SYSTEMIC V/S INHALED STEROIDS EFFICACY AND SIDE EFFECT PROFILE

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Systemic vs. Inhaled Steroids - Efficacy and Side Effect Profile

ANCC Accredited NCPD Hours: 2 hrs

Target Audience: RN/APRN

Need Assessment

Inhaled corticosteroids are a mainstay of chronic obstructive pulmonary disease for patients with a history of exacerbations. Increasing treatment options for chronic obstructive pulmonary disease add to the complexity of treatment and require review of clinical data to inform treatment decisions. Inhaled corticosteroids in combination with long acting β2-agonists reduce the risk of exacerbations and improve lung function and health status in patients with chronic obstructive pulmonary disease compared with inhaled corticosteroids or long acting beta agonist therapy alone.

Objectives

- Discuss the role of inflammation in chronic obstructive pulmonary disease
- Identify the types of inflammation in chronic obstructive pulmonary disease
- Describe the role of corticosteroids in inflammation
- Discuss and compare the efficacy of systemic corticosteroids and inhaled corticosteroids

Goal

The goal of this article is to review the current role of systemic and inhaled corticosteroids in severe COPD treatment including their efficacy and side effects

Introduction

Chronic obstructive pulmonary disease is an umbrella term used to describe different pathologies that contribute to patient symptoms of breathlessness, coughing, sputum production, chest tightness and wheezing. Patients diagnosed with chronic obstructive pulmonary disease may experience symptoms of differing severity that can vary from day to day. Many patients with chronic obstructive pulmonary disease will have some degree of lung hyperinflation, defined as an increased volume of air remaining in the lung at the end of a spontaneous expiration. Hyperinflation is closely associated with dyspnoea; limitation of physical activity and exercise intolerance, thus a reduction in hyperinflation may result in an improvement in physical activity, reduced dyspnoea and other clinical benefits (as shown in figure 1).

Systemic and local inflammation is central to the pathophysiology of chronic obstructive pulmonary disease (COPD) (as shown in figure 2). ***Increased levels of inflammation have been linked to a more progressive course in chronic obstructive pulmonary disease and have been shown to be present during an exacerbation.*** Chronic obstructive pulmonary disease treatment consists of drug therapies to alleviate the patient's symptoms, stabilize lung function and reduce the patient's risk of chronic obstructive pulmonary disease exacerbation (increased symptoms that require urgent and additional medical treatments). The mainstay of chronic obstructive pulmonary disease treatments is a class of drugs called "anticholinergics". These drugs prevent the binding of acetylcholine to the M3 receptors on the airway surface. ***Decrease in inflammatory cytokines, C-reactive protein and inflammatory cells have been observed with corticosteroid use, suggesting a possible mechanism for a therapeutic benefit of steroids.*** No available data support the routine use of systemic corticosteroids in stable chronic obstructive pulmonary disease; however, ***short courses during exacerbations are likely to improve length of hospitalization, lung function and relapse rate. Inhaled corticosteroids (ICS) decrease the rate of exacerbation and may improve the response to bronchodilators and decrease dyspnoea in stable chronic obstructive pulmonary disease.*** No study shows that inhaled corticosteroids reduce the loss of lung function; however, recent data suggest a possible survival benefit when combined with long-acting β agonists. There are limited data on the use of inhaled corticosteroids in the treatment of acute exacerbations

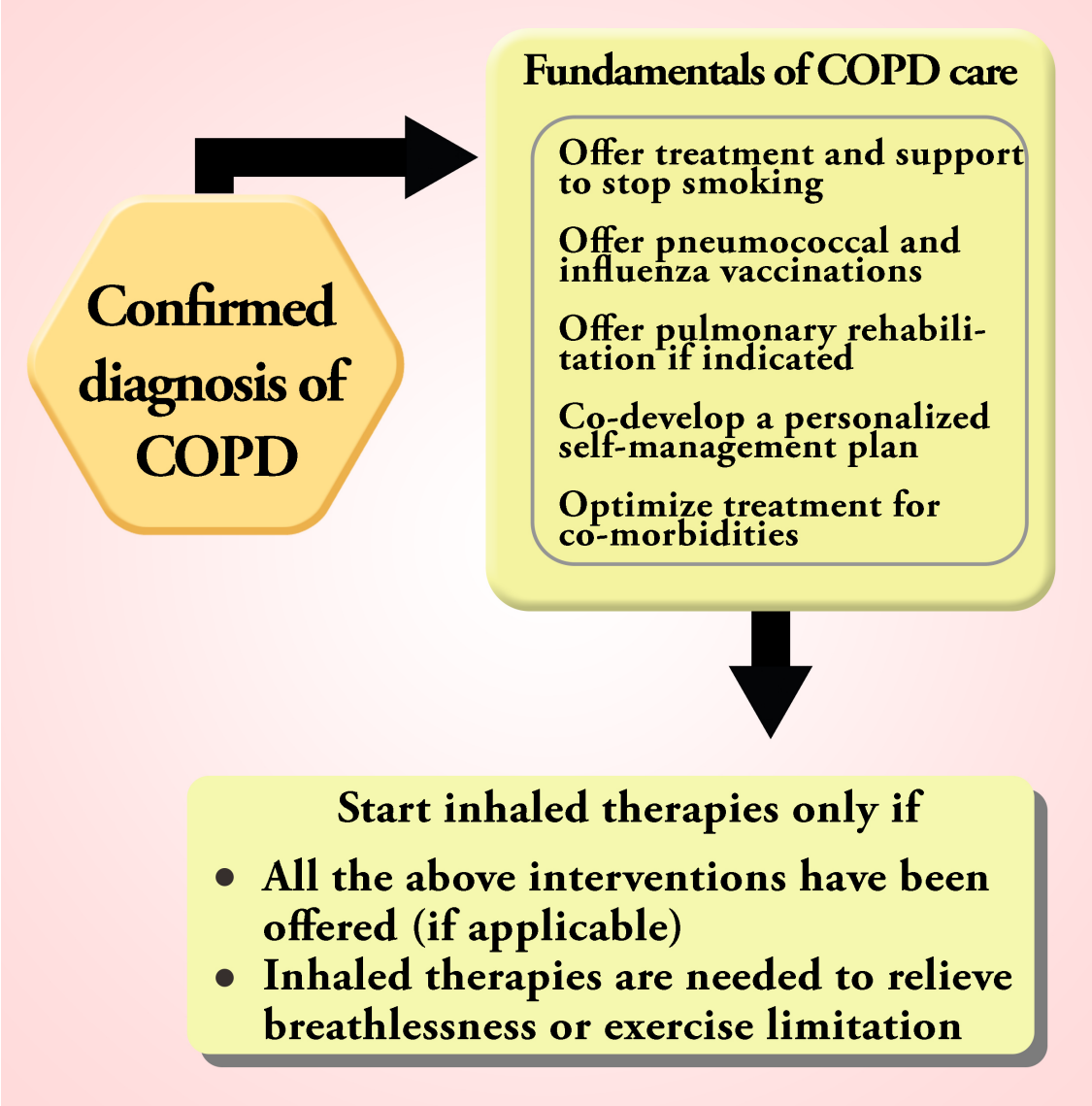

Figure 1: Fundamentals of COPD care

of chronic obstructive pulmonary disease and its role in this setting must be more clearly defined. The empiric use of systemic corticosteroids perioperatively represents another area of uncertainty.

The role of pharmacogenetics in the metabolism of corticosteroids in chronic obstructive pulmonary disease is evolving but may be partially responsible for the observed variability in patient responsiveness. The potential benefits of systemic or inhaled corticosteroid use must be weighed against the risk of known toxicities. [1, Rank 5]

Role of Inflammation in COPD

The chronic inflammatory process in chronic obstructive pulmonary disease involves both innate and adaptive immunity and is most pronounced in the bronchial

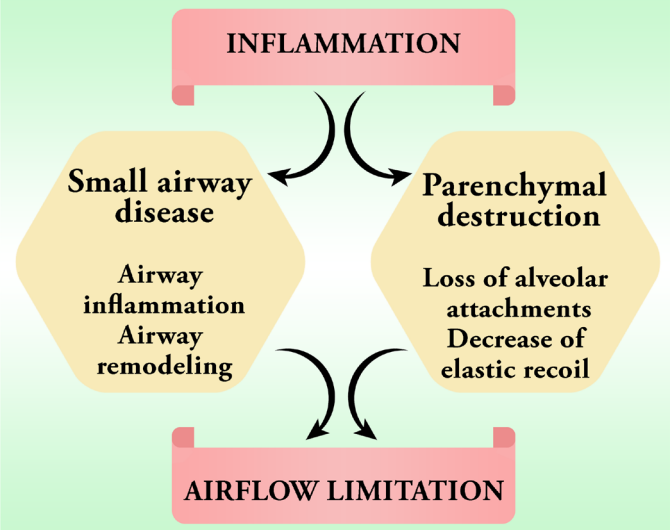

Figure 2: Pathophysiology of COPD

walls of the small airways. The inflammatory process in chronic obstructive pulmonary disease does have marked heterogeneity. It results in both emphysema with parenchymal involvement and chronic bronchitis, which predominantly affects the small airways. A characteristic feature of chronic obstructive pulmonary disease is the presence of acute exacerbations, which is typically associated with increased inflammation

Inflammatory cell types prominent in chronic obstructive pulmonary disease

There are a variety of cell types that contribute to inflammation in chronic obstructive pulmonary disease, of which the most important are the macrophages, the neutrophils and the lymphocytes (as shown in figure 3). Macrophages have a key role in the pathogenesis of chronic obstructive pulmonary disease and are found in markedly increased numbers in both airways and lung parenchyma. Neutrophils are generally more inflammatory than macrophages and are most prominent in acute exacerbations in the lung airways. As chronic obstructive pulmonary disease progresses, a distinctive feature is the development of lymphoid follicles in the small airways. These lymphoid follicles are composed of T cells and B cells. Other inflammatory cell types involved in chronic obstructive pulmonary disease include eosinophils, dendritic cells and mast cells. The presence of eosinophils in chronic obstructive pulmonary disease may be associated with co-existent asthma. Increased numbers of activated pulmonary dendritic cells are found in patients with chronic obstructive pulmonary disease and are a marker of disease severity. Mast cells are widely distributed in the airways and have a well established role in asthma inflammation.

"The mainstay of chronic obstructive pulmonary disease treatments is a class of drugs called "anticholinergics"."

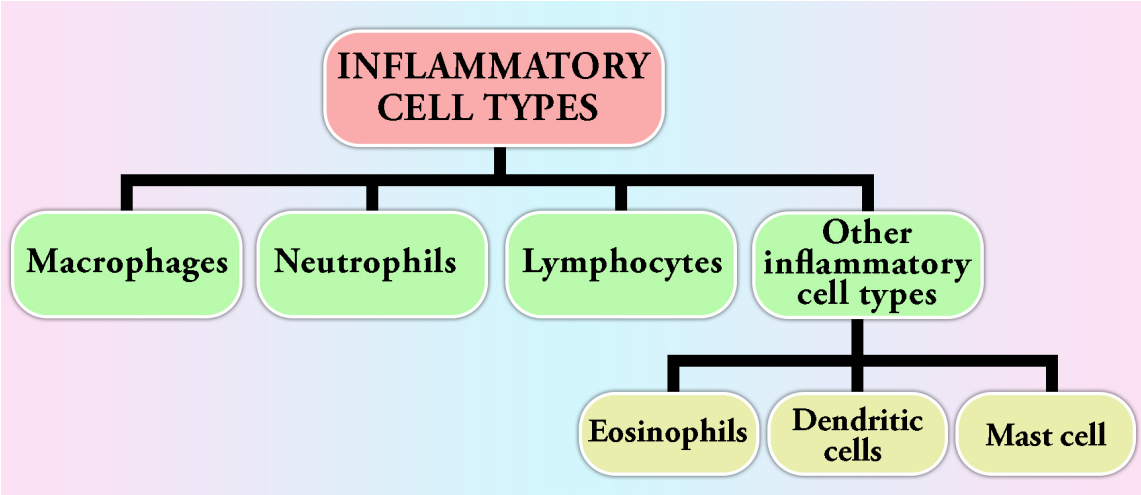

Figure 3: Inflammatory cell types

Structural lung cells and their contribution to lung inflammation

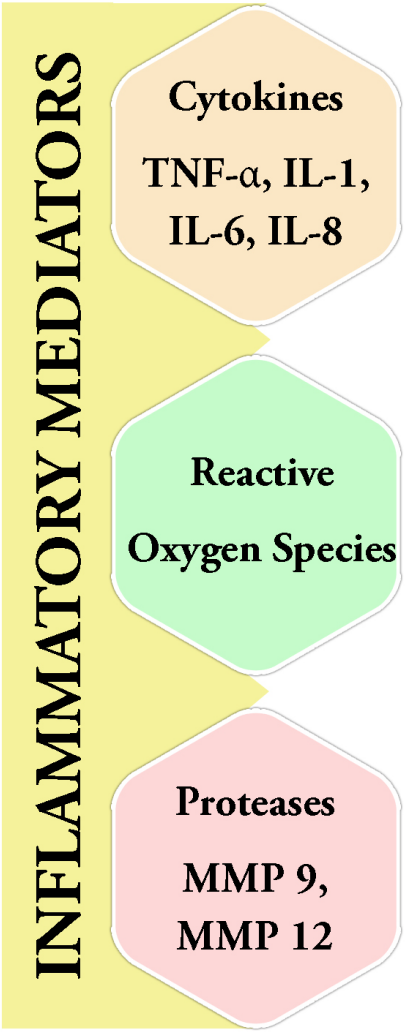

Figure 4: Inflammatory mediators

The epithelial cells have an important role in mediating inflammation in chronic obstructive pulmonary disease. These cells are activated by inhaled toxins, such as cigarette smoke and biomass smoke as well as microorganisms. This results in the production of a variety of inflammatory mediators including cytokine, chemokines and reactive oxygen species (as shown in figure 4).

