thought to involve interactions between smoking and asthma-related airway inflammation (Figure 4). Exposure to cigarette smoke induces oxidative stress[83] and the release of proinflammatory mediators by activated neutrophils, macrophages, and $CD8^+$ cytotoxic T (Tc1) cells.[84] Exposure to allergens in sensitized individuals or other stimuli induces pro-inflammatory mediator release from activated eosinophils, T helper 2 (Th2) cells, type 2 innate lymphoid cells (ILC2), and mast cells. Collectively these inflammatory pathways cause T2 low and/or T2 high airway inflammation, and tissue damage to the epithelium and other structures. Innate immune responses mediated by epithelial cells, alveolar macrophages, dendritic cells, and natural killer cells can be suppressed by exposure to cigarette smoke and thus impair host

responses against infection.[85] Corticosteroid insensitivity occurs due to refractory eosinophilic, neutrophilic or paucigranulocytic airway inflammation, in addition to other causes such as non-adherence. Possible molecular mechanisms of corticosteroid insensitivity include altered glucocorticoid receptor (GR) subtypes, such as increased inactive GRβ and decreased active GRα expression,[86] and increased pro-inflammatory transcription factors activity, such as NF-κB, or decreased histone deacetylase activity (HDAC)2 activity.[87] In addition to airway inflammation, low-grade systemic inflammation is found in current and former smokers with asthma,[7] which in one study was associated with comorbidities, a higher pack-year history, and lower lung function.[88] Whether low-grade systemic inflammation is a causative factor for adverse clinical outcomes in smokers with asthma is not known.

MANAGEMENT

The management strategy for current smokers with asthma starts with smoking cessation. Global Initiative for Asthma (GINA) provides recommendations for drug treatment,[42] although evidence for the effectiveness of therapies in current smokers with asthma and those with heavier smoking history is uncertain since clinical trial data were generated among never smokers or former smokers with a very low pack-year history, typically 5 pack-years or less. Recently, the identification and targeting of treatable traits have been proposed as a personalized approach to the management of chronic airway diseases,[64] although data are limited on its effectiveness for the management of current smokers with asthma.[89] In addition to smoking cessation, management involves the identification and targeting of high-yield treatable risk factors and behavioral traits, such as infection and poor

adherence with asthma therapies, pulmonary traits, such as exacerbations, airflow obstruction, and T2 eosinophilic inflammation, and extrapulmonary traits, such as comorbidities (figure 5). Published evidence for the effectiveness of specific components of a management plan for adults with asthma and a smoking history is reviewed below.

Smoking cessation

All smokers with asthma should be advised to quit. This advice should be personalized by listing the improvements in asthma outcomes soon after quitting. In several studies in asthma, quitting smoking is associated with improvements in symptoms,[90-92] asthma-related quality of life,[90] lung function,[92] and AHR.[90, 91] Furthermore, former smokers with asthma often have better symptom control than current smokers.[21, 93] A COPD risk-prediction model estimated that a 43-year-old female unskilled worker with asthma who smoked 20 cigarettes/day for 30 years had an estimated 42% risk of COPD in the next 10 years, but only 4.5% if she stopped smoking at age 43.[94] Cigarette smokers with asthma and COPD are no more likely to receive smoking cessation counseling and pharmacotherapy from physicians compared to the general smoking population.[95] Cigarette smoking quit rates are improved with behavioral counseling in combination with pharmacotherapies, such as nicotine replacement products, varenicline, and bupropion.[96] A tailored approach to the smoking cessation of the smokers with asthma has been described previously.[97, 98] While the preferred goal is abstinence, this is not always achievable and substitution of conventional cigarettes with alternatives that do not require combustion to deliver nicotine such as E-cigarettes may be an alternative for those smokers with asthma who do not wish to stop smoking. [99, 100]

Targeting non-adherence, poor inhaler technique, and infection risk

Cigarette smoking has been associated with poorer adherence to drug therapies for asthma in some[101] but not all studies.[102] An international cross-sectional study of over 4000 adults with asthma identified current smoking as a risk factor for ≥1 inhaler technique errors and worsening asthma outcomes among those who used a metered-dose inhaler but not among those who used a dry powder inhaler device.[103] Infection risk reduction for current smokers with asthma including smoking-related ACO involves annual influenza vaccination,[42] COVID-19 vaccination, and pneumococcal vaccination for patients >65 years.[49]

Drug treatments and other therapies

Published studies on the influence of current smoking status on GINA recommendations for the treatment of symptoms, exacerbations, and airflow obstruction in adolescents and adults with asthma are summarized in the following section.

