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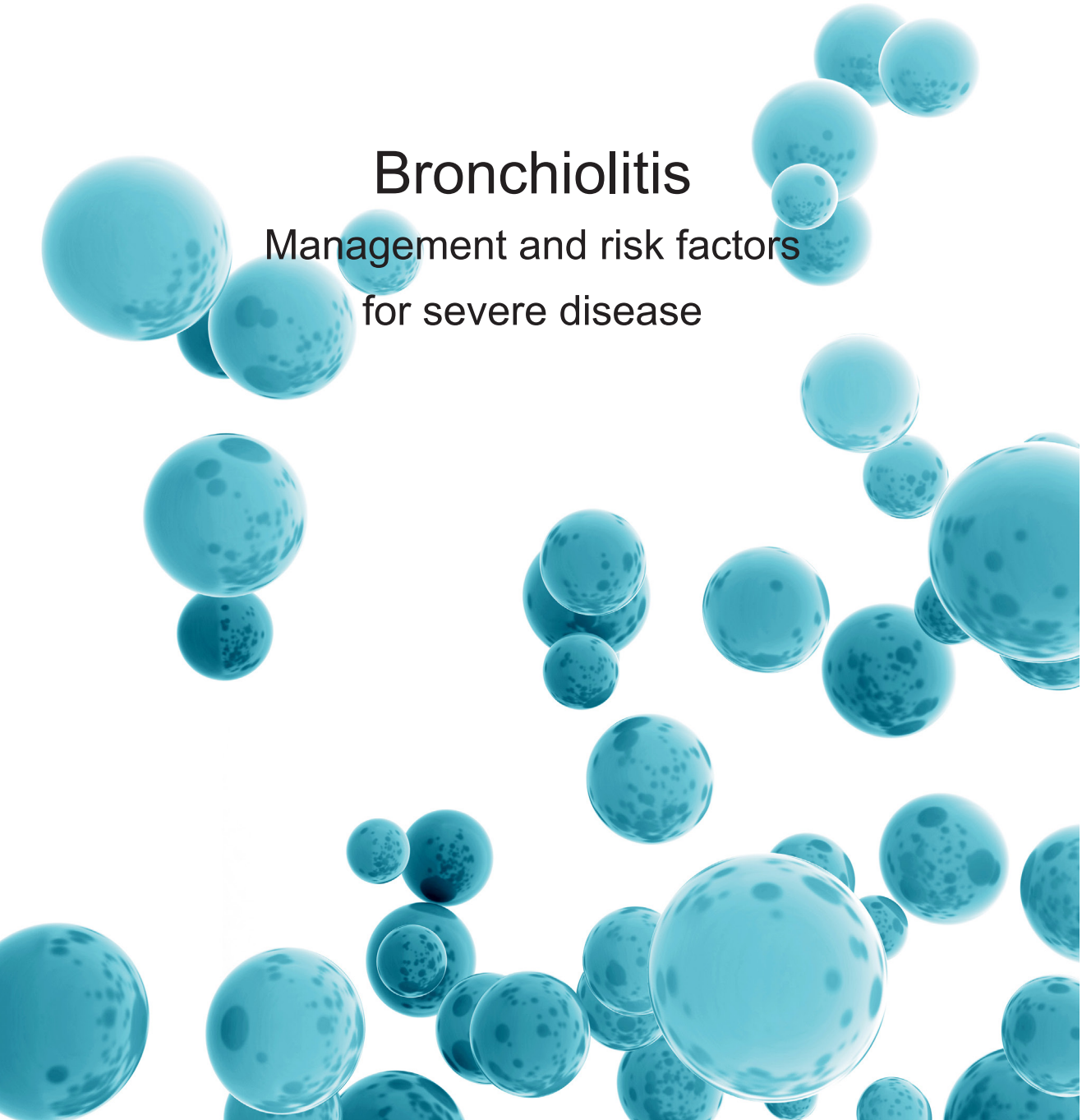
MINNA MECKLIN

Bronchiolitis

Management and risk factors for severe disease



MINNA MECKLIN

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Management and risk factors for severe disease

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ACADEMIC DISSERTATION
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UNIVERSITY OF TAMPERE

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To my family

ABSTRACT

Bronchiolitis is the primary reason for the hospitalisation of infants younger than 12 months worldwide and respiratory syncytial virus its most common causative agent. Even though bronchiolitis is both common and clinically important, there is no unified consensus on either its treatment or its diagnostic criteria. Its primary symptoms resemble those of an upper respiratory tract infection prior to the onset of typical symptoms of breathing difficulty—such as tachypnoea, chest retraction and auscultatory findings. Hospitalisation due to bronchiolitis is required for 3% of infants less than 12 months of age, of which 2–6% necessitate admission to the paediatric intensive care unit (PICU). For decades, bronchiolitis has been treated with different medications that included corticosteroids, inhaled agents (such as salbutamol, adrenaline, and saline) and anticholinergic agents, while respiratory failure has been treated with non-invasive and invasive support if needed. However, most of the medications previously used have failed to improve the course of the disease and opting fewer diagnostic tests and less invasive respiratory supports has not led to worse outcomes. Hence, the current guidelines recommend only supportive treatment for bronchiolitis.

The aim of this thesis is to describe a definition for bronchiolitis and its management in Finland and Sweden, as well as to evaluate the changes in its management with a special focus on the influence of evidence-based clinical practice guidelines. In addition, this thesis also examines the incidences of severe bronchiolitis treated in the Tampere district PICU, the risk factors for PICU admission and the need for respiratory support in infants with bronchiolitis.