Cytokines

Cytokines in the lungs are principally produced by macrophages and T cells. Important mediators produced by macrophages and neutrophils include tumor necrosis factor alpha (TNF α), interleukin-1 (IL-1), IL-6 and IL-8.

> "The most commonly associated factor with lung inflammation in COPD is autoimmunity."

Reactive oxygen species

The excessive production of reactive oxygen species damages the lung tissue and results in oxidative stress, which is a primary pathogenic process in chronic obstructive pulmonary disease. The phagocytes (neutrophils and macrophages) and epithelial cells all produce reactive oxygen species and this process is enhanced in patients with chronic obstructive pulmonary disease.

Proteases

Proteases are produced by neutrophils and macrophages. These include neutrophil elastase and matrix matalloproteinases (MMP) 9 and 12.

Tissue Inflammation

Although systemic inflammation is clearly present in chronic obstructive pulmonary disease, ***local inflammation within the airways and lung parenchyma is a likely starting point for the inflammatory cascade. Airway inflammation is significantly increased during exacerbations of chronic obstructive pulmonary disease, with evidence of increased neutrophils, lymphocytes and eosinophils seen in airways and in sputum.***

> **"Histone deacetylase (HDAC) is reduced in the alveolar macrophages of cigarette smokers and inhibits the production of inflammatory cytokines in alveolar macrophages.**
>
> **Reduced histone deacetylase activity and increased histone acetyltransferase correlate with increased exacerbation and chronic obstructive pulmonary disease severity and are associated with corticosteroid insensitivity in these patients."**

patients who had abstained from smoking for several years, suggesting a persistent, perhaps maladaptive response to previous injury. [2, Rank 3]

Systemic Inflammation

Chronic obstructive pulmonary disease affects more than just the lungs. Muscle wasting, cachexia, atherosclerosis and cardiac disease have been associated with chronic obstructive pulmonary disease (as shown in figure 5). ***These non-pulmonary manifestations of chronic obstructive pulmonary disease suggest a systemic disorder that is likely mediated by circulating inflammatory cells and inflammatory cytokines.***

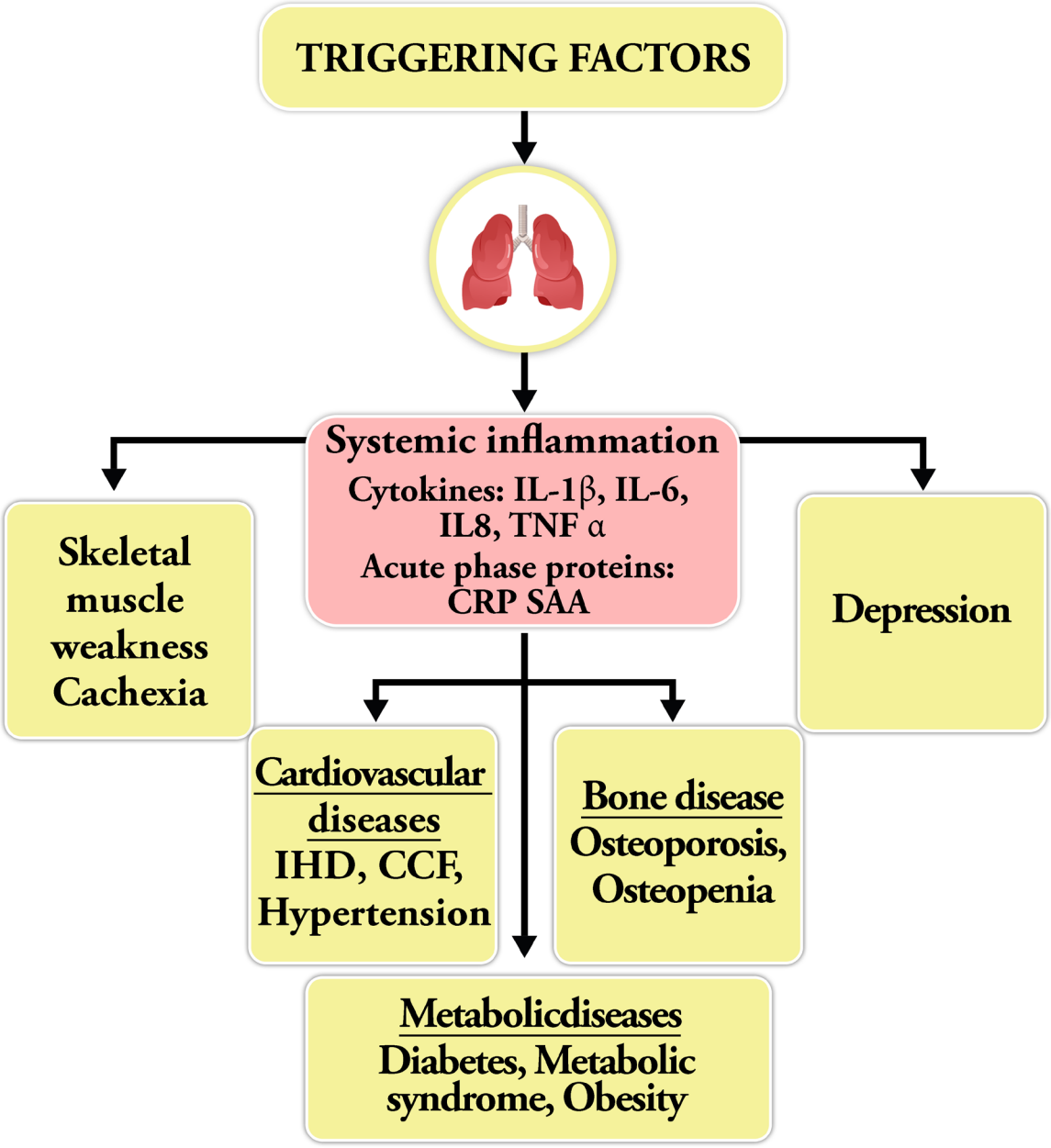

Figure 5: Non pulmonary manifestations of COPD

Neutrophil activation seems to play a central role in the pathogenesis of chronic obstructive pulmonary disease. Several recent studies have shown heightened neutrophil activation in patients with chronic obstructive pulmonary disease compared with normal individuals. Researchers showed that ***peripheral neutrophils taken from patients with stable chronic obstructive pulmonary disease had significantly increased in vitro chemotactic and proteolytic activity compared with neutrophils obtained from normal individuals.*** Genetic evidence of peripheral neutrophil activation has been provided by some researchers, who obtained peripheral neutrophils from normal volunteers and from patients with chronic obstructive

pulmonary disease after stimulation with tumor necrosis factor-α and/or granulocyte-macrophage colony–stimulating factor. ***The severity of chronic obstructive pulmonary disease as determined by the FEV1 correlated with concentrations of IL-1β, MIP-1β, CD83, IL-1 receptor 2 and IL-1 receptor antagonist as measured by gene microarray.*** Although it seems that peripheral neutrophilic activation occurs in chronic obstructive pulmonary disease, its clinical significance has yet to be elucidated. [3, Rank 4]

Less information is available regarding the role of peripheral lymphocyte function in chronic obstructive pulmonary disease. Increased lymphocyte apoptosis and the production of transforming growth factor-β have been shown in stimulated peripheral lymphocytes of patients with chronic obstructive pulmonary disease. Increased peripheral lymphocyte activation has also been seen in chronic obstructive pulmonary disease, as well as up-regulation of Toll-like receptor 2 (TLR-2), matrix metalloproteinase-9, IL-6 and monocyte chemoattractant protein-1 (MCP-1) from peripheral monocytes.

Many circulating inflammatory mediators have been observed to be elevated in stable chronic obstructive pulmonary disease and during exacerbations (as shown in figure 6). ***C-reactive protein (CRP) is a known marker of systemic inflammation and a likely participant in the inflammatory cascade. C-reactive protein has been implicated as a marker of infection and cardiovascular disease;*** however, the relationship between C-reactive protein and chronic obstructive pulmonary disease is less clear. Researchers first described an association between C-reactive protein and exacerbations of chronic obstructive pulmonary disease in 50 patients admitted for exacerbations of chronic obstructive pulmonary disease. C-reactive protein levels were significantly elevated on admission and dropped to near normal levels after treatment. Although the marked elevation in C-reactive protein was more pronounced for patients with proven bacterial infection, patients with no identified pathogen had a similar rise and fall in C-reactive protein level. ***Elevated C-reactive protein levels have also been shown in stable chronic obstructive pulmonary disease when compared with smokers without chronic obstructive pulmonary disease and seem to be independent of the presence of cardiovascular disease.*** Elevations in C-reactive protein in chronic obstructive pulmonary disease have also been linked to exercise limitation, increased airflow limitation, and dyspnoea. Last, ***elevations in C-reactive protein levels in***

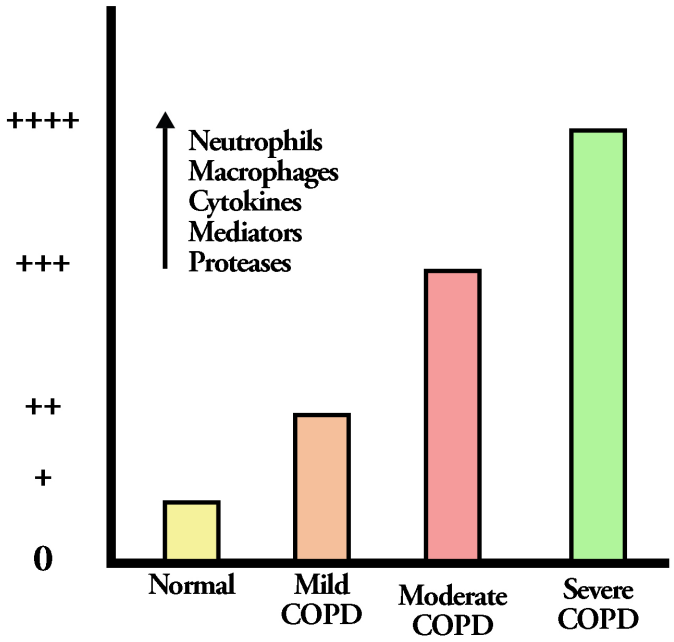

Figure 6: Inflammatory mediators and severity of COPD

patients with chronic obstructive pulmonary disease have been shown to be a strong indicator of important clinical outcomes, including hospitalization and death. [4, Rank 5]

Role of Corticosteroids in Inflammation

Corticosteroids are a class of steroid hormones that are produced in the adrenal cortex. Corticosteroids are involved in a wide range of physiologic systems such as stress response, immune response and regulation of inflammation, carbohydrate metabolism, protein catabolism, blood electrolyte levels and behaviour. In cases of chronic obstructive pulmonary disease and asthma, inflammation tends to be chronic and severe. Therefore oral glucocorticosteroids are often prescribed for these types of conditions due to their powerful ability to decrease inflammation. As more evidence mounts implicating inflammation in the pathogenesis and maintenance of chronic obstructive pulmonary disease, therapeutic strategies meant to halt or reverse inflammation are desirable. ***The use of inhaled or systemic corticosteroids has been the cornerstone in anti-inflammatory therapy in all settings of chronic obstructive pulmonary disease. The use of steroids in chronic obstructive pulmonary disease remains controversial because of questionable benefit and potentially significant drug toxicity.*** Because neutrophils, T lymphocytes and macrophages have been implicated in the pathogenesis of chronic obstructive pulmonary disease, investigators have sought evidence that steroids may alter the biological behaviour of these cell lines and other inflammatory mediators. ***The effect of steroids on neutrophils has traditionally been considered to be minimal;*** however, there are data indicating that steroids induce neutrophil death in vitro. Additionally, ***decreased neutrophils and IL-8 levels in bronchoalveolar lavage samples have been demonstrated in patients with chronic obstructive pulmonary disease*** who were treated with inhaled budesonide, suggesting a potential mechanism of action

for steroids in this patient population. Biopsies of airways of smokers with chronic obstructive pulmonary disease given inhaled fluticasone showed decreased CD8:CD4 ratios and decreased sub endothelial mast cells when compared with patients receiving placebo. In this study, patients receiving inhaled fluticasone had fewer chronic obstructive pulmonary disease exacerbations, suggesting that alterations in airway inflammation may have played a role in the beneficial effect of inhaled corticosteroids. One plausible explanation for the therapeutic effect of corticosteroids in chronic obstructive pulmonary disease suggests that ***histone deacetylase in the presence of corticosteroids down-regulates the transcription of inflammatory cytokines. Clinical observations made with the use of systemic and inhaled corticosteroids support the notion of corticosteroids exerting an inhibitory effect on inflammatory mediators.*** Additionally, patients with chronic obstructive pulmonary disease whom inhaled corticosteroids were withdrawn showed reductions in C-reactive protein level when retreated with inhaled corticosteroids and systemic corticosteroids; whereas patients retreated with placebo do not. [5, Rank 3]

Efficacy of Systemic Corticosteroids

Early clinical trials evaluating the efficacy of systemic corticosteroids in the treatment of chronic obstructive pulmonary disease offered conflicting results. While some published reports documented efficacy in the administration of systemic corticosteroids to patients with chronic obstructive pulmonary disease, others conveyed little if any benefit. However, the ***interpretation and applicability of early data are limited by a dearth of randomized, placebo-controlled, blinded studies, a lack of clearly defined end points and assessment of efficacy in multiple chronic obstructive pulmonary disease patient populations.***

