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Determinants Of Oral corticosteroid Responsiveness in Wheezing Asthmatic Youth (DOORWAY): protocol for a prospective multicentre cohort study of children with acute moderate-to-severe asthma exacerbations

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ABSTRACT

Introduction: Oral corticosteroids are the cornerstone of acute asthma management in the emergency department. Recent evidence has raised doubts about the efficacy of this treatment in preschool-aged children with viral-induced wheezing and in smoking adults. The aims of the study were to: (1) document the magnitude of response to oral corticosteroids in children presenting to the emergency department with moderate or severe asthma; (2) quantify potential determinants of response to corticosteroids and (3) explore the role of gene polymorphisms associated with the responsiveness to corticosteroids.

Methods and analysis: The design is a prospective cohort study of 1008 children aged 1–17 years meeting a strict definition of asthma and presenting with a clinical score of ≥4 on the validated Pediatric Respiratory Assessment Measure. All children will receive standardised severity-specific treatment with prednisone/prednisolone and cointerventions (salbutamol with/without ipratropium bromide). Determinants, namely viral aetiology, environmental tobacco smoke and single nucleotide polymorphism, will be objectively documented. The primary efficacy endpoint is the failure of emergency department (ED) management within 72 h of the ED visit. Secondary endpoints include other measures of asthma severity and time to recovery within 7 days of the index visit. The study has 80% power for detecting a risk difference of 7.5% associated with each determinant from a baseline risk of 21%, at an α of 0.05.

Ethics and dissemination: Ethical approval has been obtained from all participating institutions. An impaired response to systemic steroids in certain subgroups will challenge the current standard of practice and call for the immediate search for better approaches. A potential host–environment interaction will broaden our understanding of corticosteroid responsiveness in children. Documentation of similar effectiveness of corticosteroids across determinants will provide the needed reassurance regarding current treatment recommendations.

Results: Results will be disseminated at international conferences and manuscripts targeted at emergency physicians, paediatricians, geneticists and respirologists.

Trial registration number: This study is registered at Clinicaltrials.gov (NCT02013076).

Strengths and limitations of this study

- The proposed work will be the largest published cohort study exploring determinants of responsiveness to oral corticosteroids in children treated according to evidence-based acute asthma guidelines.
- The documentation of exposure using biomarkers to confirm parental reports enhances accuracy and precision of the determinants.
- The selection of a primary endpoint, that is, failure of emergency department (ED) management, the only clinical outcome that can be documented in all patients irrespective of age, carries enormous weight for modifying practice.
- A prospective cohort study is subject to potential biases inherent to this design. Loss to follow-ups will be quasi non-existent for the main and most secondary outcomes due to the short duration of follow-up in the emergency department. Confounding by indication will be minimised by the standardised severity-specific therapy.
- The inherent variability of admission and assessment of the Paediatric Respiratory Assessment Measure add noise to the data, which was taken into account in the sample size.

INTRODUCTION

Asthma is the most common chronic disease in childhood. It affects over half a million Canadian children aged 4–11 years.[1] Of all

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respiratory illnesses, asthma is one of the most frequent paediatric diagnoses requiring hospital admission.[1] The burden of illness is much higher in preschool-aged children, who account for over 50% of emergency department (ED) visits[1–4] and who have three times the hospital admission rate of older children and adolescents.[5] The difficulty in measuring asthma severity in young children has resulted in a dearth of comparative therapeutic evidence between preschoolers and older children.[6–9]

Treatment of acute asthma

National and international guidelines for the management of acute asthma recommend: (1) inhaled β_2-agonists for all patients; (2) systemic (usually oral) corticosteroids for those with moderate and severe asthma; and (3) repeated doses of inhaled β_2-agonists and anticholinergics for severe cases.[6 7 9 10] The latter two recommendations independently reduce admission rates by 25% in studies of predominantly school-aged children.[11 12] Several features must be noted. First, recommendations are severity-specific; patients with mild asthma do not appear to benefit from oral corticosteroids.[11 13] Second, the concept of the 'golden first hour of treatment' supports early and aggressive asthma management, as the risk of admission is reduced only when oral corticosteroids are administered 3–4 h prior to the decision to admit. Third, of all treatments administered in the ED, oral corticosteroids are by far the most effective for preventing admission.[14] Fourth, there is no equally effective substitute for oral corticosteroids; promising contenders such as high-dose inhaled steroids,[15 16] intravenous antileukotrienes[17] or magnesium sulfate[18] have been shown to be inferior to oral corticosteroids and are used as an add-on therapy. Fifth, systemic corticosteroids are inexpensive generic drugs. Short treatment with oral corticosteroids is generally devoid of significant side effects,[19] though rare cases of fatal or disseminated varicella have been reported.[20] Sixth, while recommendations are relatively similar in young children, older children and adults, the evidence for the former is weaker due to the under-representation of preschool-aged children in relevant trials.[11 12] While oral corticosteroids are the cornerstone of management of acute, moderate or severe asthma,[6] several reports have recently shaken the belief that they are equally effective for all patients with asthma, showing that children with viral-induced wheezing[21] and smoking adults[22] are corticosteroid-resistant. Indeed, in a large placebo-controlled randomised controlled trial of 700 children aged 10–60 months with mild-to-moderate viral-induced wheezing, oral corticosteroid was not superior to placebo for reducing the length of stay in hospital or improving the Pediatric Respiratory Assessment Measure (PRAM) clinical score, despite adequate study power.[21] Critics have suggested that: (1) in most children, the disease may not have been asthma (documented in only 16% of patients) but rather the North American definition of bronchiolitis; (2) some patients (with mild asthma) may not have needed corticosteroids[23]; (3) the prolonged stay in hospital did not seem to be supported by severity[24] and (4) the dose of 1 (instead of 2) mg/kg may have been insufficient. Yet, this study elicited major discomfort regarding acute asthma management in young children.[24] In another adequately powered landmark trial, a 2-week treatment with prednisone showed a marked blunting of response in adult smokers, with an improvement in forced expiratory volume in 1 s (FEV_1) of 237 mL (95% CI 43 to 431) in never-smokers compared to no change or 47 (−148 to 243) mL in current smokers.[22] The question remains as to whether smoking adolescents and children with environmental tobacco smoke (ETS) respond as well as those not exposed. None of these aforementioned findings have been replicated, thus prompting us to review the potential determinants of responsiveness.