Several methods have been used to conduct the research and gather the data for this thesis. A questionnaire on treatment strategies and bronchiolitis definition was sent to paediatricians who were responsible for the treatment of bronchiolitis in Finland and Sweden. Their responses were weighted by the number of infants living in their catchment areas. The questionnaire covered 74% and 100% of Swedish and Finnish infants younger than 12 months, respectively. Subsequently, a retrospective case-control study on the risk factors for intensive care admission and respiratory support requirement was performed at the Tampere University Hospital, covering the period from 2000 to 2015. All infants with bronchiolitis needing admission to

the PICU were identified (n = 105), as well as two controls with bronchiolitis for each case: the first, arriving to the emergency department immediately before the case needing admission to the PICU and the second arriving immediately afterwards (n = 210). For the case-control study, the multivariable logistic regression analyses were used to identify the risk factors for PICU admission. Three time periods were distinguished (2000–2005, 2006–2010, and 2011–2015) and used to describe the changes in the management of severe bronchiolitis. The data on the use of racemic adrenaline in four attending university hospitals in Finland were collected from their hospital pharmacy registers for the 2012–2016 period.

On average, the upper age limit for bronchiolitis diagnosis was 12.7 months in Finland and 12.5 months in Sweden. Adrenaline inhalations were given to patients in both countries, but the Swedish paediatricians preferred using inhaled levo-adrenaline while inhaled racemic adrenaline was the preferred choice of the Finnish paediatricians. Corticosteroids were used rarely. The average annual age-specific incidence of infants with bronchiolitis who were younger than 12 months and required admission to the PICU was 1.5/1,000/year during the 16-year follow-up period in the Tampere district. The independent significant risk factors for PICU admission included: being less than two months old, a birth weight of less than 2,000 g, a presence of congenital heart disease (CHD), a presence of apnoeas and the absence of wheezing. Correspondingly, the independent significant risk factors for respiratory support included: being less than two months old, a birth weight of less than 2,000 g and a presence of CHD. When the three study periods (2000–2005, 2006–2010 and 2011–2015) were compared, the use of inhaled beta-agonists and systemic corticosteroids decreased, while the use of racemic adrenaline and hypertonic saline inhalations increased in the Tampere University Hospital. In contrast, the use of racemic adrenaline was reduced in the four attending university hospitals during the 2012–2016 study period, particularly in the two hospitals where the baseline consumption was highest.

The definitions of and treatment strategies for infant bronchiolitis were found to be rather similar in Finland and Sweden. A young age, low birth weight and CHD were independent significant risk factors for severe cases of the disease that need intensive care and respiratory support. During the 16-year period, the influences of the current literature and guidelines is observed in the management of the disease, as the use of unproven medications diminished. Substantial differences existed in the yearly consumption of racemic adrenaline between the four participating university hospitals, both before and after the publication of the Finnish Current Care Guidelines for bronchiolitis in 2014.

TIIVISTELMÄ

Bronkioliitti eli ilmatiehyttulehdus on yleisin alle vuoden ikäisten lasten sairaalahoidon syy. Sen aiheuttajana on useimmiten respiratory syncytial virus. Vaikka bronkioliitti on tavallinen ja hyvin tunnistettu tauti, ei sille ole kansainvälisesti yhtenäistä määritelmää tai yhtenäisiä hoitosuosituksia. Bronkioliitin ensimmäiset oireet muistuttavat tavallista ylähengitystieinfektiota ja vasta muutaman päivän sisällä ilmaantuvat alahengitystieinfektion oireet: hengityksen tihentyminen, kylkivälivetäymät ja poikkeava keuhkojen kuuntelulöydös. Kolme prosenttia alle vuoden ikäisistä lapsista tarvitsee sairaalahoitoa bronkioliitin vuoksi ja heistä 2-6 prosenttia tarvitsee tehohoitoa. Viimeisten vuosikymmenten aikana bronkioliittia on hoidettu monenlaisilla lääkkeillä kuten kortikosteroideilla, hengitettävillä lääkkeillä salbutamolilla, adrenaliinilla ja keittosuolalla ja antikolinergeillä. Kaikki nämä on todettu tutkimuksissa kuitenkin tehottomiksi. Tämänhetkiset näyttöön perustuvat hoitosuositukset suosittelevat supportiivista hoitoa. Hengitysvaikeutta hoidetaan tarvittaessa hengitystuella. Tutkimusten mukaan näytteenoton vähentäminen, lääkehoitojen karsiminen ja non-invasiivisten hengitystukihoitojen käyttö eivät johda huonompaan lopputulokseen.

Väitöskirjani tavoitteena on kuvata bronkioliitin määritelmää, hoitoa sekä hoidon muutosta suhteessa näyttöön perustuviin hoitosuosituksiin. Lisäksi työssä arvioidaan vaikean tehohoitoa vaativan bronkioliitin ilmaantuvuutta ja riskitekijöitä tehohoitoon joutumiselle ja hengitystukihoidolle.

Kyselykaavake lähetettiin kaikkiin lastensairaaloihin Suomessa ja Ruotsissa ja bronkioliitin hoidosta vastaavaa lastenlääkäriä pyydettiin vastaamaan bronkioliitin määritelmää ja hoitoa koskevaan kyselyyn. Vastaukset painotettiin alueella asuvien alle vuoden ikäisten lasten määrän mukaan. Kyselyalueet kattoivat 74 prosenttia Ruotsin ja 100 prosenttia Suomen alle vuoden ikäisistä lapsista. Retrospektiivisen tapaus-verrokkitutkimuksen aineisto kerättiin Tampereen yliopistollisesta sairaalasta vuosilta 2000-2015. Tutkimuksessa kartoitettiin tehohoitoon ja hengitystukihoitoon joutumisen riskitekijöitä bronkoliittipotilailla. Yhteensä 16 vuoden aikana 105 lasta oli hoidettu teho-osastolla bronkioliitin vuoksi. Jokaista tehohoidettua potilasta kohden kerättiin kaksi bronkioliittia sairastanutta verrokkia päivystyspoliklinikkakäynneistä: yksi ennen tapausta ja yksi tapauksen jälkeen. Tapaus-verrokkiaineistosta

tutkittiin tehohoidon muutosta jakamalla aineisto kolmeen ajanjaksoon: 2000-2005, 2006-2010 ja 2011-2015. Aineisto raseemisen adrenaliinin käytöstä kerättiin neljän yliopistosairaalan sairaala-apteekkien rekistereistä vuosilta 2012-2016.

