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# Suboptimal use of inhaled corticosteroids in children with persistent asthma: Inadequate physician prescription, poor patient adherence or both?

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Ce mémoire intitulé:

**Suboptimal use of inhaled corticosteroids in children with persistent asthma: Inadequate physician prescription, poor patient adherence or both?**

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## ABSTRACT

Recent Canadian surveys report that many asthmatic children continue to experience uncontrolled asthma. The literature informs us that the lack of adherence to the guidelines from the Canadian Asthma Consensus regarding the use of inhaled corticosteroids (ICS) may be one of the obstacles faced by children living with this disease. The primary objectives of this study are to describe the use of ICS, including both the prescribing patterns and patient adherence using a new adherence measure which allows estimating the relative proportion attributable to the physicians and patients.

A cohort of 2,355 children aged 5-15 years with asthma and having had used more than 3 doses of inhaled short-acting β2-agonists (SABA) per week on average during a 12-month period prior to treatment initiation with ICS was reconstructed using Quebec administrative health databases, between 1997 and 2005. The new adherence measure was defined as the total days' supply dispensed to the total days' supply prescribed.

During the 12-month follow-up period, 20% of the children received only 1 prescription of ICS with no prescribed renewals. The median number of prescriptions (including prescribed renewals) was 4 corresponding to only 120 days' supply prescribed. The median percent physician and patient adherence to the prescribed therapy were 32.9% and 58.6%, respectively. The proportion of the non adherence value attributable to the lack of prescribing daily long term therapy was 51.2%.

A large percentage of children with persistent asthma were not prescribed ICS for chronic daily use and patient adherence was suboptimal.

Keywords: asthma, paediatric, children, inhaled corticosteroids, prescribing patterns, adherence

# RÉSUMÉ

Les résultats de récents sondages nous ont démontrés que l'asthme demeure mal maîtrisé chez les patients asthmatiques canadiens. Selon la littérature, le non respect des lignes directrices du consensus canadiens sur l'asthme quant à l'utilisation des corticostéroïdes en inhalation (CSI) est potentiellement un obstacle dans la prise en charge de cette maladie. Les objectifs principaux de cette étude sont d'évaluer les profils d'adhésion des médecins ainsi que des patients quant à l'utilisation des CSI en utilisant une nouvelle mesure d'adhésion nous permettant de déterminer la proportion relative attribuable à chacun.

Une cohorte de 2 355 enfants âgés asthmatiques de 5 à 15 ans et ayant utilisé en moyenne plus de 3 doses hebdomadaires de bronchodilatateurs à courte action (BCA) durant l'année précédant l'initiation au traitement des CSI a été reconstruite à partir de données extraites des banques de données administratives en santé du Québec, entre 1997 et 2005. La nouvelle mesure d'adhésion représente le nombre de jours de prescriptions reçues divisé par le nombre de jours de traitement prescrit.

Durant le suivi de 12 mois de l'étude, 20% des enfants n'ont reçu qu'une ordonnance d'un CSI. Le nombre médian d'ordonnance (incluant le renouvellement autorisé d'une ordonnance) reçu était de 4.0 correspondant à 120.0 jours de traitement prescrit. L'adhésion médiane des médecins et des enfants au traitement était de 32.9% et de 58.6%, respectivement. La proportion de non adhésion attribuable au manque de traitement prescrit à long terme était de 51.2%.

La majorité des enfants n'ont pas reçu un traitement quotidien de CSI et l'adhésion du traitement de ces patients était sous-optimale.

Mots-clés: asthme, pédiatrie, enfants, corticostéroïdes en inhalation, ordonnance, observance

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| | |
|---|---|
| AIA | Asthma in America survey |
| AIR | Asthma Insights and Reality surveys |
| BCA | Bronchodilatateurs à Courte Action |
| CAC | Canadian Asthma Consensus guidelines |
| CAIA | Children and Asthma in America survey |
| CAMP | Childhood Asthma Management Program |
| CI | Confidence Interval |
| CR | Compliance Rate |
| CSI | Corticostéroïdes en Inhalation |
| $FEV_1$ | Forced Expiratory Volume in 1 second |
| GINA | Global Initiative for Asthma |
| GOAL | Gaining Optimal Asthma Control |
| HEICA | Helsinki Early Intervention Childhood Asthma study |
| HR | Hazard Ratio |
| ICD-9 | International Classification of Diseases, 9th Revision |
| ICS | Inhaled Corticosteroids |
| IMPACT | Improving Asthma Control Trial |
| LABA | Long-Acting $\beta_2$-Agonists |
| LTRA | Leukotrienes Modifiers |
| NAEPP | National Asthma Education and Prevention Program |
| OCS | Oral Corticosteroids |
| OPTIMA | Optimal Treatment for Mild Asthma study |
| OR | Odds Ratio |
| PDC | Proportion of Days Covered |
| PEF | Peak expiratory flow |
| PPDC | Proportion of Prescribed Days Covered |
| PRN | Pro Re Nata implies that the patient may take the medicine in the prescribed dosage *if needed.* |
| RAMQ | *Régie de l'Assurance Maladie du Québec* |

| | |
|---|---|
| RR | Relative Risk |
| SABA | Inhaled Short-Acting $\beta_2$-Agonists |
| SARE | Severe Asthma-Related Event |
| SAS | Superior Software and Services |
| START | Inhaled Steroid Treatment as Regular Therapy in Early Asthma study |
| TRAC | The Reality of Asthma Control survey |
| U.S. | United States |

# PREFACE

This MSc thesis consists of six chapters including an introduction, a review of the literature, a methodology and results sections, the manuscript of an article submitted for publication in a scientific journal and a discussion section. These chapters are followed by an overall conclusion, a bibliography and appendices.

The introduction provides the rationale and objectives of the study presented herein. This chapter is followed by a review of the literature covering different aspects relevant to this project with an emphasis on findings pertaining to children 5 years and older when available. The methodology and discussion chapters encompass the information found under the 'Methods' and 'Discussion' sections of the manuscript more comprehensively while the chapters on results and appendices present findings not reported in the manuscript. The article reports the results on the use of inhaled corticosteroids in children with persistent asthma. The overall conclusion provides a brief summary of the results of the study together with a few proposals for future research interest. The bibliography covers all articles cited in the thesis; however, the manuscript includes its own bibliography.

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# CHAPTER 1: INTRODUCTION

Asthma is a chronic respiratory disease characterized by airway inflammation and acute symptomatic episodes of varying bronchial constriction. Clinical symptoms consistent with asthma include episodic or constant wheezing, chest tightness, dyspnea and cough. It is one of the most common chronic conditions in childhood and affects approximately 15.6% of children aged 4 to 11 years and 11.7% aged 12 to 19 years in Canada. (1)

The goal of pharmacological therapy, as advocated by the widely distributed treatment guidelines including the Canadian Asthma Consensus (CAC) guidelines, is to achieve and maintain long-term control of asthma symptoms with the use of inhaled corticosteroids (ICS) as a first-line therapy for the initial treatment of persistent asthma, such that no more than three doses of short-acting $\beta_2$-agonists (SABA) per week are required as rescue medication, excluding one additional daily dose per day for exercise-induced bronchoconstriction. (2;3) Regular use of ICS has been shown to reduce the impact of asthma on morbidity. (4-6) Despite the beneficial effect of ICS, Canadian surveys continue to show a significant gap between treatment goals and levels of asthma control.(7;8) As a result, patients continue to experience poor asthma control and thus, require emergency care.(1;9)

A major barrier for the optimization of pharmacological outcomes identified in the literature is the suboptimal use of ICS. Rates of non adherence among asthmatic patients have been reported to range from 32% to 50% through the use of electronic monitoring devices suggesting that inappropriate use of ICS therapy remains a problem for a majority of patients. (10-12)

Based on this information, the objective of an initial research project which has led to the study presented herein was to evaluate the impact of ICS therapy non-adherence on the occurrence of moderate to severe asthma exacerbations in asthmatic children. Further methodological attempts to evaluate this relationship using various subpopulations, and different adherence measures and regression

models, it was found that the beneficial effect of adherence to ICS on exacerbations was very difficult to demonstrate using observational data due to the overall suboptimal use of ICS and the strong presence of an indication bias (i.e., ICS was more likely to be used in patients with more severe asthma who, in turn, have a greater probability of having an exacerbation).

It remained unclear from the data obtained in the initial research project whether the suboptimal use of ICS was attributable to physicians' non adherence to treatment guidelines for the prescription of ICS as maintenance therapy or patients' non adherence to their prescribed regimen.

Although patients' non adherence to their prescribed ICS therapy is well documented, there is less evidence on the prescribing patterns among physicians. Surveys conducted in the United States (U.S.) in 1999 and 2004 found that only half of the primary care physicians reported adherence to guideline recommendations for the prescription of daily ICS for children with persistent asthma.(13;14) Recently, a Canadian study surveying primary care physicians found that 20% of uncontrolled patients used SABA alone and the most frequently reported recommended change for these patients was the initiation of ICS, but in only 52% of them.(15)

To our knowledge, there are no studies using administrative data that have simultaneously assessed the prescribing patterns of ICS and the adherence to this medication. Using administrative claims data from the province of Québec (Canada), the primary objectives of the study presented herein were to describe the use of ICS in children with persistent asthma, including both prescribing patterns and patient adherence to prescribed ICS therapy using a new adherence measure. A secondary objective of the study was to describe markers of uncontrolled asthma as a function of the use of ICS.

# CHAPTER 2: REVIEW OF THE LITERATURE

## 2.1 Prevalence and economic burden

Asthma, a chronic inflammatory disease of the airways, is a major public health concern. It is one of the most common chronic diseases in the world and, in 2003, it was estimated that as many as 300 million people in the world suffer from asthma. (16)

The prevalence of diagnosed asthma in the United States (U.S.) and Canada is amongst the highest in the world for both children and adults. (16) In 2005, the National Center for Health Statistics estimated 7.7% of people had asthma in the U.S. Prevalence rates were highest among children aged 5 to 17 years; 9.9% of children aged 5 to 11 years and 9.6% of children aged 12 to 17 years compared to 7.2% of adults. (17) Asthma is the most common chronic respiratory disease in Canada, accounting for approximately 80% of the respiratory disease and affecting, in 2007, approximately 8.0 % and 8.1% of the population aged 12 years or older in Canada and Québec, respectively. (18;19) Consistent with the U.S. data, asthma prevalence rates are highest in children. In 2007, the prevalence of asthma among children 12 to 19 years of age was approximately 11.5% in Canada and 9.9% in Québec. (18) According to the 2000/01 National Population Health Survey, asthma prevalence among children 0 to 11 years of age reached 13.4% and 15.1% in Canada and Quebec, respectively. (9)

Asthma continues to be a major cause of hospitalization for children in Canada. In 2004, asthma contributed to 10% and 8% of all hospital admissions in the 0-4 years and 5-14 years age groups, respectively. (1) In 1999/2000, asthma was the leading cause of hospitalizations among children aged 1 to 9 years and accounted for one quarter of the 78,221 hospitalizations due to respiratory diseases among children and youth under 15 years. (20)

The economic burden of asthma is considerable in North America. (16) The Canadian average annual direct costs of asthma, including hospital, physician and

medications, were reported to be 705.4 million dollars in 2000. (1) In 1995, the annual direct cost of asthma per children over the age of 4 years was estimated to be $663 from the Ontario Minister of Health perspective which excludes medication costs. The largest cost component was hospital admissions, accounting for 77% of the total costs. The medication costs and dispensing fees from the combined societal and patient perspectives were estimated to be $446 per year. (21)

Using U.S. data from the 1987 Medical Expenditure Survey, Lozano and colleagues estimated that children with asthma incurred an average of 2.8 fold increase in total health care expenditures, including prescriptions, ambulatory visits, emergency department visits and hospitalizations, compared with children without asthma. (22) Further analysis of the 1987 data showed that the largest proportion of costs was due to hospitalizations followed by prescriptions and emergency department visits. (23)

Asthma is an increasingly common chronic disorder. It is a leading cause of hospitalization in children and brings significant direct costs to societies. The data on hospitalization suggest that many individuals with asthma continue to have inadequate control of their disease. (1)

### 2.2 Diagnosis and management of asthma in children

Asthma is a chronic respiratory disease characterized by airway inflammation and acute symptomatic episodes of varying bronchial constriction. The diagnosis of asthma as suggested by both the Canadian Asthma Consensus guidelines (CAC) and the Global Initiative for Asthma (GINA) guidelines for children over 5 or 6 years of age is mainly based on family history, the reported symptoms, physical examination as well as the measurements of lung function and allergic status. (2;3)

Clinical symptoms consistent with asthma include episodic or constant wheezing, chest tightness, dyspnea and cough. Symptoms can be provoked by allergic or nonallergic environmental stimuli such as after exposure to specific irritants, cold air or by seasonal changes. Nocturnal occurrence is common. Symptoms can be acute, also known as exacerbations of asthma or asthma attacks, which are characterized by episodes of increase in patient's symptoms, such as shortness of breath, cough, wheezing and/or chest tightness or chronic. The patterns of asthma symptoms are variable and non-specific, especially in children which may more easily result in misdiagnosis (e.g. wheezy bronchitis). Alternative conditions which can also cause wheezing such as upper respiratory tract infections, pneumonia, gastroesophageal reflux or cystic fibrosis must be considered and excluded. (2;3)

Measurement of allergic status is warranted especially because of the strong association between asthma and allergic rhinitis. Skin testing or measurement of specific IgE in serum can help identify risk factors that cause asthma in some patients. (2;3)

Objective measurements of lung function, and particularly the demonstration of reversibility of lung function abnormalities, are highly recommended for children over the age of 5 or 6 years to help confirm the diagnosis and to assess its severity. (2;3) This is especially important as diagnosis based on the presence of symptoms alone may be inaccurate as asthma patients, including caregivers, generally underestimate current discomfort. (2;24) Measurements of lung function are not reliable in younger children as they may have difficulty in performing reproducible results.

