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Intravenous β_2-agonists in the treatment of patients who present to the Emergency Department with severe acute asthma. a meta analysis and prospective observational cohort study

by

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A thesis submitted to the Faculty of Graduate Studies and research in partial fulfillment of the requirements for the degree of Master of Science

in

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Brian H. Rowe

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Carlos Camargo

Dr. Carlos Camargo

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Dr. Duncan Saunders

Dr. Pat Hessel

19 APR 99

Date

Dedication

I would like to dedicate this thesis to my wife, Heather, whose love, support, encouragement, and endurance have been a constant source of strength for me. Thank you.

I want to give thanks to my daughter Emma, who sat on my lap for the many hours that I spent in front of the computer - she never touched the delete key.

Abstract

Objectives: (1) to determine the benefit of intravenous β_2-agonists (IVB) for emergency department (ED) treatment of severe acute asthma; (2) to determine characteristics of patients treated with parenteral β_2-agonists (PB) for acute asthma in Multicenter Asthma Research Collaboration (MARC) EDs.

Methods: (1) meta-analysis of the IVB literature; (2) MARC prospective cohort study in 77 North American EDs where acute asthmatics, aged 2-54, were interviewed in the ED and again by telephone two weeks later.

Results: (1) IVB use did not lead to any significant differences in pulmonary functions, laboratory measures, or clinical success. (2) 5% of the 3031 MARC patients received PB therapy (all subcutaneous, no IVB) which was associated with more severe acute and chronic asthma characteristics, more ED multi-drug treatment; and higher admission rates.

Conclusions: Evidence is lacking to support the use of IvB in ED patients with severe acute asthma. North American PB use is rare.

Word Count: 149

Preface

The thesis is presented in the paper format. It comprises an introductory chapter, two related research papers, and a concluding chapter. Each chapter is presented with its own introduction, body of text, conclusion and set of references. Chapters Two and three of this thesis have been written with the intention that they will be submitted for publication.

Acknowledgments

It is with heartfelt appreciation that I thank the following individuals who helped bring this work to its conclusion:

Dr. Brian Rowe, my thesis supervisor, Associate Professor and Research Director of Emergency Medicine. Thank you for your patience and clarity of thought.

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Dr. Carlos Camargo Jr., Chair of the MARC Operations Committee and Data Coordinating Center
Dr. Duncan Saunders, Professor of Public Health Sciences
Dr. Pat Hessel, Director, Epidemiology Program

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Abbreviations

β_2 agonist	beta 2 agonist
χ^2	chi-square statistic
%pred PEFR	percent predicted peak expiratory flow rate
95% CI	95% confidence interval
ABG	arterial blood gas
ARG	Airways Review Group
ASE	autonomic side effects
ATS	American Thoracic Society
BHR	bronchial hyperreactivity
BTS	British Thoracic Society
DBP	diastolic blood pressure
CAEP	Canadian Association of Emergency Physicians
CC	Cochrane Collaboration
CCG	Canadian Concensus Guidelines
CCTR	Cochrane Controlled Clinical Trials
CDSR	Cochrane Database of Systematic Reviews
CPG	Clinical Practice Guidelines
CRG	Cochrane Review Group
CTS	Canadian Thoracic Society
df	degrees of freedom
FEV_1	forced expiratory volume in one second
FRV	forced residual volume
FVC	forced vital capacity
HR	heart rate
i.v.	intravenous
IVBA	intravenous beta-agonist
MARC	Multicentre Asthma Research Collaboration
MDI	metered dose inhaler
MetaView	program within RevMan to view graphs
min	minute
N	number of studies
n	sample size
NAEPP	National Asthma Education & Prevention Program
OR	odds ratio
$PaCO_2$	arterial oxygen tension
PaO_2	arterial carbon dioxide tension
PEEP	peak end-expiratory flow rate
PEFR	peak expiratory flow rate
PFT	pulmonary function test
PP	pulsus paradoxus
RCT	randomised controlled trial
RevMan	Review Manager 3.0.1 Software Program
RR	respiratory rate
SD or sd	standard deviation
SOB	shortness of breath
var	variance
WMD	weighted mean difference
z	z-statistic

az'ma

n. Pathol

Gk. *azein* to breathe hard

SECTION 1.1 INTRODUCTION

Asthma is a chronic respiratory disease characterized by airway hyperreactivity, and variable degrees of reversible airflow obstruction (both partial and complete) in response to a variety of specific and nonspecific triggers.[1] Current pathophysiological paradigms emphasize the role of tracheobronchial inflammation in the pathogenesis of this disease, which, in conjunction with smooth muscle mediated bronchoconstriction and intraluminal mucous, results in airflow obstruction.[1,2] The spectrum of symptomatology is diverse and may fluctuate with acute episodes interrupting periods of relative stability.[3] Fortunately, most patients do not have debilitating disease, and instead have their symptoms easily controlled with a limited number of medications and education.[4] However, in others the disease confers a daily affliction of daily breathlessness and persistent functional impairment, similar to those patients burdened with emphysema and fixed airflow limitation.[1]

Clinical presentations of asthma are the result of airway reactivity, which is normally distributed in the population. At one end of the spectrum are individuals who never manifest airway reactivity to any trigger. This is followed sequentially by those people who need major irritants to precipitate an airway response; those who have episodic symptoms and respond once or twice a year to common irritants (e.g. viruses, pollen, etc.); and those who have persistent symptoms requiring regular medical care and avoidance of environmental triggers.

All patients with asthma are at risk of developing a severe asthma attack which places them at risk of respiratory failure and death. Whereas some patients develop sudden and unexpected increases in airflow obstruction

resulting primarily from bronchial smooth muscle-mediated spasm, others follow a more gradual course of airway inflammation and mucous production.[5] Successful therapy in this condition lies in respecting the potential for the devastating consequences of the disease.

SECTION 1.2 DEFINITION

Definition of Asthma

One of the pervading difficulties in asthma education, treatment and research is the widely different definitions of the disease itself.[6] The American Thoracic Society (ATS) defines asthma as a chronic disorder of the airways characterized by paroxysmal or persistent symptoms (dyspnea, chest tightness, wheeze, and/or cough), with variable airflow limitation and airway hyper-responsiveness to a variety of stimuli.[7,8] This reflects a functional/physiological approach where the 'asthma definition' has been broadened to include spontaneous fluctuations in severity, a paroxysmal nature to symptoms, and a temporal relief with bronchodilators and steroid treatment.[7,8] However, the various pathophysiologic mechanisms and clinical manifestations make it difficult to formulate a clear cut definition. The difficulty is magnified in children because of the overlap of symptoms with other respiratory disorders (i.e. bronchitis, bronchiolitis), and limitations of diagnostic tools in this group.[9,10] Other investigators have attempted to define asthma in clinical (recurrent wheezing)[3], immunologic (allergic vs. nonallergic)[10], or descriptive terms.[11]

Regardless of the definition, a designation of 'mild', 'moderate', and 'severe' can be used to classify severity of asthma exacerbations.[12,13] These definitions are based on history and clinical presentation, some form of airflow measurement, and response to therapy (this is discussed further in Section 1.4). The term "status asthmaticus" characterizes those attacks in which the degree of bronchial obstruction is either severe from the onset or worsens rapidly, and is not relieved by usual therapy in 30 to 60 minutes. The term "refractory status asthmaticus" has been coined and describes those cases in which the patients condition continues to deteriorate despite aggressive pharmacological interventions.[1]

SECTION 1.3 THE EPIDEMIOLOGY OF ASTHMA

1.3.1 Prevalence of Asthma

Asthma comprises a significant burden of disease worldwide with traditional estimates that place asthma in 1.5 to 7.0% of the total population in developed countries.[14-17] Many researchers claim that variations in the definition of asthma over time and between countries, coupled with the different denominators used in population estimates (number of asthma cases per either total population size, or number of emergency department visits, etc.), make any estimate of incidence or prevalence inaccurate.[14,18]

A 1995-96 survey of Canadian students aged 5-19 demonstrated a prevalence of approximately 13% (diagnosed by physician, or within the past 12 months had asthma symptoms or had taken asthma medications).[19] In addition over 3% of students had 'non-current asthma', and 21% had asthma-like conditions in the previous 12 months[19]. At the same time, this survey demonstrated regional variation across provincial boundaries: 10% in cities such as Sherbrooke and Saskatoon, and 16%, 17%, and 18% in Kingston, Halifax, and Prince Edward Island respectively.[19] Through other surveys the prevalence of asthma in adult Canadians is estimated to be approximately 5-7%.[20,21]

Asthma is a common emergency department (ED) presentation in North America. For example, acute asthma accounts for approximately 1.5-2.0 million ED visits and 460,000 hospitalizations in the US annually[22,23], together costing at least $2 billion per year.[24] In Canada, acute asthma care both in the ED and inpatient wards is responsible for over 300 million dollars in direct health care costs.[25] Approximately 10-20% of patients presenting to the ED will require admission to the hospital.[23]

In summary, despite the varied asthma definitions and methodological criticisms about the epidemiologic studies of asthma, the evidence suggests

that the burden of disease is significant and increasing.[14-18,26-33] Further methodologically strong studies are required before more accurate estimates of asthma prevalence will emerge.

1.3.2 Prevalence of Severe Acute Asthma

The literature demonstrates an increasing trend in morbidity and mortality over the past 15 years for both pediatric and adult patients.[23,26-42] The trend of fatal cases appears stable in developing countries such as Canada, Sweden, Wales, and West Germany[43], with unstable and higher rates (10 to 20 times) in Australia and New Zealand.[43-45] Plausible explanations for these increased death rates include:

- An over-reliance on bronchodilators at expense of anti-inflammatory agents.[36,46,47] It is not clear if worsening of the disease despite β_2-agonist use reflects progression of disease or drug-related effect[1,48,49]
- Increased prevalence or severity of asthma[50-54]
- Change in physician practice for earlier admission for "flare-ups", and decreased outpatient care access[26]
- Inadequate perception or denial of degree of illness by the patient[55-57]
- Autopsy inaccuracies in assuming causes of death[58]
- Identification of sociologic and biologic risk factors[51,59,60]
- Change in ICD-8 and 9 coding reclassifications of the disease[14,51,54]
- Possible effects of drug-disease toxicity[36,61-64]
- Interaction with geographic and environmental effects[28,65-67]
- The bulk of data in Canada are obtained from records of ED visits and hospital admissions and therefore reflect treatment failures rather than successes[68]

In summary, there is unresolved debate whether the international prevalence of severe acute asthma are stable[26] or increasing[14]; however, placed in perspective, deaths from asthma exacerbations are fortunately rare.

SECTION 1.4 THE SEVERE ACUTE ASTHMATIC PATIENT

1.4.1 Historical characteristics of the severe pediatric asthmatic

Death from asthma appears to occur in two clinical situations: [1] new or mildly affected asthmatic children who experience a sudden, severe bronchospastic attack resulting in cardiopulmonary arrest[69]; and [2] known steroid dependent children who have poor asthma control, often with previous history of respiratory failure.[70] In a simple descriptive study in British Columbia, Robertson et al interviewed families of 51 patients under the age of 20 who died from asthma between 1986 and 1989: 33% were judged to have trivial or mild asthma; and 32% had no previous hospitalizations for asthma.[69] In this cohort of 51 patients, 63% had sudden collapse within minutes of developing dyspnea; 78% died before reaching the hospital; and 25% had acute progression of their chronic asthma that resulted in death. This work has been supported by others who found that the final attack rate was less than one hour for 21% of children, and less than two hours for 50%, with half of the cases dying prior to reaching the hospital.[40,71] Other authors have defined characteristics of children who suffer severe acute asthma:

- Black and urban children have a higher death rates than white and suburban children, possibly attributable to economic differences between the two groups[1]
- Boys under 15 years of age had 50% higher morbidity than girls[42]
- Severe disease characterized by history of prior intubation, hypoxic seizures, nighttime wheezing, and rapid progression of attacks[1]
- Severe exacerbations precipitated by foods[1]
- A lack of perception of severity of attacks, and self weaning of corticosteroids[53]
- Lack of support systems (parental and medical), and psychological disease including overt depression and manipulative use of asthma disease[72]

1.4.2 Historical characteristics of the severe adult asthmatic

Fewer authors have defined characteristics of adults who suffer from severe acute asthma.

- Typical patients have had recurring attacks, are middle age or older, with a history of asthma less than 10 years[1]
- Smokers who require systemic steroids, and comply poorly with outpatient surveillance attempts[35,73-75]
- Patients with physical indicators of airway instability, namely short lived relief with inhaled bronchodilators, wide variance in daily bronchodilator use, worsening of symptoms resulting from viral illness, nocturnal symptoms, and/or history of intubation[1]
- Regular use of β_2-agonists appears to diminish the control of asthma, potentially due to the down-regulation of receptors [47]

In summary, a number of studies have attempted to identify predictors for pediatric and adult patients at risk of developing severe or life-threatening asthma, and these have demonstrated a variety of potential clinical, physiological, psychological, sociological, and environmental factors.[1,10] These factors could be classified as modifiable or nonmodifiable characteristics and were found between the prehospital environment, emergency department, and inpatient wards.

SECTION 1.5 THE EMERGENCY DEPARTMENT PRESENTATION

1.5.1 ED presentation of the severe acute asthmatic

Patients with severe asthma are typically anxious, breathless, fatigued, sitting upright in bed, and preoccupied with the task of breathing. A swift and directed assessment of disease severity and risk for deterioration is critical. Generally this requires an analysis of the medical history, physical examination, bedside pulmonary function tests, observation for response to initial therapy, arterial blood gas measurements and radiographic studies. A multifactorial analysis is required because no single clinical measurement has been found to predict outcome reliably.[1,10] A thorough history is impractical, but focused historical details can direct therapy, such as: previous similar attacks, hospitalizations, and intubations.[20] A rapid progression (less than three hours from onset to extremis) has been associated with increased risk of near death in acute asthma.[2,76,77] Additional history items should include precipitating factors, allergies, drug use that may have precipitated an attack (i.e. NSAIDs in ASA sensitive patients) and drug use to prevent an attack (i.e. beta-agonist inhalers, steroids, etc.).[2]

The assessment of acute asthma includes the following clinical, pulmonary function, and laboratory parameters (see Table 1.1).

Table 1.1 Assessment of acute asthma

clinical	vital signs & oxygen saturation level of consciousness position of patient cyanosis retractions accessory muscle use wheezing or silent chest pulsus paradoxus
pulmonary function	FEV1 % predicted FEV1 PEFR % predicted PEFR
laboratory	arterial oxygen tension arterial carbon dioxide tension

It has been consistently shown that the severity of airflow limitation in patients with asthma correlates poorly with the physical examination and traditionally assessed vital signs.[20] Moreover, physician estimates of PFTs are inaccurate[20], and changes in clinical signs after treatment correlate poorly with changes in spirometric test results.[20] When possible, the best PFT value of three attempts should be recorded, however all asthma consensus groups recommend withholding PFT testing in either the moribund patient, or those who appear confused, cyanotic, or exhausted.[4,8,20,76,78]

1.5.2 ED classification of mild, moderate, and severe asthma

There are slight variations in the definition of asthma severity as mild, moderate, or severe. The organizations involved in emergent asthma care in Canada (CAEP: Canadian Association of Emergency Physicians)[20], the USA (NAEPP: National Asthma Education and Prevention Program)[13], and the UK (BTS: British Thoracic Society)[76], all use somewhat different features to define severity. The definitions for 'mild' and 'moderate' are summarized in Table 1.2 and 1.3. Tables 1.4 and 1.5 illustrate the variability in the 'severe' and 'pre-cardiopulmonary arrest' definitions of asthma. Samples of the guidelines from which these definitions are cited are found in Appendix 1.1.

In summary, despite slight variations across the three clinical practice guidelines, each are based on history and clinical presentation, some form of airflow measurement, and response to therapy.

Table 1.2 Mild asthma

	CAEP	NAEPP	BTS
PEFR	PEFR > 60% predicted* PEFR > 300 L/min	PEFR > 80% predicted	PEFR > 75% predicted*
FEV_1	FEV_1 > 60% predicted* FEV_1 > 2.1 L	-	-
SaO_2	-	> 95%	‡
PaO_2	-	normal	‡
$PaCO_2$	-	< 42 mmHg	‡
History	• exertional dyspnea/cough • ± nocturnal symptoms • increased β-agonist use • good β-agonist response	• SOB while walking • can lie down • talks in sentences • may be agitated	‡
Physical	-	• increased RR • HR < 100 • no accessory muscles • no retractions • moderate expiratory wheeze • pulsus paradoxus < 10	‡

‡ absence of life-threatening features (see Table 1.5); * or best PEFR; SOB shortness of breath

Table 1.3 Moderate Asthma

	CAEP	NAEPP	BTS
PEFR	PEFR 40-60% predicted* PEFR 200-300 L/min	PEFR 50-80% predicted	PEFR 50-75% predicted*
FEV_1	FEV_1 40-60% predicted* FEV_1 1.6-2.1 L	-	-
SaO_2	-	> 91%	‡
PaO_2	-	> 60 mmHg	‡
$PaCO_2$	-	< 42 mmHg	‡
History	• dyspnea/cough at rest • congested, chest tightness • nocturnal symptoms • partial relief from β-agonist • β-agonist more often than every four hours	• SOB while talking • prefers sitting • talks in phrases • usually agitated	‡
Physical	-	• increased RR • HR 100-120 • accessory muscles & retractions common • loud expiratory wheeze • pulsus paradoxus 10-25	‡

‡ absence of life-threatening features (see Table 1.5); * or best PEFR; SOB shortness of breath

Table 1.4 Severe Asthma

	CAEP	NAEPP	BTS
PEFR	unable to perform PEFR < 40% predicted* PEFR < 200 L/min	PEFR <50% predicted	PEFR < 50% predicted*
FEV_1	unable to perform FEV_1 < 40% predicted* FEV_1 < 1.6 L	-	-
SaO_2	< 90%	< 91%	‡
PaO_2	-	< 60 mmHg	‡
$PaCO_2$	-	> 42 mmHg	‡
History	• difficulty speaking • no prehospital relief with β-agonist • agitated • β-agonist more often than every four hours	• SOB while at rest • sits upright • talks in words • usually agitated	• can't complete sentences
Physical	• diaphoretic • tachycardic	• RR > 30 • HR > 120 • accessory muscles & retractions usual • loud inspiratory and expiratory wheeze • pulsus paradoxus > 25	• RR > 25 breaths per minute • HR > 110

‡ absence of life-threatening features (see Table 1.5); * or best PEFR; SOB shortness of breath

Table 1.5 Pre-cardiopulmonary Failure Asthma

	CAEP	NAEPP	BTS
	"near death"	**"respiratory arrest imminent"**	**"life threatening"**
PEFR	"not appropriate to test"	-	PEFR < 33predicted*
FEV_1	"not appropriate to test"	-	-
SaO_2	< 90%, despite supplemental oxygen	unable to do	< 92%
PaO_2	-	unable to do	< 60 mmHg
$PaCO_2$	-	unable to do	> 36 mmHg
History	• exhaustion • confusion • agitated • β-agonist more often than every four hours	• drowsy or confused	• exhaustion • confusion • coma
Physical	• diaphoretic • cyanotic • decreased respiratory effort • falling HR • silent chest	• paradoxical thoraco-abdominal movement • bradycardia • absent wheeze • absent pulses	• cyanosis • feeble respiratory effort • bradycardia • hypotension • silent chest

SECTION 1.6 PATHOPHYSIOLOGY OF ASTHMA

1.6.1 Pathophysiology of severe acute asthma

Asthma is characterized by the triad of airway obstruction, airway hyperresponsiveness, and airway inflammation with mucous plugging. Although each have important roles in airway narrowing, no single mechanism can be shown to be present in all cases of severe asthma[1], nor do they all follow the same sequence of appearance. Through complex inflammatory[1,3,79] and neurohormonal cascades[80], two overlapping pathophysiological states emerge: (1) fixed airflow defects, and (2) reversible airflow defects.[3] These are not static or permanent defects, but instead refer to the relatively dynamic process of airway obstruction associated with asthma. 'Fixed airflow defects' occur when the degranulation of mast cells and other mediator-releasing inflammatory cells[1], results in increased vessel permeability, mucosal edema, fluid transudation, epithelial desquamation, and increased mucous production.[1] 'Reversible airflow defects' refers primarily to the hyperresponsive contraction of the smooth muscles that line the airways of the lung.[3]

Overlaying this model with the therapeutic options explains why early treatment with bronchodilators may correct 'reversible airflow defects', whereas 'fixed airflow defects' require anti-inflammatory agents to prevent or ameliorate the attack. The longer an acute attack persists the more inflammation takes place, the more hyperreactive the airway becomes, and the more mucous plugging occurs - thereby accounting for the difficulty encountered by physicians in controlling longer standing flare ups, and the relatively minor stimulus necessary to produce an exacerbation in symptoms.[1]

Pulmonary function tests (PFTs) in the severe asthmatic show increased residual volume (RV), FRV, total lung capacity (TLC), and an increased ratio of RV to TLC. Vital capacity (TLC minus RV) is reduced. Forced expiratory volume in one second (FEV1, litres) and peak expiratory flow rate (PEFR, litres/min) are the parameters most frequently studied as outcome measures. Carbon dioxide

retention often occurs when the FEV1 is less than 25% of predicted (about 0.75 litres).[81] Significant air trapping can lead to mechanical disruption of the bronchial tree, with air escaping into the pleura (pneumothorax), the mediastinum (pneumomediastinum), pericardial tissues (pneumopericardium), subcutaneous tissues (subcutaneous emphysema), or pulmonary veins (air embolism). Complications of acute asthma can be found in Table 1.6.[2,77]

Table 1.6 Complications of acute asthma

Failure of Oxygenation (Type 1)	mucus plugging
Failure of Ventilation (Type 2)	atelectasis
pneumothorax	noncardiogenic pulmonary edema
pneumomediastinum	myopathy
pneumopericardium	lactic acidosis
subcutaneous emphysema	anoxic brain injury
myocardial infarction	electrolyte disturbances (hypokalemia, hypophosphatemia, hypomagnesemia

In summary, the complex pathophysiology of asthma mandates therapy which both targets key steps in the neuro-inflammatory cascade, and prevents the serious complications associated with the disease.

SECTION 1.7 TREATMENT

1.7.1 General Management

Treatment approaches vary between and within emergency departments across North America, and perhaps, this may be in part the result of a lack of evidence-based summaries of the research pertinent to this field.

The goals of treatment are to rapidly restore airway diameter, reverse airflow obstruction, and attenuate the inflammatory cascade which perpetuates the exacerbation. The treatment strategies for severe asthma are an extension of the standard therapies for mild and moderate asthma, consisting of bronchodilators and anti-inflammatory agents augmented mainly in terms of frequency or route of administration of the medications (see Table 1.7).

Table 1.7 Medical treatment of severe acute asthma

Inhaled Medications	oxygen beta-adrenergic agonists cholinergic antagonists steroids
Intravenous Medications	beta-adrenergic agonists steroids methylxanthines Magnesium
Subcutaneous Medications	beta-adrenergic agonists

1.7.2 Bronchodilator Agents

Beta-adrenergic agents. Beta-adrenergic agents (β-agonists) are effective in relieving asthma by stimulating sympathetic beta-adrenergic receptors in the bronchial smooth muscle, thereby effecting bronchodilatation, and protecting against bronchoconstrictive stimuli. Although a variety of β-agonists are available, β_2-selective agents are preferred and can be given by inhalation (nebulization, metered-does inhaler, dry powder), intravenously, endo-tracheally, or subcutaneously.[3] The dose of β_2-agonists needed to reverse an exacerbation of asthma cannot be standardized; instead the principle of cumulative, sequential dosing is followed where clinical success is built upon the therapeutic effects of previous doses.[20] Their role is predominantly in the

early, bronchospastic phase of asthma. Treatment with β_2-agonists prior to arrival to the emergency department does not preclude successful reversal of airflow obstruction with continued β_2-agonist therapy.[20] In two recent systematic reviews, with comparative dosing, aerosol β_2-agonist therapy administered by wet nebuliser or metered-dose inhaler are equally effective for acute asthma.[82,83] Furthermore, in formal economic reviews, MDI plus spacers when reliably self-administered without supervision lead to increased cost savings.[84]

In summary, all consensus statements for asthma management recommend inhaled β_2-agonists as first-line therapy for the management of acute asthma in the emergency department.[8,13,20,76,78,85] The body of evidence for this recommendation comes from several randomized clinical trials, in addition to well-designed cohort and case-control studies, and expert opinion.[8,13,20,78] The consensus statements recommend the use of parenteral β_2-agonists when the inhaled route is impractical - for those patients who are coughing excessively, too weak to inspire adequately, or who are moribund.[8,13,20,78]

Anticholinergic agents. The airway smooth muscle tone is balanced between sympathetic (bronchodilatation) and parasympathetic (broncho-constriction and secretagogue) control.[81] Pharmacological agents that influence this pathway include the competitive muscarinic antagonists atropine, ipratropium, and glycopyrolate, all of which cause bronchodilatation and decreased mucous production. The significant systemic side effects of cholinergic blockade (tachycardia, urinary retention, confusion) may limits its use in chronic asthma[2,3], and for acute asthma nebulized ipratropium bromide has a slower onset of action than β_2-agonists therapy.[20,78] In children, controlled, double-blind clinical trials demonstrated the combination of ipratropium bromide with β_2-agonists was better than β_2-agonist alone.[20] Consequently, current CPGs recommend inhaled anticholinergic therapy as an additive to β_2-agonist therapy in the severe cases of asthma[8,20,76,78], with possible benefits in less severe cases.

Methylxanthines. Conventionally, the therapeutic benefit of methylxanthines has been ascribed to weak bronchodilatation, however they also interact with respiratory muscles to reduce respiratory muscle fatigue.[81] Aminophylline was once a mainstay in the management of acute severe asthma, however, based on many clinical trials, and several systematic reviews[86], the weight of evidence does not support its routine use in the initial phase of asthma treatment.[8,13,20,78] In a frequently cited paper, Littenberg conducted a meta-analysis of thirteen studies and found insufficient evidence for the use of aminophylline in the emergency treatment of asthma.[86] Littenberg concluded that aminophylline as a single agent is less effective than a β_2-agonist as a single agent, however no conclusion could be made regarding aminophylline as an adjunctive agent. As a consequence, aminophylline is not indicated in the management of acute exacerbation of asthma that responds to inhaled beta-agonists.[8,13,20,78]

With the growing recognition that theophyllines could modulate airway inflammation in asthma, there is a potential application in the use of these drugs in a synergistic role with other anti-inflammatory agents.[77]

1.7.3 Anti-inflammatory Agents

Steroids. Regulation of the inflammatory cascade that accompanies both early and late phase responses of asthma is paramount to the successful treatment of the disease. Glucocorticoids have been the particular subgroup of steroids that have been examined in asthma management. This thesis uses the current nomenclature of corticosteroids which is commensurate with steroids and glucocorticoids. The corticosteroids have been shown to have effects at a number of cellular levels, and are considered non-specific anti-inflammatory agents. Their cellular actions are purported to include:[1,3,78]

- interference with synthesis of inflammatory mediators such as arachadonic acid, prostaglandins, leukotrienes, and other eicosanoids. These agents have a variety of effects including: vasodilation, bronchoconstriction, chemotaxis, chemokinetics, platelet activation, etc.

