

Utilization of Inhaled Corticosteroids by Hospital Patients with Chronic Obstructive Pulmonary Disease, with a Review and Update on the Current Literature

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ABSTRACT

Objective: To review the evidence-based literature on the role of inhaled corticosteroids (ICS) in the management of chronic obstructive pulmonary disease (COPD) and to assess the utilization of ICS in patients admitted to hospital with exacerbations of COPD.

Methods: A MEDLINE search with the terms “chronic obstructive pulmonary disease”, “COPD management”, “inhaled corticosteroids”, and “inhaled steroids” was conducted for the period 1978 to 2003, to assess the published evidence for ICS therapy. A chart review of inpatients with a diagnosis of COPD exacerbation was conducted for the 13-month period January 1, 2000, to January 31, 2001.

Results: The literature review identified some weaknesses in the published evidence. Patients have not always been treated optimally with bronchodilators, and different outcomes have been measured in different trials. Recent trials have shown a reduction in exacerbations, and there is probably a subpopulation that would benefit from ICS. A total of 103 patients (46 men and 57 women) were identified for the chart review. Fifty-one (50%) of these patients had a prescription for ICS. However, bronchodilator therapy was optimized for only 13 (27%) of 49 ICS users. Ex-smokers receiving specialist care were more likely to be receiving an ICS. They were also more likely to be receiving oral theophylline, although no other historical or clinical factor leading to institution of ICS therapy could be identified. Fluticasone (28 patients or 55% of those receiving ICS therapy) was the most frequently prescribed ICS. Spirometry results were documented for only 77 patients (75%).

Conclusions: Although smoking cessation and initiation of home oxygen therapy are the only accepted evidence-based disease-modifying therapies for COPD, there has been a recent focus on adjuvant treatment with ICS as a disease-modifying therapy, in particular to prevent or reduce exacerbations. The literature review suggested that therapy for COPD should be encouraged and should adhere to recent national guidelines. Bronchodilation should be optimized — with focus on compliance, inhaler tech-

RÉSUMÉ

Objectif : Examiner le rôle des corticostéroïdes en inhalation (CSI) dans le traitement de bronchopneumopathie chronique obstructive (BPCO) à partir d'une revue de la littérature sur les données fondées sur les résultats et évaluer l'utilisation des CSI chez les patients hospitalisés pour l'exacerbation de leur BPCO.

Méthodes : On a effectué des recherches dans MEDLINE à l'aide des termes anglais « chronic obstructive pulmonary disease », « COPD management », « inhaled corticosteroids » et « inhaled steroids » pour la période s'échelonnant de 1978 à 2003, pour évaluer les données publiées sur le traitement par les CSI. On a évalué les dossiers des patients hospitalisés pour l'exacerbation de leur BPCO, pendant une période de treize mois s'échelonnant du 1^{er} janvier 2000 au 31 janvier 2001.

Résultats : L'examen de la littérature a révélé certaines faiblesses. En effet, les patients n'ont pas toujours reçu le traitement bronchodilatateur optimal, et différents résultats ont été mesurés dans divers essais. En revanche, de récentes études ont montré une réduction des exacerbations, et il semble y avoir une sous-population qui pourrait bénéficier des CSI. Au total, les dossiers médicaux de 103 patients (46 hommes et 57 femmes) ont été retenus pour évaluation. De ces patients, 51 (50 %) avaient reçu une prescription de CSI. Toutefois, le traitement bronchodilatateur n'a été optimisé que pour 13 (27 %) des 49 utilisateurs de CSI. Les anciens fumeurs soignés par un spécialiste étaient plus susceptibles de recevoir des CSI. Ils étaient aussi plus susceptibles de recevoir de la théophylline par voie orale, malgré qu'aucun autre facteur historique ou clinique commandant l'instauration du traitement par les CSI n'ait pu être identifié. Le fluticasone était le CSI le plus prescrit (28 ou 55 % des patients recevant des CSI). Les résultats de la spirométrie n'ont été documentés que chez 77 patients (75 %).

Conclusions : Bien que l'arrêt du tabagisme et l'instauration de l'oxygénothérapie à domicile soient les seuls traitements de fond reconnus contre la BPCO qui sont fondés sur les résultats, on a accordé récemment de l'intérêt au traitement adjuvant par les CSI comme traitement modificateur de cette maladie, plus

nique, and optimal therapy with short-acting anticholinergics, β^2 -agonists, or long-acting agents — before addition of ICS therapy is considered. Cost-effectiveness trials, along with consideration of advances in therapy, are necessary to identify the COPD patients most likely to benefit from ICS therapy.

Key words: chronic obstructive pulmonary disease (COPD), inhaled corticosteroids, quality review

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) continues to be a challenging condition to manage, constituting an enormous burden on the health care system.^{1,3} Many physicians approach the disease with misplaced complacency, and there is significant inertia toward any practice change.⁴ Recent epidemiological trends show an insidious increase in the incidence and prevalence of COPD, which is expected to be the third leading cause of death worldwide by 2020.⁵

The risk factors for COPD are presented in Table 1.^{1,2,6-9} The disease is characterized by progressive dyspnea, sputum production, recurrent exacerbations, respiratory tract infections, and eventually respiratory failure. In sharp contrast to the situation for asthma, there have been fewer significant advances that benefit patients in the management of COPD. Because of the proven efficacy of inhaled corticosteroids (ICS) in asthmatic patients, there has been a steady increase in the prescription of ICS therapy for COPD, but there is less scientific evidence for this use of these drugs.^{10,11} This increase may be explained by physicians not wishing to miss or undertreat a concomitant reversible asthmatic component in patients with COPD.

