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Feasibility Study to Derive a Clinical Decision Rule for Predicting Severe Bronchiolitis

By

Dr. Amy Catherine Plint

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of the requirements for the MSc degree in Epidemiology**

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ABSTRACT

Statement of Problem: Bronchiolitis is a common childhood lower respiratory tract infection. Determining risk of developing severe disease is important.

Methods: 312 children, aged ≤ 12 months, with bronchiolitis were prospectively enrolled over 5 months at 2 emergency departments. We assessed 22 standardized variables and clinical outcome. A decision rule predicting severe bronchiolitis (apnea, intubation, pediatric ICU admission, death) was derived using χ^2 recursive partitioning techniques.

Results: 8 children (2.6 %) developed severe bronchiolitis. Age, length of breastfeeding, heart rate (HR) and systolic blood pressure outside normal, respiratory exam score, oxygen saturation, and lung atelectasis were associated ($p < 0.05$) with severe bronchiolitis.

Preliminary decision rule included (1) heart rate outside normal range and (2) oxygen saturation $< 88\%$. Rule sensitivity was 100% (95% CI 68,100) and specificity was 93% (95% CI 90,96).

Conclusion: Small sample size resulted in the rule's large CIs. Successful model development suggests a decision rule is feasible.

SUMMARY

CONTEXT: Bronchiolitis is an acute viral lower respiratory track of young children characterized by rhinorrhea, cough, wheezing, respiratory distress and often hypoxia. It is the most common lower respiratory tract infection of young children. While many studies have described risk factors for admission, no study has prospectively examined the risk factors for developing severe bronchiolitis (as defined by need for intubation, apnea, ICU admission or death) among emergency department (ED) patients. For emergency physicians, who often provide the first line of care in bronchiolitis, it would be useful to determine which children are at risk of developing severe disease. Such information would allow community emergency physicians to determine whether children need transfer to a pediatric centre as well as assist pediatric emergency physicians in determining which patients need admission for medical reasons such as risk of severe illness.

OBJECTIVES: (1) To describe the occurrence of severe bronchiolitis among children presenting to the ED and (2) to develop a preliminary decision rule predicting the development of severe bronchiolitis.

DESIGN: Prospective cohort study conducted from December 2004 to April 2005, in which children were prospectively assessed for 22 standardized clinical variables.

SETTING: Two Canadian tertiary care pediatric EDs.

STUDY POPULATION: Children presenting to the EDs with bronchiolitis, which was defined as a first episode of wheezing in a child ≤ 12 months, associated with signs of an upper respiratory track infection (such as fever, corzya, cough).

MAIN OUTCOME MEASURES: The development of severe bronchiolitis (defined as need for intubation, apnea, death and admission to a pediatric ICU). The clinical decision rule was derived using logistic regression analysis and χ^2 recursive partitioning techniques.

RESULTS: 312 of 372 eligible patients (83.9%) were enrolled. Among the study sample, 8 (2.6%) developed severe bronchiolitis. No missed, eligible patients developed severe bronchiolitis. Median age was 20 weeks (range 2 to 52 weeks) and 42% of the cohort was female. In the univariate analysis age, length of breastfeeding, heart rate (HR) and systolic blood pressure outside the normal age range, respiratory distress assessment instrument (RDAI) score, oxygen saturation on room air, and atelectasis on chest x-ray were significantly associated ($p < 0.05$) with the development of severe bronchiolitis. The preliminary decision rule (derived through recursive partitioning) included (1) HR outside normal range and (2) oxygen saturation $< 88\%$. This model had 100% sensitivity (95% CI 68,100) and 93% specificity (95% CI 90,96) for predicting the development of severe bronchiolitis. Several other models with 100% sensitivity were also developed through recursive partitioning.

CONCLUSION: Since our overall sample size and number of severe outcomes is small, the 95% CI around the preliminary decision rule's sensitivity is large. Nevertheless, our success in developing several models suggests that development of a decision rule is feasible.

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CHAPTER 1: BACKGROUND AND REVIEW OF THE LITERATURE

1.1 Introduction to the Problem

Bronchiolitis is an acute viral lower respiratory tract infection of young children characterized by rhinorrhea, cough, wheezing, respiratory distress and often hypoxia. It is the most common lower respiratory tract infection of young children and typically affects children less than one year of age (1,2). While mortality is low in high-income countries, bronchiolitis is an important illness worldwide due to the frequency with which affected infants require medical care and hospitalization, the burden on patients and families due to the length and severity of symptoms, and its possible association with the development of asthma in later life (3). Furthermore, the seasonal nature of bronchiolitis (typically occurring over the winter months) increases the impact of this disease on the health care system. In Canada 35/1000 children less than one year of age are hospitalized annually (4) and a conservative estimate is that this costs Canadian taxpayers more than \$35 million dollars per year (5). Studies show that hospitalization accounts for maximal bronchiolitis related health care expenditures (5,6). One Canadian study has also shown that, even when adjustments are made for severity, age, gender, and socio-economic status, general emergency departments have close to double the admission rate for bronchiolitis than a pediatric emergency department (43% vs. 24%) (7). A pediatric emergency department is one in which only children are treated, is an academic centre, and is typically staffed by paediatricians with fellowship training in emergency medicine. A general emergency department treats patients of all ages, may or may not be affiliated with an academic centre, and is typically staffed by physicians with greater training in adult than pediatric medicine.

The clinical course of bronchiolitis can be extremely variable. Children may develop only mild respiratory symptoms and distress, others may be require oxygen or intravenous fluids, while others may develop respiratory failure or apnea, require intubation and even die. Determining which patients are at risk for severe bronchiolitis is difficult. Many studies have described risk factors for hospital admission in bronchiolitis but patients may be admitted for various factors that are unrelated to severity of illness. There are no published studies that prospectively examine the risk factors for developing severe bronchiolitis (as defined by need for intubation, apnea, pediatric ICU admission or death) among patients presenting to an emergency department.

For emergency physicians, who often provide the first line of care in bronchiolitis, it would be useful to have a decision rule using easily available clinical variables to determine which children are at risk of developing severe disease. The discrepancy between adjusted admission rates for general emergency departments and pediatric emergency departments (7) suggest that community emergency physicians may be uncomfortable in determining which children are at risk of severe bronchiolitis. In this situation a clinical decision rules may be helpful. A clinical decision rule is commonly defined as a decision making tool that is derived from original research and incorporates three or more variables from the history, physical exam or simple tests (8). A clinical decision rule would also allow community emergency physicians to determine whether a child needs transfer to a pediatric centre, as well as assist pediatric emergency physicians in determining which children definitively need admission to a tertiary care hospital. For example, at several Canadian children's hospitals, pediatric emergency physicians must triage all children requiring admission into those requiring tertiary care and those who can be cared for in a community hospital. A decision

rule predicting development of severe bronchiolitis would allow these emergency physicians to appropriately triage these children to community hospital admission or tertiary care hospital admission.

The goal of this study is to determine the occurrence of severe disease in an outpatient cohort of patients with bronchiolitis and to develop a decision rule that will predict which patients are at risk of severe disease.

1.2 Introduction to Bronchiolitis

1.2.1 Pathophysiology of bronchiolitis:

The pathophysiology of airway obstruction in bronchiolitis has been debated. It is unclear what role bronchospasm and bronchial smooth muscle hyperreactivity play versus airway inflammation, edema and accumulation of debris in the development of clinical signs of bronchiolitis (1,9). Initial abnormalities of the lower respiratory tract in respiratory syncytial viral (RSV) related bronchiolitis include necrosis of the respiratory epithelium, destruction of ciliated epithelial cells and peribronchiolar infiltration with lymphocytes (9,10). The submucosa becomes edematous while cellular debris and fibrin form plugs within the bronchioles. There may also be host specific factors that influence the course of RSV infection.

1.2.2 Viral causes of bronchiolitis:

Respiratory syncytial virus (RSV) is the most commonly identified viral cause of bronchiolitis, detected in 40-100% of infants with bronchiolitis (11-13) hence the seasonal distribution of this disease mirrors RSV activity within a community. Of note however is that the majority of published studies examining the etiology and pathophysiology of bronchiolitis tend to concentrate on RSV (14-20). As a result, the role that other respiratory

viruses play in bronchiolitis is not as clear. Other common respiratory viruses including adenovirus, rhinoviruses, parainfluenza and influenza viruses are known to cause bronchiolitis. As well newly identified viruses such human metapneumovirus (hMPV) and coronavirus [CoV] NL63 have been associated with bronchiolitis, but to date have not been adequately studied. The role of co-infections in bronchiolitis also remains unclear but two recent studies have suggested that co-infection with RSV and hMPV are associated with increased disease severity (13,21). As new viral detection methods with high sensitivity and specificity become increasingly available, the role that common respiratory viruses and newly discovered pathogens play in the etiology and progression of bronchiolitis will be determined.

1.2.3 Clinical presentation of bronchiolitis:

Bronchiolitis is usually preceded by several days of mild symptoms such as rhinorrhea, mild cough and a low-grade fever. With time the cough becomes more severe and frequent and is often associated with choking and vomiting. Within a few days of symptom onset many develop respiratory distress. When examined these children often have tachypnea, tachycardia, accessory respiratory muscle use, wheezing and decreased air entry. If the respiratory distress worsens the infant can become hypoxic, hypercarbic and dehydrated. Many infants are also irritable, sleep and feed poorly. Although uncommon some do progress to respiratory failure, apnea and death. For the majority of children though the illness is self limited although symptoms do last for several weeks (22,23).

1.3 Treatment of Bronchiolitis

The treatment of bronchiolitis may be divided into broadly divided into supportive and drug therapy. Supportive treatment may include ensuring hydration through intravenous fluids, supplemental oxygen, or ventilation for respiratory failure and apnea. These treatments are not particularly controversial and are guided by the clinical status of the patient (IV fluids for dehydrated patients with poor oral intake, supplemental oxygen for hypoxic patients, and ventilation for those with respiratory failure and apnea).

The choice of drug therapy and the efficacy of drug therapy in bronchiolitis however is less clear. Although studies have demonstrated significant practice variation (5,22) overall, bronchodilators (used here broadly to refer to beta-agonists and epinephrine) are frequently used acutely in the emergency department and many children are prescribed these medications upon discharge (22). Furthermore, despite the lack of strong evidence supporting the use of steroids, studies have suggest that 5 to 80% of clinicians use some form of steroid treatment (22-27).

Use of epinephrine and salbutamol: Several meta-analyses of bronchodilator efficacy in bronchiolitis have been published. A meta-analysis by Flores and Horwitz evaluated eight studies that used purely β -2 agonists and found no conclusive evidence for their benefit in either outpatients or inpatients (28). Kellner et al published a meta-analysis of 15 trials in 1996 and concluded that bronchodilators produced modest short-term improvement in clinical features of mild or moderately severe bronchiolitis but did not influence oxygen saturation or hospital admission rate (29). However, this meta-analysis grouped both inpatient and outpatient studies, as well as studies utilizing albuterol or epinephrine in the treatment arm. Since inpatients likely have more severe disease or may be later in their

illness course, it is difficult to compare these groups. Furthermore, albuterol and epinephrine, although often referred to together as “bronchodilators”, may work in different ways. Albuterol results in bronchodilation through its beta-agonist properties, while epinephrine may in addition decrease mucosal edema through vasoconstriction (30). In order to address these concerns, a systematic review of nine RCTs evaluating the efficacy of epinephrine for the treatment of acute bronchiolitis (31) was completed. In this review studies were divided into outpatient and inpatient studies. Among outpatient studies there was some evidence that epinephrine is superior to placebo and salbutamol for short-term benefits but no longer-term benefits were found in hospitalized patients. While the evidence for inpatients seems to be strong with adequate sample size (32,33), the evidence for outpatients has been based on 3 studies with small sample sizes.

Use of steroids: Two meta-analysis of RCTs has been published in full (34,35). Garrison published a meta-analysis of six trials in 2000 (34). The three outcomes assessed were length of stay, duration of symptoms and clinical scores. In the combined analysis, infants treated with corticosteroids had a mean length of stay or duration of symptoms that was 0.43 days less than placebo and the effect size for mean clinical score favoured treatment. However, the study results were highly heterogeneous and only inpatients were included in the data analysis. More recently, the Cochrane Collaboration published a systematic review of 13 (35). This review included both inpatient (with length of stay and clinical score as main outcomes) and outpatient studies (clinical score, admission rate as outcomes). Marked heterogeneity of the outpatient studies limited the meta-analysis of these trials. Overall, there was a slight decrease in length of stay and improvement in clinical score favouring steroids but no difference in admission rates.

1.4 Epidemiology of Bronchiolitis

1.4.1 Burden of disease:

Bronchiolitis is the most common disease of the lower respiratory tract in children under 1 year of age (1,2). Between 1987 and 1997, Canadian hospitalization rates among infants have climbed by 55% among boys and 45 % among girls (4). Recent statistics show that admission rates in the first year of life vary regionally, ranging from 2,478 admissions/100 000 (British Columbia) to 11,162/100,000 (NWT) (4). In the United States similar statistics are found with annual bronchiolitis hospitalization rates among children less than one year of age increasing 2.4 fold from 1200/100,000 infants in 1980 to 3120/100,000 in 1996 (15). Conservative estimates of the annual cost of only RSV bronchiolitis in Canada are close to 35 million dollars (5). In the United States the annual hospital charges for RSV associated bronchiolitis among infants are estimated at 365 to 585 million dollars (36). The reason for the increasing admission rates for bronchiolitis is not clear. Several authors have postulated that it may in fact be related to changes in the evaluation and monitoring of young children with bronchiolitis rather than an increasing incidence of bronchiolitis or an increasing severity of illness (15,37). For example, the expansion of pulse oximetry use may have resulted in a lowered threshold for admission of children with mild hypoxia (15,37).

1.4.2 Bronchiolitis and the Emergency Department:

Little has been published regarding population-based estimates of Emergency Department (ED) visits for bronchiolitis. A recent study from the US using large administrative databases did attempt to estimate the number of ED visits related to RSV (38). It reported that during the RSV season (November-April) there were 22.8 ED visits per 1000 children < 1 years of age with a primary diagnosis of bronchiolitis or pneumonia. Data for

bronchiolitis visits alone was not given. More recently a large retrospective cohort study using an American administrative database estimated that among children < 2 years of age, 26 (95% CI 22-31) per 1000 visit an ED annually with bronchiolitis. Interestingly this rate appeared constant over the 8 years of the study (39). The same study also estimated that bronchiolitis accounts for 31 (95% CI 26-36) per 1000 ED visits among children < 2 years of age.

1.4.3 Spectrum of disease:

While an estimated 20 % of all infants will have RSV related bronchiolitis in the first year of life, only about 2 to 3% with this illness require hospitalization (40). Bronchiolitis-associated mortality rates in the United States have been estimated as 2.4/100,000 live births (15). Thus, it appears that the majority of children with bronchiolitis do well with this common disease. When patients are ill enough to present to the ED, reported admission rates range from 22% to 46% for bronchiolitis and/or RSV infection (7,22,38). In the only cross-Canada cohort of admitted patients with RSV infection, 16 % were admitted to the ICU, 9 % required mechanical ventilation, and 1% died (14). Other studies have given ranges of 1.5-28% of admitted patients requiring ventilation (41-44). Published data on the incidence of apnea in admitted patients with bronchiolitis ranges from 2% to 21% (18,44).

1.5 Risk factors for “Severe Disease”

1.5.1 An overview:

There have been many studies published regarding risk factors associated with “severe” disease in bronchiolitis. These studies however are limited in that most are retrospective, consider admitted patients, and often include a high proportion of children typically considered “high risk” (such as preterm infants). As well the studies have focused

primarily on RSV bronchiolitis or have included other lower respiratory tract illnesses (14, 19,20, 44-50). No study has prospectively examined an outpatient cohort with bronchiolitis to determine risk factors for severe disease. A review of the relevant studies in this area follows.

Severe bronchiolitis has often been defined as that requiring hospitalization (19,20,47,51,52) but has also been defined as requiring extended hospitalization, ICU admission, intubation, resulting in apnea, or death (18,40,44,45,53). Study designs have ranged from retrospective or prospective cohort to case control and have focused primarily on admitted patients (14,18,44-46,53-55). Studies have variably examined prematurity (19,47,51) chronic lung disease (20,48), congenital heart disease (56), and immunodeficiency (49), and consistently found that these are risk factors for severe bronchiolitis. A recent systematic review of other risk factors for severe RSV lower respiratory track infection (defined primarily as admission to hospital) concluded that male sex, age<6 months, birth during the first half of the RSV season, crowding/siblings, and day care exposure are significant risk factors (52). The authors also conclude that there was insufficient evidence to unequivocally implicate a lack of breast feeding and tobacco smoke exposures as risk factors, and that the evidence for race, socio-economic status, and malnutrition as risk factors was indeterminate. The authors suggest that future studies should collect detailed data that quantify and qualify non-medical risk factors. Other studies have also reported variation in severity according to viral agent (55) and chest x-ray findings (14). These were not examined in the systematic review.

While it is probable that admitted patients, overall, are sicker than non-admitted patients, patients may be admitted for various factors unrelated to severity of illness. In a

prospective cohort study of infants with bronchiolitis presenting to the ED, we found that that age, comorbidity, and pulse oximetry were associated with admission (22). However, the sample size did not allow us to examine which factors were associated with more severe disease, as defined above. We are unaware of any other study that has prospectively examined outpatients with bronchiolitis with regards to factors associated with admission and/or severe disease. As well, no model predicting development of severe disease has been published.

Predictors of admission or severe disease reported to date can be broadly divided into demographic factors, past medical history, environmental factors, physical exam and chest x-ray findings, and etiological agents. The following review will focus on (1) predictors of hospital admission and (2) predictors of ICU admission, intubation, apnea, or death

1.5.2 Potential predictors for hospital admission identified from the literature review:

Age, sex, and race:

Young infants appear to be at increased risk for hospitalization due to bronchiolitis and/or RSV disease. In a large retrospective cohort study (248,652 child-years) of US Medicaid patients less than 3 years of age, Boyce *et al* found that among otherwise healthy infants < 6 months of age, 4.4 hospitalizations for RSV infection occurred per 100 child-years of observations (57). Among children 6 to 12 months, only 1.5 hospitalizations occurred per 100 child-years. Similarly in a study of children less than 2 years in rural England, hospitalization rates, at least among premature infants, was greater for those under 6 months of age (9.2 % versus 6.3% overall) (41). This is further supported by a detailed review of RSV hospitalizations across several studies that found 10-28 % of infants hospitalization with RSV are < 6 weeks of age, 49-70% < 6 months of age, and 66 % to

100% < 1 year of age. This same review found that in analysing representative studies over the last 30 years that the risk ratio of boys to girls admitted to hospital was 1.425:1 (95% CI 1.40, 1.45) (52). Young infants may be at greater risk for disease requiring admission for several reasons including the absence of maternal antibodies (58), narrower airways (59), and an immature immune response (60). Since male infants have shorter and narrow airways than female infants they may be more likely to develop airway obstruction with RSV infection (59).

The effect of race on admission from bronchiolitis is not clear and may be confounded by factors such as socio-economic status, breastfeeding, household crowding, and smoke exposure. Within this limitation though several studies have shown higher rates of admission in RSV disease among Hispanic infants (39) and aboriginal infants (14,61,62) relative to white infants. As well it appears that, at least among Inuit children, the higher admission rates may not be related to a lower admission threshold (61).

Socio-economic status:

Socio-economic status may be associated with admission for bronchiolitis. In a case control study of infants < 12 months old living in an industrial area, it was found that the risk of admission significantly increased with increasing level of socio-economic deprivation. Deprivation was defined using the Townsend Score which considers unemployment, overcrowding, and not owning a home or a car as markers of socio-economic deprivation. Higher Townsend Scores reflect increasing levels of socio-economic deprivation. Children in the most deprived group were 1.5 times more likely to be admitted (and require some kind of medical intervention) than those in all other groups even when adjusted for exposure to smoke (53). Similarly, Jansson *et al* examined hospital and census data in a Swedish city and

found that found that infants living in the area with highest social burden (as measured by percentage of immigrants, per capita income, unemployment rate and socio-economic factors) were almost twice as often admitted as those from rest of city. Furthermore the severity of illness, as measured by length of oxygen treatment, among all admitted children seemed similar (63).

Medical history:

Prematurity has been repetitively found to be a risk factor for admission (19,47,51,57). In Boyce's study of Medicaid children premature infants have an increased risk of admission up to two years of age when compared to full term infants (57). This is particularly marked at less than six months of age where they have almost double the risk of hospitalization. Interestingly though the degree of prematurity *per se* appears to make less difference. For example, for infants born between 33-35 weeks gestational age (GA), RSV hospitalizations were 8.0 per 100 child-years, for those born between 29-32 weeks GA hospitalizations were 8.2 per 100 child years and for those born at ≤ 28 weeks GA the hospitalizations were 9.4 per 100 child years.

Chronic lung disease (such as bronchopulmonary dysplasia (BPD) and cystic fibrosis), congenital heart disease (CHD), and immunodeficiency have also been found to be associated with admission. In Boyce's study, infants less than 6 months of age with CHD and bronchopulmonary dysplasia had 3-12 times the admission rates of their otherwise healthy peers (57). In a Canadian cohort study of hospitalized children with RSV infection it was found that 16.4 % of infants had underlying CHD (64).

In a prospective study of 608 patients (less than 5 years of age) admitted with RSV infection, it was found that 8% had some form of immunocompromise (including chemotherapy, steroid therapy or primary immunodeficiency disorder) (65).

Environmental factors:

Childhood exposure to tobacco smoke has been shown in many studies to be associated with an increased risk for admission to hospital with respiratory illness. A meta-analysis of 13 studies found that the results of community and hospital studies consistently show that a child of a parent who smokes has an almost double the risk of being hospitalized with a lower respiratory tract infection and that even when adjusted for confounding factors the risk changes little (66). Specifically for children less than two year the combined odds ratio of hospitalization for lower respiratory tract infection was 1.71 (95% CI 1.33-2.20). Two studies have also examined urinary cotinine levels (the major metabolite of nicotine) in patients with bronchiolitis. Both showed elevated urinary levels of cotinine in children admitted to hospital with bronchiolitis as compared to those admitted with other illnesses (67,68).