Once diagnostic has been made, a stepwise approach is used for therapy decisions based on asthma severity. Two different approaches have been proposed to assess asthma severity. The CAC guidelines advocate assessing severity once treatment

has been initiated and incorporates the level of treatment needed to achieve control in their assessment while the GINA guidelines advocate assessing severity based on the underlying disease of the subjects on initial presentation. (2;3)

As a result of the two different approaches, the CAC guidelines recommend initial treatment based on asthma control while the GINA guidelines recommend initial treatment based on the degree of asthma severity to achieve asthma control. Although different, they both use similar clinical features in their assessment as shown in the following two tables. These clinical features include respiratory symptoms, lung function abnormalities, limitations of activities and need for reliever treatment. Once treatment has been initiated, both guidelines involve the responsiveness to treatment to form the basis for ongoing treatment decisions. The responsiveness refers to the degree of clinical control achieved by therapy. The criteria for determining whether asthma is controlled depend on the frequency or value of the clinical features as described in the following table. (2;3)

| Indicators of controlled asthma | | |
|---|---|---|
| | Frequency or value | |
| Characteristics | Goals of CAC guidelines | Goals of GINA guidelines |
| Daytime symptoms | < 4 days/week | Twice or less/week |
| Nocturnal symptoms/awakenings | < 1 night/week | None |
| Limitations of activities | None | None |
| Exacerbations | Mild, infrequent | None |
| Need for reliever/rescue treatment | < 4 doses/week[1] | Twice or less/week |
| Lung function ($FEV_1$ or PEF)[2,t] | ≥ 90% of personal best | Normal or near normal |
| Absence from work or school | None | -- |
| PEF diurnal variation[3,t] | < 10-15% | -- |

[1] May use 1 dose/day for prevention of exercise-induced symptoms
[2] $FEV_1$ denotes the forced expiratory volume in 1 second and PEF denotes the peak expiratory flow
[3] Diurnal variation is calculated by subtracting the lowest PEF from the highest and dividing by the highest PEF multiplied by 100 for morning and night over a 2-week period.
[t] lung function is not reliable for children below the age of 5 or 6 years
Source: CAC guidelines 2004 and GINA guidelines 2007

In addition to guiding clinicians in initial treatment decisions, the GINA classification of severity also serves as a basis for the selection of subjects in clinical trials as cited under subsection 2.3.1. There are four categories: intermittent, mild persistent, moderate persistent or severe persistent. The characteristics of each category are provided in the following table.

| Classification of Asthma Severity by Clinical Features Before Treatment |
|---|
| Intermittent |
| Symptoms less than once a week<br>Brief exacerbations<br>Nocturnal symptoms not more than twice a month<br>$FEV_1$ or PEF $\geq$ 80% predicted<br>$FEV_1$ or PEF variability < 20% |
| Mild Persistent |
| Symptoms more than once a week but less than once a day<br>Exacerbations may affect activity and sleep<br>Nocturnal symptoms more than twice a month<br>$FEV_1$ or PEF $\geq$ 80% predicted<br>$FEV_1$ or PEF variability < 20 - 30% |
| Moderate Persistent |
| Symptoms daily<br>Exacerbations may affect activity and sleep<br>Nocturnal symptoms more than once a week<br>Daily use of short-acting $\beta_2$-agonists<br>$FEV_1$ or PEF 60 - 80% predicted<br>$FEV_1$ or PEF variability > 30% |
| Severe Persistent |
| Symptoms daily<br>Frequent exacerbations<br>Frequent nocturnal asthma symptoms<br>Limitation of physical activities<br>$FEV_1$ or PEF $\leq$ 60% predicted<br>$FEV_1$ or PEF variability > 30% |

Source: GINA 2007

This classification does not take treatment exposure into account and is therefore most appropriately used for patients who are controller therapy naïve. (2) This classification is very similar to the classification used by the 2002 National Asthma Education and Prevention Program (NAEPP) coordinated by the U.S.

National Heart, Lung, and Blood Institute of the National Institutes of Health which is also cited in this review. (25)

Despite widely available treatment guidelines, the evaluation of the patients' disease course remains suboptimal. Challenges in assessing asthma control may in part be due to the varying feature of an individual patient's asthma and the frequency and rapidity an individual patient's feature change over time. (26;27) These challenges appear to be more so in children than for adults according to Chipps and colleagues who found, over a 12-week period, that controller therapy naïve pediatric subjects spent, on average, 27%, 18%, 48% and 8% of weeks meeting all criteria of the NAEPP, for intermittent, mild, moderate or severe persistent asthma, respectively. (26) Unless periodic assessment of asthma control is conducted to optimize the value of treatment, as recommended by treatment guidelines, underestimation of asthma severity may be likely contributing to inadequate therapy, and ultimately to asthma morbidity and mortality. (2;3;26)

Although there is no cure for asthma, effective clinical management can reduce the impact of asthma on morbidity, and decrease the economic burden associated with asthma-related emergency department and hospitalizations visits. Interventions that can help asthma be controlled include taking adequate asthma controller therapy, avoiding contact with environmental "triggers" such as tobacco smoke, indoor allergens such as dust and fungi, outdoor allergens such as pollens, treating conditions associated with asthma such as upper respiratory tract infections, and receiving regular monitoring from health-care professionals. (2;3)

### 2.3 Pharmacological management

The goal of pharmacological management is to achieve and maintain clinical control. There are two main categories of pharmacological therapy, namely controllers and relievers. In children, controllers include inhaled corticosteroids, leukotrienes modifiers, long-acting $\beta_2$-agonists and anti-allergic agents such as

cromoglycate and nedocromil. These agents are considered preventive therapy and are usually taken daily on a long-term basis to keep asthma under control, mainly through their anti-inflammatory effects. The most effective of these agents are the inhaled corticosteroids (ICS) and are currently the recommended first-line controller therapy for children of all ages. (2;3) Relievers are best represented by the short-acting $\beta_2$-agonists (SABA), which are very effective for acute relief of symptoms, but their frequent use is associated with a heightened future risk of severe asthma attacks. (2;3;28-30)

It is recommended that low-dose ICS be introduced as initial maintenance therapy even if patients present fewer than 3 symptoms per week. (3) For children not sufficiently controlled with a low-dose of ICS, an alternative to increasing the ICS dose is the addition of long-acting $\beta_2$-agonists (LABA) or leukotrienes modifiers (LTRA) although evidence of effectiveness of combination therapy is not as well established in younger children. The use of oral corticosteroids (OCS) is recommended for the treatment of acute severe exacerbations. (2;3)

It has been well demonstrated from clinical trials that regular use of ICS is associated with improvements in symptoms and lung function. (31-33) More recent clinical trials and observational studies have also shown the beneficial effect of ICS on severe asthma-related events such as exacerbations among patients with various degree of asthma severity. A few of these studies conducted in children or in population including children with mild to more severe asthma are discussed below.

### *2.3.1 Evidence of efficacy of inhaled corticosteroids in children from randomized clinical trials*

The Inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study conducted in patients 5 to 66 years of age with new-onset mild persistent asthma, based on the GINA criteria for symptoms and lung function abnormalities,

reported that early use of low-dose ICS was associated with a significant 44% reduction in severe exacerbations (HR 0.56, 95% CI 0.45 to 0.71, p<0.0001) over a period of 3 years. (34) A separate analysis was conducted in a subgroup of patients, those < 11 years of age, to evaluate whether ICS was associated with the risk of a severe asthma-related event (SARE), as defined by an event requiring an unscheduled admission to hospital or emergency treatment, or which resulted in death due to asthma, over the 3 years. It was found that the low-dose ICS group relative to usual care (placebo) was associated with a significantly reduced risk of SARE (HR 0.60, 95% CI 0.40 to 0.90, p=0.012). (35) The Optimal Treatment for Mild Asthma (OPTIMA) study, conducted in patients ≥ 12 years of age with mild persistent asthma based on the GINA criteria for symptoms and lung function abnormalities, showed a 60% reduction in the risk for the first severe asthma exacerbation (RR 0.40, 95% CI 0.27 to 0.59) in treatment-naïve patients receiving low-dose ICS compared to patients receiving placebo and a 19% reduction (RR 0.81, 95% CI 0.65 to 1.01) in treatment-experienced patients receiving high-dose ICS compared to patients receiving low-dose ICS. (36)

Daily low-dose ICS has also been compared with intermittent 'as needed' treatment with ICS in two small studies, one of which was conducted in children. The Helsinki Early Intervention Childhood Asthma (HEICA) study compared the effect of continuous and intermittent 'as needed' ICS treatments following 6 month of continuous ICS therapy in patients 5 to 10 years of age. According to symptoms and lung function tests, the majority of patients met the GINA criteria for mild persistent asthma. Over a one year period, the mean number of exacerbations was significantly lower for patients receiving continuous ICS treatment (0.97) compared with patients receiving intermittent ICS treatment (1.69). (37) The HEICA study followed the Improving Asthma Control Trial (IMPACT) conducted in patients 18 to 65 years of age following a 10 to 14 days of intense combined therapy (OCS and ICS). With the exception of accepting a baseline $FEV_1$ as low as 70% of the predicted value, patients met the GINA

criteria for mild persistent asthma. This study showed similar rates of asthma exacerbations between daily use of ICS and intermittent short-course use of ICS or OCS, together with an action plan, over a one year period. However, the authors conclude that larger studies, conducted for a longer period of time, are needed to examine the clinical benefits of an intermittent symptom-based therapy. (38)

The Childhood Asthma Management Program (CAMP) was conducted in patients 5 to 12 years of age with mild to moderate persistent asthma, as defined by the presence of symptoms or by the use of SABA more than twice weekly or by the use of daily asthma medication and a concentration of 12.5 mg or less of methacholine causing a 20% fall in $FEV_1$. This study also found beneficial effect of medium-dose ICS monotherapy, as indicated by 43% lower rate of hospitalization ($p=0.04$), a 45% lower rate of urgent care visits ($p<0.001$), and a 43% lower rate of courses of prednisone treatment ($p<0.001$) relative to the placebo group over a four to six-year period. (39)

There are few studies conducted in children which have evaluated and compared different therapy strategies for those needing a step up in their asthma treatment (e.g. an increased in dose of ICS and/or the addition of a second controller therapy, such as a LABA or a LTRA) in order to achieve asthma control.

Evidence for effectiveness of the addition of LABA controller therapy to ICS in patients below the age of 12 with uncontrolled asthma on symptoms control and particularly on exacerbations is not well established. (2;3) Findings of a systematic review of eight randomized controlled trials of add-on LABA therapy in patients ranging in age from 4 to 17 years showed a lack of evidence for the control of asthma exacerbations in children. (40) However, more recently, a study conducted in children aged 4 to 11 years has found that fixed dose combination therapy for maintenance plus additional doses for as-needed symptom relief reduces rates of asthma exacerbation by 70 to 79% compared to fixed dose

combination therapy alone or high dose ICS. (41) The Gaining Optimal Asthma Control (GOAL) study conducted in patients ≥ 12 years of age has shown that the longitudinal effect of the ICS/LABA combination therapy in achieving guideline-defined asthma control was significantly greater compared to ICS monotherapy and the mean annual rates of exacerbations were significantly lower for the combination therapy. (42)

There is little evidence to date for effectiveness of the combined ICS and LTRA therapy in children as a substitute to increasing the dose of ICS. (2;3) Add-on LTRA treatment to children aged 6 to 14 years with persistent asthma reduced the mean percentage exacerbation days significantly compared to those receiving ICS alone. (43) More recently, a study conducted in children aged 6 to 14 years with moderate persistent asthma found that the overall control of asthma with the combined LTRA and low dose ICS therapy was inferior to that of high dose ICS. (44)

Treatment remains problematic for a minority of patients with severe, difficult-to-treat asthma. The natural history of asthma severity is poorly understood in this cohort of severe, difficult-to-treat asthmatic patients. (45-47) High dose of corticosteroids remain the most effective therapy for most patients. (2)

*Overview of safety from randomized clinical trials*

The long-term safety of low to medium dose ICS has been well established. (48;49) However, both the START and the CAMP trials showed evidence of a small decline in height velocity during treatment of ICS (1.1 to 1.34 cm over 3 to 6 year period). (34;39) The decline in the rate of growth was greatest in the first year of treatment. The CAMP study suggests that the projected adult height, by bone age determinations, to be similar to the placebo group. (39) This finding corroborates those of a separate study, which found that after a 10-year follow-up period (mean 9.2 years), the budesonide-treated children, at a mean daily dose of

412 μg, attained adult height. (50) Furthermore, in previous study conducted in the same children population, the authors reported no correlation between bone mineral density, bone mineral capacity, bone calcium and body composition and the duration of treatment or dose (averaged daily dose of budesonide was 504 μg) after 3 to 6 years of treatment. (51) Patients requiring higher dose ICS should be monitored for adverse effects. (3;49)

### *2.3.2 Evidence of effectiveness of inhaled corticosteroids from observational studies*

Although evidence of clinical effectiveness based on observational studies is not easy to demonstrate, in part due to the fact that ICS is more likely to be prescribed for patients with more severe disease and who are at greater risk of having an exacerbation, the effectiveness of ICS on reducing the risk of first hospitalization, hospital readmissions or death due to asthma has been shown. A few recently published studies are discussed below.

In a case-control study of newly treated asthmatics between 5 and 44 years of age, it was found that regular users of ICS were 40% less likely to be hospitalized for asthma compared to theophylline regular users (OR 0.6; 95% CI 0.4 to 1.0) during the first 12 months of treatment. Regular use was defined as the dispensing of at least 1 prescription every 3 months. Both treatments had been initiated within the year of the recognition of asthma. (4)

Similarly, early initiation of ICS following hospitalization for asthma also reduces the risk of a readmission for asthma. Based on a large cohort of 1 year duration in newly treated asthmatics between 5 and 54 years of age, it was found that subjects taking regular use of ICS, for at least 16 days and as long as 6 months, following discharge of an initial hospitalization for asthma were 40% less likely to be readmitted for asthma than non ICS users (RR 0.6; 95% CI: 0.4-0.9). The author suggested that the lack of effect of ICS within the first 15 days of treatment is

consistent with the minimum length of time required to affect chronic inflammation while the fading of the effect of ICS over 6 month of use may be due to confounding as subjects using ICS regularly for 6 months or more may have more severe asthma. (5)

The effectiveness of ICS over a longer period of time was subsequently evaluated using a case-control design within each of two cohorts of newly treated asthmatics between 5 and 44 years of age. The first cohort consisted of all subjects from the initiation of their asthma treatment, while the second consisted of subjects hospitalized for asthma from the date of discharge. The mean duration of follow-up was 10.8 and 7.6 years, for the first and second cohort, respectively. This study showed that regular use of ICS was associated with a 31% reduction in the rate of hospital admissions for asthma (OR 0.69; 95% CI 0.57 to 0.83) and 39% reduction in the rate of hospital readmissions (OR 0.61; 95% CI 0.50 to 0.75). The rate of reduction found during the first 4 years of follow-up was sustained over the longer term. (6)

In another three large retrospective studies of similar design, but using different source cohorts of which one was exclusively conducted in children, it was found that ICS was significantly associated with a decrease risk of a first hospitalization relative to patients with no ICS dispensing, after simultaneous adjustment for markers of disease severity (rate ratio ranged from 0.4 to 0.8). The ICS-associated protection was most pronounced among high-SABA users. In these studies, ICS drug use was measured by dispensing rates, which was the number of canisters dispensed over the duration of follow-up in two studies or based on the quantity and strength of drug dispensed over the duration of follow-up in one study. The duration of follow-up for these studies was between 1 to 10 years. (52-54)

To evaluate whether and to what extent the use of ICS prevents death from asthma, a case-control study of newly treated asthmatics between 5 and 44 years of

age was conducted over a period of 6 years. Findings from a continuous dose-response analysis showed that the rate of death among users of ICS decreased by 21% (RR 0.71; 95% CI 0.65 to 0.97) for every additional canister of ICS used during the year and by 54% (RR 0.46; 95% CI 0.26 to 0.79) for every additional canister of ICS used during the previous six months. Also, the rate of death during the first 3 months following ICS discontinuation was significantly higher than the rate among those who continued to use ICS (RR 4.6; 95% CI 1.1 to 19.1). (55)

Overall, the findings from both randomized clinical trials and observational studies support regular use of ICS therapy to reduce the risk for exacerbations and other severe asthma-related events. Regular use of ICS has been shown to reduce the risk of having a severe exacerbation by 40% to 45% among children aged 12 years or younger and by 60% among older children and adults in clinical trials. Consistent with these findings, observational studies have shown that regular use of ICS reduces the risk of asthma-related hospital admissions by 40% to 60% and hospital readmissions by 39%. Moreover, the rate of death was reported to decrease by 54% for every additional canister of ICS used during the previous six months. As recommended by the treatment guidelines, once therapy has been initiated, effectiveness of ICS should be evaluated periodically and treatment should be stepped up or down in order to maintain asthma control and to minimize the risk of side effects. (2;3)

### 2.4 Suboptimal control of asthma and underlying risk factors

Despite widely available treatment guidelines and therapeutic advances aimed at preventing onset of symptom and providing long-term control of asthma symptoms in children and adults, large surveys continue to show significant gap between treatment goals and levels of asthma control around the world. As a result, patients continue to have symptoms and lifestyle restrictions and to require emergency care.