Bronkioliitin määritelmän yläikärajan keskiarvo oli 12.7 kk Suomessa ja 12.5 kk Ruotsissa. Adrenaliini-inhalaatioiden käyttö oli yleistä molemmissa maissa, mutta Ruotsissa lastenlääkärit suosivat levo-adrenaliinia, kun taas Suomessa suosittiin raseemista adrenaliinia. Kortikosteroideja käytettiin harvoin. Alle vuoden ikäisillä lapsilla keskimääräinen ikävakioitu ilmaantuvuus vaikealle tehohoitoa vaativalle bronkioliitille oli 1.5/1000/vuosi. Itsenäisiä riskitekijöitä tehohoidolle olivat alle 2 kuukauden ikä, syntymäpaino alle 2000 g, synnynnäiset sydänsairaudet, hengityskatkokset ja hengityksen vinkumisen puuttuminen. Lisäksi itsenäisiä riskitekijöitä hengitystuen tarpeelle olivat alle 2 kk:n ikä, syntymäpaino alle 2000 g ja synnynnäinen sydänsairaus. Ajanjaksoina 2000-2005, 2006-2010 ja 2011-2015, inhaloitavien beeta-agonistien ja systeemisen kortikosteroidin käyttö laski. Sen sijaan raseemisen adrenaliinin ja hypertonisten keittosuolainhalaatioiden käyttö lisääntyi Tampereen yliopistollisessa sairaalassa. Raseemisen adrenaliinin käyttö kuitenkin väheni yliopistollisissa sairaaloissa vuosina 2012-2016. Tämä muutos näkyi selvimmin sairaaloissa, joissa käyttö oli ollut yleisintä.

Yhteenvetona bronkioliitin määritelmä ja annettu hoito olivat hyvin yhdenmukaisia Suomessa ja Ruotsissa. Nuori ikä, alhainen syntymäpaino ja synnynnäinen sydänsairaus olivat itsenäisiä riskitekijöitä vaikealle tehohoitoa ja hengitystukea vaativalle taudille. Vuosien 2000-2015 aikana tehottomaksi todetut hoidot vähenivät tutkimustiedon ja hoitosuositusten vaikutuksen myötä. Neljässä yliopistollisessa sairaalassa raseemisen adrenaliinin käyttö vaihteli merkittävästi. Käypä hoito -suosituksen myötä raseemisen adrenaliinin käyttö väheni sairaaloissa ja merkittävin muutos oli nähtävissä yksiköissä, joissa käyttö oli ollut runsainta.

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ABBREVIATIONS

AAP	American Academy of Pediatrics
aOR	Adjusted odds ratio
BPD	Bronchopulmonary dysplasia
CHD	Congenital heart disease
CI	Confidence interval
CLD	Chronic lung disease
CPAP	Continuous positive airway pressure
ED	Emergency department
HFNC	High-flow nasal cannula
HS	Hypertonic saline
ICD-10	International Classification of Diseases, 10th Revision
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IQR	Interquartile range
IVH	Intravenous hydration
LOS	Length of stay
MD	Mean difference
nCPAP	Nasal continuous positive airway pressure
NGH	Nasogastric hydration
NICE	the National (UK) Institute for Health and Care Excellence
NICU	Neonatal intensive care unit
NIPPV	Non-invasive positive pressure ventilation
NIV	Non-invasive ventilation
NO	Nitric oxygen
NS	Normal saline
OR	Odds ratio
PEEP	Positive end-expiratory pressure
PICU	Paediatric intensive care unit
PRISM III	Pediatric Risk of Mortality III

RCT	Randomised control trial
RDS	Respiratory distress syndrome
RDSS	Respiratory distress severity score
RR	Relative risk
RSV	Respiratory syncytial virus
SaO2	Oxygen saturation
SD	Standard deviation
SIGN	Scottish Intercollegiate Guidelines Network
UK	United Kingdom
US	United States
URTI	Upper respiratory tract infection
WHO	World Health Organization

LIST OF ORIGINAL PUBLICATIONS

These original publications are referred to throughout the thesis by their Roman numerals:

I Mecklin M, Hesselmar B, Qvist E, Wennergren G, Korppi M. Diagnosis and treatment of bronchiolitis in Finnish and Swedish children's hospitals. *Acta Paediatr.* 2014;103(9):946–950.

II Mecklin M, Heikkilä P, Korppi M. Low age, low birth weight and congenital heart disease are risk factors for intensive care in infants with bronchiolitis. *Acta Paediatr.* 2017;106(12):2004–2010.

III Mecklin M, Heikkilä P, Korppi. The change in management of bronchiolitis in the intensive care unit between 2000-2015. *Eur J Pediatr.* 2018;177:1131–1137.

IV Palmu S, Mecklin M, Heikkilä P, Backman K, Peltola V, Renko M, Korppi M. National treatment guidelines decreased use of racemic adrenaline for bronchiolitis in four Finnish university hospitals. *Acta Paediatr.* 2018;107(11):1966–1970.