While there has been no published meta-analysis examining the effect of breastfeeding on the risk of hospitalization for bronchiolitis specifically, this question has been examined for hospitalization from lower respiratory tract infection in general (69). A meta-analysis of 9 studies examining breastfeeding in healthy full term infants from industrialized nations studies found that all studies indicated a protective association between breastfeeding and risk of hospitalization from lower respiratory tract. Results from seven of these studies were pooled (all cohort studies) and the resulting summary relative risk of hospitalization for LRTI 0.28 (95% CI 0.14-0.54). When the results were adjusted for socio-

economic status and smoking, breastfeeding remained a protective factor. In a study examining the effects of an intervention to increase breastfeeding within a community, it was found over the course of the study there was an increased risk in the development of bronchiolitis in only the formula feed population than breastfeeding population (70).

Several cohort (71,72) and case-control (73-75) studies have shown that the presences of siblings (71,73,74), as well as living in large households (71-74), are independent risk factors for admission from RSV disease. Daycare attendance may also be a risk factor (71).

Physical exam findings:

While several studies have examined admitted patients to try and determine clinical criteria that may predict need for supplemental oxygen (76) or length of stay (77-79), only one study has prospectively examined risk factors for admission (22). In this study, a prospective cohort study of infants with bronchiolitis presenting to the ED, age, comorbidity, and pulse oximetry were associated with admission in a multivariate analysis. A large American retrospective cohort study (utilizing a national outpatient database) found that multivariate predictors for admission were Hispanic ethnicity and urgent/emergent status at triage (39).

1.5.3 Potential predictors of severe disease identified from the literature review:

While there are many studies that have examined risk factors for hospital admission with bronchiolitis, fewer have examined risk factors for ICU admission, intubation, apnea, and death due to bronchiolitis.

ICU admission and mechanical ventilation:

Perhaps one of the best studies of predictors of severe RSV disease is the PICNIC (Pediatric Investigators Collaborative Network on Infections In Canada) study (14). This prospective cohort study at 7 pediatric tertiary care hospitals included 689 admitted patients with RSV lower respiratory track infection. They found that aboriginal race (First Nations or Inuit), age < 6 weeks, underlying lung disease, hypoxia on admission, pulmonary consolidation on chest x-ray at admission, and history of apnea or respiratory arrest prior to admission were independently associated with an increased risk of ICU admission. Only the latter three factors were independently associated with mechanical ventilation. Similarly in a retrospective cohort of 3308 children admitted to a children's hospital with RSV infection, those admitted to the PICU were more likely to have a history of prematurity, age < 6 weeks, congenital heart disease, neurological disease, multiple congenital anomalies and metabolic disease (80). In a smaller prospective study of 102 patients with RSV infection (81) age, weight on admission, and prematurity were associated with the need for mechanical ventilation in the univariate analysis, however in a multivariate analysis only low weight was an independent risk factor (infants less than 5 kg, the relative risk was 4.4). A cohort study (that included both a retrospective and prospective component) of 636 infants less than one year of age admitted to hospital with bronchiolitis found that ICU admission was more common among premature infants and those with documented RSV infection (82). Finally in a retrospective cohort study of admitted RSV bronchiolitis patients, Chan *et al* found that prematurity (gestation age < 37 weeks) to be the only independent risk factor associated with mechanical ventilation (OR 1.14, 95 CI 1.02-2.07) (46).

Apnea:

Few studies have examined risk factors for the development of apnea. One, a retrospective cohort study of 179 admitted infants with RSV infection, found that age less than 2 months of age to be the strongest independent risk factor (18). A case controlled study by Meert *et al* found that otherwise previously healthy premature infants with RSV infection were more likely to present with apnea than health term infants (83). These findings were echoed by Church *et al* who found among their cohort of 261 admitted infants with RSV that apnea was more common among younger children and those born prematurely (≤ 37 weeks gestation) (84).

Mortality:

One large administrative database study has examined risk factors for bronchiolitis-associated deaths among infants in the United States (85). It found that the majority of deaths due to bronchiolitis occurred among infants aged 1-3 months of age and among normal birth weight. Univariate risk factors related to the infant included birth weight < 2500 g, birth weight < 1500 g, black race, prematurity, a low 5 min Apgar score, multiple births and a high live birth order. Maternal risk factors included receiving little prenatal care, young (<925 years) age, tobacco use and lower educational level. In the multivariate analysis, very low (<1500 g) and low birth weight (<2500 g) were most strongly associated with increased risk for death. A similar study among infants with RSV infection found that prematurity and low birth weight significantly increased RSV mortality rates (86).

Viral etiology, co-infections and bronchiolitis severity:

The role of viral etiology in predicting severity of bronchiolitis has, in the past, been hampered by a lack of sensitive detection methods (87). The advent of nucleic acid

amplification (NAA) technology has revolutionized the field of diagnostic virology by expediting the detection of viruses and increasing the sensitivity of detection. Using this technique, the role of respiratory viruses other than RSV in bronchiolitis is now being examined. Using NAA techniques, Andreoletti studied respiratory specimens from infants admitted to hospital with bronchiolitis and observed dual infections with any two of RSV, rhinoviruses, enteroviruses, and adenoviruses in 21.4% of tested specimens, but did not assess the impact of these on severity of illness (88). In a study of the role of rhinoviruses in acute bronchiolitis, Papadopoulos reported that successive or concomitant infection with RSV and rhinovirus increased the severity of bronchiolitis 5-fold. Two recent publications provide compelling evidence that hMPV-RSV coinfection leads to increased severity of bronchiolitis in infants (89). Greensill reported that in a study of 30 infants with bronchiolitis, 70% of those with illness severe enough to require admission to the pediatric ICU and ventilatory support were found to be RSV and hMPV positive (13). Semple studied bronchiolitis patients under 2 years of age admitted to hospital in Liverpool, and observed that dual infection with hMPV and RSV was strongly associated with increased severity of illness, leading to a 10-fold increase in the relative risk of admission to a pediatric ICU for mechanical ventilation (21). More work is required to define and clarify the contribution of multiple virus infections in the progression and severity of bronchiolitis.

1.6 Methodological Standards for Clinical Decision Rules:

A clinical decision rule is commonly defined as a decision making tool that is derived from original research and incorporates three or more variables from the history, physical exam or simple tests (8,90). Methodological standards have now been proposed for the

development and validation of clinical decision rules (8,90). These standards were summarized in 1997 by Laupacis (8) as follows:

- a) The outcome should be clearly defined and clinically important.
- b) The presence or absence of an outcome should ideally be determined without knowledge of the predictor variable. If the outcome is not subjective (for example, death) blinding is of less importance.
- c) Predictive variables should be assessed prior to the knowledge of the outcome, clearly defined, clinically sensible, and reproducible.
- d) The study population should be representative of the target population. It must be selected in a non-biased fashion.
- e) The statistical methods used for deriving the rules must be defined.
- f) The decision rules must be sensible. They should have a clear purpose, be clinically relevant, be valid, and easy to remember.
- g) The accuracy of the decision rules needs to be established. The sensitivity and specificity of the rule must be reported.
- h) The rule should be prospectively validated on a new, separate patient population.
- i) The rule should be implemented to determine its true effect on patient care.

1.7 Rationale for the Study

Bronchiolitis is the most common disease of the lower respiratory tract during the first year of life. Over twenty percent of children develop this infection in the first year of life with 35/1000 children (≤ 12 months) hospitalized annually with the illness. Symptoms include nasal congestion, cough, wheezing, and at times respiratory distress. While most children with bronchiolitis do well, a small proportion become very ill – requiring admission

to intensive care units, ventilatory support, having apneic episodes and even dying. There have been many studies that describe risk factors for hospital admission in bronchiolitis but patients may be admitted for various factors unrelated illness severity. To our knowledge this is the first study to prospectively examine the risk factors for developing severe bronchiolitis (as defined by need for intubation, apnea, pediatric ICU admission or death) among patients presenting to the emergency department.

For emergency physicians, who often provide the first line of care in bronchiolitis, it would be useful to have a decision rule using easily available clinical variables to determine which children are at risk of developing severe disease and which children are not. The discrepancy between adjusted admission rates for general emergency departments and pediatric emergency departments suggest that community emergency physicians may be uncomfortable in determining which children are at risk of severe bronchiolitis and that a clinical decision rule would be useful. A clinical decision rule would also allow community emergency physicians to determine whether a child needs transfer to a pediatric centre, as well as assist pediatric emergency physicians in determining which children definitively need admission to a tertiary care hospital.

CHAPTER 2: HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

We hypothesize that the subset of infants with bronchiolitis that will develop severe disease can be predicted in the emergency department with a clinical decision rule based on available clinical patient variables.

2.2 Objectives

- (1) To determine the proportion of children with bronchiolitis presenting to the Emergency Department that go on to develop severe bronchiolitis, defined as need for intubation, apnea, ICU admission, or death.
- (2) To develop a decision rule for predicting which children with bronchiolitis are at risk of severe bronchiolitis.

CHAPTER 3: METHODS

3.0 Study Design

The feasibility study which comprises this thesis (“Severity Study”) was conducted as a prospective cohort and occurred in conjunction with a multi-centre randomized controlled trial (RCT) of interventions in bronchiolitis (the Canadian Bronchiolitis Epinephrine Steroid Trial or CanBEST). Dr. Amy Plint, the principal investigator (PI) on the Severity Study, is the nominated PI for CanBEST.

3.1. Description of CanBEST Methodology

3.1.1 Study design: CanBEST is a randomized, double blind trial with a 2 by 2 factorial design. The four study groups are (1) oral dexamethasone plus nebulized epinephrine, (2) oral placebo plus nebulized epinephrine, (3) oral dexamethasone plus nebulized placebo, and (4) oral placebo steroid plus nebulized placebo.

3.1.2 Study period: CanBEST will enroll patients over three bronchiolitis seasons (December 1st, 2004 to April 30th 2005, December 1st, 2005 to April 30th 2006, and December 1st 2006 to April 30th 2006).

3.1.3 Study population: Children presenting with bronchiolitis are enrolled from Emergency Departments (ED) of eight children’s hospitals across Canada. Bronchiolitis is defined as the first episode of wheezing, in a child less than 12 months, associated with signs of an upper respiratory track infection during the period deemed to be peak season for RSV bronchiolitis (December to April).

3.1.4 Inclusion criteria:

(1) Age 6 weeks to 12 months. Children less than 6 weeks are not enrolled due to the risk of concomitant infection (91). Children over 12 months are not enrolled to minimize the risk of enrolling children with their first episode of asthma.

(2) Respiratory distress assessment instrument (RDAI) score of > 3 and ≤ 15 (Figure 1).

This range of RDAI ensures enrollment of children with a range of respiratory distress but excluding the extremes – those with mild and severe respiratory distress.

3.1.5 Exclusion criteria:

(1) Previous diagnosis of asthma by a physician.

(2) Any previous episode of wheezing and/or cough treated with bronchodilators.

(3) Previous episode of wheezing confirmed by a physician.

(4) Chronic disease that may affect cardiopulmonary status of the patient, such as bronchopulmonary dysplasia, cystic fibrosis, congenital heart disease, and immune deficiency.

(5) Severe respiratory distress as evidenced by pulse rate > 200 beats/min, a respiratory rate > 80 breaths/min, RDAI > 15 , or profound lethargy.

(6) Recent treatment with oral or inhaled steroids (within 2 weeks) and history of reaction to steroids.

(7) Presence of varicella or recent close contact (less than 3 weeks) without a history of prior infection.

(8) Insurmountable language barrier (for example, patient is unable to understand French or English well enough to give informed consent and participate in the follow-up).

(9) Any child born at less than 37 weeks gestation who is less than 6 weeks corrected age.

3.1.6 Interventions: Subjects are recruited upon arrival in the ED by a research nurse.

Following informed consent (Appendix 1), eligible children receive two treatments of 1:1000 epinephrine (3 mL) or placebo by nebulizer 30 minutes apart. Following completion of the first nebulization, the child also receives 1.0 mg/kg of dexamethasone or oral placebo.

Children also receive dexamethasone 0.6 mg/kg or placebo once daily for 5 days following study enrollment. ED discharge disposition (admission to hospital, discharge home) is at the discretion of the treating emergency department physician.

3.1.7 Outcomes: The primary outcome measure is admission to hospital up to 7 days after enrollment in the study. Secondary outcomes include time to discharge from the ED or hospital, length and severity of symptoms, and change in clinical score (respiratory distress assessment instrument) from baseline at time 60, 120, 180 and 240 minutes. An economic analysis is also planned. Planned subgroup analyses include those with risk factors for atopy, those patients who are early in their illness, and by viral etiology.

3.1.8 Measurements and follow-up: Enrolled children are followed for up to 4 hours by a research nurse in the ED, blinded to group assignment, who is responsible for administering study medications, obtaining relevant clinical data, and collecting all physical exam measurements. All children are contacted daily by a research nurse for 7 days and every other day for days 8-22 postenrolment. For those children who are discharged home this contact is by phone and for those who are admitted, the contact is in person. During this follow-up, the research nurse administers a previously developed bronchiolitis questionnaire that examines symptom severity and length and collects data regarding returns for medical assessment (33,35). A review of medical chart is completed at 22 days following enrollment

to collect information regarding further emergency department visits, admissions to hospital, treatment at any subsequent visits, and results of investigations.

3.2 Severity Study Methods

3.2.1 Study period: Children were enrolled during the December 1st, 2004 to April 30th, 2005 bronchiolitis season.

3.2.2 Setting: Recruitment and enrolment of patients occurred at two Canadian pediatric emergency departments - the Isaac Walton Killam (IWK) Health Centre and the Children's Hospital of Eastern Ontario (CHEO). The IWK and CHEO are tertiary care pediatric hospitals with annual ED census of 35,000 and 55,000 respectively. The study hospitals are members of a collaborative research group known as Pediatric Emergency Research Canada (PERC).

3.2.3 Study population:

Inclusion criteria: All patients presenting with bronchiolitis to the ED of a participating hospital were eligible for inclusion. Bronchiolitis was defined as a first episode of wheezing in a child less than or equal to 12 months of age, associated with signs of an upper respiratory track infection (such as fever, coryza, cough) during the period deemed to be peak season for RSV bronchiolitis (December to April).

Exclusion criteria:

- (i) Previous diagnosis of asthma by a physician
- (ii) Any previous episode of wheezing/cough treated with bronchodilators or inhaled steroids
- (iii) Any previous episode of wheezing diagnosed by a physician.

3.2.4 Sampling method: During the study period (December 2004-April 2005 and December 2005-April 2006), research assistants (RAs) were in the ED 16 hours per day recruiting. The RAs (who were all experienced nurses) were present in the ED during the 16 hours/day when most bronchiolitis patients present. Children with bronchiolitis who presented to the ED during these time periods only were screened for CanBEST and Severity Study eligibility (Appendix 2). These children then fell into three groups – (1) CanBEST eligible and enrolled; (2) CanBEST eligible and not enrolled (i.e., refused consent for RCT); or (3) not eligible for CanBEST but eligible for Severity Study. Those children enrolled in CanBEST were automatically enrolled in the Severity Study and the data collected during the screening, baseline measurements, and follow-up for those in CanBEST was extracted for the Severity Study. We asked the parents of those children in groups (2) and (3) for their consent for the Severity Study (Appendix 3). The same initial physical measurements and medical/social history questions asked in CanBEST were obtained for these children (Appendix 4) and a complete review of the child's hospital chart was completed by a research nurse 22 days after their enrollment visit (Appendix 5). We also kept a study log detailing screening status, consent to RCT and consent to severity study (Appendix 6). An illustrative figure of the sampling method and participant flow can be found in Figure 2.

3.2.5 Predictor variables:

Selection of variables: Information collected was divided into history, home environment, physical exam, and laboratory features. These variables were selected from prior studies that have suggested they may relate to risk for both admission for bronchiolitis and/or severe disease. These variables were also considered possibly relevant by the steering committee of CanBEST, many of who are considered experts in the field of bronchiolitis, and by the

individual site investigators for CanBEST, all of who are experienced pediatric emergency physicians. The research assistants collected historical and physical exam features prospectively in the ED. Laboratory and viral culture results were obtained during review of the patient's chart. Each variable was collected in a standardized method with a standardized definition. Variable definition and examples were detailed in the study manual and reviewed at the study orientations.

Variables from the history:

1. Age
2. Gestational Age at birth
3. Sex
4. Chronic disease (defined as disease requiring ongoing monitoring such as congenital heart disease, bronchopulmonary dysplasia, renal disease, etc.)
5. Race (as defined by child's parents)
6. Personal history of atopy (such as eczema)
7. Length of symptoms related to bronchiolitis

Variables related to home environment:

1. Maternal smoking during pregnancy
2. Current Maternal Smoking
3. Current smokers living in the home
4. Siblings living in the home
5. Numbers of individuals living in the home
6. Attendance at daycare
7. Breast feeding

8. Proxy Indicator of Social economic status (median family income reported by Stats Canada for resident postal code)

Variables related to physical exam:

1. Temperature
2. Baseline oxygen saturation
3. Baseline heart rate
4. Baseline respiratory rate
5. Respiratory distress assessment instrument (RDAI). The RDAI has been validated in previous bronchiolitis RCTs and has been used widely in studies of bronchiolitis (30,92,93) It reflects clinical parameters typically used by physicians to estimate respiratory distress. The RDAI captures information regarding respiratory rate, work of breathing, and presence/location of wheezing (Figure 1).

Laboratory variables/Investigations:

1. Respiratory viruses isolated from nasopharyngeal aspirate and reported in the patient's chart by the individual site laboratory.
2. Chest x-ray findings as reported by the individual centre's radiologist in the final radiology report (findings recorded include presence of pneumonia, atelectasis, infiltrate, hyperinflation, and consolidation, and a descriptive category of "other").

3.2.6 Outcome measures:

Primary outcome:

The primary outcome was the development of severe bronchiolitis. Severe bronchiolitis was defined as any of the following: (1) need for intubation, (2) apneic episodes, (3) ICU admission and (4) death. Apnea was defined as: 1) observed cessation of

respiration for > 15 seconds and/or 2) observed cessation of respiration accompanied by observed colour change, decrease in heart rate, oxygen saturation, or tone (41). While many authors have defined severe bronchiolitis as that requiring admission, we feel that many factors may influence admission, but that all clinicians would agree that intubation, apneic episodes and death constitute severe disease. We have chosen ICU admission as well, as we believe that any child who required ICU admission at a tertiary pediatric hospital, regardless of possible differing criteria for ICU admission between study hospitals, is a child who would be considered to have severe disease, require at least ward admission, and be best managed at a pediatric hospital.

Determination of primary outcome:

The primary outcome measure (need for intubation, ICU admission, apneic episode, and death) was determined by review of the patient's hospital chart at 22 days following their presentation. ICU admission was also confirmed by review of the ICU admission logs. We reviewed the patient's chart only at the initial hospital of presentation (i.e. children's hospital) for the following reasons: (1) our previous work has shown that most patients requiring admission are admitted at their preliminary ED visit and only occasionally within the several days following (22); (2) within the areas served by these hospitals, most children requiring admission are admitted to these same hospitals; and (3) any child requiring pediatric ICU care would only be admitted to these hospitals. As the primary outcome was not subjective, the research assistant was not blinded to the predictor variables collected. All predictor variables however were assessed prior to knowledge of the primary outcome.

3.2.7 Data collection and study management:

Data collection: Predictor variables were prospectively collected by the research nurse in the ED. These variables were collected through standardized questions (Appendices 2 and 4) asked of the child's parent by the research nurse during the child's enrollment visit.

Standardized physical exam variables were also collected prospectively, shortly after patient triage and registration in the ED, and prior to any treatment in the ED (Appendix 4). Viral study results, chest x-ray findings, and patient outcome were determined through chart review at 22 days following the patient visit (Appendix 5). Twenty two days after the ED visit was chosen as previous research has suggested that the symptoms of can persist for up to three weeks (22,23).

Research nurse training and quality assurance: All research nurses received a two-day orientation by the principal investigator and research coordinator and formal training regarding patient screening, recruitment, and data collection. A detailed research manual was also developed as a resource to the research assistants. Throughout the study there was on-going monitoring of data completeness by the research coordinator and principal investigator. Feedback was given to research assistants regarding any problems with their data recording and percentage of eligible patients enrolled.

Interobserver Reliability: A subset of patients was assessed for the clinical variables (details of the history and physical exam) by a second research nurse, who was blinded to the findings of the first assessor (Appendices 7 and 8). These assessments were done throughout the study period. We aimed for 10% of all patients to be assessed by a second research nurse. Furthermore, 10% of all patient charts were re-reviewed by a second reviewer, blinded to the

primary assessment, to determine interobserver reliability for the primary outcome (Appendix 8).

3.2.8 Sample size estimates and recruitment feasibility:

As this was a feasibility study, subjects were enrolled for a 5 month period corresponding to one “bronchiolitis season”. ED utilization data showed that approximately 2500 children less than one year of age are seen at the 8 CanBEST study hospitals during a typical bronchiolitis season (December to April). Initially we had planned that the Severity Study would run concurrently at all 8 CanBEST study hospitals but due to the length of time required for ethics approval only two hospitals (IWK and CHEO) were able to participate. From previous studies (22) at the CanBEST study hospitals, we had assumed that at least 75% of parents of children with bronchiolitis would consent to participation in either CanBEST or the Severity Study. Previous studies had also suggested that about 31% of the cohort would be admitted (22) and of these admitted children, approximately 16% would require ICU admission (27). Assuming similar proportions in our planned study, we expected 5% our ED cohort to develop severe bronchiolitis.

3.2.9 Data analysis:

Data verification: All data was entered in SPSS 12 and checked for accuracy by frequencies and visual inspection. Ten percent of data was double entered to check for data entry accuracy. Any queries were confirmed by review of the original data collection form, review of the patient’s hospital chart, and discussion with the research staff at each study site as necessary.

Baseline characteristics: Descriptive statistics were used to describe patient characteristics. Dichotomous variables were expressed as percentages and continuous variables were

expressed as medians and interquartile ranges or means and standard deviations as appropriate.

Interobserver Agreement: Interobserver agreement for each predictor variable and for the primary outcome was measured using the kappa coefficient along with 95% CIs.

Interobserver agreement for such variables as age and sex was not be calculated.