Because ***early clinical trials almost exclusively evaluated the effect of therapy with corticosteroids in patients with stable chronic obstructive pulmonary disease,*** a study was conducted to evaluate whether systemic corticosteroids improved spirometry results and/or arterial blood-gas levels in patients with chronic obstructive pulmonary disease and acute respiratory distress. In this study, patients hospitalized with acute respiratory insufficiency and chronic obstructive pulmonary disease were randomized to receive either intravenous (IV) methylprednisolone (n=22) or match

ing placebo (n=22) for 72 hours. ***All patients received standardized treatment consisting of oxygen, aminophylline, nebulized isoproterenol and antibiotics.*** The mean percentage change in both pre and post bronchodilator forced expiratory volume in 1 second (FEV1) was significantly greater in patients receiving methylprednisolone in comparison to placebo at all measured time points. No significant differences were observed in forced vital capacity (FVC), arterial pH or partial pressure of carbon dioxide (PaCO2) between the methylprednisolone treated and placebo groups. The authors noted, however, that perhaps there were too few patients included in this study to determine such differences. Of the potential adverse events associated with systemic corticosteroid administration, hyperglycemia (mean serum glucose concentration 164±42 mg/dL for methylprednisolone treated patients versus 139±29 mg/dL for placebo, P<0.05), acute psychosis (n=1) and upper gastrointestinal hemorrhage (n=1) were observed. However, only hyperglycemia could be definitively attributed to the administration of methyl prednisolone. [6, Rank 2]

Following studies indicating the emergent administration of systemic corticosteroids in acute exacerbations of chronic obstructive pulmonary disease did not acutely affect forced expiratory volume in 1 second or rate of hospitalization, but may reduce the rate of readmission, a small trial was conducted to assess the efficacy of oral corticosteroids in the outpatient treatment of acute exacerbation of chronic obstructive pulmonary disease. Patients experiencing acute exacerbations of chronic obstructive pulmonary disease were randomized to receive either a 9-day course of oral prednisone (n=13) in a tapering dose or matching placebo (n=14). All patients were instructed to increase the dose and frequency of their inhaled β-agonist. Any patients taking ipratropium, inhaled corticosteroids and/or theophylline preceding study enrollment were allowed to continue the use of these medications. Antibiotics were prescribed to patients with evidence of infective bronchitis. All patients were examined on study days 3 and 10 as well as at all unscheduled hospital visits during the study period. Measured end points included airflow obstruction (as measured by spirometry), gas exchange, dyspnea and treatment failure.

"Short courses (2wks or less) of systemic corticosteroids are effective in improving lung function and reducing morbidity associated with COPD exacerbations in patients with moderate to severe COPD"

Significant increases in forced expiratory volume in 1 second were observed at both day 3 and 10 in patients receiving prednisone in comparison to placebo (184 mL versus –14 mL [P=0.05] and 383 mL versus 9 mL [P=0.01], respectively). In addition to significantly improving the rate of airflow recovery, prednisone treatment significantly improved gas exchange (as measured by partial pressure of oxygen arterial blood [PaO2]) at both days 3 and 10 in comparison with placebo. There was, however, no difference in PaCO2 response between the prednisone-treated group and placebo. Although there was a trend toward more rapid improvement with prednisone, the degree of dyspnoea did not differ significantly between the prednisone-treated group and placebo. The rate of treatment failure in the placebo group was 57% (n=8) versus 0 in the prednisone group. [7, Rank 5]

In a prospective double-blind study designed to determine if the administration of systemic corticosteroids hastened recovery, patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease were randomized to receive either 30 mg oral prednisolone once daily (n=29) or matching placebo (n=27) for 14 days. All patients received standard treatment with controlled oxygen, nebulized short-acting β-agonist (salbutamol) and an anticholinergic (ipratropium) every 6 hours and antibiotics as per the admitting physician's discretion. Any patient receiving an inhaled corticosteroid at the time of study enrollment was allowed to continue this therapy. Patients were followed until hospital discharge and then re-examined 6 weeks after admission. Spirometry, health status and length of hospital stay were assessed.

At discharge, post bronchodilator percentage predicted forced expiratory volume in 1 second in patients receiving prednisolone had increased significantly in comparison to placebo (47% increase versus 25% increase, respectively; P<0.05). Until day 5, post bronchodilator forced expiratory volume in 1 second of the corticosteroid treated group increased at a significantly accelerated rate compared to placebo (90 mL per day [50.8–129.2] versus 30 mL per day [10.4–49.6], P=0.048). Health-status scores had improved significantly in both groups by hospital discharge. Patients receiving prednisolone had a significantly shorter median length of hospitalization when compared to placebo (7 days versus 9 days, respectively; P=0.027). At 6 weeks, there was no significant difference in percentage predicted post bronchodilator forced expiratory volume in 1 second or health status in either the corticosteroid-treatment group or placebo in comparison to discharge. In addition, there

was no difference in exacerbation rate or rate of hospital admission between the two groups observed at 6 weeks. [8, Rank 2]

A large multicenter trial was conducted to further evaluate the efficacy of systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Within 12 hours of hospital admission, patients were randomized to receive one of three treatments: an 8-week course (n=80) of systemic glucocorticoids (intravenous methylprednisolone for 72 hours, followed by once-daily oral prednisone taper over the next 57 days), a 2-week course (n=80) of systemic glucocorticoids (intravenous methylprednisolone for 72 hours, followed by once-daily oral prednisone taper over the next 12 days, then placebo for the next 45 days), or placebo (n=111). All patients received a broad-spectrum antibiotic for 7 days. In addition, all patients were required to use an inhaled β-agonist, inhaled ipratropium bromide and starting on day 4, inhaled triamcinolone acetonide at standardized doses for 6 months. The use of high-dose inhaled corticosteroids (other than triamcinolone as part of study protocol), theophylline, or additional open-label systemic corticosteroids was not allowed. Patients were evaluated on each of the first 3 days of hospitalization, and at 2 weeks, 8 weeks and 6 months. The primary end point was a composite of treatment failure, comprised of death from any cause or the need for invasive mechanical ventilation, readmission for exacerbation of chronic obstructive pulmonary disease, or intensification of pharmacologic therapy. Secondary end points included change in forced expiratory volume in 1 second and length of hospital stay.

Because there were no differences in outcomes observed between the 8-week and 2-week treatment groups, they were considered equivalent and combined for further analysis. Systemic corticosteroids significantly reduced the rate of first treatment failure compared to placebo at 30 days (23% versus 33%, P=0.04). There was not a significant difference between corticosteroid treatment and placebo at 6 months. Forced expiratory volume in 1 second improved significantly faster in patients receiving systemic corticosteroids than those receiving placebo. The maximum difference in forced expiratory volume in 1 second (approximately 100 mL) was observed by the end of day 1 and maintained until day 3. However, a significant difference was not seen between the active-treatment and placebo groups by the end of 2 weeks. Patients receiving systemic corticosteroids experienced a significantly shorter length of hospital stay in comparison to placebo (8.5 versus 9.7 days,

P=0.03). All-cause mortality and chronic obstructive pulmonary disease related mortality were similar between the treatment and placebo groups at 6 months. Subgroup analysis revealed that the administration of systemic corticosteroids was associated with more favourable outcomes in patients previously hospitalized for exacerbation of chronic obstructive pulmonary disease. In these patients, the failure rate at 6 months was 49.5% for patients treated with glucocorticoids and 66.7% for those receiving placebo (P=0.01). [9, Rank 5]

Hyperglycemia requiring treatment occurred in a greater proportion of patients treated with systemic corticosteroids in comparison to placebo (15% versus 4%, P=0.002). However, when compared to the placebo group, significantly more patients in the corticosteroid treatment group had a diagnosis of diabetes mellitus and 16 of the 24 instances of hyperglycemia in the corticosteroid treatment group occurred in known diabetics. The rate of secondary infections did not differ significantly among the three groups, but the highest percentage of patients with a serious infection occurred in the 8-week corticosteroid group (13.8%) in comparison to the 2-week corticosteroid group (1.2%) and placebo (3.6%).

Following the results of two randomized clinical trials that suggested systemic corticosteroids prevent treatment failure and reduce the length of hospital stay in acute exacerbations of chronic obstructive pulmonary disease, a study designed to assess the effect of systemic corticosteroid administration on relapse rates, lung function and health-related quality of life following discharge from the emergency department was carried out. Prior to discharge from the emergency department, patients presenting with an acute exacerbations of chronic obstructive pulmonary disease were randomized to receive either oral prednisone once daily for 10 days (n=74) or matching placebo (n=73). After being counselled on proper inhaler technique, all patients received a standardized regimen of an inhaled β-agonist (albuterol) and an inhaled anticholinergic (ipratropium) via a metered-dose inhaler with a valve holding chamber for 30 days. In addition, all patients completed a 10-day course of oral broad-spectrum antibiotics. Patients were allowed to continue all medications they were taking prior to study enrollment, including inhaled corticosteroids. Patients were assessed 3, 10, and 30 days after randomization. The primary study outcome was treatment failure, as defined by an unscheduled health care visit or return to the emergency room secondary to worsening dyspnoea within 30 days of randomization. Secondary outcomes included change from

day 1 to day 10 in post bronchodilator forced expiratory volume in 1 second, severity of dyspnoea, and chronic obstructive pulmonary disease specific quality of life. [10, Rank 1]

In comparison to placebo, oral prednisone significantly reduced the rate of relapse at 30 days (27% versus 43%, P=0.05). The relative risk of relapse with prednisone treatment at 30 days was 0.63 (95% confidence interval [CI] 0.40–1.01). Prednisone significantly prolonged the time to relapse compared with placebo (hazard ratio [HR] 0.56, 95% CI 0.32–0.99; P=0.04). Although treatment with prednisone did not induce a significant improvement in the total quality-of-life score compared to placebo, the administration of prednisone was associated with a significant improvement in dyspnoea. Patients receiving prednisone had significant improvement in lung function at day 10 when compared to placebo (mean forced expiratory volume in 1 second increase of 34% in prednisone-treated group versus 15% in placebo group, P=0.007). There was no significant difference in hospitalization rates between the two groups (21% of patients in the placebo group required hospitalization for chronic obstructive pulmonary disease within 30 days compared to 11% in the prednisone group). Significantly more patients receiving prednisone reported insomnia, increased appetite, and weight gain in comparison to placebo (P<0.01). A subgroup analysis revealed that patients taking inhaled corticosteroids were more likely to respond to systemic corticosteroid therapy (relative risk of 30-day relapse 0.44, 95% CI 0.22–0.86).

A systematic review of eleven studies (n=1,081), including each of the above mentioned studies, found that systemic corticosteroids significantly reduced the risk of treatment failure (odds ratio [OR] 0.48, 95% CI, 0.34–0.68) and relapse (HR 0.78, 95% CI 0.63–0.97) within 30 days in acute exacerbations of chronic obstructive pulmonary disease. In addition, treatment with systemic corticosteroids in acute exacerbations of chronic obstructive pulmonary disease hastened recovery (significantly increased FEV1 by a mean of 140 mL [95% CI 90–190 mL] at 72 hours in comparison to placebo), thereby decreasing length of hospital stay (–1.22 days, 95% CI –2.26 to –0.18). Systemic corticosteroids did not significantly affect mortality, but did increase the likelihood of adverse events (OR 2.33, 95% CI 1.60–3.40). This systematic review concluded that evidence supported the early administration of systemic corticosteroids in the treatment of acute exacerbations of chronic obstructive pulmonary disease, but because of the

> "Steroids can raise blood sugar levels by reducing the action of insulin, causing insulin resistance and making the liver release stored glucose into the blood stream
>
> Normally only a short term course of steroid will be advised to reduce the inflammations in the airway, as long term use of steroid tablets can cause troublesome side effects"

considerable heterogeneity of the included studies, could not offer a recommendation regarding optimal duration, dose or route. [11, Rank 3]

Efficacy of Inhaled Corticosteroids

Although low-dose oral corticosteroids are recommended for acute exacerbations of chronic obstructive pulmonary disease, systemic exposure predisposes patients to a significant adverse-effect profile. Adverse effects, such as hyperglycemia, myopathy, osteoporosis, thinning of the skin and posterior subscapular cataract formation, more than any other factor, are most influenced by cumulative steroid dose. Those with frequent exacerbations are of particular concern, as they receive multiple courses of corticosteroid treatment and often higher-dose regimens to control acute exacerbations.

As an alternative to systemic steroids, nebulized corticosteroids have minimal bioavailability, negligible systemic absorption, and minimal systemic adverse effects. In addition, inhaled corticosteroids have a high level of anti-inflammatory activity at the local level. Currently, GOLD guidelines (as shown in figure 7) offer nebulized budesonide as an alternative to oral corticosteroids for the treatment of exacerbations. [12, Rank 5]

In a double-blind, randomized, placebo-controlled trial, they compared nebulized budesonide, oral prednisolone and placebo in 199 patients requiring hospital admission for acute exacerbations of chronic obstructive pulmonary disease. Patients were randomized to one of three treatment groups: group 1 nebulized budesonide 2 mg every 6 hours for 72 hours (plus placebo tablets), then inhaled budesonide 2 mg for 7 days, group 2 prednisolone 30 mg by mouth every 12 hours (plus placebo nebulization), then prednisolone 30 mg by mouth daily for 7 days, or group 3 placebo group (placebo tablets + placebo nebulization). All patients were administered terbutaline or salbutamol/ipratropium nebulizer

COPD Maintenance Treatment by Airflow Limitation/Risk
GOLD G uidelines(2013)

FEV1% PREDICTED (AIRFLOW LIMITATION)	EXACERBATION GRADE (RISK)	TREATMENT CONSIDERATIONS
> 80%	LOW	Smoking cessation; Vaccinations; SABA prn
50-80%	MEDIUM	Add to above : Nebulized LABA-LAMA daily; Pulm Rehab;Exacerbation action plan
30-50%	HIGH	Add to above : ICS for exacerbation prone; Referral to pulmonologist
<30%	VERY HIGH	Add to above: long-term oxygen therapy; Consider surgical options

Figure 7 GOLD therapy at each stage of COPD

treatment after receiving one of the three study drugs, as well as antibiotics and supplemental oxygen.

