Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Asthma & COPD Guidelines Review***
-May 2019-

Background:

In May 2019, the National Pharmacy and Therapeutics Committee (NPTC) reviewed the current guidelines as well as different classes of drugs with indications for asthma and COPD to determine if changes to the IHS National Core Formulary were necessary. The NCF currently lists the following medications for use in asthma and/or COPD: mometasone, mometasone/formoterol, and tiotropium.

Discussion:

Asthma:

Asthma is chronic disease characterized by airway inflammation and obstructive limitations in expiratory airflow due to bronchoconstriction as well as airway edema, vascular congestion, and luminal occlusion. As airways constrict there is an increase in airway resistance resulting in wheezing and leading to airway closure, air trapping, and lung hyperinflation. Drug targets for therapy include inflammation and airway hyper-responsiveness. In 2004, the global burden of asthma report estimated 300 million people of all ages suffer from asthma and projected that by 2025 the prevalence would increase to 400 million worldwide. American Indian/Alaska Native (AI/AN) children are the 2nd most likely racial group to have an asthma diagnosis (12.9%) and AI/AN adults are the 3rd most likely racial group to have ever been diagnosed (10%) and still carry the diagnosis (7.7%) of asthma. The death rate among AI/AN from asthma is 1.1 per 100,000 compared to 0.9 per 100,000 among non-Hispanic white Americans.

The diagnosis of asthma is based on the frequency of clinical symptoms (daytime wheeze, nighttime cough) as well as documented airflow limitations through pulmonary function testing (PFT) or peak expiratory flow (PEF, less reliable) with or without a bronchodilator or methacholine challenge. Classification of asthma severity (intermittent versus mild/moderate/severe persistent) is essential for directing a stepwise approach to asthma treatment. Various guidelines exist for the treatment of asthma, including the NIH National Asthma Education and Prevention Program (NAEPP), the WHO Global Initiative for Asthma (GINA), and the British National Institute for Health and Care Excellence (NICE). These guidelines all promote early diagnosis based on history, physical examination, and clinical testing; reassessment every 3-6 months for treatment optimization; reduction in modifiable risk factors and exposures to triggers; education, evaluation and reinforcement of proper inhaler use at every visit; assessment of potential side effects of treatment; and de-escalation of therapy when possible.

The NAEPP guideline provides detailed guidance for age-based stepwise therapy. For pediatric patients 0-4 years, intermittent asthma requires only a short acting beta agonist (SABA) as needed. For mild persistent asthma, low dose inhaled corticosteroids (ICS) should be added. Progressive intensification of therapy in a stepwise manner is based on clinical worsening and/or lack of improvement in measurements of expiratory airflow. Increased ICS dose is recommended first, followed by addition of a long-acting beta agonist (LABA) or montelukast, reserving oral corticosteroids (OCS) as the last line of therapy to control severe-persistent asthma. Safety and efficacy of ICS for children under 1 year of age have not been established. Children younger than 4 years of age typically need to have their inhalers delivered via a face mask that fits snugly over the nose and mouth. For ages 5-11, intermittent asthma is again managed with a SABA as needed. Diagnosis of persistent asthma requires ICS therapy in an appropriate dose, based on severity. This may be followed by introduction of a long acting beta-2 agonist (LABA), a leukotriene modifier/leukotriene receptor agonist (LTRA), and theophylline as warranted by symptom frequency and/or measurement of airway obstruction. OCS may be required for severe-persistent asthma.

The management of adult asthma is similar with the exception that omalizumab may be considered prior to adding OCS for patients suspected to have an allergic component to their asthma. If clear benefit is not demonstrated within 4-6 weeks and medication technique and adherence is satisfactory, then adjustment of therapy or alternate diagnoses should be considered. The NICE and GINA guidelines are similar to the NAEPP guideline in the stepwise approach to asthma management. One notable exception is that GINA now recommends that all adults and adolescents with asthma should receive either symptom-driven (in mild asthma) or daily low-dose ICS-containing controller treatment, to reduce their risk of serious exacerbation. GINA has also developed guidelines for the management of difficult-to-treat and severe asthma. Difficult-to-treat asthma is defined as uncontrolled symptoms despite GINA step 4 or 5 treatment (medium or high dose