Potential determinants of response

Disease diagnosis

Children with bronchiolitis do not respond to oral corticosteroids, although a recent trial has demonstrated a significant response only in association with nebulised epinephrine.[25–27] It is thus critical to distinguish asthma from bronchiolitis in young children.[28] Bronchiolitis is clinically defined in North America as the first wheezing illness in a child ≤12 months, with respiratory syncytial virus (RSV) as the most frequent pathogen. Asthma, defined as airway obstruction (cough, dyspnoea and wheezing) with hyper-reactivity and reversibility with bronchodilator or corticosteroids, begins early in life.[29 30] While children and adults meeting these criteria can be diagnosed at the first episode, generally three wheezing episodes are required for children ≤12 months to reduce the risk of misclassification with bronchiolitis.[8 31] Heterogeneous groups of children with bronchiolitis and asthma may explain the poor response to oral corticosteroids in studies including infants and toddlers.[21 24] Thus, an operational definition of asthma, clinically applicable to children aged 1–17 years, is needed to reasonably exclude bronchiolitis.

Upper respiratory tract infections

Upper respiratory tract infections (URTIs), usually viral in origin, are the most frequent (60–80%) triggers of asthma exacerbation in children.[32–34] RSV, parainfluenza virus and rhinovirus are frequently implicated in children under 2 years of age, while picornavirus, coronavirus and influenza are usually associated with asthma in older children.[35–38] The incidence of viral-induced asthma peaks in September continues throughout the fall and winter.[32] In adults with acute asthma, viral infection is associated with longer hospital admission[39] and increased sputum neutrophils, suggesting a predominantly neutrophilic airway inflammation.[39] In a study of children aged 3–36 months, those infected with rhinovirus showed fewer relapses when treated with oral prednisone compared to placebo, suggesting that rhinovirus did not impair responsiveness to steroids.[40] In another

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placebo-controlled trial of 283 young children with wheezing, prednisolone did not significantly decrease the overall time to discharge; however, it reduced by half the length of stay in children infected with picornavirus and by fourfold that of children with enterovirus, suggesting that response may be organism dependent.[41] Clearly, oral corticosteroids may not be as effective in patients with viral infections as in those without, perhaps due to neutrophilic airway inflammation, a condition associated with poor response to corticosteroids. Moreover, response may be organism specific, a hypothesis that requires careful documentation of aetiology.

Exposure to tobacco smoke

In addition to the aforementioned trial demonstrating no response to oral corticosteroids in asthmatic adult smokers,[22] a blunted response to inhaled corticosteroids was also documented in adult smokers in two randomised controlled trials.[42 43] While the mechanism behind the lack of response is not known, one can certainly point to smoking's direct toxicity, proinflammatory action or interference with the transcription of genes associated with corticosteroid response.[22] Indeed, smoking has frequently been associated with airway neutrophilia.[44] In paediatrics, exposure to tobacco smoke has been associated with a higher incidence of URTIs and prevalence of asthma, and a greater severity of exacerbations.[45] However, the impact on the therapeutic response has not been documented in children, as asthma trials have not examined or failed to report subgroup analyses on ETS exposure or active smoking. Heavier ETS exposure in preschoolers who spend more time at home than school-aged children[46 47] may explain a poorer response in young children. Objective documentation of smoking would also be important if possible, even before high school where many already smoke.[48] Of particular concern is whether a blunted response to oral corticosteroids would be found in children exposed to tobacco smoke and adolescents with a short history of active smoking. With 25% of asthmatic children exposed to ETS and 25% of teenagers actively smoking,[49–51] such an assessment appears critical.

Several reports highlight the need for objective measurement of nicotine exposure, because of parental underreporting of their child's exposure to ETS.[46 52] Cotinine, a nicotine metabolite with a half-life of 20 h, is a widely accepted indicator of recent tobacco use and exposure.[53] Serum cotinine requires blood sampling, a major deterrent for study participation in paediatrics.[47 53] Good correlations exist between serum and either salivary (r=0.71) or urine (r=0.69) cotinine measures.[53] With a 1:10 ratio of cotinine level between saliva and urine,[54] passive exposure may lead to saliva levels of 5–10 ng/mL[55 56] and urine levels of 10–100 ng/mL.[45] However, as urine sampling in young children may not occur for several hours and is more complex to obtain in children not yet toilet-trained, saliva cotinine measured by the quantitative enzyme immunoassay kit is a well-validated, non-invasive solution that offers required precision with minimal volume and a detectable level of 0.05 ng/mL.[56 57]

Other determinants

A number of other factors could possibly modulate the responsiveness to oral corticosteroids including, among others, gender,[1] race,[58 59] perceived asthma phenotype (derived from age, common asthma triggers and interim symptoms),[31 60 61] inhaled corticosteroids,[2 73 62] allergens, the alleged trigger,[63] and other environmental triggers, all of which can be documented clinically by questionnaire.