The most recent major Canadian survey, The Reality of Asthma Control (TRAC), conducted in 2004 reported that 53% of the 893 patients aged 18 to 54 years old had symptomatic uncontrolled asthma defined as failing to meet two of the six symptom-based criteria for asthma control of the CAC guidelines (i.e., minimal daytime and night-time symptoms, no limitations on physical activity, mild and infrequent exacerbations, no absences from work or school, and fewer than 4 doses of SABA per week). Patients with uncontrolled asthma required significantly more acute care visits (unscheduled physician visit, emergency department visit, or overnight hospitalization) due to asthma exacerbations compared to patients with controlled asthma. The TRAC survey concluded that patients as well as physicians continue to fail to recognize the seriousness of acute asthma episodes leading to increase burden to patients and on the health care system. (56)

The proportion of patients with uncontrolled asthma in TRAC is consistent with findings from a similar national survey conducted in 1999 in 1001 adults or parents of children aged 4 to 15 years where 57% of patients were found to have uncontrolled asthma (measured by the same criteria as in TRAC), indicating that little has changed over a period of 5 years. (8)

Similarly in the U.S., the Children and Asthma in America (CAIA) survey, conducted in 2004 to assess knowledge, attitudes and behaviours toward asthma in 801 children aged 4 to 18 years old, concluded that a significant number of children do not have asthma under control according to the symptom-based criteria for asthma control of the NAEPP guidelines (similar to the GINA criteria) which include frequency and severity of symptoms, utilization of emergency care, missed work and/or school and use of SABA. Poorly controlled asthma also caused a significant number of acute care visits (unscheduled physician visit, emergency department visit, or overnight hospitalization) and to interfere with everyday lives of children and their families. (24) Furthermore, the overall findings of this survey were similar to those of the previous Asthma in America (AIA) survey conducted

in 721 children (<16 years) and 1788 adults in 1998, indicating that little has changed over a period of 6 years. (57)

The Asthma Insights and Reality (AIR) surveys conducted in 29 countries between 1998 and 2001 to determine international variations in the severity, control, and management of asthma according to the GINA criteria for asthma control in 3153 children and 7786 adults also found that a significant proportion of patients continue to have symptoms and lifestyle restrictions and to require emergency care. (58)

These surveys reveal that for a majority of patients, asthma control as defined by current treatment guidelines is not being met. There are many aspects of asthma management that may be contributing to suboptimal asthma control. A few of these aspects which have been highlighted in the surveys are commented below.

*2.4.1 Perception of asthma control*

It is recognized that some patients may not accurately perceive the limitations caused by their condition especially if their asthma is long-standing. (2;59) Unfortunately, poor perception of asthma control can have many implications in the management of asthma. Patients may not seek medical help for their asthma symptoms when they should. Physicians who often base their assessment of the patient's condition on symptoms reported by the patient may also underestimate asthma control and subsequently under prescribe preventive therapy. (60) Moreover, poor perception of asthma control is a major determinant of pediatric adherence to their prescribed pharmacological therapy. (61;62) Despite these implications, surveys indicate that poor perception of asthma control continues to be prevalent.

Among patients who claimed their asthma was well controlled in the TRAC survey, 45% believed that making 1 or 2 visits to an emergency department was an

expected part of their condition. (56) The Canadian survey conducted in 1999 reported that among participants with uncontrolled asthma, 85% believed that their asthma was adequately or well controlled. (8) The CAIA survey indicated nearly 80% of respondents believed their or their children's asthma was well controlled; however, for a significant number of these children, asthma was uncontrolled based on the frequency and severity of the reported symptoms. (24) The AIR surveys indicated that 32% to 49% of patients with severe symptoms and 39% to 70% of patients with moderate symptoms felt that their asthma was well controlled. (58)

Poor perception of asthma control is not limited to children as indicated by the CAIA survey where caregivers represented 85% of the respondents. Furthermore, a communication gap within the family was found when responses between parents and children 10 and 15 years of age were compared. (24) These findings are consistent with those from several other studies which have shown the discrepancy between the parents' perception of their children asthma control and their children actual disease status. (63)

*2.4.2 Asthma management education*

It is agreed that patients must understand and accept their disease, the role of their therapy, the importance of adhering to prescribed therapy and avoid possible risk factors to gain asthma control and avoid exacerbations. (64-66) This is especially important given the variability of the disease and the unpredictable nature of asthma attacks. (27) Yet, surveys suggest that many patients have insufficient asthma knowledge to self-manage their condition.

The TRAC survey reported that 33% of the participants had not been taught to recognize the early signs of asthma worsening and 25% had not received instruction on what to do if their asthma symptoms worsened. Moreover, up to 33% of patients could not make the distinction between controller and reliever

medications, and did not know how to use them. (56) Medication awareness was also poor among the participants of the Canadian survey conducted in 1999 and often resulted in inappropriate use of ICS (i.e., during asthma attacks or to prevent exercise-induced asthma). (8) In the CAIA survey, it was concluded that patients' lack of understanding about asthma risk factors, treatment and symptom prevention remained a major obstacle for the management of asthma.

Two of these surveys have also indicated that the standards set forth by the treatment guidelines for ongoing monitoring, including follow-up healthcare visits, lung function testing and written action plans were not met. (8;24) These activities are integral components of asthma education. (2;3)

*2.4.3 Patterns of asthma medication use*

Lack of adoption to the pharmacological therapy recommendations of the treatment guidelines may also be one aspect contributing to suboptimal asthma control. Although these guidelines advocate the use of ICS as the first-line therapy for the treatment of persistent asthma, underuse of ICS and overuse of SABA are still evident.

The Canadian survey conducted in 1999 reported that 26% of the patients with uncontrolled asthma were not using ICS and among those using ICS, only 64% were using ICS regularly. SABA was overused by 37% of all patients surveyed. (8) The CAIA survey conducted in 2004 found that 42% of patients surveyed overused SABA in the previous month. (24) The AIR surveys also found that patients with persistent asthma had low use of controller therapy and high use of quick-relief medication (data not shown). (58) This pattern of medication use corroborate with findings from the AIA conducted in 1998, reporting current use of anti-inflammatory medications in only 26.2% of patients with persistent asthma. ICS represented 72.5% of the anti-inflammatory medication. Of these patients, 79.7% reported current use of reliever medication. Inadequate pharmacological

management was more apparent in the younger age patients (adolescents, young adults and preschool age children) than adults over the age of 35 years. (67)

Without a doubt, reasons for the widespread suboptimal asthma control reported by the recent surveys are most likely multi-factorial and beyond the aspects presented herein. Nevertheless, it is clear from the surveys' findings that improvements in promoting the disease and the appropriate management of the disease are warranted in helping patients meeting asthma control as defined by current treatment guidelines.

### 2.5 Prescribing patterns of inhaled corticosteroids

Physicians' adherence to treatment guideline recommendations for the prescription of ICS as maintenance therapy is essential to the successful pharmacological management of asthma. A few of the studies which have examined the prescribing patterns of ICS and underlying factors which may affect the prescription of ICS are summarized below.

Two large surveys evaluating factors that may affect prescribing habits conducted in the U.S. in 1999 and 2004 found that only half of the primary care physicians (paediatricians and family physicians) reported adherence to guideline recommendations for the prescription of daily ICS for children with persistent asthma. Among other factors, physicians' non adherence to daily ICS prescription was significantly associated with lack of agreement with the guideline recommendations and the presence of external barriers (e.g. lack of reimbursement and parent hesitancy regarding ICS). (13;14) In another large U.S. survey conducted in 1998 to describe asthma care for children, it was found that 47% of the primary care physicians reported 1 or more concerns regarding potential side effects of corticosteroids and 20% were maintaining the most severe patients (with continuous symptoms) on the same dose of ICS. (68)

A U.S. retrospective cohort study over a 5-yr period (1994-1998) examining prescribing patterns among prescribers specialty revealed that generalists and especially paediatric emergency department physicians and paediatricians were among the lowest proportions of prescribers of ICS. In 1998, prescriptions of ICS represented 24% of all asthma medications for patients aged 5 to 45 years with moderate to high risk asthma, defined by those with $\geq$ 3 outpatient visits, 2 outpatient visits and > 3 asthma medication claims, $\geq$ 1 emergency department visit or $\geq$ 1 hospitalization prior to study entry, suggesting that many patients continued to be managed without ICS therapy. (69)

Under recognition of uncontrolled asthma by physicians could also be a factor affecting prescribing behaviours. A recent Canadian study surveying primary care physicians and their patients $\geq$ 12 years found that physicians regarded 42% of their patients as having uncontrolled asthma while 59% of the patients reported not meeting one of the five symptoms based criteria of the CAC (daytime symptoms, sleep disturbances, physical activities, absenteeism and use of SABA). An explanation provided by the survey findings for the under recognition of uncontrolled asthma was that physicians' assessment of asthma control was not concordant with guidelines assessment recommendations, particularly regarding the overuse of SABA. Physicians were more likely to propose follow-up visits and to report plans to alter medication regimens for their patients with uncontrolled asthma. (15)

These studies suggest that under prescription of ICS is still very prevalent for patients with persistent asthma.

### 2.6 Patient adherence to inhaled corticosteroids

Patient non adherence to their prescribed ICS therapy is also another obstacle to the successful pharmacological management of asthma. The effectiveness of ICS therapy can be greatly compromised in the presence of inadequate adherence. The

consequences of inadequate adherence include increased symptoms and asthma exacerbations, both of which can lead to increased morbidity and increased health care costs.

### *2.6.1 Definition*

Adherence to a drug regimen may be defined as the extent to which a patient's actual history of drug administration corresponds to the agreed upon prescribed regimen. (2;70;71) Studies presented in this section have assessed adherence in terms of medication consumption or medication acquisition. Some of these studies use the term compliance in the same way as adherence.

### *2.6.2 Adherence assessment*

A range of indirect methods with varying degree of validity and utility have been used to measure adherence in asthmatic patients. Some of these methods include canister weights, electronic devices attached to metered dose inhalers in order to record date and time of medication use, self-reports from patients or caregivers and pharmacy refill records. (10;12;72-76)

Among the several different indirect methods measuring adherence, the electronic devices is currently considered the 'gold standard' as they offer the most objective, reliable measurements. (77) A study comparing adherence assessment methods among asthmatic patients found that electronic adherence was significantly more accurate than self-reports (mother and child) or canister weight measures. This study was conducted over a period of 6 month in 27 children 7 to 12 years of age with mild to moderate asthma and requiring daily use of ICS according to the frequency of asthma symptoms. The Doser-Clinical Trials version (Doser CT; Meditrac, Inc, Hudson, MA) was used for the electronic recording. Mother and child reports similarly yielded higher adherence than the two other methods. When evaluating the adjusted Doser CT data, which consisted of truncated values to the prescribed daily doses, adherence was found to be low as 50%. (10) The objective

data derived from electronic monitoring has also been supported in other studies conducted in children comparing electronic devices monitoring with canister weight or self-reports. (12;73;74;78)

Although considered the 'gold standard', electronic devices monitoring are best suited for small clinical studies because of the costs and time required to obtain measurements and, are not feasible for retrospective population-based studies. (77) For large studies, pharmacy refill records from administrative prescription claims databases have been shown to provide efficient and accurate indirect measure of 'adherence' or medication exposure over time for regular and long term medication therapy. (79;80) Few studies to date have used pharmacy refill records to measure adherence in asthma patients. These studies are discussed in the following section. (75;76)

*Prescription claims databases*

Prescription claims databases typically include the patient identifier, drug code which identifies the product name, the unit dose, the form and other product information, the quantity of medications dispensed, the duration for each dispensed prescription and the date of prescription fills. This information is filed in the databases for the purpose of reimbursement of drug claims. The membership depends on the database in question.

Adherence measured by prescription claims database represents the degree of prescription filing in a given interval; a divergence from adherence could indicate either treatment gaps (undersupply) or drug stockpiling (oversupply). Although infrequent, the latter is more likely to occur if the patients are exempt from payment. (81)

Measures of refill adherence can vary from one another depending on various characteristics. (77;82) For example, the choice of the exposure period for the

denominator may differ (e.g. between refills in lieu of study evaluation period). It is important to note that when adherence is calculated between refills, it is assumed that adherence is consistent through study completion as individuals who may discontinue medication prior to study completion are not captured after the last refill. This is especially of concern if the denominator (time between refills) is much shorter than the study evaluation period which could result in a significant overestimation of adherence. (82) The adherence measure may include or exclude oversupply in the numerator. When oversupply is not permitted, adherence may be underestimated if capping is applied at each refill interval (e.g., excess medication is not permitted to carryover from one interval to the next). This is not the case when the total supply dispensed is truncated not to exceed the study evaluation period. (82) Adherence measure may assess treatment gaps instead of medication availability. In the absence of oversupply, the assessment of treatment gaps is most attractive when the objective is to identify drug withdrawal effects whereas the assessment of medication availability is useful in testing dose-response effects or the use of medication in general. (77;82) A few examples of measures of refill adherence are provided in Table IX under the section entitled 'Appendices'.

Two studies conducted in patients with asthma to examine the relationship between medication adherence and disease exacerbation have used pharmacy refill records to measure adherence. (75;76)

The first study used the continuous, multiple-interval measure of medication availability (CMA) and the continuous, multiple-interval measure of medication gaps (CMG) adherence measures which was defined as the total days' supply dispensed (for CMA) or the total days' treatment gaps (for CMG) divided by the total days' between refills during the observation period. These two measures are essentially complementary in the absence of oversupplies; the CMA provides an overall study adherence value based on cumulative drug dosage while the CMG

provides an overall study non adherence value based on the lack of available medication. A weakness of the CMG measure is that it cannot distinguish between periods of chronic and intermittent under dosing. Moreover, both measures share a limitation of not being able to correct for changes in the prescribing patterns. To correct for the latter limitation, the author abstracted the medical records of all patients for ICS use and dosage information and ensured that gaps in ICS refills were not a result of physicians stopping the prescription. The overall adherence to ICS, as estimated by the CMA or CMG, was approximately 50% over a two year period.