The primary end point was change in post bronchodilator forced expiratory volume in 1 second at 72 hours. Clinical success was predefined as an increase in forced expiratory volume in 1 second of at least 0.15 L and a reduction of PaCO2 of at least 5 mmHg. The mean change in post bronchodilator forced expiratory volume in 1 second (95% CI) at 72 hours was greater with active treatments than with placebo: budesonide versus placebo, 0.10 L (0.02–0.18 L); prednisolone versus placebo, 0.16 L (0.08–0.24 L). The difference in forced expiratory volume in 1 second between budesonide and prednisolone was not significant, at –0.06 L (–0.14 to 0.02 L). Rates of adverse events were similar in all three groups. As expected, a greater percentage of patients developed hyperglycemia in the prednisone group (n=7) versus budesonide (n=1). In summary, nebulized budesonide and prednisone improved airflow limitation versus placebo. [13, Rank 4]

Researchers also evaluated nebulized budesonide as an alternative to systemic corticosteroids. In this prospective study, patients were also randomized into three groups: group 1 received standard

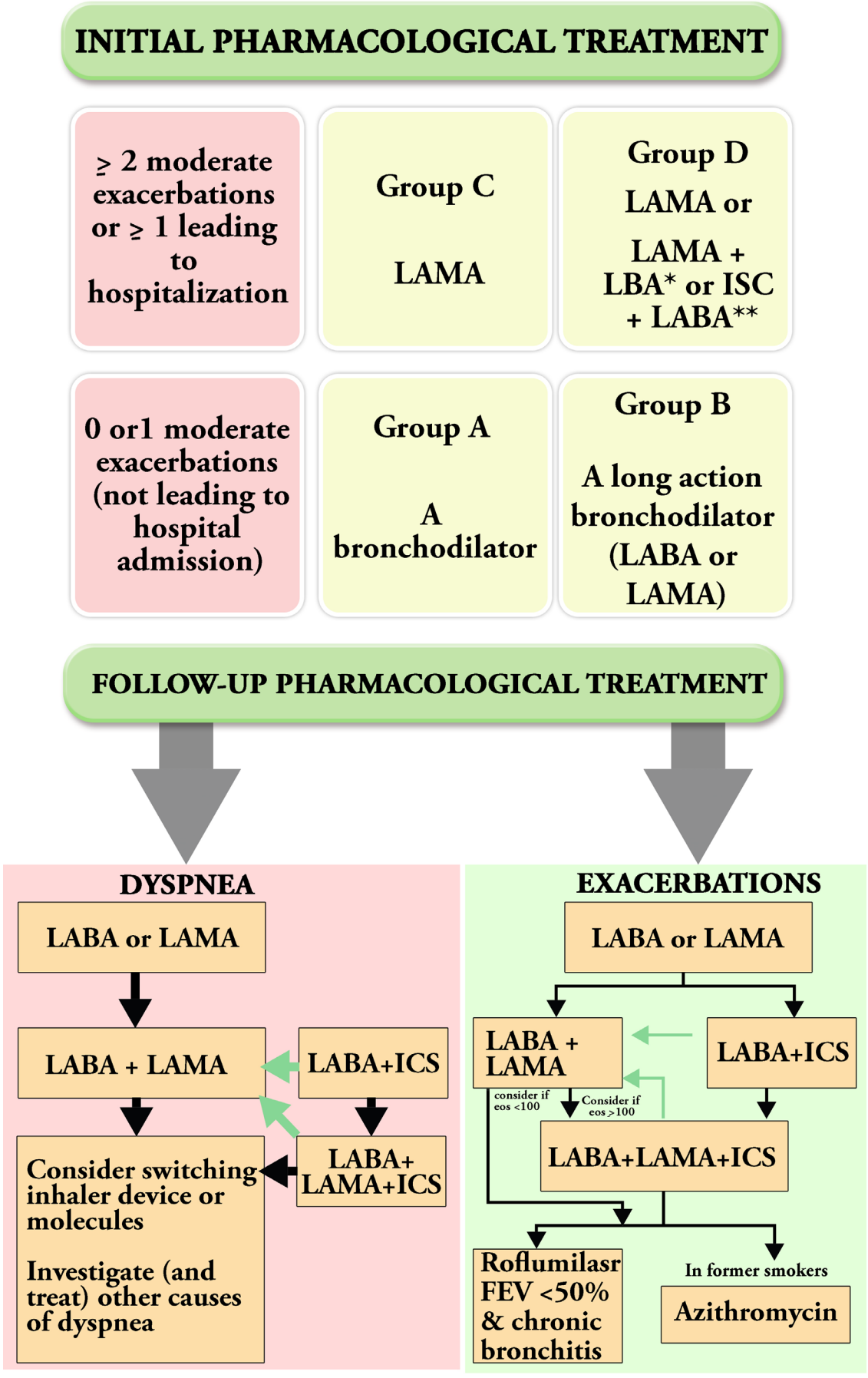

Figure 8: Standard bronchodilator therapy

> "Inhaled corticosteroids are a mainstay of COPD treatment for patients with history of exacerbations
>
> Inhaled corticosteroids decrease the rate of exacerbations and may improve response to bronchodilators and decrease dyspnoea in stable COPD"

bronchodilator therapy (as shown in figure 8). group 2 received 40 mg of prednisolone plus standard bronchodilator therapy and group 3 received 1,500 µg of nebulized budesonide plus standard bronchodilator therapy. Improvement during 10-day hospitalization was compared with exacerbation and hospitalization rates post discharge.

Similar to the previous study, the recovery rate in terms of both spirometry and arterial blood-gas results did not differ between the nebulized budesonide and systemic prednisone group. However, patients in the systemic prednisolone group did experience a significant upward trend in blood glucose. Although GOLD guidelines now list nebulized budesonide as an alternative yet expensive option to oral corticosteroids, larger studies are needed to confirm the long-term impact of clinical outcomes of nebulized corticosteroids for acute exacerbations of chronic obstructive pulmonary disease, as well as to differentiate nebulized steroid choice and optimal dosage. [14, Rank 5]

Variable Responsiveness of Corticosteroids

Despite large prospective trials showing modest benefits for the use of corticosteroids in chronic obstructive pulmonary disease, there seems to be a great deal of patient-to-patient variability regarding efficacy. Pharmacogenetics provides a potential rationale for this variability. Researchers identified a single gene that had several single nucleotide polymorphisms in adult and paediatric patients with asthma that correlated well with response to inhaled corticosteroids. More recently, a study showed a decreased concentration of histone deacetylases in peripheral lung tissue from patients with chronic obstructive pulmonary disease. The concentration of histone deacetylases correlated with the severity of chronic obstructive pulmonary disease. Histone deacetylases suppresses inflammatory gene expression, thus giving rise to more robust inflammatory responses and may be central to the pathogenesis of chronic obstructive pulmonary disease. Histone deacetylases -2, one of 11 histone deacetylases isoenzymes located within the cell nucleus, is vital to the ability of

corticosteroids to turn off inflammatory genes. Lung concentrations of histone deacetylases -2, or perhaps polymorphisms of the genes, may confer varying degrees of steroid resistance to patients with chronic obstructive pulmonary disease. [15, Rank 3]

Systemic Corticosteroids

Stable COPD

As the pathogenesis of chronic obstructive pulmonary disease has become better understood, it has become clear that systemic inflammation may be responsible for many of the symptoms and the reduction in quality of life (QOL). It therefore seems reasonable that the chronic use of systemic corticosteroids (as shown in figure 9) to reduce inflammation may be beneficial in chronic obstructive pulmonary disease. However, no study has shown a significant long-term benefit of systemic corticosteroids in stable chronic obstructive pulmonary disease. In fact, there is a suggestion that the use of systemic steroids in patients over the age of 65 with stable chronic obstructive pulmonary disease may increase mortality. Additionally, chronic use of systemic corticosteroids is associated with significant toxicity, including

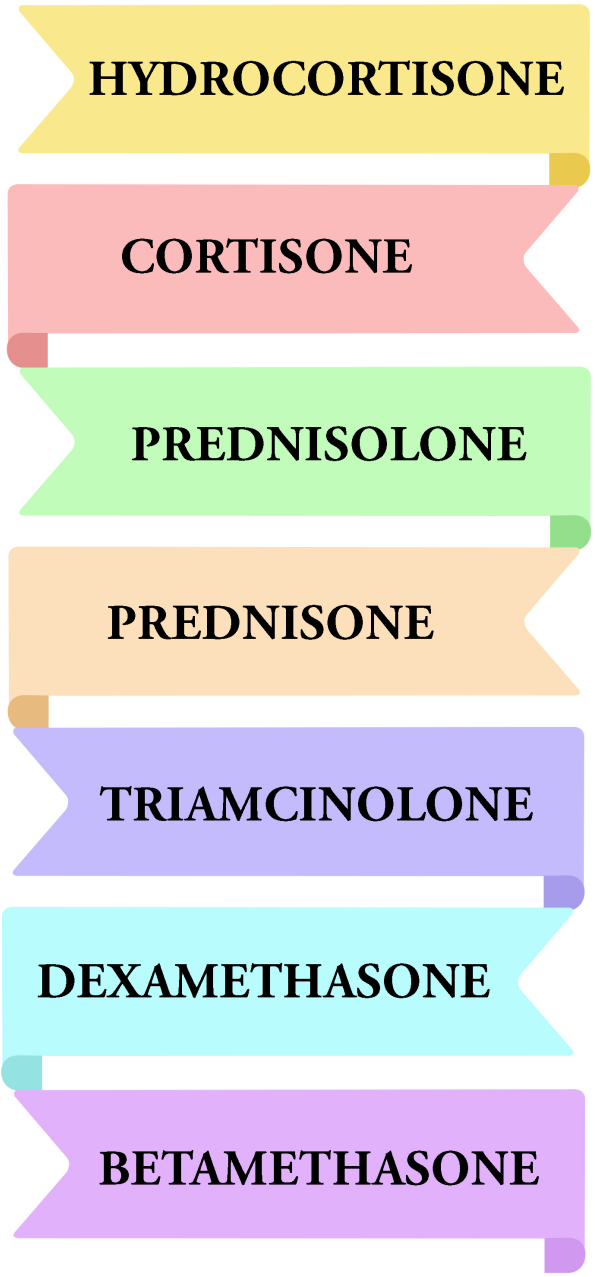

Figure 9: Examples of systemic corticosteroids

hyperglycemia, myopathy, hypertension and osteoporosis. Systemic steroids may be safely weaned from chronic users with chronic obstructive pulmonary disease without adversely affecting lung function, dyspnoea and exacerbation rate. The most notable physiological change in patients weaned from corticosteroids was a significant loss of weight. [16, Rank 5]

Exacerbations of COPD

Systemic corticosteroids have been shown to improve pulmonary function, shorten hospitalizations, improve dyspnea and decrease relapse rate in the treatment of exacerbations. Three prospective, randomized controlled trials have looked at the use of systemic steroids in the treatment of in patients with chronic obstructive pulmonary disease exacerbations. A study randomly assigned patients admitted for chronic obstructive pulmonary disease exacerbations to 0.5 mg/kg of intravenous methylprednisolone every 6 hours for 72 hours or to placebo. There was a significant improvement in pre and post bronchodilator forced expiratory volume in 1 second in those treated with methylprednisolone. In another large trial comparing placebo with 2 and 8 weeks of systemic corticosteroids, the rate of treatment failure (defined as death from any cause, need for intubation and mechanical ventilation, readmission to the hospital for chronic obstructive pulmonary disease, or intensification of drug therapy) was found to be significantly higher in the placebo group at 30 and 90 days. Additionally, patients in the corticosteroid arms showed improvements in forced expiratory volume in 1 second for the first 3 days and had shorter lengths of stay. There were no significant differences between 2 and 8 weeks of corticosteroids. Patients in the steroid groups had an increased incidence of hyperglycemia compared with those in the placebo group. [17, Rank 4]

Inhaled Corticosteroids

Figure 10: Examples of inhaled corticosteroids

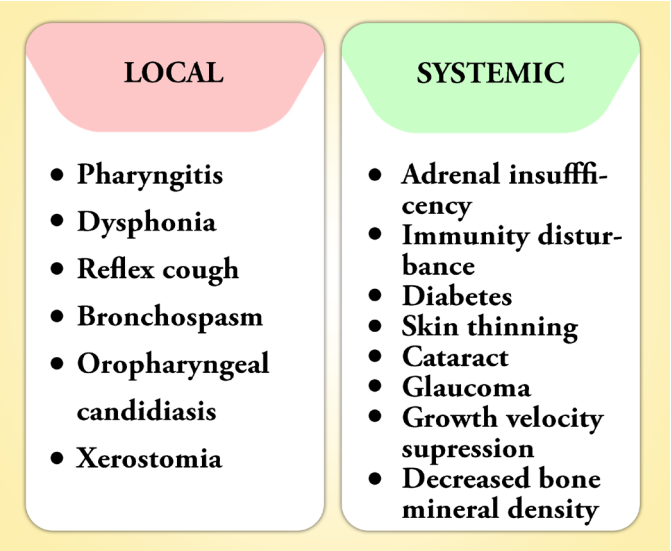

Figure 11: Side effects if ICS

Regular treatment with inhaled glucocorticosteroids (as shown in figure 10) does not modify the long term decline of forced expiratory volume in 1 second in patients with chronic obstructive pulmonary disease. However regular treatment with inhaled glucocorticosteroids is appropriate for symptomatic chronic obstructive pulmonary disease patients with an forced expiratory volume in 1 second <50 % (Stage III, Stage IV) and repeated exacerbations. This treatment has been shown to reduce the frequency of exacerbations and thus improve health status and withdrawal from treatment with inhaled glucocorticosteroids can lead to exacerbations in some patients. The possibility of side effects increases as the dose of the medicine increases. Side effects are less likely to occur when you use the inhaled form of the medicine (as shown in figure 11).