Pathophysiologically, COPD is a progressive disease encompassing both chronic bronchiolar fibrosis (obstructive bronchitis) and alveolar destruction (emphysema).^{12,13} Chronic bronchitis is defined by the presence of a productive cough of more than 3 months' duration for more than 2 successive years.¹² The cough is due to hypersecretion of mucus, often accompanied by airflow obstruction.^{13,14} Most patients with COPD have all 3 pathologic conditions (bronchitis, emphysema, and mucus plugging), characterized by a continuing slow decline in forced expiratory volume in the first second

particulièrement pour en prévenir ou en réduire les exacerbations. L'analyse de la littérature porte à croire que le traitement des BPCO doit être encouragé et conforme aux récentes lignes directrices nationales. Le traitement bronchodilatateur doit être optimisé — en portant un intérêt particulier à l'observance, aux méthodes d'inhalation et au traitement par les anticholinergiques à action rapide, les bêta-agonistes ou les agents à libération prolongée — avant d'envisager l'ajout d'un CSI. Des études coût-efficacité et l'examen des avancées thérapeutiques sont nécessaires pour déterminer les patients atteints de BPCO qui sont le plus susceptible de bénéficier d'un traitement par les CSI.

Mots clés : bronchopneumopathie chronique obstructive (BPCO), corticostéroïdes en inhalation, examen de la qualité

(FEV₁, measured in litres) over time.^{6,13,14} Objective data from spirometry represent the gold standard for diagnosis of COPD, and confirmation of therapeutic response (i.e., FEV₁ as a percentage of its predicted value) is the single best correlate of mortality.¹⁵

It is now apparent that COPD involves a chronic inflammatory process that differs from what is seen in asthma with respect to type of inflammatory cells, mediators, and responses to treatment.¹⁶⁻²⁴ The mechanism of inflammation is outlined in Figure 1.⁶ Most of the inflammation in COPD occurs in the peripheral airways and lung parenchyma, yielding increases in macrophages, T lymphocytes, and cytokines, and — in contrast to asthma — an absence of eosinophils except in acute exacerbations.^{17-21,23} Both ex-smokers and smokers with COPD have increased sputum neutrophil counts, which are associated with rapid decline in FEV₁.¹⁸ This preponderance of neutrophilic rather than eosinophilic inflammation may explain the lesser role of ICS in COPD, as these drugs have little if any activity against neutrophils.

Most studies examining the usefulness of specific drugs for COPD have been aimed at slowing the progression of the disease by either improving FEV₁ or reducing the patient's decline, as has been observed with smoking cessation.²⁵ Because survival among patients with COPD correlates directly with the level of FEV₁, any treatment that slows the accelerated rate of decline will likely reduce the mortality rate.²⁵ Recent studies have focused on reducing COPD exacerbations, which affect the patient's health status and quality of life, as well as the costs of disease management, especially those associated with hospital admission. Functional improvement without disease modification can occur by increasing the patient's fitness level, which



Table 1. Risk Factors for the Development of Chronic Obstructive Pulmonary Disease^{1,2,6-9}

Cigarette smoking
Passive smoking
Environmental pollutants
Air pollution (sulphur dioxide, particulates)
Occupational chemicals (e.g., cadmium)
Possible familial association
Childhood respiratory illness (may cause susceptibility to tobacco-induced lung damage)
Low birth weight (poor nutrition in fetal life results in smaller lungs)
Female sex*

*Forced expiratory volume in the first second decreases at a higher rate with age among women than among men. This factor may have been previously obscured by the once-higher proportion of men who used tobacco.

is achieved by pulmonary rehabilitation programs. On average, patients with COPD have 1 to 4 exacerbations per year,²⁵ which translates into a total of 15 to 16 million episodes per year in the United States.

ICS therapy is now widely prescribed for COPD.²⁶⁻²⁸ In a 1997 analysis of prescribing data from 9 UK general practices (a total of 434 patients), Peperell²⁶ found that ICS had been used in 72% of those with a diagnosis of COPD. It has been suggested that if this reflects typical practices in the United Kingdom, the financial consequences of prescribing ICS for 70% to 80% of patients with COPD would be equivalent to US\$67 million in drug acquisition costs alone.²⁷ A review of medical records in a Canadian teaching hospital in the same year showed similar trends, with 43% of patients receiving an ICS on admission and 99% of those patients being discharged on the same drug.²⁸

Use of ICS can precipitate adverse drug reactions in patients with COPD, as has been observed in asthmatic patients. Several studies and case reports have implicated ICS in such adverse events, and there is an increased risk of adrenal suppression, osteoporosis, glucose intolerance, cutaneous effects, cataracts, and corticosteroid myopathy.²⁹⁻³¹ There may also be a therapeutic gap between the frequency of prescribing ICS in COPD and studies showing long-term efficacy.^{26,28,32,33}

The study reported here involved a review of the evidence-based literature on the role of ICS in COPD management. In addition, a chart review was performed to determine the utilization of ICS in a population of inpatients with COPD. The specific objectives were to identify the evidence-based literature on the efficacy of ICS therapy for COPD, to identify clinically relevant outcomes (e.g., reduction of exacerbations) for the COPD population, and to identify the frequency of ICS use for patients with COPD.