- prevention of migration and activation of inflammatory cells
- mast cell stabilization
- potential up-regulation of airway smooth muscle beta-adrenergic receptors
- promotion of vasoconstriction, reduction of capillary permeability, and diminution of mucous production
- altered gene expression

Asthmatic exacerbations may be characterized by fast and slow responses to treatment.[87] Patients presenting to the ED may respond rapidly or slowly to treatment, and slow responders may represent those patients who have more inflammation and/or are corticosteroid resistant. The literature demonstrates that admitted patients (slow responders) respond slowly to treatment, even when steroids are added.[87,88] Fast responders may benefit from early administration of corticosteroids, possibly due to influences on the β_2-receptors of the lung and stabilization of the initial inflammatory cells that perpetuate the inflammatory cascade.[1,78,87]

Steroids can be given to the severe asthmatic patient via the inhaled, oral, intramuscular or intravenous routes. Through clinical trials and systematic reviews, steroid therapy has demonstrated rapid resolutions of airflow limitation, decreases in admissions, and decreases in relapses to the emergency department.[88] Based on such evidence, steroid therapy (both therapeutic and prophylactic) should be administered as soon as possible after β_2-agonist therapy has been initiated in the emergency department.[8,13,20,78]

Intravenous steroid therapy has no advantage over oral therapy in terms of the rate of resolution of airflow obstruction. The parenteral route is preferred when the patients are unable to absorb an oral dose (e.g. because of vomiting) or unable to take an oral medication (e.g. the patient who is too breathless to

swallow and the patient who is intubated).[8,13,20] The benefits of inhaled steroids in severe, acute asthma remains to be determined.

1.7.4 Alternative Therapies

There have been a variety of interventions reported in the literature which may be added to first-line therapy with traditional agents. These include: intravenous magnesium[89] inhalational anaesthetics[1]; intravenous ketamine[1,3]; helium oxygen mixtures[3,81]; and non-invasive positive pressure ventilation.[3,77,90] Current CPG's variably list these alternative therapies for those 'severe' and 'life-threatening' cases that are failing first-line treatments.[8,13,20,78]

SECTION 1.8 SUMMARY

This brief review has highlighted the varying definitions of asthma; the increasing prevalence of severe disease; and the treatment options for severe acute asthma. The chapter has concentrated on the fundamental principle of rapid patient assessment, combined with decisive measures to treat bronchoconstriction, hypoxemia, and to reverse airway inflammation. The emphasis on breaking the bronchospasm has lead to the use of β_2-agonists in many forms. We have clear evidence for the efficacy of the inhaled route, but we are less clear about the efficacy of parenteral agents. Despite the publication of previous overviews dealing with the use of steroids[12,88], aminophylline[86], ipratropium bromide[91,92] and inhalers vs. nebulizers[82], no systematic review of the intravenous β_2-agonist literature for the treatment in asthmatic exacerbations has been published to date.

Chapter Two evaluates the clinical evidence for the use of intravenous β_2-agonists in the treatment of patients with severe acute asthma exacerbation's that present to the emergency department. Chapter Three examines the current prevalence and patient characteristics of intravenous and subcutaneous β_2-agonist use in North America. Chapter Four summarizes the implications for both clinical practice and research with respect to intravenous β_2-agonist therapy.

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ABSTRACT

Objectives: To determine the benefit of intravenous β_2-agonists (IvB) for severe acute asthma treated in the emergency department (ED).

Methods: Randomised controlled trials (RCTs) were identified using electronic databases; the Cochrane Airways Review Group database; hand searching; bibliographies; pharmaceutic company and author contact. Studies where IvB were compared to placebo and/or standard care were considered. Trials were combined using odds ratios (OR) or weighted mean differences (WMD).

Results: From 746 identified references, 55 potentially relevant articles were identified and 15 were included. All trials were performed outside North America, and published prior to 1997. Compared to all treatments, IvB use did not lead to significant differences in vital signs, pulmonary functions, laboratory measures, adverse effects, or clinical success. Although statistically nonsignificant, IvB use was associated with an increased risk of autonomic side effects (neurological, cardiovascular, gastrointestinal), and higher heart rates (4-10 beats per minute).

Conclusions: Evidence is lacking to support the use of IvB in ED patients with severe acute asthma. Moreover, no subgroups were identified in which it's use should be considered. Future acute asthma research should focus on alternative treatment options.

Word count: 183

SECTION 2.1 INTRODUCTION

The general approach to treating the severe acute asthmatic is to use β_2-agonist bronchodilators and corticosteroids. For rapid bronchodilatation, penetration of inhaled drug to the affected small conducting airways may be impeded, and consequently responses may be a result of drug reaching the receptors via the systemic circulation. In these circumstances, if bronchodilatation occurs predominantly in response to the systemic distribution of the drug, intravenous (IV) rather than inhaled administration of bronchodilators may provide an earlier clinical response.[1]

The research investigating the role of IV β_2-agonists in the emergent treatment of asthma has spanned more than 25 years. At present, each of the guidelines in North America and Europe recommend inhaled β_2-agonist therapy for all cases of asthma that present to the emergency department.[2-5] IV or subcutaneous (SC) β_2-agonists are described as second line therapy for use in patients unresponsive to inhaled bronchodilator and systemic corticosteroid therapy, or if the inhaled route is not practical for the patient.[2-5] However, debate regarding the benefit of this route of delivery remains. No systematic review of the IV β_2-agonist literature for the treatment of asthmatic exacerbations has been published to date. The purpose of this study was to determine if the evidence from randomised trials supports the use of IV β_2-agonists in the treatment of patients with severe acute asthma who present to the emergency department (ED). The questions specifically addressed are:

1. What is the clinical effect of administration of IV β_2-agonists on pulmonary function tests, laboratory parameters, vital signs, adverse effects, and clinical improvement/failure?
2. Does the age of the patient, β_2-agonist type, treatment strategy or rate of administration influence the magnitude of effect?
3. Is the magnitude of effect is influenced by the methodological quality of the included studies or the statistical model used for analysis?

SECTION 2.2 METHODS

Identification of Studies

The Cochrane Airways Review Group (ARG) has developed an "Asthma and Wheez* RCT" register through a comprehensive and standardized search of EMBASE, MEDLINE, and CINAHL. In addition, hand searching of the 20 most commonly cited journals for articles on respiratory care has been completed and relevant RCTs have been added to the register. This register contains a variety of studies published in languages other than English, and is up-dated every six months. The register has been shown to retrieve 92% of the RCTs identified by hand searching the two top respiratory journals from 1989 to 1993, with a specificity estimated to be 17%.[6]

Randomised controlled trials were identified in the both the ARG database and Cochrane Controlled Trials Register (CCTR) using the following search strategy: (placebo* OR trial* OR random* OR double-blind OR double blind OR single-blind OR single blind OR controlled study OR comparative study). An advanced search of this database, and the Cochrane Controlled Trials Register, was completed using the following terms: (1) Asthma OR Wheez* AND (2) Emerg* OR acute* OR status* AND (3) Discharge* OR admi* OR hospit* AND (4) beta-agonist OR betaagonist OR beta agonist OR bronchodilat* OR adrenaline OR albuterol OR bricanyl OR epinephrine OR isoprenaline OR isoproterenol OR hexoprenaline OR reproterol OR salbutamol OR terbutaline OR ventolin OR *erol. This model was adapted from the Cochrane search strategy described in the handbook.[7] Several other databases were also searched separately using the same search terms, including: MEDLINE, EMBASE, CINAHL, Current Contents. Reference lists of all available primary studies and review articles were reviewed to identify potential relevant citations. Trials were not excluded on the basis of language.

Inquiries regarding other published or unpublished studies known and/or supported by the authors of the primary studies were made so that these results

could be included in this review. Several pathways were used to locate authors including letters to an address presented in the article (Appendix 2.1), Internet 'People and Hospital Searches', electronic author searches in library databases for the address on the most recent article published by the author, and contact with other reviewers on the ARG. Scientific advisors of the various pharmaceutical industries that manufacture beta-agonists were contacted for any unpublished, published, or interim results on β_2-agonist research (Appendix 2.2). Personal contact with colleagues, collaborators and other trialists working in the field of asthma was made to identify potentially relevant studies.

Selection of Studies

The reference lists from the search strategy was independently reviewed by two researchers (A.H.T., B.H.R.), and clearly irrelevant articles were discarded. If the title, abstract, or descriptors suggested any potential relevance, the full text article was retrieved. The following inclusion criteria were used to select studies for review and inclusion: (1) design: randomised, placebo-controlled, clinical trials; (2) population: adult or pediatric patients with severe acute asthma presenting to the emergency room (or its equivalent); (3) interventions: treatment with either IV β_2-agonist or one of the following: inert placebo, other intravenous bronchodilators, or other inhaled bronchodilators; (4) outcomes - any of: pulmonary functions, vital signs, clinical scores, were considered for inclusion. Agreement for relevance for review was measured using simple agreement and kappa statistics.

Each relevant paper was assessed by two independent reviewers (B.H.R., A.J.) for inclusion in this review (see Criteria for Inclusion, Appendix 2.3). The reviewers were not blinded to the authors, journal of publication, or results of the studies as investigator bias was deemed unlikely. Agreement for relevance for inclusion was measured using simple agreement and kappa statistics. Disagreement was resolved by consensus or third party adjudication (A.H.T.).

Following selection, each paper was independently subjected to quality assessment using two methods. These criteria were used to provide methodological weights for the included papers, and were to be used in the sensitivity analyses [8]. In the first method, using the Cochrane approach to assessment of allocation concealment, trials were scored independently by two reviewers (A.H.T., C.S., see Appendix 2.4).[7] In the second method, each study was assessed independently by two reviewers (C.C., A.J.) for validity using a ordinal scale (0-5) described by Jadad (Appendix 2.5).[9] Inter-rater reliability was measured by using simple agreement, kappa, and weighted kappa statistics, and disagreement was resolved by third party adjudication (B.H.R.).

Data Collection

A data collection form was completed for all papers meeting the inclusion criteria. Abstracted data included: title, author(s), year of publication, population studied, patient demographics, intervention, and outcomes (see Appendix 2.6). Data for the trials were independently extracted by two reviewers (A.H.T., C.S.) and entered (S.J.B.) into the Cochrane Collaboration software program (Review Manager Version 3.0). In cases where tables were unavailable, graphs were enlarged and values were approximated. This technique was required for seven studies.[10-16]

For those main outcome measures with statistical heterogeneity, a priori subgroup analyses were used (Population: adult versus pediatrics, severity of illness; Intervention: infusion versus bolus, IV with inhaled versus IV alone). Sensitivity analyses were completed on the strength of methodological quality and statistical method of analysis.

Data analysis

A simple agreement (SA) and kappa coefficient (k) of agreement between reviewers was calculated for the 'review for relevance', 'review for inclusion', and for the 'quality scores'.[17] When only the standard error of the mean (SEM) were reported in the studies, the standard deviation (SD) was calculated using: $SD = SEM * \sqrt{n}$, where 'n' represents the treatment sample

size. When only a pooled SD of the mean difference between treatments was described in a single study, several options were employed: (1) if individual patient data were provided in the publication, a SD for each group was calculated; (2) a pooled SD was imputed using the method by Follman (Pooled SD = ($\sqrt{}$(n1-1)*var1 + (n2-1)*var2 + ... + (nk-1)*vark) / Σ(n-k); where var = the variance of the study group in study 'I', and K= the number of studies with variance provided).[18] When no SD data was available from these sources, the initial SD from the particular subset was used.

All trials were combined using the Review Manager, Version 3.0. For continuous variables, a random effects weighted mean difference (WMD) and 95% confidence interval (CI) were calculated for each study. All similar studies were pooled using random effects WMD and 95% CIs. For dichotomous variables, a random effects odds ratio (OR, 95% CI) was calculated for individual studies. All similar studies were pooled using random effects OR and 95% CIs. For pooled effects, heterogeneity was tested using the Breslow-Day test; $p < 0.05$ was considered statistically significant. Data for IV β_2-agonist versus all other treatments were pooled for the following groups (data type): (1) serial pulmonary function (continuous); (2) serial heart rate (continuous); (3) serial arterial blood gasses (continuous); (4) adverse effects (dichotomous); and (5) clinical failure/success (dichotomous).

Sensitivity & Subgroup Analyses

Differences between study results (heterogeneity) may be qualitative or quantitative, and can arise from a variety of sources including: the result of chance; the result of differences between studies with respect to study design, population, intervention, or outcome measurement. When heterogeneity was encountered, these subgroup and sensitivity analyses were performed in an attempt to explain the findings: (1) design: strong vs. weak methodological quality; (2) population: adults vs. pediatrics; (3) intervention: treatment strategy, bolus vs. infusion; (4) statistical model used for analysis: random vs. fixed effects model.

SECTION 2.3 SYSTEMATIC REVIEW

Selection

The ARG database search revealed 976 references which represented 740 (76%) original publications: 258 (35%) in EMBASE; 250 (34%) in MEDLINE; 2 (0.3%) from CINAHL; 224 (30%) from both MEDLINE and EMBASE; and 6 references (0.7%) were cited in all three. Independent review of the abstracts and titles of these publications identified 31 potentially relevant studies. The agreement for relevance was high (SA: 98%; kappa: 0.83). Twenty-four additional references were added from bibliographic searching of relevant articles and overviews; a total of 55 papers were reviewed for inclusion. Unpublished literature was requested from pharmaceutical companies and the authors of all included studies, but none were identified.

Forty studies were excluded at this stage as they were: nonrandomised - 55% (30/55); included treatment of nonacute asthmatics or nonasthmatics - 13% (7/55); examined non-IV routes of administration 5% (3/55). The discussion is confined to included papers only.

Of these 55 articles, a total of fifteen studies (27%) were included in the overview (SA: 94%, k = 0.87) (see Appendix 2.7 for 'Included Studies', and Appendix 2.8 for 'Excluded Studies'). The ARG database identified 12 (80%) of the articles: six were from MEDLINE[10,12,14,19-21], two from EMBASE[13,15], and four from both.[1,11,22,23] The remaining three papers were found from separate MEDLINE searches.[16,24,25]

Description of Included Studies

The evidence for intervention with IV β_2-agonists spans a period of twenty-five years (see Table 2.1): seven (47%) articles published in the 1970s; five (33%) papers in the 1980s; and three (20%) trials in the 1990s. Twelve (80%) of the studies were conducted in Europe, one (7%) in Asia, and two

(13%) in Australia. No trials meeting our inclusion criteria were conducted in North America.

Table 2.1 Year of publication

1970	1980	1990
Bloomfield et al, 1979	Cheong et al, 1988	Browne et al, 1997
Femi-Pearse et al, 1977	Hussein et al, 1986	Salmeron et al, 1994
Hambleton et al, 1979	Sharma et al, 1984	Swedish Society et al, 1990
Johnson et al, 1978	van Renterghem et al, 1987	
Lawford et al, 1977	Williams et al, 1981	
Tribe et al, 1976		
Williams et al, 1975		

Many of the included papers were double-blind, placebo controlled trials, however the methodological quality varied across studies. For example, using the Jadad method, seven studies were rated as "strong" (47%) and eight (53%) were rated as "weak" (see Table 2.2). Agreement between the two independent assessments of study quality was as follows: Randomization (kappa=1.0); Method of Randomization (kappa= 0.76); Double Blind (kappa= 0.81); Method Blinded (kappa= 0.59); and Withdrawals / Dropouts (kappa=1.0). There was no significant correlation between higher Jadad quality scores and the year of publication of the trial (Pearson $r = 0.38$, p=0.17).

Table 2.2 Jadad level of methodological quality

Strong	Weak
Bloomfield et al, 1979	Femi-Pearse et al, 1977
Browne et al, 1997	Hambleton et al, 1979
Cheong et al, 1988	Hussein et al, 1986
Lawford et al, 1977	Johnson et al, 1978
Salmeron et al, 1994	Sharma et al, 1984
Tribe et al, 1976	Swedish Society et al, 1990
Williams et al, 1975	Van Renterghem et al, 1987
	Williams et al, 1981

Using the Cochrane methodology, five papers (33%) were rated as having clearly blinded allocation and ten (67%) were rated as having unclear allocation blinding (kappa = 1.0, see Table 2.3).

Table 2.3 Cochrane concealment of allocation

Clear	Unclear
Browne et al, 1997	Bloomfield et al, 1979
Cheong et al, 1988	Femi-Pearse et al, 1977
Lawford et al, 1977	Hambleton et al, 1979
Williams et al, 1975	Hussein et al, 1986
Williams et al, 1981	Johnson et al, 1978
	Salmeron et al, 1994
	Sharma et al, 1984
	Swedish Society et al, 1990
	Tribe et al, 1976
	Van Renterghem et al, 1987

There was no statistically significant association between those papers that were rated as strong methodologically and those that had blinded allocation (χ^2 2.04, df=1, p>0.05).

Study Design

Thirteen (87%) of the studies followed a parallel protocol, whereas two (13%) of the studies followed a crossover model [12,19]. Eleven (73%) of the fifteen studies introduced IV β_2-agonists immediately upon entry. The remaining four papers introduced IV β_2-agonists 30 to 75 minutes after entry into the study during which time the patients received either inhaled β_2-agonists[1,13,22] or IV aminophylline[10].

There were three main treatment strategies utilized in the studies under review (see Table 2.4). Strategy I compared IV β_2-agonists to inhaled β_2-agonist, where both groups of patients received a 'run in phase' of inhaled β_2-agonist therapy. Essentially, this was equitable to comparing IV β_2-agonists with standard of care versus standard of care. Strategy II compared IV β_2-agonists with inhaled agents, with no inhalational therapy in the IV β_2-agonist arm. Essentially this approach compared IV to inhaled β_2-agonist delivery. Strategy III compared IV β_2-agonists with IV methylxanthines, where neither group received inhaled β_2-agonist therapy.

Table 2.4 Treatment strategies

Strategy	Intervention	Comparison Treatment	Author
Strategy I	IV + inhaled β_2-agonists	inhaled β_2-agonists	Browne 1997 Cheong 1988 van Renterghem 1987
Strategy II	IV β_2-agonists	inhaled β_2-agonists	Bloomfield 1979 Hussein 1986 Lawford 1977 Salmeron 1994 Swedish Society 1990 Williams 1981
Strategy III	IV β_2-agonists	IV methylxanthines	Femi-Pearse 1977 Hambleton 1979 Johnson 1978 Sharma 1984 Tribe 1976 Williams 1975

Populations

Participants were selected from a sample of patients who presented to the emergency department or its equivalent with severe acute asthma (see table 2.5). The majority of studies focused on adult patients only (range 15 to 65 years), with only three papers evaluating the pediatric population (range 0.8 to 14.7 years)[1,15,16] The prehospital asthma medication profile, and asthma history of the patients could not be easily determined from these studies. The median sample size across the 15 studies was 23 with a range of 13 to 176 patients.

All papers enrolled 'severe asthmatics', however there was variety in the parameters and definitions used for inclusion criteria. Nine papers used vital signs (heart rate greater than 100) and pulmonary function tests (PFT less than 20% expected) as primary inclusion criteria.[11,13,14,19,20,22-25] Five papers required derangements in arterial blood gas (ABG) measurements.[13,14,16,20,23] Four papers listed simple clinical symptoms and signs of "severe shortness of breath or wheezing" as inclusion criteria.[10,12,16,21] Two papers described standardized clinical assessment scales or definitions for severe asthma as inclusion criteria. One author utilized the National Australian Asthma Campaign guidelines[26] of any four features of respiratory distress (wheeze, sternal retraction, accessory

muscle use, dyspnea) or any absolute criteria (cyanosis, pulsus paradox, altered level of consciousness, silent chest).[1] Another author[23] enrolled only those patients who met the definition for severe asthma as defined by the American Thoracic Society.[27]

Table 2.5 Study populations

Author	Country	N	Age
Bloomfield 1979	Scotland	20	μ_o 27.35
Browne 1997	Australia	29	μ_{iv} 8.4, μ_c 6.3
Cheong 1988	England	61	μ_{iv} 37, μ_c 35
Femi-Pearse 1977	Nigeria	50	adults
Hambleton 1979	England	18	range 1.5 - 7
Hussein 1986	Germany	20	range 0.8 - 14.7
Johnson 1978	England	39	range 16 - 65
Lawford 1977	England	13	range 15 - 65
Salmeron 1994	France	47	μ_{iv} 39 (± 13), μ_c41 (± 17)
Sharma 1984	India	30	μ_{salb} 33.6 (± 14.4), μ_{terb} 33.1(± 13.0), μ_c 31.7 (± 8.0)
Swedish Society 1990	Sweden	176	μ_{iv} 55 (± 13), μ_c 35
Tribe 1976	Australia	23	adults
van Renterghem 1987	Belgium	23	μ_{iv} 49.8 (± 13.5), μ_c52 (± 7.6)
Williams 1975	England	20	adults
Williams 1981	England	15	adults
		total: 584 (μ 37.6, ± 41.1), range: 0.8 - 75 years	

μ_o mean age overall; μ_{iv} mean age IV group; μ_c mean age comparison group;
salb salbutamol, **terb** terbutaline

In summary, despite the variability of definitions, based on review, all patients entered into these studies could be considered to be suffering "severe acute asthma" requiring admission to hospital as defined by the organizations involved in asthma care.[2-5]

Interventions

A variety of co-interventions were administered across studies, however all patients received supplemental oxygen by face mask; and IV or oral corticosteroids (see Tables 2.6 and 2.7). Most of the trials introduced the steroids to all patients on entry into the study, however in one study an unspecified dosage of steroids was held until two hours into the study in only a selected subgroups of patients.[11] No patients received inhaled steroids, or inhaled anticholinergic agents in any of the studies.

Nine papers gave IV β_2-agonists as a bolus (range 100 - 500 ug, or 4 - 15 ug/kg)[1,11-14,16,19,21,25], whereas six studies administered the IV β_2-agonist as an infusion (range: 8.3 - 20 ug/min to total doses of 500ug - 3000 ug).[10,16,20,22-24] Most studies used salbutamol, except for three studies in which terbutaline was evaluated[13,20,21], and one study where reproterol was used.[15] One study ran a triple parallel protocol comparing IV salbutamol versus IV terbutaline versus IV aminophylline.[21] Consequently this paper were treated as two studies of IV salbutamol versus aminophylline (Sharma1, 1984), and IV terbutaline versus aminophylline (Sharma2, 1984).

Table 2.6 Interventions used in the adult population

Author	Intravenous	Comparison	Steroid
Bloomfield	**salb 500 ug IVB**	salb 5 mg inh	hydro 500 mg iv
Cheong 1988	salb 12.5 ug/min inf*	salb 5 mg neb	hydro 200 mg iv
Femi-Pearse 1977	**salb 200 ug IVB**	amino 250 mg iv	N/A
Johnson 1978	salb 10 ug/min inf	amino 1 mg/min	hydro 200 mg iv
Lawford 1977	salb 20 ug/min inf	salb 10 mg inh	hydro 250 mg iv
Salmeron 1994	salb 8.3 ug/min inf	salb 10 mg inh	hydro 200 mg iv
Sharma 1984	**salb 250 ug IVB**	amino 250 mg iv	N/A
	terb 250 ug IVB	amino 250 mg iv	N/A
Swedish Society 1990	**salb 5 ug/kg IVB**	salb 0.15 mg/kg inh	unknown amt
Tribe 1976	**salb 100 ug IVB**	amino 250 mg iv	hydro 100 mg iv
van Renterghem 1987	**terb 6 ug/kg IVB**	terb 0.1 mg/kg inh	hydro 125 mg iv
Williams 1975	salb 8.3 ug/min inf	amino 500 mg iv	hydro 1000 mg iv
Williams 1981	**terb 250 ug IVB**	terb 2.5 mg	hydro 200 mg iv

*: intravenous salbutamol given with inhaled salbutamol; **amino:** aminophylline; **inf:** infusion; **inh:** inhaled; **IVB:** intravenous bolus; **hydro:** hydrocortisone; **meth:** methylprednisolone; **N/A:** not applicable; **repro** reproterol **salb:** salbutamol; **terb:** terbutaline; **bold denotes intravenous bolus**

Table 2.7 Interventions used in the pediatric population

Author	Intravenous	Comparison	Steroid
Browne 1997	**salb15 ug/kg IVB***	salb 2.5 - 5.0 mg neb	hydro 5 mg/kg iv
Hambleton 1979	**salb 4 ug/kg IVB**	amino 4 mg/kg iv	hydro 4 mg/kg iv
Hussein 1986	repro 0.2 ug/kg/min inf	salb 75 ug/kg inh	meth 2 mg/kg iv

*: intravenous salbutamol given with inhaled salbutamol; **amino:** aminophylline; **inf:** infusion; **inh:** inhaled; **IVB:** intravenous bolus; **hydro:** hydrocortisone; **meth:** methylprednisolone; **N/A:** not applicable; **repro** reproterol **salb:** salbutamol; **terb:** terbutaline; **bold denotes intravenous bolus**

Outcomes

Each paper evaluated their primary outcome determinants within a two hour period. However, six papers extended the observation interval longer:

three hours[21], five hours[22], six hours[23], twenty-four hours[1,16], and thirty-six hours[10,15]. Multiple statistical tests were performed in each study, with a mean of 23.7 (varying from 0 to 80). No mention of adjustments for multiple testing were identified in these papers, and 73.3% (11/15) made no mention of possible type I errors.

Over 240 individual outcome measurements were abstracted from the fifteen papers. Unfortunately, there was a wide variety of outcome measures reported (see Table 2.8).

Table 2.8 Reported outcome parameters

Clinical	vital signs (HR, BP, RR) subjective impression of improvement by patient subjective impression of improvement by physician pulsus paradoxus clinical scoring systems autonomic side effects (CVS, GI, CNS) % successful treatment recovery time need for continued supplemental O2
Pulmonary Function	PEFR, Δ PEFR FEV1, Δ FEV1, Δ%FEV_1 % predicted PEFR, Δ percent predicted PEFR Δ MMFR FVC SaO2
Laboratory	arterial oxygen tensions arterial carbon dioxide tensions serum glucose serum potassium

Scores from a variety of symptom scales were occasionally used to describe outcomes, however due to the different scores used, no pooled analyses were conducted. In addition, a number of PFT results were employed (including PEFR, FEV_1, FVC, % predicted PEFR, % predicted FEV_1), however variability in the type of PFT used limited comparisons between studies (see Table 2.9). There were no descriptions of any patients who were intubated or died during any of the study observation periods.