Maintenance low to high dose inhaled corticosteroids

Data from several small randomized controlled trials have shown reduced improvement in lung function after low to medium dose ICS administered from <1 month to 6 months among current smokers with mild to moderate asthma compared to never-smokers (Table 1).[69, 104-107] In one study, current smokers with asthma who were insensitive to low dose ICS improved lung function after high-dose ICS therapy for 12 weeks[105] suggesting that smokers with mild to moderate asthma may require a higher dose ICS treatment to overcome

corticosteroid insensitivity and improve airflow obstruction. The beneficial effect of low dose ICS on allergen-induced early asthmatic responses is attenuated in current smokers with asthma.[108] A *post hoc* analysis of the GOAL (Gaining Optimal Asthma Control) trial showed that 1-year treatment with medium to high dose ICS was less effective in preventing severe exacerbations in current compared to never smokers with asthma.[109] Data from a *post hoc* analysis of the START (inhaled Steroid Treatment As Regular Therapy) trial in recent-onset mild asthma[110] and observational studies[111, 112] have shown that long-term ICS treatment (≥1 year) reduced the decline in lung function among current smokers with asthma, although in one observational study, a beneficial effect of ICS was restricted to men and smokers with a <5 pack-year history.[111] Two systematic reviews have shown that current smoking was associated with a reduced improvement in FEV_1 after low and high-dose ICS treatment compared to non-smokers.[113, 114] Exploratory analysis of UK General Practice Database has found a lower rate of severe exacerbations and improvement in asthma control for current and former smokers with asthma after one year's treatment with extra-fine-particle ICS compared to standard-particle ICS,[115] although other studies have not found better outcomes with extra-fine-particle ICS in current smokers with asthma.[116] Data from one study in asthma have shown that a higher pack-year history was associated with reduced improvement in FEV_1 after 2 weeks and 1-year treatment with ICS.[69] Collectively, these findings suggest that the improvement in lung function after short-term low to medium dose ICS is impaired among current smokers with asthma compared to never smokers. In current smokers with asthma, long-term treatment with ICS may reduce the decline in lung function but it is less effective in preventing exacerbations compared with never smokers with asthma. Preliminary data from clinical trials in current and former

smokers with asthma[109, 110] or COPD[117-119] suggest that the beneficial effects of ICS on exacerbations and lung function are greater in former smokers than in current smokers.

As-needed low dose ICS-formoterol reliever

The GINA recommendation for the use of as-required ICS-formoterol in symptomatic mild or moderate asthma is based on evidence from large clinical trials generalizable to current or former smokers with a low cumulative smoking history.[120-123] Currently, there are no clinical trials that have assessed the as-needed low dose ICS-formoterol reliever strategy in smokers with medium to high tobacco use.[124]

Maintenance low to high dose ICS-long-acting beta-agonist (LABA)

Maintenance medium to high dose standard-particle ICS-LABA combination in current and former smokers with asthma produced greater improvement in asthma control and reduction in exacerbations than high dose ICS.[107, 109, 116] Data on the effectiveness of low-dose ICS-LABA maintenance treatment, including extra-fine particle ICS-LABA[125] are limited to findings from a small number of observational studies.