1 INTRODUCTION

Bronchiolitis is a virus-induced inflammation of the small airways that leads to morbidity in young infants. The respiratory syncytial virus (RSV) is the most common causative agent, especially in infants who are less than six months of age (1,2). Approximately 20% of each birth cohort requires either medical inpatient or outpatients care for RSV infections (3,4). Bronchiolitis is primary impetus for the hospitalisation of infants worldwide (5). Approximately 3% of all infants require hospitalisation in their first year of life due to bronchiolitis, of which 2–6% necessitate admission to the paediatric intensive care unit (PICU) due to acute respiratory distress (6–8). The initial symptoms of bronchiolitis, such as rhinitis, fever, and cough, resemble those of the common cold; however, the infection subsequently progresses to the lower respiratory tract and leads to expiratory breathing difficulties that manifest through an increased respiratory rate, chest retractions, and hypoxia (9). Virus-induced upper respiratory tract infections are common among infants and the same viruses can cause a wide variety of symptoms (10). One-third of all children contract a virus-induced lower respiratory tract infection accompanied by wheezing by the age of three; for some the wheezing occurs only once in their lives while in others it occurs repeatedly, and for some the wheezing represents the first episode of asthma exacerbation (11). A group of young children with similar wheezing symptoms consists of different clinical entities and should thus be separated into different subgroups. Nevertheless, the identification of these subgroups has proven to be difficult and lacks consensus. Thus, while the first episode of expiratory breathing difficulty is often considered to be bronchiolitis (9), some authors consider every episode of wheezing at the age of less than 24 months of age as bronchiolitis (12).

The management of bronchiolitis in the past decade reflects that of asthma treatment (3), however, none of the medication used for asthma treatment is beneficial in bronchiolitis (13,14). Hence, bronchiolitis management is mostly supportive using treatment such as supplementary oxygen and fluid support (15–17). In cases of severe respiratory distress, respiratory support is needed and is provided primarily in the form of non-invasive ventilation (NIV), including a high-flow nasal cannula (HFNC) or nasal continuous positive airway pressure (nCPAP), but,

nevertheless, 2–3% of hospitalised infants require invasive ventilation and intubation (18). While evidence-based guidelines are available for the management of bronchiolitis in ambulatory settings and in hospital (15–17), research-based evidence for treatment is lacking for severe bronchiolitis cases that need intensive care and respiratory support since medication is used as a rescue treatment on the basis of clinical experience alone (19).

This thesis evaluates the diagnostic criteria and treatment strategies for bronchiolitis in two Nordic countries: Finland and Sweden. The risk factors for intensive care and respiratory support among infants with bronchiolitis were evaluated through a 16-year single-hospital case-control study. In addition, the impact of the guidelines on real-life medical practice was investigated by following bronchiolitis management in this 16-years study and by monitoring the inhaled adrenaline prescriptions in four university hospitals in the two years prior and subsequently to the introduction of national guidelines.

2 REVIEW OF THE LITERATURE

2.1 Pathophysiology, aetiology, and epidemiology of bronchiolitis

A respiratory infection begins in the upper airways where the respiratory viruses are replicated in the nasopharyngeal epithelium (4). The sloughed epithelial cells from the upper airways transplant the infection to the lower respiratory tract and these infected cells produce the pro-inflammatory cytokines (20) and further activate the inflammatory cells, mostly neutrophils (21). The epithelial damage, large amount of mucus, and necrotic tissue create small-airway obstruction (3,20) and the inflammation and oedema in the submucosa lead to further obstruction. This obstruction in small airways induces impaired gas exchange, air-trapping and hypoxia (3). Such changes manifest in respiratory distress symptoms, such as tachypnoea, use of accessory muscles and chest retractions, leading to exhaustion and lethargy.

While bronchiolitis is caused by different viruses, the RSV is by far the most common one and is responsible for 50–70% of all bronchiolitis cases (1–3,8,22), and triggers 80% of them in infants less than six months of age (1,2). Nearly all children are infected with the RSV by the age of two years and re-infections happen throughout their lifetime (4). The initial infection is typically more severe due to the underdeveloped adaptive immune response in infancy (3). In Finland, the RSV epidemics occurs every other year, peaking in the autumn and winter months (23). In Sweden, the more recent instances of the RSV epidemic are an annual occurrence, peaking in the months between January and April (24). There are two types of RSV: type A and type B (3). Primary RSV infections, especially the type A infections, are associated with the more severe disease, the longer lengths of stay (LOS) in hospital, and the need for intensive care (2,25). Globally, the RSV is estimated to cause 1.4 million hospital admissions annually in the first six months of life (26) and has an annual cost of over $500 million in the United States (US) alone (27). The second most common causative bronchiolitis agent is rhinovirus, which is responsible for 26% of hospitalised bronchiolitis cases (2) and is detected more steadily than RSV throughout the year (28,29). Other viruses that can result in bronchiolitis are the parainfluenza virus (types 1, 2, and 3) in 3–25%, the influenza (types A and B) in 1–5%, the human metapneumovirus in 7%, the coronaviruses in 5–10%, the

enterovirus in 1–5%, the adenovirus in 5–10% and the human bocavirus in 3% of cases (2,3,30). Coinfections are common in up to 61% of all cases (31). The role of human bocavirus is still obscure and, it has been mainly identified in coinfections with other viruses.

The majority of bronchiolitis cases are self-limited and no medical intervention is necessary; nevertheless, bronchiolitis remains the main reason behind hospital admissions among infants younger than 12 months. While third of infants suffer from at least one episode of breathing difficulty by the age of two, the vast majority of cases are mild and do not involve any health care services (11). The rate of emergency department (ED) visits resulting from bronchiolitis in children less than two years of age was 31/1,000/year, of whom 19% required hospitalisation (32). In Finland, among infants younger than six months, the rate of ED visits were 37/1,000/year (8), and of whom 70% were hospitalised (2.6% of all infants younger than 12 months). In the developed countries, the hospitalisation rates have been reported to be 2–3% of all infants younger than 12 months (4,11,33,34), with these rates increasing as age decreases (35). A global estimate for 2015 indicates that RSV leads to 1.4 million hospital admissions among infants less than six months of age, and in a meta-analysis of 26 countries, the incidence rate was 20 per 1,000 (33). Studies of hospitalisation rate trends have shown conflicting results for recent decades (18,34–37). Some studies conducted between the 1980s and early 2000s reported an increase in the hospitalisation rates in the US and in Canada (36,37), while others have reported stable rates for the same time period in the US and in Europe (34,35). Nevertheless, the hospitalisation rates decreased from 17.9 to 14.9 per 1,000 person-years in the US between 2000 and 2009 (7).