The second study used the Medication Possession Ratio (MPR) adherence measure which was calculated by dividing the total days' supply dispensed by the total days' of study participation which was 365 days for all participants and capped at one to exclude oversupply. It is worth noting that the authors definition of MPR is equivalent to another adherence measure, the Proportion of Days Covered (PDC), discussed under subsection 3.5.2 of this document, as the denominator is the same for all participants. This measure provides essentially the same overall adherence value as the CMA measure in the absence of changes in the prescribing patterns and oversupplies. The authors of this study did not correct for the prescribing patterns and reported a median one year adherence ratio of 0.14 for all controller medications (ICS, ICS/LABA, LABA, LTRA, mast cell stabilizers and theophylline).

A major strength of exposure data found in prescription claims databases is that it is objective as it can be collected independently of the patients and is not subject to interview 'social desirability' or recall bias. (12;83) Most databases provide complete and accurate exposure data as long as patients are eligible for services. (79;80) Other advantages of using prescription claims databases for exposure data include being convenient, non-invasive and inexpensive for the obtention of large sample sizes. (79;82)

A limitation of using prescription claims databases for exposure data is that it can overestimate adherence as it reflects drug dispensing and not drug consumption. For example, patient may not consume the drug starting the day of dispensing, use the drug as prescribed, and consume all medications obtained. (82) Prescription claims databases are of little use in assessing adherence for drugs used on an as needed basis (PRN), a prevalent management strategy for patients with intermittent asthma symptoms. (3) For these patients, a prescribed change in the direction of use could lead to higher computed non adherence rates. In the absence of medical records, it remains unclear, when using prescription claims databases, whether little medication refill adherence is attributable to physician non adherence to treatment guidelines or patient non adherence to their physicians' instructions. Furthermore, databases may include a skewed population and, if not representative of the entire population, may have implications on the generalizability of the study. (79)

Despite these limitations, prescription claims databases provide a rich source of data for research applications and an effective mean to assess and monitor adherence in population-based studies for regular and long term medication therapy. (77;79;80;82)

*2.6.3 Prevalence*

Rates of non-adherence among asthmatic patients of all ages have been reported to range from 30% to 70%, regardless of the method of measurements. (84) In asthmatic pediatric patients, rates of non-adherence have been reported to range from 32% to 50%, when using electronic monitoring devices, suggesting no evidence of improvement of adherence rates for this age group. (10-12) Among pediatric patients, adolescents are less likely to use controller therapy compared to younger age groups. (11;52;85) Lack of adherence persists in patients with more severe asthma, even among those with 2 or more hospitalizations over the previous

year suggesting that disease severity may not influence adherence behaviour. (67;86-89)

Overreliance on SABA is still prevalent in children with persistent asthma not receiving adequate controller therapy. (86;90-93) For example, in a study evaluating variability in drug use based on pharmacy claims data in 1093 patients aged 7 years and over, it was found that for those using high doses of SABA, defined as more than 8 puffs per day, 37 % did not receive ICS and another 31% only received low-dose ICS. (93) In another U.S. cross-sectional study, evaluating the pattern of asthma therapy in 13,352 children aged 3 to 15 years old, 40% were dispensed a controller therapy (ICS or cromolyn) during a one year period, with ranges of 15 to 77% by level of SABA dispensing. At the highest level of SABA dispensing (6 or more SABA), 23% of children had no records of controller dispensing. (91)

There are also several studies which have examined whether ICS was used as prescribed. A survey conducted in adults and parents of children aged 1 to 17 years revealed that while 75% of patients were using ICS, only 38% used ICS daily as prescribed and 40% used ICS on an as needed basis. (94) In a separate survey, the frequency of under users of controller therapy as reported by parents of children aged 2 to 16 years was 73%, with 49% reporting no controller use and 24% reporting less than daily use. (95) A review of 10 studies conducted in children and adults to measure adherence using electronic device found that patients took ICS as directed on 20 to 73% of days and took less than 50% of prescribed dose on 24 to 69% of days. (96) In patients 14 to 65 years of age with moderate to severe asthma based on the NAEPP severity classification, the proportion of respondents who reported having an ICS ranged from 55 to 69%. Of those respondents who had an ICS, less than 50% reported using the inhaler daily as recommended by the guidelines. (89)

Rates of non adherence among asthmatic patients suggest that inappropriate use of controller therapy remains a problem for a majority of patients.

*2.6.4 Factors influencing adherence*

There are many potential factors which have been described to influence adherence behaviour of the patients. Some of these factors are summarized below.

*Patient-related factors influencing adherence*

The patient's or parent's poor perception of asthma control as well as their lack of understanding of the disease and the role of therapy as highlighted under section 2.4 are major determinants of poor adherence. (61;97) Patients are less likely to be adherent if they do not accurately perceive their limitation and underestimate the severity of their disease. (27;62;98;99) For some patients, asthma is only a problem when they experience an exacerbation. (62) Underestimating the disease may also lead to lack of confidence in the medication prescribed. (27) Patients may stop taking ICS if they have not experienced an exacerbation for an extended period. (100;101) Other patients may stop taking ICS prematurely because they do not feel an immediate improvement of asthma symptoms. (27;62;70;96;100;102)

Embarrassment or stigmatization is another factor which may impede adherence especially in adolescents. Adolescents with asthma often feel isolated from their peers, and may choose not to take their medication in situations that involve social barriers. (102;103)

Psychological dysfunction in patient and family, low socioeconomic status and level of education have also been associated with problematic adherence. (66;100;104-106)

*Treatment-related factors influencing adherence*

Treatment-related factors contributing to non adherence include the choice and complexity of the regimens (e.g. route of medication delivery, multiple daily administration or use of multiple drugs), difficulties with inhalation techniques, even in healthy children over the age of 5 years, and the patient's perception of the side effect profile (2;3;66;70;96;102;107;108) In a U.S. survey identifying issues among caregivers that could adversely affect adherence, over 80% reported being concerned with side effects. (109) Although less common, steroid phobia is still an issue. (12;61;66;71) For some patients, concerns regarding the risk of impaired growth of anabolic steroids may incorrectly be associated with ICS. (71)

## 2.7 Conclusion

Asthma is a prevalent chronic respiratory disease especially among children and many of these individuals continue to have inadequate asthma control symptoms and require emergency care according to recent Canadian surveys. .The treatment guidelines advocate the use of ICS as first-line daily long-term use therapy based on a wealth of data which have demonstrated the efficacy and effectiveness of ICS in the symptomatic treatment of asthma.

Among the reasons for the widespread suboptimal control of asthma suggested in large surveys, there is a high prevalence of children with persistent asthma not being treated with ICS according to guidelines (i.e., daily long-term use of ICS).

Suboptimal use of ICS could potentially be attributable to the physician's non adherence to the treatment guidelines and/or the patient's non adherence to their prescribed regimens. In the U.S., only half of the primary care physicians participating in two surveys have reported prescribing ICS for children with persistent asthma. In addition, the estimated percentage adherence among asthmatic children ranges from 32 to 50%. These studies suggest that both the physicians and patients contribute to the suboptimal use of ICS.

No studies to date have simultaneously assessed the prescribing patterns of ICS and the patient adherence to this medication.

# CHAPTER 3: METHODOLOGY

This chapter encompasses the methodological aspects presented in the manuscript more comprehensively.

## 3.1 General research objectives

To describe the use of ICS in children with persistent asthma, including both prescribing patterns and patient adherence to the prescribed therapy using a new adherence measure.

### *3.1.1 Specific primary objectives*

1. To develop a new patient adherence measure that takes into account variability in prescribing patterns, the Proportion of Prescribed days Covered (PPDC);
2. To estimate the prescription patterns for ICS therapy among asthmatic children;
3. To estimate patient adherence to ICS therapy among asthmatic children using the PPDC;
4. To compare the PPDC with another commonly used patient adherence measure, the Proportion of Days Covered (PDC), and estimate the proportion of the PDC that is due to variations in prescription patterns.

### *3.1.2 Specific secondary objective*

To describe the frequency of markers of uncontrolled asthma as a function of the use of ICS in the year following treatment initiation with ICS.

## 3.2 Source of data

This population-based study utilized data from two of the province of Québec's administrative databases; the *Régie de l'Assurance Maladie du Québec* (RAMQ) and the MED-ECHO databases for the period from 1 January 1997 through 31 December 2005. The RAMQ provides medical coverage to all residents of Québec and pharmaceutical coverage to the elderly ($\geq$ 65 years), persons receiving social

assistance, persons who do not have access to a private insurance plan, and children of persons covered by the public plan, which in 2005 represented over 42% of the population. (110) All children covered by the public plan have free access to prescription medications. Prescription claims in the RAMQ database is only available for insured drugs (i.e. drugs listed on the Québec formulary) dispensed from community pharmacies. All ICS medications are covered by the RAMQ drug plan and were permitted in this study (i.e., beclomethasone, budesonide, fluticasone and flunisolide).

The RAMQ database provides information, through a patient unique identifier (encrypted), related to the patient characteristics such as age, gender, area of residence and social aid status, the diagnosis, the encrypted identification and specialty of the treating physician, and the identification and date of the dispensed medical services as well as where they were dispensed – clinics, emergency department or hospitals. The RAMQ database also provides information on prescription claims including the drug code which identifies the product name, the unit dose, the form and other product information, the type of prescription (new or refill), the number of prescribed refills (potential renewals associated with a new prescription), the duration of the prescription, the dispensing date, the encrypted identification, and specialty of the prescribing physician. The asthma diagnoses and prescription claims data recorded in the RAMQ database have been previously validated.(80;111)

The MED-ECHO database provides information on acute care hospital admissions including data on the patient unique identifier (encrypted), the discharge diagnoses, and the duration of the hospitalization for all residents of Québec. The patient's encrypted unique identifier was used to link the RAMQ database with the MED-ECHO database.

### 3.3 Cohort definition

As shown in Figure 1 under the 'Appendices' section, new ICS treatment episode were selected retrospectively from the RAMQ database between 1 January 1998 and 31 December 2004. To ensure a resulting homogenous population with respect to the maintenance ICS therapy, new treatment episodes were defined as the absence of an ICS dispensation during the 12 months prior to treatment initiation.

Moreover, prescriptions for adjunct controller therapies consisting of LTRA and/or LABA were excluded on the day of treatment initiation with ICS. Individuals were aged between 5 to 15 years on the day of treatment initiation and needed to be enrolled in the RAMQ pharmacy insurance plan in the year prior to treatment initiation.

A correct diagnosis of asthma is important for the appropriate pharmacological intervention. As asthma symptoms are non specific (e.g., recurrent wheezing and nocturnal cough), the administration of an objective pulmonary function testing for children > 5 years of age is highly recommended by the treatment guidelines to help confirm the diagnosis. (2;3) However, pulmonary function testing is rarely used and in fact, it was administered to only 50 (2.1%) children in our cohort.

To ensure the identification of patients with asthma, we initially applied the following selection criteria in the year before treatment initiation with ICS: (1) diagnosis of asthma (ICD-9 code 493), and (2) utilization of more than 3 doses of SABA per week on average, or (3) 1 or more asthma-related event (an emergency visit with primary discharge diagnosis of asthma, a hospitalization with primary discharge diagnosis of asthma and/or utilization of a short course of OCS) indicating the presence of asthma exacerbations. The latter two criteria are markers of uncontrolled asthma according to the CAC guidelines and helps

confirm the exclusion of patients with misdiagnosed asthma (e.g., patients with various forms of bronchitis).

However, the presence of an asthma-related event may not indicate persistent asthma symptoms (e.g., patient may have an occasional asthma-related event triggered by a viral, upper respiratory tract infection but otherwise be asymptomatic). For these patients, optimal treatments have not been clearly defined according to the CAC guidelines and, are often treated with intermittent ICS therapy. We therefore further restricted our selection criteria to only those patients with a diagnosis of asthma and who had used more than 3 doses of SABA per week on average in the year before treatment initiation with ICS in order to ensure the identification of patients with persistent asthma that would most benefit from daily chronic ICS maintenance therapy.

In addition, we have excluded patients with a documented diagnosis for conditions whose symptoms overlap those of asthma (i.e., cystic fibrosis (ICD-9 code 277.0) or false croup (ICD-9 code 478.75)) or if they had a medication dispensation related to these conditions (acetylcysteine, racemic epinephrine, pancrelipase, pancreatine and tobracymine) or if they were oral corticosteroid (OCS) dependent, defined as having been dispensed more than 182 days of an OCS, in the year prior to treatment initiation to exclude patients with difficult-to-treat asthma or conditions other than asthma.

We also only considered the first episode of treatment with ICS and patients with a new prescription (not a refill of a previous prescription) on the day of treatment initiation to ensure that patients had been evaluated by a physician just prior to treatment initiation.

An assessment period of 12 months following treatment initiation was finally considered for all patients to allow for a long-term assessment of prescribing and patient adherence behaviours to this chronic ICS therapy.

## 3.4 Study design

A retrospective cohort study design was utilized.

### *3.4.1 Justification of the study design*

It is well established that the review of prescription claims data from computerized administrative databases such as the RAMQ pharmacy database provides a suitable strategy for the long-term monitoring of the use of medications in large populations in a real-life setting. (77;82) An important requirement when assessing adherence (also referred as compliance in some studies) to a medication regimen from prescription claims data is that the dataset must contain all prescription claims for the study cohort and the claims data must be complete and accurate. The RAMQ database has been validated for this purpose and found to be accurate and complete. (80)

When assessing the validity of adherence measures, we need to consider both the sensitivity and specificity of the measures. Within the context of our study, we can define sensitivity as the proportion of adherent patients that is correctly identified as adherent while specificity as the proportion of non-adherent patients that is correctly identified as non-adherent. (112)

It is agreed that refill adherence measures are specific but insensitive of 'partial' adherence as it provides an 'upper bound' of medication consumption by assessing medication possession. (77) In other words, we could be overestimating adherence for patients who do not consume all medications dispensed. Nonetheless, the high specificity of the refill adherence measure allows identifying

and examining patients who are not using sufficient therapy in order to achieve control of their conditions which meets the objective of our study.