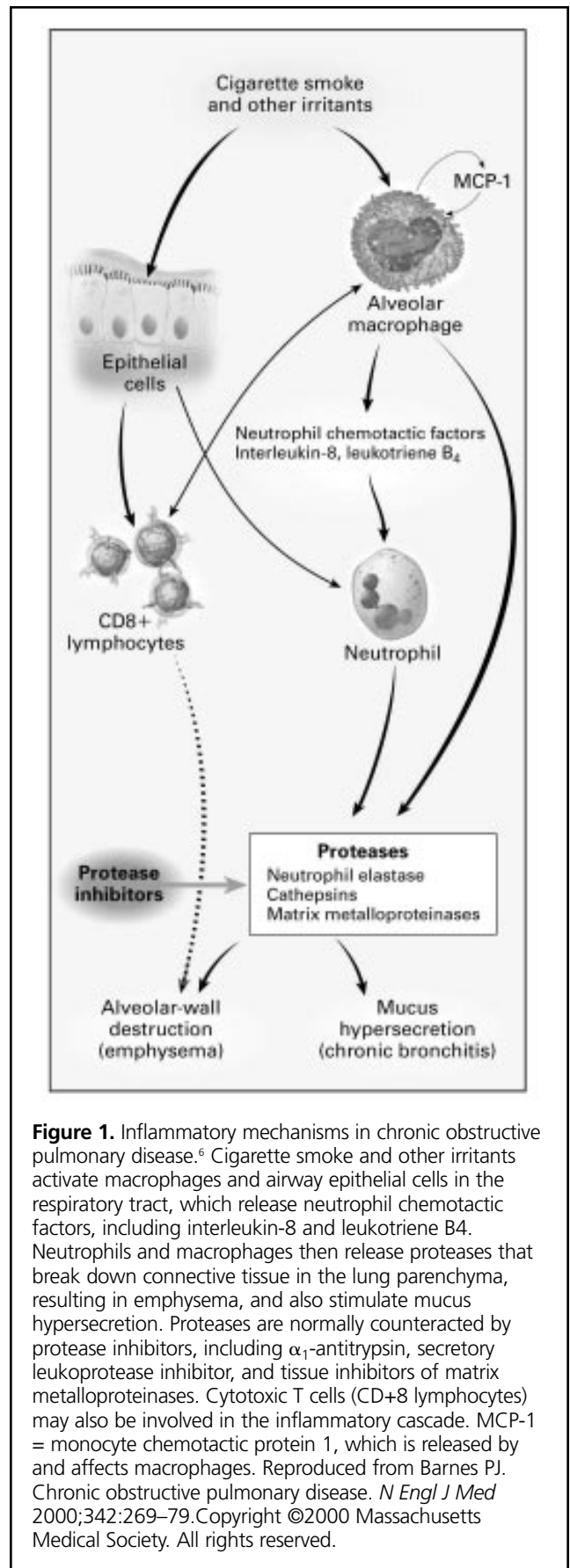


Figure 1. Inflammatory mechanisms in chronic obstructive pulmonary disease.⁶ Cigarette smoke and other irritants activate macrophages and airway epithelial cells in the respiratory tract, which release neutrophil chemotactic factors, including interleukin-8 and leukotriene B₄. Neutrophils and macrophages then release proteases that break down connective tissue in the lung parenchyma, resulting in emphysema, and also stimulate mucus hypersecretion. Proteases are normally counteracted by protease inhibitors, including α_1 -antitrypsin, secretory leukoprotease inhibitor, and tissue inhibitors of matrix metalloproteinases. Cytotoxic T cells (CD+8 lymphocytes) may also be involved in the inflammatory cascade. MCP-1 = monocyte chemotactic protein 1, which is released by and affects macrophages. Reproduced from Barnes PJ. Chronic obstructive pulmonary disease. *N Engl J Med* 2000;342:269-79. Copyright ©2000 Massachusetts Medical Society. All rights reserved.

METHODS

Literature Review

The published literature and national consensus guidelines were reviewed. A MEDLINE search for the period 1978 to 2003 was conducted with the terms “chronic obstructive pulmonary disease”, “COPD management”, “inhaled corticosteroids”, and “inhaled steroids”. In addition, the Cochrane, Evidence Based Medicine, Bandolier, Ovid, CINAHL, and HealthStar databases were searched with the same Medical Subject Heading (MeSH) terms. All clinical trials evaluating the use of ICS in the treatment of COPD were gathered, and data from them were tabulated.

Chart Review

A chart review, approved by the Research Ethics Committee of the authors' institution, was performed. The medical record code for COPD was used to identify and retrieve the medical records for all patients with a primary admission or discharge diagnosis of COPD exacerbation. Charts of patients who were discharged in the 13-month period between January 1, 2000, and January 31, 2001, were obtained from Patient Information Services. To avoid bias, charts were selected consecutively and in reverse chronological order beginning from January 31, 2001.

We included any patient who was admitted or discharged with a primary diagnosis of COPD exacerbation. We excluded patients with documentation of a history or evidence (postbronchodilator increase in FEV₁ greater than 15%) of reversible airway disease, such as asthma. We also excluded patients with a documented history of antitrypsin deficiency, cystic fibrosis, or tuberculosis. For patients with multiple admissions, the most recent admission was reviewed.

The chart analysis documented the following baseline patient characteristics: age, sex, comorbidities, smoking status (including pack-years), results of pulmonary function tests, medications, spacer use, home oxygen use, and whether the patient was under the care of a specialist. Any changes in these characteristics during the admission were recorded. The optimum dose of ipratropium was defined as more than 8 puffs per day.³⁵ Data from pulmonary function tests were compiled from the amalgamated hospital pulmonary function laboratories; these data were cross-referenced with spirometry testing completed at the Queen Elizabeth II Health Sciences Centre within the previous 5 years.

Data were entered into an SPSS database, then grouped and analyzed with descriptive statistics (i.e., summary percentages, means, ranges, and frequencies). Proportions were compared with χ^2 and Fisher's exact tests.

RESULTS

Literature Review

Short-Term Trials

Fourteen short-term (duration 2 to 12 weeks) randomized, placebo-controlled trials of ICS in COPD have been reported.³⁴⁻⁴⁷ A summary of these trials is provided in Table 2. The studies generally showed equivocal or no significant effect on the degree of airway obstruction (as indicated by FEV₁ or peak expiratory flow) or airway hyperresponsiveness to histamine. However, some studies showed that several individuals, more often among patients receiving ICS than among those receiving placebo, had substantial benefit in terms of pulmonary function^{34,42}; however, these “responders” could not be predicted. The studies were limited by small sample sizes (10 to 127 patients) and the fact that various dosage regimens of different ICS formulations were used. The studies were not designed to look at exacerbations or quality-of-life measurements as primary outcomes.

