

Pharmacological Treatment in Asthma and COPD

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ABSTRACT

Many lines of previous studies have reported that differences and similarities between bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD). The pathological and physiological abnormalities of these diseases have been also discussed. BA and COPD have some similarities such as airflow obstruction, pulmonary inflammation, and airway hyperresponsiveness (AHR). However, both two diseases are regarded different diseases since their mechanisms of development are quite different. Therefore, both two diseases require different assessment, monitoring, and pharmacological treatments. In this paper, we describe the pharmacological treatment of asthma in adults and COPD based on recently updated guideline by the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD), respectively.

KEY WORDS

asthma, bronchodilators, COPD, inhaled glucocorticosteroids

PHARMACOLOGICAL TREATMENT FOR STABLE ASTHMA IN ADULTS (GREATER THAN OR EQUAL TO 12 YEARS OF AGE)

Since BA has airflow obstruction due to airway inflammation and hyperresponsiveness, anti-inflammatory therapy and bronchodilating therapy should be considered.¹ Airway inflammation in BA responds to steroid very well, thus inhaled glucocorticosteroids are the first choice for the treatment for BA. Assessment should address daytime symptoms, nighttime symptoms, use of short acting inhaled beta agonists to relieve symptoms, and difficulty in performing normal activities and exercise at each visit. A simplified scheme for recognizing controlled, partly controlled and uncontrolled asthma has been published by GINA¹ (Table 1). The management approach to pharmacological treatment is based on increasing medications until asthma is controlled, and decreasing medications when possible to minimize side effects. The patient's management should be adjusted, if needed, at every visit¹ (Fig. 1). For example, if asthma is not controlled on the current regimen, treatment should be stepped up until control is achieved. If control has been maintained for at least three months, treatment can be stepped down. The

scheme of the pharmacological treatment for BA is shown in Figure 2.¹ Commonly used drugs including bronchodilators and glucocorticosteroids are shown in Table 2.

Intermittent (Step 1): Patients with mild intermittent asthma are best treated with a short-acting inhaled beta-2-selective agonist such as salbutamol and procaterol, taken as needed for relief of symptoms.

Mild persistent (Step 2): The distinction between intermittent and mild persistent asthma is important, because the GINA guideline calls for initiation of long-term controller medication in patients with mild persistent asthma.¹ The preferred long-term controller for mild persistent asthma is low dose inhaled glucocorticosteroids (Fig. 2). Regular use of inhaled glucocorticosteroids reduces the frequency of symptoms and the need for SABAs for symptom relief. In addition, it improves the overall quality of life, and decreases the risk of serious exacerbations.² Alternative pharmacological treatment of mild persistent asthma includes leukotriene receptor antagonists. Patients receiving long-term controller therapy also should continue to use their short-acting beta agonist as needed for relief of symptoms.

Moderate persistent (Step 3): The pharmacological treatments for moderate persistent asthma are either

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Table 1 Levels of asthma control: a scheme for recognizing controlled, partly controlled and uncontrolled asthma

Characteristic	Controlled (All of the following)	Partly controlled (Any measure present in any week)	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV1) [†]	Normal	<80% predicted or personal best (if known)	
Exacerbation	None	One or more/year [‡]	One in any week [§]

[†]Lung function is not a reliable test for children 5 years and younger.

[‡]Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.

[§]By definition, an exacerbation in any week.

Quoted from reference 1.