Inhaled corticosteroids are usually delivered usually using a metered dose inhaler (MDI) but are also often available for dry powder inhalers (DPI).

Stable COPD

The use of inhaled corticosteroids in the treatment of stable chronic obstructive pulmonary disease has been in clinical practice for decades; however, the precise role of inhaled corticosteroids remains controversial. There have been many prospective, placebo-controlled trials examining the benefit of inhaled corticosteroids in stable chronic obstructive pulmonary disease. Two large early trials examining the benefits of inhaled budesonide in patients with mild airflow obstruction had similar results. A meta analysis conducted a 3-year study of 1,277 smokers with mild chronic obstructive pulmonary disease who were given inhaled budesonide or placebo. Although there was no slowing in the rate of decline in lung function over the study period, there was an initial significant improvement in forced expiratory volume in 1 second and a slowing of the progression of disease over the initial 6 months of the study when compared with placebo. In a similar study, researchers prospectively followed 290 patients with mild to moderate chronic

obstructive pulmonary disease and found no change in the rate of decline of forced expiratory volume in 1 second. There was no decrease in the rate of exacerbation with inhaled corticosteroids in this patient population. The Lung Health Study in many ways mirrored the findings previously reported on the absence of benefit of inhaled corticosteroids on decline in lung function; however, there were positive secondary benefits, including improved symptoms, decreased physician visits and less airway hyper reactivity. [18, Rank 5]

Evidence supporting the use of inhaled corticosteroids in patients with severe chronic obstructive pulmonary disease has been provided by the ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe) trial in which 751 patients with chronic obstructive pulmonary disease were randomized to receive inhaled fluticasone twice daily or placebo over a 3-year period. Although there was no difference between groups in the rate of decline in lung function, the group treated with inhaled corticosteroids had significant reductions in rate of exacerbation, improved response to bronchodilator therapy and improved quality of life as measured by the St. George's Respiratory Questionnaire. The Inhaled Steroids in Obstructive Lung Disease in Europe trial did not examine treatment effect by severity of disease. In a follow-up to the Inhaled Steroids in Obstructive Lung Disease in Europe trial, Jones and colleagues looked at the efficacy of inhaled fluticasone in reducing the rate of exacerbations in patients with moderate/ severe versus mild chronic obstructive pulmonary disease as determined by an forced expiratory volume in 1 second of less than 50% predicted or above 50% predicted, respectively. Improvements in the rate of exacerbation were limited to patients with severe disease; however, when patients who had at least one exacerbation were examined, both the mild and severe groups showed decreased rates of exacerbation with the addition of inhaled corticosteroids. Further support for the role of inhaled corticosteroids in chronic obstructive pulmonary disease comes from the COPE study in which patients were treated with high-dose inhaled fluticasone for 4 months. The inhaled corticosteroids were discontinued in half of the patients, who then received placebo. Patients discontinuing fluticasone had increased rates of exacerbation and worse quality of life as measured by the St. George's Respiratory Questionnaire. [19, Rank 3]

With the recent availability of combined long-acting β-agonists (LABAs) and inhaled corticosteroids, there have been a

number of trials examining their efficacy in chronic obstructive pulmonary disease. Two similar 24-week trials of combined fluticasone and salmeterol have shown improved lung function and measures of dyspnea when compared with placebo or either individual component, which were sustained throughout the study period. In a 12-month study, researchers evaluated 1,465 patients with moderate to severe chronic obstructive pulmonary disease and examined the effect of combined fluticasone and salmeterol on lung function over 1 year. Pre-treatment forced expiratory volume in 1 second improved significantly when compared with placebo or with inhaled cortiosteroids or long-acting β-agonists given alone. Combined treatment improved quality of life and decreased the rate of exacerbation, particularly in patients with a forced expiratory volume in 1 second of less than 50% predicted. Patients with severe chronic obstructive pulmonary disease may show particular benefit to combined inhaled corticosteroids and long-acting β-agonists as when compared with long-acting β-agonists alone because patients with an forced expiratory volume in 1 second of less than 50% predicted had a 35% reduction in moderate and severe chronic obstructive pulmonary disease exacerbations over a 44-week study period. A Cochrane review of prospective, randomized controlled trials examining the role of combined long-acting β-agonists and inhaled corticosteroids revealed an overall improvement in pre-dose forced expiratory volume in 1 second in patients receiving both long-acting β-agonists and inhaled corticosteroids compared with placebo or with long-acting β-agonists or inhaled corticosteroids alone. No differences in rates of exacerbation were observed with combined long-acting β-agonists and inhaled corticosteroids compared with inhaled corticosteroids alone. There were conflicting results regarding quality of life measures, although fluticasone/ salmeterol and budesonide/ formoterol were superior to placebo. [20, Rank 4]

Until recently, no large, prospective, controlled trials had shown that use of inhaled or systemic corticosteroids altered the natural history of chronic obstructive pulmonary disease or affected survival. Several recent observational studies have provided conflicting results with regards to survival. The TORCH (Towards a Revolution in Chronic obstructive pulmonary disease Health) trial randomized approximately 6,000 patients with chronic obstructive pulmonary disease to combined fluticasone/ salmeterol, fluticasone alone, salmeterol alone, or placebo and treated them for

a 3-year period. The primary endpoint was death from any cause. There was a 17.5% risk reduction for death in the combined group compared with placebo, which nearly (P = 0.052) met statistical significance. In addition to a reduction in all-cause mortality, there were statistically significant improvements in yearly exacerbation rate (P < 0.001) and pulmonary function in the combined group (62-ml decrement over 3 yr in placebo group vs. 29-ml increase in the combined group; P < 0.001). There was a significant increase in the rate of pneumonia in the two corticosteroid arms when compared with placebo (19.6 and 18.3% vs. 12.3%, respectively; P < 0.001). This increase in pneumonia rate did not translate into increased mortality. Another recent study followed 449 patients with moderate to severe chronic obstructive pulmonary disease were randomized to 1 year of inhaled tiotropium, tiotropium plus salmeterol, or tiotropium plus salmeterol and fluticasone. There were no statistically significant differences in the three groups regarding having at least one exacerbation during a year, but the fluticasone-containing arm did show improvements in lung function (P = 0.04), QOL (P = 0.01) and a reduction in hospitalizations for chronic obstructive pulmonary disease exacerbations (P < 0.01). In contrast to the TORCH

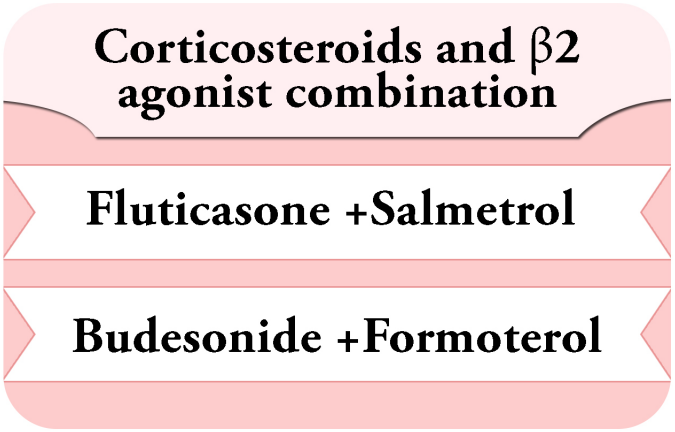

Figure 12: Corticosteroids and β-agonists combination drugs

trial, no increase in rate of pneumonia was observed for the corticosteroid-containing arm; in fact, the percentage of patients reporting pneumonia over the course of the 1-year study was only 0.7%.

Although the clinical observation that an additive benefit of inhaled corticosteroids and long-acting β-agonists (as shown in figure 12) for patients with chronic obstructive pulmonary disease exists, the mechanism of this finding is less clear. Some have proposed that the addition of long-acting β-agonists to inhaled corticosteroids promotes bronchodilation and thus improved delivery of drug to distal airways. On a molecular level, steroids may have a beneficial effect on β2-adrenoceptors, including receptor up-regulation and a reduction in tachyphylaxis, thus maximizing the effect of β-agonists. Alternatively, β-agonists have been shown to augment glucocorticoid receptor function. [21, Rank 3]

Exacerbations of COPD

The possibility of using inhaled corticosteroids rather than systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease is theoretically attractive because patients may be spared the toxicity associated with systemic corticosteroids. Studies reported successful use of nebulized budesonide in treating acute exacerbations of chronic obstructive pulmonary disease. Patients were randomized to 2 mg nebulized budesonide every 6 hours, 30 mg of prednisolone every 12 hours, or placebo for 72 hours. The budesonide and prednisolone groups had statistically significant improvements in post bronchodilator forced expiratory volume in 1 second when compared with the placebo group, but no differences were noted between the budesonide and prednisolone groups. A significantly increased number of patients in the prednisolone groups became hyperglycemic. [22, Rank 2]

Duration of Therapy

Following clinical trials documenting the efficacy of systemic corticosteroids in the treatment of acute exacerbations of chronic obstructive pulmonary disease, studies were conducted in an attempt to establish the optimal treatment duration. A parallel-group, single-blind, single-centre study compared the efficacy of different durations of corticosteroid therapy in improving airflow obstruction and gas exchange, relieving symptoms and preventing recurrence in patients with acute exacerbations of chronic obstructive pulmonary disease (n=36). Patients with severe chronic obstructive pulmonary disease were randomized to receive intravenous methylprednisolone for 3 days or tapered over 10 days. All patients were hospitalized for at least 10 days and received a high-dose inhaled β-agonist, ipratropium, theophylline, and histamine H2-receptor antagonists. Antibiotics were administered if indicated. Primary outcomes were post bronchodilator forced expiratory volume in 1 second and PaO2 levels on days 3 and 10. Secondary outcomes included symptoms related to exacerbation of chronic obstructive pulmonary disease (eg, dyspnea, cough), recurrence of exacerbation within 6 months of study enrolment and treatment-related adverse events.

> "People using fluticasone combined with β agonists were more likely to develop pneumonia."

While forced expiratory volume in 1 second in both treatment groups increased significantly from baseline, the increase in forced expiratory volume in 1 second in the 10-day treatment group was significantly higher than the increase in the 3-day treatment group (236 mL versus 68 mL, P=0.019). Compared to baseline, there was significant symptom-score improvement in both the 3-day and 10-day treatment groups. Symptoms related to exacerbation of chronic obstructive pulmonary disease were significantly better in the 10-day treatment group compared to the 3-day treatment group (P=0.009). There was no observed difference in the rate of recurrence between the treatment groups at 6 months (35% in 3-day treatment group versus 29% in 10-day treatment group). There was no significant difference in the rate of hyperglycaemia between the two treatment groups. However, one patient in the 10-day treatment group developed steroid-associated psychosis.

A systematic review comprised of two published studies (including the aforementioned trial) and two published abstracts (n=146) inconclusively found no significant difference in the risk of treatment failure between a short duration (7 days or less) and longer duration (greater than 7 days) of corticosteroid therapy in the treatment of acute exacerbation of chronic obstructive pulmonary disease (OR 0.82, 95% CI 0.24–2.79). In addition, the mean differences in forced expiratory volume in 1 second did not differ significantly by treatment duration, nor did the likelihood of an adverse event. [23, Rank 3]

Considering data that suggested a short course of systemic corticosteroids was not associated with worse outcomes in comparison to longer treatment courses in the treatment of acute exacerbations of chronic obstructive pulmonary disease, a non inferiority trial was conducted to evaluate the efficacy of a reduced duration of systemic corticosteroid therapy in comparison to conventional systemic corticosteroid treatment. All patients presenting with acute exacerbations of chronic obstructive pulmonary disease were given a one-time dose of intravenous methylprednisolone on day 1 and then randomized to receive oral prednisone once daily to complete a total of either 5 days (n=155) or 14 (n=156) days of systemic corticosteroid therapy. In addition to systemic corticosteroids, all patients received an inhaled β2-agonist twice daily, tiotropium once daily and inhaled glucocorticoids twice daily throughout the study. All patients received a broad-spectrum antibiotic for 7 days and as-needed nebulized short-acting bronchodilators while

hospitalized. Patients were assessed daily while hospitalized and on days 6, 15, 30, 90 and 180 following hospital discharge. The primary end point was time to next chronic obstructive pulmonary disease exacerbation during a follow-up of 6 months. Secondary end points included all-cause mortality, change in forced expiratory volume in 1 second, cumulative corticosteroid dose and clinical performance. Duration of hospital stay and corticosteroid-related adverse effects were also assessed. Non inferiority was defined a priori as an HR of less than 1.515.