Univariate Analysis: Univariate analyses were used to determine the strength of association between each variable and the primary outcome. The appropriate univariate techniques were chosen according to the type of data. The Chi-square or Fisher's exact test was used for nominal variables. The unpaired 2-tailed t-test, using pooled or separate variance estimates, was used as appropriate, for continuous variables.

Multivariate Analysis:

This analysis was performed to develop a preliminary clinical decision rule predicting the development of severe bronchiolitis. Multivariate techniques used in developing models included multivariate logistic regression and recursive partitioning. Variables found to be associated with the outcome variable ($p < 0.30$), with reliable kappa's (>0.60), and that made clinical sense, were used in the multivariate models. As the primary purpose of this thesis was to determine the feasibility of a larger derivation study, less stringent criteria than normal were used to determine variable entry for the multivariate analysis.

For the multivariate logistic regression model, a backwards likelihood ratio model with a p-to enter of 0.30 and a p-to remove of 0.25 was used to generate parsimonious model. Adjusted odds ratios and 95% CIs were reported for statistically significant risk factors. Recursive partitioning was performed using Knowledge Seeker software to determine the most significant variables for the primary outcome. This procedure

progressively divided the patients using a Chi-squared analysis until a sub-population containing all the cases of severe bronchiolitis was found.

Narrative decision rules were then created based on the multivariate models. The classification of each patient based on the clinical decision rule was compared to his or her actual outcome and the sensitivity and specificity of rule (with 95% CIs) was determined. The final preliminary decision rule was chosen based on ease of use, classification performance, sensitivity and specificity.

3.2.10 Ethical Concerns

This study was approved by the IWK and CHEO as an amendment to the CanBEST protocol (Appendices 9 and 10). All patient identifiers were kept strictly confidential.

CHAPTER 4: RESULTS

4.1 Study Flow

Four hundred and twenty children under the age of one year presented to the IWK and CHEO EDs during the study period with an episode of wheezing. Of these, 372 presented with their first episode of wheezing and were eligible for inclusion in the study. Three hundred and twelve were enrolled in the study (83.9%) and had data forms completed. Among the enrolled patients, eight (2.6%) developed severe bronchiolitis. The study flow is illustrated in Figure 3. Sixty six (21.1%) children were enrolled through the IWK and 246 (78.8 %) through CHEO. Sixty of 80 (82.5%) eligible IWK patients and 246 of 292 (84.2%) eligible CHEO patients were recruited. Review of ICU logs confirmed that no missed eligible patients were admitted to the ICU and that no patient who presented outside the 16 hour time period of research assistant coverage developed severe bronchiolitis.

4.2 Enrolled Cohort Characteristics

4.2.1 Demographics:

The median age of the cohort was 19.8 weeks with a range of 1.7 to 52 weeks (Table 1). Forty two percent of the cohort was female and the majority (79.5%) were Caucasian. Annual household income ranged from \$40,338 to \$152,209 with a median of \$69,975.

4.2.2. Medical history:

Most children (88.8%) were born at term (≥ 37 weeks gestation). While only 1.9% of enrolled subjects had confirmed chronic disease affecting their cardiopulmonary status, 6.4% had a past history of a significant illness (defined as condition requiring surgery, admission to hospital, or ongoing follow-up). Ten percent of children had a personal history of atopy (such as eczema or environmental allergies). Thirteen children (4.2%) had a past history of

intubation and all were intubated in the newborn period for respiratory distress or for a surgical intervention.

4.2.3. Home environment:

Twenty four percent of the cohort was exposed to maternal smoking *in utero* (Table 2). Thirty eight percent currently lived in households with smokers. Most children (75.3%) had siblings and the mean number of individuals living in the home was 4.34. Most children had been breastfed at some point during their life (72.2%) but only 23.4% were being breastfed at the time of their ED visit. Twenty nine (9.3%) children attended daycare.

4.2.4 Physical exam findings:

Given that normal ranges for heart rate, respiratory rate, and blood pressure vary by age, each child was classified as falling within their age-related normal range for these variables (Table 3). Most children were tachypneic (92.6%) and 7.1% were tachycardic. Not all children had blood pressures completed but among those that did (67%), 15.1% and 16.6% had systolic and diastolic blood pressures outside the normal range. All children but one with abnormal systolic blood pressures were hypertensive. Among children with abnormal diastolic blood pressures, 19 (55.8%) were hypertensive. About a quarter (26.8%) of children were febrile and 7.0% had room air oxygen saturations of less than 92%.

4.2.5 Treatments, investigations and outcomes:

On arrival in the ED, 13.8% and 9.3% of children were already being treated with salbutamol inhalers and antibiotics respectively (Table 4). In the ED 206 (66%) received nebulized epinephrine, 49 (16%) received salbutamol (by nebulizer or metered dose inhaler), and 90 (28.8%) received steroids. Among the 181 patients not in CanBEST (in which patients might receive epinephrine or steroids as part of their protocol), 139 (76.8%) patients

received some type of bronchodilator, 115 (63.8%) received at least one epinephrine nebulization, 38 (21%) received at least one salbutamol treatment, and 6.6% received steroids. Seventy (22.4%) children had chest x-rays with only 17.1% of these being reported as normal. The most common finding on chest x-ray was hyperinflation (53.9% of patients receiving chest x-rays). Respiratory viral testing was done in 68.6% of children with RSV being the most commonly isolated virus (78.0%). Examining only those children who were not also part of CanBEST (in which viral testing is mandated), 45.9% had viral testing and RSV (83.1%) was the most commonly isolated virus.

The majority (67.7%) of children were never admitted. Only 8 children (2.6%) developed severe bronchiolitis. Of those admitted, 77.2% were admitted at their initial ED visit. Two children who developed severe bronchiolitis were admitted to hospital at their second ED visit for bronchiolitis. The mean length of hospital stay was 5.0 days. For those who were admitted to the ICU, their average ICU stay was 2.9 days. Two children in the cohort required intubation and ventilatory support. No child in the cohort is known to have died.

4.2.6 Description of the first ED visit of two children who developed severe bronchiolitis and were admitted at a later visit:

Due to lack of research nurse coverage two patients who developed severe bronchiolitis were not enrolled in the Severity Study at their first ED visit for bronchiolitis. The medical records for these visits were retrospectively reviewed. One child was three weeks old and was seen two days prior to their admission visit. The other was five weeks and was seen one day prior to their admission visit. For the three week old child, the entrance complaint was “choking spells” and the triage heart rate was 183 while the respiratory rate

was 60. Respiratory exam findings reported by both the triage nurse and examining physician (a trainee) were indrawing of the chest and wheezes bilaterally. No treatment, oxygen saturation, repeat vital signs, or repeat respiratory reassessment is recorded in this patient's ED record. The primary ED discharge diagnosis was gastroesophageal reflux and viral URTI was indicated as a secondary diagnosis. The child was not discharged on any medications. The other child, aged five weeks, had an entrance complaint of "difficulty breathing". This child was born at 34 weeks gestation. Triage vitals were 152 for heart rate, 38 for respiratory rate, and oxygen saturation of 100%. Both the triage nurse and examining physician's notes report bilateral wheezing and moderate work of breathing. The child was treated with one epinephrine nebulization followed by two salbutamol nebulizations. The child's heart rate increased during the course of their ED visit. The final vital signs recorded were a heart rate of 194 beats per minute, respiratory rate of 60 breaths per minute, and an oxygen saturation of 95%. These vitals were recorded one hour prior to ED discharge and two hours after the third bronchodilator treatment. The discharge diagnosis was bronchiolitis and the child was discharged on oral steroids and salbutamol by MDI.

4.3 Univariate Analysis

The univariate association of demographic, medical history, home environment, and treatment received with the development of severe bronchiolitis is shown in Tables 5 to 7. Children developing severe bronchiolitis were significantly younger than those who did not (10.7 weeks versus 21.9 weeks, $p = 0.016$). No other variable from this group, except for mean length of breastfeeding, was significantly associated ($p \leq 0.05$) with the development of severe bronchiolitis. Of note is that preterm birth, sex, race, cardiopulmonary disease, previous significant illness, or previous intubation are not associated with the development of

severe bronchiolitis. The association of a shorter length of breastfeeding with the development of severe bronchiolitis is related to the observation that younger children are at greater risk for severe bronchiolitis and due to their young age have had less “days of breastfeeding.

Table 8 provides the results of the univariate analysis for physical exam findings. Children developing severe bronchiolitis had significantly higher mean systolic and diastolic blood pressures, heart rates, respiratory rates and RDAI. They had significantly lower mean rectal temperature and oxygen saturation. Since vitals signs change with age, univariate analysis was also completed for whether or not the child’s vital signs were outside the normal range. This analysis demonstrated that children with severe bronchiolitis were significantly more likely to have a heart rate outside the normal range than those without severe bronchiolitis (75% vs. 5.3%, $p < 0.005$) but that this was not true for respiratory rate or blood pressure. Oxygen saturation $< 92\%$ on room air was also significantly associated with severe bronchiolitis.

A univariate analysis was also completed on the subset of patients who received chest x-rays and respiratory virus testing in the ED. Only atelectasis on chest x-ray was associated with the development of severe bronchiolitis. These results are shown in Table 9.

4.4 Interobserver Agreement for Predictor Variables

There were only 8 interobserver cases for predictor variables. The kappa statistics were overall good with only length of bronchiolitis symptoms ($\text{kappa} = 0.788$), the presence of other smokers in the home ($\text{kappa} = 0.696$), breastfeeding at any time ($\text{kappa} = 0.588$), and $\text{RDAI} > 10$ ($\text{kappa} = 0.696$) showing less than perfect agreement. For all variables found to

be significant predictors in the univariate analysis the agreement was perfect. Ninety five percent confidence intervals were not calculated due to the small number of cases.

4.5 Interobserver Agreement for Primary Outcome

Thirty eight patient charts (12%) were randomly selected to be re-reviewed for the primary outcome by another research nurse or by the principal investigator. The kappa for the primary outcome was 0.84 (95% CI 0.54,1). Only one patient was misclassified. The child was incorrectly classified as having developed severe bronchiolitis. This error likely occurred because the hospital discharge summary stated that the child was admitted to the ICU. In fact, although the ICU service was consulted, the child remained on the ward and never met the definition of severe bronchiolitis. Following the review of these 38 charts and the discovery that the kappa was not 1.0 for the primary outcome, medical charts of all patients identified as having severe bronchiolitis were again reviewed to confirm the accuracy of that assignment. No other misclassification was found. Review of ICU admission logs also confirmed that no patient classified as “nonsevere” was in fact admitted to the ICU.

4.6 Multivariate Analysis

4.6.1 Initial logistic regression model:

All possible predictor variables were analyzed with logistic regression individually with the outcome variable of severe bronchiolitis (Appendices 11 to 13). Due to the presence of cells with no cases the standard errors were very high for variables “presence of cardiopulmonary disease”, “personal history of atopy”, “received RSV immunoglobulin”, “day care attendance”, and “breast feeding at any time”.

4.6.2. Multivariate logistic regression models:

Variable selection:

There were 17 variables with a p-value of less than 0.30 that could have been offered to a model. The continuous physical exam variables of systolic BP, diastolic BP, heart rate and respiratory rate are not clinically useful as these values vary by age and as a result the categorical variables of “outside of normal range” for each of these physical exam variables were considered initially. Similarly the continuous variable of temperature is not clinically useful but rather whether a child is febrile or not. When temperature was converted to such a categorical variable, the p-value was greater than 0.30. The reliability of several variables was also affected by large amounts of missing data. For example, over 100 children did not have blood pressure measurements due to the inherent difficulty in taking blood pressures on irritable, crying infants. As well, only 22 % of children had chest x-rays taken so the presence of atelectasis or hyperinflation on chest x-ray was not included in the initial models. Treatment with epinephrine was also not included although it had a p-value of 0.225. At CHEO (the major recruiting site) there is a triage nurse initiated pathway that starts treatment with epinephrine for all children who present to the ED with their first episode of wheezing. Thus, the apparent positive association of epinephrine with the development of severe outcome likely reflects the practice at CHEO to treat children with bronchiolitis, particularly those in any distress, with epinephrine (even outside of the CanBEST protocol). As well, current breastfeeding and a shorter length of breastfeeding appeared in individual regression analysis to be associated with the development of severe bronchiolitis. However, this is a reflection of the fact that children who developed severe bronchiolitis are much younger than

those who did not develop severe bronchiolitis and as result were more to be still breastfeeding.

Models developed:

After these considerations, there were seven clinically relevant and reliable variables to be offered to the model (age, preterm birth, previous intubation, family income, heart rate outside normal range, RDAI and oxygen saturation). A backwards likelihood ratio model with a p to enter of 0.30 and a p-to remove of 0.25 was conducted. This resulted in age and previous intubation being excluded from the model. As physicians might be unwilling to ask about family income, this variable was excluded and the resulting model included only heart rate outside normal range, RDAI and oxygen saturation. The model coefficients and odds ratio for these models are reported in Table 10.

In an effort to make the model more clinically relevant, oxygen saturation was changed to a categorical variable of oxygen sat < 92% (where most clinicians begin treatment with oxygen) and several cut points of the RDAI were explored ($\text{RDAI} \geq 10$, $\text{RDAI} \geq 12$) and age was converted to a categorical variable of age < 6 weeks (which has been previously suggested as high risk for developing severe bronchiolitis). Each of these variables, in an individual regression model, had a p-value of less than 0.30. Thus six variables were now offered to the model (age < 6 weeks, preterm birth, previous intubation, oxygen saturation < 92%, heart rate outside of normal and RDAI as a categorical variable). The final models included RDAI at both cut points, oxygen saturation < 92% and heart rate outside normal range. If age was offered to the model as a continuous variable, rather than a categorical variable, the models were no different. The model coefficients and odds ratios are reported in Table 10.

4.6.3. Sensitivity and specificity of logistic regression models:

The sensitivity and specificity of the regression models were determined using probability classification cut points from 0.01 to 0.95 and the receiver operating curve for the final model is chosen is shown in Figure 4. The area under the curve for the models ranged from 0.984 to 0.993.

4.6.4 Goodness-of-fit test for logistic regression models:

The Homer and Lemeshow test for goodness of fit was performed for the models proposed and is shown in Table 11. The R square for each model is also indicated in Table 11.

4.6.5. Final logistic regression model:

The final regression model chosen included the terms heart rate outside normal range, oxygen saturation $< 92\%$ and $RDAI \geq 10$. This model was chosen on (1) the basis of statistical modeling, (2) by ensuring clinically important variables were included, (3) that the model made clinical sense and (4) could be put in a narrative decision rule form.

4.6.6 Narrative form of final logistic regression model:

The final regression model was then converted into a narrative format called the “Bronchiolitis Severity Rule” (Figure 5). Each variable was represented by a question: (1) “Is the heart rate outside of normal?”, (2) “Is the $RDAI \geq 10$?”, and (3) “Was the oxygen saturation $< 92\%$?”. As the coefficients for each of the variables in the regression model were almost equal, an affirmative answer to any of these questions was given equal weight in this rule. The rule was considered positive (predictive of severe bronchiolitis) if there was one affirmative answer. The classification performance of “Bronchiolitis Severity Rule” is given in Figure 6. Using one affirmative answer as a positive rule, the rule had a sensitivity

of 100% (95% CI 60,100) and a specificity of 61% (95% CI 55, 66) (Table 12) but if applied to the current cohort would require 40% of the patients to be admitted to a pediatric hospital due to risk of severe bronchiolitis. Requiring two affirmative answers, decreased the rule's sensitivity to 88% (95% CI 0.47, 0.99), but increased the specificity to 97% (95% CI 95, 99) (Table 12), and if used as a cut point for admission would require 4.8 % of the current cohort to be admitted.

4.7 Recursive Partitioning

4.7.1 Variables offered to the model:

As with the logistic regression models, variables were eligible for inclusion in the recursive partitioning model if they had a $p < 0.30$ and were clinically sensible. As recursive partitioning however requires categorical variables, only categorical variables that had a $p < 0.30$, were clinically sensible and easy to use were considered. This resulted in the following variables being examined: age less than 6 weeks, preterm birth, previous history of intubation, heart rate outside normal, oxygen saturation $< 92\%$, oxygen saturation $< 88\%$, $RDAI \geq 10$, $RDAI \geq 12$, and $RDAI \geq 15$.

4.7.2 Sensitivity and specificity of models developed

Table 13 shows the initial clinical decision rules developed using recursive partitioning. All included heart rate outside the normal range. The sensitivity of all the rules was 100% but the specificity ranged from 61% to 93%. The recursive partitioning development of these models is shown in Appendices 14 to 21 and for the final model in Figure 7.

4.7.3. Final clinical decision rule based on recursive partitioning

The final clinical decision rule chosen included the variables oxygen saturation (on room air) less than 88% and heart rate outside the normal range (Figure 8). This clinical decision rule was chosen on the basis of ease of use, clinical sensibility, sensitivity/specificity parameters, and classification performance. The rule's sensitivity was 100% and specificity of 93%. When applied to the current cohort, the rule would result in 9.0% of children requiring admission due to the risk of severe disease (Figure 9).

CHAPTER 5: DISCUSSION

5.1 Success in Enrollment

Three hundred and twelve children with bronchiolitis were enrolled in the study between December 1st, 2004 and April 31st, 2005. This represents 83.9 % of eligible children who presented during the study time period. The lack of complete capture is due in part to the busy nature of the ED and that this time period is the “peak season” for pediatric EDs. Other published emergency department based decision rule studies have had 70 to 77% capture of all eligible patients (94, 95, 96, 97).

Although more patients were recruited at CHEO than IWK, both sites obtained similar recruitment rates of eligible patients. The lower number of patients recruited from IWK reflects their lower ED census (35,000 patients/year versus 55,000 patients/year at CHEO) and the fact that the bronchiolitis season is typically shorter in areas with milder winters.

5.2 Generalizing Results From Our Study Cohort

Questions may be raised about the generalizability of a cohort collected at two Pediatric Emergency Departments to the population of children with bronchiolitis presenting to other Emergency Departments. However, our cohort appears to be similar to the three published ED bronchiolitis emergency department studies (7,22,39) (Table 14). The only prospective study enrolled 237 children with bronchiolitis at seven pediatric emergency departments across Canada and defined bronchiolitis in an identical manner as our cohort (22). IWK and CHEO also participated in this seven site study contributing 26% of the final sample size. The two cohorts are almost identical in age, sex distribution, home smoking environment, admission rates, treatment with bronchodilators and steroids, and viral testing.

The cohorts differed only in the use of chest x-rays (with 42% of patients in seven centre cohort receiving chest x-rays). Two large retrospective studies have also been published (7,39). One, a Canadian study, included 3091 children with bronchiolitis who presented to 1 pediatric ED and 4 general EDs in the Calgary Health Region over a five year period (7). Children were included if they were less than 2 years of age and had a discharge diagnosis by the ED physician of bronchiolitis or “if wheezing was noted on physical examination, the child was < 2 years of age, and had either no previous history of wheezing or a nasopharyngeal aspirate that was positive for RSV”. Despite defining bronchiolitis slightly different than in our cohort, the children were similar overall in age, sex, steroid use, and admission rate (27.5%). The cohorts differed slightly in incidence of prematurity and in bronchodilator use. The difference in prematurity (6% vs. 12%) may in part be due to the strict definition of prematurity used in our study (gestational age < 37 weeks) and the reliance upon retrospective medical chart data in the Calgary Health Region cohort. As a selection bias might occur by studying only patients seen at a pediatric ED, we can also compare our cohort to those seen in the CHR general EDs. The cohorts were very similar with the CHR general ED cohort being just slightly older. A large American study analyzed nine years of National Hospital Ambulatory Medical Care Survey data about bronchiolitis (39). The National Hospital Ambulatory Medical Care Survey is a 4-stage probability sample of visits to randomly selected general and short stay hospitals. The study reviewed data for children less than two years of age with a discharge diagnosis of bronchiolitis. Data from the US Census Bureau was used to extrapolate population-based estimates. In this study, the sex distribution (60% male) was similar to our cohort, 53% of children were treated with salbutamol, and 46% had chest x-rays. Admission rates were however lower at only 19%.

5.3 Differences in Occurrence of Severe Bronchiolitis

We had initially estimated that approximately 5% of children presenting to the ED with bronchiolitis would develop severe bronchiolitis (as defined by ICU admission, apnea, intubation, or death). This was based on extrapolating data from Canadian pediatric hospital studies reporting an admission rate of 31% among children with bronchiolitis (22) and a 16% rate of ICU admission among patients admitted with RSV infection (14).

Overall in our study overall only 2.6% of cohort developed severe bronchiolitis, 6.9% of admitted patients went to the ICU, less than 1% were intubated or had apnea, and no deaths were known to occur. In the only published Canadian study of admitted patients with RSV lower respiratory tract infection, 16% were admitted to the ICU, 9% required intubation, and 1% died (14). This cohort, known as the “PICNIC study”, included children less than 2 years of age with RSV proven lower respiratory tract infection and those greater than 2 years of age with RSV lower respiratory tract infection who also had underlying lung or heart disease or with immunosuppression. While the differences in ICU admission rates may have to do with the differing study populations, it is important to note that only 3% of the PICNIC study cohort actually had congenital heart disease, chronic lung disease, or were immunosuppressed and median age of the sample was 19 weeks. Almost 2% of our cohort had congenital heart disease or chronic lung disease and the median age was 19.8 weeks. Thus, it would appear that this difference in ICU admission rates is not solely on the basis of very different study populations. Other reasons for the difference may include (1) the fewer study sites in our study (2 vs. 7 hospitals), (2) change in indicators for ICU/admission or ventilation (given that the studies are 10 years apart) over time, and (3) hospital specific patient populations or practices.

Other studies (18,81) have also reported much higher rates of apnea, intubation and ICU admission among admitted patients with bronchiolitis but these studies were also retrospective and included significantly higher proportions of either very preterm infants or children with congenital heart disease and chronic lung disease than our study (18,81). Other retrospective studies have however reported slightly lower ICU admission rates than our study with from 2.7% to 6.2% of admitted patients requiring ICU admission (41,46,82).

Despite the lower than anticipated occurrence of severe bronchiolitis we cannot conclude that bronchiolitis is becoming a milder disease. The prevalence of severe bronchiolitis in our cohort does fall within previously published ranges. As well, all studies in this area have followed admitted patients, many have been retrospective, and many have included a high number of traditionally “high risk” patients (for example, those who were born very premature). There are no published studies that have followed an outpatient bronchiolitis cohort.