Mechanistic pathways

Two promising mechanistic pathways may explain the variations in the magnitude of response observed in clinical effectiveness, namely (1) gene polymorphisms that may reveal potential gene–environment interactions and (2) the type of airway inflammation.

Gene polymorphisms

There is increasing evidence that inherited genes are not a deterministic genotype, but rather a genotype that encodes a potential range of phenotypes that will develop in response to a variety of environments.[64] Consequently, a minor polymorphism between individuals in genes that modulate response to corticosteroids may predispose some people to environmentally induced problems, such as smoke-induced or viral-induced asthma.[65 66] Two major groups of genes are of interest: (1) those affecting susceptibility to asthma and (2) those directly interfering with response to corticosteroids by coding for major components of the pathway involved in corticosteroid action (table 1). In the first group, we selected eight polymorphisms in seven genes that can be divided into those coding for xenobiotic metabolising enzymes and those coding for mediators of inflammation and immunity, specifically the ones demonstrated to affect lung function, disease severity and interaction with exposure to ETS.[67 68] We selected polymorphisms affecting gene function, top-ranking single-nucleotide polymorphisms (SNPs) in a number of associated studies. Transforming growth factor β 1 polymorphisms were found to correlate with disease severity[69]; CC16 polymorphisms play a role in the development and persistence of the asthma phenotype in childhood[70]; CD14 polymorphisms have been linked to pathogenesis of asthma and lung function in smokers.[71] The ORMDL3 gene confers susceptibility to early-onset asthma, particularly through interaction with early life exposure to ETS[67 72]; GSTM1 and GSTP1 are involved in the metabolism of polycyclic aromatic hydrocarbon derivatives and reactive oxygen species[73 74]; GSTM1 null and GSTP1 genotypes have been associated with an increased risk of asthma[75] and rapid decline of lung function among smokers.[76] The ADRB2 receptor gene was found to contribute to the occurrence of wheeze among children who were exposed to tobacco smoke in utero and in early childhood[77] and was related to β_2-agonist response.[68 78] Among genes affecting the corticosteroid and inflammatory

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Table 1 Summary of the polymorphisms in subset of candidate genes of relevance for asthma phenotype and corticosteroids response

Gene		Location	Position/SNP annotation
TGF-β11	Transforming growth factor β	Promoter	-C-509T rs1800469
		Coding	T869C rs1982073
CD141	Monocyte differentiation antigen CD14	Promoter	C-159T rs2569190
CC161	Clara cell 16 kDa secretory protein	5′UTR	A38G rs3741240
ADRB21	β-2-adrenergic receptor	Coding	Arg16Gly rs1042713
GSTM1*	Glutathione S transferase M1	Gene deletion	GSTM1 null genotype
GSTP1*	Glutathione S transferase P1	Coding	Ile105Val rs1695
ORMDL3*	Orm1-like protein 3	Intronic	A/C rs4795405
CRHR1†	Corticotropin-releasing hormone receptor 1	Intronic	A/G rs242941
TBX21†	Tbox 21	Coding	H33Q rs2240017
		Promoter	T-1514C rs17250932
			G-999A rs11650451
			T-1993C rs4794067
FCER2†	Fc fragment of IgE, low affinity II, receptor for (CD23)	Intronic	T2206C rs28364072
GLCCI1†	Glucocorticoid-induced transcript 1	5′UTR	C/T rs37972
SERPINE1†	Plasminogen activator inhibitor-1,	Promoter	−675 4G/5G rs1799889
STIP1†	Stress-induced phosphoprotein		G/T rs4980524
STIP1†	Stress-induced phosphoprotein		rs2236647

*Relevance for asthma phenotype.
†Relevance for corticosteroid response.
SNP, single-nucleotide polymorphism.

pathways, we selected genes (CHRH1, TBX21, FCER2, GLCC1, STIP1 and SERPINE1) that were shown to correlate with response to corticosteroids in patients with asthma; the finding for some of them was replicated in several cohorts.[79–84] All selected polymorphisms with the gene name, position and corresponding reference are summarised in table 1. Genotyping is essential to link the observed corticosteroid response to genotype and to evaluate the potential host–environment interaction.

Airway inflammation

Induced sputum is a valid, reproducible and non-invasive method of assessing the magnitude and pattern of airway inflammation in adults and children.[85] Sputum cell counts and differentials (ie, eosinophils and neutrophils) determine the inflammatory phenotype; analysis of supernatants for eosinophil cationic protein (ECP), interleukin-8 (IL-8) and myeloperoxidase provides measures of cellular activation. Sputum eosinophils and ECP increase with exposure to allergens and decrease with corticosteroid treatment.[86] A higher proportion of neutrophils is associated with smoking[22 44 87] and with viral infection.[39 88] The non-eosinophilic inflammatory phenotype in adults has been associated with poor response to corticosteroids.[89 90] Markers of this phenotype include an increased proportion of neutrophils, IL-8 and myeloperoxidase, all of which are easily quantifiable.[91 92] Contrary to adult findings and criteria, three distinct inflammatory cell patterns have been reported during paediatric exacerbations: non-eosinophilic (<2.5% eosinophils) in 22%, eosinophilic (≥2.5% eosinophils) in 43% and combined eosinophilic/neutrophilic (≥2.5% eosinophils and >54% neutrophils) in 35%, with paucigranular inflammation not described in acute paediatric asthma.[62] Combined eosinophilic/neutrophilic exacerbations show more mast cells and higher sputum ECP levels than eosinophilic exacerbations. There is increasing evidence that eosinophilic asthma is more responsive to corticosteroids than non-eosinophilic asthma; a promising mechanistic pathway to explore.[93 94]