Moreover, a number of studies have validated measures of refill adherence through association with measures of drug presence or drug effect. (77) For example, one study reported that pharmacy refill records of centralized pharmacies for patients taking an anticonvulsant medication phenytoin correlated significantly ($r = 0.31$; $p = 0.03$) with mean phenytoin plasma level. (113) In another study, it was found that each 10% increase in pharmacy-based refill adherence was statistically significantly associated with a decrease of viral load (0.12 log copies/mL; 95% CI 0.01 to 0.23 log copies/mL) for patients taking antiretroviral therapy. (114)

Other studies have assessed the predictive validity of measures of refill adherence through association with clinical outcomes, health services utilization, or healthcare costs. For example, one study has found that among community-dwelling elderly women, noncompliance with alendronate or risedronate assessed through the use of prescription claims data was associated with a statistically significant increased risk of nonvertebral fracture (RR: 1.27; 95% CI 1.12 to 1.44). (115)

Refill adherence has also been found to correlate strongly with pill counts ($r = 0.68$; $p < 0.001$). (116) When compared to self-reporting measures, which may also be applicable to larger populations, refill adherence is found to be more convenient and inexpensive to use, and it is a much more sensitive measure as the exposure data is prospectively collected independently of the physicians and patients and is therefore not subject to interview 'social desirability' bias and recall bias which tends to overestimate adherence. (112) In fact, studies comparing the two measures have found that adherence based on refill adherence measures have not correlated with self-reported adherence. (114;117)

Furthermore, the RAMQ pharmacy database provides for each prescription dispensed, the identification of the type of prescription (i.e., whether the dispensed prescription is a new prescription or a refill of a previous prescription) and the number of prescribed refills (i.e., when a prescription includes at least one refill, the pharmacist records the number of refills prescribed by the physician in the RAMQ database). When the prescribed renewals correspond to an end validation date, the pharmacist must determine and record the number of renewals corresponding to the allowed time period or record the number 99 in the field pertaining to the number of renewals when the number of prescribed renewals cannot be determined precisely. The RAMQ pharmacy database also provides the duration of prescriptions which is determined by the pharmacists based on the supplied quantity divided by the prescribed dose. These variables are available as soon as a new prescription has been dispensed and can be used to estimate the total number of prescriptions (new and refills) prescribed by the physicians without having to consult the patients' medical records. This information allows the determination of the physicians' prescribing pattern and the identification of whether suboptimal use of medication can be attributable to physicians' under prescribing and/or the patients' non adherence to their prescribed regimen.

## 3.5 Outcomes definitions

### *3.5.1 Prescribing patterns*

We estimated the prescribing patterns by reporting the total number of prescriptions for ICS which was defined as the sum of all new prescriptions dispensed plus prescribed refills from all physicians a patient could have consulted during the 12-month follow-up period. The numbers of new prescriptions dispensed and prescribed refills were also reported separately. The sum of the duration of all prescriptions of ICS was then calculated to determine the total days' supply prescribed during the study period.

We also estimated the physicians' adherence to the CAC guidelines for the daily long-term use of ICS for treatment of persistent asthma. The physicians' adherence was calculated by dividing the total days' supply prescribed by the duration of the study.

$$\text{Physicians' adherence} = \frac{\text{Total days' supply prescribed}}{\text{Total days' of study duration}}$$

The numerator was truncated to 365 days to exclude excess medication prescription.

*3.5.2 Patient adherence*

Adherence to a drug regimen as defined under section 2.6.1 is the extent to which a patient's actual history of drug administration corresponds to the agreed upon prescribed regimen. (2;70;71) Initially, a measure of refill adherence frequently used in previous studies was explored. This adherence measure, referred as the Proportion of Days Covered (PDC), is defined as the ratio of the total days' supplies dispensed by the duration of the study as shown below:

$$\text{PDC} = \frac{\text{Total days' supply dispensed}}{\text{Total days' of study participation}}$$

We noted that although the PDC adherence measure provides an accurate reflection of the use of medication throughout the duration of the study, it may not accurately reflect patient adherence to their prescribed medication if the latter is not prescribed for daily long-term use. In the presence of differing prescribing patterns, the PDC may fail to provide information about whether the patient is using the medication as prescribed.

It is for this reason that we have developed a new treatment adherence measure for the study presented herein which we named the Proportion of Prescribed Days Covered (PPDC). The PPDC which is based on the PDC measure is defined as the total days' supply dispensed to the total days' supply prescribed during the 12-month follow-up period. The total days' supply dispensed was calculated by summing the duration of all prescriptions of ICS (new and refills) dispensed from all physicians over the 12-month follow-up period as shown below:

$$\text{PPDC} = \frac{\text{Total days' supply dispensed}}{\text{Total days' supply prescribed}}$$

Both numerator and denominator were truncated to 365 days to exclude excess medication possession and medication prescription, respectively.

Patient adherence was estimated for all patients as well as stratified by prescription categories (1 prescription, 2 to 6 prescriptions and $\geq$ 7 prescriptions) to describe patients' adherence behaviour among those prescribed episodic and chronic ICS therapy. Patient adherence was also estimated for the two age groups (5-11 years and 12-15 years) separately. For comparison, we also estimated the overall patient adherence using the PDC.

In addition, the proportion of the non adherence value attributable to the lack of prescribing daily long term therapy was estimated using the following formula:

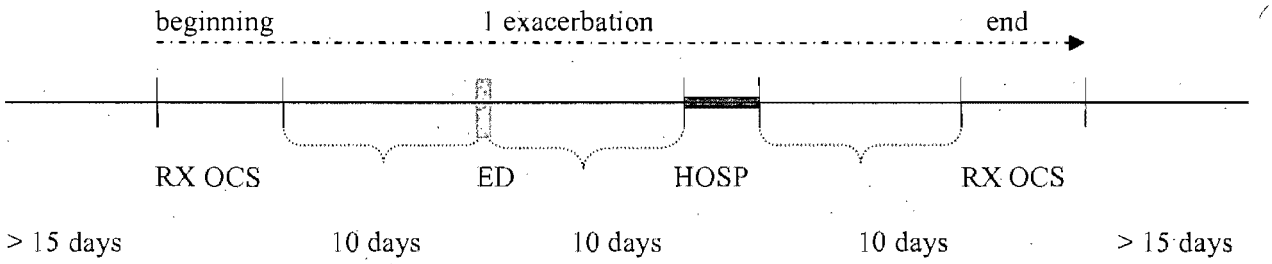
$$\frac{(1 - \text{PDC}) - (1 - \text{PPDC})}{(1 - \text{PDC})}$$

where 1 – PDC = 1 – (total days' supply dispensed/study duration) and represents the non adherence measure of the patients that includes the effect of the prescribing patterns and 1 – PPDC = 1 – (total days' supply dispensed/total days' supply prescribed) and represents the non adherence measure of the patients that corrects for the effect of the prescribing patterns.

We did not assess therapy persistence in our study, which examines more specifically the act of continuing therapy for the prescribed duration, by reporting the proportion of patients continuing to use a therapy after specified time intervals during the study period. (118) Although therapy persistence is often reported for chronic preventive therapies, it is difficult to assess in asthmatic patients as many physicians do not prescribed ICS for daily long term use (please see subsection 2.5).

*3.5.3 Markers of uncontrolled asthma*

We have described markers of uncontrolled asthma which are commonly used in administrative databases studies. (75;119) Markers of uncontrolled asthma over the 12-month follow-up period included moderate to severe asthma exacerbations which was defined as a composite outcome of a dispensed prescription for a short course OCS (14 days or less), an asthma-related emergency department visit or an asthma-related hospitalization. As shown below, the date of the first event constituted the beginning of the exacerbation. Exacerbations occurring within 15 days of a previous exacerbation were excluded to avoid double counting of the same event.




The three elements of this composite outcome were also reported separately. These markers of uncontrolled asthma were classified as dichotomous variables (0/≥1). Furthermore, we have assessed SABA use as a marker of asthma control based on the average number of doses per week and categorized into 3 groups: 0-3 doses per week, >3-10 doses per week and >10 doses per week.

### 3.6 Characteristics of the patients and physicians

The patient characteristics which we described included demographics at treatment initiation, co-morbid conditions such as diseases of the upper respiratory tract (ICD-9 codes: 460 (acute nasopharyngitis [common cold]), 461 (acute sinusitis), 465 (acute upper respitatory infections of multiple or unspecified sites), 466 (acute bronchitis and bronchiolitis), 471 (nasal polyps), 472.0 (chronic rhinitis), 473 (chronic sinusitis), 477 (allergic rhinitis)), pneumonia and influenza (ICD-9 codes: 480 (viral pneumonia), 482 (other bacterial pneumonia), 483 (pneumonia due to other specified organism), 484 (pneumonia in infectious diseases classified elsewhere), 485 (bronchopneumonia, organism unspecified), 486 (pneumonia, organism unspecified) and 487 (influenza), gastro-oesophageal reflux disease (ICD-9 code: 530.8), use of medications related to respiratory diseases (e.g., anti-allergy therapies, corticosteroids for nasal use and oral SABA), use of OCS, average number of doses of SABA used per week, number of moderate to severe asthma exacerbations, outpatient visits for asthma and for all causes (asthma and other diagnoses), and emergency department visits and hospitalizations due to asthma assessed in the year prior to treatment initiation. Characteristics related to

the first prescription of ICS included the prescribed daily dose categorized into three groups (>0-250 $\mu$g per day, >250-500 $\mu$g per day and >500 $\mu$g per day), type of ICS, specialty of the prescribing physician, location of the prescribing physicians, number of prescribed refills as well as the presence of markers of uncontrolled asthma (use of OCS, asthma-related emergency department visits, hospitalizations due to asthma and moderate to severe asthma exacerbations) at treatment initiation and 15 days prior. During the 12-month follow-up period, we assessed variables reflecting the use of health care services including the number of different prescribing physicians for asthma medications and the number of outpatient visits for asthma (at 6 weeks, 3 months and 12 months time points) and the number of outpatient visits for all causes (asthma and other diagnoses). Moreover, we estimated the average daily doses of ICS during the 12-month follow-up period for the two to six and seven or more prescriptions categories only, since the calculation of the average daily dose of ICS over a 12-month period is irrelevant when the patient had only received one prescription of ICS.

Events preceding each new and refill prescription dispensations (dispensing date and prior 15 days) such as moderate to severe asthma exacerbation, asthma-related emergency department visits, hospitalizations due to asthma and use of OCS were examined during the follow-up period. The observation period included 15 days prior to a dispensation to ensure capturing events for patients who may not obtain their prescriptions the day the medication is prescribed.

Patients were allowed to switch ICS medications during the follow up period. ICS medications were reported into fluticasone-equivalent based on equivalencies provided in the CAC guidelines and SABA medications were converted to dose equivalencies between the different SABA agents using the algorithm suggested by Blais et al.(120)

This study was approved by the Scientific and Ethics Committee of the *Hôpital du Sacré-Cœur de Montréal*, Québec, Canada.

### 3.7 Statistic analyses

Descriptive statistics were used to summarize the characteristics related to the patients 12-month prior to and 12-month following treatment initiation as well as to the physicians 12-month following treatment initiation. Data were reported as both medians and means with 95% confidence intervals for the prescribing patterns, use of health care services, patient adherence, and average daily doses of ICS; and as proportions for the markers of asthma control. Markers of uncontrolled asthma were stratified by three prescription categories (one prescription, two to six prescriptions and seven or more prescriptions) and by two patient adherence categories ($\geq$50% and <50%). All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC).

# CHAPTER 4: RESULTS

The objective of this chapter is to supplement the results presented in the manuscript. Results presented under the manuscript are not repeated in this chapter. All tables referred below are found under the section entitled 'Appendices'.

The locations of the prescribing physicians for the initial prescription of ICS are presented in Table I. Among the available locations (62%), the majority of prescriptions were obtained at outpatient clinics (75.7%) followed by emergency departments (20.5%) and hospitals (3.7%). Fewer patients received prescribed refills from emergency departments (39.1%) than from outpatient clinics (56.4%) and hospitals (51.9%).

In order to avoid overestimating the prescribing patterns and patient adherence to ICS during the study follow-up period, we have truncated the total days supply prescribed and the total days supply dispensed to 365 days affecting 5 to 10% and less than 1 % of the patients, respectively.

As shown in Table II, the overall median physicians' adherence to the CAC guidelines recommendation for the prescription of ICS for persistent asthma, representing the number of days of prescribed daily dose during the 12-month follow-up period, was 32.9%. When determining the overall median physicians' adherence to the CAC guidelines, we have found 267 new prescriptions (6.6%) with a recorded end validation date for potential renewals affecting 228 patients (9.7%). The majority of these prescriptions were valid for a duration of 365 days. The first analysis consisted of assigning the maximum potential number of renewals for the 267 new prescriptions with a recorded end validation date while the second analysis consisted of removing from the analyses the 228 patients who had at least one prescription with an end validation date. As shown in Table III, the overall median physicians' adherence to the CAC guidelines during the 12-month follow-up period obtained from the first and second sensitivity analyses

was 34.2%and 32.9%, respectively and the overall median patients' adherence rates obtained from the first and second sensitivity analyses was 50.0% and 53.8%, respectively.

Table IV presents adherence to the CAC guidelines for the re-evaluation of asthma control and effectiveness of the prescribed maintenance therapy. The number of patients with at least one outpatient visits for asthma at 6 weeks and 3 months following treatment initiation were 13.4% and 21.0%, respectively. The number of patients with at least one outpatient visits for asthma during the 12-month follow-up period was 45.4%.

As shown in Table V, the overall median patient adherence rate during the 12-month follow-up period was 58.6% when calculated using the newly developed PPDC measure compared to 15.1% when calculated using the PDC measure. The proportion of the non adherence value attributable to the lack of prescribing daily long-term ICS therapy is 51.2%. The comparison of adherence rates among children aged 5 to 11 years with those aged 12 to 15 years during the 12-month follow-up period are presented under Table VI. The median patient adherence rate obtained from the PPDC measure was 61.5% for the younger age group compared to 52.4% for the older age group. Similarly, the median patient adherence rates among children who had seven or more prescriptions were 32.9% and 28.9% for the younger and older age groups, respectively.

Table VII presents asthma-related events occurring 15 days prior to or on the day of an ICS dispensation throughout the 12-month follow-up period. Moderate to severe exacerbations preceded 14% of all prescriptions dispensed (new and refills) and were more frequent prior to a dispensation of a new prescription (18.1%) compared to a refill prescription (2.2%).

The number of patients with controlled asthma stratified by the number of prescription categories and patient adherence during the 12-month follow-up period is presented in Table VIII. Overall, patients with controlled asthma based on an average use of 3 doses or less of SABA per week, on average, and the absence of exacerbations represented 25% of the cohort. The number of patients with controlled asthma decreased with increasing ICS exposure.

# CHAPTER 5: MANUSCRIPT

# Use of Inhaled Corticosteroids in Children with Persistent Asthma:

# A Descriptive Analysis

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## ABSTRACT

The objective of this study was to measure simultaneously patient adherence and prescribing patterns of inhaled corticosteroids in asthmatic children with a new adherence measure.

A cohort of 2,355 children aged 5-15 years with asthma and having had used > 3 doses of short-acting beta-agonists per week on average during a 12-month period prior to treatment initiation with inhaled corticosteroids was reconstructed using Canadian administrative databases, between 1997 and 2005.

During the 12-month follow-up period, 20% of the children received only 1 prescription of inhaled corticosteroids with no prescribed renewals. The median number of prescriptions (including prescribed renewals) was 4 corresponding to only 120 days' supply prescribed. The median percent patient adherence to the prescribed therapy was 58.6%. Only 25% of the patients had controlled asthma based on the use of $\leq 3$ doses of short-acting beta-agonists per week and absence of moderate to severe exacerbations.

A large percentage of children with persistent asthma were not prescribed inhaled corticosteroids for chronic daily use and patient adherence was suboptimal. Many of these patients continued to experience poor asthma control.