Table 2.9 Types of pulmonary functions reported as outcomes

	PEFR	Δ PEFR	Δ % Pred*	FEV_1	Δ FEV_1
Bloomfield	✓	✓			
Browne 1997					
Cheong 1988	✓	cbi	✓		
Femi-Pearse 1977		✓			
Hambleton 1979					
Hussein 1986			✓		
Johnson 1978	✓	cbi		✓	cbi
Lawford 1977	✓	✓		✓	✓
Salmeron 1994	✓	✓			
Sharma 1984		✓**			✓
Swedish Society 1990	✓	cbi			
Tribe 1976				unable to use	unable to use
van Renterghem 1987	✓	cbi	✓		
Williams 1975	✓	cbi			
Williams 1981				✓	cbi

* % Response = ((PEFR after treatment - initial PEFR) / (predicted PEFR - initial PEFR)) X 100
** ΔMMFR (maximum mid-expiratory flow rate), **cbi** can be imputed from graphs

Five trials used improvements in PFTs (namely PEFR) as the primary outcome of choice.[10,14,19,20,22] Five papers described a primary outcome variable of "Clinical Improvement", however the definition varied widely between papers. Three of these relied on the 'impression by the patient or physician of improvement in symptoms'.[11,12,24] The remaining two papers described predefined clinical determinants of success.[1,23] The first defined three unique primary clinical measures of success: earlier ED discharge time (defined as the start of hourly inhaled salbutamol therapy); faster recovery time (to cessation of nebulised β_2-agonists every thirty minutes, and sixty minutes); and less oxygen dependence (defined at the two hour window as the requirement for medical oxygen to maintain oxygen saturations above 93%).[1] The second paper defined 'Clinical Success' as the presence of at least two of the following points at 60 minutes: (1) a decrease in a "clinical index rating" of at least three points; (2) a decrease in PaCO2 of at least three mmHg; (3) an increase in PEFR of at least 50 L/min.[23]

Consequent to the variety of outcomes, only seven domains were pooled where data was sufficiently available and similarly derived. These are defined and listed in Table 2.10.

Table 2.10 Outcomes used for summary statistics

Outcome	Domain	Stratum
PFT	PEFR	PEFR at 15, 30, 45 min
		PEFR at 1, 2, 2-6 hours
	% predicted PEFR	% pred PEFR at 1, 2, 3, 6 hr
	FEV_1	FEV_1 at 15 and 45-90 min, 3-4 hours
Clinical	Heart Rate	HR at 15, 30, 45 min
		HR at 1, 2, 2-6 hours
	Autonomic Side Effects	ASE over study period
	Clinical Failure	proportion who fail to improve with therapy
Laboratory	Arterial Blood Gasses	arterial oxygen tension at 1 hour
		arterial carbon dioxide tension at 1 hour

SECTION 2.4 RESULTS

Objective One: combined result for all treatment options

Pulmonary Function

A pooled estimate of the WMD of PEFR over a six hour period after IV β_2-agonist therapy or comparison therapy were calculated for seven of the fifteen papers.[10-12,19,20,22,23] Table 2.11 summarizes the WMD and pooled estimate of treatment effect over the 15 minute to six hour period. (Figure 2.1 in Appendix 2.9 is a 'MetaView' representation of the WMD in the individual studies and of the pooled estimate of treatment effect).

Table 2.11: Summary statistics for PEFR trials

PFT	N	WMD L/min §	95% CI REM	Chi-square*
15 min	5	10.06	-1.67, 21.78	4.63 (df=4), ns
30 min	4	9.48	-10.45, 29.41	5.75 (df=3), ns
45 min	3	-0.42	-29.94, 29.10	0.55 (df=2), ns
60 min	7	19.42	-3.70, 42.55	18.83 (df=6) ‡
120 min	4	16.91	-18.60, 52.42	15.42 (df=3) ‡
2 to 6 hours	5	-3.38	-21.55, 14.79	4.46 (df=4), ns

REM Random Effects Model, * Breslow-Day Test for Heterogeneity, ‡ $p \leq 0.05$
§ negative numbers favor IV treatment, positive numbers favors control

Across all six strata in the PEFR domain no statistical differences in PEFR were identified between those patients who received IV β_2-agonists versus inhaled β_2-agonists or IV methylxanthines. Moreover, differences between the summary outcome measures in each stratum were also of questionable clinical significance with pooled estimates of treatment effect ranging from -0.42 L/min to 19.42 L/min. The heterogeneity present in the 60 and 120 minute strata is addressed in the sensitivity analysis later in this section.

Three papers reported serial changes in percent predicted peak expiratory flow rates, with pooled estimates of WMD listed in Table 2.12.[13,15,22] Two papers followed treatment Strategy I in adults patients[13,22], with the third paper following Strategy II in pediatric patients.[15]

Table 2.12: Summary statistics for % predicted PEFR trials

PFT	N	WMD % §	95% CI REM	Chi-square*
1 hr	3	-1.42	-7.00, 4.16	2.96 (df=2), ns
2 hr	2	-2.64	-6.14, 0.86	0.89 (df=1), ns
3 hr	2	-6.85	-17.03, 3.33	1.85 (df=1), ns
6 hr	2	-8.75	-17.90, 0.39	1.54 (df=1), ns

REM Random Effects Model, * Breslow-Day Test for Heterogeneity, ‡ $p \leq 0.05$
§ negative numbers favor IV treatment, positive numbers favors control

Although there was no statistically significant difference between treatments across the four strata, the results demonstrated an increasing treatment effect over a six hour period favoring IV β_2-agonists (compare -1.42% at one hour versus -8.75% at six hours). However, such marginal differences in percent predicted PEFR are of questionable clinical importance. There was no visual or statistical heterogeneity across the strata in this analysis (See Figure 2.2 in Appendix 2.9).

Two papers reported serial changes in forced expiratory volume in one second, with pooled estimates of WMD reported in Table 2.13.[10,21] Each of these studies followed treatment Strategy III in adult patients (See Figure 2.3 in Appendix 2.9)..

Table 2.13: Summary statistics for FEV_1 trials

serial FEV_1	N	WMD Litres §	95% CI REM	Chi-square*
15 min	3	-0.11	-0.19, -0.02	13.33 (df=2), ‡
45-90 min	5	-0.06	-0.18, 0.06	10.98 (df=4), ‡
> 90 min*	3	-0.06	-0.22, 0.10	3.28 (df=2), ns

REM Random Effects Model, * Breslow-Day Test for Heterogeneity, ‡ $p \leq 0.05$
§ negative numbers favor IV treatment, positive numbers favors control

Across all three time periods there were clinically insignificant differences in FEV1 of 60 - 110 ml. Statistically significant heterogeneity was only absent in the greater than 90 minute stratum where there was no significant difference in effect between treatments.

Serial Heart Rates

Less than 50% of the papers described trends in vital signs, which predominantly included serial heart rates. Nine papers described heart rate

over a six hour period with pooled estimates described in Table 2.14.[10-13,15,19,20,22,23] Table 2.11 summarizes the WMD and pooled estimate of treatment effect over the 15 minute to six hour period. (See Figure 2.4 in Appendix 2.9)..

Table 2.14: Summary statistics for heart rate

serial HR	N	WMD beats/min §	95% CI REM	Chi-square*
15 min	5	7.70	0.87, 14.51	8.69 (df=4), ns
30 min	5	4.03	-2.98, 11.03	11.81 (df=4) ‡
45 min	3	13.07	1.56, 24.50	3.59 (df=2), ns
60 min	9	3.65	-2.90, 10.19	31.23 (df=8), ‡
120 min	6	3.95	-6.85, 14.76	45.21 (df=5), ‡
2 to 6 hours	6	10.82	5.00, 16.64	9.91 (df=5), ns

REM Random Effects Model, * Breslow-Day Test for Heterogeneity, ‡ $p \leq 0.05$
§ negative numbers favor IV treatment, positive numbers favors control

Across all six strata there were lower heart rates in those patients who received the comparison treatment (range 3.95 to 12.26 beats per minute). These differences were statistically significant in the 15 and 45 minute, and the two to six hour strata, each of which had absent heterogeneity amongst the pooled estimates. However, the differences in heart rate are of questionable clinical significance. For the remaining three strata (30 min, 60 min, and 120 min) there was significant heterogeneity present.

Arterial Blood Gas Measurements

Six papers described arterial blood gas measurements for oxygen tensions, and five papers described carbon dioxide tensions all within a two hour period.[10,13,15,19,20,24] Table 2.15 summarizes the WMD and pooled estimate of treatment effect (see Figure 2.5 in Appendix 2.9).

Table 2.15: Summary statistics for arterial gas tensions

ABG	N	WMD mmHg §	95% CI REM	Chi-square*
oxygen	6	-3.18	-8.69, 2.33	1.11 (df=5), ns
carbon dioxide	5	1.66	-0.94, 4.25	3.69 (df=4), ns

REM Random Effects Model, * Breslow-Day Test for Heterogeneity, ‡ $p \leq 0.05$
§ negative numbers favor IV treatment, positive numbers favors control

There was no statistical difference in either the arterial oxygen tension, or carbon dioxide tension between IV β_2-agonists and comparison treatments. In addition there was no heterogeneity across each stratum.

Autonomic Side Effects

Despite concern regarding the potential side effects of IV β_2-agonists, only 10 (67%) studies reported this information. Nine papers reported proportions of cardiovascular (palpitations, tachycardia, hypertension), neurological (tremor, headache), and/or gastrointestinal (nausea) side effects associated with therapy.[11,12,14,19-24] The tenth paper reported a significantly higher proportion of tremor in the IV β_2-agonist group, but did not list specific data.[1] Table 2.16 summarizes the OR and pooled estimate of treatment effect (see Figure 2.6 in Appendix 2.9).

Table 2.16: Summary statistics for autonomic side effects

side effects	N	OR §	95% CI REM	Chi-square*
side effects	9	1.98	0.48, 8.18	36.80 (df=8), ‡

REM Random Effects Model, * Breslow-Day Test for Heterogeneity, ‡ $p \leq 0.05$
§ < 1 favor IV treatment, > 1 favors control

The pooled OR suggests that the proportion of patients who experienced adverse effects from IV treatment were approximately twice as frequent as those who received the comparison treatment. However, this result was not statistically significant and significant heterogeneity was present in the pooled estimate (χ^2 36.8, df=8, $p < 0.05$).

Clinical Failure

Five papers reported a primary outcome variable of "Clinical Improvement", however there was variability in the subjective and objective measures used.[1,11,12,23,24] For entry into RevMan v3.0, the proportion of patients who had 'clinical success' as defined by each author, were converted to the proportion of patients with clinical failure. Table 2.17 summarizes the pooled estimate of treatment effect (see Figure 2.7 in Appendix 2.9).

Table 2.17: Proportion who failed to improve with therapy

	N	OR §	95% CI REM	Chi-square*
Fail to improve	5	2.08	0.32, 13.47	24.48 (df=4), ‡

REM Random Effects Model, * Breslow-Day Test for Heterogeneity, ‡ $p \leq 0.05$
§ < 1 favor IV treatment, > 1 favors control

The pooled OR suggests that the proportion of patients who failed to improve with IV therapy was approximately twice that of the proportion who received the comparison treatment. However, this result was not statistically significant, moreover, significant heterogeneity was present in the pooled estimate (χ^2 24.48, df=4, $p < 0.05$).

Objective Two: Subgroup Analyses

Population:

An insufficient number of pediatric papers with similar outcome measures, precluded any subgroup comparison on the basis of age of the patients. Only three of the fifteen included papers (20%) evaluated the pediatric population.[1,15,16]

Intervention:

Three types of β_2-agonist were evaluated - the majority examined salbutamol, however terbutaline was reviewed in three papers[13,14,21], and reproterol in one paper[15] An insufficient number of similar outcomes excluded any formal comparison of results. There was no statistical difference in any of the outcome domains when comparing β_2-agonists administered as an IV bolus versus infusion.

Three of the 15 papers evaluated the question of whether IV β_2-agonist improves the initial bronchodilator response when given in addition to nebulised β_2-agonist therapy.[1,13,22] Amongst these studies, the only domain where sufficient similar outcomes were reported, were in two papers in the stratum of %predicted PEFR.[13,22] In this stratum there was a trend showing increasing percent predicted responses over six hours for those patients who received intravenous β_2-agonist therapy. These results were non-significant at each point in time, and were also of minimal clinical significance. In the remaining paper utilizing treatment Strategy I, there were no reports of

pulmonary function data thereby limiting comparisons with the other two papers.[1]

There was no change in the trends of the summary statistics for any of the outcome domains when Strategy II was compared to Strategy III (see MetaViews in Appendix 2.9). Too few studies with sufficient similar outcomes limited any meaningful comparison of Strategy I versus Strategy III.

Sensitivity Analysis: Methodological Quality

There was significant heterogeneity in pooled estimates in 9 (37.5%) of the 24 stratums. Sensitivity analysis of clinically significant outcome strata, by strength of methodological quality yielded the results in Table 2.18. Using Jadad's methods a strong methodological paper was defined as having a Jadad score of three to five, and a weak paper as having a Jadad score of zero to two.

Table 2.18 Subgroup analysis by methodological quality

Stratum	Strong Quality WMD* or OR§ (95%CI) Breslow Day Test	Weak Quality WMD* or OR§ (95%CI) Breslow Day Test
PEFR at 60 min	WMD 8.30 (-17.63, 34.22), N=4 χ2 4.97 (df=3), ns	WMD 32.67 (1.18, 64.16), N=3 χ2 5.80 (df=2), ns
PEFR at 120 min	WMD -1.27 (-21.42, 18.88), N=2 χ2 0.63 (df=1), ns	WMD 27.22 (-28.19, 82.63), N=4 χ2 4.66 (df=3), ns
PEFR Final	WMD -10.76 (-32.84, 11.33), N=3 χ2 2.14 (df=2), ns	WMD 27.25 (-6.20, 60.69), N=3 χ2 5.87 (df=2), ns
HR at 60 min	WMD 4.89 (-1.08, 10.86), N=5 χ2 7.12 (df=4), ns	WMD -0.69 (-13.41, 12.04), N=3 χ2 10.68 (df=2), ‡
HR at 120 min	WMD 8.92 (1.38, 16.46), N=4 χ2 6.03 (df=3), ns	WMD -4.44 (-19.03, 10.14), N=2 χ2 5.93 (df=1), ‡
Autonomic Side Effects	OR 2.25 (0.49, 10.39), N=5 χ2 7.19 (df=4), ns	OR 0.26 (0.06, 1.15), N=5 χ2 7.19 (df=4), ns
Clinical Failure/Success	1.17 (0.12, 11.66), N=4 χ2 15.03 (df=3), ‡	OR 12.79 (5.32, 30.76), N=1 ns

‡ $p \leq 0.05$
* negative numbers favor IV treatment, positive numbers favors control
§ < 1 favor IV treatment, > 1 favors control

It is evident that the stronger methodological papers fail to demonstrate a clinical or statistical difference between IV agents or the comparison treatment arm in terms of PEFR and clinical success. Moreover, although not statistically

significant, IV β_2-agonists appear to have an increased risk of adverse effects and increased heart rate compared to the comparison treatment. By comparing the two groups it is clear that the weak methodological papers had larger effect favoring the comparison treatment. Although these were statistically non-significant, the treatment effects from the weak methodological were clearly orders of magnitude larger or even discordant to the results from the strong methodological studies.

Subgroup analysis by fixed effects modeling demonstrated no differences in results except for more strata with statistically significant lower serial heart rates for the non-IV groups (range: 0.1 to 14.1 beats/min).

SECTION 2.5 DISCUSSION

Physicians who assess and treat patients presenting with severe acute asthma are faced with many difficult decisions, including how aggressively to treat and what medications to use. The literature is conflicting regarding the use of IV agents, and this systematic overview is the first to examine evidence of the effect of treating asthmatics with IV β_2-agonists following diagnosis in the ED. This meta-analysis included fifteen randomised parallel and crossover trials over twenty-five years that included 584 adults and children across nine countries. Several important conclusions arise from the analyses.

First, this meta-analysis fails to demonstrate a statistically significant difference in effect between IV β_2-agonists and all other treatments combined (inhaled β_2-agonists, or IV methyxanthines) in the management of patients with severe acute asthma who present to the ED. Intravenous β_2-agonists administered either by bolus or infusion did not lead to significant improvements in any of the outcome measures of clinical success. It was consistently shown through subgroup and sensitivity analysis that the use of intravenous β_2-agonists was associated with an increased risk of autonomic side effects (2-12 times), and higher heart rates (4-10 beats per minute). However, while important information, they were never shown to be statistically significant.

Second, when examining the quality of papers involving intravenous agents in acute asthmatic presentations, it is obvious that greater care must be incorporated into further work if clarity is to emerge. There were broad discrepancies among outcomes from studies where methodological quality was scored using two accepted methods.[7,9] Moreover, statistical planning and sample size calculations were not carefully considered in most studies. No papers were large enough to protect against type II error, and sample size calculations were rarely reported. Furthermore, multiple statistical testing was performed in many studies, increasing the risk of type I error. Factors confounding the relationship of IV β_2-agonist use and outcome measures are

the weak methodologies of the studies included in the summary measures. When analysed by methodological quality, the treatment effects were less pronounced in the methodologically stronger studies.

Third, the literature has examined three treatment strategies involving IV β_2-agonists. Originally, IV β_2-agonists were compared to IV aminophylline in most clinical trials in the 1970s and early 1980s (40% of the included papers). However, as the standard of care for asthma has been refined, the routine use of aminophylline has diminished, and inhaled β_2-agonists have been increasingly used. Consequently, there was a shift in focus to compare IV versus nebulised IV β_2-agonists (40% of the included papers).

However, whether IV β_2-agonists improve bronchodilator response when given in addition to nebulised bronchodilators was only addressed in 20% (3/15) of the studies under review.[1,13,22] These papers evaluated differing populations (two adult and one pediatric population) and used different primary outcomes thereby limiting any pooling of results. Each in isolation concluded that IV β_2-agonists administered with β_2-agonists resulted in better primary outcomes. In one study of adults, a salbutamol infusion started after an initial treatment of both nebulised salbutamol and IV hydrocortisone, resulted in a greater improvement in PEFR than three successive nebulised treatments over 2 hours[22] In another study of children, a single IV bolus of salbutamol was given in addition to nebulised salbutamol.[1] The recovery time to cessation of repetitive 30 minute administrations of nebulised salbutamol was four hours in the IV group versus 11.1 hours in the control group. In addition IV salbutamol also lead to both a faster discharge from the ED (9.7 hours earlier than controls), and lower dependency on supplemental oxygen. Consequently, although the evidence suggests that IV β_2-agonists alone are no better than inhaled, the role of IV β_2-agonists in addition to inhaled β_2-agonists remains unclear.

Fourth, data regarding the IV route of administration in patients with severe acute asthma suggest changes in treatment approaches. For instance, the current recommendations for parenteral β_2-agonist therapy varies slightly amongst the clinical practice guidelines produced by the Canadian, American, and British organizations involved in acute asthma care.[3,5,28] All CPG's recommend that IV or subcutaneous (SC) agents be introduced as second line therapy only if the patient is unresponsive to inhaled bronchodilator and systemic corticosteroid therapy, or if the inhaled route is not practical for the patient (i.e. excessive coughing, too weak to inspire adequately, or moribund patient). All CPG's variously describe "near-death asthma", or "life-threatening asthma" as qualifying terms for adult candidates for IV bolus therapy or infusion therapy. These are listed as alternative therapies paralleling inhalational anaesthetics and IV methylxanthines.

However, most of the CPG recommendations for IV or SC agents originate from low grade and/or low levels of evidence. For example, the CAEP guidelines on parenteral agents cite evidence from 15 studies; however they only included seven (four of which were methodologically strong) of the 15 papers which were included in this analysis.[3] The remainder of the studies were non-trials, or studies evaluating SC routes of administration. The CPGs need to continue to assimilate new information on the contextual pillars of evidence-based medicine. Furthermore, the CPGs should illustrate the importance of pursuing other modalities of treatment including the optimization of corticosteroids, and potential treatments with magnesium.

In summary, use of IV β_2-agonists did not lead to any significant differences in pulmonary functions, laboratory measures of ventilation and oxygenation, and clinical failure. However, the findings suggest that IV β_2-agonists produce more autonomic side effects and higher heart rates. Thus, the clinical benefit appears questionable, while the risks are more obvious. Such 'lack of difference' between the two treatment arms does not equate to 'equivalence' between the treatment arms, as much larger samples sizes would

be needed to confirm the latter conclusion. The discordance between the outcome domains of clinical failure despite improving pulmonary function illustrates a potential flaw in using the latter domain as a measure of "successful treatment.

EVALUATION OF THE SYSTEMATIC REVIEW

Methodological Strengths

When reading and reporting meta-analysis results, it is necessary to have an organized approach. There have been recent publications that specifically address this issue[29-31], and following their criteria, the following strengths are illustrated.

First, unbiased and complete identification of all relevant studies is of paramount importance in assuring the validity of systematic review and meta-analytic results, and therefore requires a comprehensive search involving multiple overlapping strategies.[32] The search strategies included in this meta-analysis included comprehensive and reproducible electronic databases, book chapters, cited bibliographies, experts, and personal contact with authors and pharmaceutical companies. The trail of the exhaustive search of the published, unpublished, English, and foreign papers is described fully in the Methods section. Unpublished literature was solicited but not forthcoming from those authors with expertise in the field. While these methods are not foolproof, it seems unlikely that rigorous clinical trials exist that would substantially alter these results. Restricting the analysis to randomised controlled trials resulted in the inclusion of only the strongest available clinical evidence.[29]

Second, using two independent reviewers and explicit inclusion criteria (for relevance and review) addressed biases in study selection.[29,30] The agreement for inclusion was high, and the comprehensive nature of the search reduced the opportunity to introduce personal bias in study selection.

Third, the validity of a trial is dependent on the degree to which its design and conduct are likely to prevent systematic errors[33]; however as Greenhalgh postulates, there is no 'true gold standard' against with to judge the 'true' methodological quality of a trial.[34] Quality and design features are known to influence results[9], for example, studies using poor methodology have been shown to overestimate the treatment effect.[35] Moreover, other features including concealment of allocation[36], blinding and randomisation, have all been found to influence the effect size.[37] In this review, the validity of included studies were independently appraised using accepted scoring systems defined by Jadad and the Cochrane Collaboration.[7,9]

Justification for Pooling of Results

A systematic review is secondary, retrospective research defined as the application of strict, and rigorous scientific strategies that limit bias in the systematic assembly, appraisal, and synthesis of all relevant studies addressing the same fundamental question.[8,38] Consequently the result reflects a valid representation of whether the findings are consistent and generalisable across populations, settings and treatment variations; and whether findings differ by particular subgroups.[39] A meta-analysis is a statistical technique that incorporates the quantitative results from independent studies in a review into a single 'pooled-estimate of effect' coupled with a measure of precision.[40] The advantages are: (1) combining results across trials increases the sample size, thereby increasing the statistical power to determine the presence or absence of treatment effect; (2) a meta-analysis may unveil a significant effect from treatment when individual trials are too small to reach statistical significance; and (3) the 'pooled-estimate' provides an 'on average' measure of the overall effectiveness of interventions [39,41].

In summary, the general purpose of pooling individual studies is to provide a general effect of treatment. Based on sound methodological principles, this systematic review combined the highest quality evidence from similar trials. Furthermore, it would be sensible and efficient to combine those

studies using IV β_2-agonists, since the sample sizes of the individual studies are insufficient to reach a firm conclusion on their own. In addition, the decision to combine results is based on demonstration of similarities in populations, interventions, and outcome measurements between studies. By dividing the papers into their respective categories, the issue of similarity was addressed. As a result of these steps, the pooling of data was reasonable. Despite these features, statistically significant heterogeneity was still found in some of the analyses.

Methodological limitations

First, due to the small number of trials included in this meta-analysis, and the overall small number of patients upon which the results are based, no firm conclusions regarding subgroups by treatment (i.e. intravenous with nebuliser, versus intravenous without nebuliser) or age can be made. Also, this review analysed only the intravenous route of administration, and did not evaluate the literature on subcutaneous routes of administration.

Second, there was significant heterogeneity in pooled estimates in nine of the twenty-four outcome strata. However, on further sensitivity analysis it appeared that papers of low methodological quality helped to explain much of the heterogeneity. In particular, one paper (Swedish Society, 1990) was responsible for the majority of the heterogeneity based on the following points: (1) Differential Methodological Quality: The Swedish Society paper was rated as the weakest paper amongst those in the review (Jadad score = 1); (2) Different Populations: All papers studied extremely severe asthmatic patients, however the majority of papers enrolled patients with mean PEFRs in the range of 50 to 100 L/min, whereas the Swedish study evaluated patients with mean PEFRs in the 160 to 170 l/min range (still defined as "severe < 200 L/min" by international guidelines). (3) Different cointerventions: The Swedish study did not administer any steroid therapy until two hours into the study protocol, whereas all other papers introduced steroid therapy at time of enrollment into the study. The effects of each of these factors on the homogeneity of the

outcome domains were confounding in isolation and in whole by the very large sample size of the Swedish study (n=176) in relation to the relatively smaller studies (range n=14 to 71).

Third, despite the intensive search strategy employed, there still exists a possibility of study selection bias or publication bias in this meta-analysis. For example, through missing unpublished negative or positive trials we may be estimating erroneously the non-significant effects of IV β_2-agonists. However, a comprehensive search of the published English and non-English literature for potentially relevant studies was conducted, using a systematic strategy to avoid bias. In addition, attempts were made to contact first and corresponding authors. Despite these endeavors, no unpublished or non-English papers were uncovered, however we recognize that they may exist.

Fourth, the best outcome measure for "success" in treating acute asthma was measured variably between studies, and perhaps also within studies (particularly in those studies relying on the subjective impression of improvement by the patient or physician). Better standardization of this outcome would improve study comparability. Most studies included PFT outcome measures, namely: absolute PEFR, percent change in predicted PEFR, FEV_1, or percent change in predicted FEV_1. The inherent variability of these PFTs, particularly in the acute exacerbation, emphasizes the need for further research into alternative measures, particularly assessment of factors that are important to the patient. In addition, the evaluation of adverse side effects was complicated by a lack of standardized reporting.