The majority of study participants were classified as GOLD chronic obstructive pulmonary disease grade 4 (52.1%); mean baseline forced expiratory volume in 1 second was 31.5% predicted. Time to exacerbation did not differ significantly between a 5-day course of systemic corticosteroids and a 14-day course. A total of 56 patients (35.9%) experienced acute exacerbations of chronic obstructive pulmonary disease within 6 months of hospital discharge in the short-term group compared to 57 patients (36.8%) in the conventional treatment group (HR 0.95 per intent-to-treat analysis, 90% CI 0.7–1.29; P=0.006). Among patients who experienced re-exacerbation of chronic obstructive pulmonary disease during follow-up, the median time to event was 43.5 days in the short-term group and 29 days in the conventional treatment group. [24, Rank 2]

Overall survival did not differ between the two treatment groups, nor did the need for mechanical ventilation during hospitalization. Alleviation of dyspnoea and improvement of bronchitis-associated quality of life and patient-assessed overall performance occurred over the first 5 days of treatment and did not vary significantly between the two groups. Patients randomized to receive short-term systemic corticosteroid treatment had a significantly shorter duration of hospital stay (median duration of hospital stay of 8 days, 95% CI 7–9 days) compared to patients receiving conventional systemic corticosteroid treatment (median duration of hospital stay of 9 days, 95% CI 8–10 days; P=0.04). Forced expiratory volume in 1 second improved significantly from baseline to day 6 and remained stable thereafter in both groups. Although patients receiving conventional therapy were exposed to significantly higher cumulative doses of systemic corticosteroids (median cumulative prednisone dose of 379 mg versus 560 mg in the short-term therapy and conventional therapy groups, respectively; P<0.001), a detectable difference in corticosteroid-related adverse events between the two groups was not reported. New or worsening hyperglycemia was

observed in 74 patients (56.9%) in the short-term and 74 patients (57.4%) in the conventional treatment group (P>0.99); hypertension developed or worsened in 15 patients (11.6%) in the short-term and 23 patients (17.8%) in the conventional treatment group (P=0.22). [25, Rank 5]

Route of Administration

Intravenous vs. Oral Administration

Current guidelines for the management of chronic obstructive pulmonary disease recommend low-dose oral corticosteroids for the treatment of exacerbations. Oral corticosteroids have very good bioavailability (generally >85%), greater ease of administration, and lower costs. Despite evidence of the efficacy of oral corticosteroids compared to placebo and guideline recommendations, intravenous corticosteroids are still routinely used for the treatment of acute exacerbations of chronic obstructive pulmonary disease. Studies comparing intravenous to oral corticosteroids in the asthma population also support the use of oral steroids. To date, only two studies have directly compared intravenous and oral regimens for the treatment of acute exacerbation of chronic obstructive pulmonary disease.

The first was a single-centre, double-blind, double-dummy trial that randomized 435 patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease to equivalent doses of intravenous or oral prednisolone (60 mg) once daily for 5 days. After day 5, all patients were prescribed an oral tapering schedule beginning with prednisolone 30 mg daily. Patients were all older than 40 years of age with at least a 10 pack-year smoking history and evidence of airflow limitation. Those experiencing very severe exacerbations (arterial pH <7.26 or PaCO2 >9.3 kPa) or with unstable co-morbidities were excluded. The primary outcome was treatment failure: a composite end point of all-cause mortality, intensive care unit admission, readmission due to chronic obstructive pulmonary disease or intensification of treatment. The proportion of patients experiencing treatment failure in the intravenous group was 61.7% compared to 56.3% in the group receiving oral prednisolone, and was non inferior to intravenous prednisolone therapy. Secondary outcomes of forced expiratory volume in 1 second, quality-of-life scores and length of hospital stay were comparable between the two groups. The use of equipotent doses of intravenous and oral corticosteroids provides data to support the use of the oral route for the

treatment of chronic obstructive pulmonary disease exacerbations, when feasible. This finding is further supported by several studies in patients with asthma reporting no benefit with intravenous corticosteroids compared to oral corticosteroids. The trial did not answer whether high-dose intravenous corticosteroids are more efficacious than low-dose oral corticosteroids, nor can these findings be applied to patients experiencing very severe exacerbations, as they were excluded from this trial. [26, Rank 2]

A large observational study utilizing claims data from 414 US hospitals evaluated the effects of high-dose intravenous corticosteroids versus low-dose oral corticosteroids in 79,985 patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. Patients were identified for inclusion by International Classification of Diseases, ninth revision, clinical modification codes representative of acute exacerbations of chronic obstructive pulmonary disease, and received either low-dose oral corticosteroids (20–80 mg of prednisone equivalents daily) or high-dose intravenous corticosteroids (120–180 mg of prednisone equivalents daily) as initial therapy (hospital days 1–2). Key exclusion criteria included initial admission to the intensive care unit, diagnosis of pneumonia or pulmonary embolism, hospitalization less than 2 days and transfer from other acute care facilities. The primary outcome was a composite end point of treatment failure, including mechanical ventilation after day 2, inpatient mortality or readmission within 30 days for acute exacerbations of chronic obstructive pulmonary disease. Ninety-two percent of patients (73,765) were initially treated with high-dose intravenous corticosteroids, whereas only 8% (6,220) were treated with low-dose oral corticosteroids. Median total corticosteroid doses for the first 2 days of hospitalization were 600 mg and 60 mg of prednisone equivalents for the intravenous and oral groups, respectively. The use of oral corticosteroids was not associated with greater rates of treatment failure, but was associated with lower hospital cost and length of stay. Limitations of this study were its observational design and use of claims data that did not allow the investigators to adjust for clinical findings.

These studies, in addition to the high bioavailability of corticosteroids and the vast literature supporting the efficacy of corticosteroids in asthma exacerbations, provide evidence to support the use of low-dose oral corticosteroids for the treatment of patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease who are not admitted to the intensive care unit. [27, Rank 5]

Inhaled Corticosteroids

Although low-dose oral corticosteroids are recommended for acute exacerbations of chronic obstructive pulmonary disease, systemic exposure predisposes patients to a significant adverse-effect profile. Adverse effects, such as hyperglycemia, myopathy, osteoporosis, thinning of the skin and posterior subscapular cataract formation, more than any other factor, are most influenced by cumulative steroid dose. Those with frequent exacerbations are of particular concern, as they receive multiple courses of corticosteroid treatment and often higher-dose regimens to control acute exacerbations.

As an alternative to systemic steroids, nebulized corticosteroids have minimal bioavailability, negligible systemic absorption, and minimal systemic adverse effects. In addition; inhaled corticosteroids have a high level of anti-inflammatory activity at the local level. Currently, GOLD guidelines offer nebulized budesonide as an alternative to oral corticosteroids for the treatment of exacerbations.

In a double-blind, randomized, placebo-controlled trial, researchers compared nebulized budesonide, oral prednisolone and placebo in 199 patients requiring hospital admission for acute exacerbations of chronic obstructive pulmonary disease. Patients were randomized to one of three treatment groups: group 1 nebulized budesonide 2 mg every 6 hours for 72 hours (plus placebo tablets), then inhaled budesonide 2 mg for 7 days, group 2 prednisolone 30 mg by mouth every 12 hours (plus placebo nebulization), then prednisolone 30 mg by mouth daily for 7 days, or group 3 placebo group (placebo tablets + placebo nebulization). All patients were administered terbutaline or salbutamol/ipratropium nebulizer treatment after receiving one of the three study drugs, as well as antibiotics and supplemental oxygen. [28, Rank 5]

> **"Oral corticosteroids may be used to treat COPD when symptoms rapidly get worse (COPD exacerbations) especially when there is increased mucus production"**

The primary end point was changed in post-bronchodilator forced expiratory volume in 1 second at 72 hours. Clinical success was predefined as an increase in forced expiratory volume in 1 second of at least 0.15 L and a reduction of PaCO2 of at least 5 mmHg. The mean change in post-bronchodilator forced expiratory volume in 1 second (95% CI) at 72 hours was greater with active treatments than with placebo: budesonide versus placebo, 0.10 L

(0.02–0.18 L); prednisolone versus placebo, 0.16 L (0.08–0.24 L). The difference in forced expiratory volume in 1 second between budesonide and prednisolone was not significant, at –0.06 L (–0.14 to 0.02 L). Rates of adverse events were similar in all three groups. As expected, a greater percentage of patients developed hyperglycemia in the prednisone group (n=7) versus budesonide (n=1). In summary, nebulized budesonide and prednisone improved airflow limitation versus placebo.

Another study evaluated nebulized budesonide as an alternative to systemic corticosteroids. In this prospective study, patients were also randomized into three groups: group 1 received standard bronchodilator therapy (SBDT), group 2 received 40 mg of prednisolone plus standard bronchodilator therapy, and group 3 received 1,500 µg of nebulized budesonide plus received standard bronchodilator therapy. Improvement during 10-day hospitalization was compared with exacerbation and hospitalization rates post discharge.

Similar to the previous study, the recovery rate in terms of both spirometry and arterial blood-gas results did not differ between the nebulized budesonide and systemic prednisone group. However, patients in the systemic prednisolone group did experience a significant upward trend in blood glucose.

Although guidelines now list nebulized budesonide as an alternative yet expensive option to oral corticosteroids, larger studies are needed to confirm the long-term impact of clinical outcomes of nebulized corticosteroids for acute exacerbations of chronic obstructive pulmonary disease, as well as to differentiate nebulized steroid choice and optimal dosage. [29, Rank 2]

Perioperative Use of Corticosteroids

There are scant prospective, randomized data examining the use of systemic corticosteroids in the perioperative management of the patient with chronic obstructive pulmonary disease. Researchers studied 40 patients with moderate chronic obstructive pulmonary disease who underwent coronary artery bypass surgery. Half of the patients were randomized to receive 20 mg of prednisolone 10 days before surgery and then continued with prednisolone until the day of surgery, after which the dose was halved every third day; the other 20 patients received placebo. The steroid group had a significant improvement in forced expiratory volume in 1 second on the day of surgery and just before discharge; however, by 3 months there was no difference in lung function. Patients receiving steroids had

> "Inhaled corticosteroids may be used to treat stable symptoms of COPD or symptoms that are slowly getting worse.
>
> Inhaled corticosteroids may decrease the number of COPD exacerbations in people with severe COPD, particularly those with chronic bronchitis and frequent exacerbations"

shorter duration of mechanical ventilation, shorter ICU stays and shorter overall hospital days. Although this study was limited in size, it provides a basis for a larger trial. [30, Rank 3]

Steroid Toxicity

Inhaled Corticosteroids

The rationale for the use of inhaled corticosteroids is multifactorial. It allows delivery of a drug directly to the target organ and the ability to use lower cumulative doses of corticosteroid and to avoid systemic absorption. Although a complete absence of systemic absorption of inhaled corticosteroids would be ideal, this is not the case. Because of first-pass metabolism (as shown in figure 13) of the liver, virtually none of the inhaled corticosteroids typically used for the treatment of chronic obstructive pulmonary disease, fluticasone proprionate and budesonide, are absorbed through the gastrointestinal tract. Therefore, the vast majority of systemically absorbed corticosteroid occurs through the lungs. In the case of fluticasone, less systemic absorption occurs in patients with diseased lung than in patients with normal lung function. Despite the theoretical bene

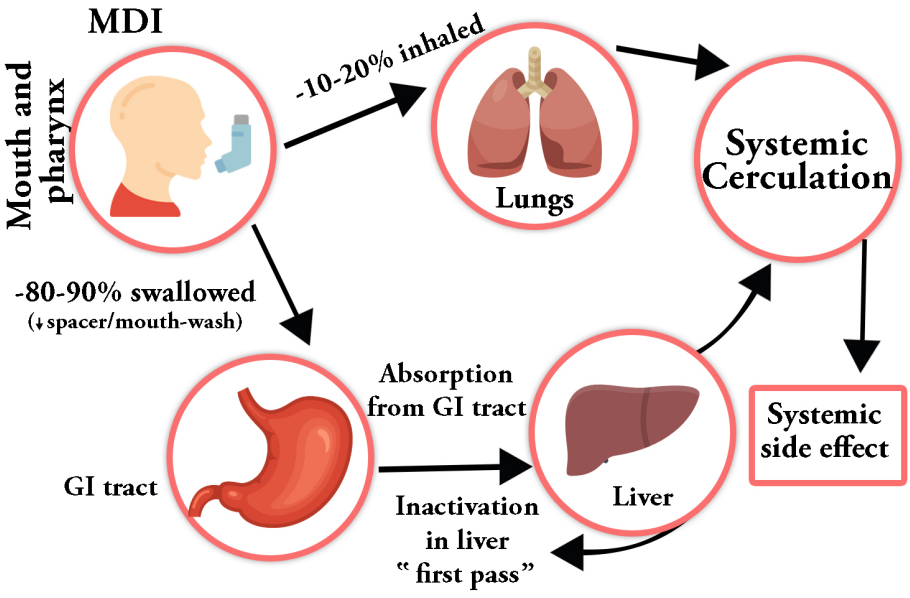

Figure 13: First pass metabolism of ICS

fit of lower overall systemic corticosteroid levels, there are documented adverse biological effects of inhaled corticosteroids use, including adrenal suppression, loss of bone mass density and increased risk of fracture, glaucoma, and skin bruising. The TORCH trial showed no increase in the rate of fractures in either of the groups receiving inhaled corticosteroids. [28, Rank 2-

Systemic Corticosteroids

The toxicities associated with short- and long-term use of systemic corticosteroids are extensive and have been well described previously. Regarding treatment of chronic obstructive pulmonary disease, toxicities seem to be linked to cumulative dose and duration of therapy. Patients with stable chronic obstructive pulmonary disease treated with systemic corticosteroids have been noted to have increased risk of glucose intolerance, decreased serum levels of osteocalcin, and increased risk of adrenal insufficiency. In addition, the degree of respiratory and peripheral muscle weakness has been shown to correlate with dose and duration of systemic steroid use in chronic treatment of chronic obstructive pulmonary disease. Courses of systemic steroids for exacerbations have been associated with hyperglycemia, weight gain, insomnia, anxiety, and depression. [27, Rank 4]

Mechanism of Action of Corticosteroids

Corticosteroids have many cell- and tissue-specific anti-inflammatory effects that have been extensively described. The corticosteroid enters the cell cytoplasm and binds with the inactive glucocorticoid receptor complex. Consequently, the activated glucocorticoid receptor binds to DNA at the glucocorticoid response element sequence and promotes synthesis of antiinflammatory proteins (transactivation) and inhibits transcription and synthesis of many proinflammatory cytokines (transrepression). Transactivation is also responsible for many adverse systemic effects of corticosteroids. Corticosteroids also reduce the number of T lymphocytes, dendritic cells, eosinophils, and mast cells in airways and reduce inducible nitric oxide production. [22, Rank 4]

Pharmacodynamics

As with other drugs whose mechanisms are receptor mediated, corticosteroids exhibit a log–dose linear effect; thus, the clinical dose response is often described as flat because doubling the dose is relatively ineffective in producing significant changes in outcomes. The inhaled corticosteroids dose response is further complicated

because the various measures of response (lung function, bronchial hyper responsiveness, asthma symptom control, exacerbations, sputum and exhalation markers of inflammation) are downstream events from the direct anti inflammatory effects that have been extensively reviewed. Most studies and meta-analyses of the dose response suggest that most of the benefit from inhaled corticosteroids occurs in the low to medium dose range with minimal additional improvement with higher doses, although some patients may benefit from these higher doses.

