Clinical Management Review

Cigarette Smoking and Asthma

Neil C. Thomson, MD[a], Riccardo Polosa, MD[b,c,d], and Don D. Sin, MD[e] *Glasgow, United Kingdom; Catania, Italy; and Vancouver, BC, Canada*

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List of Design Committee Members: Neil C. Thomson, MD, Riccardo Polosa, MD, and Don D. Sin, MD (authors); Robert S. Zeiger, MD, PhD (editor)

Learning objectives:

1. To describe the adverse clinical outcomes associated with cigarette smoking in asthma.
2. To recognize the main issues that clinicians should consider when making a diagnosis of asthma in adults with a smoking history.
3. To identify mechanisms linking cigarette smoking with adverse health outcomes in patients with asthma.
4. To describe a management plan for symptomatic current and former smokers with asthma.

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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

[a]Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, United Kingdom
[b]Department of Clinical & Experimental Medicine, University of Catania, Catania, Italy
[c]Centre for the Prevention and Treatment of Tobacco Addiction (CPCT), Teaching Hospital "Policlinico-V. Emanuele", University of Catania, Catania, Italy
[d]Center of Excellence for the Acceleration of HArm Reduction (CoEHAR), University of Catania, Catania, Italy
[e]Division of Respirology, Department of Medicine, Centre for Heart Lung Innovation, St. Paul's Hospital, University of British Columbia, Vancouver, BC, Canada

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Corresponding author: Neil C. Thomson, MD, Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow G12 OYN, United Kingdom. E-mail: neil.thomson@glasgow.ac.uk.
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Abbreviations used

ACO- Asthma-COPD overlap
AHR- Airway hyperreactivity
COPD- Chronic obstructive pulmonary disease
CT- Computed tomography
FeNO- Fractional concentration of exhaled nitric oxide
FEV_1- Forced expiratory volume in 1 second
GINA- Global Initiative for Asthma
GR- Glucocorticoid receptor
ICS- Inhaled corticosteroid
LABA- Long-acting β_2-agonist
LAMA- Long-acting muscarinic antagonist
MART- Maintenance and reliever therapy
T2 inflammation- Type 2 inflammation
WHO- World Health Organization

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 the 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. **(J Allergy Clin Immunol Pract 2022;10:2783-97)**

Key words: *Asthma; Asthma–chronic obstructive pulmonary disease overlap; Chronic obstructive pulmonary disease; Cigarette smoking; Smokers with asthma; Smoking cessation*

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 because of 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 50% 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 with 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 with 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

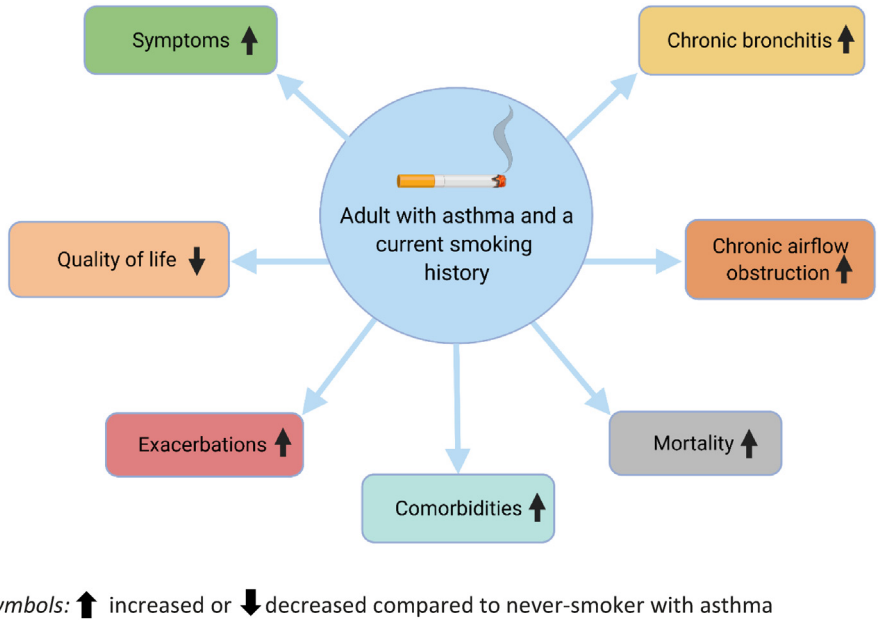

FIGURE 1. Summary of adverse clinical outcomes in current smokers with asthma compared with never smokers with asthma. Created with BioRender.com.