Finnish studies have shown that approximately 6% of infants are admitted to the PICU from the paediatric ED (6,8). Similarly, in Australia and New Zealand, 6% of hospitalised infants with bronchiolitis aged two to 12 months with bronchiolitis required PICU admission (38). In England, the annual admission rate for the intensive care unit (ICU) was 1.3–1.6 per 1,000 infants aged less than 12 months between 2004 and 2012 (39). In Australia and New Zealand, 18% of infants admitted to the PICU at the age of two to 12 months required intubation (38). In a recent study, that is based on a nationally representative database of US paediatric hospitalisations, the need for mechanical ventilation has increased between the years 2000 and 2009 (7).

In developed countries, the mortality rate for bronchiolitis is low and occurs among patients with underlying illnesses, such as neuromuscular disease, chronic lung disease (CLD), congenital heart disease (CHD) and immunodeficiency (40,41).

In the US, the mortality rate stands at two per every 100,000 live births (37,42). Since the mortality rates are higher in developing countries, where deaths often occur at home (43), the exact global bronchiolitis mortality rates are impossible to calculate. Globally, it is estimated that the RSV-related lower respiratory tract infections instigate 45% of all deaths in infants younger than six months, totalling to 30,000 deaths annually (26).

2.2 Assessment of bronchiolitis

2.2.1 Clinical features

The initial symptoms of bronchiolitis resemble those of the common cold: rhinitis, low-grade fever, and cough (9). When the infection spreads to the lower respiratory tract the symptoms progress. Three to five days after the onset of initial symptoms, the children begin to show symptoms of respiratory distress such as tachypnoea, use of accessory muscles, abnormal findings in auscultation, chest retractions, apnoea, and hypoxia (3,9). Of those, apnoea—the cessation of breathing—has been reported to be the first sign of bronchiolitis, especially in premature babies (15). Nasal congestion blocks the upper respiratory tract and further increases respiratory effort, in particular during feeding. This constantly increasing respiratory effort eventually leads to lethargy and feeding difficulties.

Auscultation is a relevant part of the clinical examination for bronchiolitis, even though auscultatory findings alone are not sufficient to reveal the course of the disease (44). The breathing of children—and especially that of infants—is noisy, and both the inspiration and expiration are normally audible (45). The task force of the European Respiratory Society concluded that four terms of abnormal lung sounds should be used for describing auscultatory findings: wheezing, fine crackles, coarse crackles, and rhonchi (46). In bronchiolitis, the typical auscultatory findings are wheezing and fine crackles, although different terms have been used for the same findings in different countries (Table 1). These two typical findings are not specific to bronchiolitis. Fine crackles are a classical finding in pneumonia and wheezing is also associated with asthma. In addition, the auscultatory findings may change over the time and thus confound the assessment of the severity of the disease (47).

Table 1. National clinical practice guidelines for bronchiolitis in different countries.

	Finland, 2016 (16)	NICE, 2015 (17)	AAP, 2014 (12)	Canada, 2014 (48)	Italy, 2014 (49)	Australia, 2008 (50)	SIGN, 2006 (51)
Upper age limit for definition	< 12 months	< 24 months, most common in <12 months	< 24 months	< 24 months	< 12 months	< 18 months	< 24 months, most common in <12 months
Signs and symptoms	Signs of URTI, wheezing or crackles, respiratory distress	Signs of URTI, tachypnoea or chest retraction, wheezing or crackles	Rhinorrhoea, cough, tachypnoea, wheezing, rales, chest retraction	Signs of URTI, cough, rhinorrhoea, tachypnoea, chest retraction, wheezing or crackles	Rhinorrhoea, wheezing or crackles, chest retraction	Signs of URTI, cough, tachypnoea, crepitation, wheezing	Rhinorrhoea, cough, tachypnoea, chest retraction, wheezing or crackles
Diagnosis	Clinical	Clinical	Clinical	Clinical	Clinical, viral testing	Clinical	Clinical
Risk factors for severe disease	CHD, Down syndrome, neuromuscular disease, immunodeficiency	CHD, CLD, age < 3 months, premature birth, neuromuscular disease, immunodeficiency	CHD, CLD, age < 12 weeks, premature birth	CHD, age < 3 months, premature birth, immunodeficiency	CHD, CLD, premature birth, immunodeficiency, airway malformation, severe neurological deficit	CHD, CLD, cystic fibrosis, premature birth, other chronic illnesses	CHD, CLD, premature birth, immunodeficiency
Chest radiograph	Not mentioned	Not routinely recommended, only for high-risk patients	Not recommended	Not routinely recommended, only for severe disease or atypical symptoms	Not routinely recommended	Not routinely recommended, only for severe disease or atypical symptoms	Not routinely, only for atypical symptoms
Viral testing	May be taken from hospitalized patients	Not mentioned	Not routinely recommended	Not routinely recommended, only for cohort arrangement	Recommended in hospital setting	Not routinely recommended, may be considered in febrile infants	Not routinely recommended, only for cohort arrangement
Pulse oximetry	Not mentioned	In all children at admission, no mention of continuous monitoring	Continuous monitoring not recommended	At admission	Continuously in high-risk patients and those with supplemented oxygen	Not mentioned	Not mentioned
Limit of SaO2 for initiation of oxygen	Not mentioned	< 92%	< 90%	< 90%	< 90—92%	Not mentioned	< 92% indication for hospitalisation, >94% for discharge

AAP, American Academy of Pediatrics; CHD, congenital heart disease; CLD, chronic lung disease; NICE, National Institute for Health and Care Excellence; SaO2, oxygen saturation; SIGN, Scottish Intercollegiate Guidelines Network; URTI, upper respiratory tract infection.