## Introduction

Asthma is one of the most common chronic conditions in childhood. In Canada, approximately 15.6% of children aged 4 to 11 years and 11.7% aged 12 to 19 years have been diagnosed with asthma.[1] Despite widely distributed treatment guidelines including the Canadian Asthma Consensus (CAC) guidelines [2;3] and therapeutic advances aimed at preventing the onset of symptoms and providing long-term control of asthma symptoms, Canadian surveys continue to show a significant gap between treatment goals and levels of asthma control.[2;4] As a result, patients continue to experience poor asthma control and thus, require emergency care.[1;5]

Lack of adoption to the pharmacological therapy recommendations of the treatment guidelines may be one aspect contributing to suboptimal asthma control. Surveys conducted in the United States (U.S.) in 1999 and 2004 found that only half of the primary care physicians reported adherence to guideline recommendations for the prescription of daily ICS for children with persistent asthma.[6;7] Recently, a Canadian study surveying primary care physicians found that 20% of uncontrolled patients used SABA alone and the most frequently reported recommended change for these patients was the initiation of ICS, but in only 52% of them.[8] Moreover, rates of non-adherence to ICS in asthmatic paediatric patients have been reported to range from 32% to 50% through the use of electronic monitoring devices.[9-11]

Use of ICS has also been assessed using administrative data. A recent Canadian retrospective study conducted by Klomp et al has found that among those with poor asthma control, 37% were not dispensed any ICS.[12] The findings of this study are consistent with previous studies conducted in both Canada and the U.S.[13;14] However, it remains unclear from these studies whether the suboptimal use of ICS is attributable to physicians' non adherence to treatment

guidelines for the prescription of ICS as maintenance therapy or patients' non adherence to their prescribed regimen.

To our knowledge, there are no studies using administrative data that have simultaneously assessed the prescribing patterns of ICS and the adherence to this medication. Using administrative claims data from the province of Québec (Canada), the primary objective of this study was to describe the use of ICS in children with persistent asthma, including both prescribing patterns and patient adherence to prescribed ICS therapy using a new adherence measure. A secondary objective of this study was to describe markers of uncontrolled asthma as a function of the use of ICS.

**Methods**

Data Source

This study was completed using data from two of the province of Québec's administrative databases; the *Régie de l'Assurance Maladie du Québec* (RAMQ) and the MED-ECHO databases for the period from 1 January 1997 through 31 December 2005. The RAMQ provides medical coverage to all residents of Québec and pharmaceutical coverage to the elderly ($\geq$ 65 years), persons receiving social assistance, persons who do not have access to a private insurance plan, and children of persons covered by the public plan, which in 2005 represented over 42% of the population. All children covered by the public plan have free access to prescription medication.

The RAMQ database provides information, through a patient unique identifier (encrypted), related to the patient characteristics such as age, gender, area of residence and social aid status, the diagnosis, the encrypted identification, specialty of the treating physician, and type & date of the dispensed medical services as well as where they were dispensed – clinics, emergency department or hospitals. The RAMQ database also provides information on prescription claims

including the drug code which identifies the product name, the unit dose, the form and other product information, the type of prescription (new or refill), the number of prescribed refills (potential renewals associated with a new prescription), the duration of the prescription, the dispensing date, the encrypted identification, and specialty of the prescribing physician. The asthma diagnoses and prescription claims data recorded in the RAMQ database have been previously validated.[15;16]

The MED-ECHO database provides information on acute care hospital admissions including data on the patient unique identifier (encrypted), the discharge diagnoses, and the duration of the hospitalization for all residents of Québec. The patient's encrypted unique identifier was used to link the RAMQ database with the MED-ECHO database.

Cohort Definition

Patients with a newly filled prescription for an ICS in monotherapy were retrospectively selected from the RAMQ database between 1 January 1997 and 31 December 2004. The inclusion criteria were being between 5 and 15 years of age at treatment initiation with ICS (date of the first filled prescription of ICS which defined cohort entry), having received a diagnosis of asthma (ICD-9 code 493), and having used more than three doses of SABA per week on average in the year prior to treatment initiation to ensure that only patients with persistent asthma were included in the study. Patients had to have pharmaceutical insurance coverage one year prior to treatment initiation and throughout the follow-up period. Patients did not qualify for the study if they filled a prescription for an ICS in the year prior to treatment initiation or for a leukotriene modifier and/or a long-acting beta-agonist at treatment initiation and throughout the follow-up period. All patients were followed for a period of 12 months. Patients were excluded if they had a diagnosis of cystic fibrosis (ICD-9 code 277.0) or false croup (ICD-9 code 478.75), if they had been dispensed a prescription for an acetylcysteine, racemic epinephrine,

pancrelipase, pancreatine and tobracymine or if they were oral corticosteroid (OCS) dependent, defined as having been dispensed more than 182 days of an OCS, in the year prior to treatment initiation.

Outcomes

The primary outcomes were the prescribing patterns of ICS and patient adherence to ICS. Markers of uncontrolled asthma were secondary outcomes.

*Prescribing Patterns of ICS*

To describe the prescribing patterns, we reported the total number of prescriptions for ICS which was defined as the sum of all new prescriptions dispensed plus prescribed refills (i.e., when a prescription included at least one refill, the pharmacist records the number of refills prescribed by the physician in the RAMQ database) from all physicians a patient could have consulted during the 12-month follow-up period. The numbers of new prescriptions dispensed and prescribed refills were also reported separately. The sum of the duration of the total number of prescriptions of ICS was then calculated to determine the total days' supply prescribed.

*Patient Adherence to ICS*

A new treatment adherence measure which we named the Proportion of Prescribed Days Covered (PPDC) was developed for this study to account for differing prescribing patterns. The PPDC was defined as the total days' supply dispensed to the total days' supply prescribed during the 12-month follow-up period. The total days' supply dispensed was calculated by summing the duration of the dispensed prescriptions of ICS (new and refills) over the 12-month follow-up period.

$$\text{PPDC} = \frac{\text{Total days' supply dispensed}}{\text{Total days' supply prescribed}}$$

Both numerator and denominator were truncated to 365 days to exclude excess medication possession and medication prescription, respectively.

Patient adherence was estimated for all patients as well as stratified per prescription categories (one prescription, two to six prescriptions and seven or more prescriptions) to describe patients' adherence behaviour among those prescribed episodic and chronic ICS therapies. Patient adherence was also estimated for the two age groups (5-11 years and 12-15 years) separately.

*Markers of Uncontrolled Asthma*

Markers of uncontrolled asthma over the 12-month follow-up period included moderate to severe asthma exacerbations, which were defined as a composite outcome of a dispensed prescription for a short course OCS (14 days or less), an asthma-related emergency department visit, or an asthma-related hospitalization. The date of the first event constituted the start of the exacerbation. Exacerbations occurring within 15 days of a previous exacerbation were excluded to avoid double counting of the same event. The three elements of this composite outcome were also reported separately. These markers were classified as dichotomous variables ($0/\geq 1$). Furthermore, we have assessed SABA use as a marker of asthma control based on the average number of doses per week and categorized into three groups: 0-3 doses per week, 4-10 doses per week and >10 doses per week.

ICS medications were reported into fluticasone-equivalent based on equivalencies provided in the CAC guidelines and SABA medications were converted to dose equivalencies between the different SABA agents using the algorithm suggested by Blais et al.[17]

This study was approved by the Scientific and Ethics Committee of the *Hôpital du Sacré-Cœur de Montréal*, Québec, Canada.

**Statistical Analyses**

Descriptive statistics were used to summarize the characteristics related to the patients 12-month prior to and 12-month following treatment initiation as well as to the physicians 12-month following treatment initiation. Data were reported as both medians and means with 95% confidence intervals for the prescribing patterns, use of health care services, patient adherence, and average daily doses of ICS; and as proportions for the markers of asthma control. Markers of uncontrolled asthma were stratified by three prescription categories (one prescription, two to six prescriptions and seven or more prescriptions) and by two patient adherence categories (≥50% and <50%). All statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC).

**Results**

A total of 2,355 ICS-naïve children with persistent asthma met the study criteria. Baseline characteristics of the study population are shown in Table 1. The majority of patients (67.3%) were 5 to 11 years of age, male (56.4%), residing in urban areas (78.7%), and 40.3% were children of families receiving social assistance. During the year prior to treatment initiation with ICS, 40.5% of children had received a diagnosis for comorbid diseases of the upper respiratory tract, 10.9% had received a diagnosis related to pneumonia and/or influenza while none of the children had received a diagnosis of gastro-oesophageal reflux disease. As many as 13.2% of children had used an average of more than 10 doses of SABA per week and 28.3% had experienced at least one moderate to severe asthma exacerbation in the year prior to treatment initiation with ICS.

We then examined the characteristics related to the initial ICS prescription as shown in Table 2. For almost half of the patients (47.6%), there was no prescribed refill with their initial prescription and as much as 20.2% had experienced a moderate to severe exacerbation just prior to or on the day of the initiation of the

treatment with ICS. Among children with prescribed refills, the median number of refills was 1.0. Almost 95% of prescribers were family physicians and pediatricians.

Table 3 presents the prescribing patterns, use of healthcare services and patient adherence to ICS during the 12-month follow-up period. Twenty percent of the children received only one new prescription of ICS (no prescribed refills) and 50% had only 4 or fewer prescriptions from all physicians consulted during the 12-month follow-up corresponding to 120.0 days' supply prescribed. The median number of prescribing physicians was 2.0, with one outpatient visit for asthma and four outpatient visits for all causes. The overall median patient adherence value during the 12-month follow-up period was 58.6% and as low as 31.5% among children who had seven or more prescriptions. The median average daily dose of ICS was 73.2 and 118.7 μg per day among children who had two to six and seven or more prescriptions, respectively.

Markers of uncontrolled asthma stratified by prescription and patient adherence categories during the 12-month follow-up period are presented under Table 4. The continued high use of SABA and frequencies of moderate to severe exacerbations indicate that many patients were inadequately controlled during the follow-up.

**Discussion**

The prescribing patterns that we have identified suggest that ICS is often not prescribed for daily long-term use as recommended by the CAC guidelines for patients with persistent asthma. Indeed, during the 12-month follow-up period, 20% of patients had received only one prescription of ICS and 50% had 4 or fewer prescriptions corresponding to 120 days' supply prescribed. It is worth noting that regular use of ICS was clearly indicated for all patients in our cohort since they all

used on average more than three doses of SABA per week in the year prior to the first prescription of ICS.

There are many potential barriers to prescribing ICS that may explain our findings including lack of agreement with the ICS guidelines, lack of familiarity with guidelines criteria of asthma control, concerns regarding potential side effects of corticosteroids, and family-level barriers such as the cost of the medication which, in our study, is not a barrier since all patients had free access to their medications. [6;7;18] Our data suggest that for some patients, ICS may be used only to manage exacerbations. Indeed, we found that 20.2% of children had experienced a moderate to severe exacerbation just prior to or on the day of their initial ICS prescription. During the follow-up period, 27.1% of children with seven or more prescriptions had experienced a moderate to severe exacerbation excluding those occurring on the day of treatment initiation compared to 21.3% among children with two to six prescriptions and 13% among children with one prescription. We have also found that patients had few regular follow-up visits for asthma with their physicians which may also explain the under prescribing of ICS. Moreover, the median number of different prescribing physicians consulted was two indicating that patients have less than optimal continuity of care for the treatment of asthma.[19]

In addition to the suboptimal prescription of ICS by physicians, the overall median patient adherence value during the 12-month follow-up period was 58.6% and as low as 31.5% among children who had seven or more prescriptions. These results are consistent with the adherence rates reported in the literature. [9-11;20] As anticipated, the 12 to 15 age group had a lower overall median adherence than the younger age group (52.4% versus 61.5%), which is also consistent with the literature.[10;13;21]

Poor adherence to prescribed ICS therapy can be a result of many different underlying causes.[22;23] For some patients, asthma is only a problem when they experience an exacerbation. [24] Misunderstanding the role of therapy is also common in parents of children with persistent asthma.[25]

This study also showed that many patients did not attain control of their asthma by the observed frequencies of moderate to severe exacerbations and the continued high use of SABA during the follow-up period highlighting the importance of treating asthma with maintenance ICS therapy. In fact, only 25% of the patients had controlled asthma based on low use of SABA (three doses or less per week on average) and absence of moderate to severe exacerbations (data not shown). We observe that our two markers of uncontrolled asthma increases with increased ICS exposure. However, the majority of the patients had a median average daily dose below 125 µg, which may not be sufficient for patients with uncontrolled asthma.

There are several important methodological strengths to our study. We have selected patients who would most likely benefit from chronic daily use of ICS therapy as all patients had used more than three doses of SABA per week on average, a guideline defined marker of poor asthma control, during the one year period prior to treatment initiation. We have used a large validated healthcare administrative database to assess the use of ICS, which provides prospectively collected data on a population level. We were able to identify whether the low use of ICS was attributable to physicians not prescribing ICS for chronic daily use and/or the patient not filling their prescriptions using our newly developed adherence measure, the PPDC, which takes into account the quantity of medication prescribed, thereby correcting for the effect of varying prescribing patterns. Indeed, we would have obtained a median adherence value of 15.1% (data not shown) had we used the proportion of days covered (PDC), a frequently used adherence measure, instead of 58.6% when using the PPDC measure.[26]

Our findings must be interpreted in light of some limitations. Our study excluded patients covered by private drug plans; families with higher income may have been underrepresented. However, a previous Canadian study has shown that socioeconomic status had little influence on medication prescription patterns for the treatment of asthma in a population of children that had free access to prescribed medications. [17] Our findings may not generally apply to populations that pay for their medications. Our inability to determine whether patients booked and kept follow-up appointments with their physician and whether patients have filled their new prescription may have resulted in an underestimation of the prescribing patterns as only prescriptions dispensed at the pharmacy are accounted for in the database.[27] Conversely, the prescribing patterns were based on the total number of prescriptions a patient could have received from all physicians consulted during the 12-month follow-up period, which may overestimate the prescribing patterns of individual physicians. The adherence value derived from administrative databases assumes that patients filled their new prescription, used the drug as prescribed, and consumed all medications, thus providing the highest potential adherence.

Our study showed that many children with persistent asthma did not use their newly prescribed ICS therapy on a daily chronic basis, continued to overuse SABA, and experienced moderate to severe exacerbations. The consequences of poor compliance with the CAC guidelines recommendation to use ICS as maintenance therapy for patients with persistent asthma have been shown to reduce the effectiveness of the medication regimen, increase symptoms as well as being associated with a significantly higher number of annual emergency and hospitalization visits.[28-30] Our efforts to disentangle the behaviours of physicians and patients regarding the use of ICS therapy can be very useful in providing a better understanding of the gap between treatment goals and asthma control and in the planning of interventions aiming at the optimal use of ICS therapy.