We also have no evidence that bronchiolitis is becoming less prevalent. One American study examined temporal trends in ED bronchiolitis visits and found them constant from 1992 to 2000 at 26 (95% CI 22-31) per 1000 children < 2 years of age (39). Admission rates for bronchiolitis however appear to have increased. Specifically, Njoo found within Canada that between 1987 and 1997 admission rates for bronchiolitis have increased by 55% among males and 45% among females (4). In 1997, this meant that 35 of every 1000 children less than one year of age were admitted to hospital with bronchiolitis in Canada. In the US, hospitalization for bronchiolitis increased by 2.4 fold from 1980 to 1996 in the US (1200/100,000 to 3120/100,000 in 1996) (15).

5.4 Potentially Important Predictor Variables

5.4.1 Age and pre-existing medical conditions as predictor variables:

The univariate analysis demonstrated several statistically significant differences in variables between those children who developed severe bronchiolitis and those who did not. With regards to demographic factors, younger age was significantly related ($p < 0.05$). This has been previously reported as a risk factor in the literature (41, 52, 57, 80,81). No other demographic or medical history factors were significantly related to the development severe bronchiolitis. Specifically, premature birth, congenital heart disease, and chronic lung disease were not found to be associated with severe disease unlike other studies (14, 19, 41, 46, 47, 51, 57, 64). Given however that our study was small and examined an outpatient cohort it is perhaps not surprising that prematurity, congenital heart disease, and chronic lung disease were not found to be associated with severe disease. We know that many children with bronchiolitis do not progress to needing hospital admission (3), let alone develop severe disease. As well most children are born at term (98) and few have significant CHD or chronic lung disease. As a result most children who develop bronchiolitis are otherwise healthy. Most of the studies that have suggested these associations have examined admitted patients or used a case control design. As well the use of RSV immunoglobulin prophylaxis may have made these variables less important with time. RSV immunoglobulin has been shown to reduce the risk of severe disease for certain “high risk” populations (99,100). As a result, the Canadian Pediatric Society and the American Academy of Pediatrics recommend RSV immunoglobulin for children born less than 32 weeks as well for those children with chronic lung disease who are less than 2 years of age during the bronchiolitis season. Currently RSV immunoglobulin is not routinely recommended for healthy children born at

33-35 weeks gestation (99,100). Marked prematurity, significant congenital heart disease, and chronic lung disease may be important individual risk factors for severe bronchiolitis but they may not be useful variables in an emergency department based clinical decision rule. Collection of a larger outpatient cohort should help delineate the importance of these variables.

5.4.2 Exposure to tobacco smoke:

Childhood exposure to tobacco smoke has been shown in many studies to be associated with an increased risk for admission to hospital with respiratory illness (66-68). As well studies have shown elevated levels of urinary cotinine (an marker of exposure to tobacco smoke) in children admitted to hospital with bronchiolitis as compared to those admitted with other illnesses (67,68). Over one third of our cohort was exposed to tobacco smoke at home according to parental history but this was not associated with development of severe bronchiolitis. We did try to quantify exposure by ascertaining whether mother smoked, other members of the household smoked and number of cigarettes smoked by mother in the previous 2 weeks. There was no association between the number of cigarettes smoked per day by a child's mother in the last two weeks, whether just the mom smoked, or there whether there was more than one smoker in the home, and the development of severe bronchiolitis. This data was dependent on self report by the parents and thus might be self censored (101-104) but even if accurately reported may not reflect the actual amount of tobacco smoke exposure for the infant. It is possible that urinary cotinine levels might have been predictive in our study for severe bronchiolitis but they were not measured. Unless such a test became rapidly and cheaply available in the ED such a measure would also not be useful in a clinical decision rule.

5.4.3 Physical exam findings, atelectasis and treatment received as predictor variables:

Significant physical exam findings included heart rate outside the normal range, systolic blood pressure outside normal, RDAI ≥ 10 , and oxygen saturation $< 92\%$. Several studies have examined the use of physical exam parameters (such as heart rate, respiratory rate, presence of fever, oxygen saturation, work of breathing) in predicting “severity” as measured by length of hospital stay or need for supplemental oxygen but almost all have studied admitted patients. One prospective study found intercostal recessions and sternal retractions were predictive of low oxygen saturations but the interobserver agreement on the presence of these signs was only fair (76). Two studies found patient weight was associated with prolonged hospital admission (105,106). Another study examined whether or not they could determine which children are at risk of returning to the ED after their first bronchiolitis visit and require admission. They found that children with HR > 150 were almost 2.5 times more likely to return requiring admission (107).

The finding of atelectasis was also associated with the development of severe bronchiolitis among those who had chest x-rays. While pulmonary consolidation on chest x-ray has been previously reported to be associated with severe bronchiolitis (14), atelectasis has not. Not surprisingly, no drug therapy provided prior to ED presentation by the primary care provider or in the ED (with regards to antibiotics, bronchodilators, or steroids) was related to the development of severe bronchiolitis. This is in keeping with the current medical literature that suggests minimal to no benefit from treatment with bronchodilators or steroids (28,29,31,32,35).

Given our small sample size and few “positive outcomes”, it is possible that other variables will be determined to be associated with severe bronchiolitis when the final sample

size is collected. The finding of several strongly associated variables (such as age, heart rate outside normal, oxygen saturation < 92%, RDAI) is encouraging though and make the development of a decision rule feasible. These variables noted thus far are also clinically sensible and would be easy to apply. With a larger sample size, other variables may also be relevant.

5.5 Reliability of Predictor Variables

Although the agreement was perfect for all variables found to be associated in the univariate analysis with severe bronchiolitis, this needs to be interpreted with caution give the small number (eight) of interobserver forms completed.

5.6 Models Derived Using Multivariate Logistic Regression

We found logistic regression was less useful than recursive partitioning in deriving a decision rule. Given the small sample size and small number of “positive” outcomes, the models developed were extremely unstable with very large 95% CI around the coefficient estimates. As well, accurate assessment of interaction and collinearity among variables was not feasible given the small sample size. The high area under the ROC curve also suggests that the model was likely overfitted.

Assuming that development of a stable model was feasible, there are several possible ways in which logistic regression models can be converted into a decision rule. Accepting the limitations of our logistic regression model described above, we chose to convert our model into a narrative format where the presence of one variable resulted in a positive rule. As a clinical decision rule must have a high sensitivity (and particularly for a serious outcome such as severe bronchiolitis) our rule required only one variable to be present in order to be “positive”. This gave the rule 100% sensitivity for predicting the development of

severe bronchiolitis but resulted in 40% of the cohort requiring admission. If a positive rule required the presence of two variables, the admission rate dropped to only 9% but the sensitivity was inadequate at only 88%. Other methods of converting logistic regression models into decision rules include determining the probability cut point where all positive outcomes are detected. Using some form of computational aid, clinicians can then enter the value of predictor variables into the logistic equation to determine whether an individual patient is above or below this probability cut point. The advantage of this method is that continuous variables can be easily included in the model and there is no loss of sensitivity by converting them to categorical variables. The disadvantages however include the need to use a computational device and the complexity of such a rule. Previous research has shown that rules that are considered an efficient use of time and not difficult to apply are more likely to be utilized in the ED (108).

5.7 Models Derived Using Recursive Partitioning

Recursive partitioning was found to be superior to logistic regression for developing the clinical decision rule. The final rule derived using recursive partitioning in this study had better classification performance than the logistic regression model and is easy to utilize. Other investigators have also found recursive partitioning to be a superior method for deriving a decision rule (95,96,109).

We were able to create several different models that captured all cases of severe bronchiolitis. Given, however, the small sample size of the study and the low number of “positive cases” the 95% CI around the sensitivities and specificities are very large. Further cases with positive outcomes must be collected in order to develop a decision rule with more precision. Our success in developing several models though does suggest that developing

such a decision rule will be feasible with a larger sample size. The current model proposed would result in 9% of patients being admitted to a tertiary care centre due to the risk of severe bronchiolitis. Currently 32% of the cohort was admitted. While we are not suggesting that those children who were admitted did not require admission (they may have needed monitoring, oxygen, or fluids), it does not appear that admission to a tertiary care hospital is necessarily indicated.

While our preliminary decision rule contained only two variables, the published standards for clinical decision rules suggest that at least three variables are needed for a rule (8,90). Previous published emergency department decision rules to date have included at least three variables (94, 95, 96,97). It is likely that our final rule will similarly have more than two variables.

5.8 Is a Decision Rule Necessary?

One Canadian study has also shown that, even when adjustments are made for clinical signs of respiratory distress (oxygen saturation, respiratory rate), age, gender, and socio-economic status, general emergency departments have close to double the admission rate for bronchiolitis than a pediatric emergency department (43% vs. 24%) (7). The discrepancy between adjusted admission rates for general emergency departments and pediatric emergency departments suggest that community emergency physicians may be uncomfortable in determining which children are at risk of severe bronchiolitis. Certainly even clinicians experienced in treating infants with bronchiolitis worry that a young infant discharged with bronchiolitis may worsen, develop apnea at home, or return to the ED sicker. Two of the eight children who developed severe bronchiolitis, were in fact discharged upon their initial visit to the ED. They presented to the ED in the following few days and were

admitted to the ICU from the ED. It is these cases that cause ED physicians feel particularly anxious. Although unfortunately these patients were not enrolled in our study at the time of their initial visit (due to lack of research nurse availability), retrospective review of these visits show that both these patients would have been admitted according to our preliminary clinical decision at this first visit. Of note is that both these patients were less than six weeks of age and in fact one patient was only 1 week corrected age. It is possible that the final decision rule may include age as an important predictor variable.

5.9 Comparison to Other Models Predicting Clinical Outcomes in Bronchiolitis

There have been no studies published that attempt to develop prediction models or clinical decision rules for developing severe bronchiolitis as defined in our study. There are two published studies that have developed models for predicting long hospitalization with RSV related illness (≥ 7 days in one, ≥ 9 days in the other). In the first study, known as the “Michigan model”, data from a retrospective cohort study of children hospitalized with RSV was used (105). Variables found to be associated in a univariate model with length of stay ≥ 7 days were included in a multivariate logistic regression model. Using a stepwise method, nine variables remained in the model – weight, congenital heart disease, two groups of lung disease, history of significant illness (such as genetic syndromes, major disability of an organ system), failure to thrive, early mechanical ventilation (day 1 of hospitalization), and early ribavirin therapy. This model seemed to have good discrimination with the area under the curve for this model was 0.894. A second study (106) attempted to validate the Michigan model in their population. The Michigan model did not perform as well in this population with an area under the ROC curve of 0.70 (95% CI, 0.59, 0.80). The authors then attempted to develop their own predictive model (“Rochester model”) for length of stay > 9 days (their

median duration of stay) using multivariate logistic regression and found only weight and oxygen supplementation were independently associated with the outcome variable. In their derivation population the ROC curve area to be 0.65 (95% CI, 0.57-0.73) but in their small validation study (42 patients) the ROC area was only 0.53 (95% CI, 0.34, 0.72). It is interesting that these models, as in our model, did not include age or prematurity despite these factors having been cited as risk factors for severe bronchiolitis. The only similarity to our final model is the Rochester model which found the need for supplemental oxygen (presumably an indicator for low oxygen saturation and increased respiratory distress) predicted prolonged hospitalization.

5.10 Study Strengths

Although this study is small, there is no larger prospective cohort study of ED patients with bronchiolitis published. This is the first study to prospectively following ED patients with bronchiolitis for the development of severe bronchiolitis and to collect a wide range of predictor variables. We also followed published standards in developing decision rules (8,90). The outcome, severe bronchiolitis, was clearly defined and important to patients, parents, and clinicians. The predictor variables were assessed prospectively and prior to the knowledge of the outcome. They were clearly defined, clinically sensible and in our small sample, reproducible. The prospective nature of the data collection also helped eliminate recall bias.

The study occurred at more than one site and the population enrolled was similar to other published ED bronchiolitis patient cohorts. Thus it appears that our study population was representative of our target population. We also tracked all patients with bronchiolitis throughout the study period. Although some eligible patients were missed, none of the

missed patients developed severe bronchiolitis. Our overall capture rate was in keeping with other ED based decision rule studies. Although one site contributed the majority of patients, there was no evidence of differential recruitment as both sites had similar recruitment rates of eligible patients.

The statistical methods for deriving the rule were clearly defined and the preliminary decision rule is sensible. It appears to be clinically relevant, sensible and easy to remember.

5.11 Study Limitations

The major limitation of this study is the small overall sample size and low numbers of “positive” outcomes. This made derivation of a stable logistic regression model extremely difficult. It also resulted in wide confidence intervals around the sensitivity and specificity of the preliminary decision rules developed and of the proposed decision rule. Given the small sample size and resultant low power, variables may have been excluded from the model that are in fact predictor variables for the development of severe bronchiolitis. For example, our power for including “preterm birth” in the model with a sample size of 312 and an alpha of 0.05 was only 0.12. if we used an alpha of 0.30 to include variables in the model, then the power for this variable increased to 0.372. For a variable such as “past history of significant illness” we would need significantly more subjects (a total of 6442) to detect a significant difference between groups using an alpha of 0.05 and a power of 0.80. Thus it is apparent that if the distribution of possible predictor variables between the severe and nonsevere bronchiolitis groups is, in fact, representative of the true distribution, we would need significantly more patients to obtain adequate power.

Approximately 30% of young infants who present to the ED with bronchiolitis make more than one ED visit during the course of their illness (22). Ideally these children should be enrolled in the study on their first visit but given the realities of a busy ED this did not have happened in all cases. For children who do not develop severe bronchiolitis the issue is less important but for those that do it is important that the patients be enrolled on their first visit. We know that for two of the patients that developed severe bronchiolitis they were not enrolled in the study on their first visit. While possible history predictor variables (such as age, preterm birth, etc) would not change between visits, the physical exam parameters may change. While we can retrospectively collect some of these variables (such as heart rate, respiratory rate, oxygen saturation), this is not ideal.

Another limitation of this study is the use of chart review to ascertain the child's final outcome. It is possible that a child may have been admitted to another hospital or died following discharge from the ED. However, this is extremely unlikely as in the communities served by the study hospitals they are the only hospitals that admit children and we know from previous work that children who visit these pediatric EDs tend to return to the same ED for care (22).

The low number of interobserver forms completed is also a limitation of this study. As it is essential that the variables included in a decision rule are reliable this must be improved in the subsequent study. This will be obtained through reminders and incentives for the research nurses.

5.12 Feasibility of a Definitive Study and Future Directions.

Despite the lower than anticipated sample size and occurrence of severe bronchiolitis in our study, a definitive study appears feasible. We had initially anticipated that all 8

CanBEST sites would participate in this study but only two sites were able to participate. This was not due to a lack of interest or support among the CanBEST sites but rather that individual ethics committees had differing processes for approval. IWK and CHEO allowed the Severity Study to proceed as an amendment to CanBEST, the remaining sites required a new ethics application. As well, the successful recruitment of 84% of all eligible patients (a higher recruitment than many other emergency department studies) and the ability to collect almost all predictor variables also supports the feasibility of this study. Furthermore, the ability to derive a preliminary decision rule that was 100% sensitive for predicting severe bronchiolitis supports the feasibility of a definitive study. While the interobserver rate for predictor variables was suboptimal this can be addressed in a definitive study by reporting to each site their weekly interobserver rates, providing incentives, and overlapping research shifts.

Previous decision rule studies found that 60-120 “positive outcomes” are needed to produce a decision rule with nearly 100% sensitivity and narrow confidence intervals. Such sensitivity is needed given the seriousness of the outcome we wish to detect. Assuming that 2.6 % of the children presenting to the ED with bronchiolitis develop severe disease, we will need a cohort of at least 2300 children. Five other pediatric emergency departments have already agreed to participate in this definitive study and have obtained ethics approval.

Although only a few variables were found to have a strong association with severe bronchiolitis in this feasibility study, we will not drop any variables for the definitive study given our small sample size and low number of severe outcomes. We plan on using recursive partitioning for developing the final decision rule. It is probable that this rule will contain more than the two variables in our preliminary model.

Following derivation of a final decision rule, a prospective validation in a second population will be needed. If validity of the rule were confirmed, the final step would involve a study to determine if the rule can be successfully implemented into clinical practice and is cost-effective (8,90).

5.13 Importance and Relevance

This feasibility study has shown that recruitment of patients during the busiest time of year in pediatric emergency departments and prospective collection of predictor variables is feasible. The derivation of a preliminary decision rule with such a small number of patients suggests that an accurate and reliable clinical decision rule can be obtained. This supports expanded research in this area to obtain sufficient sample size. To our knowledge, this is the first study to prospectively assess the risk of developing severe bronchiolitis in an emergency department cohort.

As previously stated, bronchiolitis is the most common disease of the lower respiratory tract during the first year of life. While most children with bronchiolitis do well, a small proportion become very ill – requiring admission to intensive care units, ventilatory support, having apneic episodes and even dying. For emergency physicians, who often provide the first line of care in bronchiolitis, it would be useful to have a decision rule using easily available clinical variables to determine which children are at risk of developing severe disease and which children are not. A clinical decision rule would also allow community emergency physicians to determine whether a child needs transfer to a pediatric centre, as well as assist pediatric emergency physicians in determining which children definitively need admission to a tertiary care hospital.

5.15 Conclusions

There were eight children who developed severe bronchiolitis among the 312 prospectively enrolled emergency department patients. Two of the eight children who subsequently developed severe bronchiolitis were discharged home at their initial ED visit, only to return within several days in extreme respiratory distress. One hundred and one children (32%) were admitted to hospital from the cohort.

We found several variables to be highly correlated in a univariate model with the development of severe bronchiolitis. These variables included age, heart rate outside range of normal, decreasing oxygen saturation, increasing respiratory distress assessment instrument score, and the presence of atelectasis on chest x-ray.

The preliminary model derived in this study through recursive partitioning included heart rate outside of normal and oxygen saturation (on room air) of less than 88%. The preliminary model has 100% sensitivity for predicting severe bronchiolitis but large confidence intervals due to the small sample size of this study. It is feasible that with a larger sample size, a highly sensitive decision rule can be derived for predicting the development of severe bronchiolitis.

Table 1: Demographic and medical history characteristics from a prospective cohort of Emergency Department patients with bronchiolitis

Characteristic	Number of patients, n = 312
Demographics	
Mean age (SD), weeks	21.6 (13.0)
Range	1.7 to 52.0
Median age, weeks	19.8
Female n (%)	132 (42.3)
Race	
Caucasian, n (%)	248 (79.5)
Black, n (%)	20 (6.4)
First Nations, n (%)	3 (1.0)
Asian, n (%)	3 (1.0)
Other*, n (%)	38 (12.1)
Household Income (median dollars/year)	69,975
Range	40,338 to 152,209
Variables from Medical History	
Mean gestational age at birth (SD), weeks	39 (2)
Range	26-42
Gestational age $\geq$ 37 weeks, n (%)	277 (88.8)
Gestational age, 34-37 weeks, n (%)	28 (9.0)
Gestational age < 34 weeks, n (%)	7 (2.2)
Chronic Disease affecting cardiopulmonary status, n (%)	6 (1.9)
Significant illness including cardiopulmonary disease*, n (%)	20 (6.4)
History of atopy, n (%)	32 (10.3)
Length of Bronchiolitis Symptoms	
Mean, days (SD)	5 (4)
Range	0-28
$\leq$ 2 days, n (%)	73 (23.4)
> 2 days, n (%)	239 (76.6)
Received RSV immunoglobulin, n (%)	5 (1.6)
Previously intubated, n (%)	13 (4.2)

*Majority of "other" were biracial children.

*Defined as illness requiring hospitalization, surgery, or continued medical care. Prematurity per se not included.

Table 2: Home environment characteristics from a prospective cohort of Emergency Department patients with bronchiolitis

Characteristic	Number of patients, n = 312
Home Environment	
Maternal smoking during pregnancy, n (%)	75 (24)
Any smokers in the home, n (%)	118 (37.8)
Current maternal smoking, n (%)	77 (24.7)
Other smokers in the home, n (%)	102 (32.7)
Mean Number of individuals in home (sd)	4.34 (1.3)
Daycare attendance, n (%)	29 (9.3)
Breastfeeding [†]	
Breastfeeding at any time during child's life, n (%)	208 (72.2)
Currently breastfeeding, n (%)	66 (23.4)
Mean length of breastfeeding (SD), days	60 (71.2)

[†] The breastfeeding questions were left off 24 emergency enrollment forms giving an n of 288. On the 288 forms where the breastfeeding questions were present, 10 had incomplete data regarding length of breastfeeding.

Table 3: Physical exam findings from a prospective cohort of Emergency Department patients with bronchiolitis*

Physical Exam Finding*	
Mean temperature (SD), °C, n= 306	37.7 (12.5)
Range	36-41
Mean systolic BP (SD), mm Hg n= 205	98 (14)
Range	60-147
Mean diastolic BP (SD), mm Hg n= 205	60 (13)
Range	33-96
Mean oxygen saturation [†] (SD), % n = 310	97 (4)
Range	54-100
Mean HR (SD), beats per minute n=312	155 (18)
Range	90-21
Mean RR (SD), breaths per minute n=312	50 (11)
Range	14-84
RDAI (SD) n= 311	8 (3)
Range	2-17
Febrile [‡] , n (%)	82 (26.8)
Systolic BP outside normal range, n (%)	31 (15.1)
Diastolic BP outside normal range, n (%)	34 (16.6)
HR outside normal range, n (%)	22 (7.1)
RR outside normal range, n (%)	289 (92.6)
Oxygen saturation [†] < 92%	22 (7.0)

*As not all physical exam variables were collected on all patients, the sample size for each variable is indicated next to the variable.