ICS-LABA MART (Maintenance and Reliever Therapy) regimen

A study of medium-dose maintenance budesonide/formoterol (200/6 µg) two puffs twice daily showed that the reduction in severe exacerbations with low dose budesonide/formoterol (200/6 µg) one puff (MART regimen) compared with SABA for

symptom relief was unrelated to smoking status among 303 adults with asthma of whom half were current or former smokers with <10 pack-year smoking history.[126] A six-month open-label study in light smokers with asthma found that the reduction in symptoms and severe exacerbations was greater with the MART regimen using medium-dose budesonide/formoterol (200/6 µg) two puffs twice daily compared with one inhalation twice daily suggesting that a higher maintenance dose of budesonide/formoterol may be required in smokers with asthma.[127] Collectively, these findings suggest that the MART regimen is effective in current smokers with asthma who have a low cumulative smoking history.

Add-on long-acting muscarinic antagonist (LAMA)

A *post hoc* analysis of phase 3 trials of once-daily tiotropium add-on therapy in symptomatic patients with asthma despite treatment with medium to high dose ICS with or without LABA reported a reduced time to first severe exacerbation in former smokers with persistent airflow obstruction.[128] A 12-week randomized placebo-controlled study in 472 current and former heavy cigarette smokers (34 pack-year history) with ACO reported improvements in FEV_1 and a decrease in rescue medication use with add-on tiotropium.[129] A randomized cross-over trial in 16 current smokers with asthma found that the addition of tiotropium to medium dose ICS-LABA improved trough small airway flow rates, but had no added effect on symptoms or reliever use.[130] Collectively, these findings suggest benefits from the addition of tiotropium to symptomatic ever smokers with asthma associated with persistent airflow obstruction despite treatment with medium to high dose ICS-LABA.

Biologics

Post-hoc analysis of the PROSPERO (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab) study showed that omalizumab for 48 weeks improved symptom control, but not lung function, among 50 current and former smokers with ACO compared to 663 adults without ACO, of whom two-thirds were never smokers.[131] Data from a global observational cohort study of 368 real-world patients newly prescribed mepolizumab for severe asthma, of whom 39% were current smokers or former smokers demonstrated reductions in exacerbations and maintenance oral corticosteroid use similar to those reported in clinical trials of mepolizumab.[132] A *post-hoc* analysis of a phase 2b trial of the anti-interleukin (IL)-4 receptor α monoclonal antibody dupilumab in patients with severe asthma reported improvements in FEV_1 and reduced severe exacerbations in a subgroup of patients with a smoking history and ACO.[133] Collectively, these data and other observational studies[116] provide low-certainty evidence of clinical benefits from treatment with anti-IgE omalizumab, anti-IL5 mepolizumab, and anti-IL4 receptor α dupilumab in patients with smoking-related ACO.

Add-on azithromycin

Add-on azithromycin treatment for 12 weeks did not affect clinical outcomes and inflammatory biomarkers among current smokers with mild to moderate asthma.[134] The AMAZES (Asthma and Macrolides: The Azithromycin Efficacy and Safety) trial, which recruited 420 never and former smokers (38% of participants; <10 pack-year history) with persistent uncontrolled asthma , showed that the addition of azithromycin for 48 weeks

reduced severe and moderate exacerbations and improved asthma-specific quality of life compared to placebo. [135] In COPD, daily azithromycin decreased acute exacerbations in former smokers, but not in current smokers [136]. Collectively, these findings suggest that the addition of azithromycin is not effective in current smokers with mild to moderate asthma, whereas it may reduce exacerbations in former smokers with asthma who have a low cumulative smoking history.

Low dose maintenance oral corticosteroid

Several clinical trials showed that the improvement in lung function after short-term high-dose oral corticosteroid treatment was impaired in current smokers with asthma compared to never smokers.[137, 138] The influence of smoking status on low dose maintenance oral corticosteroid treatment or the efficacy of high dose oral corticosteroid treatment of exacerbations is not known.