Factors associated with a diminished dose response to inhaled corticosteroids include genetic polymorphisms, chronic obstructive pulmonary disease, smoking, severe asthma, obesity and vitamin D insufficiency. Patients with asthma who are homozygous for the variant allele rs37973, which maps to the glucocorticoid-induced transcript 1 gene (GLCCI1), show about one third the lung function response of that of those homozygous for the wild-type allele. The variant occurs in about 16% of the population. Smoking, chronic obstructive pulmonary disease and severe asthma result in oxidative stress and influx of multiple inflammatory cytokines that produce glucocorticoid resistance through a number of heterogeneous molecular mechanisms that have been extensively reviewed. Even in utero smoke exposure has been associated with diminished response to inhaled corticosteroids in school-aged children. There are ongoing prospective clinical trials to determine whether vitamin D supplementation restores inhaled corticosteroids responsiveness in patients with insufficiency. [25, Rank 5]

Dosing Strategies

All of the current inhaled corticosteroids are more effective when administered twice daily in moderate to severe asthma; however, they have been shown to control mild asthma with once-daily dosing. The issue of improving compliance with once-daily administration of the inhaled corticosteroids remains to be evaluated in controlled clinical trials.

In patients with mild or intermittent asthma, the use of inhaled corticosteroids as needed with rescue bronchodilator or intermittently at high doses for a prescribed duration (5–10 d) has been investigated in paediatric and adult populations. These studies have been inconsistent and confirm greater efficacy of daily use of inhaled corticosteroids for controlling the impairment domain and mixed effects on preventing exacerbations requiring oral corticosteroids. Although the combination budesonide

with the long-acting β2 agonist (LABA) formoterol in a single inhaler has been approved in Europe and other countries for maintenance and reliever therapy, it has not been approved for this use in the United States and recently concerns have been expressed that patients receiving this therapy are not well controlled and may have inadequately treated airways inflammation. The use of intermittent inhaled corticosteroids therapy for preschool children with viral-induced wheezing is of particular interest. Two recent trials suggest that intermittent high-dose use is as effective as continuous low-dose therapy and placebo in infants and young children. However, the children in the latter trial who received very-high-dose fluticasone (1.5 mg/d via metered dose inhalers plus valve holding chambers) experienced systemic effects of weight and growth retardation, whereas the children who received high-dose budesonide (2.0 mg/d via jet nebulization) did not. Thus, optimal dosing for this strategy needs to be determined. [21, Rank 4]

It has been posited that the newer, small-particle–generating (or ultrafine particle) inhaled corticosteroids metered dose inhalers may provide enhanced control because of their improved delivery to the peripheral small airways. It has been well documented that small airways (<2 mm diameter) inflammation results in increased air trapping and bronchial hyper responsiveness and is associated with increased nocturnal asthma and severe uncontrolled asthma phenotypes. Small airways dysfunction is also common in chronic obstructive pulmonary disease. Although initial investigations in small numbers of patients have demonstrated preferential improvement in some measures of small airways disease, results have been inconsistent and confounded by differential dosing of the ultrafine versus standard particle delivery devices and study design flaws. In addition, large-scale studies comparing ultrafine and standard-particle inhaled corticosteroids have failed to demonstrate improved asthma outcomes for the ultrafine devices when administered in the clinically comparable doses, although this may be due to the inclusion of patients that do not have significant small airways disease. Improved methods of measuring small airways disease and large-scale trials targeted at patients with significant small airways inflammation are required to determine if targeted therapy provides clinically relevant improvement in asthma and chronic obstructive pulmonary disease control. [20, Rank 3]

Adverse Effects

When used appropriately, inhaled corticosteroids have few adverse events (as shown in figure 14) at low and medium doses. The local side effects result from the deposition of the inhaled corticosteroids in the oropharynx and include hoarseness, candidiasis, cough, and dysphonia. Potential systemic side effects of inhaled corticosteroids include suppression of the hypothalamus-pituitary-adrenal (HPA) axis, Cushing syndrome, osteoporosis, cataracts, dermal thinning and bruising, adrenal insufficiency, and growth suppression in children. Cushing syndrome and associated adrenal insufficiency have been reported with high doses of inhaled corticosteroids or as a result of drug interaction with CYP3A4 inhibitors. Additionally, inhaled corticosteroids therapy increases the risk of pneumonia in patients with chronic obstructive pulmonary disease.

Several methods have been used to measure HPA axis function with 24-hour serum area-under-the-curve cortisol, low-dose adrenocorticotropin stimulation and 24-hour and overnight urinary free cortisol being the most sensitive indicators of exogenous corticosteroid exposure. The standard test to evaluate the full integrity of the hypothalamus-pituitary-adrenal axis is insulin-hypoglycemic stimulation, but standard-dose adrenocorticotropin stimulation has been used for regulatory purposes. Although 24-hour urinary cortisol excretion has been approved to compare relative systemic activity from the inhaled corticosteroids, the degree of suppression does not correlate with risk of adrenal insufficiency. Patients exposed to high doses of inhaled corticosteroids should have their HPA axis monitored. [15, Rank 5]

Reduced bone mineral density and increased risk of fracture have been reported in older patients on high doses of inhaled corticosteroids. Patients with chronic obstructive pulmonary disease have increased risk factors, including smoking, vitamin D insufficiency and immobility; furthermore, the doses of inhaled corticosteroids currently used are in the high-dose range. Recent analyses of prospective trials of inhaled corticosteroids in chronic obstructive pulmonary disease have not demonstrated an increased bone mineral density decline or an increased risk of fractures. However, as many as 60% of patients with chronic obstructive pulmonary disease, particularly patients with more severe disease, may have osteoporosis, so bone mineral density measures should be considered. In children, medium doses of budesonide for 4 to 6 years did not result in

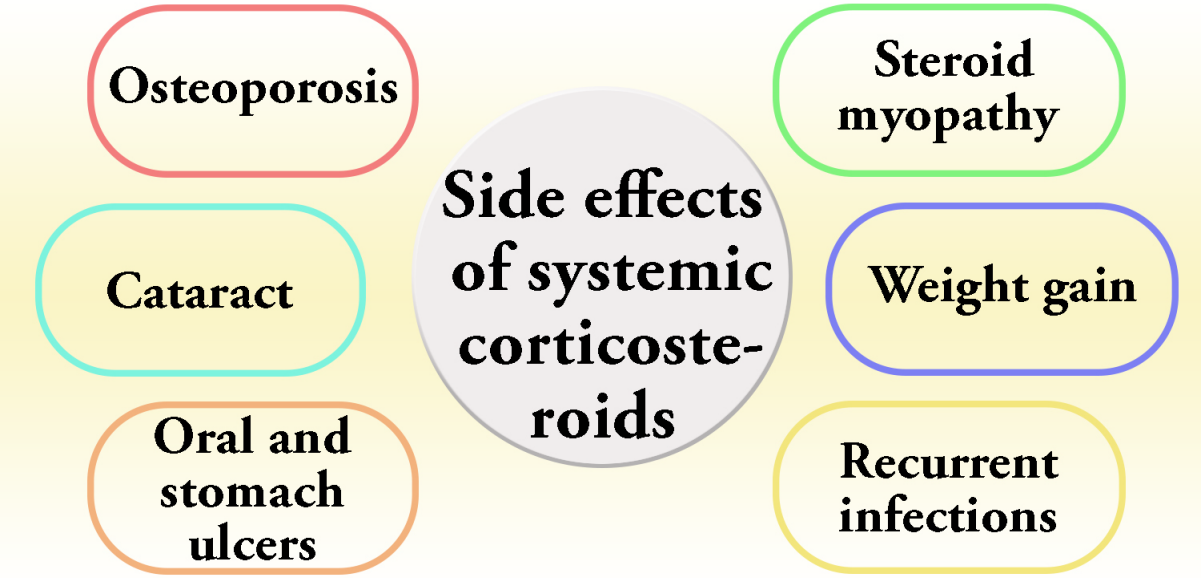

Figure 14: Side effects of systemic corticosteroids

increased risk of osteoporosis or fractures. Elderly patients and patients with severe chronic obstructive pulmonary disease receiving high-dose inhaled corticosteroids should receive appropriate prophylaxis with vitamin D and calcium. Similar to osteoporosis, the risk of cataracts has been reported to be associated with dose and duration of inhaled corticosteroids in elderly patients; however, a long-term prospective trial of 4 to 6 years plus an additional 8-year follow-up with continuous and intermittent therapy did not find an association between inhaled corticosteroids and cataracts.

A major concern for inhaled corticosteroids therapy in young children is the effect on growth. A recent publication reported that the growth suppression seen in the first few years of therapy, although it was dose-dependent and not cumulative, persisted into adulthood. Growth suppression is dose and device dependent and has been reported with low to medium doses of beclomethasone dipropionate metered dose inhaler and budesonide dry-powder inhaler (DPI) in children 4 to 17 years of age and in infants 2 years of age or younger with fluticasone metered dose inhaler plus valve holding chambers but not with low- to medium-dose fluticasone dry-powder inhaler, mometasone furoate dry-powder inhaler, or ciclesonide metered dose inhaler. Several large studies have shown that inhaled corticosteroids alone or in combination are associated with increased pneumonia risk and even death from pneumonia, with a dose-related risk. [19, Rank 4]

Current Use of Corticosteroids

Many of the side effects of inhaled corticosteroids, including pneumonia, bone fracture risk, tuberculosis and diabetes, are dose-related, in terms of both daily dose and lifetime exposure. Despite this, fluticasone/ salmeterol combination is approved in the EU for use in chronic obstructive pulmonary disease only at a daily fluticasone propionate dose of 1000 µg, which is double the 500 µg daily dose approved for chronic obstructive pulmonary disease in the US and Japan. In their review of data on fluticasone/ salmeterol combination 500/50 and 250/50 µg b.i.d. for use in chronic obstructive pulmonary disease, the US FDA reported both a higher frequency of adverse events (78 vs 70%) and no treatment benefit for the higher versus the lower dose. The dosage of budesonide in combination with the long-acting β2 agonist formoterol is also lower in the US than that approved in the EU (200 and 400 µg b.i.d., respectively). Evidence to support the use of the higher rather than the lower doses in the EU is lacking. Comparative efficacy data are also lacking for other inhaled corticosteroids agents, as a 2014 Cochrane network meta-analysis identified only a few prospective head-to-head trials evaluating different doses of the same inhaled corticosteroids (administered alone or with a long-acting β 2 agonist) on relevant chronic obstructive pulmonary disease outcomes. Additionally, the majority of studies powered to investigate the effects of inhaled corticosteroids on important chronic obstructive pulmonary disease outcomes used a single inhaled corticosteroids dose that was the highest dose given among studies included in the meta-analysis. Exceptions include trials of the newer formulation of fluticasone, the furoate salt, which is approved for chronic obstructive pulmonary disease in the EU and the US at the same q.d. dose of 100 µg (in combination with the long-acting β2 agonist vilanterol), after studies showed no additional benefit on lung function or exacerbation frequency of a combination containing a higher (200 µg) dose of fluticasone furoate. Short-term (12-week) head-to-head comparisons showed similar bronchodilator efficacy and also suggested a comparable incidence of pneumonia between fluticasone/ salmeterol combination 500/50 µg b.i.d. and fluticasone furoate/vilanterol 100/25 µg q.d. In duplicate 1-year studies in patients with a history of exacerbations, the incidence of pneumonia with fluticasone furoate/vilanterol 100/25 µg q.d. was higher than with vilanterol 25 µg q.d. alone (6 vs 3%) and similar to the