Long-Term Trials

Nine long-term (duration 6 months to 3 years) randomized, placebo-controlled trials have evaluated the long-term effect of ICS therapy in COPD⁴⁸⁻⁵⁶ (Table 3).

Two studies with 6-month follow-up yielded conflicting results. In the first, by Bourbeau and others,⁴⁸ there was no difference in FEV₁ between 39 patients who received 1600 $\mu\text{g}/\text{day}$ of inhaled budesonide (and who previously had not responded to 2 weeks of treatment with oral prednisone) and 40 patients who received placebo. Assessments of dyspnea score, 6-min walk test, and quality of life led to the same conclusion. The sample size was small, with a total of 13 dropouts at 6 months, which rendered the study's power weak. However, these results are supported by the larger and longer-duration Copenhagen trial of patients with mild disease (mean FEV₁ 86% of predicted), which also showed a lack of benefit from inhaled budesonide (800 $\mu\text{g}/\text{day}$) for any outcome measure.⁴⁹ The FEV₁ was above 100% of predicted in 22% of the patients. Their mean age was 59 years, and because of their mild disease, few were likely to have frequent exacerbations,



Table 2. Short-term Randomized Placebo-Controlled Trials of Inhaled Corticosteroid (ICS) Therapy in Chronic Obstructive Pulmonary Disease

Study	Duration (weeks)	ICS Dose (µg/day)	No. of Patients	Mean Age (years)	FEV ₁ (% of Predicted)*	Current Smokers (%)
Robertson et al. ³⁸	2	1500 (BDP)	83	61	44	51
Weir et al. ⁴²	2	1500 (BUD)	127	63	44	38
Wempe et al. ³⁵	3	1600 (BUD)	10	57	59	60
Weiner et al. ⁴¹	4	800 (BUD)	30	Not reported	1.4 L	100
Nishimura et al. ⁴⁵	4	3000 (BDP)	30	65.2	37.4	20
Thompson et al. ³⁴	6	1000 (BDP)	100	49	72	100
Wesseling et al. ⁴³	6	1600 (BUD)	35	52	96	46
Rutgers et al. ³⁹	6	1600 (BUD)	44	60	60	100
Auffarth et al. ³⁶	8	1600 (BUD)	24	57	53	100
Engel et al. ³⁷	12	800 (BDP)	18	50	97	18
Watson et al. ⁴⁰	12	1200 (BUD)	14	60	80	100
Boothman-Burrell et al. ⁴⁴	12	2000 (BDP)	18	>40	52.4	50
Thompson et al. ^{46†}	12	1000 (FP)	36	Not reported	1.1 L	Not reported
Hattotuwa et al. ⁴⁷	12	1000 (FP)	31	65	46	12

FEV₁ = forced expiratory volume in the first second, BDP = beclomethasone dipropionate, BUD = budesonide, FP = fluticasone propionate.

*Except where indicated otherwise.

†Included patients with significant reversibility.

Table 3. Long-term Randomized Placebo-Controlled Trials of Inhaled Corticosteroid (ICS) Therapy in Chronic Obstructive Pulmonary Disease

Study	Duration (weeks)	ICS Dose (µg/day)	No. of Patients	Mean Age (years)	FEV ₁ (% of Predicted)	Current Smokers (%)
Paggiaro et al. ⁵⁰	24	1000 (FP)	281	63	55	69
Bourbeau et al. ⁴⁸	24	1600 (BUD)	79	66	43	39
Van der Valk et al. ⁵¹	24	1000 (FP)	244	64	57	27
Renkema et al. ⁵⁶	104	1600 (BUD)	58	57	63	45
Kerstjens et al. ⁵²	130	800 (BDP)	22	46	70	73
Copenhagen ⁴⁹	130	1200/800 (BUD)*	290	59	86	76
EUROSCOP ⁵⁴	156	800 (BUD)	1277	53	77	100
ISOLDE ⁵³	156	1000 (FP)	990	64	50	48
Lung Health Study ⁵⁵	160	1200 (TRI)	1116	56	67	90

FEV₁ = forced expiratory volume in the first second, FP = fluticasone propionate, BUD = budesonide, BDP = beclomethasone dipropionate, TRI = triamcinolone acetate.

*1200 µg/day of budesonide for the first 6 months, then 800 µg/day.

which perhaps made this a poor outcome measure for this population.

The second 6-month trial, by Paggiaro and others,⁵⁰ compared fluticasone 500 µg twice daily with placebo in current smokers and ex-smokers with mild to moderate COPD (mean FEV₁ 55% of predicted). A greater proportion of patients in the placebo group than in the fluticasone group experienced moderate to severe exacerbations (86% and 60%, respectively; $p < 0.001$). The total number of exacerbations was lower after treatment with fluticasone (76 in 45 patients receiving fluticasone and 111 in 51 patients receiving placebo; $p = 0.07$), and the distribution of number of exacerbations per patient was narrower in this group, although not significantly so. However, the main

outcome measure (at least one exacerbation in the 6-month period) was the same in both groups. At 6 months, results for the 6-min walk test were significantly better in the fluticasone group, as was FEV₁ (more than 10% of predicted), relative to the placebo group, and there was a trend toward less breathlessness. Paggiaro and others⁵⁰ also suggested that some subjects might have had an asthmatic component to their disease, although attempts were made to exclude such patients from the trial. The average serum cortisol level was lower in the treated group, and 14% of these patients (but only 11% of those receiving placebo) had subnormal morning cortisol levels, although this was not associated with any clinical effects.