Other therapies

The number of participants with a smoking history included in real-world patient observational studies of bronchial thermoplasty is too small to establish the efficacy or safety of the procedure in current or former smokers with severe asthma.[139] A small number of clinical studies have reported the benefits of the leukotriene receptor antagonist montelukast as a first-line controller therapy in current smokers with asthma.[106, 140] In a controlled clinical trial among 1019 current smokers with asthma, a better clinical response to montelukast was found in those with a higher cumulative exposure to tobacco smoke

(>11 pack-year), whereas a better response to medium-dose ICS was shown in those with lower cumulative exposure to tobacco smoke (≤11 pack-year).[141]

Drugs used to treat symptoms of chronic bronchitis, such as thiol compounds[142] and the phosphodiesterase $(PDE)_4$ inhibitor roflumilast, which is an add-on option to reduce exacerbations in current and former smokers with severe COPD and chronic bronchitis [49] have not been studied in smokers with asthma and chronic bronchitis. Preliminary studies with statins [143, 144] or low-dose theophylline,[145] have shown clinical benefits in current smokers with mild to moderate asthma, but larger trials are required.

T2 eosinophilic inflammation status

Current cigarette smoking alters biomarkers of T2 inflammation in asthma, for example, by reducing FeNO,[45] and serum periostin concentrations.[146] Blood eosinophil numbers in current smokers with asthma can be increased,[147] reduced[69] or similar [7 21, 148] to never smokers with asthma. Among current smokers (≥10 pack-year smoking history) with mild to moderate asthma, a single blood eosinophil count (>2%) was shown to be a good predictor of airway eosinophilia.[149] Blood eosinophils are used to identify individuals with T2 high airway inflammation who are potentially suitable for ICS or biologic treatment among adults with asthma (data mainly from non-smokers) and ICS use in smoking-related COPD. Based on these findings, it is likely that blood eosinophils can be also used to predict ICS responsiveness among adults with asthma and a smoking history, although published clinical data are limited. Current smoking is associated with elevated total IgE antibody levels in the general population,[150] whereas most studies in asthma have found that total IgE levels are

494 not influenced by smoking status.[7, 21] Smoking is associated with a reduced sensitization to
495 common aeroallergens,[151] except for increased sensitization house dust mites in some
496 studies.[21, 151]
497
498 *T2 high eosinophilic inflammation*
499
500 Over one-third of current smokers with asthma have biomarker evidence of T2 high
501 inflammation.[146, 152, 153] In a large UK primary care asthma cohort, of whom over 50% were
502 current and former smokers, a multidimensional eosinophil algorithm classified an
503 eosinophilic phenotype in the majority.[154] Current and former smokers with poorly
504 controlled asthma despite moderate dose ICS-LABA who have persistently raised blood
505 eosinophils should be considered for high dose ICS-LABA and/or biologics. The optimum
506 blood eosinophil count cut-off value for high-dose ICS or biologic treatment is uncertain in
507 smokers with asthma. In smoking-related COPD, the addition of ICS to LABA or LABA and
508 LAMA reduced moderate and severe exacerbations[117, 118] at all blood eosinophil counts
509 among former smokers, but among current smokers, clinical benefits were lacking at lower
510 eosinophil counts (<200cells/µl), whereas exacerbations were reduced at higher eosinophil
511 counts (>200cells/µl).[117, 118] In smoking-related ACO, observational data suggested that a
512 blood eosinophil count of >300cells/ul predicted a decrease in exacerbations with ICS.[155].
513 Possible blood eosinophil values predicting ICS responsiveness in current smokers with
514 asthma are: >300 cells/µl, good ICS response; >100 to 300 cells/µl, uncertain ICS response;
515 ≤100 cells/µl, low probability of ICS response. Collectively, these findings suggest that
516 former smoking status and elevated blood eosinophil count may predict ICS responsiveness
517 in adults with asthma and a smoking history, although further studies are required to assess

the interrelationships between smoking status, blood eosinophil count, ICS responsiveness, exacerbations, and severity of asthma.

T2 low neutrophilic and/or paucigranulocytic inflammation

Around fifty percent of adults with asthma and a smoking history have neutrophilic or paucigranulocytic airway inflammation. T2 low inflammation is associated with a high cumulative exposure to tobacco smoke.[52, 156] Specific drug therapies are not currently available to target T2 low inflammation.