SECTION 2.6 CONCLUSIONS

Despite the methodological limitations, the results of this work clarifies the use of intravenous β_2-agonists in the treatment of severe acute asthma. The use of IV β_2-agonists did not lead to any significant differences in pulmonary functions, laboratory measures of ventilation and oxygenation, and clinical failure. However, the findings suggest that IV β_2-agonists produce more autonomic side effects and tachycardia than do comparison treatments. Consequently, the clinical benefit appears questionable, while the clinical risks are obvious. The only recommendations for IV β_2-agonist use should be in those patients in whom inhaled therapy is not feasible, or in the context of a controlled clinical trial comparing IV β_2-agonists with standard care versus standard care alone. Future acute asthma research should focus on alternative treatment options, and there is a need to adjust national and international practice guideline recommendations for IV β_2-agonists.

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ABSTRACT

Rationale: β_2-agonists may be given by inhaled or systemic routes for the treatment of acute asthma. However, little is known about the epidemiology of the use of systemic β_2-agonists in North American Emergency Departments (ED).

Objectives: To determine the prevalence of systemic (intravenous: IV, subcutaneous: SC, intramuscular: IM, oral: PO) β_2-agonist use in North American Eds, and the factors associated systemic β_2-agonist use for acute asthma in EDs.

Methods: This prospective cohort study was performed in 77 North American EDs affiliated with the Multicenter Asthma Research Collaboration (MARC). Patients aged 2-54 presenting to the ED with acute asthma were interviewed during their visit and by telephone two weeks later. Treatment decisions were left to the discretion of the treating ED physician.

Results: Of 4099 eligible patients, 3031 were enrolled in the study (74%); 1,847 were adult (18-54) and 1,184 were children (2-17). Overall, 5% (144/3031) received systemic β_2-agonists; 117 (81%) within and 27 (19%) prior to ED arrival. No patients received IV β_2-agonists. Univariate analysis demonstrated that adults receiving SC β_2-agonist required more frequent inhaled β_2-agonist treatment (4 vs 3 during their stay), more systemic corticosteroids (92% vs 67%) and stayed longer in the ED (243 minutes vs 180 minutes). Finally, admission rates were higher in the SC group (80% vs 54% in adults; 77% vs 46% in children). Multivariate analysis of patient characteristics revealed that increasing age (OR 1.2 per 10 years, 95%CI: 1.0-1.3), use of oral β_2-agonists during the past four weeks (OR 1.8, 95%CI: 1.1-2.9), maximum severity scores (OR 3.3, 95%CI: 1.8-6.1), and ED length of stay (OR 1.1, 95%CI: 1.0-1.2) were independent predictors of systemic β_2-agonist use.

Conclusions: The use of systemic β_2-agonists in North American EDs is uncommon, and most frequently seen in patients with more severe exacerbations of asthma. Clinicians should re-evaluate the role of systemic agents and optimize other proven modalities of treatment such as corticosteroids and inhaled β_2-agonists.

Word count: 317

SECTION 3.1 INTRODUCTION

Acute asthma is a common emergency department (ED) presentation in North America. For example, acute asthma accounts for approximately 2.0 million ED visits and 460,000 hospitalizations in the US annually[1,2], together costing at least $2 billion per year.[3] In Canada, acute asthma care both in the ED and inpatient wards is responsible for over 300 million dollars in direct health care costs.[4] Approximately 10-20% of patients presenting to the ED will require admission to the hospital.[5]

Generally, the ED approach to acute asthma includes therapy with agents that address the bronchospasm (inhaled β_2-agonists) and inflammatory (corticosteroids) components of the disease. In more severe cases, systemic therapy with intravenous (IV) or subcutaneous (SC) β_2-agonists may be warranted, however, there is debate over the effectiveness of this strategy.[6-9] Theoretically, patients may require alternative delivery of bronchodilators due to the ineffectiveness of inhaled delivery to the airway in severe acute asthma. IV or SC delivery has the potential to speed the bronchodilation in such cases.

Recommendations regarding IV or SC β_2-agonist use exist in current national guidelines.[7,9,10] However, far less is known about this aspect of acute asthma care than other components such as inhaled β_2-agonist and corticosteroid use. The purpose of this study was to determine the prevalence of systemic β_2-agonist use in North American ED sites involved in the Multicenter Asthma Research Collaboration (MARC) studies. In addition, this study examined the differences in asthmatic presentation, treatment and outcomes between those patients who received β_2-agonists via the systemic versus inhaled route.

SECTION 3.1 METHODS

Design

MARC was created in May 1996. The first study, MARC-1, was performed in late 1996 at 12 EDs across the USA. The subsequent MARC studies (MARC 2, MARC 2_X, MARC 2_{X2}, MARC 3, and MARC 3_X) have built upon this foundation by recruiting additional sites for the MARC network. The MARC studies were a series of prospective cohort studies examining the diagnostic and therapeutic details of adult and pediatric patients presenting to North American EDs. Their purpose has been to develop an ED research network for future participation in randomized trials of acute asthma therapy, and to describe current management of acute asthma. At present, investigators from 77 EDs in 22 US states and 8 EDs from five Canadian Provinces are involved in MARC trials.

This study combined data from six prospective MARC cohort studies (see Table 3.1: four adult and two pediatric) performed during October-December 1996, April-June 1996, October-December 1997, April-June 1997, and March-April 1998, respectively. [5] Using a standardized protocol, 24-hour per day coverage was provided at each site for a median of two weeks. The Institutional Review Board at each of the participating hospitals approved the study, and informed consent was obtained for all participants (See Appendix 3.1 and 3.2).

Table 3.1 MARC demographics

	Date	Population
MARC 1	Fall 96	adults
MARC 2	Spring 97	adults
MARC 2_x	Fall 97	adults
MARC 2_{x2}	Spring 98	adults
MARC 3	Fall 97	pediatrics
MARC 3_x	Spring 98	pediatrics †

† ages 12-17 years

Eligible patients were those patients who presented to the ED and had a physician diagnosis of acute asthma, were between 2 and 54 years of age, and were able to provide informed consent (parental consent for pediatric cases).

Ineligible patients were those with prior enrollment in a MARC study, major concomitant disorders (i.e., pneumonia, bronchopulmonary dysplasia, emphysema, or COPD); and patients with an ED visit which was not prompted primarily by acute asthma. Minimal data were recorded for patients who refused, were missed or were otherwise excluded from the study. Patients with lost medical records were excluded because a diagnosis of asthma could not be confirmed.

Data Collection

Consenting patients were examined in the ED using a standardized questionnaire by MARC research assistants who could not influence patient management. The ED interview assessed demographic characteristics, asthma history, and details of the current asthma exacerbation. Information was collected until admission or discharge had been reached (see Appendix 3.3). Further data on ED management and disposition were obtained from chart review completed by study personnel. Follow-up data were obtained by telephone interview two weeks after the initial ED visit and included details of any urgent asthma visits, general health status, relapses to additional care, changes in medical management, compliance with prescribed steroid therapy, and current asthma symptoms.

Patients were asked to report use of short-acting oral β_2-agonists (e.g., albuterol [Ventolin, Proventil]) or long-acting β_2-agonists (e.g., salmeterol [Serevent]) during the four weeks prior to ED visit. Patients who received subcutaneous (SC), parenteral (intravenous: IV, or intramuscular: IM), or oral β_2-agonist treatments during the six hours preceding ED arrival (pre-ED) or during the ED visit were classified as having received a systemic β_2-agonist. Inhaled short-acting and long-acting β_2-agonist were not classified as systemic β_2-agonist treatments.

Median family income was estimated using patients' home ZIP codes.[11] Primary Care Provider (PCP) status was assigned on the basis of the question:

"Do you have a primary care provider (such as a family doctor, internist, or nurse practitioner)?". If yes, patients were asked to provide the name and address of their PCP. Symptoms were classified as severe if patients answered 'yes' to one of two questions referring to the 24 hours preceding their ED presentation (i.e., asthma symptoms "most of the time" *or* "severe" discomfort and distress due to their asthma). Smoking status was coded as never smoker, current smoker, and ex-smoker.

For pediatric patients, questions pertaining to smoking status were asked for patients age 12-17. Smoke exposure for pediatric patients was derived from three questions about smoking status and passive smoke exposure in the home (i.e., current smoking status and exposure to someone who frequently smokes in the same room, asked of patients age 12-17, and exposure to someone who frequently smokes in the same room, asked for all patients).

A severity score was derived using the Pulmonary Index (PI) for pediatric patients and PEFR for adult patients. PI scores were calculated for pediatric patients using respiratory rate, accessory muscle use, wheezing, and Inspiratory:Expiratory (I:E) ratio. Based on a scale of 0 to 3 for each component of the PI, a total was calculated with a maximum PI of 12.[12] Peak expiratory flow rate (PEFR) was expressed as percentage of patient's predicted value, based on race, age, gender, and height.[13] Changes in PEFR were expressed as the absolute change in percent of predicted (e.g., an improvement from 40% predicted to 70% predicted would be expressed as a change of 30%). To allow combination of pediatric and adult data, each variable (PI and PEFR) was divided approximately into quartiles: one, PI>6 or PEFR<33%; two, PI 5-6 or PEFR 33%-45%; three, PI 3-4 or PEFR 46%-60%; four, PI<3 or PEFR>60%. A severity score of 1 to 4 was assigned based on these quartiles.

Site characteristics, such as the type of ED (i.e., general ED, ED in a pediatric-only hospital, or ED in an adult-only hospital), and number of ED visits for asthma over one year, were obtained from a site questionnaire completed by

the principal investigator at each site. The questionnaire also ascertained presence of standardized asthma treatment protocols in each ED. Published sources provided additional information, such as presence of an emergency medicine residency, hospital type, and estimated household income by hospital ZIP (USA)[11] or postal (CANADA) code (Statistics Canada, Ottawa, 1999). Sites were stratified into three domains of no systemic β_2-agonist use; infrequent systemic β_2-agonist use (defined as less than 5% of all treatments); and frequent systemic β_2-agonist use (defined as greater than 5% of all treatments).

Data preparation

Following complete data collection, all forms were reviewed by site investigators before submission to the MARC Coordinating Center in Boston, where they underwent further review by trained personnel and then double data entry.

Data analysis

All analyses were performed using STATA 5.0 (StataCorp, College Station, TX). Data are presented as proportions (with 95% confidence intervals [CI]), means (with standard deviation [SD]), or medians (with interquartile range [IQR]). Imputed values were used to calculate the PI score when one of the elements (i.e., respiratory rate, accessory muscle use, wheezing, and I:E ratio) were missing; patients missing more than one of the parameters were not assigned a pulmonary index score. The association between systemic β_2-agonist use and other factors was examined using Chi-squared statistics, Student's t-test, and the Wilcoxon rank sum test, as appropriate. All p-values were two-tailed, with $p<0.05$ considered statistically significant. For those variables with two or more strata, standardized cell deviates for differences in Chi-square statistics were calculated for each domain.

Logistic regression analysis was used to determine the factors associated with systemic β_2-agonist use. Variables associated with systemic β-agonist use ($p < 0.10$) in univariate analysis were evaluated for inclusion in

multivariate logistic regression models. Age, sex, and estimated median household income were included in multivariate logistic regression models because of their clinical importance. The area under the receiver operator curve (ROC) was calculated for the final multivariate logistic regression model. Factors were removed from the model to evaluate their influence on the area under the ROC curve. All odds ratios (OR) are presented with 95% CI. All p-values are two-tailed, with $p<0.05$ considered statistically significant.

There were two study populations under review, with subgroups based on age (pediatric: 2-17 years, and adult: 18-54 years). The first comparison group (termed 'systemic group') were those patients who received IV or SC β_2-agonists during the study period. The second group, referred to as the 'non-systemic group' (also termed 'inhalation group') received therapy with inhaled β_2-agonists alone.

SECTION 3.3 RESULTS

Patients:

Of 2,496 eligible adult patients with acute asthma presenting to the ED 1,847 (74%) were enrolled (100 refused entry, 500 were missed, and 49 had other classifications). From 1,603 eligible pediatric patients presenting to the EDs over the study periods 1,184 (74%) were enrolled (45 refused, 346 missed, 28 other). All descriptive statistics described in the body of the results follow the same sequence of (systemic group vs. non-systemic group, p-value).

MARC Site Characteristics

Table 3.2 illustrates the general ED characteristics of the MARC sites according to frequency of systemic β_2-agonist use. For the 77 sites, there were no significant differences in general ED profiles, except for a higher proportion of pediatric EDs in the hospitals with infrequent systemic β_2-agonist use (22% vs 5% vs 6% for infrequent, nonuse, and frequent use sites respectively, $p<0.05$), and a higher proportion of General EDs with frequent systemic β_2-agonist use (94% vs 73% vs 61% for frequent, nonuse, and infrequent use sites respectively, $p<0.05$).

Table 3.3 illustrates the asthma ED characteristics of the MARC sites according to frequency of systemic β_2-agonist use. There were higher percentages of total ED visits for asthma in the sites with frequent systemic β_2-agonist use (median 3.4), compared to those with infrequent use (median 3.0) and no use (median 2.1) - these trends were statistically significant ($p = 0.04$). In addition, 81% of the hospitals that did not use systemic β_2-agonists had less than 2500 cases of asthma per year; 64% of the hospitals with infrequent systemic β_2-agonist use had less than 2500 cases per year; and 54% of the hospitals with frequent β_2-agonist use had more than 2500 asthma cases per year.

Overall, systemic β_2-agonist use was low in participating EDs; however, use varied slightly across sites with a median of 1% (Interquartile Range (IQR) across sites, 0% to 5%). While 48% (37/77) of participating sites reported no systemic β_2-agonist use (nonusers), 30% (23/77) reported using systemic β_2-agonists in less than 5% of patients (infrequent users), and 22% (17/77) report using β_2-agonists in more than 5% of patients (frequent users). One smaller site (n=13 patients) reported use in 31% (95% CI, 9% to 61%) of their patients.

Systemic β-agonist Use During Index Asthma Exacerbation

Among the 3031 ED asthma patients enrolled in the study, only 144 (5%; 95% CI, 4% to 6%) received systemic β_2-agonist medications during their current asthma exacerbation. In total, 3% (37/1184) of the pediatric patients and 6% (107/1847) of the adult patients received systemic therapy. Overall, 27 (19%) received systemic β_2-agonists pre-ED but not while in the ED (18 oral medication, 9 SC/IM epinephrine), while 26 (18%) received SC epinephrine in the ED only. The remaining 91 patients (63%) received SC terbutaline or salbutamol in the ED. No patients received IV β_2-agonists either in the ED or in the 6 hours prior to the ED.

Demographic Characteristics

Table 3.4 illustrates the demographic characteristics of pediatric and adult patients who received systemic versus inhaled β_2-agonists alone in the ED. There were few major differences in demographic characteristics in both the adult or pediatric subgroups with respect to route of administration. Pediatric patients given systemic β_2-agonists were less likely to have parents who were high school graduates compared to the inhalation group (54% vs. 71%, $p < 0.05$), yet there was no statistical difference in age of patients between the two groups. For the adult population there was a higher percentage of African Americans among those who received systemic β_2-agonists compared to those who did not (33% vs. 21%, $p<0.05$). Furthermore, adults given systemic β_2-agonists had lower estimated household incomes than the

inhalation group ($23,235 vs. $27,724, $p<0.01$). There were statistically significant variations in the insurance status between adults with more patients in the systemic group having Medicaid (41% vs. 27%, $p<0.05$), and more adults in the inhalation group having 'other public insurance plans' (4% vs. 15%, $p< 0.05$).

Chronic Asthma Characteristics

Table 3.5 illustrates the chronic asthma characteristics of pediatric and adult patients who received either systemic or inhaled therapy. In the pediatric subgroup, there were no statistically significant differences in chronic asthma characteristics between the systemic and inhalational groups, except for a higher percentage of the latter group using the ED as a usual source for asthma medication prescriptions (9% vs. 31% respectively, $p\leq 0.01$).

For the adult population, there were more previous hospitalizations and more previous asthma ED visits in those patients who received systemic β_2-agonists than those who received inhaled therapy (73% vs. 61%, $p\leq 0.05$ for "ever hospitalized for asthma", and 45% vs. 29%, $p\leq 0.001$ for "admitted for asthma in the past year" and 3 vs. 2, $p\leq 0.01$ for "ED visits"). Furthermore, in the four weeks prior to presentation those patients who received systemic therapy in the ED were more likely to have taken inhaled β_2-agonists (93% vs. 85%, $p\leq 0.05$), and more likely to have used other adjunctive therapies for their asthma including: oral β_2-agonists, non-β_2-agonist and non steroid medications (46% vs. 35%, $p\leq 0.05$). Likewise, the systemic group was more likely to have received corticosteroid medication for asthma at some point in the past (86% vs. 72%, $p\leq 0.01$).

The majority of the patients utilized the ED as their usual source for asthma care (60% of the pediatric patients, and 70% of the adult patients using the ED for primary asthma care). This was seen in both the systemic and inhalational groups. There were no statistical differences in the remaining

variables including: hayfever comorbidity, smoking status, history of intubation, and ownership of a spacer and /or a peak flow meter.

Acute Asthma Characteristics

Table 3.6 illustrates the acute asthma characteristics of pediatric and adult patients who received systemic β_2-agonists and those that received non-systemic therapy. In both age groups those patients who received systemic β_2-agonists generally had more severe disease than those who received inhaled agents alone. In the pediatric population, the systemic group had a shorter duration of symptoms prior to ED arrival (24% less than 3 hours vs. 10% less than 3 hours, $p<0.05$), with higher respiratory rates (39±16 vs. 32±11, $p\leq 0.001$), lower oxygen saturations (92±10 vs. 95±4, $p\leq 0.001$), and more severe Pulmonary Index Scores on ED presentation (6±4 vs. 4±2, $p\leq 0.001$).

Likewise, in the adult population the systemic group took more inhaled β_2-agonist therapy in the six hours prior to ED arrival (6 vs. 4, $p\leq 0.01$); and presented with higher respiratory rates (25±6 vs. 24±5, $p\leq 0.01$), lower oxygen saturations (95±3 vs. 96±3, $p\leq 0.01$), lower initial peak expiratory flow rates (187±83 vs. 225±97, $p\leq 0.001$), and lower percent predicted PEFRs (42±20 vs. 49±21, $p\leq 0.01$), than those receiving inhaled agents.

ED Course For Index Asthma Exacerbation

For the pediatric sample, those who received systemic β_2-agonists had significantly more treatments with inhaled β_2-agonists within the first hour (2 vs. 2; $p\leq 0.001$) and over the entire ED stay (4 vs. 3; $p\leq 0.0$ 1) than the non-systemic group (Table 3.7). Although not statistically significant, there were more children in the systemic group who were admitted to hospital (46% vs. 21%, $p>0.05$).

For the adult population, those who received systemic β_2-agonists had significantly more treatments with inhaled β_2-agonists within the first hour (2 vs.

2; p≤ 0.001) and over the entire ED stay (4 vs. 3; p≤ 0.01). Furthermore, there were more adults in the systemic group who received steroid therapy in the ED than in the inhalational group (92% vs. 67%, p≤ 0.001). Patients who received systemic therapy remained in the ED longer than those who received inhaled therapy alone (243 minutes vs. 180 minutes, p≤ 0.001). Finally, systemic therapy had significantly greater improvement in percent predicted PEFR compared to inhaled therapy (30±21 vs. 24±19, p≤ 0.05). More patients given inhaled treatment were discharged home (54% vs. 80%, $p<0.05$), whereas more patients given systemic β_2-agonist treatment left against medical advice (8% vs. 2%, $p<0.05$). Those patients who were given systemic treatment had higher admission rates for continued treatment than the inhaled group (32% vs. 16%, $p<0.05$).

Multivariate Analysis

A multivariate analysis of patient characteristics associated with using systemic β_2-agonists (Table 3.8) in the ED revealed the following independent factors: increasing age (OR 1.2 for each increase in age of 10 years, 95%CI: 1.0-1.3), use of oral β_2-agonists during the past four weeks (OR 1.8, 95%CI: 1.1-2.9), symptom Severity Score 4 (OR 3.3, 95%CI: 1.8-6.1), and longer ED length of stay (OR 1.1, 95%CI: 1.0-1.2). For the multivariate logistic regression model which includes both patient and site factors related to systemic β_2-agonist use in the ED there were minimal changes in each odds ratio except for an increase in OR from 3.3 to 4.0 for the most severe symptoms category. When the strongest patient factor (severity) was removed from the model the area under the ROC curve only decreased from 0.79 to 0.77.

Table 3.2 MARC ED site general characteristics

	No Systemic β_2-agonist Rx (n=37)	< 5% Systemic β_2-agonist Rx (n=23)	> 5% Systemic β_2-agonist Rx (n=17)	p
Type of ED (%)				*
General ED	73	61	94	
Pediatric ED	5	22	6	
Adult ED	22	17	0	
Emergency Medicine Residency Program (%)	79	83	76	
Public Hospital (%)	35	43	29	
Estimated Household Income, mean ± SD	28,605 ± 11,081	33,745 ± 9,347	33,474 ± 14,681	
Number of ED visits in one year				
< 40,000 visits	19	13	18	
40,000 - 59,999 visits	46	35	35	
60,000 - 79,999 visits	19	22	24	
≥ 80,000 visits	16	30	24	

ED = emergency department; IQR = interquartile range; SD = standard deviation; * $p \leq 0.05$

Table 3.3 MARC ED site asthma characteristics

	No Systemic β_2-agonist Rx (n=37)	< 5% Systemic β_2-agonist Rx (n=23)	> 5% Systemic β_2-agonist Rx (n=23)	p
No. of ED asthma visits in one year (%)				*
< 1,500 visits	58	30	33	
1,500 - 2,499 visits	23	35	13	
2,500 - 3,499 visits	16	9	27	
≥ 3,500 visits	3	26	27	
Percentage of total ED visits for asthma, median (IQR)	2.1 (1.4 - 3.2)	3.0 (1.9 - 5.9)	3.4 (2.5 - 5.1)	*
Has asthma room (%)	19	30	25	
Has guideline for managing asthma (%)	61	39	56	
Has standard form for recording asthma history and physical exam (%)	17	22	31	
Has standard form for ordering asthma treatments (%)	22	35	19	

ED = emergency department; IQR = interquartile range; SD = standard deviation

* $p \leq 0.05$, † $p \leq 0.01$, ‡ $p \leq 0.001$

Table 3.4 Demographic characteristics of patients with acute asthma

	age 2-17			age 18-54		
	Systemic β_2-agonist (n=37)	Inhaled β_2-agonist (n=1146)	p	Systemic β_2-agonist (n=107)	Inhaled β_2-agonist (n=1726)	p
Age (years), (mean, SD)	9 ± 5	8 ± 4		35 ± 10	35 ± 10	
Female (%)	46	40		36	34	
Race (%)						*
White	27	18		15	25	
Black	43	58		50	51	
Hispanic	24	22		33	21	
Other	5	2		2	2	
High School Graduate (%)	54	71	*	66	68	
Estimated Household Income, (median, IQR)	$31,008 (21,858-37,962)	$28,582 (21,858-36,608)		$23,235 (16,995 - 36,093)	$27,724 (19,675 - 37,155)	†
Insurance Status (%)						‡
Private	51	38		22	29	
Medicaid	26	31		41	27	
Other public	17	17		4	15	
None	6	14		33	30	
Primary Care Provider Status (%)	100	91		67	66	

IQR = interquartile range

* $p \leq 0.05$, † $p \leq 0.01$, ‡ $p \leq 0.001$

Table 3.5 Chronic asthma characteristics of patients with acute asthma

	age 2-17			age 18-54		
	Systemic β_2-agonist (n=37)	Inhaled β_2-agonist (n=1146)	p	Systemic β_2-agonist (n=107)	Inhaled β_2-agonist (n=1726)	p
Ever taken steroid medicine for asthma (%)	59	72		86	72	†
Ever hospitalized for asthma (%)	51	59		73	61	*
Ever intubated for asthma (%)	11	5		17	16	
Hayfever (%)	41	43		57	63	
Current smoker (%)§	18	11		30	35	
Inhaled β-agonist during past 4 weeks (%)	68	74		93	85	*
Inhaled corticosteroid during past 4 weeks (%)	33	21		51	44	
Other asthma meds during past 4 weeks (%)	35	18		46	35	*
Owns a peak flow meter (%)	39	29		36	40	
Owns a spacer (%)	44	45		36	38	
No. of urgent clinic visits in past year, median (IQR)	1 (0 - 3)	1 (0 - 3)		0 (0 - 2)	0 (0 - 2)	
No. of ED visits in past year , median (IQR)	2 (1 - 4)	2 (1 - 4)		3 (1 - 6)	2 (0 - 5)	†
Admitted for asthma in past year (%)	30	29		45	29	‡
ED usual site for problem asthma care (%)	61	63		74	74	
ED usual source of asthma prescriptions (%)	9	31	†	52	46	

SD = standard deviation; IQR = interquartile range; ED = emergency department.

* $p \leq 0.05$,† $p \leq 0.01$, ‡ $p \leq 0.001$

§ For pediatric patients, restricted to age 12-17.

Table 3.6 Acute asthma characteristics of index case

	age 2-17			age 18-54		
	Systemic β_2-agonist (n=37)	Inhaled β_2-agonist (n=1146)	p	Systemic β_2-agonist (n=107)	Inhaled β_2-agonist (n=1726)	p
ED triage time (%)						
00:00 - 7:59	19	17		24	18	
8:00 - 15:59	43	41		37	45	
16:00 - 23:59	38	42		38	37	
Duration of symptoms, (%)			*			
≤ 3 hours	24	10		16	15	
4-23 hours	49	54		51	39	
1-7 days	27	33		27	38	
>7 days	0	2		6	8	
No. of inhaled β-agonist puffs within 6 hours of ED, median (IQR) §	6 (0 - 16)	4 (0 - 12)		6 (2 - 18)	4 (0 - 12)	†
Severe symptoms (%) ¶	68	65		75	74	
Initial respiratory rate (breaths/min) , mean±S D	39 ± 16	32 ± 11	‡	25 ± 6	24 ± 5	†
Initial O2 saturation, mean ± SD	92 ± 10	95 ± 4	‡	95 ± 3	96 ± 3	†
Initial PEFR (L/min), mean ± SD	-	-		187 ± 83	225 ± 97	‡
Initial PEFR (% predicted), mean ± SD	-	-		42 ± 20	49 ± 21	†
Pulmonary Index Score, mean ± SD ¶	6 ± 4	4 ± 2	‡	-	-	

ED = emergency department; IQR = interquartile range; SD = standard deviation; PEFR = peak expiratory flow rate

* $p \leq 0.05$, † $p \leq 0.01$, and ‡ $p \leq 0.001$

§ Each nebuliser treatment was counted as equivalent to six "puffs" from a metered-dose inhaler.