ICS with a second controller; or need for OCS). Severe asthma is a subset of difficult-to-treat asthma defined as uncontrolled despite maximal optimized therapy and treatment of contributing factors, or asthma that worsens when high-dose treatment is tapered. Of note, many cases of asthma may appear difficult to treat because of modifiable factors such as incorrect inhaler technique, poor adherence, smoking, comorbidities, or because the diagnosis is incorrect. Once a patient is thought to have "severe persistent asthma," the next step is to assess phenotype, factors contributing to symptoms, quality of life, and exacerbations. Presence or absence of type 2 inflammation (~50% of asthma patients) characterized by atopy, eosinophils, and over-activation of the IL-4 inflammatory cytokine pathway determines the next step in therapy. For non-type 2 severe disease, recommendations are to: (1) review techniques with inhalers, adherence, and modifiable risk factors, (2) prescribe a trial of non-biologic add-on therapy, (3) consider daily low dose OCS and, (4) evaluate for thermal bronchoplasty. For patients with type 2 inflammation, biologic therapy may be considered, in consultation with an asthma specialist.

COPD:
Chronic Obstructive Pulmonary Disease (COPD) is characterized by partially-reversible airflow limitation with pathophysiologic features including emphysema (destruction and enlargement of alveoli), chronic bronchitis (chronic cough and phlegm production), and/or small airways disease (narrowing of small bronchioles). Pathologic diagnosis is aided by clinical testing which demonstrates persistent reduction in forced expiratory flow rates (FEV1) as well as increases in residual volume, non-uniform distribution of ventilation, and ultimately ventilation-perfusion mismatch. Risk factors for COPD include cigarette smoking, airway hyper-responsiveness, occupational exposures (mining, cotton textile dust), smoke due to biomass combustion (indoor cooking or wood/coal stove heating), and alpha-1 anti-trypsin deficiency. Prevalence of COPD in the US in 2017 was 1.2% in the general population and 0.8% in the American Indian/Alaska Native (AI/AN) population. COPD is twice as common among people with low family income, residence outside a major metropolitan area, and/or enrollment in Medicaid or Medicare.

The diagnosis of COPD is based on a combination of clinical examination (presence of prolonged expiratory phase, expiratory wheezing, hyperinflation, accessory muscle use) and spirometry measurement (FEV1 [Forced Expiratory Volume], FVC [Forced vital capacity], FEV1/FVC ratio). Symptoms of an exacerbation include increased respiratory symptoms (dyspnea, cough), sputum or sputum purulence, and need for PRN controller medications. COPD exacerbations negatively impact quality of life, accelerate disease progression, promote hospitalization, and increase risk of death. Prevention of exacerbation is therefore the focus of most COPD therapies. Correct diagnosis and classification of severity of disease is essential for proper treatment.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has developed both diagnostic criteria and treatment guidelines. For stable COPD, treatment goals include prevention of disease progression through reduction in symptoms, prevention and treatment of exacerbation, and mortality reduction.

GOLD classification of airflow limitation permits categorization of disease severity with the following criteria:
GOLD 1 (mild) = FEV1 ≥ 80% of predicted
GOLD 2 (moderate) = FEV1 < 80% and ≥ 50% of predicted
GOLD 3 (severe) = FEV1 < 50% and ≥ 30% of predicted
GOLD 4 (very severe) = FEV1 < 30% of predicted

Once diagnosis is determined using the GOLD classification based upon spirometry data, clinical symptom assessment is necessary to assess the level of therapy indicated.

Patients complete a COPD Assessment Test (CAT) to determine disease category, including the following;
Category A (0-1 exacerbation per year and CAT score <10)
Category B (0-1 exacerbations per year and CAT score ≥ 10)
Category C (2-3 exacerbations per year and CAT score <10)
Category D (2-3 exacerbations per year and CAT score ≥ 10).

All group A patients should be offered bronchodilator treatment (either a SABA or LABA) based on its effect on breathlessness. For group B patients, initial therapy should consist of a LABA or long acting muscarinic antagonist (LAMA). Long-acting inhaled bronchodilators are superior to short-acting bronchodilators when used on an as-needed basis. In group B patients with severe breathlessness, initial therapy with two bronchodilators may be considered. Group C patients should initially be placed on LAMA monotherapy, but LABA monotherapy is also acceptable if LAMA is contraindicated or not tolerated. For group D, initial therapy

should be a LAMA for improvement of both breathlessness and exacerbations. In more symptomatic group D patients, initial therapy with combination LAMA/LABA may be appropriate.