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Table 1: Characteristics of the Study Population

| **Number of patients** | **2355** |
|---|---|
| **Variables** | **Number (%)** |
| **At treatment initiation** | |
| Age (years) | |
| 5-11 | 1584 (67.3) |
| 12-15 | 771 (32.7) |
| Male gender | 1329 (56.4) |
| Area of residence | |
| Urban | 1852 (78.7) |
| Rural | 500 (21.3) |
| Missing | 3 (0.1) |
| Social aid recipients | 950 (40.3) |
| **One year prior to treatment initiation** | |
| Comorbidities: | |
| Diseases of the Upper Respiratory Tract | 954 (40.5) |
| Pneumonia and Influenza | 257 (10.9) |
| Dispensed prescription related to respiratory diseases: | |
| Anti-allergy therapies | 16 (0.7) |
| Corticosteroids for nasal use | 305 (13.0) |
| Oral short-acting beta-agonists | 85 (3.6) |
| Number of outpatient visits for asthma | |
| 0 | 888 (37.7) |
| 1 | 972 (41.3) |
| ≥ 2 | 495 (21.0) |
| ≥ one pulmonary function test | 50 (2.1) |
| Use of SABA | |
| >3-10 doses per week | 2043 (86.8) |
| >10 doses per week | 312 (13.2) |

| **Number of patients** | **2355** |
|---|---|
| **Variables** | **Number (%)** |
| ≥ one dispensed prescription of OCS (14 days or less) | 389 (16.5) |
| ≥ one visits to an emergency department for asthma | 492 (20.9) |
| ≥ one hospitalizations for asthma | 103 (4.4) |
| ≥ one moderate to severe asthma exacerbation | 666 (28.3) |

Table 2: Characteristics Related to the Initial Prescription

| **Number of patients** | **2355** |
|---|---|
| **Variables** | **Number (%)** |
| **At treatment initiation** | |
| Fluticasone-equivalent dose prescribed, in µg per day, | |
| >0-250 | 424 (18.0) |
| >250-500 | 809 (34.4) |
| >500 | 1122 (47.6) |
| Type of ICS | |
| Fluticasone | 1564 (66.4) |
| Budesonide | 580 (24.6) |
| Beclomethasone | 211 (9.0) |
| Number of prescribed refills [1] | |
| 0 | 1122 (47.6) |
| ≥ 1 | 1233 (52.4) |
| Median (95% CI) | 1.0 (1.0-1.0) |
| Mean (95% CI) | 2.2 (2.0-2.3) |
| Prescribing physician specialty | |
| Family physician | 1579 (67.0) |
| Pediatrician | 657 (27.9) |
| Pneumologist | 37 (1.6) |
| Other | 82 (3.5) |
| **At treatment initiation and prior 15 days** | |
| ≥ one dispensed OCS | 298 (12.7) |
| ≥ one visit to an emergency department for asthma | 367 (15.6) |
| ≥ one hospitalization for asthma | 51 (2.2) |
| ≥ one moderate to severe asthma exacerbation | 476 (20.2) |

[1] Truncated to 365 days

Table 3: Prescribing Patterns, Use of Healthcare Services and Patient Medication Adherence during the 12-month Follow-up Period

| **Number of patients** | **2355** | |
|---|---|---|
| **Variables** | **Median (95% CI)** | **Mean (95% CI)** |
| **Prescribing patterns of ICS** | | |
| Number of dispensed new prescriptions | 1.0 (1.0-1.0) | 1.7 (1.7-1.7) |
| Number of prescribed refills | 2.0 (2.0-2.0) | 3.3 (3.1-3.5) |
| Total number of prescriptions | 4.0 (4.0-4.0) | 5.0 (4.9-5.2) |
| Total days' supply prescribed | 120.0 (105.0-120.0) | 152.0 (146.5-157.4) |
| **Use of health care services** | | |
| Number of different prescribing physicians for asthma medications | 2.0 (2.0-2.0) | 1.9 (1.9-2.0) |
| Number of outpatient visits for asthma[1] | 1.0 (1.0-1.0) | 1.3 (1.2-1.3) |
| Number of outpatient visits all causes[1] | 4.0 (4.0-4.0) | 5.1 (4.9-5.3) |
| **Patient adherence to ICS** | | |
| All patients | 58.6 (54.8-62.5) | 62.4 (61.1-63.7) |
| Patients with 1 prescription (n=468) | 100.0 (100.0-100.0) | 100.0 (100.0-100.0) |
| Patients with 2-6 prescriptions (n=1270) | 55.8 (50.7-60.0) | 60.9 (59.3-62.5) |
| Average ICS dose[2], in µg per day, | 73.2 (68.3-78.4) | 87.9 (84.7-91.2) |
| Patients with ≥ 7 prescriptions (n=617) | 31.5 (28.9-33.9) | 36.8 (35.1-38.6) |
| Average ICS dose[2], in µg per day, | 118.7 (106.4-126.3) | 143.6 (135.2-152.0) |

[1]Includes 15 days prior to treatment initiation

[2]Fluticasone-equivalent dose

Notes: The number of prescribed refills, total number of prescriptions, total days' supply prescribed, patient adherence and average daily dose of ICS were truncated to 365 days. The average daily dose of ICS was not calculated for patients who had received only one prescription over the 12-month follow-up period as it is irrelevant.

Table 4: Markers of Uncontrolled Asthma during the 12-month Follow-up Period as a Function of the Use of ICS

| **Use of ICS** | | | | | |
|---|---|---|---|---|---|
| Total number of prescriptions | 1 | 2-6 | | ≥7 | |
| Patient adherence, % | 100% | <50% | ≥50% | <50% | ≥50% |
| **Markers of uncontrolled asthma**[1] | | | | | |
| Number of patients | 468 | 469 | 801 | 475 | 142 |
| Use of SABA, (%) | | | | | |
| 0-3 doses per week | 262 (56.0) | 159 (33.9) | 164 (20.5) | 74 (15.6) | 8 (5.6) |
| 4-10 doses per week | 174 (37.2) | 246 (52.5) | 490 (61.2) | 272 (57.3) | 46 (32.4) |
| >10 doses per week | 32 (6.8) | 64 (13.6) | 147 (18.4) | 129 (27.2) | 88 (62.0) |
| ≥ one dispensed OCS, (%) | 32 (6.8) | 58 (12.4) | 157 (19.6) | 93 (19.6) | 36 (25.4) |
| ≥ one visit to an emergency department for asthma, (%) | 47 (10.0) | 55 (11.7) | 117 (14.6) | 81 (17.1) | 33 (23.0) |
| ≥ one hospitalization for asthma,(%) | 6 (1.3) | 4 (0.9) | 18 (2.2) | 12 (2.5) | 9 (6.3) |
| ≥ one moderate to severe exacerbation, (%) | 61 (13.0) | 81 (17.3) | 189 (23.6) | 117 (24.6) | 50 (35.2) |

[1] excluding the day of treatment initiation

# CHAPTER 6: DISCUSSION

This chapter encompasses the discussion of the results presented in the manuscript as well as those presented under chapter 4.

The prescribing patterns that we have identified suggest that ICS is often not prescribed for daily long-term use as recommended by the CAC guidelines for patients with persistent asthma. Indeed, during the 12-month follow-up period, 20% of patients had received only one prescription of ICS and 50% had 4 or fewer prescriptions corresponding to 120 days' supply prescribed. It is worth noting that regular use of ICS was clearly indicated for all patients in our cohort since they all used on average more than three doses of SABA per week in the year prior to the first prescription of ICS.

We have also found that the overall median physicians' adherence to the CAC guidelines recommendation for the prescription of ICS for persistent asthma was 32.9% during the 12-month follow-up period. It may be argued that physicians from emergency departments are most likely to refer patients to their family physicians for continued care and therefore less likely to prescribe refills with a new prescription. Indeed, at treatment initiation, there were fewer patients (39.1%) who had prescribed refills from an emergency department than from an outpatient clinic (56.4%) or from a hospital (51.9%). However, the majority of initial prescriptions were obtained at outpatient clinics (75.7%) and as many as 43.6% of these patients did not have prescribed refills.

There are many potential barriers to prescribing ICS that may explain our findings including lack of agreement with treatment guidelines recommendations for the prescription of daily ICS to patients with daily symptoms, concerns regarding potential side effects of corticosteroids, and family-level barriers such as the cost of the medication which, in our study, is not a barrier since all patients had free access to their medications. (13;14;68) Moreover, a recent Canadian survey reported that physicians' assessment of asthma control was not concordant with

guidelines assessment recommendations, particularly regarding the overuse of SABA which may lead physicians to overestimate control and under prescribe ICS.(15)

Our data suggest that for some patients ICS may be used only to manage exacerbations. Indeed, we found that 20.2% of children had experienced a moderate to severe exacerbation just prior to or on the day of their initial ICS prescription. During the follow-up period, 27.1% of children with seven or more prescriptions had experienced a moderate to severe exacerbation excluding those occurring on the day of treatment initiation compared to 21.3% among children with two to six prescriptions and 13% among children with one prescription.

When we specifically examined asthma-related events occurring 15 days prior to or on the day of a prescription dispensation, for all prescriptions (new and refills) dispensed throughout the 12-month follow-up period, we found that moderate to severe exacerbations preceded 14% of ICS dispensation. Interestingly, when stratified by prescription status (new and refills), it was found that moderate to severe exacerbations preceded 18.1% of new ICS dispensations compared to 2.2% of refill dispensations. Since most claims throughout the 12-month follow-up period were for new prescriptions (74.3%), these findings again suggest that a moderate to severe exacerbation is an important motivator for prescribing or obtaining a new prescription of ICS. In addition, the lower proportion of refill prescriptions (25.7%) dispensed throughout the 12-month follow-up period may suggest that ICS is not used as maintenance therapy.

We have also found that patients had few regular follow-up visits for asthma with their physicians which may also explain the under prescribing of ICS. The median number of outpatient visits for asthma during the 12-month follow-up period including the date of their initial prescription was one which is considered suboptimal for newly-treated asthma patients according to the CAC guidelines.

However, the median number of outpatient visits for all causes was four suggesting there may have been sufficient medical encounters to obtain prescriptions if the patients or caregivers reported poor asthma control. Moreover, the median number of different prescribing physicians consulted was two indicating that patients have less than optimal continuity of care for the treatment of asthma.(121)

When we examined the physicians' adherence to the CAC guidelines for the re-evaluation of asthma control and effectiveness of the prescribed maintenance therapy, we found that as few as 13.4% and 21.0% of patients had an outpatient visits for asthma at 6 weeks and 3 months following treatment initiation, respectively. Moreover, only 45.4% patients had an outpatient visits for asthma during the 12-month follow-up period following treatment initiation.

In addition to the suboptimal prescription of ICS by physicians, the overall median patient adherence value during the 12-month follow-up period was 58.6% and as low as 31.5% among children who had seven or more prescriptions. These results are consistent with the adherence rates reported in the literature. (10-12;122)

We hypothesize that the lower median adherence rates observed among patients with seven or more prescriptions is, among other factors, due to the patients' motivation to control their symptoms rather than to prevent symptoms. This hypothesis is consistent with the literature which informs us that asthmatic patients often stop prematurely taking their long-term ICS therapy in the absence of symptoms or if they have not experienced an attack for an extended period of time. (66;102) Patients may also be reluctant to fill long-term ICS prescriptions, particularly if they are asymptomatic, because of fear of side effects. (62;102) Poor adherence to prescribed long-term ICS therapy can also be a result of the patient's or caregiver's poor perception of the severity of the disease. (99;123) The intermittent nature of asthma may also lead some patients to perceive asthma

as an acute rather than a chronic disease. (102) Also commonly reported, many asthmatic patients or their caregivers have a lack of understanding of the role of ICS therapy and perceive ICS as symptom relieving rather than preventive. (97) A Canadian survey conducted in adults and parents of children aged 4 to 15 years revealed that 48% of patients with poorly controlled asthma who used an ICS did not understand the role of ICS, 45% reported using ICS when having an asthma attack and 28% before doing an exercise.(8)

As anticipated from the literature, the 12 to 15 age group had a lower overall median adherence than the younger age group (52.4% versus 61.5%). (11;85;90) In addition to the factors influencing adherence described above, it has been reported that adolescents may be less prone to take their medication because of inconvenience, embarrassment or forgetfulness. (102;103)

This study also showed that many patients did not attain control of their asthma by the observed frequencies of moderate to severe exacerbations and the continued high use of SABA during the follow-up period highlighting the importance of treating asthma with maintenance ICS therapy. In fact, only 25% of the patients had controlled asthma based on low use of SABA (less than three doses per week on average) and absence of moderate to severe exacerbations. We observe that our two markers of uncontrolled asthma increases with increased ICS exposure which suggests, as described earlier, that the most symptomatic patients are more likely to be adherent to their ICS. To explain the high frequencies of markers of uncontrolled asthma even in the most adherent patients, we estimated the median average daily doses of ICS during the 12-month follow-up period among patients with the highest ICS exposure (i.e., $\geq 7$ prescriptions of ICS and had an adherence of $\geq 50\%$). The median average daily dose was found to be less than 125 $\mu$g. It is important to note that a daily dose of $\leq 200$ $\mu$g represents a low dose according to the asthma treatment guidelines. Our finding suggests that ICS was not used

appropriately even among patients with the highest ICS exposure to keep asthma under control.

There are several important methodological strengths to our study. We have selected patients who would most likely benefit from chronic daily use of ICS therapy as all patients had used more than three doses of SABA per week on average, a guideline defined marker of poor asthma control, during the one year period prior to treatment initiation. We have used a large validated healthcare administrative database to assess the use of ICS on a population level, which provides objective exposure data as it is prospectively collected independently of the physicians and patients and thus, is not subject to interview 'social desirability' and recall biases. Another major strength of our study is that we were able to identify whether the low use of ICS was attributable to physicians not prescribing ICS for chronic daily use and/or the patient not filling their prescriptions. The Proportion of Prescribed Days Covered (PPDC) adherence measure developed for this study is based on a frequently used measure to estimate patient adherence from administrative databases, the proportion of days covered (PDC), which is defined as the total days' supply dispensed to the number of days of study participation.(82) Although both the PPDC and PDC measures provide an adherence value that represents the proportion of days with medication possession, the PDC is most useful when the medication is prescribed for chronic use. In the presence of differing prescribing patterns, the PDC may fail to provide information about whether the patient is using the medication as prescribed. The adherence value provided by the PPDC in our study more accurately represents the patients' adherence to the prescribed therapy as it takes into account, in the denominator, the quantity of medication prescribed, thereby correcting for the effect of varying prescribing patterns. Indeed, we would have obtained a median adherence value of 15.1% had we used the PDC adherence measure instead of 58.6% when using the PPDC measure.

Our findings must be interpreted in light of some limitations. Our study excluded patients covered by private drug plans; families with higher income may have been underrepresented. However, a previous Canadian study has shown that socioeconomic status had little influence on medication prescription patterns for the treatment of asthma in a population of children that had free access to prescribed medications. (120) Our findings may not generally apply to populations that pay for their medications. Our inability to determine whether the patients' booked and kept follow-up appointments with their physician if indeed recommended for reassessment of symptoms and therapy and whether the patients receiving a new prescription from their physician have obtained their prescription may have resulted in an underestimation of the prescribing patterns as only prescriptions dispensed at the pharmacy are accounted for in the database.(124) Conversely, the prescribing patterns were based on the total number of prescriptions a patient could have received from all physicians consulted during the 12-month follow-up period, which may overestimate the prescribing patterns of individual physicians. The adherence value derived from administrative databases assumes that patients filled their new prescription and consumed all medications, thus providing the highest potential adherence.