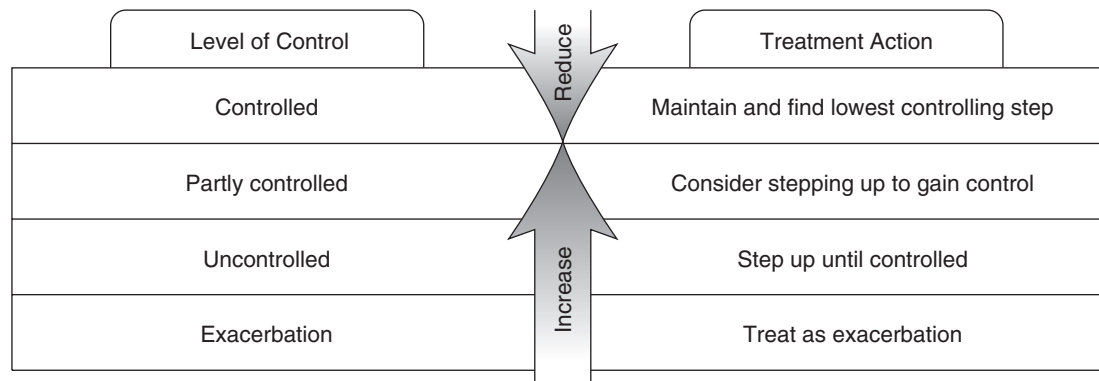


Fig. 1 The management approach to pharmacological treatment for asthma. Quoted from reference 1.

low-doses of an inhaled glucocorticosteroids plus a long-acting inhaled beta agonist (LABAs), medium- or high-doses of an inhaled glucocorticosteroids, low doses of an inhaled glucocorticosteroids plus leukotriene receptor antagonists, or low doses of an inhaled glucocorticosteroids plus sustained release theophylline. The combination of low-doses of an inhaled glucocorticosteroids plus LABAs may be more effective in controlling asthmatic symptoms than increasing the dose of inhaled glucocorticosteroids alone.

Severe persistent (Step 4): The preferred treatments for severe persistent asthma are medium- or high-doses of an inhaled glucocorticosteroids in combination with LABA. When patients are inadequately controlled on high-dose inhaled glucocorticosteroids plus LABAs, add a leukotriene modifier (leukotriene receptor antagonist or lipoxigenase inhibitor) and/or sustained release theophylline.

Severe persistent (Step 5): The preferred treatments for severe persistent asthma are high doses of an inhaled glucocorticosteroids plus LABAs. In addition, for patients who are inadequately controlled on high-dose inhaled glucocorticosteroids and LABAs,

add lowest dose of oral glucocorticosteroids. Recently, anti-IgE humanized monoclonal antibody omalizumab (Xolair[®]) is available in Japan. The anti-IgE therapy omalizumab may be considered in combination with other treatments for very severe asthma patients who are resistant against treatment with high doses of an inhaled glucocorticosteroids plus LABAs.

PHARMACOLOGICAL TREATMENT FOR ACUTE EXACERBATIONS OF ASTHMA IN ADULTS

Patients with mild asthma attack require inhaled rapid-acting beta2-agonists in adequate doses using a metered dose inhaler (MDI). Begin with 2 to 4 puffs every 20 min for first hour. However, patients with acute exacerbations of asthma often require systemic glucocorticosteroids. The best strategy for management of acute exacerbations of asthma is early recognition and intervention, before asthma attacks become severe and potentially life threatening. Previous studies have frequently revealed that failures on the part of both patients and clinicians to recognize the severity of the disease and to intensify treatment ap-