In patients whose blood eosinophil counts are ≥ 300 cells/µL, initial therapy with combination LABA/ICS may be the first choice, although consideration of increased risk of pneumonia should be weighed against benefits of therapy. In general, GOLD guidelines for inhaled bronchodilators are as follows: LABA and LAMA are recommended over short acting agents except in patients with occasional dyspnea, inhaled bronchodilators are recommended over oral bronchodilators, and theophylline is not recommended unless other long-term bronchodilator therapy is unavailable or unaffordable. With regards to anti-inflammatory agents, GOLD guidelines do NOT recommend monotherapy with ICS, though they may be considered as add-on therapy in patients with a history of multiple exacerbations despite appropriate use of long acting bronchodilators. Long term therapy with OCS is not recommended.

Additional guidelines have been published by the British National Institute for Health and Care Excellence (NICE), European Respiratory Society/American Thoracic Society (ERS/ATS), American College of Chest Physicians (CHEST), and the Canadian Thoracic Society (CTS). These guidelines differ from GOLD criteria by promoting use of SAMA and SABA for prevention of mild to moderate COPD exacerbations.

The CHEST/CTS guidelines recommend use of a SAMA (compared with SABA monotherapy) to prevent acute mild-moderate exacerbations of COPD for patients with mild to moderate disease. Patients with moderate to severe disease should be treated with SAMA plus SABA (compared with SABA alone) to prevent acute exacerbations.

Recommendations for the treatment of acute exacerbations vary between guidelines. All guidelines recommend OCS for acute exacerbation although there is no consensus regarding duration or dose. Antibiotics are recommended for exacerbations depending on presenting symptoms and local sensitivity patterns, but no consensus exists on duration or selection of agent. Prophylactic antibiotic therapy is recommended only by NICE and CHEST/CTS, with varying criteria.

NICE, CHEST/CTS and GOLD guidelines also provide recommendations regarding non-inhaled therapeutic options for COPD. Phosphodiesterase Type 4 Inhibitors (PDE-4i) are recommended by all three for patients with moderate to severe COPD with more than 1-2 exacerbations or 1 hospitalization in the previous year. Theophylline is recommended by NICE only after failure of SABA and LABAs or in patients who cannot tolerate inhaled therapy. The CHEST/CTS guideline recommends theophylline for stable patients who need additional treatment to prevent exacerbation. The GOLD guideline states that there is limited evidence favoring theophylline and cautions against use based on a narrow therapeutic window. The GOLD guideline does not recommend mucolytics, including N-acetyl-cysteine and carbocysteine. The NICE guideline recommends consideration of mucolytics in patients with chronic productive cough. The CHEST/CTS guideline recommends mucolytics in stable outpatients with acute exacerbations despite maximal therapy.

Findings:

Asthma guidelines promote strategies to establish a correct diagnosis and determine the level of severity. A stepwise approach to therapy is advocated, ensuring adherence and proper inhaler use prior to intensifying treatment, while addressing modifiable risk factors. SABA, ICS, and LABA are all advocated as initial treatments based on disease severity. Secondary agents include theophylline, montelukast, cromolyn, and LTRA, without consensus on guidelines for use. Biologic therapies are recommended in severe, persistent asthma, also without consensus on guidelines for use.

In summarizing contemporary COPD guidelines, the following generalizations can be made. Correct diagnosis requires thorough evaluation, including history, physical examination, and pulmonary function testing. Thereafter, guidelines promote frequent re-evaluation of symptom control as well as assessment of proper inhaler use prior to treatment escalation. ICS monotherapy is not appropriate for long term control in COPD patients. OCS should be used for all COPD exacerbations. Antibiotics are indicated for most COPD exacerbations, while there is no consensus on preventive use of macrolides. A PDE-4i is recommended by all guidelines for severe, difficult to control disease. There is no consensus regarding use of theophylline or mucolytic drugs.

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