[†]On room air

[‡]Defined as rectal temperature > 38 °C

Table 4: Medications, investigations, and outcomes of prospective cohort of Emergency Department patients with bronchiolitis

Medications received prior to ED visit, n (%)	n = 312
Salbutamol	43 (13.8)
Inhaled Steroids	9 (2.9)
Antibiotics	29 (9.3)
Medications received in the ED, n (%)	
Epinephrine**	206 (66.0)
Salbutamol	49 (16)
Steroids	90 (28.8)
Oral**	77 (24.7)
Intravenous	2 (0.6)
Investigations in the ED, n (%)	
Chest x-ray	70 (22.4)
Results of x-ray, n/# who had chest x-rays	
Normal	12 (17.1)
Pneumonia	10 (14.3)
Atelectasis	14 (20.0)
Infiltrate	4 (5.7)
Hyperinflation	37 (53.9)
Consolidation	1(1.4)
Respiratory virus testing done*	214 (68.6)
Results of viral testing, n/# who had viral testing (%) [‡]	
RSV positive	167 (78.0)
Influenza positive	3 (1.4)
Adenovirus positive	1 (0.5)
Outcome, n (%)	
Never admitted	211 (67.7)
Admitted	101 (32.3)
Admitted at Enrollment Visit	78 (25.0)
Admitted subsequent to enrollment visit	23 (7.3)
Developed “severe” bronchiolitis [†]	8 (2.6)
ICU admission	7 (2.2)
Intubation	2 (0.6)
Apnea	1 (0.3)
Died	0 (0.0)

*CanBEST patients had RSV testing as per protocol. [‡]Both hospitals test first for RSV and do further tests only if RSV negative **Includes CanBEST patients who received steroid and epinephrine as per protocol (data provided by an analyst not otherwise involved in the study in order for the PI to remain blinded to group assignment). Among nonCanBEST patients: epinephrine 115/181 (63.5%), steroids 12/181 (6.6%), and any bronchodilator (includes epinephrine and salbutamol) 139/181 (76.0%).

Table 5: Univariate correlation of variables from history for development of severe bronchiolitis from a prospective cohort of Emergency Department patients with bronchiolitis

History Variable	Severe bronchiolitis n=8	Not Severe n=304	p-value
Demographics			
Mean Age (SD), weeks	10.7 (8.7)	21.9 (12.9)	0.016
Age < 6 weeks, n (%)	3 (37.5)	29 (9.5)	0.039
Female, n (%)	4 (50)	128 (42.1)	0.726
Race, n (%)*			0.359
Caucasian	8	240	
Black	0	20	
First Nations	0	3	
Asian	0	3	
Other	0	38	
Mean annual household income (SD), dollars	63,048 (12,277)	73,003 (17,249)	0.106*
Variables from Medical History			
Mean gestational age (SD), weeks	38.6 (1.8)	38.8 (2.1)	0.855
Preterm (< 37 weeks gestation), n (%)	2 (25.0)	33 (10.9)	0.223
Cardiopulmonary disease, n (%)	0 (0.0)	6 (2.0)	1.000
Significant illness including cardiopulmonary disease, n (%)	1 (12.5)	19 (6.2)	0.415
Personal history of Atopy, n (%)	0	32	1.000
Mean length of Bronchiolitis Symptoms (SD), days	6.25 (4.7)	4.8 (4.2)	0.344
Symptoms ≤ 2 days, n (%)	2 (25)	71 (23.4)	1.000
Received RSV immunoglobulin, n (%)	0 (0)	5 (1.6)	1.000
Previously intubated, n (%)	1 (12.5)	12 (3.9)	0.291

* Compared Caucasian race to all others using Fisher's Exact Test.

Table 6: Univariate correlation of variables from home environment on development of severe bronchiolitis from a prospective cohort of Emergency Department patients with bronchiolitis

Home Environment Variable	Severe bronchiolitis n=8	Not Severe n=304	p-value
Maternal smoking during pregnancy, n (%)	2 (25)	73 (24.0)	1.00
Any smokers in the home, n (%)	3 (37.5)	115 (37.8)	1.00
Current maternal smoking, n (%)	2 (25)	75 (24.7)	1.00
Other smokers at home, n (%)	2 (25)	100 (32.9)	1.00
Presence of siblings, n (%)	5 (62.5)	230 (75.7)	0.413
Mean # of individuals living in home (SD)	4 (1.3)	4.4 (1.3)	0.436
Daycare attendance, n (%)	0 (0)	29 (9.5)	1.0
Breastfeeding*	n=7	n=281	
Breastfeeding at any time, n (%)	7 (100)	201 (70.8)	0.196
Current breastfeeding, n (%)	7 (100)	201 (71.3)	0.360
Mean length of breastfeeding (SD), days	26.0 (18.4)	60.8 (71.8)	0.001

*The breastfeeding questions were left off 24 emergency enrollment forms giving an n = 288. On the 288 forms where the breastfeeding questions were present, 10 had missing data regarding the length of breastfeeding.

Table 7: Univariate correlation of medications received prior to ED visit and those received in the Emergency Department with the development of severe bronchiolitis from a prospective cohort of Emergency Department patients with bronchiolitis

Medications	Severe bronchiolitis, n=8	Not Severe, n=304	p-value
Received prior to ED visit, n (%)			
Salbutamol, n (%)	1 (12.5)	42 (13.8)	1.000
Inhaled Steroids, n (%)	0 (0.0)	9 (3.0)	1.000
Antibiotics	0 (0.0)	29 (9.5)	1.000
Received in the ED*, n (%)			
Epinephrine, n (%)	7 (87.5)	199 (65.5)	0.273
Salbutamol, n (%)	2 (25.0)	47 (15.5)	0.616
Oral steroids, n (%)	1 (20.0)	76 (25)	0.685

* In order for the PI to remain blinded to CanBEST drug assignment the univariate analysis of the relationship between epinephrine and oral steroids and the development of severe bronchiolitis was calculated by a data analyst not otherwise involved in the Severity Study or CanBEST.

Table 8: Univariate correlation of variables from physical exam and results of investigations on development of severe bronchiolitis from a prospective cohort of Emergency Department patients with bronchiolitis

Physical Exam	Severe bronchiolitis, n =8	Not Severe, n = 308*	p-value
Mean temperature (SD), °C	37.1 (0.9)	37.7 (0.7)	0.035
Mean Systolic BP (SD), mm Hg	108 (17)	98 (14)	0.040
Mean Diastolic BP (SD), mm Hg	68 (13)	59 (12)	0.049
Mean heart rate (SD), beats/minute	187 (18)	154 (17)	<0.001
Mean respiratory rate (SD), breaths/minute	59 (7)	50 (10)	0.018
RDAI	12 (3)	8 (3)	<0.001
Oxygen saturation (SD), %	87 (14)	97 (3)	<0.001
Febrile*, n (%)	1 (12.5)	81 (27.2)	0.687
Systolic BP outside normal range, n (%)	3 (37.5)	28 (14.9)	0.097
Diastolic BP outside normal range, n (%)	2 (25.0)	32 (16.2)	0.622
Heart rate outside normal range, n (%)	6 (75.0)	16 (5.3)	<0.001
Respiratory rate outside normal range, n (%)	8 (100.0)	281 (92.4)	1.000
RDAI $\geq$ 10	6 (75.0)	77 (24.8)	0.005
RDAI $\geq$ 12	5 (62.5)	45 (14.8)	0.003
RDAI $\geq$ 15	2 (25.0)	7 (2.0)	0.018
Oxygen saturation < 92%	5 (71.4)	16 (5.3)	<0.001
Oxygen saturation < 88%	4 (50.0)	4 (1.3)	<0.001

Not all variables were measured for all 312 patients.

Temperature n =306; Systolic BP n= 10, Diastolic n=205; Oxygen saturation n=310

Table 9: Univariate correlation of chest x-rays (CXR) findings and RSV status on development of severe bronchiolitis from a prospective cohort of Emergency Department patients with bronchiolitis

Investigations	Severe bronchiolitis	Not Severe	p-value
For patients in whom a CXR was done (n=70)	n=8	n=62	
Pneumonia, n (%)	1 (12.5)	9 (14.5)	1.000
Atelectasis, n (%)	5 (62.5)	9 (14.5)	0.006
Infiltrate, n (%)	0 (0)	4 (6.5)	1.000
Hyperinflation, n (%)	6 (75)	31 (50.0)	0.266
Consolidation, n (%)	0 (0)	1 (1.6)	1.000
Other finding, n (%)	2 (25)	15 (24.2)	1.000
Respiratory virus testing done (n=214)	n=8	n=206	
RSV positive, n (%)	7 (89.5)	161 (78.2)	1.00

Table 10: Odds ratios of clinical variables in the final 4 regression models from a prospective cohort of Emergency Department patients with bronchiolitis

Variable	Co-efficient	OR (95%)
Model 1		
Intercept	14.58	
Preterm birth	2.11	8.3 (0.28, 240.8)
Family income	-0.0001	1
HR outside normal range	4.88	131.1 (4.9, 3503.2)
RDAI	0.42	1.5 (1.0, 2.3)
Oxygen saturation	-0.19	0.8 (0.6, 1.1)
Model 2		
Intercept	19.27	
HR outside normal range	4.21	67.2 (5.3, 850.6)
RDAI	0.30	1.4 (1.0, 1.9)
Oxygen saturation	-0.31	0.74 (0.59, 0.93)
Model 3[¶]		
Intercept	-8.925	
HR outside normal range	4.71	110.6 (7.9, 1544.4)
RDAI ≥ 10	3.01	26.2 (1.1, 359.1)
Oxygen saturation < 92%	3.27	20.2 (2.5, 282.9)
Model 4		
Intercept	-7.04	
HR outside normal range	4.24	69.5 (6.5, 746.5)
RDAI ≥ 12	1.63	5.1 (0.66, 39.2)
Oxygen saturation < 92%	2.81	16.6 (2.2, 123.7)

[¶]Final model selected

Table 11: Homer Lemeshow Goodness of Fit of final 4 regression models from a prospective cohort of Emergency Department patients with bronchiolitis

Model (variables included)	χ^2	R square
5 variables: preterm birth, family income, heart rate outside normal range, RDAI and oxygen saturation	0.413	0.730
3 variables*: heart rate outside normal range, RDAI, oxygen saturation	0.549	0.682
3 variables[¶]**: heart rate outside normal range, RDAI ≥ 10 , oxygen saturation $< 92\%$	0.278	0.686
3 variables**: heart rate outside normal range, RDAI ≥ 12 , oxygen saturation $< 92\%$,	0.819	0.638

*Variables offered to model include age (as a continuous variable), preterm birth, previous intubation, heart rate outside normal range, RDAI and oxygen saturation

** Variables offered to model include age < 6 weeks, preterm birth, previous intubation, heart rate outside normal range, RDAI cut points, oxygen saturation $< 92\%$

[¶]Final model selected

Table 12: Sensitivity and specificity of alternate decision rules developed using logistic regression

Decision Rule*	Sensitivity (95% CI)	Specificity (95% CI)
Bronchiolitis Severity Rule, 1 affirmative answer	1.0 (0.60, 1.0)	61 (0.55, 0.66)
Bronchiolitis Severity Rule, 2 affirmative answers	0.88 (0.47,0.99)	0.97 (0.95, 0.99)

Table 13: Sensitivity and specificity of alternate decision rules developed using recursive partitioning

Rule	Sensitivity (95% CI)	Specificity (95% CI)
O ₂ sat < 88% <i>or</i> HR* outside normal range	1.0 (0.68, 1.0)	0.93 (0.90, 0.96)
O ₂ sat < 92% <i>or</i> HR outside normal range	1.0 (0.68, 1.0)	0.90 (0.86, 0.93)
RDAI $\geq$ 15 <i>or</i> HR outside normal range	1.0 (0.68, 1.0)	0.92 (0.89, 95)
RDAI $\geq$ 12 <i>or</i> HR outside normal range	1.0 (0.68, 1.0)	0.84 (0.80, 0.88)
RDAI $\geq$ 10 <i>or</i> HR outside normal range	1.0 (0.68, 1.0)	0.61 (0.56, 0.67)
Preterm birth <i>or</i> HR outside normal range <i>or</i> RDAI $\geq$ 15	1.0 (0.68, 1.0)	0.83 (0.78, 0.87)
Age < 6 weeks <i>or</i> HR outside normal range <i>or</i> RDAI $\geq$ 15	1.0 (0.68, 1.0)	0.85 (0.81, 0.89)
History of intubation <i>or</i> HR outside normal range <i>or</i> RDAI $\geq$ 15	1.0 (0.68, 1.0)	0.89 (0.85, 0.92)

* HR = heart rate

Table 14: Comparison of Severity Study Cohort with published ED bronchiolitis studies

Characteristic	Severity study cohort	Study	CHR cohort (Johnson)	CHR cohort - General EDs (Johnson)	US ED cohort (Mansbach)
	n=312*	Canadian Pediatric ED cohort (Plint)	n=3091	n=595	n=**
Median age (weeks)	19.4	20	24	30	
Female sex, n (%)	132 (42.3)	97 (41)	1236 (40.0)	238 (40.0)	39%
Premature birth, n (%)	35 (12.2)	----	156 (6.3)	30 (5.0)	---
Congenital heart disease, n (%)	1.9	0 (0)	25 (0.8)	0 (0)	---
Home smoking environment, n (%)	118 (37.8)	29 [†] (36.0)	---	---	---
Viral testing*, n (%)	214 (68.6)	124 (53)	---	---	---
RSV positive, n (%)	167 (78)	94 (76)	---	---	---
Chest x-rays, n (%)	70 (22.4)	99 (42)	---	---	46%
Bronchodilator*, n (%)					53%***
Steroids*, n (%)		12 (5.0)	217 (7.0)	26 (5.0)	13%
Hospital admission, n (%)			850 (27.4)	221 (37.1)	19%

*Children in the study cohort who were also part of CanBEST had viral testing mandated and may have received bronchodilators and steroids as part of the study protocol. Examining only those children who were NOT part of CanBEST (n = 181), viral testing was completed in 83 (45.9%); bronchodilators were given in 139 (76%), and steroids in 12 (6.6%).

[†]Home smoking environment was recorded for only 80 children in this cohort.

This data was generated from a large electronic database that randomly samples hospitals across the US. The data was then extrapolated using US Census Bureau data. So an "n" per se is not reported in the published paper. ** Only salbutamol is reported

Figure 1: Respiratory Distress Assessment Instrument

Points

	0	1	2	3	4	Max
Wheezing						
Exp	none	end	½	¾	all	4
Inspir	none	part	all			2
Location	none	≤ 2 lung fields	≥ 3 lung fields			2
Retractions						
Supercrav	none	mild	moderate	marked		3
Intercost	none	mild	moderate	marked		3
Subcostal	none	mild	moderate	marked		3
TOTAL						17

From: Lowell DI, Lister G, Von Koss H, McCarthy P. Pediatrics, 1987; 79: 939-45.

Figure 2: Sampling Method and Participant Flow

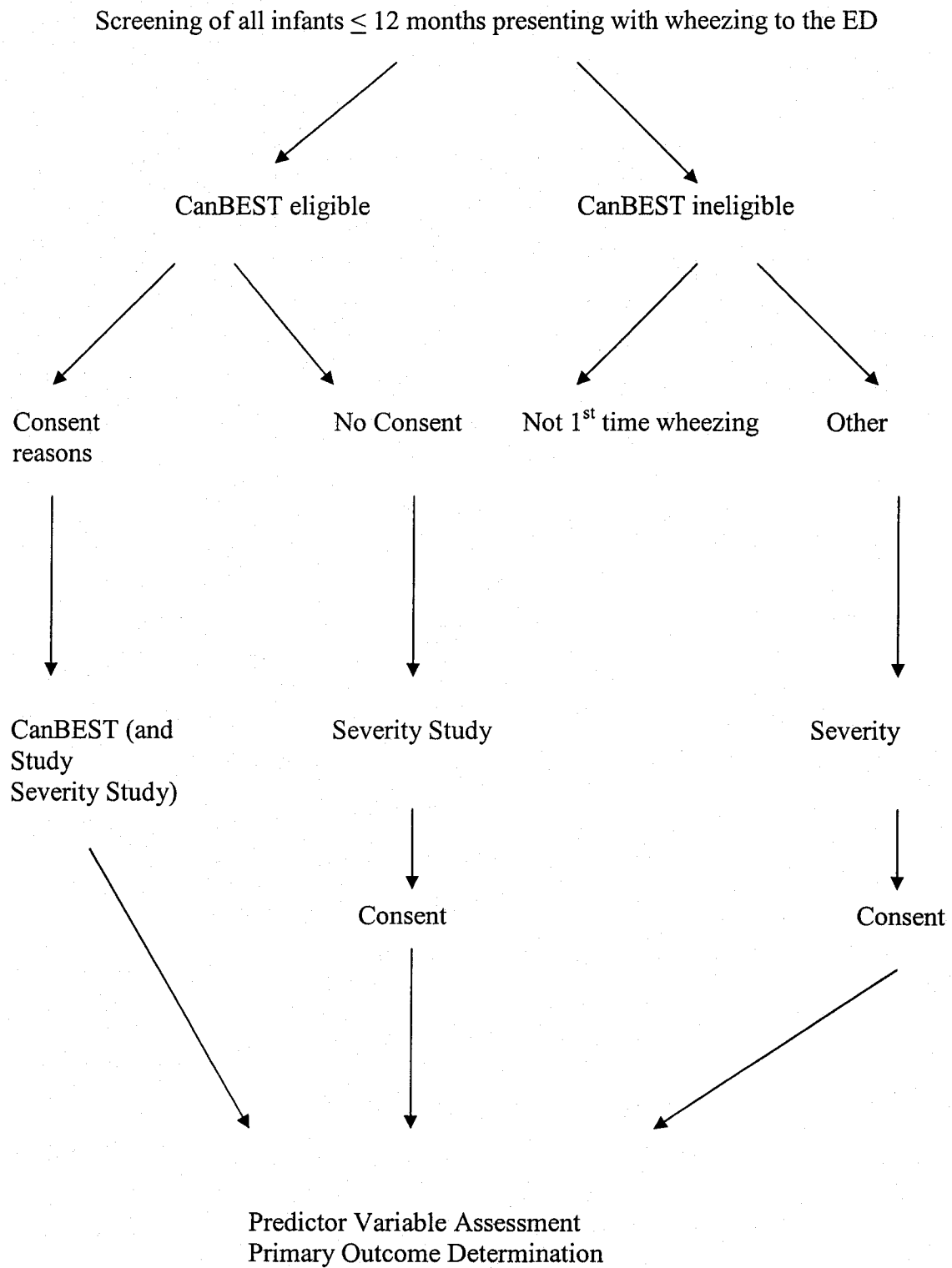


Figure 3: Flow of participants through the study

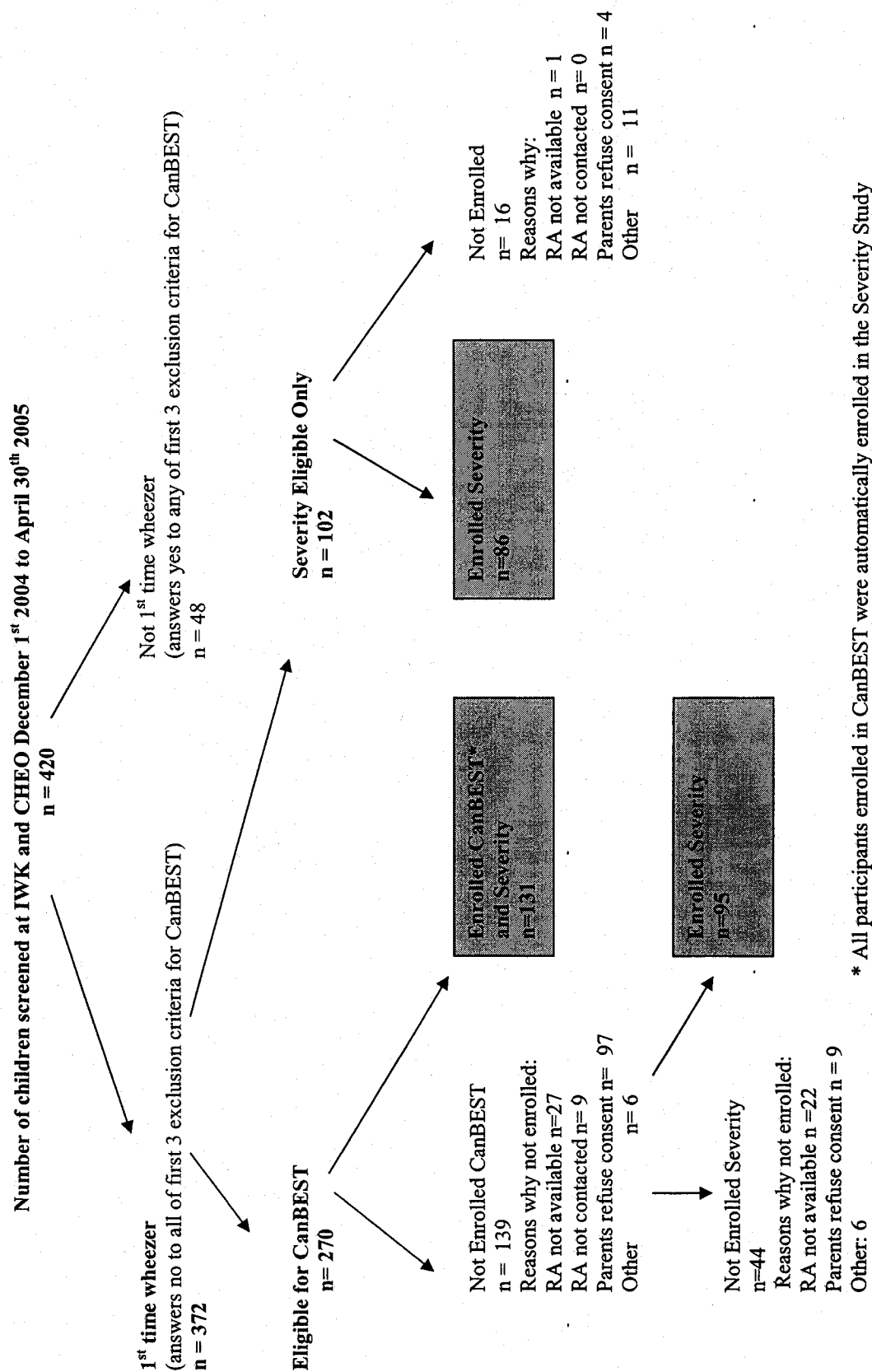


Figure 4: Receiver operating characteristic curve for final logistic regression model developed for predicting the development of severe bronchiolitis

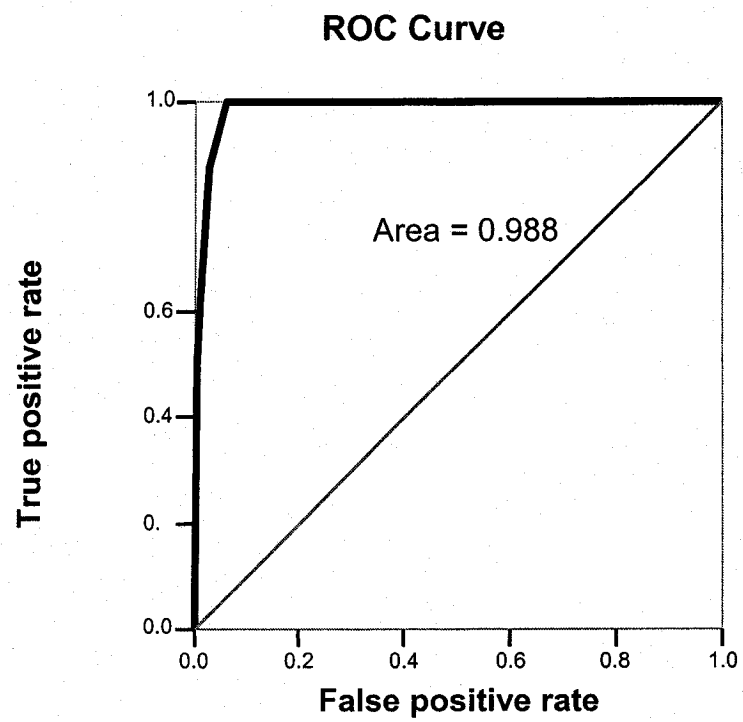


Figure 5: Preliminary decision rules derived using logistic regression model from a prospective cohort of children presenting to the Emergency Department with bronchiolitis

Bronchiolitis Severity Rule

Clinical Variable	Present	
	Yes	No
Is the heart rate outside normal range?	Yes	No
Is the RDAI ≥ 10 ?	Yes	No
Is the oxygen saturation $< 92\%$ on room air?	Yes	No

Bronchiolitis Severity Rule is considered positive if “yes” is the answer for any of the three questions. A positive rule indicates the child is at risk of developing severe bronchiolitis.