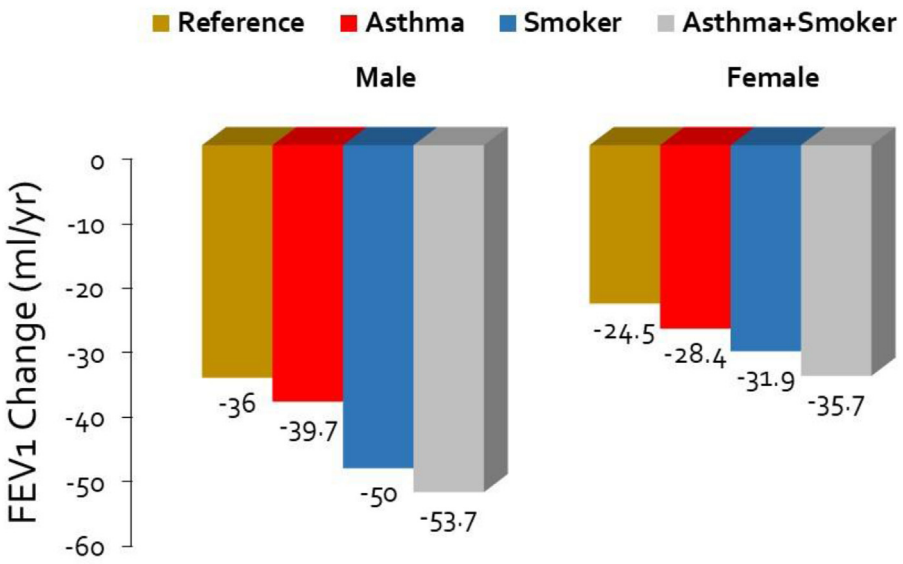

FIGURE 2. The average annual rate of decline in FEV_1 of a typical 49-year-old heavy smoker and never smoker with and without asthma according to sex. Reference indicates lifetime never smokers without asthma. *FEV_1*, Forced expiratory volume in 1 second. Created from James et al.[34]

late-onset asthma subgroup (25-fold increase) compared with 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 with 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,

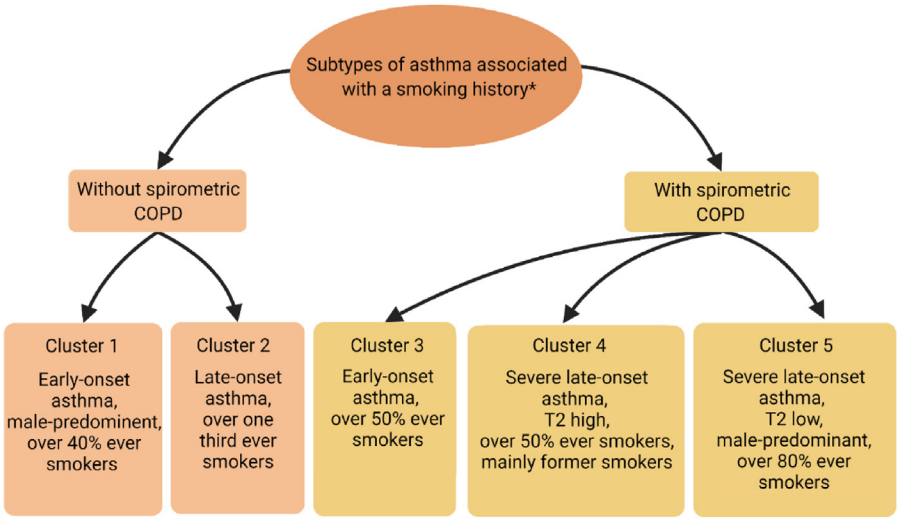

FIGURE 3. Asthma smoking phenotypes identified from cluster analysis studies that included current and former smokers with asthma. COPD, Chronic obstructive pulmonary disease. *Summary data from cluster analysis studies that included current and former smokers with asthma.[50-61] Created with BioRender.com.