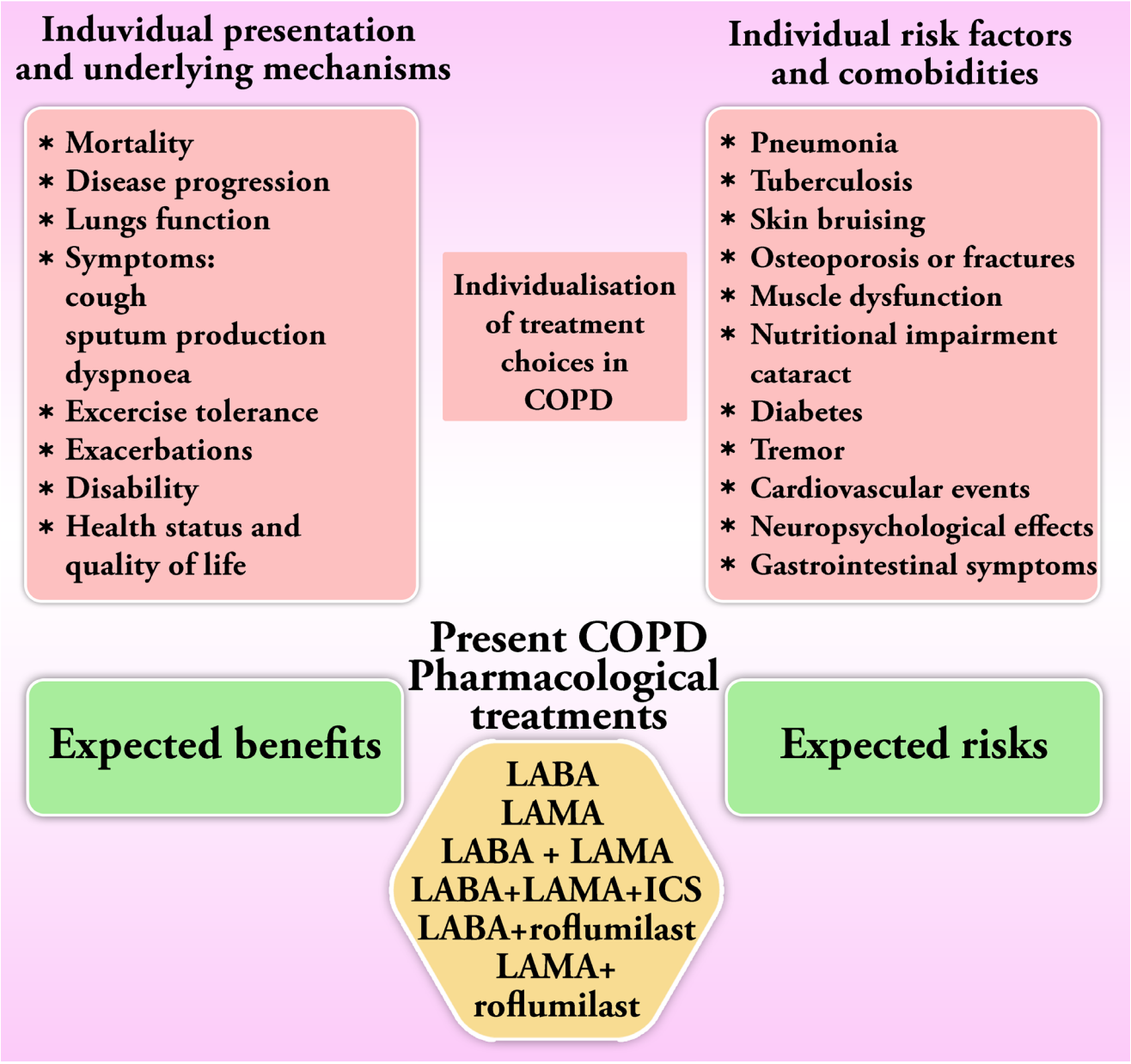

Figure 15: Risk benefit balance on decision of treatment of COPD

incidence of 5% with FSC 500/50 µg b.i.d. reported by Kardos et al. in a comparable patient population. [17, Rank 4]

Benefit risk balance (as shown in figure 15) and its determinants with personalized chronic obstructive pulmonary disease treatment choices have to be kept in mind while deciding on treatment options. When the clinician is deciding which pharmacological treatment options to prescribe to a patient, they have to consider expected benefits (determined by individual presentation and underlying mechanism of the disease) and possible risks (which depend on individual risk.

Asthma-COPD Overlap Syndrome (ACOS)

Some patients present with features of both chronic obstructive pulmonary disease and asthma, described as asthma–chronic obstructive pulmonary disease overlap syndrome. As yet, there is no universally accepted definition of asthma –chronic obstructive pulmonary disease overlap syndrome and no validated diagnostic criteria, although the GINA/GOLD collaboration provides a clinical description: "asthma –chronic obstructive pulmonary disease overlap syndrome is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with chronic obstructive pulmonary disease. Asthma– chronic obstructive pulmonary disease overlap syndrome is therefore identified by the features that it shares with both asthma and chronic obstructive pulmonary disease". The definition of asthma– chronic obstructive pulmonary disease overlap syndrome used in the COPDGENE study is similar and is increasingly used: chronic obstructive pulmonary disease based on usual spirometric criteria and a history of smoking, plus history of asthma before the age of 40 years. The reported prevalence rates of asthma–chronic obstructive pulmonary disease overlap syndrome have varied widely, likely as a result of differences in definition, but 10 – 20% of patients with chronic obstructive pulmonary disease may have asthma–chronic obstructive pulmonary disease overlap syndrome. Although reliable biomarkers for asthma–chronic obstructive pulmonary disease overlap syndrome are not currently available, it is important to identify the syndrome due to different therapeutic strategies for asthma–chronic obstructive pulmonary disease overlap syndrome and chronic obstructive pulmonary disease.

In patients with asthma –chronic obstructive pulmonary disease overlap syndrome, the default is to start treatment (as shown in figure 16) as for asthma, that is, inhaled corticosteroids at low or moderate dose plus a long-acting β2 agonist, in recognition of the potentially life-saving role of inhaled corticosteroids in asthma. Long acting muscarinic acid treatment can also be considered in addition to inhaled corticosteroids/ long-acting β2 agonist. In the previously mentioned cohort study comparing new users of inhaled corticosteroids/ long-acting β-agonists or long-acting β2 agonist, there was only a modest overall benefit for inhaled corticosteroids/ long-acting β2 agonist but the greatest

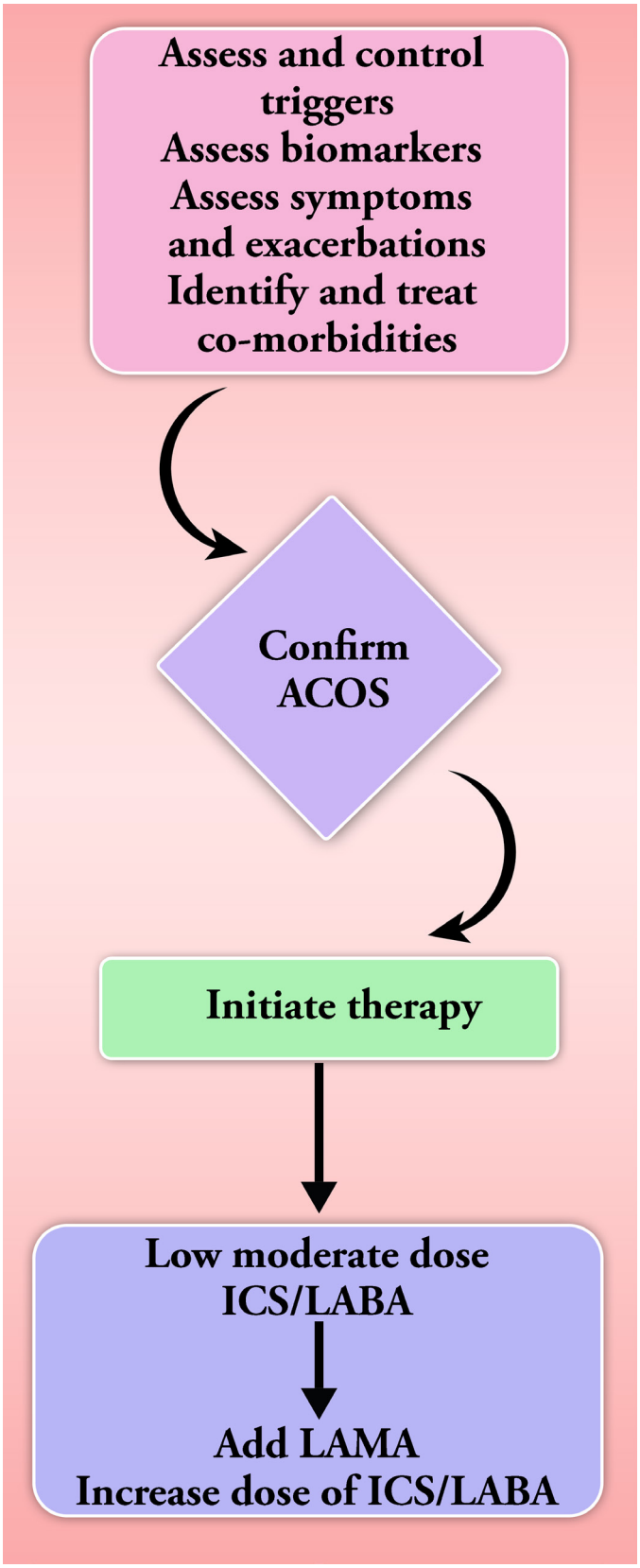

Figure 16: Management of ACOS

difference was observed among chronic obstructive pulmonary disease patients with a co-diagnosis of asthma (difference of –6.5% in the composite outcome of hospitalization or death at 5 years), supporting the use of inhaled corticosteroids in this population. [10, Rank 4]

Recommendations

Existing evidence indicates that short courses (2 wk or less) of systemic corticosteroids are effective in improving lung function and reducing morbidity associated with chronic obstructive pulmonary disease exacerbations in patients with moderate to severe chronic obstructive pulmonary disease. The use of systemic steroids in stable conditions is not recommended. Any potential benefit with systemic corticosteroids should be weighed against their potential toxicities on an individual basis. Based on the available literature, it is reasonable to initiate stable patients with moderate to severe chronic obstructive pulmonary disease on an inhaled corticosteroids/long-acting β2 agonist combination regimen or inhaled corticosteroids alone with the goal of improving lung function, reducing the frequency of exacerbations, and improving QOL. Results from the TORCH trial are promising, with hopes of

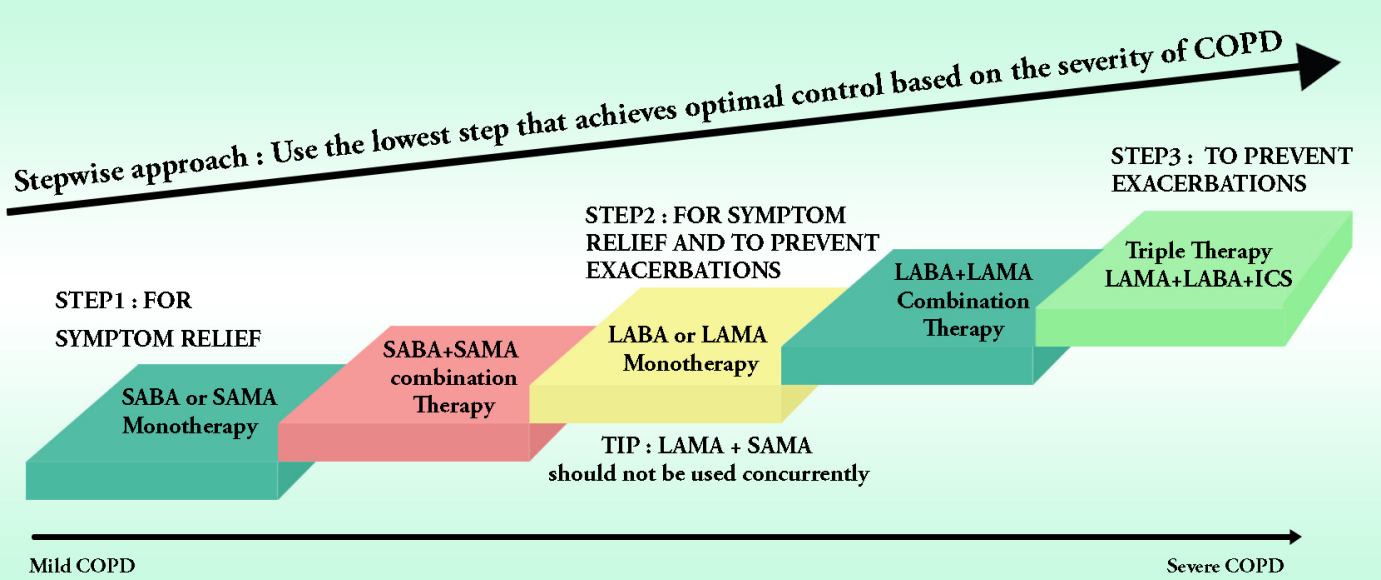

Figure 17: Recommended treatment modalities in COPD

improving survival with the use of combined long-acting β2 agonist and inhaled corticosteroids, but this needs to be further studied in light of a potential for increasing rates of pneumonia. In addition, the combination of tiotropium, long-acting β-agonists and inhaled corticosteroids may have some benefit but further studies are needed. This recommendation is in line with the current recommendations of the Global Initiative for Chronic Obstructive Lung Disease (as shown in figure 17).

Targeting inhaled corticosteroids to those patients who are likely to respond would minimize unnecessary exposure and costs while increasing the chance of improved outcomes. Some of the indicators of a probable inhaled corticosteroids response in patients with obstructive lung disease (such as a previous history of asthma, atopy, positive bronchodilator test [reversibility], bronchial hyper responsiveness, high levels of the fraction of exhaled nitric oxide and eosinophilia in sputum or blood) [5, Rank 4]

Conclusion

Chronic obstructive pulmonary disease is a systemic disorder that carries significant morbidity. Local and systemic inflammation seem to be central to its pathogenesis and will likely be targets of future therapeutic modalities aimed at ameliorating symptoms and perhaps altering the natural history of the disease. There is a growing body of data suggesting that corticosteroids can reduce systemic and local inflammation providing a plausible mechanism for clinical benefit in chronic obstructive pulmonary disease. Ample evidence

exists to recommend short courses of systemic corticosteroids for chronic obstructive pulmonary disease exacerbations. The use of inhaled corticosteroids in stable chronic obstructive pulmonary disease improves lung function, decreases rates of exacerbation and seems to improve survival when combined with long-acting β 2 agonist but must be weighed against the potential for increased vulnerability to pneumonia. Although the data are limited, there may be a role for peri-operative use of systemic corticosteroids in chronic obstructive pulmonary disease, although more investigation is warranted. As with all medical interventions for chronic obstructive pulmonary disease, a careful examination of risk–benefit ratio must be partaken, particularly in light of the significant adverse effects associated with corticosteroid usage. [6, Rank 3]

***Important information for post-test is highlighted in red letters, boxes and diagrams.**

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