The COPE study⁵¹ had an unusual design. It examined the discontinuation of ICS in a double-blind manner and documented the subsequent development of exacerbations and impact on health-related quality of life. Discontinuation of fluticasone (1000 µg/day) after 4 months of maintenance therapy induced a more rapid onset and higher rate of recurrence of exacerbations than did discontinuation of placebo. The hazard ratio for a first exacerbation in the placebo group compared with the fluticasone group was 1.5 (95% confidence interval [CI] 1.1 to 2.1). There was also a significant deterioration in quality of life in those who stopped ICS therapy.

A Dutch trial by Kerstjens and others,⁵² which made no distinction between asthma and COPD, compared 3 inhalation regimens in which a β₂-agonist (terbutaline 2000 µg/day) was combined with either a corticosteroid (beclomethasone 800 µg/day), an anticholinergic (ipratropium 160 µg/day), or placebo; the study period was 2.5 years. A subgroup of 20 patients with COPD had a nonsignificant improvement in FEV₁ after 6 months (mean improvement ± standard deviation [SD] 7.4% ± 3.2%). There were numerous dropouts, including 44 of 91 patients assigned to the placebo group and 45 of 92 patients assigned to the anticholinergic arm; however, a smaller proportion (12 of 91 patients) in the inhaled corticosteroid arm dropped out, which might suggest that they were experiencing a benefit from this drug.

The ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe) trial⁵³ recently looked at the effect of long-term (3 years) therapy with inhaled fluticasone (1000 µg/day) on outcome measures such as FEV₁, overall health status, frequency of exacerbations, adverse events, and morning serum cortisol levels. The 990 patients in the ISOLDE trial were recruited mainly from hospital clinics, and these participants were the most severely affected (with mean FEV₁ 50% of predicted) of participants in any of the long-term trials to date. No benefit was seen in terms of rate of decline of FEV₁, which was perhaps an unexpected finding, given reports of improvement in previous shorter trials.^{29,50,52} Mean exacerbation rate, however, was 25% lower among patients in the treatment group (1.32 exacerbations/year with placebo and 0.99 exacerbations/year with fluticasone), which implies that one exacerbation could be prevented every 3 years with this therapy ($p = 0.026$). Exacerbation was defined as an episode requiring oral steroids, antibiotics, or both, in the judgement of the general practitioner; specific symptom criteria were not used. Health status did not change significantly over the first 6 months, yet thereafter, it worsened faster in the placebo-treated patients

than in the fluticasone group ($p = 0.004$). Status was assessed using the validated, disease-specific St George's Respiratory Questionnaire. The authors acknowledged a high withdrawal rate (25% in the placebo group, 19% in the treatment group; $p = 0.034$) as a limitation of the study. The fluticasone group also had higher rates of oral candidiasis, throat irritation, and bruising, but not fractures.⁵³

Another 3-year trial (the EUROSCOP study)⁵⁴ examined the effect of budesonide 800 µg/day in subjects with mild COPD (mean FEV₁ 77% of predicted) who had a moderate to severe smoking history and who continued to smoke. Budesonide was associated with a small, one-time improvement in FEV₁ after bronchodilator use, but it did not appreciably affect the long-term progressive decline in lung function. Clinical outcomes such as exacerbations were infrequent, and health status either showed no benefit of budesonide or was not assessed. Skin bruising occurred in 10% of the budesonide patients but only 4% of the controls ($p < 0.001$). More oropharyngeal candidiasis ($p < 0.001$) and throat irritation ($p = 0.04$), but not new fractures, occurred in the budesonide group.

The most recently published long-term trial (3.5 years) was the Lung Health Study-II,⁵⁵ which used triamcinolone (1200 µg/day) in current smokers (representing 90% of study participants) and ex-smokers, some of whom had asthma. The primary outcome variable was decline in FEV₁. Secondary outcome variables were respiratory symptoms, airway reactivity (response to methacholine), exacerbations, and use of health care resources. As in the EUROSCOP⁵⁴ and Copenhagen⁴⁹ trials, study patients had predominantly mild to moderate COPD (mean FEV₁ before bronchodilator was 64% of predicted). The authors observed a significant difference in moderate to severe respiratory symptoms, especially dyspnea ($p = 0.02$), as assessed by the American Thoracic Society — Division of Lung Diseases Questionnaire, but not in daily cough or phlegm ($p = 0.26$). Differences in visits to the emergency department for respiratory complaints ($p = 0.36$) and subsequent admission to hospital ($p = 0.07$) did not reach statistical significance. However, there were fewer outpatient visits to the family physician for respiratory conditions in the triamcinolone group ($p = 0.03$). These data imply that 100 patients would have to be treated with triamcinolone for 1 year to prevent 1 outpatient family physician visit. Triamcinolone did reduce airway hyperactivity at 9 and 33 months ($p = 0.02$). After 3 years, bone density of the lumbar spine ($p = 0.007$) and



the femur ($p < 0.001$) was lower in the triamcinolone group. Quality of life was assessed with the non-disease-specific SF-36 (Medical Outcomes Study Short-Form General Health Survey). No differences in any of the 8 quality-of-life aspects were associated with treatment assignment, except for score on the mental health subscales, which was slightly worse at 36 months in the triamcinolone group ($p = 0.03$). The authors felt that this association was probably spurious.

There is some indication from these longer-term clinical trials, therefore, that ICS may reduce the frequency of exacerbations. Specifically, the 6-month trial of fluticasone by Paggario and others⁵⁰ showed a trend toward a lower total number of exacerbations ($p = 0.07$). The frequency of exacerbations was lower with drug treatment in the EUROSCOP study,⁵⁴ but these patients had a low baseline incidence of exacerbations, given the mild nature of their disease. The most compelling evidence comes from the ISOLDE trial,⁵³ which found a significant reduction (by 25%) in exacerbation frequency with ICS treatment in patients with severe COPD ($p = 0.03$). This led to a decrease of 1 exacerbation per 3 years for patients in the treatment arm.