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 Global Initiative for Asthma (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 nonatopic 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 toward 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

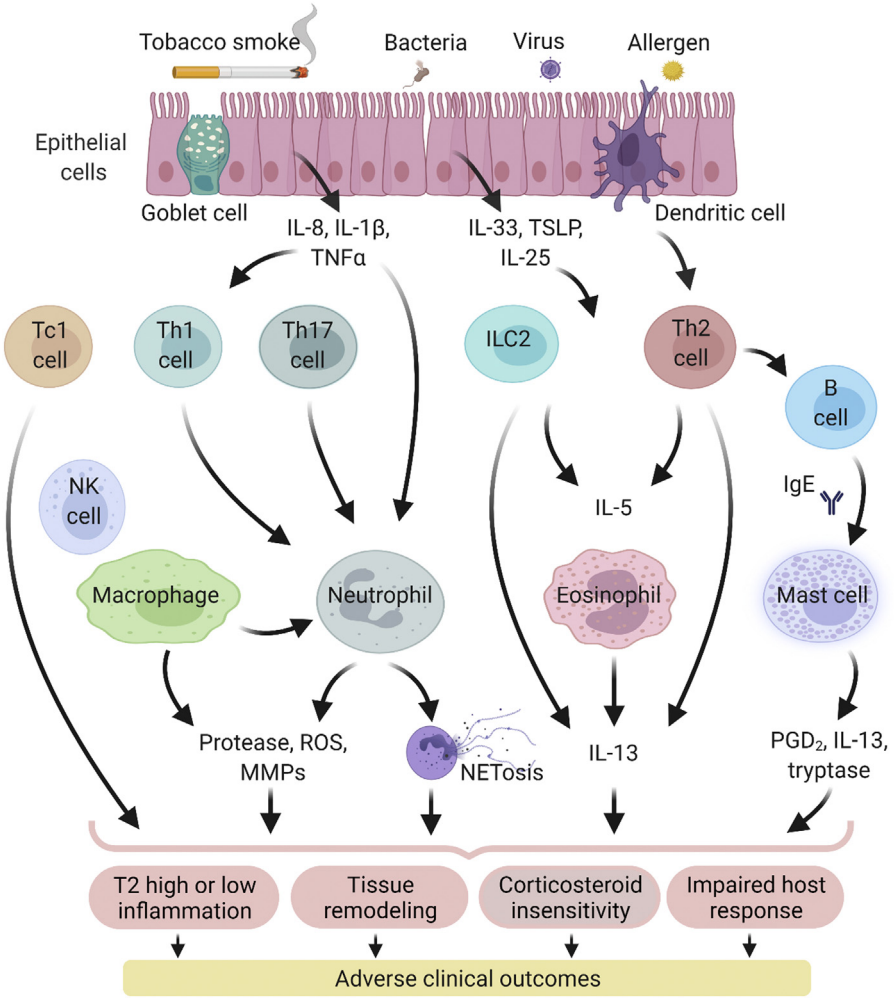

FIGURE 4. Schematic diagram illustrating potential inflammatory pathways underlying airway immunopathology of asthma in adults with a smoking history. Exposure to cigarette smoke, which contains high concentrations of reactive oxygen species (ROS), activates airway epithelial cells to synthesize proinflammatory mediators such as IL-8 and IL-1β, which recruit and/or activate neutrophils, macrophages, and $CD8^+$ cytotoxic T cells (Tc1). Activated neutrophils secrete ROS, proteases, and inflammatory mediators, such as matrix metalloproteinase (MMPs), and can form neutrophil extracellular traps (NETs). Excessive NET formation (NETosis) induces T helper (Th)17 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), and 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 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. *NK*, natural killer; *PGD_2*, prostaglandin D_2; *T2*, type 2 inflammation. Created with BioRender.com.

inflammation. In addition, 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 with 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 because increased goblet cell 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]