¶ See Methods section for details.

Table 3.7 ED course of index asthma case

	age 2-17			age 18-54		
	Systemic β_2-agonist (n=37)	Inhaled β_2-agonist (n=1146)	p	Systemic β_2-agonist (n=107)	Inhaled β_2-agonist (n=1726)	p
No. of inhaled β-agonists in first hour, median (IQR)	2 (2 - 3)	2 (1 - 2)	‡	2 (2 - 3)	2 (1 - 2)	‡
No. of inhaled β-agonists over ED stay, median (IQR)	4 (3 - 6)	3 (2 - 4)	‡	4 (3 - 6)	3 (2 - 4)	‡
Given steroid treatment (%)	86	78		92	67	‡
Final PEFR (L/min), mean ± SD	-	-		317 ± 94	337 ± 118	
Final PEFR (% predicted), mean ± SD	-	-		71 ± 22	73 ± 24	
Change in PEFR (% predicted), mean ± SD	-	-		30 ± 21	24 ± 19	*
ED length-of-stay (minutes), median (IQR)	170 (125 - 250)	150 (110 - 207)		243 (152 - 323)	180 (126 - 257)	‡
ED disposition (%)						‡
Sent home	46	77		54	80	
Observation admission	8	2		6	3	
Hospital admission	46	21		32	16	
Other (e.g., left against medical advice)	0	1		8	2	
Sent home on systemic corticosteroids (%) ‖	75	76		87	65	†

ED = emergency department; IQR = interquartile range; SD = standard deviation; PEFR = peak expiratory flow rate

* $p \leq 0.05$, † $p \leq 0.01$, and ‡ $p \leq 0.001$

‖ Restricted to patients sent home from ED (age 2-17, n=903; age 18-54, n=1442).

Table 3.8 Predictors of Treatment with Systemic β-agonist Medication in the Emergency Department.

Patient Characteristics	Multivariate OR (95% CI) *	Multivariate OR (95% CI) †
Age (per ↑10yrs)	1.2 (1.0 - 1.3)	1.2 (1.1 - 1.3)
Female	1.1 (0.7 - 1.6)	1.2 (0.8 - 1.8)
Estimated household income (per ↑$10,000)	0.9 (0.8 - 1.1)	1.1 (0.9 - 1.3)
Other asthma medication during past 4 weeks ‡	1.2 (0.8 - 1.9)	1.2 (0.8 - 2.0)
Oral β-agonist during past 4 weeks	1.8 (1.1 - 2.9)	1.9 (1.1 - 3.2)
Symptom Duration <24 hours	1.4 (0.9 - 2.1)	1.5 (1.0 - 2.2)
Severity Score §		
1 (mild)	1.0 (reference)	1.0 (reference)
2	1.2 (0.6 - 2.5)	1.1 (0.6 - 2.4)
3	1.5 (0.8 - 3.0)	1.5 (0.8 - 3.1)
4 (severe)	3.3 (1.8 - 6.1)	4.0 (2.1 - 7.6)
ED length-of-stay (hours)	1.1 (1.0 - 1.2)	1.1 (1.0 - 1.2)

OR denotes odds ratio; CI, confidence interval; ED, emergency department

* Model includes patient characteristics only.

† Model includes patient characteristics and 3 site characteristics (type of ED, number of ED visits for asthma in one year, and percentage of total ED visits for asthma)

SECTION 3.4 DISCUSSION

This study represents the largest prospective cohort study to examine the use of systemic β_2-agonists in acute asthma. This study of North American ED patients with acute asthma demonstrates that only 5% received systemic β_2-agonist medications during their visit. Most of these were administered in the ED as subcutaneous injections however a small number also received systemic β_2-agonists prior to ED arrival. In this pre-ED group, the majority were patients who received oral β_2-agonists in the six hours prior to ED arrival, with few patients receiving SC epinephrine. Overall, systemic β_2-agonist use was low in most participating EDs; however, use did vary slightly across sites. Moreover, the use of IV ß-agonists was not observed in any patients in this study.

Through univariate analysis, adult patients who received systemic β_2-agonists were more likely to have more severe acute and chronic asthma characteristics, with more aggressive multi-drug treatment, longer ED stays, and higher admission rates than those who received inhaled treatment. Demographic, acute, and chronic asthma characteristics were essentially unremarkable between those children who received systemic therapy and those who received inhaled therapy. Multivariate analysis of all patient characteristics revealed that increasing age, use of oral β_2-agonists during the past four weeks, maximum severity scores, and ED length of stay were independent predictors of systemic β_2-agonist use. Maximum severity scores had the largest magnitude of effect on systemic β_2-agonist use. Incorporating site characteristics into the regression model only increased the magnitude of association between more severe symptoms and systemic β_2-agonist use. This observation mirrors that seen in the univariate analysis, where sites using systemic β_2-agonists were shown to have higher absolute and relative ED visits for asthma.

There exists potential inter-physician and inter-departmental variability in the way that medical teams treat asthma in the ED - this is reflected by the

distribution of sites by frequency of systemic β_2-agonist use. This may reflect the general protean recommendations regarding asthma treatment, which in turn reflects a possible lack of evidence-based summaries for their recommendations. For example, Canadian and US ED physicians are provided with clinical practice guidelines (CPG) for ED asthma treatment.[7,9] While some recommendations in the CPG are based on sound evidence-based principles (i.e. aggressive use of inhaled bronchodilators and systemic corticosteroids); the areas recommending parenteral therapy are not. These CPGs recommend that systemic β_2-agonists be introduced as second line therapy only if the patient is unresponsive to inhaled bronchodilator and systemic corticosteroid therapy (CAEP), or if the inhaled route is not practical for the patient (i.e. excessive coughing, too weak to inspire adequately, or moribund patient).[7,9] These are listed as alternative therapies paralleling inhalational anaesthetics, and IV methylxanthines. The guidelines differ slightly between countries, where the Canadian CPG describes IV salbutamol or SC epinephrine therapy[7], and the American CPG describes only SC therapy with epinephrine or terbutaline.[9]

Following the CPGs in either country, it would be expected that those patients who received systemic β_2-agonists should have more severe asthma compared to those who received non-systemic therapy. This trend was observed in the cohort under study, and consequently the use of β_2-agonists is consistent with current CPGs recommendations. However, most of the CPG recommendations for IV or SC agents originates from low grade or low levels of evidence.[14] In light of a recent systematic review and meta-analysis of the IV β_2-agonist trials, there is little evidence to support IV use in severe acute asthma - IV β_2-agonists did not demonstrate any significant differences in pulmonary functions, laboratory measures of ventilation and oxygenation, or clinically successful treatment [14]. No formal systematic review of the SC β_2-agonist literature has been completed to date, but based on the consistent lack of benefit shown with the IV β_2-agonists, it is unlikely that SC agents would differ in effect.

The lack of evidence based practice patterns by North American physicians is also reflected in the variable use of corticosteroids in this cohort. Despite the wealth of evidence supporting corticosteroid use, and the CPG recommendations that inhaled bronchodilators and corticosteroids be maximized in any cases where systemic agents are used- only 86% and 92% of the pediatric and adult populations respectively received corticosteroid agents in this study. Moreover, only 53% of the MARC sites had guidelines for managing asthma within the ED (61% at the nonuser sites, 39% at infrequent use sites, and 56% at frequent use sites). The twofold increase risk of systemic β_2-agonist use in those patients who take oral β_2-agonists reflects either a more severe form of disease requiring multi-drug therapy, or inadequate treatment of asthma. Whether these oral agents were prescribed through the ED or by another non-ED caregiver is unknown.

The absence of IV β_2-agonist use in this North American cohort warrants further discussion. Differences in CPG recommendations between countries may account for its lack of use. Intravenous formulations of β_2-agonists may not be available at all sites enrolled in the studies. Practice patterns may be dictated by what evidence exists in the medical literature within that country, and since there have been no methodologically sound clinical trials of IV β_2-agonists performed in North America its use may be limited by this fact.[14] It is possible that international research may identify different rates of IV β_2-agonist use in non-North American sites, as most clinical trials in this field have been completed in these settings.

Research into the indications and evidence for SC β_2-agonist would be helpful in clarifying the effectiveness and appropriateness of this route of administration. Also, clinicians and researchers may have to re-evaluate and possibly de-emphasize the role of systemic β_2-agonist in the management of severe acute asthma. With the knowledge of asthma as having both inflammatory and bronchospastic components, other evidence-based treatment

options should be pursued and optimized. These may include systemic or inhaled corticosteroids[15,16], inhaled ipratropium bromide[17,18], and IV magnesium.[19]

Methodological limitations

The present study has a number of potential limitations. First, MARC sites are not a random sample of EDs in North America. Since these sites are predominantly large, urban, academic institutions, these results may not be generalisable to all asthma patients. However, it is the largest cohort of patients ever sampled in the ED setting, and provides a sense of distribution of β_2-agonist use among a diverse set of sites. Second, we were unable to examine the role of interviewer factors, such as interviewer bias and training, on patient response. However, sites attempted to standardize interviews as much as possible prior to the start of the study. Third, PEFR measurement was not standardized across sites. This may add some inaccuracy to the PEFR results, but this should not systematically bias particular groups within the study. Fourth, we were unable to identify prehospital factors associated with systemic therapy in a comprehensive manner. It is unclear if the prehospital systemic therapy was in the form of self-administration of medications or via dedicated pre-hospital personnel. Fifth, ED management and the admission decision were left to the discretion of the treating emergency physician, and there were undoubtedly different approaches to acute asthma management across EDs. Intravenous salbutamol is currently unavailable in the US for the ED management of asthma, and is also not described in the US CPG for asthma. Notwithstanding these concerns, the standardized methodology, large sample, high rates of enrollment and follow-up provide the most comprehensive picture of ED acute asthma care ever reported.

SECTION 3.5 CONCLUSIONS

Systemic β_2-agonists were used in approximately 5% of acute asthma patients presenting to North American EDs. Patients receiving systemic agents had consistently more severe markers of disease across each domain of acute and chronic asthma. Moreover, patients given systemic β_2-agonists had more intensive inhaled β_2-agonist and corticosteroid therapy, with more admissions to hospital. Multivariate analysis demonstrated that increasing age, use of oral β_2-agonists during the past four weeks, maximum severity scores, and ED length of stay were independent predictors of systemic β_2-agonist use. Use of systemic agents in only severe cases complies with current North American guidelines for managing asthma, however recent evidence suggests that it is of questionable clinical value The lack of universal use of corticosteroids in all severe cases reflects practice variation and lack of adherence to current CPGs. Physicians must modify their treatments of asthma to adhere to existing evidence-based practices and optimize proven therapies.

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Section 4.1 OVERVIEW AND FUTURE DIRECTIONS

The recommendations for parenteral β_2-agonists vary slightly amongst the clinical practice guidelines put forth by the agencies involved in asthma care.[1-3] Essentially, each recommend that parenteral β_2-agonists be introduced as second line therapy only if the patient is unresponsive to inhaled bronchodilator and systemic corticosteroid therapy, or if the inhaled route is not practical for the patient (i.e. excessive coughing, too weak to inspire adequately, or moribund patient). This thesis challenges this approach and suggests that many ED physicians are not following guidelines.

Chapter One has illustrated that changes in the understanding of the pathophysiology of asthma have resulted in a re-evaluation of treatment approaches. In particular more emphasis has been placed on the treatment of the underlying inflammatory component of asthma pathophysiology. Consequently, clinical practice guidelines must reflect this shift in focus and base their methods on evidence-based summaries for each treatment that they recommend. Evidence-based medicine emphasizes the importance of relying on results from randomised trials in directing therapeutic decisions.[4] The condition of asthma is well suited for a randomized trial, which requires the condition to be common, with clear end points that occur within a relatively short period.[5]

Chapter Two is the first study to systematically review and meta-analyze the clinical trials involving IV β_2-agonists in patients with severe acute asthma that present to the ED. The pooled results fail to demonstrate a statistically significant or clinically important difference in effect between IV β_2-agonists and all other treatments. Specifically, IV β_2-agonists administered either by bolus or infusion did not lead to any significant differences in pulmonary functions, laboratory measures of ventilation and oxygenation, or clinical failure. However, although statistically nonsignificant, the findings suggest that IV β_2-

agonists produce more autonomic side effects and higher heart rates. Thus, the clinical benefit appears questionable, while the clinical risks are more obvious.

Such 'lack of difference' between the two treatment arms does not equate to 'equivalence' between the treatment arms, as much larger samples sizes would be needed to confirm the latter conclusion. The majority of the studies included in the meta-analysis have compared treatment with either IV or nebulised β_2-agonists. The issue of whether IV β_2-agonists improves the initial bronchodilator response when given in addition to nebulised bronchodilator and systemic corticosteroid therapy was addressed in only 20% (3/15) of the included studies, each using slightly different primary outcomes. Consequently, with so few papers the true effect of IV β_2-agonists administered with inhaled β_2-agonists remains unproved.

Chapter Three described the results from a large prospective cohort study, and demonstrated that parenteral β_2-agonists are rarely used in North America. Furthermore, for the 5% of patients who received parenteral therapy, the subcutaneous route was mainly used. Differences in asthma characteristics were predominantly in the adult population where those patients who received parenteral β_2-agonists had more severe acute and chronic asthma characteristics, more aggressive ED multi-drug treatment, and higher admission rates. In a multivariate analysis, increasing age, use of oral β_2-agonists during the past four weeks, maximum asthma severity scores (PEFR < 33% in adults, and Pulmonary Index Scores > 6 in children)[6], and longer ED length of stay were independent predictors of systemic β_2-agonist use.

Use of parenteral agents in only severe cases complies with current CAEP and NHAEEP CPG's for managing asthma.[1-3] However, based on the consistent lack of benefit shown with the IV β_2-agonists, it is unlikely that SC agents would differ in effect. Consequently concern is raised about the strength of the CPG recommendations in this area. Furthermore, many physicians are not following guidelines, illustrated by the variable use of corticosteroids in this cohort.

Despite the wealth of evidence supporting corticosteroid use, and the CPG recommendations that inhaled bronchodilators and corticosteroids be maximized in all severe cases (before giving parenteral agents) - only 86% and 92% of the severe pediatric and adult populations respectively received corticosteroid agents in this study. The lack of any IV β_2-agonist use in North America during the MARC trials is likely multifactorial: differences in CPG recommendations between countries; availability of intravenous formulations; physician preference; or lack of North American clinical trials on IV agents.

On the basis of these chapters there are several implications both for clinical practice and research.

Section 4.2 IMPLICATIONS FOR PRACTICE

- Based on this thesis, providing intravenous β_2-agonist either as an adjunct to or replacement of inhaled bronchodilator therapy appears to offer no clinical or statistical benefit. However, physician experience, and patient preference should also be weighed in the treatment decision.
- This thesis examined only trials with severe acute asthma patients, so the benefit in ventilated patients has not been examined.
- The utility of intravenous β_2-agonists in the pediatric population remains unclear as too few pediatric clinical trials were identified.
- The only support from this thesis for IV β_2-agonist use would be in the context of a methodologically sound clinical trial comparing IV β_2-agonists, in combination with current standard of care, versus standard of care alone.

IMPLICATIONS FOR CLINICAL PRACTICE GUIDELINES

- Clinicians must evaluate and critically appraise clinical practice guidelines to determine if they are built on a foundation of evidence-based medicine.
- Collaborators who construct clinical practice guidelines must incorporate evidence-based summaries into the framework of the guideline in a timely manner.

Section 4.3 IMPLICATIONS FOR RESEARCH

Population

- The effectiveness of IV β_2-agonists in pediatric patients with severe acute asthma exacerbation's that present to the ED remains to be determined.
- Research must identify modifiable risk factors and predictors for "near death" or "life-threatening asthma", and steps taken to improve the outpatient management of asthma.

Interventions

- Despite the strength of the findings from this review, many questions still remain regarding the optimal treatment of acute asthma presenting to the ED. For example, future methodologically sound clinical trials could be justifiable to clarify whether IV β_2-agonists improve the initial bronchodilator response when given in addition to nebulised bronchodilator (β_2-agonists +/- anticholinergics) and corticosteroid therapy (intravenous, oral, or inhaled).
- The evidence for subcutaneous routes of β_2-agonists (both selective and non-selective) must be formally evaluated via a systematic review.

Outcomes

Future research on acute asthma must concentrate on well defined outcomes which may lead to more informative overviews in the future. More specifically the following areas must be refined:

- Statistical planning and sample size calculations must be more carefully considered. Trials should be large enough to protect against type II error, and when multiple statistical tests are performed the increased risk of type I error should be addressed.
- Complete reporting of PFT data in a systematic and standardised fashion would assist in further work (i.e. reporting of % predicted PEFR and changes in %PEFR).

- The inherent variability of these PFTs, particularly in acute asthma, emphasizes the need for further research into alternative measures, particularly assessment of factors that are important to the patient.
- Standardization and complete reporting of symptom data and universal descriptions of what defines a "clinical success"
- Standardization and complete reporting of adverse reactions and side effects

Section 4.3 IMPLICATIONS FOR RESEARCH

1. British Asthma Guidelines Coordinating Committee . British guidelines on asthma management. Thorax 1997; 52:s1-s24.

2. Beveridge RC, Grunfeld AF, Hodder RV, Verbeek PR. Guidelines for the emergency management of asthma in adults. CMAJ 1996; 155:25-37.

3. Egger M, Davey-Smith G, Phillips A. Meta-analysis: principles and procedures. BMJ 1997; 315:1533-1537.

4. Olson C. Understanding and evaluating a meta-analysis. Acad Emerg Med 1994; 1:392-398.

5. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. N Eng J Med 1997; 337:536-542.

6. Becker A, Nelson N, Simons F. The pulmonary index: Assessment of a clinical score for asthma. Am J Dis Child 1984; 138:574-576.

A 2.1

Working Document

Letter to Authors and Pharmaceutical Industry

Intravenous β-Agonists for Acute Asthma in the ED
~ A Meta-Analysis ~

NAME: _____

TITLE: _____

_____

I. Are you aware of any additional studies that relate to the above mentioned paper?

[ ] Yes [ ] No

If yes, please list:

1. _____

2. _____

3. _____

4. _____

5. _____

II. Would you be able to provide feedback with respect to data extracted from your article or provide other unpublished data?

[ ] Yes, please contact me at this fax number _____.

[ ] No; however, _____ would be able to provide this service to your research team. He/she can be contacted at the following address and/or fax number:

_____

_____

_____

_____

[ ] No, I would not be able to provide feedback to you.

Please FAX back to:
Dr. Andrew Travers, Chief Resident
Division of Emergency Medicine, University of Alberta
FAX: (403) -492-9857

The following articles have been excluded from the meta-analysis:

Anonymous . Intravenous versus inhaled salbutamol. Lancet 1978; 1:80.

Arnaud A, Dugue P, Orehek J, Pommier de Santi P, Vervloet D, Charpin J. Treatment of acute asthma. Comparison of the effectiveness of corticosteroids and of a combination of corticosteroids and an adrenerguc beta-stimulant. La Nouvelle Presse Medicale 1977; 6:4183-4186.

Beswick K, Davies J, Davey A. A comparison of intravenous aminophylline and salbutamol in the treatment of acute bronchospasm. The Practitioner 1975; 214:561-566.

Blumenthal I, Tormey WP. Comparison of IV salbutamol with IV aminophylline in severe acute asthma. Arch Dis Child 1979; 54:983-987.

Boe J, Carlsson L, Hetta L, Karlson B, Ljungholm K. Acute asthma - plasma levels and effect of terbutaline intravenous injection. Eur J Resp Dis 1985; 67:261-268.

Bond D, Kalloghian A, Jenkins J, Edmonds J, Barker G. Intravenous salbutamol in the treatment of status asthmaticus in children. Crit Care Med 1984; 12:892-895.

Bruguerolle B, Philip-Joet F, Lagier F, et al. Unequal day-night terbutaline IV dosing in acute severe asthma: effect on nocturnal bronchial patency, heart rate, and arterial pressure. Chronobiology International 1991; 8:194-202.

Crompton GK. Nebulized or intravenous beta2-adrenoceptor agonist therapy in acute asthma. Eur Respir J 1990; 3:125-126.

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Evans WV, Monie RDH, Crimmins J, Seaton A. Aminophylline, salbutamol and combined intravenous infusions in acute severe asthma. Brit J Dis Chest 1980; 74:385-389.

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Herman JJ, Noah ZL, Moody RR. Use of intravenous isoproterenol for status asthmaticus in children. Crit Care Med 1983; 11:716-720.

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Hirsch SR. Intravenous therapy with terbutaline. Chest 1979; 75:648.

Intravenous infusion of salbutamol in severe acute asthma (letter). Brit Med J 1978; 1:1620-1621.

Intravenous beta-agonist in severe acute asthma. BMJ 1988; 297:1046-1047.

Iodice F, Rufulo L, Piscione F, DeMichele G. Hemodynamic and ventilatory effects of intravenous salbutamol in patients affected by COLD. Respiration 1980; 40:272-277.

Janson C, Boman D. Intravenous theophylline after beta2-agonist treatment in severe acute asthma. Effect on patients who are not treated with theophylline. Ups J Med Sci 1992; 97:149-155.

Marlin GE, Turner P. Intravenous treatment with rimiterol and salbutamol. Brit Med J 1975; 2:715-719.

May CS, Paterson JW, Spiro SG, Johnson AJ. Intravenous infusion of salbutamol in the treatment of asthma. Brit J Clin Pharmac 1975; 2:503-508.

Nogrady SG, Hartley JPR, Seaton A. Metabolic effects of intravenous salbutamol in the course of acute severe asthma. Thorax 1977; 32:559-562.

Noseda A, Yernault JC. Sympathomimetics in acute severe asthma: inhaled or parenteral, nebulizer or spacer. Eur Respir J 1989; 2:377-382.

O'Connell MB, Iber C. Continuous intravenous terbutaline infusions for adult patients with status asthmaticus. Ann Allergy 1990; 64:213-218.

Parry LW, Martorano F, Cotton E. Management of life-threatening asthma with intravenous isoproterenol infusions. Am J Dis Chil 1976; 130:39-42.

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Salmeron S, Ellrodt A, Taravella O. Sympathomimetics in acute severe acute asthma. Lancet 1995; 346:257.

Schiavi EA. Efecto agudo salbutamol intravenosos en et estado de mal asmatico. Medicina 1987; 47:39-44.

Smith SR, Kendall MJ. Potentiation of the adverse effects of intravenous terbutaline by oral theophylline. Brit J Clin Pharmac 1986; 21:451-453.

Spiro SG, Johnson AJ, May CS, Paterson JW. Effect of intravenous injection of salbutamol in asthma. Brit J Clin Pharmac 1975; 2:495-501.

Subias JE, Manrique NS, Hidalgo VM, et al. Status asthmaticus treatment: beta-agonist iv therapy experience in 71 cases. An Esp Pediatr 1989; 31:435-439.

Teoh PC. Clinical evaluation of intravenous hexoprenaline in bronchial asthma. Annals Academy of Medicine 1979; 8:144-147.

Thiringer G, Svedmyr N. Comparison of infused and inhaled terbutaline i patients with asthma. Scand J Resp Dis 1976; 57:17-24.

Ting CK, Liao MH. A comparative study of epinephrine injection and beta2-agonist inhalation in the treatment of childhood asthma. Acta Pediatrica Sinica 1991; 32:372-381.

Tirot P, Bouachour G, Varache N, et al. the use of intravenous adrenaline in acute severe asthma. Rev Mal resp 1992; 9:319-323.

Tripathi S. Management of acute bronchial asthma - intravenous terbutaline or aminophylline. J Ind Med Assoc 1989; 87:75-76.

Williams SJ, Seaton A. Intravenous or inhaled salbutamol in severe acute asthma. Thorax 1977; 32:555-558.

Wood D, Downes J, Scheinkopf H, `Lecks H. Intravenous isoproterenol in the management of respiratory arrest in childhood status asthmaticus. J Allergy Clin Immunol 1972; 50:75-81.

Wood D, Downes J. Intravenous isoproterenol in the treatment of respiratory failure in childhood status asthmaticus. Ann Allergy 1973; 31:607-610.

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Working Document

Review for Inclusion Form

Efficacy of IV beta-agonists in addition to "standard care" in acute severe asthma

Citation # _____

Reviewer: BR AJ

Please assess the following questions for each paper. The inclusion criteria are listed below, however **WHEN YOU OBTAIN ONE EXCLUSION - STOP.**

Design

[ ] **Include** only randomized controlled clinical trials.

[ ] **Exclude** all non-experimental studies (cohort study, case-control study, before-after studies, case-series, letters, reviews, etc.).

Populations

[ ] **Include** if patients (adults and/or children) were enrolled due to exacerbation of their asthma requiring additional treatment in the Emergency Department.

[ ] **Exclude** papers where the patients were inpatients, had stable asthma, were volunteers, or presented to a non-ED setting (e.g. lab).

Interventions

[ ] **Include** all primary research in which patients were treated with intravenous beta-agonists compared with placebo in the Emergency Department.

[ ] **Exclude** if intravenous beta-agonists use was not the primary research question.

Outcomes

[ ] **Include** only those studies that report admission rates and/or pulmonary function test results.

[ ] **Exclude** all studies which do not report neither admission rates, nor pulmonary function test reports.

Final Decision

[ ] Included
meets all inclusion criteria above

[ ] Excluded
has at least one exclusion

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Cochrane Collaboration Criteria for Concealment of Allocation

Criteria for Concealment of Allocation		
Grade	definition	criteria
A	adequate concealment	centralised or pharmacy controlled randomisation
		pre-numbered identical containers administered serially
		on-site computersied randomisation system unlocked after entering patients
		sequentially numbered, sealed, opaque envelopes
		other explicit schemes that provide adequate concealment
B	uncertainty about adequate concealment	merely stating table or list was used
		merely stating sealed envelopes were used
		information arousing suspicion about concealment
C	inadequate concealment	alternation, days of week
		transparent allocation procedure
D	not used as criterion	

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Jadad Validity Criteria

Methodological Assessment

Author:	_____			
Year:	_____	**Reviewer:**	AJ	CC

Please read the article and try to answer the following questions (there are no in-between answers).
See "Guidelines for Assessment" on reverse.

Was the study described as randomized ? (this includes the use of words such as randomly, random, and randomization)?

No [ ] Score 0 points
Yes [ ] Score 1 point
[ ] Score 1 additional point if the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, etc).
[ ] Deduct 1 additional point if the method to generate the sequence of randomization was described and it was inappropriate (e.g. patients were allocated alternately, or according to date of birth, hospital number, etc.)
[ ] **Subtotal$_1$**

Was the study described as double blind?