Expired nitric oxide (eNO) is increasingly recognised as a non-invasive marker of airway inflammation, particularly in atopic asthma,[95 96] and correlates strongly with the percentage of airway eosinophils (r=0.78) and ECP (r=0.53) in children with asthma.[97] Although the understanding about the link between NO and airway inflammation remains incomplete, airway epithelial cells activated by inflammatory cytokines produce an increased amount of eNO due to the expression of inducible NO synthase.[98] eNO is elevated in untreated asthma[99] and improves with asthma therapy.[100 101] Of interest, eNO correlates with other markers of eosinophilic inflammation, including sputum eosinophils.[102 103] Thus, eNO appears to reflect the magnitude of eosinophilic airway inflammatory and may serve as a promising biomarker of eosinophilic inflammation in children too young or unable to cooperate with induced sputum sampling.[104] As it can be measured in preschool-aged using an offline technique[105 106] and in older children using commercially available instruments,[107 108] it could serve as a biomarker of subsequent response to corticosteroids if indeed the type of airway inflammation modulates response.

Selection of outcomes

Healthcare service utilisation

The need for *hospital admission* is a powerful marker of therapy failure, likely to alter physicians' practice and

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influence decision makers as hospital costs alone account for 43% of total asthma costs.[109] Although subject to practice variation, a physician's decision to admit is usually based on an unsatisfactory response to bronchodilators and systemic corticosteroids in the ED, indicating severe asthma or poor response to corticosteroids.[22] Admission may be affected by other reasons such as parental anxiety, distance or fatigue and, of course, availability of ED and hospital beds.[50] Adding a cut-off length of ED stay, above which a patient is considered admitted, limits the impact of external factors (bed availabilities) which may vary widely within and between institutions. Moreover, incorporating return visits resulting in admission provides an additional measure of failure of ED treatment by adding a measure of the decision appropriateness. Time to meet severity criteria for discharge (PRAM <4) and length of active treatment are two additional measures of interest that are less influenced by factors other than severity.

Indicators of airway dysfunction

Accurate and objective assessment of the severity of airway obstruction is clearly the biggest challenge in acute paediatric asthma research. Standard lung function tests, such as spirometry, require a forced expiratory manoeuvre that is extremely difficult and unreliable for preschool-aged children because of poor coordination; it is not obtainable in 35–50% of acutely ill school-aged children because of illness severity and/or poor familiarity with technique.[110–112] About three quarters of asthmatic children cannot perform standard lung function tests in the ED setting.[113] In contrast, respiratory resistance (Rrs) by forced oscillation is an effort-independent measure that can be obtained in untrained, acutely ill children aged ≥3 years[110] We and others have demonstrated the reproducibility and sensitivity to change Rrs[114] and established reference values for Canadian children.[115 116] Thus, the measure of Rrs can serve as a precise and reliable index of severity and response in acutely ill children, although still missing very young or uncooperative preschoolers and as such cannot serve as the main outcome.

Clinical scores appear to be a reasonable alternative to lung function testing as they can be used in children of all ages. Although many clinical scores have been designed, only two have been validated for use in both preschool-aged and school-aged children.[112 117] The PRAM is the only score developed and validated against a concurrent measure of lung function in children aged 3–6 years,[117] and subsequently validated in children aged 1–17 years.[23] It is a discriminative and responsive tool, with a change in scores ≥3 indicating clinical importance.[23 117] The inter-rater reliability is consistently above 70%.[23] The 12-point PRAM, rating five weighted items (oxygen saturation, suprasternal retractions, scalene muscle contraction, air entry and wheezing), has been used in landmark clinical trials.[21] It can be used to assess severity at baseline (mild: PRAM 0–3; moderate: PRAM 4–7; severe: PRAM 8–12), improvement with treatment depicted as the area under the curve, need for admission (PRAM ≥4, 4 h after the oral corticosteroids) and time until ready for discharge (delay until PRAM <4).[23]

Indicators of recovery following discharge

Among children discharged home, the time to complete recovery will vary widely between individuals. Although symptom scores are frequently used in clinical trials, only four have been specifically developed for use in children.[69 70 71] The Asthma flare-up diary for young children (formerly the Pediatric Asthma Diary) is the only one validated to detect day-to-day change in the functional status of preschool-aged children following an acute care visit[118]; it is highly sensitive to detect group differences in intensity and duration of symptoms in randomised controlled trials; however, its performance in school-aged children has not been explored.[119] Another diary has been validated for detecting change in school-aged children but not in the context of acutely ill children.[120] Use of β_2-agonists is an additional marker for the duration and intensity of symptoms, as greater use of rescue relievers is expected to occur in children with more symptoms.[119] Finally, the impact of the disease on the quality of life of the patient or the caregivers is a recognised, sensitive and unique marker of the burden of disease on the patient or family.[121] Several well-validated asthma-specific quality of life instruments are available for adults[122] and school-aged children with stable asthma.[123] To our knowledge, only one instrument, entitled 'Effects of a child's asthma flare-up on parents', is available for measuring the burden of disease on parents of preschool-aged children following an asthma exacerbation; we have developed the instrument using Kirshner and Guyatt's[124] approach for developing health instruments, validated it in a randomised controlled trial[119] and received two copyrights (French version: #1019528 English version: #1019529 (manuscript in preparation).