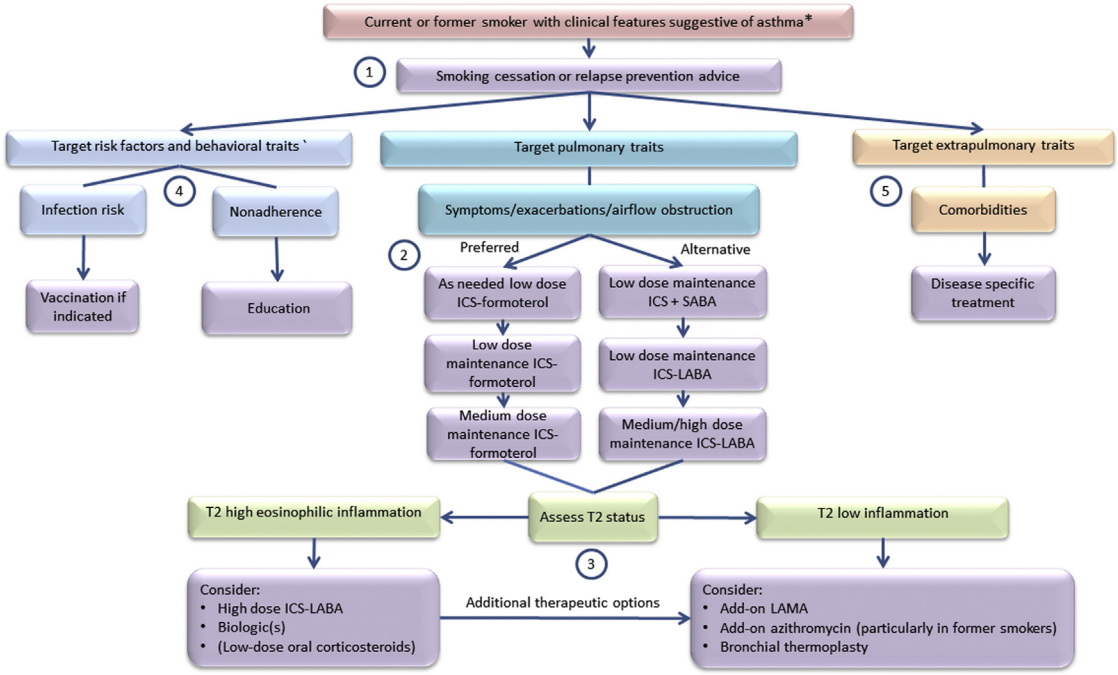

FIGURE 5. Algorithm for the management of current and former smokers with clinical features suggestive of asthma. *Some patients may have clinical features suggestive of smoking-related ACO. There is a risk of diagnostic misclassification of chronic airway disease such as COPD in symptomatic current 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.[90] ② *Pharmacological management:* based on Global Initiative for Asthma recommendations, although data are 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 nonadherence, poor inhaler technique, and infection risk. ⑤ *Target extrapulmonary comorbidities:* disease-specific treatment. *ICS*, inhaled corticosteroid; *LABA*, long-acting β-agonist; *LAMA*, long-acting muscarinic antagonist; *SABA*, short-acting β-agonist; *T2 inflammation*, type 2 inflammation.

suggesting reversal of epithelial cell remodeling after 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 with 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 cells.[84] Exposure to allergens in sensitized individuals or other stimuli induces proinflammatory mediator release from activated eosinophils, T helper 2 cells, type 2 innate lymphoid cells, 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 because of refractory eosinophilic, neutrophilic, or paucigranulocytic airway inflammation, in addition to other causes such as nonadherence. 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 proinflammatory

TABLE I. Selected studies of the efficacy of inhaled corticosteroid treatment in current smokers with asthma compared with never smokers with asthma

Reference	Study design	No. of participants	Mean age (y)	Mean baseline FEV_1% predicted	Mean pack-year history	ICS dose and duration	Main outcome
ICS treatment for ≤3 mo							
Chalmers, 2002[105]	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 wk	Improvement in morning PEF greater in NS than in CS (27 L/min vs −5 L/min) ($P = .006$) Within-group improvement in FEV_1 (0.17 L), geometric mean PC_{20} (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[106]	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 mo	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) ($P = .02$). Among those receiving 2000 μg BDP daily, the difference was reduced between CS and NS
Lazarus, 2007[107]	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 wk	Improvement in FEV_1 in NS (170 mL, $P = .0003$) and no improvement in CS Improvement in PEF and reduction in sputum eosinophils similar between NS and CS
Clearie, 2012[108]	Randomized, controlled, cross-over	CS/NS 15/16	CS/NS 38/39	CS/NS 88/83	CS 14	FP 500 μg daily for 2 wk	Improvement in methacholine PC_{20} was greater in NS than in CS: 2.5 doubling doses ($P < .01$) Improvement in FEV_1 was greater in NS than in CS: 7.9% ($P = .02$) 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 wk	Improvement in FEV_1 was lower in CS compared with NS ($P = .01$) and in FS compared with NS ($P = .07$) Improvement in FEV_1 in NS of 8% ($P < .001$) but no improvement in FEV_1 in CS (2.4%) ($P = .17$) or FS (4%) ($P = .07$) A higher pack-year history was associated with less improvement in FEV_1
ICS treatment for ≤1 y							
Pedersen, 2007[110]	*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 1 y	A higher proportion of CS receiving inhaled medium- to high-dose FP had severe exacerbations compared with NS (0.35 vs 0.17 per patient per year, respectively) ($P = .012$)