Figure 6: Classification performance of preliminary model developed using logistic regression to determine which children with bronchiolitis are at risk of developing severe bronchiolitis

One affirmative answer for a “positive” rule:

	Severe Bronchiolitis	
Bronchiolitis Severity Rule positive	Yes	No
Yes	8	118
No	0	184

Sensitivity = 100% (95% CI 60,100)

Specificity = 61% (95% CI 55, 66)

Percentage of children in cohort that would need to be admitted to a tertiary care centre due to risk of developing severe bronchiolitis 40%

Two affirmative answers for a “positive” rule:

	Severe Bronchiolitis	
Bronchiolitis Severity Rule positive	Yes	No
Yes	7	8
No	1	294

Sensitivity = 88% (95% CI 47,99)

Specificity = 97% (95% CI 95,99)

Percentage of children in cohort that would need to be admitted to a tertiary care centre due to risk of developing severe bronchiolitis 4.8%

Figure 7: Flow diagram of the recursive partitioning model using oxygen saturation $\leq 88\%$ and heart rate outside normal range

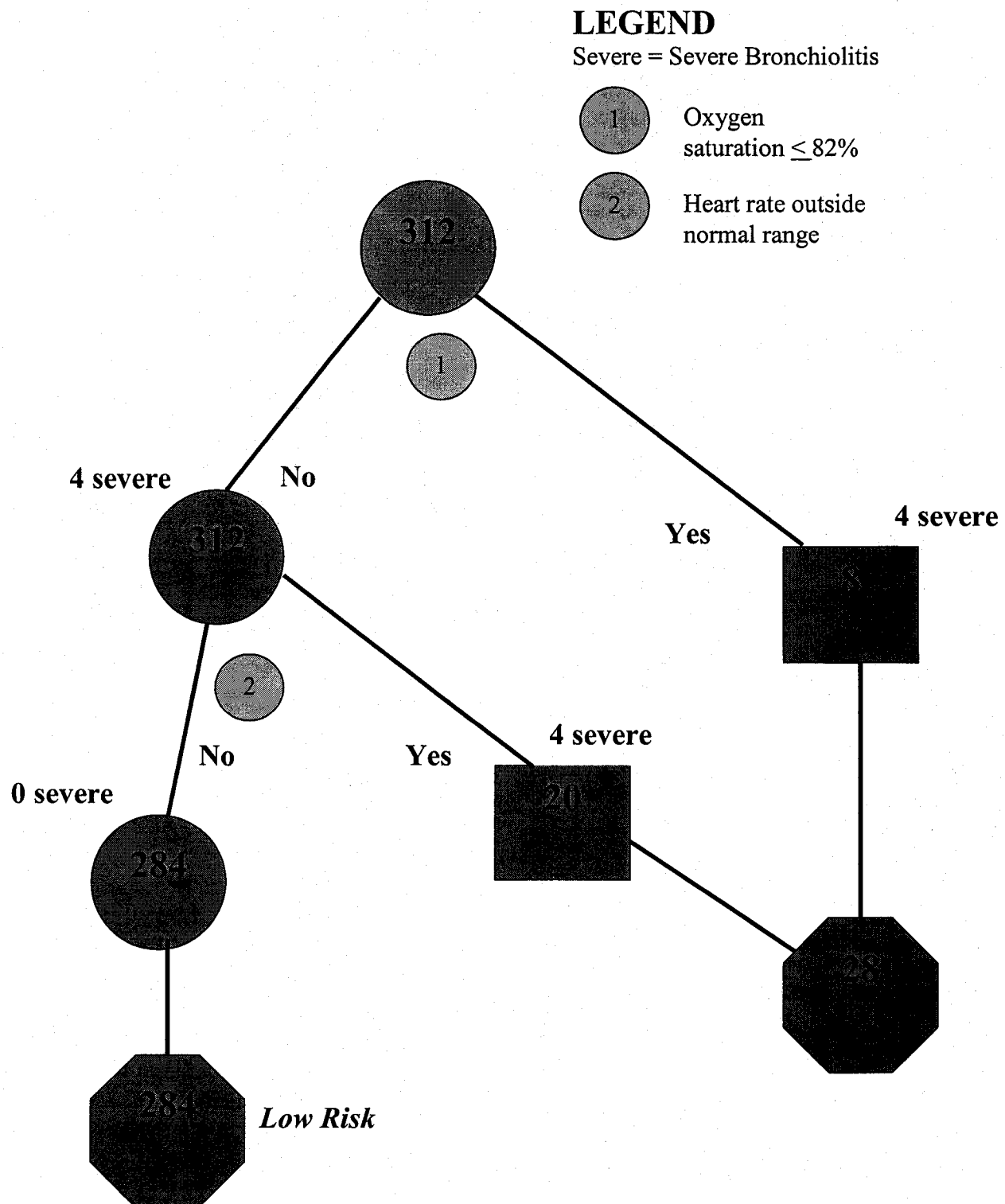


Figure 8: Preliminary decision rule by recursive partitioning analysis from a prospective cohort of children presenting to the Emergency Department with bronchiolitis

Child is at risk of developing severe bronchiolitis if:

1. Oxygen saturation less than 88% on room air

OR

2. Heart rate outside normal range for age

Figure 9: Classification performance of the preliminary decision rule determined by recursive partitioning to determine which children with bronchiolitis are at risk of developing severe bronchiolitis

	Severe Bronchiolitis	
Decision Rule	Yes	No
Yes	8	20
No	0	284

Sensitivity = 100% (95% CI 68,100)

Specificity = 93% (95% CI 90,96)

Percentage of children that would need to be admitted to a tertiary care centre due to risk of developing severe bronchiolitis 9.0%

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APPENDIX 1:

CONSENT FORM

A RANDOMIZED CONTROLLED TRIAL OF NEBULIZED EPINEPHRINE AND ORAL DEXAMETHASONE IN THE TREATMENT OF OUTPATIENTS WITH BRONCHIOLITIS

Purpose of the Study:

We are currently studying the best way of treating bronchiolitis in the emergency department. Bronchiolitis is a viral illness that is very common during the winter months. Young children that develop bronchiolitis have cough, difficulty breathing and noisy breathing (wheezing) for up to several weeks. A cross Canada study of children's hospitals showed that the treatment used varies significantly at each hospital. **While several medications have been tried in treating bronchiolitis, it remains unclear as to which, if any medications, can improve your child symptoms.**

Some physicians believe that a medication called epinephrine (given in a mist form by a face mask) may help with bronchiolitis by dilating the airways and reducing swelling inside the airways. However, while some studies have shown that it may help temporarily in improving a child's breathing, other studies have shown no benefit. Physicians have often wondered whether another type of medication, oral steroids, may help with bronchiolitis symptoms, but until one small recent study there has been almost no evidence that they help in bronchiolitis. Many physicians question whether any medications are beneficial in treating in bronchiolitis.

In order to clearly decide if either of these two medications are beneficial in treating bronchiolitis, eight children's hospitals across Canada are participating in this 2 year study. We plan to enroll 800 children into the study over the 2 year period.

Study Procedure

If you agree to your child's participation in this study your child will receive two face mask treatments 30 minutes apart that contain either epinephrine or a placebo (a solution that does not a medication). Your child will also receive one dose of dexamethasone (steroid medicine by mouth) following by 5 days of dexamethasone at home **OR** a placebo in the emergency department and followed by 5 days of placebo at home. Neither you, nor the study nurse or emergency physician, will know whether your child received a medication or placebos (this is known as "blinding"). ***However, if the emergency physician treating your child does not feel they are improving while in the emergency department they can chose to treat your child following the study treatments regardless of which medications (or placebo) they have already received.*** Decisions regarding when your child is ready to be discharged from the emergency department and any other investigations will be made by the emergency physician treating your child.

While your child is in the emergency department, a study nurse will examine your child's chest prior to each treatment and then for another 90 minutes (or until the

emergency physicians treating your child feel he/she is ready to go home). Following your return home, a study nurse will contact you by telephone to see how your child is doing. The study nurse will call daily for the first week, then every other day for the next week, then every 3 days for one more week. During this phone call, they will review with you what symptoms of bronchiolitis your child has and the effect this illness is having on your family life (such as hours of work missed and the need for visits to your family doctor). This phone call will take about 10 minutes of your time. If your child is admitted to hospital during today's visit to the emergency room, a study nurse will contact you in hospital to review your child's symptoms. In total, participation in this study from time of enrollment until follow up is concluded will be 22 days.

Your child will also have a sample of mucous taken from his/her nose by suction to determine which virus has caused your child's bronchiolitis. Most children with bronchiolitis who come to the ED have this sample taken.

If you chose to participate in this study, the time your child spends in the emergency department will not be increased.

Potential benefits:

Your child may not directly benefit from this study, although the information collected from this study will improve future treatment of bronchiolitis in children.

Potential risks:

There have been no studies addressing the safety of dexamethasone in bronchiolitis specifically but there are several studies examining their safety in other childhood diseases. It has been tested in large numbers of children with croup (an infection near the vocal cords) and is known to be safe. There are some extremely rare problems that might be related to dexamethasone. These include a severe form of chickenpox (in children who have been exposed to chickenpox before getting the dexamethasone), rare cases of bleeding from the stomach or intestines; growth problems in very ill, very small premature babies (less than 3 lbs and born about 3 months early); and very rare (estimated at no more than 1 in 30,000) of softening of the bone of the hip. However, all of these events are very rare, even in children who have needed many doses of dexamethasone. Although we do not expect any of these problems to occur, we will be monitoring for these events during telephone follow-up and by reviewing the children's medical charts. Furthermore, no child who known to be vulnerable to any of these complications would be accepted into the study.

Withdrawal from the Study:

You are free to withdraw from the study at any time and this will not affect the care your child receives.

Compensation:

In the event that you suffer injury as a direct result for participating in this study, normal legal rules on compensation will apply. By signing this consent form you are in no way waiving your legal rights or releasing the investigator and sponsor from their legal and professional responsibilities.

Study results:

At the conclusion of the research study, participants should be provided with a summary of the results of the study. During the course of the study should the investigator learn of any information that is relevant to your participation in this study we will share this information with you.

Your signature on this form indicates that you understand the information regarding this study and agree to your child's participation. If the results of this study are published your child will not be identified in any way. Your child's personal information will be kept strictly confidential except as required or permitted by law. As required by law, Health Canada, as well as representatives from the CHEO Research Ethics Board, may have access to your child's records as it pertains to this study.

If you have any questions please contact:

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Name

Date

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Witness

Name

Date

I HAVE EXPLAINED THIS STUDY TO THE PERSON AUTHORIZED TO SIGN ABOVE AND
I AM SATISFIED THAT IT IS UNDERSTOOD.

Signature

Name

Date

Parent

Witness

You may contact the Chair of the Research Ethics Committee, Dr. Carole Gentile, for information regarding patient's rights in research studies at 737-7600; however, this person cannot provide any medical information with regard to this study.

In the future as we wish to use the data collected in this study to answer other questions about bronchiolitis. If the results of this study are published your child will not be identified in any way. Any personal information that leaves the hospital will be coded such that your child cannot be identified by name. Do you consent to future use of this information in related studies? Yes No

In the future we may wish to contact you for long-term follow-up about your child's illness. Do you consent to contact in the future regarding your child's illness? Yes No

If yes, would you please give the name and contact information for someone close to your family in case you move (for example, grandparents)

Name: _____
 (first name) (last name)

Phone Number: (_____) _____ - _____

Relationship to your child : _____

Canadian Bronchiolitis Epinephrine Steroid Trial (CanBEST)

(This ID Number is for Screening purposes only)

Screening ID:

3	1	0
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-

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Patient Initials:

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Site ScreeningNumber

Patient Number

F M L

Date screened:

dd	mm	yyyy			

Date of ED Visit:

dd	mm	yyyy			

Age (in months) _____ (If less than one month of age) Age in weeks _____

Is patient preterm? ☐ Yes ☐ No If yes, eligibility/corrected age (in months) _____**Inclusion criteria (Exclude the patient if any of the answers to the following questions is 'No')**Aged 6 weeks to 12 months (check whether patient is preterm and adjust age) ☐ Yes ☐ No ☐ N/ARDAI score >3 and ≤15 (will be done by RA) ☐ Yes ☐ No ☐ N/A**Exclusion criteria (Exclude the patient if any of the answers to the following questions is 'Yes')**

Previous diagnosis of asthma by a physician	☐ Yes ☐ No
Previous episode of wheezing and/or cough treated with bronchodilators or inhaled steroids	☐ Yes ☐ No
Previous episode of wheezing that was confirmed by a physician (ie. Physician told parent they heard wheezing)	☐ Yes ☐ No
Chronic disease that may affect cardiopulmonary status of patient (such as BPD, cystic fibrosis, congenital heart disease, immune deficiency)	☐ Yes ☐ No
If yes- specify _____	
Severe respiratory distress as evidenced by:	
☐ a pulse rate > 200	
☐ a respiratory rate > 80	
☐ RDAI >15	
☐ Profound lethargy	☐ Yes ☐ No
Recent treatment with oral or inhaled steroids (within 2 weeks)	☐ Yes ☐ No
History of adverse reaction to steroids	☐ Yes ☐ No
Presence of varicella or recent close contact (less than 3 weeks) (in a child without a history of prior infection)	☐ Yes ☐ No
Born at < 37 weeks gestation – now < 6 weeks corrected age	☐ Yes ☐ No
Language barrier	☐ Yes ☐ No
No access to a telephone	☐ Yes ☐ No
Previous enrollment in the study	☐ Yes ☐ No
Not available for complete follow-up	☐ Yes ☐ No

Nov 11. 04

Fax completed forms to the coordinationg site @ CHEO (613) 738-4238

**Canadian Bronchiolitis Epinephrine Steroid Trial
(CanBEST)**

(This ID Number is for Screening purposes only)

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Patient Number

F M L

CanBEST Eligibility

If NO go to Severity Screening

If YES does not require screening for Severity Study.

_____ : _____
hh:mm (00:00-23:59)

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Site Number

Patient Number

If patient is NOT enrolled in CanBEST, specify reason:

- ☐ Research Assistant not contacted
☐ Research Assistant not available
☐ Family refused to sign consent
☐ Other, specify _____

Severity Study

If child is not eligible for CanBEST but meets inclusion/exclusion criteria listed below, approach parents for consent in Severity study. Use consent form "A".

Inclusion Criteria

☐ Yes ☐ No

☐ Yes ☐ No

Exclusion Criteria

☐ Yes ☐ No

☐ Yes ☐ No

☐ Yes ☐ No

☐ Yes ☐ No

**Canadian Bronchiolitis Epinephrine Steroid Trial
(CanBEST)**

(This ID Number is for Screening purposes only)

Screening ID:

3	1	0
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Patient Initials:

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Site ScreeningNumber

Patient Number

F M L

If the child is eligible for the CanBEST study but parents refuse consent, approach parents for consent for Severity Study. Using Consent form "B".

Is this patient eligible for the Severity Study?

☐ Yes ☐ No

If yes, is this patient enrolled?

☐ Yes ☐ No

If no, specify reason:

- ☐ Research Assistant not contacted
- ☐ Research Assistant not available
- ☐ Family refused to sign consent
- ☐ Other, specify _____

Severity Study ID

3	2	0
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Site Number

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Patient Number

Form completed by _____ Signature _____ Date ____/____/____
(please print name) dd mm yyyy

Form reviewed by _____ Signature _____ Date ____/____/____
(please print name) dd mm yyyy



APPENDIX 3: SEVERITY CONSENT FORM

Purpose of the Study:

Bronchiolitis is a viral illness that is very common during the winter months. Young children that develop bronchiolitis have cough, difficulty breathing and noisy breathing (wheezing) for up to several weeks. Doctors at eight hospitals across Canada are interested in understanding more about what factors in a child's history or physical exam predispose them to developing more severe bronchiolitis. These hospitals are participating in a two-year study about bronchiolitis. We plan to enroll 2500 patients less than or equal to one year of age who have bronchiolitis in this study. The Investigator at CHEO responsible for this study is Dr. Amy Plint.

Your decision to participate or not in this study will not influence the care your child receives at the hospital.

Study Procedure

If you agree to your child's participation in this study we will ask you some questions about their home environment. We would also like to examine your child's breathing. These questions and examination should take no more than 10 minutes of your time and should not significantly prolong your stay in the Emergency Department.

Participating in this study will not change the treatment you receive in the Emergency Department which will be determined by the doctors and nurses treating your child.

We would also like to review your child's hospital chart 22 days following your emergency department visit. When we review your child's chart we will be determining whether they were admitted to the hospital during the 22 days for bronchiolitis and if they were how they did in hospital.

Potential benefits:

Your child may not directly benefit from this study, although the information collected from this study will improve future treatment of bronchiolitis in children.

Potential risks:

There are no potential risks to participating in this study apart from the inconvenience of answering questions.

Compensation:

In the event that you suffer injury as a direct result for participating in this study, normal legal rules on compensation will apply. By signing this consent form you are in no way waiving your legal rights or releasing the investigator from their legal and professional responsibilities.

Study results:

At the conclusion of the research study, participants would be provided with a summary of the results of the study.

Your signature on this form indicates that you understand the information regarding this study and agree to your child's participation. If the results of this study are published your child will not be identified in any way. Any personal information that leaves the hospital will be coded such that your child cannot be identified by name.

If you have any questions please contact:

Study Co-ordinator: Rhonda Correll, HBSc. Nursing,
office -613-737-7600, ext. 3905
pager 239-7302

Principal Investigator: Dr Amy Plint, MD, FRCPC,
Office 613-737-7600, ext. 3237
pager 594-6031.

Signature
Parent/Guardian

Name

Date

Signature
Witness

Name

Date

I HAVE EXPLAINED THIS STUDY TO THE PERSON AUTHORIZED TO SIGN ABOVE
AND I AM SATISFIED THAT IT IS UNDERSTOOD.

Signature

Name

Date

Parent

Witness

You may contact the Chair of the Research Ethics Committee, Dr. Carole Gentile, for information regarding patient's rights in research studies at 737-7600; however, this person cannot provide any health related information about the study.

In the future as we wish to use the data collected in this study to answer other questions about bronchiolitis. If the results of this study are published your child will not be identified in any way. Any personal information that leaves the hospital will be coded such that your child cannot be identified by name. Do you consent to future use of this information in related studies?

Yes

No

Study ID:

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Site Number

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Patient Number

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Date and time of triage: _____ / _____ / _____ : _____
dd mm yyyy hh:mm (00:00 - 23:59)

Postal Code _____ - _____

Date of Birth: / /
 dd mm yyyy

Number of weeks of completed pregnancy? _____

Age (months) _____

Sex: ☐ Male ☐ Female

Rectal temperature _____ degrees celsius

[illegible]

- 1.) Has your baby ever been diagnosed with environmental allergies or eczema? ☐ Yes ☐ No
- 2.) Has either parent or any siblings ever been diagnosed with environmental allergies, asthma or eczema? ☐ Yes ☐ No
- 3.) Has your baby received RSV immunoglobulin? ☐ Yes ☐ No
- 4.) Has the baby had any other significant illness in the past?
If yes, specify _____ ☐ Yes ☐ No
- 5.) Has your baby ever required a tube to be placed down his/her throat in order to help him/her breathe?
If yes, specify _____ ☐ Yes ☐ No
- 6.) Since your child became ill, has he/she received any medication through an inhaler or puffer to help open up his/her lungs and help him/her breathe?
If yes, do you know the name of the medication or what colour the puffer was? _____ ☐ Yes ☐ No
- 7.) Has your baby been treated with antibiotics for this illness as of today?
If yes, specify _____ ☐ Yes ☐ No
- 8.) Did mother smoke during pregnancy? ☐ Yes ☐ No

Canadian Bronchiolitis Severity Study

Study ID:

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Site Number

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Patient Number

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- 9.) Are there other smokers in the household? ☐ Yes ☐ No
- 10.) Has mother been smoking in the past two weeks? ☐ Yes ☐ No
If yes, how many cigarettes per day, on average? _____
- 11.) How many people live in the patient's home (including the patient) _____
- 12.) How many children (<18 years of age) living in the home (including the patient)? _____
- 13.) Does the child attend daycare? ☐ Yes ☐ No
- 14.) Did mother breast feed the infant at any time? ☐ Yes ☐ No
If yes, how many weeks? _____
- 15.) It appears that certain races may be at higher risk for severe bronchiolitis, what race would you identify your child?
- ☐ Caucasian ☐ Black ☐ Asian ☐ Arabic ☐ East Indian
- ☐ Other (Specify) _____ ☐ Declined to Answer

RDAI Respiratory Distress Assessment Instrument						
Wheezing	0	1	2	3	4	Maximum
Expiratory	None	End	½	¾	All	4
Inspiratory	None	Part	All			2
Location	None	≤2 lung fields	≥3 lung fields			2
Retractions	0	1	2	3	4	Maximum
Supraclavical	None	Mild	Moderate	Marked		3
Intercostal	None	Mild	Moderate	Marked		3
Subcostal	None	Mild	Moderate	Marked		3

Respiratory Assessment

Time Assessment Performed		RDAI Wheeze	RDAI Retractions	RR (Breaths per min)	HR (BPM)	O ₂ Sat % on room air	Patient Status (check one only)
Time "0"	____ : ____ (00:00 – 23:59)						☐ Asleep ☐ Awake/quiet

Baseline BP (mm Hg) ____ : ____

Canadian Bronchiolitis Severity Study

Study ID:

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Site Number

-

--	--	--

Patient Number

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M

L

Form completed by _____ Signature _____ Date ____/____/____
(please print name) dd mm yyyy

Form reviewed by _____ Signature _____ Date ____/____/____
(please print name) dd mm yyyy

Canadian Bronchiolitis Severity Study

Study ID:

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Patient Initials:

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Site Number

Patient Number

F

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Emergency Enrollment Visit

Final ED diagnosis ☐ Bronchiolitis? ☐ Other? Specify _____

Medications received in the ED.