On the basis of a meta-analysis, van Grunsven and others²⁹ concluded that in a group of patients with strictly defined moderate to severe COPD, prebronchodilator FEV₁ improved over 2 years of treatment with 800 to 1600 µg/day of beclomethasone. No beneficial

effect on exacerbation rate was observed in either the treatment or the placebo arm. This meta-analysis has been questioned in a number of respects,⁵⁷ including concerns regarding the complex statistics needed to control the many relevant covariants, the inclusion of an unpublished trial in the data set, the fact that the number of exacerbations did not vary between groups, and the fact that there was no effect of smoking status in this population, which was contrary to previous reports from EUROSCOP.

Chart Review

Patient Characteristics

A total of 103 patients were identified. Patient characteristics were analyzed for the entire study population and were also compared between the 51 patients who received ICS therapy (which began before admission to hospital [44 patients or 43% of the total] or was started while in hospital [7 patients or 7%]) and the 52 patients who did not receive ICS therapy (Table 4). The mean age (\pm SD) was 72.7 ± 10.5 years (range 43 to 97 years). Fifty-five percent (57/103) of the patients were women. The mean number of comorbidities for all patients was 3.9 ± 2.3 (range 0 to 10). The mean number of pack-years for the 72 patients for whom this information was available was 59.3 ± 31.3 . There was a statistically significant difference in the mean number of pack-years between women and men

Table 4. Characteristics of Patients with Chronic Obstructive Pulmonary Disease

Characteristic	Patient Group; No. (and %) of Patients*		χ^2	p value
	ICS Therapy (n = 51)	No ICS Therapy (n = 52)		
Sex			0.008	0.93
Men	23 (45)	23 (44)		
Women	28 (55)	29 (56)		
Mean age (years)	72.0	73.3		0.56
Mean weight (kg)	64.8	72.0		0.09
Length of stay (days)	12.0	18.9		0.07
Mean no. of comorbidities	3.6	4.3		0.14
Smoking status			4.32	0.04
Current smoker	18 (35)	21 (46)		
Ex-smoker	33 (65)	25 (54)		
Pack-years	58.26	60.38		0.78
Specialist follow-up†			3.58	0.06
Yes	25 (49)	16 (31)		
No	26 (51)	36 (69)		
Death in hospital			0.002	0.96
Yes	10 (20)	10 (19)		
No	41 (80)	42 (81)		

ICS = inhaled corticosteroid.

*Unless indicated otherwise.

†In hospital or in the community.



(49.2 ± 18.8 versus 71.8 ± 38.9; $p = 0.004$). However, the mean number of pack-years for those receiving and not receiving ICS therapy was similar ($p = 0.78$) (Table 4). Overall, patient characteristics for these 2 groups did not differ significantly, except for smoking status: current smoking was more prevalent among those not receiving ICS therapy ($p = 0.04$) (Table 4). There was also a trend toward longer length of stay in this group (mean length of stay 12.0 days for those receiving ICS therapy and 18.9 days for those not receiving such therapy [overall range 2 to 67 days], $p = 0.07$) (Table 4). This trend cannot be explained, as both groups were given IV steroids for exacerbations, and ICS users had their steroid puffers withheld during this period. Finally, there was a trend toward greater specialist follow-up among those receiving ICS therapy ($p = 0.06$).

Medication Use

The use and dosages of COPD medications were recorded for each patient, including information on ICS therapy, ipratropium, salbutamol, salmeterol, theophylline, home oxygen, and spacer devices. For the purposes of this study, “admitted on” means that the patient was receiving the agent before being admitted

to hospital, “started on” means that the therapy was initiated during the hospital stay, and “switched to” means that the ICS that the patient was using at home was switched to a different agent during the hospital stay. Patients were designated as “continuing on” an agent in 3 situations: instances where there was no mention that the product was discontinued during the hospital stay; instances where the agent given at home (or an equivalent) was given to the patient while in hospital and/or they were discharged on the same agent; and instances in which patients were instructed to reinstate home medications upon discharge.

Overall, 44 (43%) of the patients were admitted on an ICS, 7 (7%) were started on an ICS, 4 (4%) were switched to another ICS, and 33 (32%) continued on an ICS. Of the 44 patients who were admitted on an ICS, 7 had their steroid discontinued while in hospital. Overall, 51 (50%) of the patients admitted during the study period were taking an ICS before admission or started taking an ICS during the hospital stay. The most frequently prescribed ICS was fluticasone (28 patients or 55% of all patients receiving an ICS).

Of the 103 patients in the study, 101 (98%) were receiving salbutamol, but only 8 (8%) were using a long acting β_2 -agonist (and salmeterol was the only agent of this class that was used).

Table 5. Use of Medications by Patients with Chronic Obstructive Pulmonary Disease

Medication*	Patient Group; No. (and %) of Patients*		χ^2	p value
	ICS Therapy	No ICS Therapy		
AeroChamber (n = 89)	41 (89)	29 (67)	6.23	0.012
Home oxygen (n = 100)			0.05	0.82
Yes	14 (28)	13 (26)		
No	36 (72)	37 (74)		
Ipratropium (n = 103)				0.68 (FE)
Yes	49 (96)	50 (96)		
No	2 (4)	2 (4)		
Ipratropium optimized (n = 99)			0.76	0.38
Yes	13 (27)	17 (34)		
No	36 (73)	33 (66)		
Salbutamo l (n = 103)			2.00	0.25 (FE)
Yes	51 (100)	50 (96)		
No	0	2 (4)		
Theophylline (n = 103)				
<i>Admitted on</i>			4.5	0.03
Yes	13 (25)	5 (10)		
No	38 (75)	47 (90)		
<i>Started on</i>			2.91	0.1 (FE)
Yes	5 (10)	1 (2)		
No	46 (90)	51 (98)		
<i>Continued on</i>			8.07	0.004
Yes	15 (29)	4 (8)		
No	36 (71)	48 (92)		

ICS = inhaled corticosteroid, FE = Fisher's exact test.