Overview of management

As an aid for clinicians, an algorithm summarizes the key components of the management of current and former smokers with clinical features suggestive of asthma and/or smoking related ACO (figure 5) and emphasizes the central place of smoking cessation for current smokers. Despite limited data on the effectiveness of therapies for current smokers with asthma, pharmacological management is based on GINA recommendations.[42] Overall, published data suggest that smoking status (current versus former smokers),[109, 110, 137] cumulative smoking exposure,[69] and biomarker evidence of T2 high eosinophilic inflammation influence the therapeutic response to pharmacological and biological interventions. Blood eosinophil count should be used to assess T2 status in current and former smokers with poorly controlled asthma despite maintenance medium-dose ICS-LABA combination treatment before considering high dose ICS-LABA and/or biologics (or low dose oral corticosteroids) for those with persistently raised blood eosinophils. Therapeutic

options for patients with persistently poorly controlled asthma despite moderate dose ICS-LABA and T2 low inflammation or with treated T2 high inflammation include add-on LAMA for patients with chronic airflow obstruction, a trial of add-on azithromycin, particularly in former smokers, and bronchial thermoplasty. Management also includes targeting risk factors, behavioral, and extrapulmonary comorbidity treatable traits. In the future, controlled trials and pragmatic trials in real-world populations should include cigarette smokers with asthma to provide evidence on the effectiveness of drug and biological treatments in this subgroup of chronic airway disease.

CONCLUSIONS

Globally, adults with asthma frequently give a history of current or previous cigarette smoking. Current smoking is a risk factor for the development of asthma and worse clinical outcomes including suboptimal asthma control, increased exacerbations, accelerated decline in lung function, persistent airflow obstruction, more comorbidities, and higher all-cause mortality. Although diagnosing asthma in symptomatic younger adults with a smoking history can be straightforward, distinguishing asthma from smoking-related chronic airway diseases such as COPD can be difficult, particularly in older individuals with a long-standing smoking history. Given the substantial risk of diagnostic misclassification in symptomatic smokers, we recommend an approach that involves an assessment of the probability that clinical features are suggestive of a diagnosis of asthma or smoking-related ACO as outlined in the GINA report and that describes clinical, physiological, pathological, and/or biomarker variables and treatable traits. Exposure to cigarette smoke and other risk factors cause pathogenic mechanisms involving smoking and asthma-related airway inflammation, tissue

566 remodeling, corticosteroid insensitivity, and low-grade systemic inflammation. Key
567 components of the management strategy for current smokers with asthma include smoking
568 cessation advice, and targeting risk factors, behavioral, and extrapulmonary comorbidity
569 treatable traits. Despite limited data on the effectiveness of therapies and evidence of
570 reduced sensitivity to ICS treatment, pharmacological management is based on GINA
571 recommendations. T2 high eosinophilic inflammation should be confirmed before a step-up
572 to high dose ICS or the use of biologics. Controlled trials and pragmatic trials are required in
573 real-world populations that include cigarette smokers with asthma to provide data on the
574 effectiveness of drug and biological treatments.
575

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Table 1. Selected studies of the efficacy of inhaled corticosteroid treatment in current smokers with asthma compared to never smokers with asthma