A formal validation of the prescription duration recorded in the RAMQ database based on the quantity dispensed and the usual dosage has not been conducted in our current study. In addition, it may be possible that the prescription duration was underestimated or overestimated in the event that the prescribed recommended use was verbally communicated to the patient and consisted of self adjusting the dose until effective control was achieved or reduced to a minimum maintenance effective dose.

We have slightly underestimated the prescribing physicians' adherence to the CAC guidelines recommendation for the prescription of ICS and overestimated the patients' adherence to ICS by not accounting for the number of potential renewals

corresponding to the 267 prescriptions with a recorded end validation date. However, based on the results obtained from the two sensitivity analyses, we can conclude that our main results for the physicians and patients adherence were robust as these estimates were only slightly affected and the conclusion was not affected. In the presence of overlapping prescriptions, we did not invalidate the permitted number of renewals of the previous prescription which may have potentially overestimated the physicians' adherence to the CAC guidelines recommendation for the prescription of ICS and an underestimated the patient's adherence. To minimize the impact of this limitation, the duration of therapy was truncated to 365 days to exclude excess medication prescription and medication possession.

Another limitation of the RAMQ database is that it does not include drugs supplied in hospitals. We do not believe this could have impacted our findings as few patients have been hospitalized and for these patients hospital stays were of short duration. Moreover, the diagnosis of asthma in children recorded in the RAMQ databases has not been validated; however, it is not anticipated to be different than in adults. What may be questionable is whether the diagnosis of asthma was correctly attributed in the absence of an objective pulmonary function test to confirm the diagnosis. However, by selecting patients who had also used, on average, more than 3 doses of SABA per week, during the year preceding treatment initiation with ICS, it provides us an additional assurance that our cohort reflects patients with persistent asthma.

# OVERALL CONCLUSION

Asthma is an increasingly common chronic disorder. It is a leading cause of hospitalization in children and brings significant direct costs to societies. National and international guidelines have been developed for the diagnosis, management and treatment of asthma. The pharmacological treatment component of these guidelines advocates first-line regular use of ICS for patients with persistent asthma. This recommendation is based on a wealth of scientific evidence from randomized, controlled clinical trials. [31-36] Regular use of ICS has also been associated with reduced asthma symptoms and severity and is associated with a significant lower number of annual emergency and hospitalizations in patients with persistent asthma based on 'real world' data from observational studies. [4-6] Yet, suboptimal use of ICS therapy is common in this population.

Consistent with the literature, we have found in our study that many physicians did not prescribed daily ICS for their patients with persistent asthma symptoms and many of these patients did not use their newly prescribed ICS therapy on a daily chronic basis, continued to overuse SABA, and experienced moderate to severe exacerbations. Differing to measures of refill adherence reported in the literature, the measure developed for this study corrected for the prescribing patterns without having to consult the patients' medical records, a major benefit in terms of study efficiency (i.e., time, manpower and cost). This is very important in asthma due to the presence of varying prescribing patterns to reflect the actual patient adherence behaviors. Indeed, in our study, the proportion of the non adherence value attributable to the lack of prescribing daily long-term ICS therapy was 51.2%. Our efforts to disentangle the behaviours of physicians and patients regarding the use of ICS therapy can be very useful in providing a better understanding of the gap between treatment goals and asthma control and in the planning of interventions aiming at the optimal use of ICS therapy.

It would be interesting to identify, as a next step, the determinants associated with the suboptimal prescription of ICS as maintenance therapy for patients with

persistent asthma. Using the same cohort, we could examine differences among prescribers and under prescribers by characteristics of the physicians such as their specialty, age, years since graduation, sex, region of practice, academic affiliation and characteristics of their patient such as age and prior asthma-related risk factors. This information could then be used to target individuals for focus groups to help elucidate some of the potential barriers to prescribing daily long-term ICS and subsequent tailor interventions to address identified barriers.

Despite the widely available treatment guidelines and the positive benefit-risk profile of ICS therapy, suboptimal asthma control continues to have a major impact in children and society. Physicians, parents and patients appear to fail to recognize that asthma is a chronic disease and the need to shift focus from treating asthma symptoms to using a more preventive approach with regular daily long-term ICS therapy. Interventions to encourage disease recognition and widespread use of ICS should continue to be advocated to reduce asthma-related morbidities, health care utilization and costs of asthma management.

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# APPENDICES

Figure 1: Cohort Selection

| | |
|---|---|
| New treatment episode with ICS[1] between 1 January 1998 to 31 December 2004 | 194 128 |
| No prescription for a leukotriene modifiers and/or long-acting $\beta_2$-agonists on the day of treatment initiation | 193 903 |
| Aged between 5 and 15 years on the day of treatment initiation | 79 835 |
| Enrolled in RAMQ pharmacy insurance plan in the year prior to treatment initiation | 65 011 |
| Diagnosed with asthma in the year prior to treatment initiation (ICD-9 code 493) | 35 664 |
| No diagnoses of cystic fibrosis (ICD-9 code 277.0) or false croup (ICD-9 code 478.75) in the year prior to treatment initiation | 35 571 |
| No prescription dispensation for an acetylcysteine, racemic epinephrine, pancrelipase, pancreatine and tobracymine in the year prior to treatment initiation | 35 475 |
| No OCS dependency (>182 days) in the year prior to treatment initiation | 35 461 |
| Observation period ≥ 3 months from treatment initiation | 32 838 |
| >3 SABA doses per week on average or ≥ 1 asthma-related event (an emergency visit, a hospitalization and/or an OCS dispensation) in the year prior to treatment initiation | 7 849 |
| First treatment episode with ICS | 7 253 |
| New prescription (not a refill of a previous prescription) for an ICS on the day of treatment initiation | 6 966 |
| Observation period of ≥ 12 months from treatment initiation | 5 836 |
| >3 SABA doses per week on average in the year prior to treatment initiation | 2 355 |

[1] New episode defined as the absence of ICS dispensation in the year prior to treatment initiation

Abbreviations: ICS = Inhaled Corticosteroids. SABA = Inhaled Short Acting $\beta_2$-Agonists. RAMQ = *Régie de l'Assurance Maladie du Québec.* ICD-9 = International Classification of Diseases, 9th Revision. OCS = Oral Corticosteroids

Table I: Location of the prescribing physicians for the initial prescription of ICS

| | |
|---|---|
| Number of patients | 2355 |
| **Location of prescribing physicians [1], %** | |
| **Outpatient clinic** | |
| All patients | 1102 (75.7) |
| Patients with no refill | 480 (43.6) |
| Patients with ≥ one refills | 622 (56.4) |
| **Emergency department** | |
| All patients | 299 (20.5) |
| Patients with no refill | 182 (60.9) |
| Patients with ≥ one refills | 117 (39.1) |
| **Hospital** | |
| All patients | 54 (3.7) |
| Patients with no refill | 26 (48.1) |
| Patients with ≥ one refills | 28 (51.9) |
| **Undefined** | |
| All patients | 900 |
| Patients with no refill | 434 |
| Patients with ≥ one refills | 466 |

[1] Day of treatment initiation and 15 days prior

Abbreviation: ICS = Inhaled Corticosteroids.

Table II: Physicians adherence to the CAC guidelines for the prescription of ICS during the 12-month follow-up period

| Number of patients | 2355 | |
|---|---|---|
| | Percent adherence | |
| | Median (95% CI) | Mean (95% CI) |
| Physicians adherence[1] | 32.9 (28.8-32.9) | 39.1 (37.9-40.4) |

[1] Physicians adherence is defined as the percent days' supply prescribed divided by the duration of the study

Abbreviations: CAC = Canadian Asthma Consensus. ICS = Inhaled Corticosteroids.

Table III: Sensitivity analyses for comparison of physicians adherence to the CAC guidelines for the prescription of ICS and patients adherence to ICS during the 12-month follow-up period

| | Main analysis | Sensitivity analysis 1[1] | Sensitivity analysis 2[2] |
|---|---|---|---|
| **Number of patients** | 2355 | 2355 | 2127 |
| | | Percent adherence | |
| **Physicians adherence**[3] | | | |
| **Median (95% CI)** | 32.9 (28.8-32.9) | 34.2 (32.9-37.0) | 32.9 (29.6-32.9) |
| **Mean (95% CI)** | 39.1 (37.9-40.4) | 43.8 (42.5-45.1) | 39.2 (37.9-40.5) |
| **Patients adherence using PPDC** | | | |
| **Median (95% CI)** | 58.6 (54.8-62.5) | 50.0 (50.0-50.0) | 53.8 (50.0-57.9) |
| **Mean (95% CI)** | 62.4 (61.1-63.7) | 57.6 (56.3-58.9) | 60.7 (59.3-62.0) |

[1] Sensitivity analysis 1 consists of assigning the maximum potential number of renewals for the 267 prescriptions with a recorded end validation date.

[2] Sensitivity analysis 2 consists of removing from the analyses the 228 patients who had at least one prescription with a recorded end validation date.

[3] Physicians adherence is defined as the percent days' supply prescribed divided by the duration of the study

Abbreviations: CAC = Canadian Asthma Consensus. ICS = Inhaled Corticosteroids. PPDC = Proportion of Prescribed Days Covered.

Table IV: Physicians adherence to the CAC guidelines for the re-evaluation of asthma control and effectiveness of the prescribed ICS therapy following initiation of therapy

| Number of patients | 2355 |
|---|---|
| Variables | Number (%) |
| Number of patients with ≥ one outpatient visits for asthma[1] | |
| During the first six weeks following treatment initiation | 316 (13.4) |
| During the first twelve weeks following treatment initiation | 494 (21.0) |

[1] Including outpatient visits to all physicians a patient could have consulted.
Abbreviations: CAC = Canadian Asthma Consensus. ICS = Inhaled Corticosteroids.

Table V: Comparison of patient adherence rates to ICS using two adherence measures (PPDC and PDC) during the 12-month follow-up period

| Number of patients | 2355 | |
|---|---|---|
| Variables | Percent adherence | |
| | Median (95% CI) | Mean (95% CI) |
| Patient adherence using PPDC | 58.6 (54.8-62.5) | 62.4 (61.1-63.7) |
| Patient adherence using PDC | 15.1 (13.7-15.1) | 18.5 (17.9-19.1) |

Abbreviations: ICS = Inhaled Corticosteroids. PPDC = Proportion of Prescribed Days Covered. PDC = Proportion of Days Covered.

Table VI: Patient adherence to ICS using the PPDC measure for all patients and per age groups (5-11 years and 12-15 years) during the 12-month follow-up period

| Variables | Percent adherence | |
|---|---|---|
| | Median (95% CI) | Mean (95% CI) |
| **Patients 5-15 years old** (N=2355) | | |
| All patients | 58.6 (54.8-62.5) | 62.4 (61.1-63.7) |
| Patients with | | |
| 2-6 prescriptions | 55.8 (50.7-60.0) | 60.9 (59.3-62.5) |
| ≥7 prescriptions | 31.5 (28.9-33.9) | 36.8 (35.1-38.6) |
| **Patients 5-11 years old** (N=1584) | | |
| All patients | 61.5 (57.1-66.7) | 62.4 (61.1-63.7) |
| Patients with | | |
| 2-6 prescriptions | 60.0 (54.8-65.0) | 60.9 (59.3-62.5) |
| ≥7 prescriptions | 32.9 (29.9-35.6) | 36.8 (35.1-38.6) |
| **Patients 12-15 years old** (N=771) | | |
| All patients | 52.4 (50.0-60.0) | 60.0 (57.7-62.3) |
| Patients with | | |
| 2-6 prescriptions | 50.0 (50.0-54.8) | 57.0 (54.1-59.9) |
| ≥7 prescriptions | 28.9 (27.4-33.0) | 36.4 (33.4-39.4) |

Abbreviations: ICS = Inhaled Corticosteroids. PPDC = Proportion of Prescribed Days Covered.

Table VII: Asthma-related events occurring 15 days prior to or on the day of an ICS dispensation throughout the 12-month follow-up period

| Variables | Number (%) of prescriptions dispensed | | |
|---|---|---|---|
| Type of prescriptions | All prescriptions (new and refills) | New prescriptions | Refill prescriptions |
| Number of prescriptions dispensed | 5425 (100) | 4030 (74.3) | 1395 (25.7) |
| Dispensed oral corticosteroids | 511 (9.4) | 489 (12.1) | 22 (1.6) |
| Visits to an emergency department for asthma | 563 (10.4) | 541 (13.4) | 22 (1.6) |
| Hospitalizations for asthma | 91 (1.7) | 85 (2.1) | 6 (0.4) |
| Moderate to severe exacerbations[1] | 759 (14.0) | 729 (18.1) | 30 (2.2) |

[1] Moderate to severe exacerbations is defined as a composite outcome of a dispensed prescription for a short course OCS (14 days or less), an asthma-related emergency department visit or an asthma-related hospitalization.
Abbreviations: ICS = Inhaled Corticosteroids. OCS = Oral Corticosteroids.

Table VIII: Number of patients with controlled asthma during the 12-month follow-up period

| Use of ICS | | | | | |
|---|---|---|---|---|---|
| Total number of prescriptions | 1 | 2-6 | | ≥7 | |
| Patient adherence, % | 100% | <50% | ≥50% | <50% | ≥50% |
| Number of patients | 468 | 469 | 801 | 475 | 142 |
| Number of patients with controlled asthma[1], (%) | 235 (50.9) | 145 (30.9) | 133 (16.6) | 68 (14.3) | 6 (4.2) |

[1]0-3 doses of SABA per week on average and absence of a moderate to severe exacerbation defined as a composite outcome of a dispensed prescription for a short course OCS (14 days or less), an asthma-related emergency department visit or an asthma-related hospitalization. Abbreviations: SABA = Inhaled Short Acting $\beta_2$-Agonists. OCS = Oral Corticosteroids

Table IX: Examples of refill adherence assessment measures

| Measure | Formula | Value |
|---|---|---|
| CSA | Total days' supply dispensed/total days' in interval | Adherence value per single refill interval |
| CSG | Total days' treatment gaps /total days' in interval | Non adherence value per single refill interval |
| CMA | Total days' supply dispensed/total days' over a series of intervals | Adherence value for cumulative period of interest[1] |
| CMG | Total days' treatment gaps/total days' over a series of intervals | Non adherence value for cumulative period of interest[1] |
| CR | [(Total days' supply dispensed-days' supply of last dispensation)/total days' between first and last dispensation] X 100 | Adherence percentage for period between first and last refill |
| MPR | Total days' supply dispensed/total days' study participation per participant | Ratio of medication availability |
| MRA | [Total days' supply dispensed/total days' study participation] X 100 | Overall adherence percentage |
| PDC | [Total days' supply dispensed/total days' study participation] X 100, capped at one | Overall adherence percentage |

[1] The end date may be the last fill or an arbitrary date such as the end of the calendar year or the end of the observation period.

Abbreviations: CMA = continuous, multiple-interval measure of medication availability (or acquisition). CMG = continuous, multiple-interval measures of medication gaps. CSA = continuous, single-interval measure of medication availability (or acquisition). CSG = continuous, single-interval measure of medication gaps. CR = compliance rate. MPR = medication possession ratio. MRA = medication refill adherence. PDC = proportion of days covered.

Adapted from Hess et al 2006 and Steiner et al 1997