*n values indicate the number of patients for whom information was available.



Seventy (68%) of the patients were using a spacer device (“AeroChamber”) before admission. Interestingly, there was no significant difference in home oxygen use between the ICS and non-ICS groups (Table 5).

Only 4 patients had not been receiving ipratropium before admission, 2 of whom were receiving ICS therapy. For 36 (73%) of 49 patients on ICS therapy and 33 (66%) of 50 non-ICS users, the ipratropium dosage was not optimized (with optimized dosage defined as more than 160 µg or 8 puffs per day), even though their disease was regarded as moderate to severe. Those receiving ICS therapy were no more likely to have their ipratropium optimized than those not receiving ICS therapy ($p = 0.38$).

Eighteen (17%) of the patients were receiving a theophylline preparation on admission (Table 5), and those receiving ICS therapy were more likely to be receiving a theophylline preparation on admission ($p = 0.03$).

Pulmonary Function Tests

For 77 of the patients enrolled in the study, evidence was available for pulmonary function testing at some point. Fifty-nine (57%) of the study patients underwent spirometry during the hospital stay, and 19 (18%) had documentation of spirometry during a previous admission or physician visit. Overall, 31 (30%) of the 103 patients underwent spirometry at the time of admission, 40 (39%) underwent this testing just before discharge, and 14 (14%) had this testing both on admission and at discharge. For 11 of the 51 patients receiving ICS therapy there was no documentation of pulmonary function testing at any point. According to the available spirometry data, patients in both groups appeared to have severe obstructive disease, as

indicated by a severe decrease in the FEV₁ (as percent of predicted) (Table 6) and thus could be considered candidates for ICS therapy.

DISCUSSION

The role of ICS in COPD has been the subject of debate for more than 40 years. As such, probably no other area in COPD management is as controversial.⁵⁷⁻⁵⁹ It has been documented that approximately 10% of COPD patients respond objectively to oral corticosteroids, and this is believed to be partially due to an asthmatic component.^{11,26} However, the effects of inhaled corticosteroids as determined by traditional measures of pulmonary function have been variable.

The retrospective chart analysis reported here revealed that a high percentage of patients at the authors’ institution were using an ICS: approximately 50% (95% CI 39% to 59%) of the patients admitted to this hospital for COPD exacerbation were admitted on or were started on an ICS. This prescribing behaviour appears to represent a significant endorsement of ICS therapy in moderate to severe COPD, as seen in 2 previous publications.^{26,28} This occurred despite the publication of 4 long-term trials showing no effect of ICS on the rate of decline of FEV₁,⁵³⁻⁵⁶ although one of these trials demonstrated a benefit in terms of exacerbation rate; however, 1 exacerbation could be prevented only with 3 years of daily use.⁵³ No obvious objective criteria could be identified to indicate how physicians selected patients with COPD to receive ICS, as there were no significant differences in sex, age, weight, comorbidities, severity of illness, pack-years, home oxygen therapy, ipratropium or salbutamol use, or FEV₁ between those receiving and not receiving ICS therapy.

Table 6. Forced Expiratory Volume in the First Second (FEV₁) for Patients with Chronic Obstructive Pulmonary Disease*

FEV ₁ variable	Patient Group; Mean Value Recorded ± SD		p value
	ICS Therapy	No ICS Therapy	
By volume (L)			
On admission	0.68 ± 0.3 (n = 16)	0.83 ± 0.5 (n = 15)	0.28
On discharge	0.78 ± 0.3 (n = 22)	1.03 ± 0.4 (n = 18)	0.56
On previous admission or physician visit	0.77 ± 0.3 (n = 8)	0.91 ± 0.3 (n = 11)	0.30
As % of predicted			
On admission	25.7 ± 12.2 (n = 16)	31.1 ± 13.4 (n = 15)	0.22
On discharge	32.5 ± 12.4 (n = 22)	40.3 ± 12.8 (n = 18)	0.06
On previous admission or physician visit	32.6 (n = 8)	39.1 (n = 11)	0.32

ICS = inhaled corticosteroid.

*Data represent 77 of the 103 patients enrolled in the study.



Most national guidelines recommend that patients with severe COPD (i.e., those needing ICS therapy) receive specialist follow-up. However, only 25 (49%) of the 51 patients receiving ICS therapy in this study were seen by a specialist (Table 4). The difference between specialists and general practitioners in utilization of ICS therapy approached statistical significance ($p = 0.06$), specialists employing this type of therapy more often. Whether all patients using an ICS are followed objectively with spirometry or quality-of-life assessment to justify continued use of these drugs is unknown. The most recent guidelines, the Global Initiative for Chronic Obstructive Lung Disease (the GOLD Guidelines),⁶⁰ recommend an ICS trial of 6 weeks to 3 months followed by reassessment. Because the patients in this study were admitted with COPD exacerbation and had severe disease (by FEV₁ criteria), they could all have been considered appropriate candidates for ICS therapy.

There was a statistically significant difference between the 2 patient groups with respect to smoking status, whereby more patients who were currently smoking were not receiving ICS therapy. The clinical significance of this observation is not the difference in smoking rates between the groups, but rather the high percentage (38%) of current smokers in the entire sample. All national guidelines attest to the importance of smoking cessation, as it is the single most important measure to slow the progression of FEV₁ decline in COPD. Education and the provision of smoking cessation tools should be endorsed, adopted, and promoted by all health care professionals.

The mean FEV₁ (as percent of predicted) that was observed in this study may have underestimated the true mean, in that patients were generally admitted during an exacerbation and might not have been able to complete the spirometry to the best of their ability. The low FEV₁ in this study population (less than 50% of predicted) was similar to that observed in the recent ISOLDE trial⁵³ and might have been the basis for the high proportion of patients receiving ICS therapy.