(continued)

TABLE I. *(Continued)*

Reference	Study design	No. of participants	Mean age (y)	Mean baseline FEV_1% predicted	Mean pack-year history	ICS dose and duration	Main outcome
O'Byrne, 2009[111]	*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 y	Improvement in pre- and post-BD FEV_1 was similar in CS and NS
Dijkstra, 2006[112]	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 y	The decline in FEV_1 was reduced in male CS with a <5-pack-year history after ICS, but no effect of ICS on the decline in FEV_1 among women or CS with a >5-pack-year history
Lange, 2006[113]	Observational	CS/NS 76/158	Total group (range 52 to 58)	Total group 83	Not recorded	ICS (dose and formulation not specified) for 10 y	ICS treatment compared with 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 wk, then FP 500 μg daily group continued for 50 wk (1 y in total)	Improvement in FEV_1 was similar between the NS, CS, and FS groups after 1 y Improvement in FEV_1 in NS of 10% ($P < .001$), in FS of 5% ($P = .01$), but no improvement in FEV_1 in CS (3%) ($P = .06$)

ACQ, Asthma Control Questionnaire; *BD*, bronchodilator; *BDP*, beclometasone dipropionate; *BUD*, budesonide; *CI*, confidence interval; *CS*, current smoker; *FEV_1*, forced expiratory volume in 1 second; *FP*, fluticasone propionate; *FS*, former smoker; *GOAL*, Gaining Optimal Asthma Control; *ICS*, inhaled corticosteroid; *NS*, never smoker; *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.

*Study included a small number of nonsmokers defined as follows: stopped smoking over 5 years ago and had smoked ≤5 pack-years.

†Study included a small number of nonsmokers defined as follows: stopped smoking at least 1 year ago and had smoked <2 pack-years.

transcription factors activity, such as nuclear factor-κB, or decreased histone deacetylase activity 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. 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 because 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,[91-93] asthma-related quality of life,[91] lung function,[93] and AHR.[91,92] Furthermore, former smokers with asthma often have better symptom control than current smokers.[21,94] 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.[95] Cigarette smokers with asthma and COPD are no more likely to receive smoking cessation counseling and pharmacotherapy from physicians compared with the general smoking population.[96] Cigarette smoking quit rates are improved with behavioral counseling in combination with pharmacotherapies, such as nicotine replacement products, varenicline, and bupropion.[97] A tailored approach to the smoking cessation of the smokers with asthma has been described previously.[98,99] Although 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.[100,101]

Targeting nonadherence, poor inhaler technique, and infection risk

Cigarette smoking has been associated with poorer adherence to drug therapies for asthma in some[102] but not all studies.[103] 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.[104] 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 (ICS). 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 with never smokers (Table I).[69,105-108] 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,[106] 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.[109] A *post hoc* analysis of the 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 with never smokers with asthma.[110] Data from a *post hoc* analysis of the inhaled Steroid Treatment as Regular Therapy trial in recent-onset mild asthma[111] and observational studies[112,113] 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.[112] Two systematic reviews have shown that current smoking was associated with a reduced improvement in forced expiratory volume in 1 second (FEV_1) after low- and high-dose ICS treatment compared with nonsmokers.[114,115] Exploratory analysis of the 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 1 year's treatment with extra-fine-particle ICS compared with standard-particle ICS,[116] although other studies have not found better outcomes with extra-fine-particle ICS in current smokers with asthma.[117] Data from one study in asthma have shown that a higher pack-year history was associated with reduced improvement in FEV_1 after 2-week 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 with 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[110,111] or COPD[118-120] 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.[121-124] 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.[125]

Maintenance low- to high-dose ICS-long-acting β-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.[108,110,117] Data on the effectiveness of low-dose ICS-LABA maintenance treatment, including extra-fine particle ICS-LABA,[126] are limited to findings from a small number of observational studies.