Epinephrine nebulized	☐ Yes ☐ No
Salbutamol MDI	☐ Yes ☐ No
Salbutamol nebulized	☐ Yes ☐ No
Oral steroids, specify	☐ Yes ☐ No
Nebulized steroids, specify	☐ Yes ☐ No
Intravenous steroids, specify	☐ Yes ☐ No

Chest X-rays

Chest Xray done during enrollment visit? ☐ NO ☐ YES If yes, indicate all findings that apply, on the table below

Pneumonia	☐ Yes ☐ No
Atelectasis	☐ Yes ☐ No
Infiltrate	☐ Yes ☐ No
Hyperinflation	☐ Yes ☐ No
Consolidation	☐ Yes ☐ No
Other, specify _____	☐ Yes ☐ No

Virology Results

Where viral studies (DFA, cultures, etc) done during ED Enrollment visit?

☐ No ☐ Yes If YES, complete table below (check if positive)

☐	RSV
☐	Adenovirus
☐	Influenza A
☐	Influenza B
☐	Parainfluenza
☐	Other, specify _____

Canadian Bronchiolitis Severity Study

Study ID:

-

Patient Initials:

Site Number

Patient Number

F

M

L

Did the patient have a preceding ED visit within 7 days?

☐ No☐ Yes If yes, was a nasal aspirate sent for viral testing?

If YES indicate the result from the nasal aspirate in the space provided

Admissions

Was this patient admitted to hospital during the enrollment visit to the ED?

☐ Yes ☐ No

If yes, date and time of hospital admission:

 / / : :
dd mm yyyy hh:mm (00:00 to 23:59)

if yes, date and time of hospital discharge:

 / / : :
dd mm yyyy hh:mm (00:00 to 23:59)
Final Discharge diagnosis ☐ Bronchiolitis? ☐ Other? Specify _____Was this patient admitted to hospital in the 22 days following their enrollment visit? ☐ Yes ☐ No

If yes, date and time of hospital admission:

 / / : :
dd mm yyyy hh:mm (00:00 to 23:59)

If yes, date and time of hospital discharge:

 / / : :
dd mm yyyy hh:mm (00:00 to 23:59)
Final Discharge diagnosis ☐ Bronchiolitis? ☐ Other? Specify _____

Canadian Bronchiolitis Severity Study

Study ID:

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Site Number

-

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Patient Number

Patient Initials:

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F

M

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COURSE IN HOSPITALDid the child have any apneic spells during their hospital admissions? ☐ Yes ☐ NoWas the child admitted to the ICU during their hospital admission? ☐ Yes ☐ No

If yes, Date of ICU admission

____	/	____	/	____
dd		mm		yyyy

Date of ICU discharge

____	/	____	/	____
dd		mm		yyyy

Was the child intubated during their hospital admission? ☐ Yes ☐ No

If yes, Date of intubation

____	/	____	/	____
dd		mm		yyyy

Date of extubation

____	/	____	/	____
dd		mm		yyyy

Did the child survive their illness? ☐ Yes ☐ No

If no, date of death

____	/	____	/	____
dd		mm		yyyy

Form completed by _____ (please print name)	Signature _____	Date ____/____/____ dd mm yyyy
--	-----------------	-----------------------------------

Form Review by _____ (please print name)	Signature _____	Date ____/____/____ dd mm yyyy
---	-----------------	-----------------------------------

Medical Examiner Review – for Coordinating Site to completeDid this child die in the 22 days following their ED visit? ☐ Yes ☐ No

Canadian Bronchiolitis Severity Study

Study ID:

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Patient Initials:

--	--	--

Site Number

Patient Number

F

M

L

If yes, specify the cause of death: _____

If yes, date of death: _____

dd

mm

yyyy

Form completed by _____ Signature _____ Date ____/____/____
(please print name) dd mm yyyy

APPENDIX 6: CanBEST Screening Log

[illegible]

Canadian Bronchiolitis Severity Study

Study ID:

3 2 0

Site Number

-

Patient Number

F

M

L

Demographics

Number of weeks of completed pregnancy? _____

Date respiratory symptoms (cough, coryza, noisy breathing) started? _____ / _____ / _____
dd mm yyyy

History

- 1.) Has your baby ever been diagnosed with environmental allergies or eczema? ☐ Yes ☐ No
- 2.) Has either parent or any siblings ever been diagnosed with environmental allergies, asthma or eczema? ☐ Yes ☐ No
- 3.) Has your baby received RSV immunoglobulin? ☐ Yes ☐ No
- 4.) Has the baby had any other significant illness in the past? ☐ Yes ☐ No
If yes, specify _____
- 5.) Has your baby ever required a tube to be placed down his/her throat in order to help him/her breathe? ☐ Yes ☐ No
If yes, specify _____
- 6.) Since your child became ill, has he/she received any medication through an inhaler or puffer to help open up his/her lungs and help him/her breathe? ☐ Yes ☐ No
If yes, do you know the name of the medication or what colour the puffer was? _____
- 7.) Has your baby been treated with antibiotics for this illness as of today? ☐ Yes ☐ No
If yes, specify _____
- 8.) Did mother smoke during pregnancy? ☐ Yes ☐ No
- 9.) Are there other smokers in the household? ☐ Yes ☐ No
- 10.) Has mother been smoking in the past two weeks? ☐ Yes ☐ No
If yes, how many cigarettes per day, on average? _____
- 11.) How many people live in the patient's home (including the patient) _____
- 12.) How many children (<18 years of age) living in the home (including the patient)? _____
- 13.) Does the child attend daycare? ☐ Yes ☐ No

Canadian Bronchiolitis Severity Study

Study ID:

3

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-

Site Number

Patient Number

F

M

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14.) Did mother breast feed the infant at any time?

☐ Yes ☐ No

If yes, how many weeks? _____

15.) It appears that certain races may be at higher risk for severe bronchiolitis, what race would you identify your child?

☐ Caucasian ☐ Black ☐ Asian ☐ Arabic ☐ Other (Specify) ☐ Declined to AnswerForm completed by _____ Signature _____ Date ____/____/____
(please print name) dd mm yyyyForm reviewed by _____ Signature _____ Date ____/____/____
(please print name) dd mm yyyy

APPENDIX 7 Canadian Bronchiolitis Severity Study

Study ID:

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--	--	--

Site Number

Patient Number

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THIS FORM WILL ONLY BE COMPLETED BY 2ND OBSERVER**Demographics**

Number of weeks of completed pregnancy? _____

Date respiratory symptoms (cough, coryza, noisy breathing) started? _____ / _____ / _____
dd mm yyyy**History**

- 1.) Has your baby ever been diagnosed with environmental allergies or eczema? ☐ Yes ☐ No
- 2.) Has either parent or any siblings ever been diagnosed with environmental allergies, asthma or eczema? ☐ Yes ☐ No
- 3.) Has your baby received RSV immunoglobulin? ☐ Yes ☐ No
- 4.) Has the baby had any other significant illness in the past? ☐ Yes ☐ No
If yes, specify _____
- 5.) Has your baby ever required a tube to be placed down his/her throat in order to help him/her breathe? ☐ Yes ☐ No
If yes, specify _____
- 6.) Since your child became ill, has he/she received any medication through an inhaler or puffer to help open up his/her lungs and help him/her breathe? ☐ Yes ☐ No
If yes, do you know the name of the medication or what colour the puffer was? _____
- 7.) Has your baby been treated with antibiotics for this illness as of today? ☐ Yes ☐ No
If yes, specify _____
- 8.) Did mother smoke during pregnancy? ☐ Yes ☐ No
- 9.) Are there other smokers in the household? ☐ Yes ☐ No
- 10.) Has mother been smoking in the past two weeks? ☐ Yes ☐ No
If yes, how many cigarettes per day, on average? _____
- 11.) How many people live in the patient's home (including the patient) _____
- 12.) How many children (<18 years of age) living in the home (including the patient)? _____
- 13.) Does the child attend daycare? ☐ Yes ☐ No

APPENDIX 7 Canadian Bronchiolitis Severity Study

Study ID:

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Site Number

Patient Number

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F

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14.) Did mother breast feed the infant at any time?

☐ Yes ☐ No

If yes, how many weeks? _____

15.) It appears that certain races may be at higher risk for severe bronchiolitis, what race would you identify your child?

☐ Caucasian ☐ Black ☐ Asian ☐ Arabic ☐ Other (Specify) ☐ Declined to AnswerForm completed by _____ Signature _____ Date ____/____/____
(please print name) dd mm yyyyForm reviewed by _____ Signature _____ Date ____/____/____
(please print name) dd mm yyyy

**APPENDIX 7 con't: Canadian Bronchiolitis Epinephrine Steroid
Trial
(CanBEST)**

Study ID: - Patient Initials:

Date: (dd/mm/yy) _____/_____/_____

Time of Assessment (hh:mm) _____;

DOB (dd/mm/yy) _____/_____/_____

Age (months) _____

RA Initials _____

RDAI Respiratory Distress Assessment Instrument						
Wheezing	0	1	2	3	4	Maximum
Expiratory	None	End	½	¾	All	4
Inspiratory	None	Part	All			2
Location	None	≤2 lung fields	≥3 lung fields			2
Retractions	0	1	2	3	4	Maximum
Supraclavical	None	Mild	Moderate	Marked		3
Intercostal	None	Mild	Moderate	Marked		3
Subcostal	None	Mild	Moderate	Marked		3

RDAI Score _____

APPENDIX 8: Canadian Bronchiolitis Severity Study

Study ID:

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Patient Initials:

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Site Number

Patient Number

F

M

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AdmissionsWas this patient admitted to hospital during the enrollment visit to the ED? ☐ Yes ☐ NoWas this patient admitted to hospital in the 22 days following their enrollment visit? ☐ Yes ☐ No**COURSE IN HOSPITAL**Did the child have any apneic spells during their hospital admissions? ☐ Yes ☐ NoWas the child admitted to the ICU during their hospital admission? ☐ Yes ☐ No

If yes, Date of ICU admission

dd	/	mm	/	yyyy
----	---	----	---	------

Date of ICU discharge

dd	/	mm	/	yyyy
----	---	----	---	------

Was the child intubated during their hospital admission? ☐ Yes ☐ No

If yes, Date of intubation

dd	/	mm	/	yyyy
----	---	----	---	------

Date of extubation

dd	/	mm	/	yyyy
----	---	----	---	------

Did the child survive their illness? ☐ Yes ☐ No

If no, date of death

dd	/	mm	/	yyyy
----	---	----	---	------

Form completed by _____ Signature _____ Date

dd	/	mm	/	yyyy
----	---	----	---	------

(please print name)Form Review by _____ Signature _____ Date

dd	/	mm	/	yyyy
----	---	----	---	------

(please print name)

APPENDIX 8: Canadian Bronchiolitis Severity Study

Study ID:

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Site Number

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--	--	--

Patient Number

Patient Initials:

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F

M

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Medical Examiner Review – for Coordinating Site to complete

Did this child die in the 22 days following their ED visit?

☐ Yes☐ No

If yes, specify the cause of death:

If yes, date of death:

dd

mm

yyyy

Form completed by _____
(please print name)

Signature _____

Date _____

dd

mm

yyyy



CHEO Research Ethics Board Approval Notice - REACTIVATION

Principal Investigator:	Dr. Amy Plint
Proposal Number:	#02/59E
Protocol Title:	A randomized, controlled trial of nebulized epinephrine and oral dexamethasone in the treatment of outpatients with bronchiolitis
Department or PSU:	Emergency
Approval date:	May 2004
Approval valid until:	May 2005
Documents reviewed and approved:	REB Protocol (November 2002), Letter of Information & Consent Form (February 26, 2004); Health Canada Letter of Non-objection (April 13, 2004)

This is to notify you that the Children's Hospital of Eastern Ontario Research Ethics Board has granted full board approval to the above named research study on the date noted above. In fulfilling its mandate, the REB is guided by the Tri-Council Policy Statement, Health Canada Division 5 of the Food and Drug Regulations, the ICH Good Clinical Practice Practices: Consolidated Guidelines; as well as the applicable laws and regulations of Ontario. The REB approval is valid until the date referenced above assuming timely and acceptable responses to the REB's periodic requests for surveillance and monitoring information.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the REB except when necessary to eliminate immediate hazards to the subject. Investigators must also promptly report to the REB all adverse events that are both serious and unexpected and any new information regarding the safety of research subjects. If these changes/adverse events require a change to the information /consent document, and/or recruitment advertisement, the newly revised information/consent document, and/or advertisement, must be submitted to the office for approval. The primary investigator must produce an annual report that includes a summary of adverse events, any study amendments, and subject recruitment. A final report is also required at the conclusion of the trial. Finally, the primary investigator must notify the REB if one of the investigators leaves the institution or the project, and if the contractual agreement between the Sponsor and the principal investigator changes in any way.

Please be reminded that the Health Canada regulations also make similar reporting requirements of Phase I, II, or III clinical trials. Specifically, the sponsor of such a trial must file with Health Canada all clinical amendments to the protocol, and report any premature discontinuation of a trial. Moreover, unexpected and serious adverse events must be filed with the Ministry. Finally, it should be noted that the Health Canada clinical trial regulations require that the Sponsor maintain information on Phase I, II, and III clinical trials for a period of 25 years after the conclusion of the study. Wishing you success in your project.

Regards,

Dr. Carole Gentile, C.Psych.
Chair, Research Ethics Board

C/G/smeh 29/04/04
c.c. Pat Brazeau, Manager, CHEO Research Institute
Rhonda Correll, Research Coordinator

This is an official document. Please retain the original for your files.

Version 01/04

June
02/59E

Dear Dr. Gentile

Please consider this proposed amendment to protocol 0259-E – A randomized controlled trial of nebulized epinephrine and oral dexamethasone in the treatment of outpatients with bronchiolitis (we have now named this trial “CanBEST” or the Canadian Bronchiolitis Epinephrine Steroid Trial).

In the course of the RCT we would like to collect further information on those patients with bronchiolitis who are not eligible for the RCT (such as those with congenital heart disease) and on those who are eligible but for whom consent is not obtained. The purpose of this information would be to develop a decision rule to predict the development of severe bronchiolitis (defined as ICU admission, intubation, apnea and death) in the overall population of children with bronchiolitis. We would collect baseline history and physical exam information on the patients and then review their charts at 22 days. Consent would be obtained from all parents for this study. This same information would be collected on those patients in the RCT. I have included a brief summary of this study as well as a more detailed protocol and a copy of the data we wish to collect. I have highlighted the proposed changes to the baseline data collection form. I have also included copies of the two consent forms we would use in this part of the study.

We have also correct a mistake in the original consent form for the RCT – it states 4 days rather than 5 days of medication will be administered at home. We have also added two check box sections. The first is to allow for the use of the data collected in this study for secondary analysis (as per the ethics committee new guidelines) and the second to allow us to contact the family for long term follow-up after this study. I have highlighted the changes to the consent form.

If you have any questions, please feel free to contact me at 737-7600, ext 3237. I look forward to your reply.

Sincerely

Amy Plint, MD, FRCPC
Division of Emergency Medicine
CHEO

CHEO Research Ethics Board
A P P R O V A L

Chair's Signature: _____

Date: November 24, 2004



IWK Health Centre

RESEARCH ETHICS BOARD

Approval

5850/5980 University Avenue

PO Box 9700

Halifax, NS B3K 6R8

Canada

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The Research Ethics Board established by the IWK Health Centre has examined the application for research involving human subjects entitled:

Canadian Bronchiolitis Epinephrine Steroid Trial (CanBEST) - A Randomized Controlled Trial of Nebulized Epinephrine and Oral Dexamethasone in the Treatment of Outpatients with Bronchiolitis.

Principal Investigator(s): Brett Taylor

and found the proposed research involving human subjects to be ethically acceptable. The Research Ethics Board operates in compliance with the Tri-Council Policy Statement and ICH/GCP Guidelines. This approval will be in effect for 12 months from the date indicated below.

Date: 29-Sep-04

Alixé Howlett, MD, FRCPC

Co-Chair, Research Ethics Board

Members of Committee	Meeting Date: 18/05/2004	Attendance *
Harry Bawden	Psychology (Clinical Researcher)	Yes
Robert Bortolussi	Chief of Research (Ex-Officio)	Yes
Kelly Cameron	Lay Representative	Yes
Peter R. Camfield	Pediatrics (Clinical Researcher)	Yes
Anne Crowe	Lay Representative	Yes
Kent Dooley	Laboratory Medicine	Yes
Mike Hadskis	Legal Representative	Yes
Alixé Howlett	Pediatrics (Clinical Researcher)(Co-Chair)	Yes
Adam M. Huber	Pediatrics (Clinical Researcher)	Yes
Leah Hill	Lay Representative	Yes
Joanne McLangley	Pediatrics (Clinical Researcher)	Yes
Anthony R. Olley	Pediatrics (Clinical Researcher)(Co-Chair)	No
Joëlynn Porter	Pharmacy	Yes
Jason Scott Robert	Biotechnicist	No
Erna Snelgrove-Clarke	Nursing (Clinical Researcher)	Yes
Joan Wenning	Obstetrics & Gynaecology (Clinical Researcher)	Yes

* REB members are not in attendance during review of their own proposed research involving human subjects or where there is a conflict of interest with the proposed research.

APPENDIX 10 (con't)

REB Approved Document List

Document Title	Version Date
Telephone Followup Form - Day 22	04/02/2005
Protocol Amendment - RSV and Other Viruses	14/02/2005
Information and Authorization Form - Non Eligible Participants - Form A	18/02/2005
Information and Authorization Form - Data Collection Only - Form B	18/02/2005
Canadian Bronchiolitis Severity Study - Interobserver Form	17/02/2005
Canadian Bronchiolitis Severity Study - Day 22 Chart Review Form	17/02/2005

Appendix 11: Univariate logistic regression analysis of the data from a prospective cohort of children presenting with bronchiolitis to an Emergency Department

Logistic regression with the following variables in the model alone	Odds Ratio	95% CI
Demographics		
Age	0.90	0.83, 0.99
Age < 6 weeks	5.69	1.29, 25.04
Female	1.38	0.34, 5.60
Mean annual household income, dollars	1.0	1,1
Variables from Medical History		
Gestational age	0.97	0.71, 1.34
Preterm (< 37 weeks gestation)	2.74	0.53, 14.12
Cardiopulmonary (CP) disease*	0	-
Significant illness including CP disease	2.14	0.25, 18.30
Personal history of atopy	0	-
Length of bronchiolitis symptoms	1.06	0.94, 1.20
Symptoms $\leq$ 2 days	1.09	0.22, 5.5
Received RSV immunoglobulin*	0	-
Previously intubated	3.48	0.40, 30.5
Variables from Home Environment		
Maternal smoking during pregnancy	1.06	0.21, 5.34
Any smokers in the home	0.99	0.24, 4.39
Current maternal smoking	1.02	0.20, 5.2
Other smokers at home	0.64	0.14, 3.43
Average number of cigarettes smoked/day by mother in last two weeks	1.03	0.924, 1.41
Presence of siblings	0.54	0.13, 2.30
# Of individuals living in home	0.78	0.41, 1.47
Daycare attendance*	0	-
Breastfeeding at any time*	5.6×10^7	-
Current breastfeeding	2.33	0.51, 10.67

* The standard errors were very high for these variables Due to the presence of cells with no cases. 95% CI were not calculated.