No [ ] Score 0 points
Yes [ ] Score 1 point
[ ] Score 1 additional point if the method of double blinding was described and it was appropriate (e.g. identical placebo, active placebo, dummy, etc.).
[ ] Deduct 1 additional point if the method of double blinding was described and it was inappropriate (e.g. comparison of tablet vs. injection with no double dummy)
[ ] **Subtotal$_2$**

Was there a description of withdrawals and dropouts?

No [ ] Score 0 points
Yes [ ] Score 1 point
[ ] **Subtotal$_3$**

Total Score (add Subtotals)

0 1 2 3 4 5

Adapted from Jadad et al. Assessing the Quality of Reports of Randomized Clinical Trials: Is blinding necessary? Controlled Clinical Trials 1996. Elsevier Science Inc. 17: 1-12.

Guidelines for Assessment

1. Randomization

A method to generate the sequence of randomization will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. Methods of allocation using date of birth, date of admission, hospital numbers, or alternation should not be regarded as appropriate.

2. Double Blinding

A study must be regarded as double blind if the word "double blind" is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned.

3. Withdrawals and Dropouts

Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described. The number and the reasons for withdrawal in each group must be stated. If there were no withdrawals, it should be stated in the article. If there is no statement on withdrawals, this item must be given no points.

Adapted from Jadad et al. Assessing the Quality of Reports of Randomized Clinical Trials: Is blinding necessary? Controlled Clinical Trials 1996. Elsevier Science Inc. 17: 1-12.

A 2.5

Working Document

Data Abstraction Form

Author:_____, Reference Number: _____, Year: _____

STUDY DESIGN

Asthma Definition

_____

_____

Inclusion Criteria

[1] _____ [5] _____
[2] _____ [6] _____
[3] _____ [7] _____
[4] _____ [8] _____

Exclusion Criteria

[1] _____ [5] _____
[2] _____ [6] _____
[3] _____ [7] _____
[4] _____ [8] _____

Study Design

_____

_____

Randomization

[ ]$_1$ Yes [ ]$_2$ Unclear [ ]$_3$ No

Method of Randomization

_____

_____

Concealment of Allocation

[ ]$_1$ Yes
[ ]$_2$ No

Blinding of the...

...Physician [ ]$_1$ Yes [ ]$_2$ No

...Patient [ ]$_1$ Yes [ ]$_2$ No

...Analyst [ ]$_1$ Yes [ ]$_2$ No

Author:_____, Reference Number: _____, Year: _____

POPULATION

Number of Patients		
	Iv beta agonist Rx	Comparison Rx
# patients considered for trial		
# patients meeting inclusion criteria		
# patients meeting exclusion criteria		
reasons for exclusion		

Demographics		
	Iv beta agonist Rx	Comparison Rx
Mean Age		
Standard Deviation		
Lower Limit		
Upper Limit		
Number Male		
Number Female		
Mean Weight		
Mean Height		

Mean Vital Signs (standard deviations)		
	Iv beta agonist Rx	Comparison Rx
Heart Rate		
Respiratory rate		
Blood Pressure		
SaO2		
Pulsus Paradoxus		
Pulmonary Symptomatology		
Clinical Index (if given: scores 0 - 15)		
Pulmonary Index >= 7		

Lab Investigations		
	Iv beta agonist Rx	Comparison Rx
pH		
PaO2		
PaCO2		
Glucose		
Potassium		

Pulmonary Function		
	Iv beta agonist Rx	Comparison Rx
PEFR		
% Predicted PEFR		
FEV1		
% Predicted FEV1		
FVC		
% Predicted FVC		

Author:_____, Reference Number: _____, Year: _____

IV BETA AGONIST

Prehospital Meds

	Iv beta agonist Rx	Comparison Rx
Unhaled Beta-agonists		
Anti-cholinergics		
Inhaled Steroids		
Oral Steroids		
Methylxanthine Derivatives		
Mast Cell Stabilizers		

Standard Treatment

[ ]1 O_2 by NPV (____% FiO_2)
[ ]2 salbutamol neb (____) mg every ____ min
[ ]3 hydrocortisone (____) mg iv
[ ]4 prednisone (____) mg po
[ ]5 O_2 by PPV (intubated)
[ ]6 crystalloid (NS / RL) (_____) ml iv
[ ]7 aminophylline (_____) mg/kg iv
[ ]8 O_2 by NPV (___% FiO_2)

[ ]9 other:

_____

_____

Intravenous Beta-agonist Treatment

Name	
Mean Time Given	
Bolus Dose	
Frequency	
Infusion Dose	

Comparison Treatment

Name	
Mean Time Given	
Bolus Dose	
Frequency	
Infusion Dose	
Placebo (if used)	

Other stuff...

	Iv beta agonist Rx	Comparison Rx
Cointervention description (if any)		
Contamination description (if any)		

Author:_____, Reference Number: _____, Year: _____

OUTCOME

Number of Subjects		
	Iv beta agonist Rx	Comparison Rx
Number Given Rx		
Number Followed Up		
% Follow-up		
Reason for drop outs		

Mean Vital Signs (standard deviation)						
	Heart Rate		Resp Rate		Blood Pressure	
	iv beta agonist	comparison Rx	iv beta agonist	comparison Rx	iv beta agonist	comparison Rx
15 min						
30 min						
45 min						
60 min						
90 min						
120 min						
3 hours						
6 hours						
other						

Mean Pulmonary Function (standard deviation)				
	PEFR		% Predicted PEFR	
	iv beta agonist	comparison Rx	iv beta agonist	comparison Rx
15 min				
30 min				
45 min				
60 min				
90 min				
120 min				
3 hours				
6 hours				
other				

Mean Pulmonary Function (standard deviation)				
	FEV_1		% Predicted FEV_1	
	iv beta agonist	comparison Rx	iv beta agonist	comparison Rx
15 min				
30 min				
45 min				
60 min				
90 min				
120 min				
3 hours				
6 hours				
other				

Author:_____, Reference Number: _____, Year: _____

Additional Notes

ee

A 2.6

Citations of Included Studies

Bloomfield P, Carmichael J, Petrie GR, Jewell NP, Crompton GK. Comparison of salbutamol given intravenously and by intermittent positive-pressure breathing in life-threatening asthma. Brit Med J 1979; 1:848-850.

Browne GJ, Penna AS, Phung X, Soo M. Randomised trial of intravenous salbutamol in early management of acute severe asthma in children. Lancet 1997; 349:301-305.

Cheong B, Reynolds SR, Rajan G, Ward MJ. Intravenous beta-agonist in severe acute asthma. BMJ 1988; 297:448-450.

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Van Renterghem D, Lamont H, Elinck W, Pauwels R, Van Der Straeten M. Intravenous versus nebulized terbutaline in patients with acute severe asthma: a double-blind randomized study. Ann Allergy 1987; 59:313-315.

Williams SJ, Parrish RW, Seaton A. Comparison of intravenous aminophylline and salbutamol in severe asthma. Brit Med J 1975; 4:685.

Williams SJ, Winner SJ, Clark TJH. Comparison of inhaled and intravenous terbutaline in acute severe asthma. Thorax 1981; 36:629-631.

A 2.7

Citations of Excluded Studies

Anonymous . Intravenous versus inhaled salbutamol. Lancet 1978; 1:80.

Arnaud A, Dugue P, Orehek J, Pommier de Santi P, Vervloet D, Charpin J. Treatment of acute asthma. Comparison of the effectiveness of corticosteroids and of a combination of corticosteroids and an adrenerguc beta-stimulant. La Nouvelle Presse Medicale 1977; 6:4183-4186.

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A 2.8

Figures of RevMan v3.0 MetaViews

MetaView representation WMD and OR and pooled estimate of treatment effect

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: PEFR @ 15 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Intravenous beta-agonist vs. Inhaled beta-agonist							
Bloomfield, 197	10	-137.00 (40.80)	10	-123.00 (31.60)		12.3	-14.000 [-45.986,17.986]
Swedish Society	89	-214.70 (52.80)	87	-235.30 (52.20)		40.6	20.600 [5.087,36.113]
Van Renterghe	11	-108.00 (40.80)	12	-111.00 (27.00)		15.1	3.000 [-25.543,31.543]
Subtotal (95%CI)	110		109			67.9	7.012 [-13.340,27.364]
Chi-square 4.10 (df=2) Z=0.68							
Intravenous beta-agonist vs. Intravenous methylxanthine							
Johnson, 1978	20	-146.00 (44.70)	19	-145.00 (65.40)		10.2	-1.000 [-36.335,34.335]
Williams, 1975	11	-90.00 (25.00)	9	-104.00 (27.00)		21.9	14.000 [-9.010,37.010]
Subtotal (95%CI)	31		28			32.1	9.533 [-9.748,28.815]
Chi-square 0.49 (df=1) Z=0.97							
Total (95%CI)	141		137			100.0	10.060 [-1.661,21.782]
Chi-square 4.63 (df=4) Z=1.68							

-100 -50 0 50 100
Favours Treatment Favours Control

Figure 2.1.1

Appendix

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: PEFR @ 30 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield, 197	10	-128.00 (28.70)	10	-132.00 (34.50)		26.2	4.000 [-23.815,31.815]
Swedish Society	89	-210.30 (53.80)	87	-238.80 (57.80)		39.1	28.500 [11.994,45.006]
Van Renterghe	11	-110.00 (47.80)	12	-104.00 (41.80)		18.9	-6.000 [-42.842,30.842]
Subtotal (95%CI)	110		109			84.2	13.174 [-8.438,34.785]
Chi-square 4.15 (df=2) Z=1.19							
Intravenous beta-agonist vs. intravenous methylxanthine							
Williams, 1975	11	-128.00 (53.00)	9	-118.00 (43.00)		15.8	-10.000 [-52.074,32.074]
Subtotal (95%CI)	11		9			15.8	-10.000 [-52.074,32.074]
Chi-square 0.00 (df=0) Z=0.47							
Total (95%CI)	121		118			100.0	9.480 [-10.445,29.405]
Chi-square 5.75 (df=3) Z=0.93							

-100 -50 0 50 100
Favours Treatment Favours Control

Figure 2.1.2

Appendix

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: PEFR @ 45 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield, 197	10	-124.00 (43.60)	10	-129.00 (40.20)		64.5	5.000 [-31.757,41.757]
Lawford, 1978	6	-123.30 (87.00)	7	-133.60 (71.40)		11.4	10.300 [-77.130,97.730]
Subtotal (95%CI)	16		17			75.9	5.796 [-28.088,39.680]
Chi-square 0.01 (df=1) Z=0.34							
Intravenous beta-agonist vs. intravenous methylxanthine							
Williams, 1975	11	-151.00 (72.00)	9	-131.00 (65.00)		24.1	-20.000 [-80.115,40.115]
Subtotal (95%CI)	11		9			24.1	-20.000 [-80.115,40.115]
Chi-square 0.00 (df=0) Z=0.65							
Total (95%CI)	27		26			100.0	-0.424 [-29.942,29.095]
Chi-square 0.55 (df=2) Z=0.03							

-100 -50 0 50 100
Favours Treatment Favours Control

Figure 2.1.3

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: PEFR @ 60 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield, 197	10	-137.00 (45.90)	10	-125.00 (47.80)		13.4	-12.000 [-53.074,29.074]
Cheong, 1988	37	-137.90 (37.20)	34	-149.00 (53.40)		19.4	11.100 [-10.484,32.684]
Salmeron, 1994	25	-123.00 (82.00)	22	-174.00 (90.00)		11.3	51.000 [1.526,100.474]
Swedish Society	89	-200.00 (58.50)	87	-256.20 (70.00)		20.1	56.200 [37.119,75.281]
Van Renterghe	11	-99.00 (40.80)	12	-111.00 (64.40)		12.7	12.000 [-31.693,55.693]
Subtotal (95%CI)	172		165			76.9	24.711 [-2.923,52.344]
Chi-square 15.53 (df=4) Z=1.75							
Intravenous beta-agonist vs. intravenous methylxanthine							
Johnson, 1978	20	-133.30 (46.10)	19	-150.00 (65.80)		14.9	16.700 [-19.128,52.528]
Williams, 1975	11	-161.00 (85.00)	9	-134.00 (64.00)		8.1	-27.000 [-92.357,38.357]
Subtotal (95%CI)	31		28			23.1	3.749 [-35.364,42.862]
Chi-square 1.32 (df=1) Z=0.19							
Total (95%CI)	203		193			100.0	19.420 [-3.694,42.533]
Chi-square 18.83 (df=6) Z=1.65							

-100 -50 0 50 100
Favours Treatment Favours Control

Figure 2.1.4

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: PEFR @ 120 min

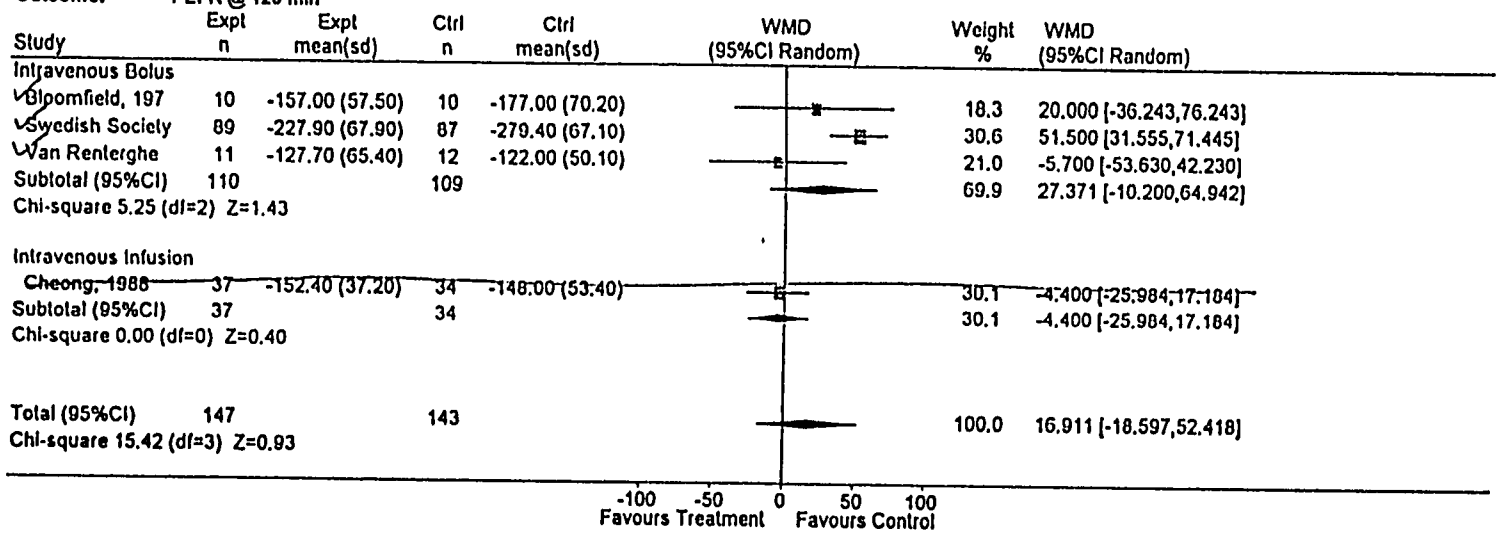

Figure 2.1.5

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: PEFR Final

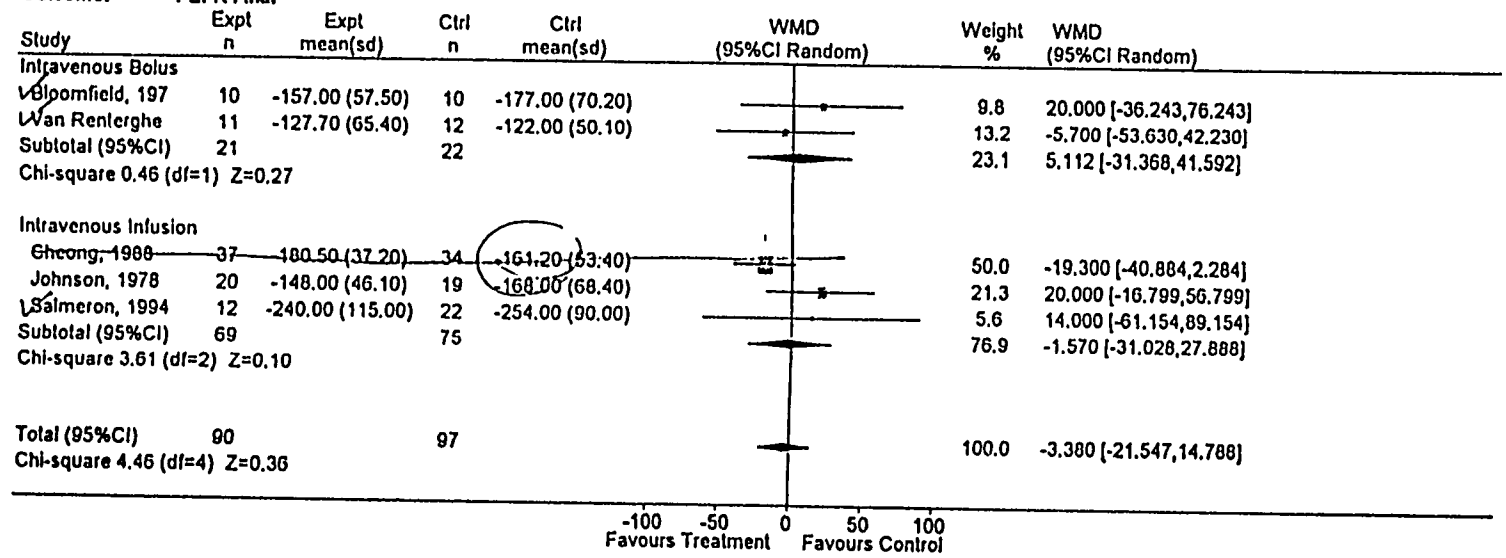

Figure 2.1.6

Appendix

Review: IV beta-agonists in acute asthma
Comparison: % Predicted PEFR Trials
Outcome: % pred PEFR at 1 hour

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Cheong, 1988	37	-31.00 (6.90)	35	-32.00 (9.10)		62.6	1.000 [-2.746,4.746]
Hussein, 1986	7	-42.00 (15.10)	7	-31.00 (10.40)		14.1	-11.000 [-24.583,2.583]
Van Renterghe	11	-21.30 (12.10)	12	-19.20 (12.10)		23.3	-2.100 [-12.000,7.800]
Total (95%CI)	55		54			100.0	-1.419 [-7.001,4.162]

Chi-square 2.96 (df=2) Z=0.50

-100 -50 0 50 100
Favours Treatment Favours Control

Figure 2.2.1

Review: IV beta-agonists in acute asthma
Comparison: % Predicted PEFR Trials
Outcome: % pred PEFR at 2 hours

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Cheong, 1988	37	-34.00 (6.90)	35	-32.00 (9.10)		87.5	-2.000 [-5.746,1.746]
Van Renterghe	11	-28.20 (12.10)	12	-21.10 (12.10)		12.5	-7.100 [-17.000,2.800]
Total (95%CI)	48		47			100.0	-2.639 [-6.142,0.865]

Chi-square 0.89 (df=1) Z=1.48

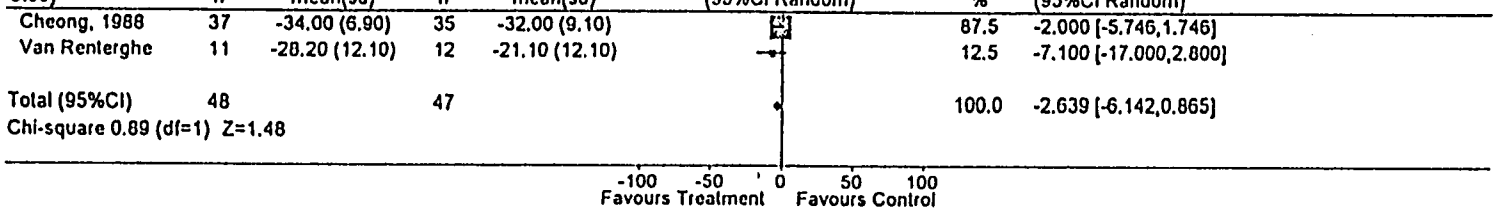

Figure 2.2.2

Review: IV beta-agonists in acute asthma
Comparison: % Predicted PEFR Trials
Outcome: % pred PEFR at 3 hours

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Cheong, 1988	37	-36.90 (6.90)	35	-33.10 (9.10)		74.4	-3.800 [-7.546,-0.054]
Hussein, 1986	7	-46.70 (21.60)	7	-31.00 (6.50)		25.6	-15.700 [-32.410,1.010]
Total (95%CI)	44		42			100.0	-6.849 [-17.032,3.333]
Chi-square 1.85 (df=1) Z=1.32							

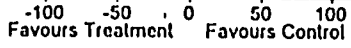

Figure 2.2.3

Figure 2.2.4

Appendix

Review: IV beta-agonists in acute asthma
Comparison: % Predicted PEFR Trials
Outcome: % pred PEFR at 6 hours

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Cheong, 1988	37	-40.40 (6.90)	35	-34.00 (9.10)		79.7	-6.400 [-10.146,-2.654]
Hussein, 1986	7	-54.00 (21.60)	7	-36.00 (10.90)		20.3	-18.000 [-35.923,-0.077]
Total (95%CI)	44		42			100.0	-8.753 [-17.095,0.390]
Chi-square 1.54 (df=1) Z=1.88							

-100 -50 0 50 100
Favours Treatment Favours Control

Appendix

Figure 2.3.1

Review: IV beta-agonists in acute asthma
Comparison: FEV1 Trials
Outcome: FEV1 at 15 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Johnson, 1978	20	-0.85 (0.21)	19	-0.82 (0.18)		48.0	-0.030 [-0.153,0.093]
Sharma 1, 1984	10	-0.85 (0.19)	10	-0.87 (0.19)		26.0	0.020 [-0.147,0.187]
Sharma 2, 1984	10	-1.24 (0.19)	10	-0.87 (0.19)		26.0	-0.370 [-0.537,-0.203]
Total (95%CI)	40		39			100.0	-0.105 [-0.190,-0.020]

Chi-square 13.33 (df=2) Z=2.43

-1 Favours Treatment 0 1 Favours Control

Review: IV beta-agonists in acute asthma
Comparison: FEV1 Trials
Outcome: FEV1 at 45 - 90 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Johnson, 1978	20	-0.80 (0.27)	19	-0.94 (0.40)		30.5	0.140 [-0.075,0.355]
Lawford, 1978	7	-1.08 (0.51)	6	-0.73 (0.22)		8.1	-0.350 [-0.767,0.067]
Sharma 1, 1984	10	-0.92 (0.31)	10	-0.93 (0.31)		19.2	0.010 [-0.262,0.282]
Sharma 2, 1984	10	-1.31 (0.31)	10	-0.93 (0.31)		19.2	-0.380 [-0.652,-0.108]
Williams, 1981	8	-0.92 (0.25)	7	-0.92 (0.24)		23.0	0.000 [-0.248,0.248]
Total (95%CI)	55		52			100.0	-0.057 [-0.176,0.062]

Chi-square 10.98 (df=4) Z=0.93

Figure 2.3.2

Review: IV beta-agonists in acute asthma
Comparison: FEV1 Trials
Outcome: FEV1 at 3 - 4 hours

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Fixed)	Weight %	WMD (95%CI Fixed)
Johnson, 1978	20	-0.97 (0.41)	19	-1.04 (0.46)		33.0	0.070 [-0.204,0.344]
Sharma 1, 1984	10	-0.89 (0.31)	10	-0.91 (0.31)		33.5	0.020 [-0.252,0.292]
Sharma 2, 1984	10	-1.17 (0.31)	10	-0.91 (0.31)		33.5	-0.260 [-0.532,0.012]
Total (95%CI)	40		39			100.0	-0.057 [-0.215,0.100]
Chi-square 3.28 (df=2) Z=0.71							

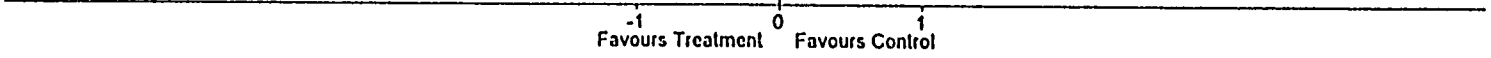

Figure 2.3.3

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: Heart Rate @ 15 min

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield, 197	10	148.00 (13.10)	10	127.00 (17.10)		15.7	21.000 [7.649,34.351]
Swedish Society	89	107.00 (14.10)	87	105.00 (14.00)		34.5	2.000 [-2.152,6.152]
Van Renterghe	11	118.00 (22.20)	12	113.00 (14.20)		13.1	5.000 [-10.384,20.384]
Subtotal (95%CI)	110		109			63.4	8.355 [-3.393,20.103]
Chi-square 7.12 (df=2) Z=1.39							
Intravenous beta-agonist vs. intravenous methylxanthine							
Johnson, 1978	20	115.00 (17.90)	19	110.00 (17.40)		19.4	5.000 [-6.080,16.080]
Williams, 1975	11	128.00 (14.00)	9	116.00 (14.00)		17.3	12.000 [-0.333,24.333]
Subtotal (95%CI)	31		28			36.6	8.126 [-0.116,16.368]
Chi-square 0.68 (df=1) Z=1.93							
Total (95%CI)	141		137			100.0	7.690 [0.867,14.512]
Chi-square 8.69 (df=4) Z=2.21							

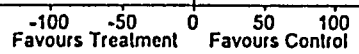

Figure 2.4.1

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: Heart Rate @ 30 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield, 197	10	136.00 (16.10)	10	126.00 (16.10)		14.2	10.000 [-4.112,24.112]
Cheong, 1988	37	105.00 (14.00)	34	101.00 (17.00)		24.6	4.000 [-3.280,11.280]
Swedish Society	89	98.00 (12.30)	87	102.40 (14.90)		30.2	-4.400 [-8.441,-0.359]
Van Renterghe	11	119.00 (17.20)	12	111.00 (15.20)		15.2	8.000 [-5.315,21.315]
Subtotal (95%CI)	147		143			84.2	2.550 [-4.690,9.791]
Chi-square 8.62 (df=3) Z=0.69							
Intravenous beta-agonist vs. intravenous methylxanthine							
Williams, 1975	11	126.00 (14.00)	9	115.00 (15.00)		15.8	11.000 [-1.825,23.825]
Subtotal (95%CI)	11		9			15.8	11.000 [-1.825,23.825]
Chi-square 0.00 (df=0) Z=1.68							
Total (95%CI)	158		152			100.0	4.028 [-2.976,11.033]
Chi-square 11.81 (df=4) Z=1.13							