A systematic review of diagnostic testing in bronchiolitis found that 43 out of 65 studies used tachypnoea as an inclusive criterion (52). Tachypnoea is referred to as the earliest and the most sensitive vital sign of bronchiolitis, but it may also be a symptom of dehydration, fever, and hypoxia (53). Furthermore, the presence of tachypnoea does not exclude other lower respiratory tract infections such as pneumonia (12). Additionally, the age of the infant must be recognised when assessing tachypnoea. Tachypnoea is considered when the respiratory rate is more than 60 breaths/min in infants younger than two months and more than 50 breaths/min at two to 13 months of age. The respiratory rate should be counted for at least one minute (12).

Apnoea is defined as a breathing pause of 20 or more seconds that is accompanied by desaturation or bradycardia in infants. Apnoea is associated with bronchiolitis that is caused by different viruses, although it was primarily thought to be associated only with an RSV infection (15,54). The incidence of apnoea in bronchiolitis depends on comorbidities and varies from 1% to 20%, even reaching as high as 38% in premature babies (15). At the same time, it should be noted that apnoea incidences are decreased in most recent studies (55). The reason for apnoea is unknown, but it is suggested that a sensorineural stimulation triggers it due to the inflammatory effect of different viruses (56). In RSV-infected rats, the threshold for apnoea was lower when the infection spreads to the lower respiratory tract (56). Still, apnoea might be the first sign of bronchiolitis in some infants, although the exact triggering mechanism beyond the central inhibition of respiratory work is unclear. The apnoea due to viral infection is associated with sudden infant death syndrome (57). Young age, premature birth, comorbidities, and low birth weight have been all associated with the risk of apnoea (54,58). A prospective observational study of 892 infants younger than 18 months attending the ED underlined that those infants less than six weeks of age, weighting less than 2.5 kg, and with parentally reported apnoea were at risk of subsequent apnoea (59).

Hypoxia is defined as a partial oxygen tension of arterial blood that is less than 8 kPa, which is equivalent to an oxygen saturation of 89%. However, this relation between a partial oxygen tension and oxygen saturation is not linear but described by the oxyhaemoglobin dissociation curve (60).

Clinical examination is a key element for diagnosing bronchiolitis, however, the fact that disease severity and clinical findings do not progress linearly and clinical condition can change quickly over time must be kept in mind. Consequently, it is difficult to establish a reliable scoring system for bronchiolitis severity (51,61–63) and thus far the scoring is mainly used for research purposes only (61). Clinical trials

have tried to assess the respiratory status by using scoring in addition to primary outcomes (64–66). The most common scoring instruments in bronchiolitis are the respiratory distress assessment instrument (RDAI) and the respiratory assessment change score (RACS), which are partially validated (62,67,68). They have been used to monitor the respiratory status and to assess the bronchodilator response to wheezing (64,66). The severity scores contain a variable on wheezing, which is not globally mandatory for the definition of bronchiolitis (16,17).

2.2.2 Diagnosis

Even though diagnosing bronchiolitis during its epidemic season may not feel ambiguous to the clinician, a unified consensus on the diagnostic criteria for bronchiolitis is still lacking (9). All national guidelines define bronchiolitis as a lower respiratory tract infection instigated by viruses that leads to acute respiratory distress in some infants and indicate that its diagnosis is based on a constellation of clinical symptoms and signs (9,12,16,17,48–51,69). However, the constellation of these clinical findings and infant age differs between countries (Table 1). In most countries, the diagnosis of bronchiolitis is clinical—i.e. that it is constituted by a combination of the patient history and physical examination—and that laboratory tests or chest radiographs are not necessary (12,17,51). Nevertheless, different guidelines suggest different upper age limits for bronchiolitis diagnosis: in North America this limit is 24 months (12,48) while in Europe it is 12 months (16,17,49,51). Furthermore, the North American guidelines underline wheezing as one of the main clinical findings and include infants with a history of wheezing (47), whereas the definition of bronchiolitis in European guidelines is more often restricted to the first episode of expiratory breathing difficulty only with different auscultatory findings (16,51,70).

2.2.3 Monitoring oxygen saturation

Pulse oximetry is a simple non-invasive method for detecting hypoxia in clinical practice (60). To estimate the arterial haemoglobin oxygen saturation, pulse oximetry calculates the oxyhaemoglobin by a ratio of light absorption from the previous three to six seconds (60). Pulse oximetry has several limitations, such as motion artefacts, arrhythmias, skin colour, tissue perfusion and changes in the haemoglobin, all of which can lead to misinterpretations (60). On average, the oxygen saturation values

in pulse oximetry during a 24-hour monitoring period are 97% to 99% in healthy infants (71) and over 93% in healthy neonates (72). For infants with bronchiolitis, there is no consensus on the levels of oxygen saturation that require hospital admission or oxygen administration, nor those needed for safe discharge from the ED (12,47). In paediatric pneumonia, pulse oximetry has a positive predictive value (73), but in bronchiolitis desaturation seems to be a poor predictor of disease severity or the need for hospital care (3,74,75). Furthermore, it has been suggested that the use of pulse oximetry leads to an over-diagnosis of hypoxemia (74) and an increased admission rates for bronchiolitis (76), ultimately leading to a longer LOSs (77–79) and incurring higher costs (80). Three randomised trials found that lowering the limit for defining hypoxia was safe and had no short-term adverse effects (75,80,81). In fact, lowering the acceptable saturation limit from 94% to 92% halved the admission rate (74). A prospective observational study of 118 infants with bronchiolitis discharged from the ED founds that 64% of them had oxygen saturation levels of less than 90% and hypoxia was not associated with subsequent medical visits (82).