Appendix 12: Univariate logistic regression analysis of the data from a prospective cohort of children presenting with bronchiolitis to an Emergency Department

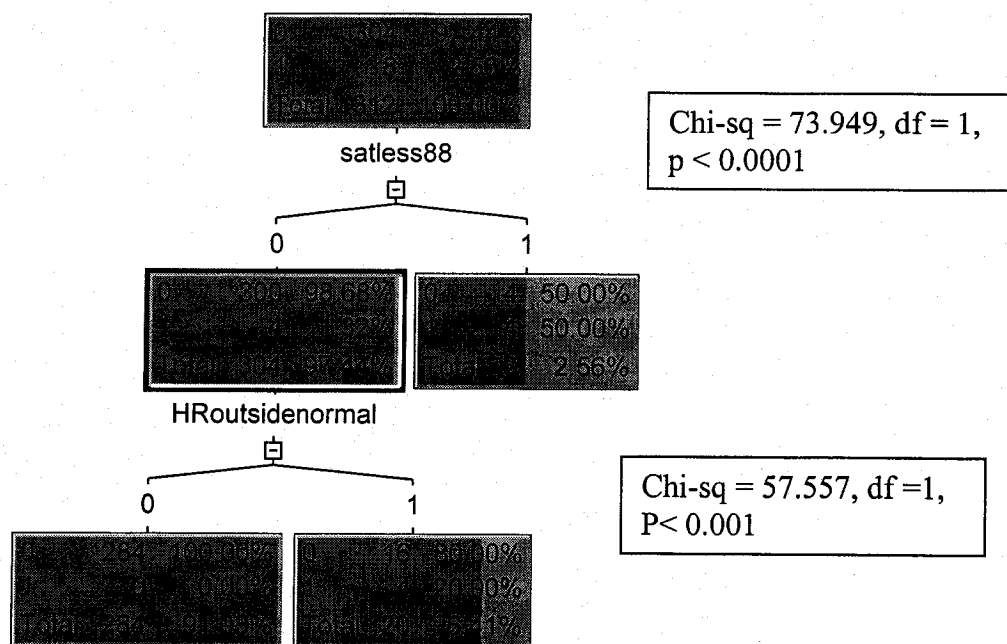
Logistic regression with the following variables in the model alone	Odd's Ratio	95% CI
Medications received prior to ED visit		
Salbutamol	0.89	0.11, 7.43
Inhaled Steroids*	0	-
Antibiotics*	0	-
Medications received in the ED		
Epinephrine	3.69	0.45, 30.42
Salbutamol	1.82	0.36, 9.31
Oral Steroids	0.42	0.05, 3.54
CXR findings		
Pneumonia	0.84	0.09, 7.68
Atelectasis	9.82	1.99, 48.43
Infiltrate*	0	-
Hyperinflation	3	0.56, 16.03
Consolidation*	0	-
Respiratory virus results		
RSV positive*	7.9 X 10 ⁷	-

*The standard errors were very high for these variables Due to the presence of cells with no cases 95% CI were not calculated

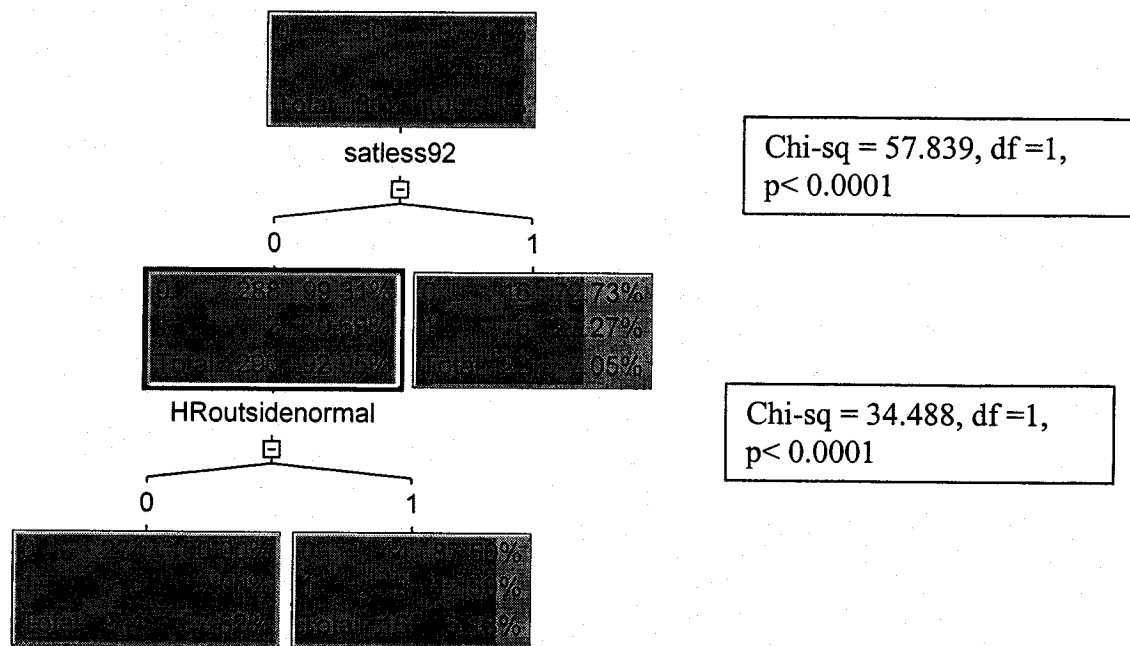
Appendix 13: Univariate correlation of variables from physical exam and results of investigations on development of severe bronchiolitis from a prospective cohort of 312 emergency department patients with bronchiolitis

Logistic regression with the following variables in the model alone	Odd's Ratio	95% CI
Temperature	0.31	0.10, 0.98
Systolic BP	1.05	1.05, 1.10
Diastolic BP	1.05	1.00, 1.10
Heart rate	1.10	1.05, 1.16
Respiratory rate	1.08	1.01, 1.15
RDAI	1.52	1.85, 1.94
Oxygen saturation	0.72	0.55, 0.79
Febrile	0.38	0.5, 3.16
Systolic BP outside normal range	3.73	0.84, 16.48
Diastolic BP outside normal range	1.72	0.33, 8.90
Heart rate outside normal range	54.00	13.74, 1016.20
Respiratory rate outside normal range*	4.60×10^7	-
RDAI ≥ 10	8.81	1.59, 107.69
RDAI ≥ 12	9.59	2.22, 41.55
RDAI ≥ 15	14.14	2.42, 82.79
Oxygen saturation < 92%	29.90	10.09, 289.05
Oxygen saturation < 88%	75.00	13.68, 411.02

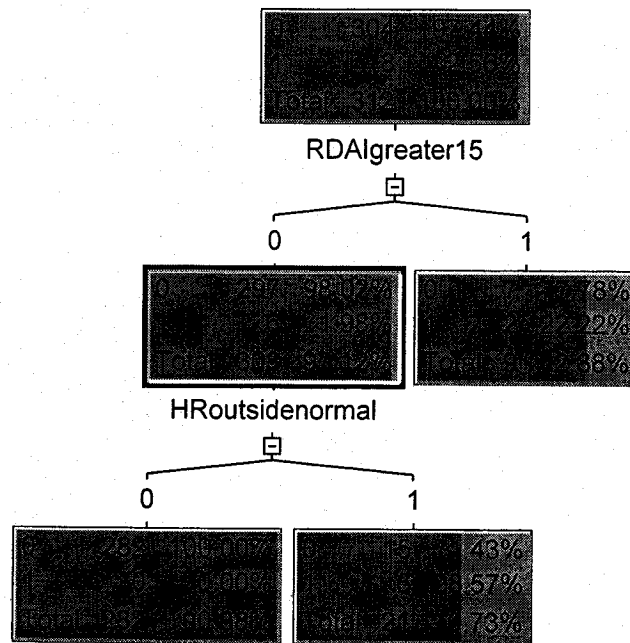
*The standard errors were very high for these variables Due to the presence of cells with no cases 95% CI were not calculated



Appendix 14: Recursive partitioning model with variables oxygen saturation < 88% and heart rate (HR) outside normal



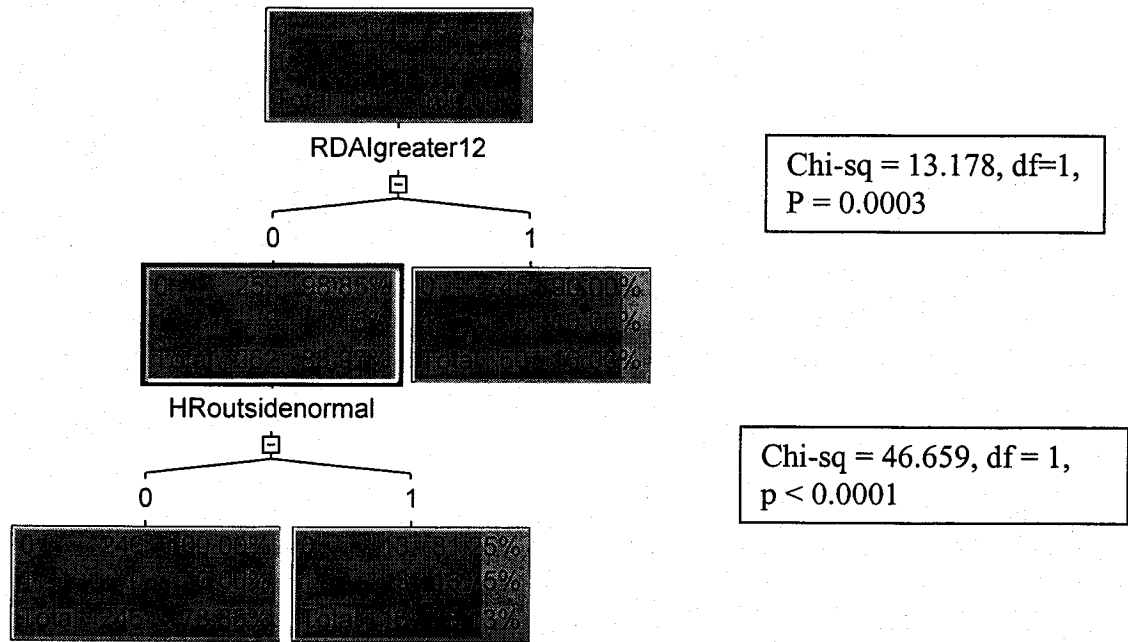
Appendix 15: Recursive partitioning model with variables oxygen saturation < 92% and heart rate (HR) outside normal



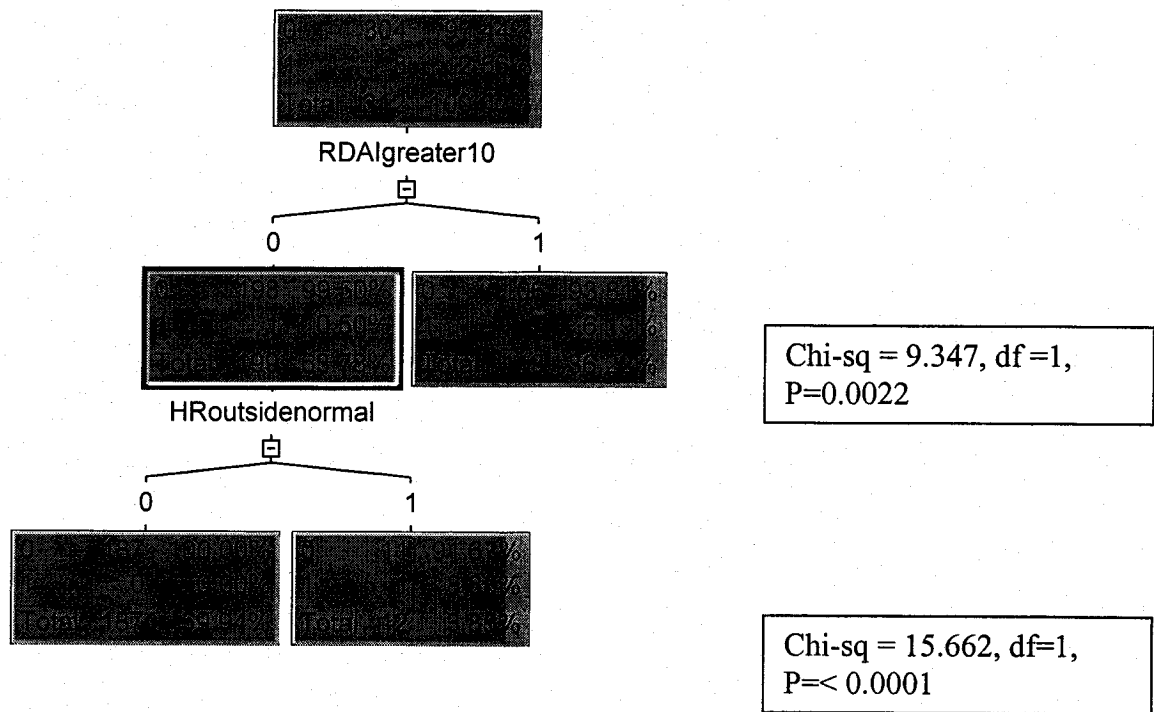
Chi-sq = 14.335, df = 1,
p = 0.002

Chi-sq = 82.199, df = 1,
p < 0.0001

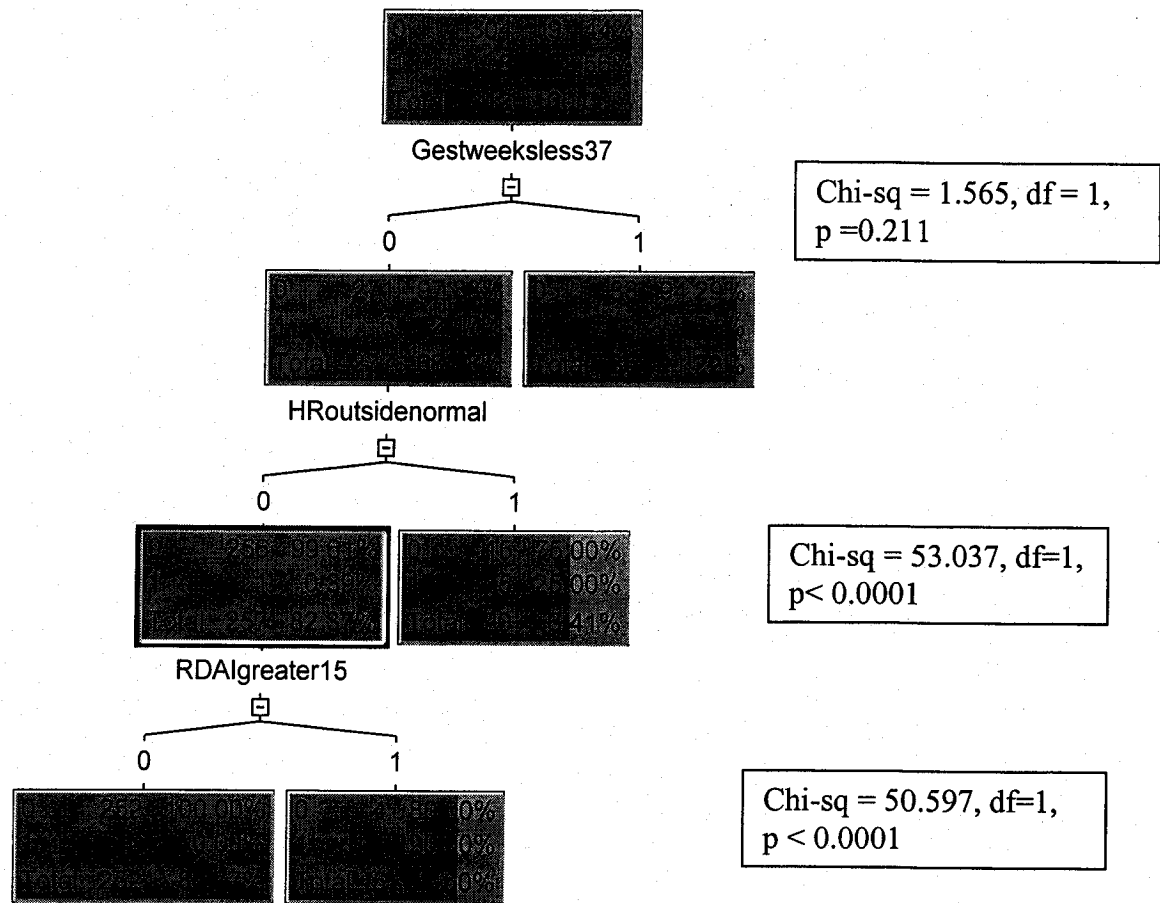
Appendix 16: Recursive partitioning model with $RDAI \geq 15$ and heart rate (HR) outside normal



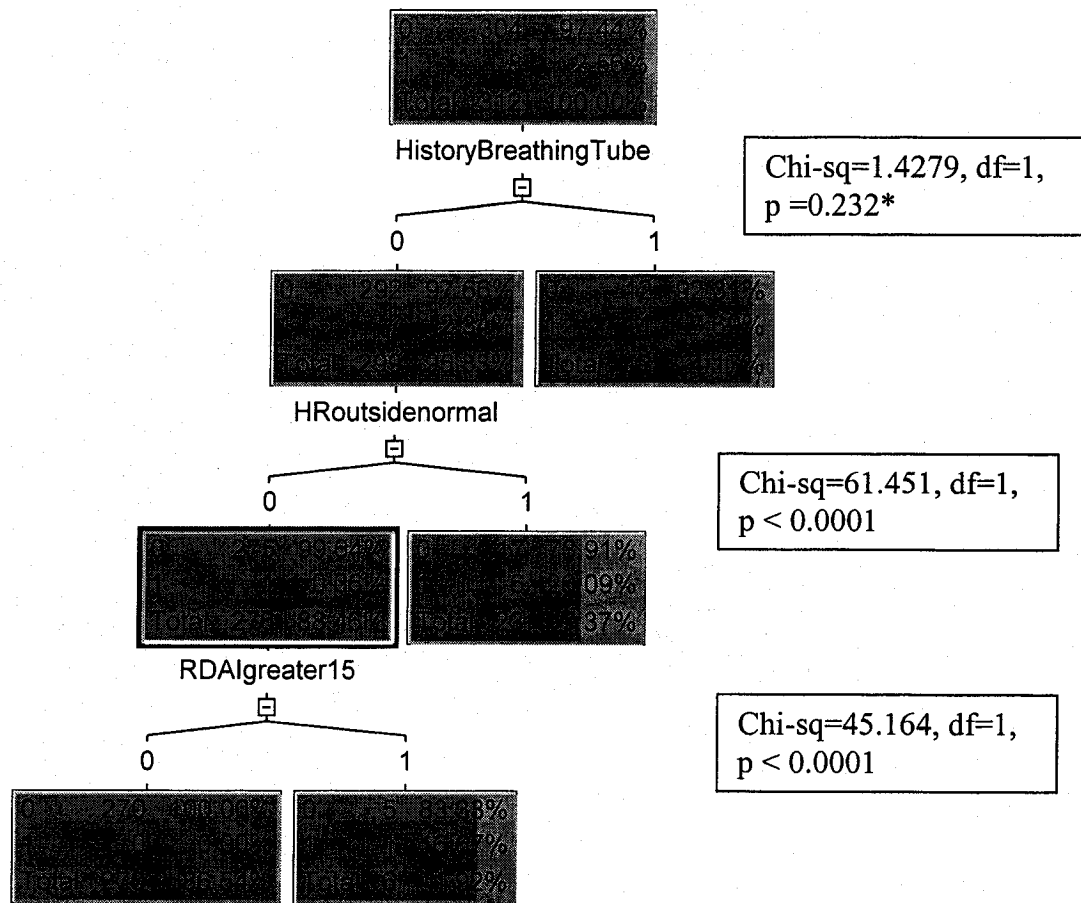
Appendix 17: Recursive partitioning model with $RDAI \geq 12$ and heart rate (HR) outside normal



Appendix 18: Recursive partitioning model with $RDAI \geq 10$ and heart rate (HR) outside normal

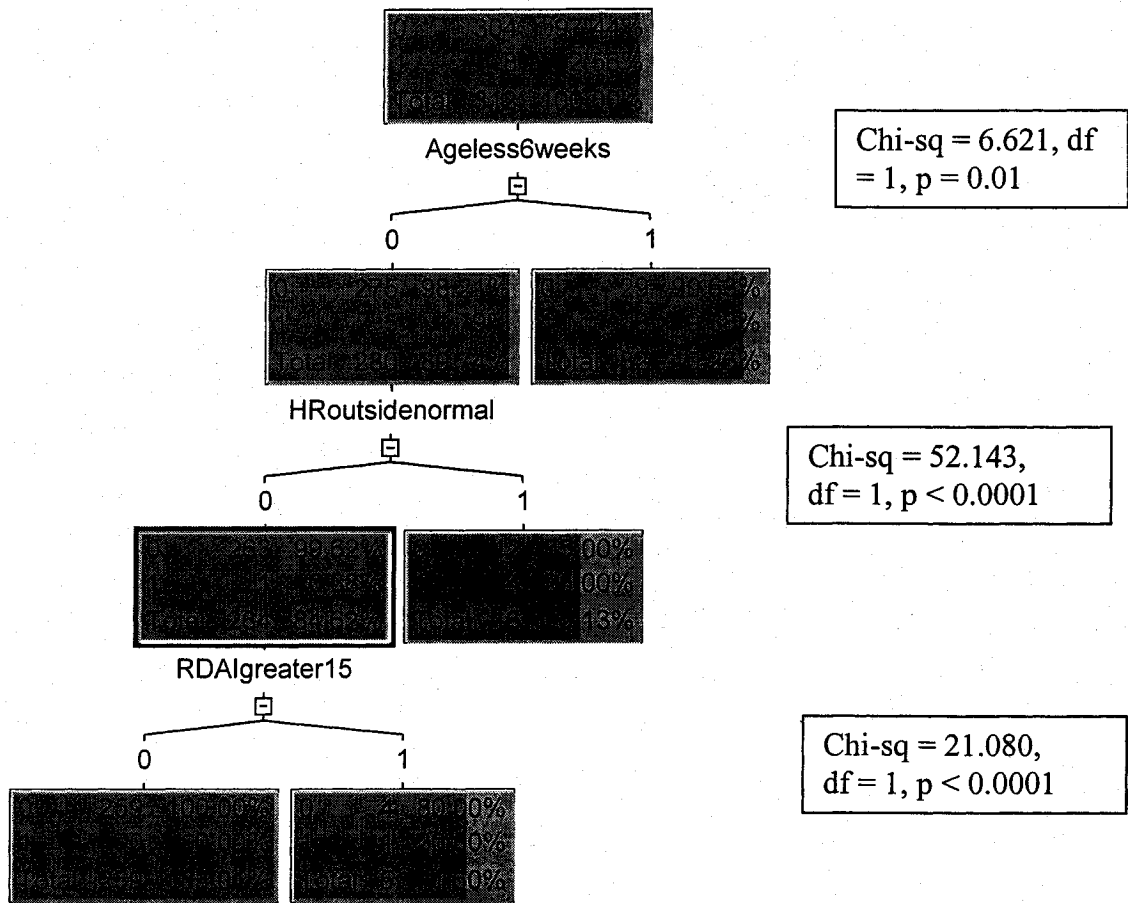


Appendix 19: Recursive partitioning model with preterm birth, heart rate (HR) outside normal, and RDAI ≥ 15



Appendix 20: Recursive partitioning model with previous intubation, heart rate (HR) outside normal, and RDAI ≥ 15

* comparison is not statistically significant but model is included as an example



Appendix 21: Recursive partitioning model with age < 6 weeks, heart rate (HR) outside normal and RDAI ≥ 15