Hypothesis

In children presenting with moderate or severe asthma to the ED:

1. Preschool age, specific viral triggers and exposure to tobacco smoke are independently associated with increased risk of failure of ED management (risk difference (RD) ≥7.5%).
2. Specific genetic polymorphisms alone or in association with environmental factors are associated with higher risk of admission.
3. An eosinophilic pattern of airway inflammation (ie, percentage of eosinophils on induced sputum and/or baseline eNO) is associated with greater clinical improvement as measured by the PRAM area under the curve over 4 h (nested cohort).

OBJECTIVES

The main objective was to identify and quantify clinically available factors (eg, age, specific viral trigger and ETS) associated with failure of ED management and other

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markers of clinical response to oral corticosteroids in preschool-aged and school-aged children presenting to the ED with moderate or severe asthma.

Secondary objectives

1. Examine the association between specific genetic polymorphisms (including potential host–environment interactions) and markers of response.
2. Determine whether the type of airway inflammation (ie, eosinophilic and eNO) is associated with the magnitude of response to corticosteroids and which host or episode characteristics are associated with a specific type of inflammation.

METHODS

Design

The study design is a multicentre prospective cohort study with a standard intervention involving 1008 children aged 1–17 years of age presenting with acute asthma to one of the five participating Canadian paediatric EDs. The study includes a nested cohort study of children who presented at selected centres and who could cooperate with eNO measurements (about 200) or induced sputum (about 60 children aged ≥8 years) to explore the pattern of airway inflammation.

Subjects

Participants will be eligible if they: (1) are aged 1–17 years; (2) have asthma, defined as: (i) prior diagnosis of asthma made by a physician; (ii) prior documented episode of acute cough, wheezing and/or dyspnoea with significant response to inhaled β_2-agonists or to oral corticosteroids; (iii) in a child aged <2 years, three or more episodes of cough, wheezing and/or dyspnoea, including the index visit or (iv) previous lung function tests showing significant reversibility postbronchodilation (≥12% FEV_1 or ≥25% Rrs at 4–8 Hz)[117] or a positive provocation test (PC_{20} ≤8 mg/mL or provocation dose (to increase Rrs by 50% or more (PD_{50}) ≤8 mg/mL), in keeping with the American Thoracic Society and European Respiratory Society criteria[125 126]; (3) present with an acute episode of cough, wheezing and/or dyspnoea; (4) have moderate-to-severe airway obstruction, defined as a PRAM score >3 at baseline; (5) have a good understanding of English or French and (6) are accompanied by parents or legal guardians.

Patients will be excluded if they present: (1) with another chronic respiratory condition (such as bronchopulmonary dysplasia or cystic fibrosis); (2) with a reasonable suspicion of bronchiolitis or foreign body aspiration; (3) a history of hypersensitivity to salbutamol, ipratropium bromide or oral prednisolone; (4) a relative or absolute contraindication to receiving oral corticosteroids such as recent exposure to varicella or live vaccine in a susceptible child or (5) with confirmed or suspected pregnancy status. As some inclusion and exclusion criteria may become evident during or after the ED stay (ie, pneumonia), a central adjudicating committee comprising a paediatrician/ED physician and respirologist will review the eligibility criteria of children who, after enrolment, appear to be ineligible due to the failure to meet one or more inclusion or exclusion criteria and who did not receive or tolerate oral corticosteroids as recommended in the protocol. The main trigger for identifying these children will be the ED physician's low degree of confidence that this child had asthma, suspicion that he/she may have bronchiolitis and the suspicion that he/she did not retain the oral corticosteroids. In this case, the relevant case report forms, relevant anonymised laboratory testing (ie, imaging, microbiology, virology and haematology) and relevant anonymised medical chart sections will be reviewed by the adjudicating committee. The adjudicating committee will be central, although we are not ruling out the possibility of creating local committees at each site, depending on the volume of cases to review. In such a case, the site would be added as a covariate in the analysis. Disagreement will be resolved by consensus or the assistance of a third observer. The proportion of excluded children, assumed to be around 10%, will be monitored and reported.

Standardised acute treatment protocol

As per the evidence-based paediatric national[127] and international guidelines,[9] children will be treated according to a standardised severity-specific protocol (table 1). All children will receive 2 mg/kg (maximum 50 mg) of oral prednisolone (or prednisone) within 60 min of triage, along with inhaled salbutamol with or without inhaled ipratropium bromide as per severity strata. Discharge medications will include a 5-day course of oral prednisolone at a dose of 1 mg/kg/day and inhaled β_2-agonists as needed. Cointerventions, such as add-on therapy with magnesium sulfate in the ED or inhaled corticosteroids at discharge, will be permitted and recorded. Comorbidities (eg, pneumonia, sinusitis, allergic rhinitis, etc) and adverse health events will be documented.

Measurements of effectiveness

The primary outcome, serving as a proxy for suboptimal response, is the failure of ED management defined as a hospital admission for asthma (as primary or secondary diagnosis if the primary diagnosis is a complication or comorbidity of asthma) or ED stay for asthma (with active treatment) of ≥8 h after intake of oral corticosteroids or a return visit within 72 hours meeting either of the two previous criteria (admission or length of active treatment ≥8 hours). The 8 h time constraint was included to account for extraneous factors affecting admissions, such as variation in bed availabilities while the child remains under treatment on site.