Reference	Study design	Number of participants	Mean age, years	Mean baseline FEV_1% predicted	Mean pack-year history	ICS dose and duration	Main outcome
ICS treatment for ≤3 months							
Chalmers, 2002 [104]	Randomized, placebo-controlled, cross-over	CS/NS 17/21	CS/NS 35/35	CS/NS 87/88	CS 17	FP 1000 µg daily for 3 weeks	Improvement in morning PEF greater in NS than in CS (27 l/min v –5 l/min) (p=0.006). Within-group improvement in FEV_1 (0.17 l), geometric mean PC20 (2.6 doubling dose), and a decrease in the proportion of sputum eosinophils (–1.75%) after FP compared with placebo among NS, with no improvement in these outcomes in CS.
Tomlinson, 2005 [105]	Randomized, parallel-group	CS/NS 40/55*	CS/NS 46/43	CS/NS 86/85	CS/NS 25/3	BDP 400 µg and 2000 µg daily for 3 months	Among those receiving 400 µg daily, the improvement in mean (95% CI) morning PEF (l/min) in CS was less than NS (-25, -45 to -4), p = 0.02). Among those receiving 2000 µg BDP daily, the difference was reduced between CS and NS.
Lazarus, 2007 [106]	Randomized, cross-over	CS/NS 39/44**	CS/NS 29/29	CS/NS 78/80	CS/NS 7/0	BDP 400 µg daily for 8 weeks	Improvement In FEV_1 in NS (170 ml, p=0.0003) and no improvement in CS. Improvement PEF and reduction in sputum eosinophils similar between NS and CS.
Clearie, 2012 [107]	Randomized, controlled, cross-over	CS/NS 15/16	CS/NS 38/39	CS/NS 88/83	CS 14	FP 500 µg daily for 2 weeks	Improvement in methacholine PC_{20} was greater in NS than in CS: 2.5 doubling doses (p<0.01). Improvement in FEV_1 was greater in NS than in CS: 7.9% (p=0.02) Within-group improvement in ACQ in NS, but not in CS.
Telenga, 2013 [69]	Randomized, controlled	CS/FS/NS 30/29/55	CS/FS/NS 27/38/25	CS/FS/NS 78/79/82	CS/FS 7/7	FP 500 µg and 2000 µg daily for 2 weeks	Improvement in FEV_1 was lower in CS compared with NS (p=0.01) and in FS compared to NS (p=0.07). Improvement in FEV_1 in NS of 8% (p<0.001) but no improvement in FEV_1 in CS (2.4%) (p=0.17) or FS (4%) (p=0.07). A higher pack-year history was associated with less improvement in FEV_1.
ICS treatment for ≤1 year							
Pedersen 2007 [109]	*Post hoc* analysis of the GOAL randomized controlled, parallel-group trial	CS/FS/NS 142/306/1259	Total group 40	CS/FS/NS 77/76/77	CS/FS <10	FP up to 1000 µg daily alone or combined with inhaled salmeterol for one year	A higher proportion of CS receiving inhaled medium to high dose FP had severe exacerbations compared to NS (0.35 versus 0.17 per patient per year respectively) (p=0.012)
O'Byrne 2009 [110]	*Post hoc* analysis of the START randomized placebo-controlled	CS/NS 263/1183	CS/NS 32/35	CSNS 88/86	Not recorded	BUD 400 µg daily for 3 years	Improvement in pre- and post-BD FEV_1 was similar in CS and NS.

Dijkstra 2006 [111]	Observational	CS/FS/NS 55/7/60	Total group 28	Total group 85	Total group 0.1	ICS (dose and formulation not specified) for a mean follow-up of 23 years	The decline in FEV_1 was reduced in male CS with <5 pack-year history after ICS, but no effect of ICS on the decline in FEV_1 among women or CS with >5 pack-year history.
Lange, 2006 [112]	Observational	CS/NS 76/158	Total group (range 52 to 58)	Total group 83	Not recorded	ICS (dose and formulation not specified) for 10 years	ICS treatment compared to no ICS treatment associated with a 27 ml per year lower decline in FEV_1 among smokers.
Telenga, 2013 [69]	Observational (Open-label follow-up from randomized, controlled	CS/FS/NS 16/16/32	CS/FS/NS 29/37/25	Not recorded	Not recorded	FP 500 µg and 2000 µg daily for 2 weeks, then FP 500 µg daily group continued for 50 weeks (1 year in total)	Improvement in FEV_1 was similar between NS, CS, and FS groups after 1 year. Improvement in FEV_1 in NS of 10% ($p<0.001$), in FS group of 5% ($p=0.01$) but no improvement in FEV_1 in CS (3%) ($p=0.06$)