2.3 Severe bronchiolitis

Studies on the severity of bronchiolitis have applied different outcomes. The severity of the disease has been categorised either by clinical findings or by the need for health care facilities. Clinical scoring and the measurement of clinical findings, such as oxygen saturation, respiratory rate and heart rate have all been used, even though a clinical examination is influenced by the experience of the attending physician and measured clinical findings may significantly fluctuate by the time the investigation is undertaken. Furthermore, the need for medical interventions has been used to describe the severity of the disease, although it may actually reflect the prescribing habits more. The need for health care facilities, such as hospital admission, has been used for defining severe bronchiolitis, but several additional factors influence to these outcomes: the local clinical practice, the circumstances on the ward or the PICU, and both social and geographical issues, such as the parents' capability to take care of the infant and distance of their home in relation to the hospital (83,84). Likewise, the same factors also influence to the LOS in hospital, and partly, the LOS in the PICU. Since the admission to the PICU and the LOS in the PICU are influenced by many confounding factors, the need for respiratory support has been considered a more reliable outcome for describing the most severe conditions. Even

in infants whose disease severity is similar, variability exists between countries and treatment sites in the use of different types of respiratory support (65,85).

2.3.1 Risk factors for hospitalisation

Several risk factors, such as genetic, epidemiological, and environmental factors, are connected to severe bronchiolitis but they are not fully understood. There are many known epidemiological risk factors for developing severe bronchiolitis and being hospitalised: young age, low birth weight, premature birth (33,86–88), male gender (87,89,90), comorbidities (41), low weight at admission (90), environmental pollution, low socio-economic status, birth by caesarean section (86,89), transient tachypnoea of a new-born (91), vitamin D deficiency (92), number of siblings, crowdedness of living conditions (10,93), and an RSV-positive infection (94).

Young age, probably due to the fact that the innate and adaptive immune responses are still immature, is a risk factor for both hospitalisation and respiratory support (4,35). Most of the risk factors are related to the maturation of the immune system and to lung development and these, in turn, are both are influenced by maternal factors and by the development of the foetus. Premature birth is a risk factor for the under-development of the lungs, and bronchopulmonary dysplasia (BPD) that relates to premature birth is a risk factor for bronchiolitis. Maternal factors, such as diet, use of alcohol and smoking, are related to impaired lung development during pregnancy and later on to the risk of bronchiolitis in infancy (2,90,92,93,95,96). All these factors affect the development of the foetus and are associated with intrauterine growth retardation.

The number of siblings has been associated with bronchiolitis, since the person who spreads the RSV infection is most likely a member of the family (10,93). The RSV is associated with a longer LOS in hospital, the need for supplementary oxygen, and the need for intensive care and respiratory support (97). However, classical clinical factors, such as BPD, premature birth, and CHD, carry more weight in predicting the severity of bronchiolitis than involved viruses (88).

2.3.2 Risk factors for paediatric intensive care unit (PICU) admission and respiratory support

Several studies have explored the predictors of bronchiolitis that requires intensive care (2,18,22,98–101) (Table 2). Young age has been associated with more severe disease (2,41,99,100,102). The age cut-off point vary from between four weeks and two months (22,100,103) and up to the age of six months, as the odds are increased in comparison to children older than one year (2). A recent population-based cohort study showed that, without the comorbidities, age was a significant predictor of admission to the ICU or of death within 14 days of discharge (Table 2) and that for every one-month decrease in age the adjusted odds ratio (aOR) increased by 64% (41). Low birth weight increases the risk for more severe disease (2,18). Infants with a birth weight of less than 2.3 kg had increased risk of needing respiratory support (2); furthermore, the birth weight of less than 2.3 kg and tachypnoea were both found to be independent significant risk factors for the PICU admissions (Table 2) (2,18). A large cohort study from Canada confirmed the association of premature birth and admission to the ICU or death 14 days after discharge (Table 2), and finding that a one-week decrease in gestational age increases the odds for admission and death by 15% (41). Late preterm infants with bronchiolitis have a three-fold higher risk for respiratory support in comparison to full-term infants (87). Older studies reveal that comorbidities also have a substantial impact on the disease severity of bronchiolitis (104,105), and consequently, some of the more recent studies have excluded children with comorbidities from their analysis (22). In contrast, a large prospective multicentre study conducted in the US did not found comorbidities to be significant risk factor for the PICU admission nor for the need for respiratory support requirement (2,18). However, the most recent cohort study of 34,270 infants with bronchiolitis confirmed that comorbidities are significant predictors of severe outcomes such as readmission to the PICU or death during two-week period following discharge (Table 2), and that if two or more risk factors are present, the risk increases 25-fold in comparison to the risk for infants without any of the risk factors (41).

Table 2. The previous studies on risk factors for PICU admission and respiratory support

	Study design	Risk factors for PICU admission	aOR (95% CI)
Schuh et al. (Canada) 2018 (41)	Population-based cohort study 2003–2014 N = 34,270, N = 102 (admitted to the PICU)	Any comorbidity CTAS 2 Younger age Younger gestational age	5.3 (2.82-10.1) 1.6 (1.03-2.33) 1.5 (1.33-1.61) 1.1 (1.06-1.22)
Hasegawa et al. (US) 2015 (18)	Prospective 16-centres study 2007–2010 N = 2104, N = 342 (admitted to the PICU on the first inpatient day)	Birth weight < 2.3 kg Respiratory rate > 70 per minute	2.3 (1.30-4.02) 4.6 (2.86-7.53)
Damore et al. (US) 2008 (100)	Prospective cohort study 2004–2006 N = 1456, N = 50 (admitted to the PICU)	Age < 2 months ED visit in previous week Moderate/severe retraction Inadequate oral intake	4.1 (2.05-8.34) 2.2 (1.05-4.37) 2.6 (1.27-5.18) 3.3 (1.55-7.07)
	Study design	Risk factors for respiratory support	aOR (95% CI)
Mansbach et al. (US) 2012 (2)	Prospective 16-centres study 2007–2010 N = 2207, N = 379 (admitted to the PICU), N = 161 (needed respiratory support)	Age < 2 months Maternal smoking during pregnancy Birth weight < 2.3 kg Breathing difficulty < 1 day before Apnoea Inadequate oral intake Severe retraction SaO2 < 85%	4.3 (1.66-11.53) 1.4 (1.05-1.91) 1.7 (1.01-2.52) 1.6 (1.15-2.09) 4.8 (2.57-8.50) 2.5 (1.34-4.26) 11.1 (2.40-33.19) 3.3 (2.02-4.82)
Papoff et al. (Italy) 2011 (22)	Prospective single-centre study 2004–2009 N = 310, N = 16 (needed respiratory support)	Age < 30 days RSV infection Lymphocytes <3200/mm^3	8.4 (2.35-29.86) 3.4 (1.01-11.27) 5.2 (1.40-19.47)

aOR, adjusted odds ratio; CI, confidence interval; CTAS, Canadian Triage Acuity Scale; ED, emergency department; OR, odds ratio; PICU, paediatric intensive care unit; RSV, respiratory syncytial virus; SaO2, oxygen saturation; US, the United States.