Table 2 Commonly used formulations of drugs used in asthma and COPD in Japan

Drug	Inhaler (µg)	Oral, flow nebulization, trans-dermal	Vials for injection (mg)	Duration of action (hours)
β2-agonists				
Short-acting β2-agonists (SABAs)				
Salbutamol	100, 200 (MDI & DPI)	*Flow nebulization 1.5-2.5 mg		4-6
Procaterol	10-20 (MDI)	25, 50 µg (Pill)		8-10
Long-acting β2-agonists (LABAs)				
Salmeterol	25-50 (MDI & DPI)			12+
Tulobuterol		*Trans-dermal 0.5, 1, 2 mg		12-24
Anticholinergics				
Short-acting				
Ipratropium bromide	20, 40 (MDI)			6-8
Oxipropium bromide	100 (MDI)			7-9
Long-acting				
Tiotropium	18 (DPI)			24+
Methylxanthines				
Aminophylline		100 mg (Pill)	250 mg	Variable, up to 24
Theophylline		50-400 mg (Pill)		Variable, up to 24
Inhaled glucocorticosteroids				
Beclomethasone	50-100 (MDI)			
Budesonide	100, 200 (DPI)			
Fluticasone	50-200 (MDI & DPI)			
Combination of long-acting β2-agonists plus glucocorticosteroids				
Salmeterol/Fluticasone	50/100, 250, 500 (DPI)			
Leukotriene receptor antagonist				
Pranlukast		112.5 mg (Pill)		1.15
Zafirlukast		20, 40 mg (Pill)		7.5
Montelukast		10 mg (Pill)		4.57

MDI, metered dose inhaler; DPI, dry-powder inhaler.

Original table is quoted from reference 4, and modified.

PHARMACOLOGICAL TREATMENT FOR STABLE COPD

Bronchodilators but not inhaled glucocorticosteroids are the therapeutic mainstay for COPD patients.⁴ They include anticholinergics, beta agonists, and theophylline. β2 agonists and anticholinergics are available in short-acting and long-acting inhaled formulations. The scheme of the treatment for COPD is shown in Figure 3. Table 2 shows commonly used drugs used in COPD in Japan. In COPD, the order of bronchodilators is inhaled anticholinergics, inhaled β2-agonists and theophylline. Most bronchodilators are administered by inhalation, orally, or intravenously. A metered dose inhaler (MDI), dry powder

inhaler (DPI), or nebulizer can be used to deliver a bronchodilator medication by inhalation. Moreover, it is known that the long acting anticholinergics and long acting β2-agonists work well in COPD.^{4,5} Combination therapy using inhaled glucocorticosteroids plus long-acting β2 agonists significantly improves some outcomes compared to placebo, long-acting β2 agonists alone, or inhaled glucocorticosteroids alone.⁶

PHARMACOLOGICAL TREATMENT FOR EXACERBATIONS OF COPD

GOLD defines an exacerbation of COPD as an acute increase in symptoms beyond normal day-to-day variation.⁴ An exacerbation of COPD includes one or