-100 -50 0 50 100
Favours Treatment Favours Control

Figure 2.4.2

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: Heart Rate @ 45 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield, 197	10	129.00 (15.40)	10	120.00 (18.00)		33.5	9.000 [-5.682,23.682]
Lawford, 1978	7	135.40 (17.10)	9	104.90 (26.20)		20.8	30.500 [9.205,51.795]
Subtotal (95%CI)	17		19			54.3	18.310 [-2.570,39.190]
Chi-square 2.65 (df=1) Z=1.72							
Intravenous beta-agonist vs. intravenous methylxanthine							
Williams, 1975	11	126.00 (13.00)	9	118.00 (11.00)		45.7	8.000 [-2.520,18.520]
Subtotal (95%CI)	11		9			45.7	8.000 [-2.520,18.520]
Chi-square 0.00 (df=0) Z=1.49							
Total (95%CI)	28		28			100.0	13.017 [1.575,24.459]
Chi-square 3.59 (df=2) Z=2.23							

-100 -50 0 50 100
Favours Treatment Favours Control

Figure 2.4.3

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: Heart Rate @ 60 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield, 197	10	129.00 (12.20)	10	118.00 (19.00)		9.3	11.000 [-2.995,24.995]
Cheong, 1988	37	114.00 (17.00)	34	106.00 (15.00)		13.4	8.000 [0.555,15.445]
Hussein, 1986	9	155.00 (17.40)	9	140.00 (23.70)		6.8	15.000 [-4.209,34.209]
Salmeron, 1994	25	122.00 (18.00)	22	115.00 (19.00)		11.4	7.000 [-3.622,17.622]
Swedish Society	89	95.00 (14.10)	87	105.00 (19.60)		14.8	-10.000 [-15.054,-4.946]
Van Renterghe	11	117.00 (19.90)	12	114.00 (16.70)		8.7	3.000 [-12.086,18.086]
Subtotal (95%CI)	181		174			64.5	4.544 [-4.892,13.979]
Chi-square 25.73 (df=5) Z=0.94							
Intravenous beta-agonist vs. intravenous methylxanthine							
Johnson, 1978	20	115.40 (16.50)	19	108.00 (15.30)		11.8	7.400 [-2.581,17.381]
Tribe, 1976	11	101.00 (9.30)	12	106.60 (12.20)		12.6	-5.600 [-14.423,3.223]
Williams, 1975	11	126.00 (14.00)	9	119.00 (11.00)		11.2	7.000 [-3.959,17.959]
Subtotal (95%CI)	42		40			35.5	2.537 [-6.283,11.358]
Chi-square 4.77 (df=2) Z=0.56							
Total (95%CI)	223		214			100.0	3.645 [-2.899,10.189]
Chi-square 31.23 (df=8) Z=1.09							

-100 -50 0 50 100
Favours Treatment Favours Control

Figure 2.4.4

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: Heart Rate @ 120 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Intravenous Bolus							
Bloomfield, 197	10	118.00 (18.90)	10	123.00 (9.80)		15.1	-5.000 [-18.195,8.195]
Brown, 1997	14	152.00 (18.90)	15	142.00 (14.00)		15.7	10.000 [-2.174,22.174]
Swedish Society	89	94.00 (15.10)	87	105.00 (14.00)		19.0	-11.000 [-15.301,-6.699]
Van Renterghe	11	114.00 (14.30)	12	110.00 (13.20)		16.1	4.000 [-7.278,15.278]
Subtotal (95%CI)	124		124			65.8	-1.258 [-11.935,9.418]
Chi-square 14.56 (df=3) Z=0.23							
Intravenous Infusion							
Cheong, 1998	37	113.00 (17.00)	34	101.00 (14.00)		18.0	12.000 [4.778,19.222]
Salmeron, 1994	12	126.00 (15.00)	19	111.00 (16.00)		16.2	15.000 [3.874,26.126]
Subtotal (95%CI)	49		53			34.2	12.889 [6.832,18.947]
Chi-square 0.20 (df=1) Z=4.17							
Total (95%CI)	173		177			100.0	3.953 [-6.853,14.759]
Chi-square 45.21 (df=5) Z=0.72							

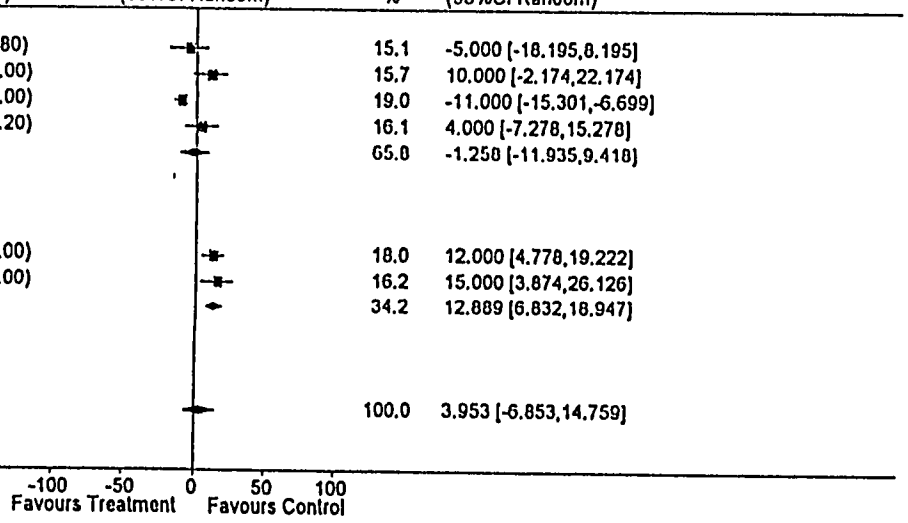

Figure 2.4.5

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: Heart Rate Final

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Intravenous beta-agonist vs. inhaled beta-agonist							
Bloomfield, 197	10	118.00 (18.90)	10	123.00 (9.80)		12.5	-5.000 [-18.195,8.195]
Browne, 1997	14	152.00 (18.90)	15	142.00 (9.80)		15.5	10.000 [-1.073,21.073]
Cheong, 1988	37	116.00 (14.00)	34	98.00 (14.40)		24.2	18.000 [11.383,24.617]
Hussein, 1986	9	152.00 (20.10)	9	138.00 (14.40)		9.5	14.000 [-2.154,30.154]
Williams, 1981	8	114.00 (8.20)	7	102.00 (9.30)		19.2	12.000 [3.069,20.931]
Subtotal (95%CI)	78		75			80.9	10.727 [3.443,18.011]
Chi-square 9.65 (df=4) Z=2.89							
Intravenous beta-agonist vs. intravenous methylxanthine							
Johnson, 1978	20	114.00 (14.30)	19	104.00 (14.40)		19.1	10.000 [0.989,19.011]
Subtotal (95%CI)	20		19			19.1	10.000 [0.989,19.011]
Chi-square 0.00 (df=0) Z=2.18							
Total (95%CI)	98		94			100.0	10.820 [5.001,16.640]
Chi-square 9.91 (df=5) Z=3.64							

-100 -50 0 50 100
Favours Treatment Favours Control

Figure 2.4.6

Appendix

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: Arterial Oxygen Tension

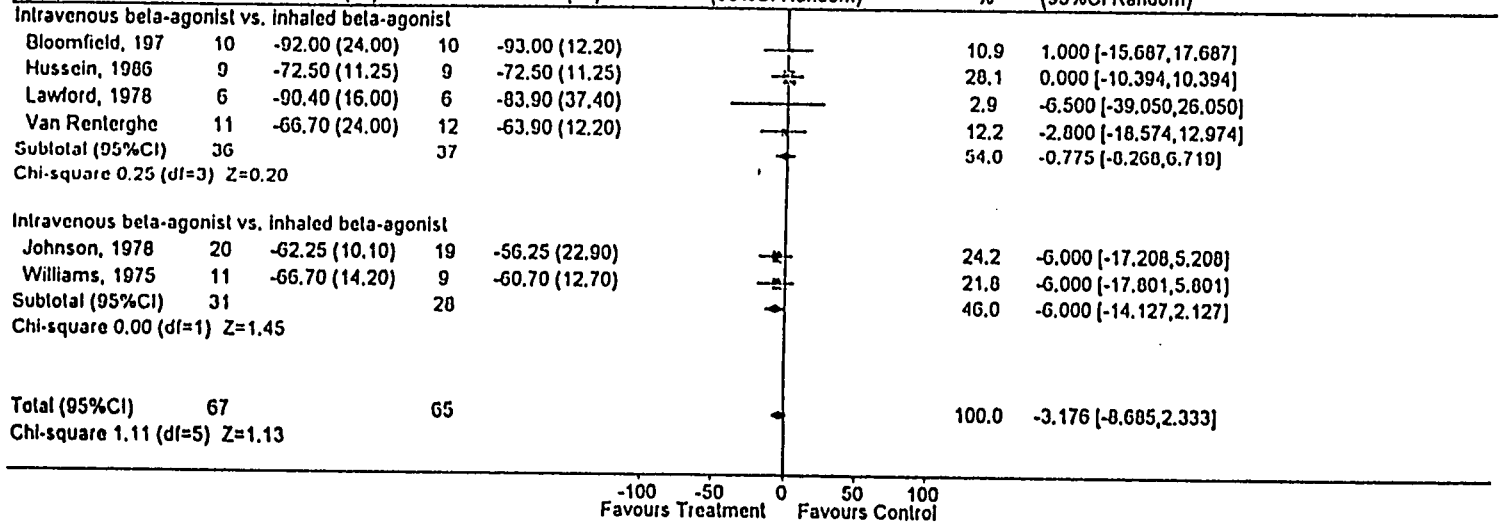

Figure 2.5.1

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: Arterial Carbon Dioxide Tension

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Intravenous beta-agonist vs. inhaled beta-agonist							
Hussein, 1986	9	30.00 (7.50)	9	30.00 (7.50)		14.0	0.000 [-6.930,6.930]
Lawford, 1978	6	36.90 (9.80)	6	36.40 (7.30)		7.1	0.500 [-9.278,10.278]
Salmeron, 1994	25	49.00 (18.00)	22	40.00 (9.00)		10.6	9.000 [1.004,16.996]
Subtotal (95%CI)	40		37			31.7	3.182 [-2.685,9.050]
Chi-square 3.13 (df=2) Z=1.06							
Intravenous beta-agonist vs. intravenous methylxanthine							
Johnson, 1978	20	38.25 (6.70)	19	37.25 (3.30)		62.3	1.000 [-2.290,4.290]
Williams, 1975	11	39.00 (6.70)	9	38.20 (15.00)		6.0	0.800 [-9.770,11.370]
Subtotal (95%CI)	31		28			68.3	0.982 [-2.159,4.124]
Chi-square 0.00 (df=1) Z=0.61							
Total (95%CI)	71		65			100.0	1.656 [-0.941,4.253]
Chi-square 3.69 (df=4) Z=1.25							

-100 -50 0 50 100
Favours Treatment Favours Control

Figure 2.5.2

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: Autonomic Side Effects

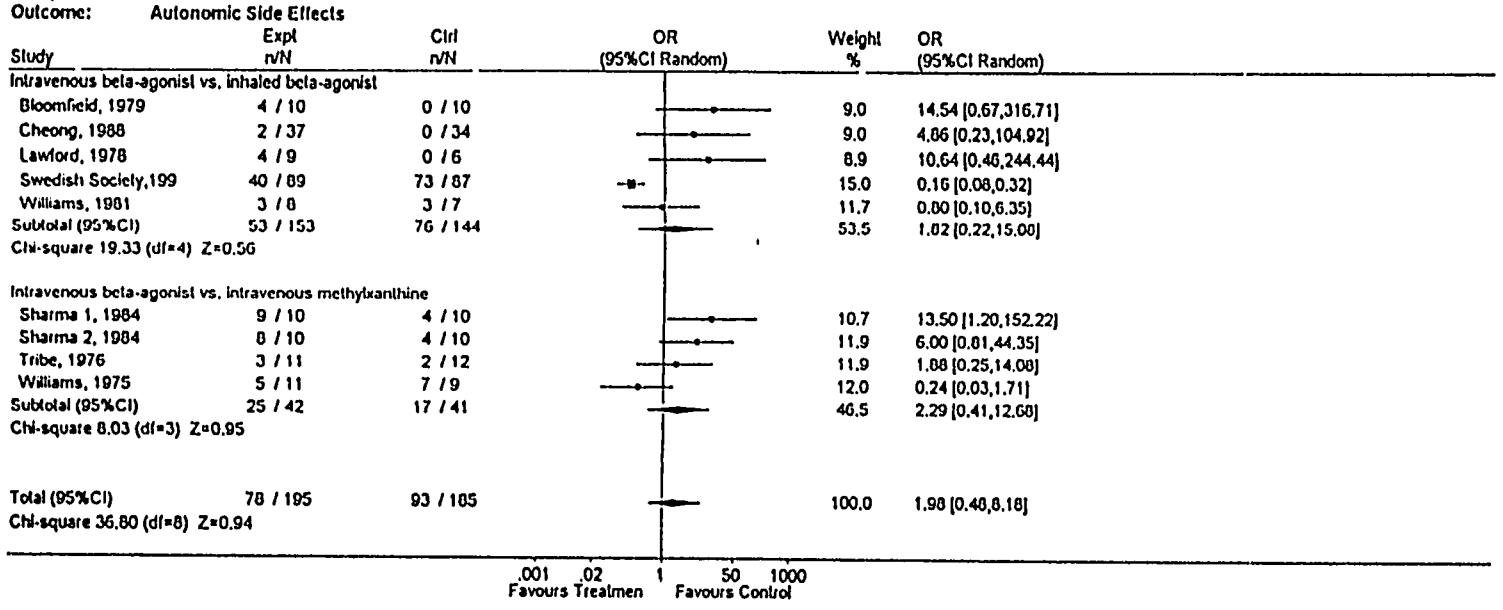

Figure 2.6

Appendix

Review: IV beta-agonists in acute asthma
Comparison: IV vs. All Treatments
Outcome: Clinical Failure

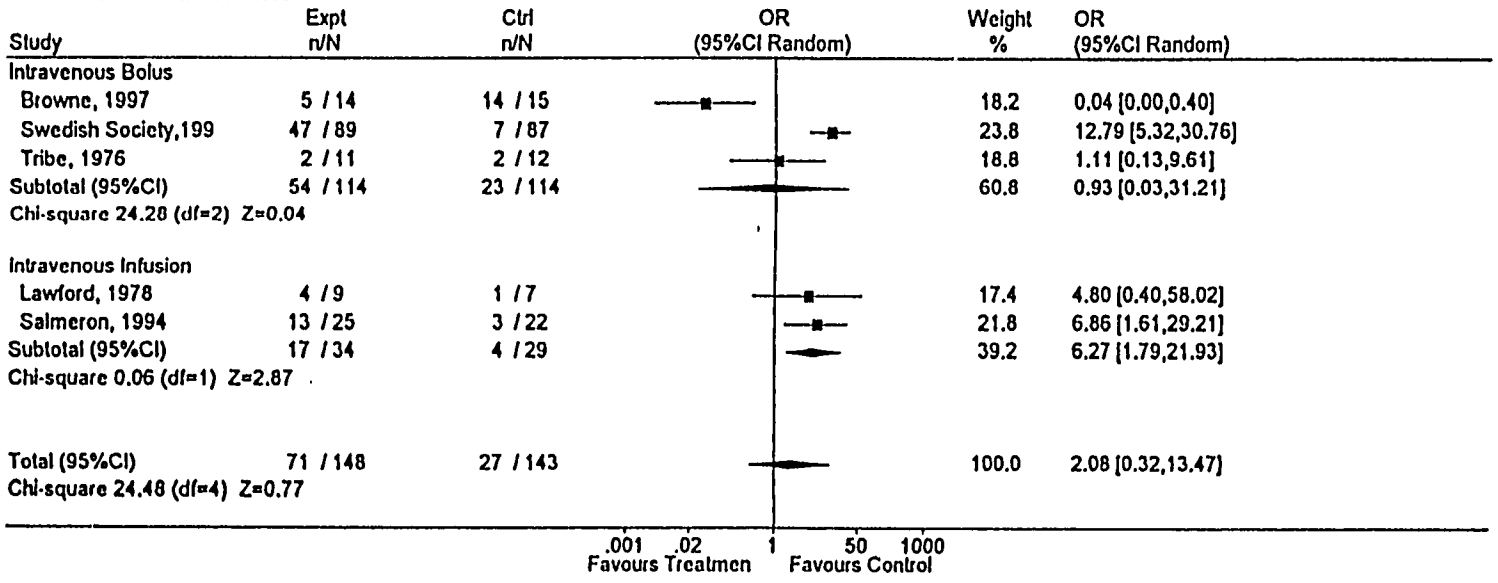

Figure 2.7

Appendix

Review: IV beta-agonists in acute asthma
Comparison: Comparison by Quality
Outcome: PEFR at 60 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Strong Methodological Quality							
Bloomfield, 197	10	-137.00 (45.90)	10	-125.00 (47.80)		13.4	-12.000 [-53.074,29.074]
Cheong, 1988	37	-137.90 (37.20)	34	-149.00 (53.40)		19.4	11.100 [-10.484,32.684]
Salmeron, 1994	25	-123.00 (82.00)	22	-174.00 (90.00)		11.3	51.000 [1.526,100.474]
Williams, 1975	11	-161.00 (85.00)	9	-134.00 (64.00)		8.1	-27.000 [-92.357,38.357]
Subtotal (95%CI)	83		75			52.2	8.295 [-17.635,34.225]
Chi-square 4.97 (df=3) Z=0.63							
Weak Methodological Quality							
Johnson, 1978	20	-133.00 (46.10)	19	-150.00 (65.80)		14.9	17.000 [-18.828,52.828]
Swedish Society	89	-200.00 (58.50)	87	-256.20 (70.00)		20.1	56.200 [37.119,75.281]
Van Renterghe	11	-99.00 (40.80)	12	-111.00 (64.40)		12.7	12.000 [-31.693,55.693]
Subtotal (95%CI)	120		118			47.8	32.670 [1.179,64.161]
Chi-square 5.80 (df=2) Z=2.03							
Total (95%CI)	203		193			100.0	19.468 [-3.634,42.570]
Chi-square 18.81 (df=6) Z=1.65							

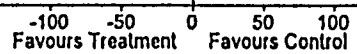

Figure 2.8.1

Review: IV beta-agonists in acute asthma
Comparison: Comparison by Quality
Outcome: PEFR at 120 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Strong Methodological Quality							
Bloomfield, 197	10	-157.00 (57.50)	10	-177.00 (70.20)		18.3	20.000 [-36.243,76.243]
Cheong, 1988	37	-152.40 (37.20)	34	-148.00 (53.40)		30.1	-4.400 [-25.984,17.184]
Subtotal (95%CI)	47		44			48.4	-1.268 [-21.419,18.883]
Chi-square 0.63 (df=1) Z=0.12							
Weak Methodological Quality							
Swedish Society	89	-227.90 (67.90)	87	-279.40 (67.10)		30.6	51.500 [31.555,71.445]
Van Renterghe	11	-127.70 (65.40)	12	-122.00 (50.10)		21.0	-5.700 [-53.630,42.230]
Subtotal (95%CI)	100		99			51.6	27.222 [-28.190,82.634]
Chi-square 4.66 (df=1) Z=0.96							
Total (95%CI)	147		143			100.0	16.911 [-18.597,52.418]
Chi-square 15.42 (df=3) Z=0.93							

-100 -50 0 50 100
Favours Treatment Favours Control

Figure 2.8.2

Review: IV beta-agonists in acute asthma
Comparison: Comparison by Quality
Outcome: PEFR Final

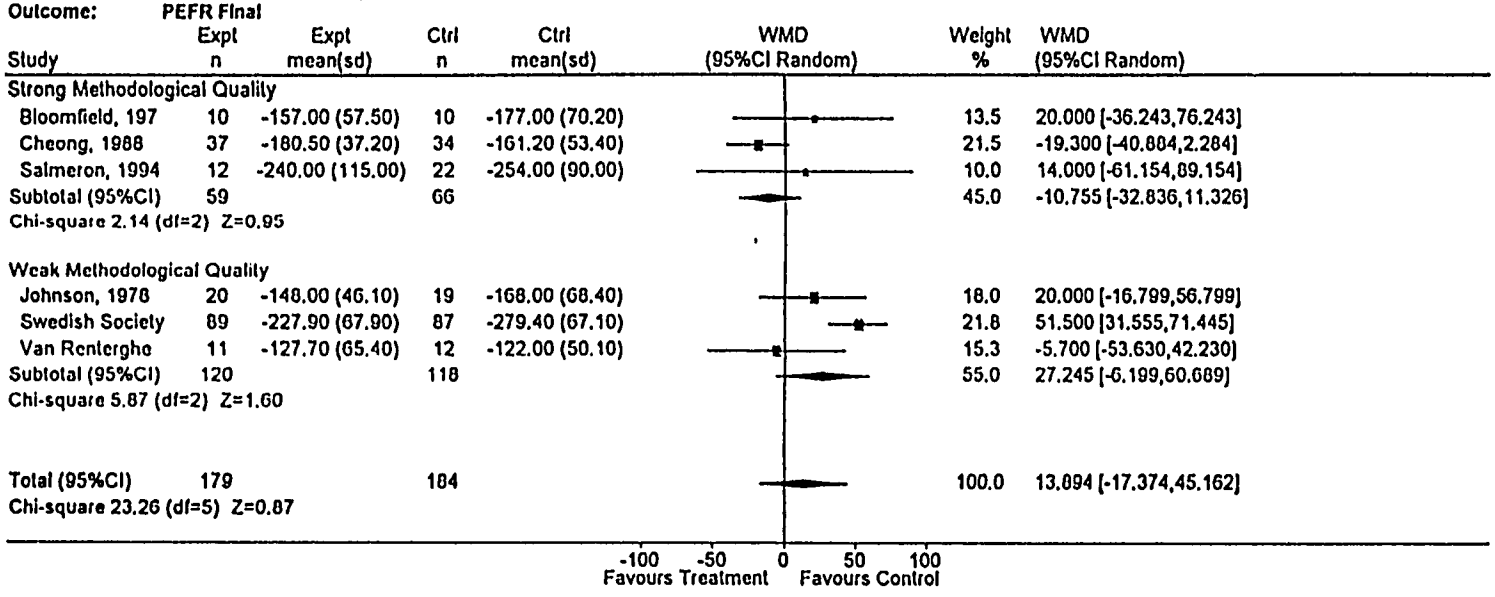

Figure 2.8.3

Review: IV beta-agonists in acute asthma
Comparison: Comparison by Quality
Outcome: Heart Rate @ 60 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Strong Methodological Quality							
Bloomfield, 197	10	129.00 (12.20)	10	118.00 (19.00)		10.0	11.000 [-2.995,24.995]
Cheong, 1988	37	114.00 (17.00)	34	106.00 (15.00)		14.4	8.000 [0.555,15.445]
Salmeron, 1994	25	122.00 (18.00)	22	115.00 (19.00)		12.2	7.000 [-3.622,17.622]
Tribe, 1976	11	101.00 (9.30)	12	106.60 (12.20)		13.5	-5.600 [-14.423,3.223]
Williams, 1975	11	126.00 (14.00)	9	119.00 (11.00)		12.0	7.000 [-3.959,17.959]
Subtotal (95%CI)	94		87			62.1	4.888 [-1.080,10.855]
Chi-square 7.12 (df=4) Z=1.61							
Weak Methodological Quality							
Johnson, 1978	20	115.40 (16.50)	19	108.00 (15.30)		12.7	7.400 [-2.581,17.381]
Swedish Society	89	95.00 (14.10)	87	105.00 (19.60)		16.0	-10.000 [-15.054,-4.946]
Van Renterghe	11	117.00 (19.90)	12	114.00 (16.70)		9.3	3.000 [-12.086,18.086]
Subtotal (95%CI)	120		118			37.9	-0.690 [-13.415,12.035]
Chi-square 10.68 (df=2) Z=0.11							
Total (95%CI)	214		205			100.0	2.806 [-3.904,9.515]
Chi-square 28.79 (df=7) Z=0.82							

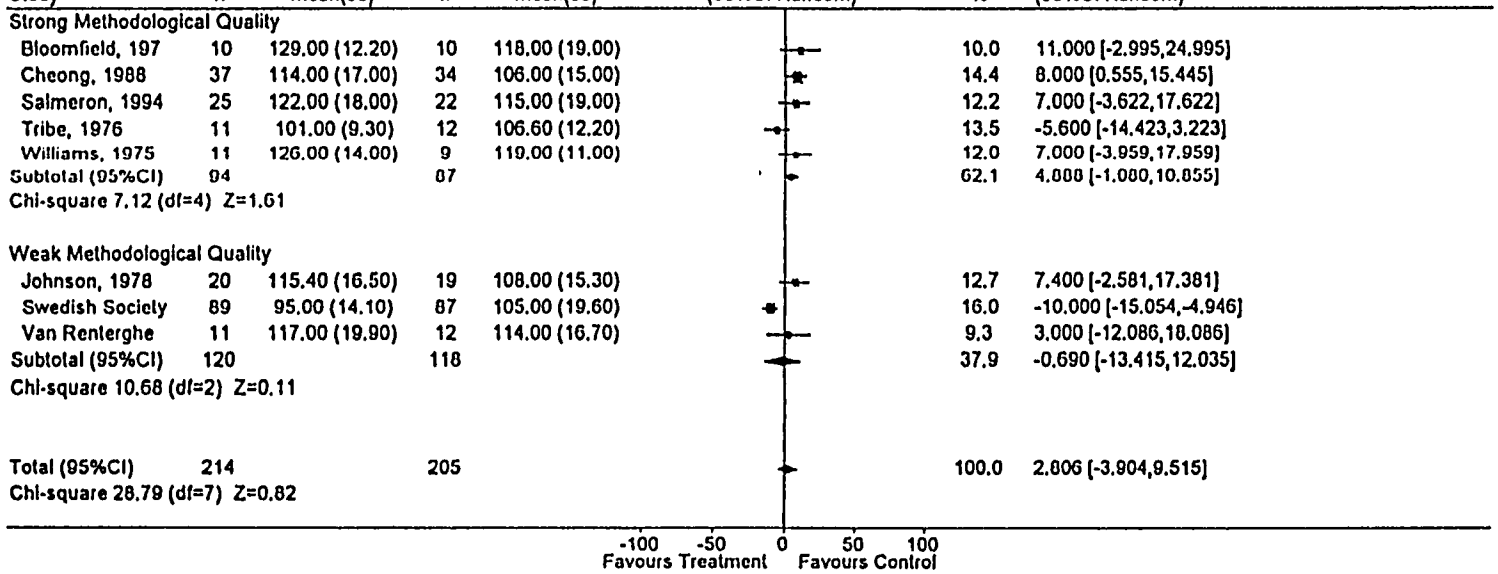

Figure 2.8.4

Appendix

Review: IV beta-agonists in acute asthma
Comparison: Comparison by Quality
Outcome: Heart Rate @ 120 minutes