Secondary measures of effectiveness in the ED include: (1) meeting the severity criteria for admission, that is, a PRAM score ≥4 within 4 h of corticosteroid administration (to account for other reasons for hospital

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admission); (2) the PRAM profile in the ED, measured hourly from baseline and every hour until disposition (or until 4 h after intake of oral corticosteroids, whichever occurs first) and reported as the area under the curve; (3) time to PRAM ≤3, that is, meeting the criteria for discharge; (4) length of active treatment defined as duration between the first and last salbutamol inhalation. Finally, to allow more objective and precise quantification of response in a nested cohort (CHU Ste-Justine), (5) change in Rrs between baseline and disposition will be documented on the MasterScreen Impulse Oscillometry (Cardinal Health Canada, Montreal, Canada) using previously described standardised techniques[110 114 126] in cooperative children aged ≥3 years, (6) change in eNO between baseline and disposition will be documented on a chemiluminescence NO analyser in cooperative children aged ≥4 years and (7) hospital admission for asthma (as primary or secondary diagnosis) within 72 h or an active ED stay of ≥8 h after intake of oral corticosteroids.

Secondary measures of resolution of exacerbation measured after discharge will be documented over the next 10 days in all patients: (8) unscheduled visits for asthma as reported by parents and confirmed by medical charts; (9) cumulative symptom score and duration of symptoms measured daily on the validated Asthma flare-up diary for young children (formerly named the Paediatric Asthma Diary)[118]; (10) parent quality of life measured on the 'Effect of a child's asthma flare-up on parents' and (11) the cumulative number of puffs and duration of use of rescue β_2-agonists as recorded on the Asthma flare-up diary for young children.

Potential determinants

Sociodemographic variables

Basic characteristics will be documented, including age, gender, neighbourhood financial income derived from six-digit postal codes from both parents (if separated), medical insurance (private or public) and ethnicity as reported by the parents and classified as per the latest Canadian Census questionnaire.

Phenotype and morbidity

Children's asthma phenotype will be documented as per the latest international recommendations (ie, viral induced, exercise induced, allergen induced and multiple trigger).[31] Prior morbidity (admissions, ED visits and rescue oral corticosteroids), asthma control using the Asthma Quiz for Kidz,[128] reported use of daily controller medications, environmental factors (eg, dust, animals and pollen) and perceived trigger of the exacerbation will be documented. Prior allergy test results, serum IgE (specific) will be obtained (with permission) as well as pollen counts in the area.

Viral trigger

Acknowledging viruses as the major trigger, all children will be tested for respiratory viruses. All children will have a nasopharyngeal aspirate or nasopharyngeal swab (Flocked swab, Copan Diagnostics, California, USA) performed. The aspirate or swab will be put in 3 mL of viral transport media (UTM, Copan Diagnostics, California, USA) and split in half on site. The first half will be tested using routine methods in each site if clinically required and the other half will be frozen at −80°C for molecular diagnosis. The frozen samples will be processed using the validated automated microarray detection,[129] which tests for 23 common respiratory viruses, including the novel influenza A/H1N1/Mexico.

Passive exposure to tobacco smoke will be quantified by a questionnaire specifically enquiring about current smoking and the amount of smoking by household members, cumulative smoke exposure in pack-years since birth and in utero exposure, using validated questions.[51 130] Active smoking will be assessed by asking school-aged children aged 10 years and older, while alone, if they smoked in the past 7 days, using standardised questions used by the Quebec Institute of Statistics.[131] A quantitative cotinine by quantitative enzyme immunoassay kit (Salimetrics, Pennsylvania, USA) will be performed on saliva sampled using three Sorbettes (a wand with a small sponge) according to a previously described protocol.[56 57]

Several other factors will be considered, including an assumed trigger. In the absence of valid biomarkers of causal relationship to the exacerbation, the alleged trigger (allergic or other) based on the parental report, physician perception, prior documented sensitisation (skin tests or specific IgE), pollen, particles, ozone (and other) levels in the child's living area will serve to infer a trigger.

Mechanistic pathway

Genetic profile

Patients' DNA will be extracted from saliva expectoration or collected on Sorbettes designed for young children, with only a small amount (1–2 mL) needed for DNA analysis. After amplification by PCR, key polymorphisms[132 133] will be determined by high throughput genotyping technology (Sequenom platform) for custom SNP panels.

eNO will be measured on a chemiluminescence analyser (the Niox Flex or the portable Niox Mino from Aerocrine, New Providence, New Jersey, USA or Sievers from GE Analytic Instrument, Boulder, Colorado, USA), using standardised techniques[98] in cooperative children aged ≥4 years; the measurements will be taken before corticosteroids and at 4 h or disposition, whichever occurs first. In children unable to cooperate with these techniques, the eNO will also be measured, using the single breath manoeuvre, in an inert balloon (offline technique) and then analysed on the chemiluminescence analyser.[105 106]

Induced sputum

After the initial salbutamol inhalation, children aged ≥7 years will be asked to expectorate spontaneously or, if

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unsuccessful, receive a nebulisation of 0.9% saline solution over 7–10 min at 5 L/min with oxygen. With this technique, a 70% success rate was obtained among acutely ill school-aged asthmatic children.[134–136] Throughout the induction, lung function tests using Rrs will be documented to ensure that the coughing effort does not induce bronchospasm.[134] Sputum will be processed according to standard techniques within 8 h. Briefly, sputum will be separated from the saliva and dispersed using dithiothreitol. The dispersed suspension is then centrifuged and filtered; cytospin slides will be prepared on site by a trained medical technologist, and the supernatant frozen at −70°C for subsequent quantification of inflammatory mediators. Differential cell counts and inflammatory mediators will each be analysed by an independent laboratory, blinded to exposure and outcome.