ICS-LABA maintenance and reliever therapy (MART) regimen. A study of medium-dose maintenance budesonide/formoterol (200/6 μg) 2 puffs twice daily showed that the reduction in severe exacerbations with low-dose budesonide/formoterol (200/6 μg) 1 puff (MART regimen) compared with short-acting β_2-agonist 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.[127] A 6-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) 2 puffs twice daily compared with 1 inhalation twice daily suggesting that a higher maintenance dose of budesonide/formoterol may be required in smokers with asthma.[128] 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.[129] 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.[130] A randomized cross-over trial in 16 current smokers with asthma found that the addition of tiotropium to medium-dose ICS-LABA improved through small airway flow rates, but had no added effect on symptoms or reliever use.[131] 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 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 with 663 adults without ACO, of whom two-thirds were never smokers.[132] 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.[133] 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.[134] Collectively, these data and other observational studies[117] provide low-certainty evidence of clinical benefits from treatment with anti−immunoglobulin E (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.[135] The 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 with placebo.[136] In COPD, daily azithromycin decreased acute exacerbations in former smokers, but not in current smokers.[137] 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 with never smokers.[138,139] 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.[140] 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.[107,141] 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-years), whereas a better response to medium-dose ICS was shown in those with lower cumulative exposure to tobacco smoke (≤11 pack-years).[142]

Drugs used to treat symptoms of chronic bronchitis, such as thiol compounds[143] and the phosphodiesterase 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[144,145] or low-dose theophylline[146] 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.[147] Blood eosinophil numbers in current smokers with asthma can be increased,[148] reduced,[69] or similar[7,21,149] 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.[150] 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 nonsmokers) and ICS use in smoking-related COPD. Based on these findings, it is likely that blood eosinophils can also be 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,[151] whereas most studies in asthma have found that total IgE levels are not influenced by smoking status.[7,21] Smoking is associated with a reduced sensitization to common aeroallergens,[152] except for increased sensitization house dust mites in some studies.[21,152]

T2-high eosinophilic inflammation. Over one-third of current smokers with asthma have biomarker evidence of T2-high inflammation.[147,153,154] In a large UK primary care asthma cohort, of whom over 50% were current and former smokers, a multidimensional eosinophil algorithm classified an eosinophilic phenotype in the majority.[155] Current and former smokers with poorly controlled asthma despite moderate-dose ICS-LABA who have persistently raised blood eosinophils should be considered for high-dose ICS-LABA and/or biologics. The optimum blood eosinophil count cutoff value for high-dose ICS or biologic treatment is uncertain in smokers with asthma. In smoking-related COPD, the addition of ICS to LABA or LABA and LAMA reduced moderate and severe exacerbations[118,119] at all blood eosinophil counts among former smokers, but among current smokers, clinical benefits were lacking at lower eosinophil counts (<200 cells/μL), whereas exacerbations were reduced at higher eosinophil counts (>200 cells/μL).[118,119] In smoking-related ACO, observational data suggested that a blood eosinophil count of >300 cells/μL predicted a decrease in exacerbations with ICS.[156] Possible blood eosinophil values predicting ICS responsiveness in current smokers with asthma are >300 cells/μL, good ICS response; >100 to 300 cells/μL, uncertain ICS response; and ≤100 cells/μL, low probability of ICS response. Collectively, these findings suggest that former smoking status and elevated blood eosinophil count may predict ICS responsiveness 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 50% 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.[52,157] 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 vs former smokers),[110,111,138] 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, and 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 biologic 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 remodeling, corticosteroid insensitivity, and low-grade systemic inflammation. The key components of the management strategy for current smokers with asthma include smoking cessation advice, targeting risk factors, and behavioral and extrapulmonary comorbidity treatable traits. Despite limited data on the

effectiveness of therapies and evidence of reduced sensitivity to ICS treatment, pharmacological management is based on GINA recommendations. T2-high eosinophilic inflammation should be confirmed before a step-up to high-dose ICS or the use of biologics. Controlled trials and pragmatic trials are required in real-world populations that include cigarette smokers with asthma to provide data on the effectiveness of drug and biologic treatments.

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