Abbreviations: ACQ, asthma control questionnaire; BD, bronchodilator; BDP, beclometasone dipropionate; BUD, budesonide; CS, current smoker; GOAL, Gaining Optimal Asthma Control; NS, never smoker; FEV_1, forced expiratory volume in one second; FS, former smoker; FP, fluticasone propionate; BDP, beclometasone dipropionate; BUD, budesonide; ICS, inhaled corticosteroid; PC_{20} provocative concentration that produced a 20% fall in FEV_1; PD_{15}, provocative dose that produced a 15% fall in FEV_1; PEF, peak expiratory flow; START, inhaled Steroid Treatment As Regular Therapy;

Symbols: *Study included a small number of non-smokers defined as follows: stopped smoking over 5 years ago and had smoked $\leq$5 pack-year; ** Study included a small number of non-smokers defined as follows: stopped smoking at least 1 years ago and had smoked <2 pack-year

FIGURES

Figure 1: Summary of adverse clinical outcomes in current smokers with asthma compared to never smokers with asthma.
Acknowledgment: Created with BioRender.com.

Figure 2: The average annual rate of decline in FEV_1 of a typical 49-year-old heavy smoker and never smoker with and without asthma according to sex.

Legend: Reference indicates lifetime never smokers without asthma. Created from James et al.[34]

Figure 3: Asthma smoking phenotypes identified from cluster analysis studies that included current and former smokers with asthma.

***** Summary data from cluster analysis studies that included current and former smokers with asthma [50-61]

Acknowledgment: Created with BioRender.com.

Figure 4: Schematic diagram illustrating potential inflammatory pathways underlying airway immunopathology of asthma in adults with a smoking history.

Legend: Exposure to cigarette smoke, which contains high concentrations of reactive oxygen species (ROS), activates airway epithelial cells to synthesize proinflammatory mediators such as IL-8 and IL-1β, which recruit and/or activate neutrophils, macrophages, and $CD8^+$ cytotoxic T cells (Tc1) cells. Activated neutrophils secrete ROS, proteases, and inflammatory mediators, such as matrix metalloproteinase (MMP)s, and can form neutrophil extracellular traps (NETs). Excessive NET formation (NETosis) induces Th17 responses that contribute to neutrophilic inflammation. Activated macrophages secrete proteases, MMPs, and chemokines that attract neutrophils, Th17, Th1 cells, and Tc1 cells. Th17 cells are chemotactic to neutrophils, Tc1 cells secrete serine protease granzyme B and Th1 cells release IFNγ. Current cigarette smoking in asthma is likely to induce predominately non-T2 inflammation, although T2 high eosinophilic inflammation may coexist due to allergen-induced pathways, NETosis causing DNA induced T2 responses, and cigarette-smoke induced release of alarmins such as IL-33, thymic stromal lymphopoietin (TSLP), IL-25. Exposure to allergens in sensitized individuals and the release of alarmins from injured epithelial cells activate Th2 cells and type 2 innate lymphoid cells (ILC2) respectively to release T2 cytokines IL-4, IL-5, and IL-13. Dendritic cells process antigens and when activated by alarmins can initiate T2 immunity. IL-4 causes immunoglobulin E (IgE) production from B cells and IL-5 recruits and activates eosinophils. Smoking and asthma-related inflammation cause T2 high and/or T2 low inflammation, tissue remodeling, corticosteroid insensitivity, and impaired host responses, which together contribute to adverse clinical outcomes in current and former smokers with asthma.