Procedures

Within each institution, potentially eligible patients aged 1–17 years will be identified on arrival in the ED. As per standard practice in each of the participating hospitals, all children will be triaged and scored on the PRAM at or shortly after triage. The first inhalation of salbutamol and, for severe exacerbations, ipratropium bromide will be administered (figure 1). Using a two-step informed consent, parents will first give their authorisation for their child to receive standardised severity-specific treatment and, at the CHU Ste-Justine, lung function testing and induced sputum in cooperative children. Parents will then receive a detailed explanation of the study and be offered study participation. Participants will receive the treatment and measures detailed in figure 1, with key measurements obtained prior to corticosteroids.

Statistical analyses

Standard summary statistics (N, mean, SD, median, minimum and maximum for continuous variables; N and proportion for categorical variables) will be computed for all variables for the whole cohort and by institutions. Two-sided 95% CIs will be presented as necessary. For the primary endpoint, failure of ED management and other dichotomous outcomes, bivariate and multivariate logistic regression models will be used to examine the association with each potential determinant and to adjust for site, baseline severity and other relevant covariates of interest. ORs will be estimated and presented with two-sided 95% CIs. Continuous outcomes, such as the area under the curve for repeated PRAM measures, daily Asthma flare-up diary for young children or intensity of both β_2-agonist use and symptom scores after discharge, will be analysed using linear regression models. Transformation of variables will be performed if necessary to account for non-normality of the residuals.

With regard to pharmacogenomics, we will compare the frequency of SNPs between patients with versus without failure of ED management using Fisher's exact tests and examine the strength of the association with failure of ED management with bivariate and multivariate logistic regression. Genotypes will be considered as variables with two (dominant or recessive models) or three (additive model) categories. The choice of the model is determined by the functionality of selected polymorphisms and previous reports. Bonferroni correction will be used to adjust for multiple testing ($p=0.005$, adjusted for 10 independent genes investigated). Host–environment interaction will be examined by adding other covariates of interest to the genotype model. For example, to investigate genetic heterogeneity according to early-life exposure to ETS, we will introduce markers of tobacco smoke exposure status.

With regard to examining eosinophilic inflammation as a marker of responsiveness, the area of the curve of serial PRAM measurements and time to PRAM <4 will serve as outcomes. Linear regression will be used to examine the bivariate and multivariate relationships between sputum eosinophils counts, patterns of inflammation (eosinophilic, non-eosinophilic and mixed) and baseline eNO with the PRAM profile (area under the curve); the standard survival curve will explore the difference in time to meet criteria for discharge, censored at 4 h.[137] All models will be checked using appropriate regression diagnostics. Results will be reported as significant when $p<0.05$.

Sample size

Sample size was estimated in two steps using hospital admission as the dependent variable in a multivariate logistic regression model. Pilot data were extracted from two large recent chart audits[14 138] totalling 1628 children presenting with acute asthma to the ED (in which age, gender, baseline PRAM, timing of oral corticosteroid intake and admission were documented) and two recently completed trials[119 139] totalling 518 children, in whom tobacco exposure was also ascertained by questionnaire; we then focused only on children meeting our current eligibility criteria (age, baseline PRAM and corticosteroids within an hour of arrival). Based on the literature, we assumed the prevalence of viral pathogen varied between 60% and 80%.[140 141] The baseline risk of admission was 41%; after recruitment of the initial 320 patients, the observed overall risk of admission was substantially lower at 16%, which substantially reduced the effective sample size from 1200 to 800. First, using the Wald test (based on the prevalence of factors and the risk of admission in unexposed children), we calculated the sample size required to detect an RD of admission of 7.5%, taking each determinant in turn as the independent variable in a bivariate logistic regression; we used 95% CIs for each estimate obtained from pilot data to examine the impact on power.[142] Then, using the method proposed by Hsieh *et al*,[143] we calculated the inflation factor to adjust the total sample size, based on the observed correlation between key determinants

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Pediatric Respiratory Assessment Measure (PRAM)	Oral corticosteroids §	Inhaled salbutamol † 100 mcg/puff	Inhaled ipratropium bromide 21 mcg/puff †
Within initial 60 ± 15 minutes of triage			
MODERATE ASTHMA **PRAM 4-7**	**Drug:** Prednisone or prednisolone 2mg/kg, max: 50 mg* **Timing**: after 1st salbutamol (and ipratropium bromide if indicated)	**Delivery device:** MDI (or nebulizer) **Dose:** 0.3 puffs/kg of 100 ug/puff (max 10 puffs) (**or** 0.3 mL/kg of 5% salbutamol solution) **Frequency**: q 20 to 30 minutes	**Not recommended**
SEVERE ASTHMA **PRAM >7**	**As above**	**MDI and dose** : as above **Frequency**: q 20 minutes	**Delivery device: MDI (or nebulizer)** **Dose:** 3 puffs (or 250 ug) **Frequency:** q 20 min
Beyond initial 60 minutes until discharge			
PRAM 4-7	—	As above q 30-60 minutes	
PRAM >7	—	As above q 30 to 60 minutes	
At discharge			
	Prednisone or prednisolone 1mg/kg x 4 days, max: 50 mg*	2-4 puffs q 4 to 6 hours as needed	