Seventy-seven (75%) of the patients underwent spirometry either during the current admission or during a previous visit or admission to the hospital. For 59 (57%) of the patients, objective measurements were performed during the current admission, a value that is similar to that reported in a previous study, in which only 53% of patients with COPD underwent FEV₁ testing during the hospital stay.⁶¹ Of the 26 patients who had no records of spirometry testing, 11 were receiving an ICS on admission, perhaps without documentation of airflow obstruction. A limitation of this observation is

that this study did not identify patients who underwent pulmonary function testing outside the institution for diagnostic or follow-up care.

At this institution, the ICS of choice for patients with COPD was fluticasone; this is the drug that was studied in the ISOLDE trial,⁵³ which has provided the most convincing evidence thus far supporting the use of ICS in severe COPD. Of interest is the fact that patients receiving an ICS in this study had shorter hospital stays (12.0 versus 18.9 days, although the difference was not statistically significant).

One disappointing observation was the suboptimal ipratropium dosage for both ICS users and non-ICS users. The GOLD and other national guidelines recommend a stepwise approach to the management of COPD.^{12,58,60} Accordingly, it might be expected that all patients receiving an ICS would already be receiving optimal ipratropium therapy (more than 8 puffs/day). However, this was not observed, and the percentage of patients whose ipratropium dose was optimized was greater among those not receiving ICS therapy, although the difference between the 2 groups was not significant. Canadian guidelines⁶² and others^{12,33} have recommended starting with inhaled anticholinergics, as was the case in this study population. Unfortunately, none of the 4 long-term trials commented on the specifics of ipratropium use. Efficacy trials of new therapies such as tiotropium bromide, the new long-acting anticholinergic, have recently been published,^{63,64} and this information is being integrated into clinical practice and updates of guidelines.

The short-term and long-term trials examining ICS utilization in COPD demonstrated various responses. Long-term trials with large, adequate numbers of patients have provided minimal evidence that ICS therapy alters the rate of decline in FEV₁. The data available to date suggest that the patients most likely to obtain benefit are those with severe disease (FEV₁ less than 50% of predicted) and frequent exacerbations. Even so, the ISOLDE trial data⁵³ imply that a patient with severe COPD would have to be treated for 3 years with 1 mg of fluticasone daily (4 inhalations of 250 µg/puff each), a relatively high dose, to prevent just 1 exacerbation. Furthermore, these agents are not benign in their side effect profile, and clinical judgement must be exercised to determine if the expense and risk of side effects justify their use. Present guidelines and editorials suggest a trial with high-dose ICS^{9,60} (but there are no data to suggest how long such a trial should last). If the number or severity of exacerbations decreases, which may take years to determine (or if the FEV₁ increases by

20% [and more than 200 mL] or more), then the patient should remain on the ICS.

Recently, concern has been raised that the withdrawal of inhaled corticosteroids may lead to worse outcomes.^{51,65} A population-based observational cohort study of 22 620 COPD patients over the age of 65, which used pharmacy administrative databases in Ontario,⁶⁵ adds to the controversy. A relationship existed between use of ICS within 3 months of discharge and the combined risk of repeat hospital admission for COPD and all-cause mortality 1 year after discharge. The authors showed that ICS therapy after discharge was associated with a 26% relative reduction in the combined risk of all-cause mortality and repeat hospital admission among elderly patients with a recent COPD exacerbation. Interestingly, use of oral steroids increased this combined endpoint. Use of antimicrobials and oral theophyllines was weakly associated with repeat admission for COPD. Although it lacked the benefits of a randomized controlled trial with minimal bias and confounders, the study may nonetheless reflect a trend toward reduced exacerbations in severe disease, which has been seen in more recent randomized controlled trials (assuming that the study populations were similar). Although observational, this study⁶⁵ may be the first to suggest a mortality benefit.

A recent meta-analysis⁶⁶ of randomized placebo-controlled trials of ICS given for at least 6 months for stable COPD showed that use of ICS therapy reduced the rate of exacerbations by 30% (relative risk 0.70, 95% CI 0.58 to 0.84), with similar benefits in those who were and were not treated with systemic steroids.

Two new studies^{67,68} in which ICS therapy was combined with a long-acting β -agonist (LABA) have shown improvement in FEV₁, peak expiratory flow, and symptoms, along with a reduction in exacerbation rate. Combinations appear to be better than either drug alone, with the ICS reducing severe exacerbation rate and the LABA improving symptoms and flow rates.

Although some aspects of COPD are positively affected by ICS, the underlying disease process and decline in FEV₁ may not be altered. More long-term studies looking at all outcomes, quality of life, prevention of exacerbations, hospital admissions, death (especially upon withdrawal), and other factors are needed. Pending further trials, extensive ICS use in COPD must be weighed against the potential adverse effects and financial consequences.^{2,6,30} This type of drug therapy is expensive, and the current monthly community acquisition cost is approximately Can\$87 for a 120-dose, 250 μ g/puff fluticasone inhaler, or

approximately Can\$1044 per year. To date, there have been no pharmacoeconomic analyses of the use of ICS in COPD management. Such studies are urgently needed to justify the financial burden of these agents. For the subgroup of patients for whom ICS therapy is believed to confer a benefit, it would be prudent to recommend follow-up and to document responses with both objective and subjective criteria.

Clearly, controversy will continue to surround the use of ICS in COPD until further prospective randomized controlled trials identify the subset of patients who best respond and the appropriate dosage that balances efficacy against side effects.^{29,31} Only when this happens can physicians feel confident that they can positively influence the disease course and outcomes of the growing population of patients with advanced COPD by more discriminate prescribing and use of ICS. The future holds significant promise, as recent trials with combination LABAs and inhaled corticosteroids and studies with long-acting anticholinergics have shown improvements in clinically relevant outcomes.^{63,67,68}

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