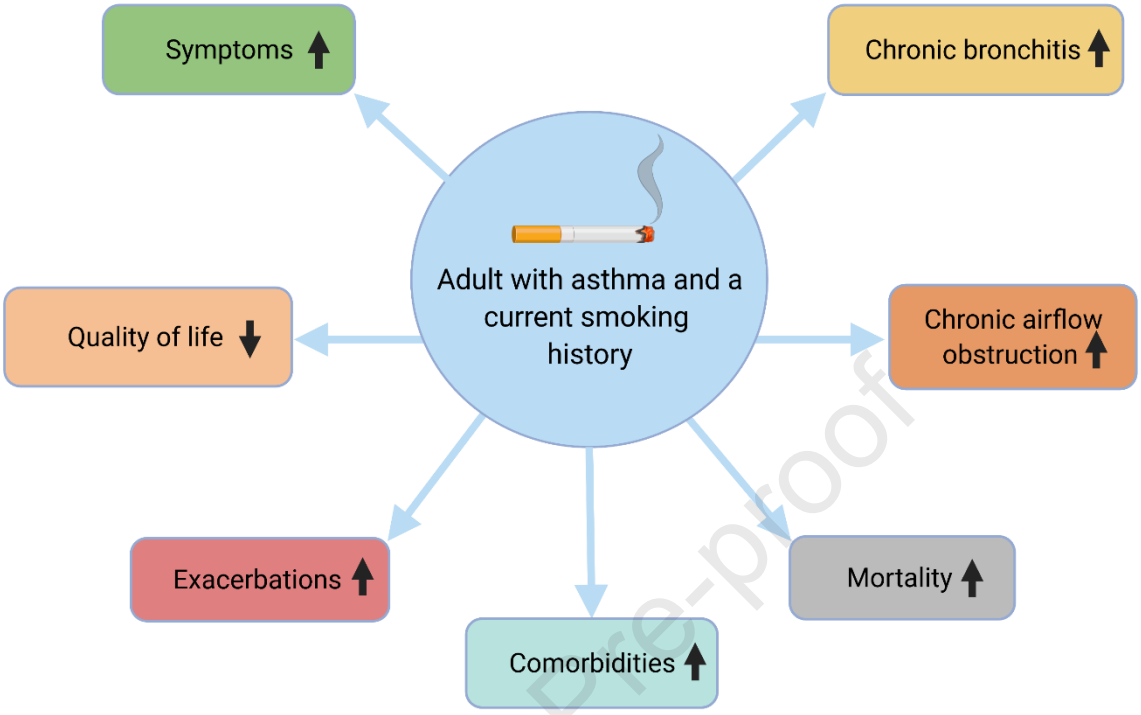
Abbreviations: IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cell, MMPs, matrix metalloproteinase; NET, neutrophil extracellular trap; NETosis, neutrophil extracellular trap formation; NK, natural killer; PGD_2, prostaglandin D_2; Tc1, $CD8^+$ cytotoxic T cells; TNF, tumor necrosis factor; ROS, reactive oxygen species; Th2, T helper 2; TSLP, thymic stromal lymphopoietin; T2, type 2 inflammation

Acknowledgment: Created with BioRender.com.

Figure 5: Algorithm for the management of current and former smokers with clinical features suggestive of asthma.

Legend:
* Some patients may have clinical features suggestive of smoking-related ACO. There is a risk of diagnostic misclassification of chronic airway disease such as COPD in symptomatic current and former smokers, particularly in older age groups.
Key components of management:
① *Smoking cessation or relapse prevention advice:* smoking cessation advice is a priority component of management among current smokers; relapse prevention advice is an option for recent quitters.[157]
② *Pharmacological management:* based on Global Initiative for Asthma recommendations, although data is limited on the effectiveness of therapies for current smokers with asthma and there is evidence of corticosteroid insensitivity to ICS treatment.
③ *Assess T2 status:* Among current or former smokers with poorly controlled asthma despite moderate dose ICS-LABA who have T2 high eosinophilic inflammation (raised blood eosinophil count), consider high dose ICS-LABA and/or biologics (or low dose oral corticosteroids). Therapeutic options for patients with persistently poorly controlled asthma associated with T2 low inflammation or associated with treated T2 high inflammation include add-on LAMA for patients with chronic airflow obstruction, a trial of add-on azithromycin, particularly in former smokers, and bronchial thermoplasty.
④ *Target risk factors and behavioral treatable traits:* such as non-adherence, poor inhaler technique, and infection risk
⑤ Target *extrapulmonary co-morbidities:* disease-specific treatment.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta-agonist; T2 inflammation, type 2 inflammation



Symbols: ↑ increased or ↓ decreased compared to never-smoker with asthma