Study	Expt n	Expt mean(sd)	Ctrl n	Ctrl mean(sd)	WMD (95%CI Random)	Weight %	WMD (95%CI Random)
Strong Methodological Quality							
Bloomfield, 197	10	118.00 (18.90)	10	123.00 (9.80)		15.1	-5.000 [-18.195,8.195]
Browne, 1997	14	152.00 (18.90)	15	142.00 (14.00)		15.7	10.000 [-2.174,22.174]
Cheong, 1988	37	113.00 (17.00)	34	101.00 (14.00)		18.0	12.000 [4.778,19.222]
Salmeron, 1994	12	126.00 (15.00)	19	111.00 (16.00)		16.2	15.000 [3.874,26.126]
Subtotal (95%CI)	73		78			64.9	8.920 [1.385,16.455]
Chi-square 6.03 (df=3) Z=2.32							
Weak Methodological Quality							
Swedish Society	89	94.00 (15.10)	87	105.00 (14.00)		19.0	-11.000 [-15.301,-6.699]
Van Renterghe	11	114.00 (14.30)	12	110.00 (13.20)		16.1	4.000 [-7.278,15.278]
Subtotal (95%CI)	100		99			35.1	-4.443 [-19.026,10.140]
Chi-square 5.93 (df=1) Z=0.60							
Total (95%CI)	173		177			100.0	3.953 [-6.853,14.759]
Chi-square 45.21 (df=5) Z=0.72							

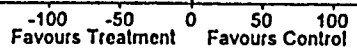

Figure 2.8.5

Review: IV beta-agonists in acute asthma
Comparison: Comparison by Quality
Outcome: Autonomic Side Effects

Study	Expt n/N	Ctrl n/N	OR (95%CI Random)	Weight %	OR (95%CI Random)
Strong Methodological Quality					
Bloomfield, 1979	4 / 20	0 / 20		11.3	11.18 [0.56,222.99]
Cheong, 1988	2 / 37	0 / 34		11.0	4.86 [0.23,104.92]
Lawford, 1978	4 / 9	0 / 6		10.8	10.64 [0.46,244.44]
Tribe, 1976	3 / 11	2 / 12		15.4	1.88 [0.25,14.08]
Williams, 1975	5 / 11	7 / 9		15.6	0.24 [0.03,1.71]
Subtotal (95%CI)	18 / 88	9 / 81		63.9	2.25 [0.49,10.39]
Chi-square 7.19 (df=4) Z=1.04					
Weak Methodological Quality					
Swedish Society,199	40 / 89	73 / 87		20.9	0.16 [0.08,0.32]
Williams, 1981	3 / 8	3 / 7		15.1	0.80 [0.10,6.35]
Subtotal (95%CI)	43 / 97	76 / 94		36.1	0.26 [0.06,1.15]
Chi-square 2.13 (df=1) Z=1.77					
Total (95%CI)	61 / 185	85 / 175		100.0	1.16 [0.28,4.89]
Chi-square 21.67 (df=6) Z=0.21					

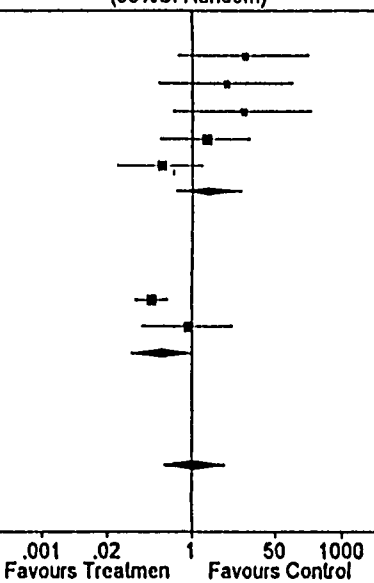

Figure 2.8.6

Review: IV beta-agonists in acute asthma
Comparison: Comparison by Quality
Outcome: Clinical Failure

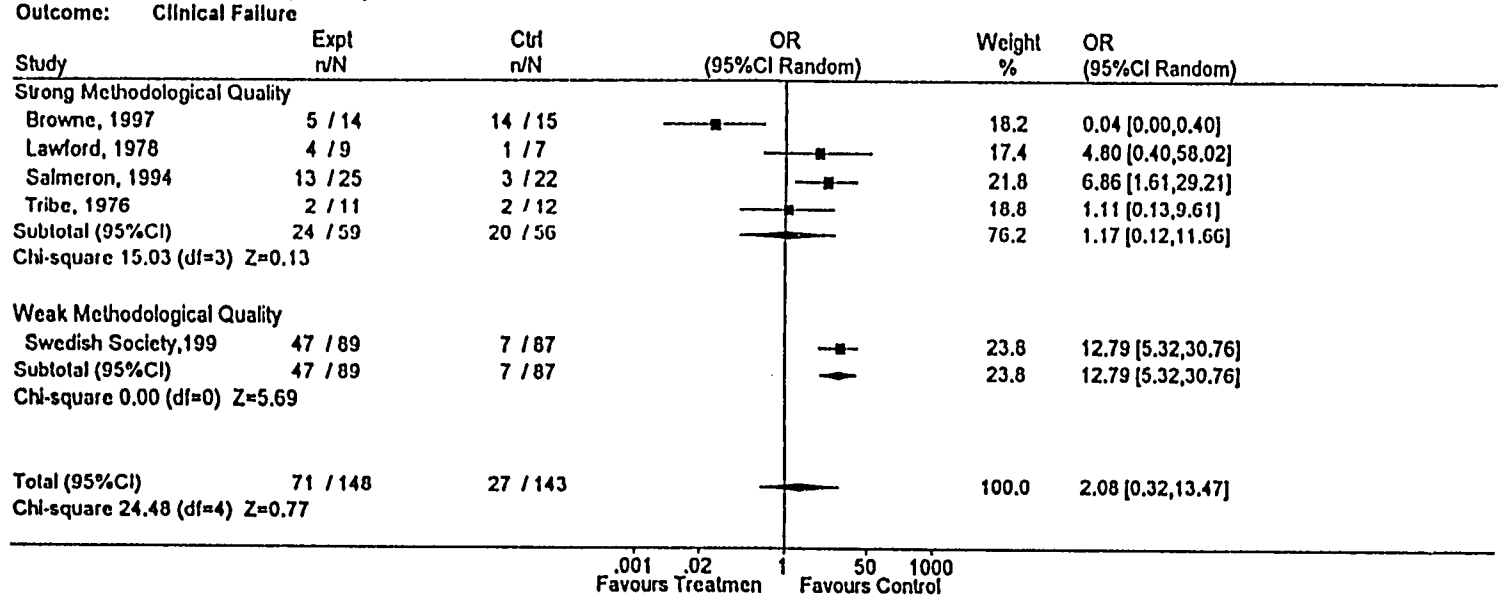

Figure 2.8.7

A 3.1

Summary of Investigators

Multicenter Asthma Research Collaboration

MARC Steering Committee:
Jill M. Baren, MD; Carlos A. Camargo, Jr., MD (Chair); Rita K. Cydulka, MD; Michael A. Gibbs, MD; Charles V. Pollack, Jr., MD; and Brian H. Rowe, MD.

Operations Committee and Data Coordinating Center:
Carlos A. Camargo, Jr., MD (Chair); Sunday Clark, MPH; Leo T. Mayer; Michael S. Radeos, MD; Caitlin R. Reed, MPhil; Anita K. Singh; and Prescott G. Woodruff, MD — all at Massachusetts General Hospital, Boston.

Principal Investigators at the 77 Participating Sites:
FC Baker III (Maine Medical Center, Portland, ME); JM Baren and S Stahmer (Hospital of the University of Pennsylvania, Philadelphia, PA); JM Basior (Buffalo General Hospital, Buffalo, NY); CA Bethel (Mercy Hospital, Philadelphia, PA); L Bielory (University Hospital, Newark, NJ); MP Blanda (Summa Health System, Akron, OH); D Bond (Grey Nun's Community Hospital, Edmonton, AB); GW Bota (Sudbury General Hospital, Sudbury, BC); ED Boudreaux (Earl K. Long Memorial Hospital, Baton Rouge, LA); BE Brenner (The Brooklyn Hospital Center, Brooklyn, NY); J Brown (Misericordia Community Hospital, Edmonton, AB); K Brown and DM Joyce (University Hospital, SUNY HSC, Syracuse, NY); CA Camargo Jr. (Massachusetts General Hospital, Boston, MA); K Camasso-Richardson (Rainbow Babies & Children's Hospital, Cleveland, OH); FL Counselman (Sentara Norfolk General Hospital, Norfolk, VA); EF Crain (Jacobi Hospital, Bronx, NY); F Cunningham and G Ramalanjaona (Newark Beth Israel Hospital, Newark, NJ); RK Cydulka (MetroHealth Medical Center, Cleveland, OH); CO Davis and A Sucov (University of Rochester Hospital, Rochester, NY); L de Ybarrondo (LBJ General Hospital, Houston, TX); DJ Dire (University of Oklahoma Medical Center, Oklahoma City, OK); MA Dolan (Medical College of Virginia, Richmond, VA); MD Dowd (Children's Mercy Hospital, Kansas City, MO); N El Sanadi (Broward General Hospital, Ft. Lauderdale, FL); SD Emond (St. Luke's/Roosevelt Hospital Center, New York, NY); F Fairfield (Sturgeon Community Hospital, St. Albert, AB); TJ Gaeta (Methodist Hospital, Brooklyn, NY); TJ Gaeta (St. Barnabas Hospital, Bronx, NY); MA Gibbs (Carolinas Medical Center, Charlotte, NC); TE Glynn (Brooke Army Medical Center, Fort Sam Houston, TX); TE Glynn (Wilford Hall Medical Center, Ft. Sam Houston, TX); LG Graff IV (New Britain General Hospital, New Britain, CT); RO Gray (Hennepin County Medical Center, Minneapolis, MN); SK Griswold (Thomas Jefferson University Hospital, Philadelphia, PA); A Guttman (Sir Mortimer B. Davis - Jewish General Hospital, Montreal, QC); JP Hanrahan (Beth Israel Hospital, Boston, MA); F Harchelroad (Allegheny General Hospital, Pittsburgh, PA); R Harrigan (Temple University Hospital, Philadelphia, PA); SE Hughes (Albany Medical College, Albany, NY); AH Idris (University of Florida Health Center, Gainesville, FL); GD Innes (St. Paul's Hospital, Vancouver, BC); ME Johnson (Jackson Memorial Hospital, Miami, FL); LW Kreplick (Christ Hospital & Medical Center, Oak Lawn, IL); EC Leibner (Detroit Receiving Hospital, Detroit, MI); S Lelyveld (University of

Chicago Hospital, Chicago, IL); LF Lobon (Beth Israel Medical Center, New York, NY); A Mangione (Albert Einstein Medical Center, Philadelphia, PA); MF McDermott (Cook County Hospital, Chicago, IL); JS Mylinski (Richland Memorial Hospital, Columbia, SC); ES Nadel (Brigham and Women's Hospital, Boston, MA); RM Nowak and H Sedik (Henry Ford Hospital, Detroit, MI); JB Orenstein (Fairfax Hospital, Falls Church, VA); E Paul (Charity Hospital, New Orleans, LA); CV Pollack Jr. (Maricopa Medical Center, Phoenix, AZ); F Qureshi (Children's Hospital of the King's Daughters, Norfolk, VA); MS Radeos (Lincoln Medical Center, Bronx, NY); DJ Robinson (University of Maryland Medical Center, Baltimore, MD); RM Rodriguez (Southwestern Medical Center, Dallas, TX); BH Rowe (University of Alberta Hospital, Edmonton, AB); G Rudnitsky (Allegheny University - MCP Division, Philadelphia, PA); RE Sapien (University of New Mexico Health Sciences Center, Albuquerque, NM); RJ Scarfone (St. Christopher's Hospital for Children, Philadelphia, PA); D Schreiber (Stanford University Medical Center, Stanford, CA); RA Silverman (Long Island Jewish Medical Center, New Hyde Park, NY); S Smith (St. Louis Children's Hospital, St. Louis, MO); H Smithline (Baystate Medical Center, Springfield, MA); D Stewart (Bronson Medical Center, Kalamazoo, MI); DM Taylor (University of Pittsburgh Medical Center, Pittsburgh, PA); CA Terregino (Cooper Hospital/University Medical Center, Camden, NJ); D Travers and JL Larson (University of North Carolina Hospitals, Chapel Hill, NC); A Walker (Royal Alexandria Hospital, Edmonton, AB); J Walter (University of Chicago Hospital, Chicago, IL); EJ Weber (UCSF Medical Center, San Francisco, CA); L White (Akron General Medical Center, Akron, OH); and JL Zimmerman (Ben Taub General Hospital, Houston, TX).

A 3.2

Working Document

Information Sheet for MARC Candidates

Capital Health Authority

Emergency Program

University of Alberta Hospitals
Medical Research Consent Form

Title of Project: Second Multicenter Asthma Research Collaboration (MARC-2x)

Principal Investigator: Brian H. Rowe, MD
Department of Emergency Medicine
Tel. (403) 492-4040

Purpose: To learn more about emergency asthma visits in adults.

Why are we doing this study?: You have been seen in the emergency room for an asthma attack. The Department of Emergency Medicine is conducting a study to learn more about the treatment of asthma, and to find out what happens to patients after we see them. Patients with asthma between 18 and 54 years old are being asked to be involved in this study. We hope following the successful completion of this study, Edmonton will be selected for further clinical asthma trials.

What do you need to do?: Nothing really, we will do everything. If you agree to be interviewed, we will talk to you for 15 minutes about your asthma. You will be asked about your medical history and how asthma affects your life. In about two weeks, we will contact you by phone and asked about your health since you left the emergency department. The telephone call will take about 5-10 minutes of your time. There will be no changes to your medication, except by your treating doctor(s).

What are the risks and benefits to you?: We do not think there are any risks nor direct benefits to you from taking part in this study. However, one possible benefit is a follow-up phone call from someone on the study team. This contact will provide you with an opportunity to discuss your asthma condition with a health care professional. The phone caller will talk to you about your asthma since we last saw you.

How do you know the information will be kept confidential?: The medical information collected from this study will be subject to the regulations of the University of Alberta. Information of a personal nature will not be part of the medical record; all information will be stored in Dr. Rowe's research files and identified only by a code number. The code connecting your name to the number will be kept in a different locked location. All data will be submitted to the coordinating centre in Boston, USA for analysis, however they will not know who you are. Members of the research team will have access to the data, but also will not be able to identify you specifically. When we present or publish the results of this research, no names will be used.

Can you withdraw or refuse to be involved?: Certainly, your involvement is voluntary, and you are free to refuse to be questioned. Also, you may stop being in the study at any time. If you refuse to be involved or stop participating, your present and future care at this hospital will not be affected.

Emergency Program
1G1 Walter C. Mackenzie Centre
8440 - 112 Street
Edmonton, Alberta, Canada
T6G 2B7

Tel: (403) 492-4040
Fax: (403) 492-9857

Do you want any more information?: You may ask questions about the study at any time. Dr. Brian Rowe at (403) 492-4040 is available to answer your questions or concerns.

If you have any further concerns about any aspect of this study, you may contact the Patient Concerns Office of the Capital Health Authority at 474-8892. This office has no affiliation with the study investigators.

You may keep a copy of this form for careful reading.

A 3.3

Working Document

Consent Sheet for MARC Candidates

Capital Health Authority

Emergency Program

Title of Project: The 2nd Multicenter Asthma Research Collaboration (MARC-2x)

Principal Investigator(s): The MARC Trials Group
Boston, USA

Co-Investigator(s): Dr. Brian H. Rowe, Edmonton, Alberta
Division of Emergency Medicine
492-4040

Part 2 (to be completed by the research subject):

Do you understand that you have been asked to be in a research study?	Yes	No
Have you read and received a copy of the attached Information Sheet?	Yes	No
Do you understand the benefits and risks involved in taking part in this research study?	Yes	No
Have you had an opportunity to ask questions and discuss this study?	Yes	No
Do you understand that you are free to refuse to participate or withdraw from the study at any time? You do not have to give a reason and it will not affect your care.	Yes	No
Has the issue of confidentiality been explained to you? Do you understand who will have access to your records?	Yes	No

This study was explained to me by: _____

I agree to take part in this study.

_____ __/__/1997 _____
Signature of Research Participant Date Witness

_____ _____
Printed Name Printed Name

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

_____ __/__/1997
Signature of Investigator or Designee Date

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH SUBJECT

Emergency Program
1G1 Walter C. Mackenzie Centre
8440 - 112 Street
Edmonton, Alberta, Canada
T6G 2B7

Tel: (403) 492-4040
Fax: (403) 492-9857

A 3.4

Working Document

MARC 2x Questionairre

VISIT FORM

Interviewer initials ____ MARC-2x Site ____

1. Patient initials (xx) __
2. ED visit date (mm/dd) __/__
3. ED triage time (hh:mm) __:__

1. yes
2. no
8's when Q does not apply
9's when response missing

4. Date of birth (mm/dd/yy. Confirm that age 18-54 at last birthday; if not, STOP). __/__/__
5. Sex 1. male 2. female __
6. Race (circle all that apply) 1. white 2. black 3. Hispanic 4. Asian 5. other _____ circle

Hello. My name is _____ and I work in the emergency department. I'd like to ask you some questions about your asthma so that we can learn ways to improve asthma treatment. Is this a good time to talk for about 10 minutes?

[If no (eg, severe dyspnea)]: Okay. I'll come back in about 20 minutes to see how you're doing.
[If yes]: Great. The questions I'll ask you have been approved by the hospital. After today's interview, in about 2 weeks, we'll call you to see how you're doing. This telephone interview will take about 5 minutes. All of your answers will be kept confidential. The study does not involve any "experimental" devices or medications. Would you like to participate in this simple but important study?
[If yes, sign Consent Forms and proceed. Give one form to patient and keep the other.]

7. Time interview began (hh:mm) __:__
[If patient Refusal, Miss, or Other problem, STOP. Please complete the RMO Form by chart review]

8. How tall are you? _____ feet _____ inches (record height in TOTAL inches) __

9. Do you have a "primary care provider" (eg, family doctor, internist, or nurse practitioner)? Y N __
[PC = coordinated, comprehensive, longitudinal care (incl. prevention). PCP usually 1 person but may be a clinic.]

If yes / If no, assign 8.

Name & location _____ text

When was your last visit with this primary care provider?
1. < 1 wk ago 2. <1 month 3. < 1 year 4. ≥ 1 year 5. have PCP but no visit yet __

10. Have you ever smoked cigarettes? 1. never smoker 2. ex-smoker 3. smoker __
[If quit smoking ≤ 28 days ago, count as smoker]

If ex-smoker or smoker / If never smoker, assign 888.

At what age did you start smoking regularly? [At what age did you stop?]
On average, how many packs do [did] you smoke per day?
[One pack = 20 cigarettes. Calculate # of lifetime pack-years = # years smoking • # packs/day] ___

11. Have you ever had hayfever or allergic rhinitis (a runny nose due to allergies)? Y N __

12. [Women only] Are you currently pregnant? Y N __

13. What is the highest grade you completed in school? __
1. 8th grade or less
2. some high school
3. high school graduate (or GED)
4. some college
5. college graduate
6. any post-graduate work

14. How old were you when a doctor first diagnosed you with asthma? (approx. age) ___

15. Have you ever been admitted overnight to a hospital because of your asthma? Y N _

If yes — If no, assign 8, 88.

When was your last overnight hospital admission because of your asthma?
1. < 1 day ago 2. <1 week 3. < 1 month 4. < 1 year 5. ≥ 1 year _

Over the past 12 months, how many times have you been admitted overnight to a hospital because of your asthma? ___

16. Over the past 12 months, how many times have you gone to a hospital emergency department because of your asthma? [Don't count current visit] ___

Over the past 12 months, how many times have you gone to a doctor's office or clinic for *urgent* treatment of your asthma? [Urgent visit = not scheduled, or scheduled < 24 hrs ahead] ___

17. Have you ever been intubated for your asthma? Y N _

18. When you are having problems with your asthma, where do you usually go?
1. primary care provider (e.g., family doctor, internist, nurse practitioner)
2. asthma specialist (e.g., pulmonologist, allergist, Asthma Clinic)
3. emergency department
4. other (specify below) _

name & location _____ text

Who usually writes your asthma medicine prescriptions? [see above list] _

19. Over the past 4 weeks, have you used a "quick relief" inhaler for your asthma? Y N
[ß-agonist MDI: eg. albuterol (Ventolin, Proventil), metaproterenol (Alupent), Primatene Mist, others]
[List does not include salmeterol (Serevent), a long-acting inhaled ß-agonist — record its use under Q23] _

If yes — If no, assign 8.

name(s) _____ Were you told by your doctor to use it:
_____ 1. everyday 2. only as needed 3. not sure _

20. In the 6 hours before you came to the ED (from ___ until ___), how many puffs did you take by inhaler? How many treatments did you get by nebulizer?
[Calculate total # of pre-ED puffs = # inhaler puffs + (# home + EMS nebs)•(6 puffs per neb)] ___

21. Over the past 4 weeks, have you used a steroid inhaler for your asthma? Y N _
[eg. triamcinolone (Azmacort), beclomethasone (Beclovent, Vanceril), flunisolide (Aerobid), fluticasone (FloVent)]

If yes — If no, assign 8, 8, 88/88.

name _____ Were you told by your doctor to use it:
1. everyday 2. only as needed 3. not sure _

On average, how often do you use your steroid inhaler?
1. almost never 2. <1/week 3. 1-3/week 4. 4-6/week 5. daily _

Did you run out of your steroid inhaler in the past week? When? (mm/dd) ___/___

MARC-2x Site ___ Pt initials ___ ED visit date ___/___

22. Over the past 4 weeks, have you taken steroid medicine for your asthma? Y N
[eg. prednisone, methylprednisolone (Medrol, SoluMedrol, DepoMedrol)] —

If yes — If no, assign 8, 88/88.

How did your doctor prescribe the steroids?
1. ≤14 day "burst" 2. chronic Rx 3. both 1 & 2 4. IM shot 5. other _____ —

[If response 1 or 3]: When was the last day you actually took it? (mm/dd) ___/___

[If no] Have you *ever* taken steroids for a severe asthma attack? Y N —

23. Over the past 4 weeks, have you used any other asthma medicines? Y N —

If yes, circle ALL that apply — If no, go to next Q.

a. salmeterol (Serevent)	e. inhaled cromolyn (Intal)	circle
b. oral ß-agonist (eg. albuterol [Ventolin, Proventil])	f. inhaled nedocromil (Tilade)	
c. inhaled anticholinergic (eg. ipratropium [Atrovent])	g. leukotriene modifier (zafirlukast, zileuton)	
d. methylxanthine (eg. theophylline [Theodur])	h. other: _____	

24. A spacer is a device that you put between your mouth and your inhaler; it helps deliver more medicine into your lungs. Do you own a spacer? Y N —

25. A peak flow meter measures how hard you can blow air out of your lungs. Do you own a peak flow meter? Y N —

If yes — If no, assign 8, 888.

On average, how often do you use your peak flow meter?
1. almost never 2. <1/week 3. 1-3/week 4. 4-6/week 5. daily —

When you're feeling well, what is your best peak flow? [Assign 999 if unknown] ____

26. How long ago did your current asthma attack begin? [time before ED triage]
1. ≤3 hrs 2. 4-12 hrs 3. 13-23 hrs 4. 1-3 days 5. 4-7 days 6. > 7 days —

27. Over the past 24 hours (from yesterday at ____ until now), how often did you experience asthma symptoms? [read options]
1 none of the time 2 some of the time 3 most of the time 4 all of the time —

Over the past 24 hours, how much discomfort or distress have you felt because of these asthma symptoms? [read options]
1 none 2 mild 3 moderate 4 severe —

That's it! Do you have any questions or comments? [pause] As you know, we're going to call you in 2 weeks to see how you're doing. What's the best number to reach you? When's the best time to call? [Consider asking for another contact if suspect difficulty with f/u call]

home tel # (___)___-____ other tel # (___)___-____

Chart Review

28. Pre-ED treatment (≤ 3 hrs before triage, *besides* inhaled ß-agonist)? Y N If yes, describe above. ___

29. Initial respiratory rate (per min) [Ideally, "initial" values are obtained before first ED neb] ___

30. Initial peak flow (L/min) [missing/not done = 999, intubated = 998, too sick = 997, refused = 996] ___

If PF done: If not done, assign 8, 88:88.

When was initial PF done? 1. before 2. during 3. after 1st neb 9. unknown ___

Actual time of initial PF (hh:mm) ___:___

31. Major, relevant, concomitant medical disorder? Y N ___
(Note: If present, ED physician must still believe that ED visit was prompted, in large part, by acute asthma.)

If yes, circle ALL that apply If no, go to next Q.

a. COPD
b. pneumonia
c. pneumothorax
d. CHF
e. significant arrhythmia (eg. SVT) _____
f. other _____

circle

32. Inhaled ß-agonist: # treatments in first 60 minutes (from time of ED triage) ___
treatments over entire ED stay ___

33. Route of inhaled treatments: 1. nebulizer 2. MDI 3. both ___

34. Steroid: 1. prednisone 2. methylprednisolone (Solu-Medrol) 3. other _____ 4. none ___

If given steroid in ED If none, assign 833, 88:88.

Dose (mg) ___

Actual time that steroid given (hh:mm) ___:___

35. Other asthma treatments? Y N ___

If yes, circle ALL that apply If no, go to next Q.

a. inhaled anticholinergic (eg. ipratropium [Atrovent])
b. subcutaneous epinephrine
c. subcutaneous ß-agonist (eg. terbutaline)
d. IV magnesium
e. IV aminophylline
f. heliox
g. non-invasive ventilation
h. intubation
i. other _____

circle

36. Discharge PF = last available value in ED (L/min) [see Q30 for coding] ___
— Actual time of "discharge" PF (hh:mm) ___:___

37. ED dispo 1. sent home 2. obsv 3. admitted 4. ama/lwt 5. died in ED 6. other _____ ___

If sent home, what were discharge medications? If obsv/etc, assign 8, 833, 8, 88, 8.

Oral steroid? 1. prednisone 2. other _____ 3. none ___
— Dose on post-ED day 1 (mg/day) ___
— Regimen: 1. tapering-dose then stop 2. fixed-dose then stop 3. other _____ ___
— Planned # days of steroid "burst" (Assign 87 if no change in chronic steroid Rx) ___
Inhaled steroid? Y N If yes, details: _____ ___