* Administered as prednisone 5 (or 50mg) or prednisolone 1 mg/mL solution

† Administered via age-appropriate valve spacer

§ If patient vomits, use oral dexamethasone 0.15-0.30 mg/kg per dose of parenteral solution (max 10 mg)
If impending respiratory failure, use methylprednisolone 1-2mg/kg (max 80 mg) or hydrocortisone 4-8 mg/kg (max 400 mg)

Figure 1 The treatment protocol is stratified on the severity of asthma exacerbation, that is, moderate or severe, as measured by the validated Pediatric Respiratory Assessment Measure (PRAM). Categories of medications are listed in the three columns. The three horizontal panels describe therapy administered in the first 60 minutes (top panel); after the initial 60 minutes (middle panel); and on discharge (bottom panel).

(age, gender and tobacco exposure, and baseline severity). As the observed correlation between determinants and severity and any pair of determinants was negligible (β coefficients <0.03), there was no need to inflate the sample size. At an α of 0.05, a sample of 800 children had 80% power to detect an RD of admission of ≥7.5% for all key determinants. We targeted the RD of 7.5%, because it was considered in a survey of researchers of the Pediatric Emergency Research in Canada (PERC) network as a clinically meaningful effect size that would support a practice change. After documenting a 1% loss after enrolment (from 10% originally estimated) and 20% missing key samples (viral or cotinine), our target recruitment sample is 1008 to obtain an effective sample of 800 children. Acknowledging that the majority of selected polymorphisms have a minor allele frequency of at least 30% and using an α of 0.005 (with a Bonferroni correction for 14 polymorphisms), 1008 children will provide 80% power to detect an OR of 1.5 between each polymorphism and admission. Finally, of the expected 400 children recruited at the University Health Centre Sainte-Justine, we estimated that 200 children would cooperate with eNO measurements and 60 with induced sputum. These sample sizes should be adequate to detect a correlation coefficient as low as 0.2–0.35, respectively, with the area under the curve of the PRAM score during the ED with 80% power and a two-sided 0.05 α.

ETHICS AND DISSEMINATION

This study poses little risk to participants, as all children will receive state-of-the-art asthma management with oral corticosteroids, an approach associated with minimal side effects.[19 144 145] Children will be assessed for potential contraindication to corticosteroids prior to enrolment. Using a two-step informed consent, parents will first give their authorisation for their child to receive the severity-specific asthma protocol and, at specific centres, lung function testing and induced sputum in cooperative children; then they will consent to the full study including sampling for cotinine, DNA and viruses. All parents will sign an informed consent form authorising the DNA analysis for the specified research purpose as well as future analyses (including biobanking of DNA in anonymised fashion), provided these are approved by the institutional ethics boards. Assent will be obtained from children aged ≥7 years. The collection of saliva by expectoration or sponge is painless and well tolerated by children. Nasopharyngeal aspiration or swab for viral diagnosis is a commonly used procedure in the ED setting; it is rapid and associated with little discomfort. The performance of Rrs and eNO is non-invasive and devoid of serious side effects. Sputum induction with 0.9% saline and salbutamol pretreatment is a safe procedure in the acute care setting.[134–136] Data safety is maximised through: restricted physical access to computers and electronically protected servers (firewall, restricted password-protected

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access, daily back-up and storage in 2 different locations). Confidentiality is also a part of standard operating procedures; a unique research code will be assigned to each patient. All research data and specimens will be kept in locked rooms with restricted access at each site, the coordination centre and the site of analysis. The protocol, consent form and any amendments are subject to the ethics review board approval of each institution. Each investigator will adhere to the principles of the Declaration of Helsinki. All serious adverse effects will be promptly reported.

This study will provide needed answers as to whether oral corticosteroids are less effective for preventing hospital admission in subgroups of children and, if so, which clinically available characteristics could be used to identify patients at risk of poorer response. An impaired response to systemic steroids in certain subgroups, resulting in a higher rate of failure of ED management and/or impaired recovery, would challenge the current standard of practice and call for an immediate search for better approaches. Given the high prevalence of suspected factors (young age (60%), viral infection (60–80%), ETS (20–30%)), the potential impact of poor response on the rate of failure of ED management is sizeable. The exploration of potential host–environment interactions will broaden our understanding of corticosteroid responsiveness in children and enable us to focus on relevant alternative/supplemental strategies to adequately manage these patients. Documentation of the similar effectiveness of systemic corticosteroids across determinants will provide the needed reassurance as to the value of national recommendations for the treatment of all children with acute asthma.

Results will be disseminated at international conferences targeting emergency physicians, paediatricians, geneticists and respirologists. Four manuscripts are envisioned: one pertaining to the identification of main determinants of the risk of failure of ED management within 72 h of the dose of oral corticosteroids (general medical journal); one pertaining to the validation of perceived triggers and clinical predictors of response to therapy during the index exacerbation (emergency medicine journal); one pertaining to the genetic polymorphisms associated with non-response to oral corticosteroids (respirology journal); and one pertaining to the gene–environment interaction modulating the response to corticosteroids in children (paediatric journal).

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Contributors FMD conceptualised the research design, wrote the research protocol, secured the funding and coordinating the project team. MCG was responsible for the sample size calculation and statistical methods. RZ, JG, DC, NP, SL, CQ, MK, CG and CL provided feedback to refine the research methodology and contributed to the implementation of the study. All authors read and approved the final version.

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