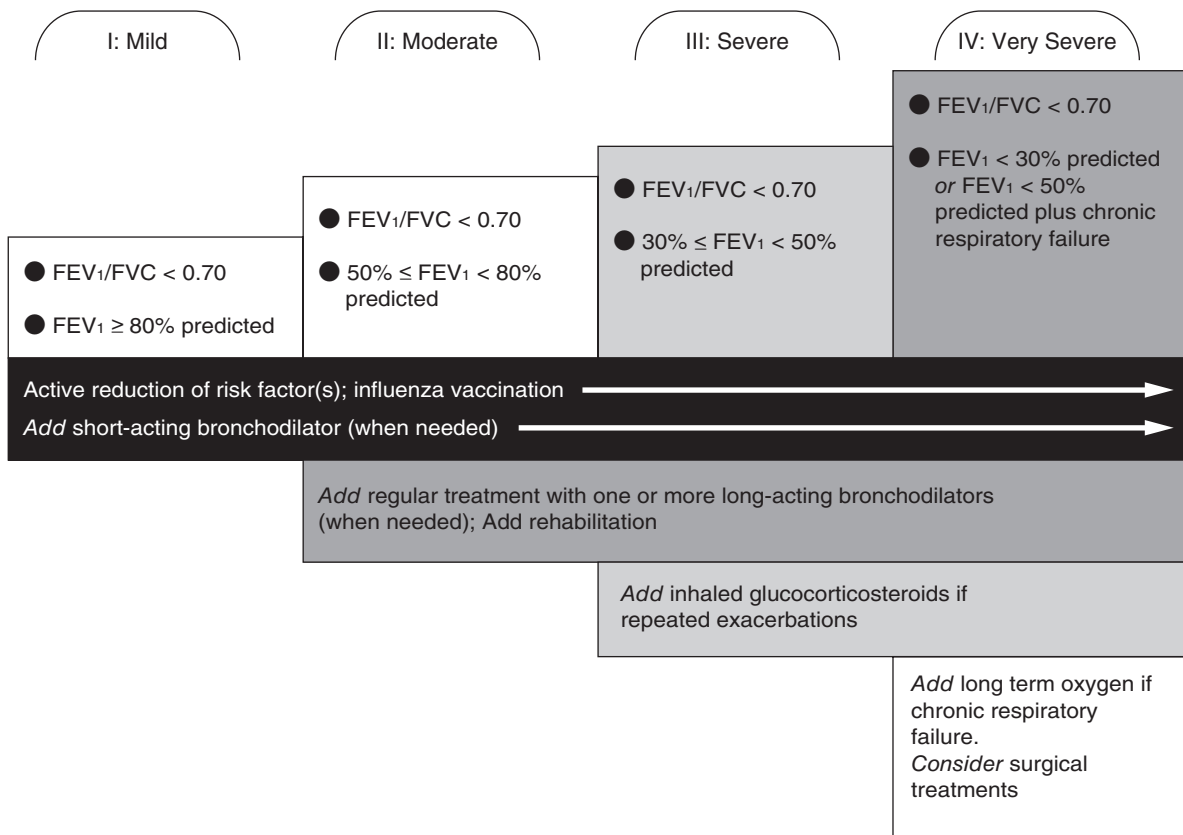


Fig. 3 The scheme of the treatment for COPD. Quoted from reference 4.

more of the following symptoms: dyspnea increases, cough increases in frequency and severity, and sputum production increases in volume and/or changes character. The major components of managing an acute exacerbation of COPD include inhaled short-acting bronchodilators (beta adrenergic agonists and anticholinergic agents), glucocorticosteroids, and antibiotics.

BRONCHODILATORS

Increase dose and/or frequency of existing short-acting bronchodilator therapy, preferably inhaled SABA such as salbutamol and procaterol in Japan. If not already used, add anticholinergic agents until symptoms improve. For example, inhaled short-acting anticholinergic agents (e.g. ipratropium bromide) can be used with SABAs to treat acute exacerbations of COPD.

GLUCOCORTICOSTEROIDS

Previous studies have shown that systemic glucocorticoid therapy improves lung function and treatment success, while reducing the length of hospital stay.^{7,8} The optimal dose of systemic glucocorticosteroids for treating a COPD exacerbation is still unknown. If baseline FEV₁ <50% predicted, prednisone (30 to 40 mg orally, once daily) should be given for 7 to 10

days to the bronchodilator regimen.⁴ Methylprednisolone (60 to 125 mg, 2 to 4 times daily) are also used intravenously. It is of note that high doses of systemic glucocorticosteroids may increase the risk of side effects. Lower doses (e.g. 30 to 40 mg of prednisone) may be equally effective and safe.⁴

ANTIBIOTICS

Antibiotics should be given to patients. Bacterial infections appear to trigger one-third to one-half of COPD exacerbations. *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae* are the bacteria most frequently isolated bronchoscopically from patients having an exacerbation of COPD.⁹⁻¹¹ Therefore, antibiotics including amoxicillin-clavulanate, azithromycin, cefpodoxime, cefprozil, cefuroxime, loracarbef, and the fluoroquinolones are commonly used against *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae* for outpatients. For hospitalized patients with risk factors for *Pseudomonas*, antibiotic choices include levofloxacin, cefepime, ceftazidime, and piperacillin-tazobactam. Hospitalized patients without risk factors for *Pseudomonas* can be treated with a respiratory fluoroquinolone (levofloxacin, moxifloxacin) or a third-generation cephalosporin (ceftriaxone or cefotaxime).¹²

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