Inadequate feeding, desaturation and signs of acute respiratory distress have been associated with more severe bronchiolitis (2,100). In a large prospective cohort study, the multivariable logistic regression showed that the presence of apnoea, severe chest retractions, oxygen saturation of less than 85% and inadequate feeding at admission all predicted the future need for respiratory support (Table 2) (2). Furthermore, a secondary analysis from the same study revealed that one day after admission to the ward, a respiratory rate higher than 70 breaths per minute was associated with later admission to the PICU (Table 2) (18). Some studies have found an association between the laboratory findings and the severity of bronchiolitis

(22,106). A retrospective cohort study of 102 critically ill children with bronchiolitis established that hyponatremia is associated with the mortality, the longer stay in the PICU and with the need of NIV treatment, but no significant association was seen with intubations, readmissions or seizures (106). In the data collected prospectively on 310 previously healthy infants with strict inclusion criteria, the age less than 30 days and lymphopenia predicted the admission to the PICU (Table 2) (22). In addition, the paediatric risk of mortality score (PRISM III), which is one of the most commonly used paediatric scores in the PICUs for a wide range of disease (107,108), has been associated with more severe forms of bronchiolitis and the use of mechanical ventilation, as well as with the failure of the NIV therapy (109,110).

2.4 Management of bronchiolitis

Drugs that are effective in the treatment of asthma have been tried for the treatment of bronchiolitis, but have all proven to be ineffective—the beta-agonists, anticholinergics, inhaled and systemic corticosteroids, and leukotriene receptor antagonists among others (13,14,111–113). The only exception seems to be inhaled racemic adrenaline which may be effective as a form of rescue on-demand therapy in selected bronchiolitis patients (114). Therefore, supportive therapies still form the basis of bronchiolitis treatment.

2.4.1 Supportive treatments

2.4.1.1 Supplementary oxygen

The monitoring of oxygen saturation and oxygen supplementation, if needed, are the current cornerstones of bronchiolitis treatment (12,47,51). Since the 1940s, supplementary oxygen has been delivered to patients through a nasal cannula and, to avoid adverse effects (such as patient discomfort and airway damage), it is recommended that the flow is restricted to 2–4 L/min. The threshold for beginning oxygen supplementation varies in different countries; the bronchiolitis guidelines from the US recommend starting supplementary oxygen when oxygen saturation falls to less than 90%, while the Australian guidelines suggest doing so once the level hits 94% or less (115,116). Furthermore, the World Health Organization (WHO) recommends starting supplementary oxygen treatments for lower respiratory tract

infections when the oxygen saturation falls to 90 %. A double-blind randomised controlled trial (RCT) revealed that targeting saturation at either 90% or 94% does not influence the time it takes for symptoms to be resolved, and that a lower targeting saturation of 90% leads to a shorter LOS, to earlier oral feeding, and to fewer readmissions for infants admitted for bronchiolitis (80).

In the 1990s, a new application was introduced to administer the oxygen—the HFNC—which delivers a heated and humidified air-oxygen mixture (117). The HFNC offers several advantages over the traditional oxygen administration. The HFNC therapy is well tolerated due to the soft cannulas and the heated and humidified oxygen, even though the flow rate has been up to 2 L/kg/min (118). In a low-flow oxygen administration, the flow cannot exceed 2 L/min, which means that the inspiratory oxygen concentration is 60% or less. Through its ability to create distending pressure in infants, this thesis considers HFNC to be an NIV mode (see 2.4.5.1 High-flow nasal cannula [HFNC]).

2.4.1.2 Fluid support

Another cornerstone of supportive bronchiolitis treatment is maintaining adequate hydration, and approximately one-third of the patients need fluid support during hospitalisation for bronchiolitis (119). Fluid support may be delivered either intravenously or via a nasogastric tube. One of the disadvantages of intravenous hydration (IVH) is entering a catabolic state, as the demand for energy is high in critically ill infants and the fluids lack high-energy fat and protein (120). There is also a risk of electrolyte disturbances (48). An advantage of IVH is that it may relieve respiratory distress, since the upper airways are not irritated. Instead, nasogastric tube hydration (NGH) provides more physiological nutrition, aids recovery, and is more cost-effective than intravenous hydration (121). However, an aspiration risk is associated with nasogastric tube feeding and it is suggested that it also increases respiratory effort by blocking the upper respiratory tract (122,123). The aspiration risk was found in a small observational prospective study, where the infants who were admitted for bronchiolitis and feeding difficulties were given barium, and one-third of the infants showed signs of aspiration (123). Hence, the American Academy of Pediatrics (AAP) recommends IVH if an infant with bronchiolitis is not capable of sustaining oral feeding (12). However, none of the recent studies has found a substantial risk for aspiration, even with respiratory support such as HFNC or nCPAP (124–127). In another RCT, 759 infants with moderate bronchiolitis between the age two and 12 months were randomly given either IVH or NGH and

no significant differences in the LOS, the escalation of treatment, and the need for supplementary oxygen or adverse events, such as aspiration, apnoea, and desaturation or bradycardia, were found (126). Furthermore, in a multicentre descriptive cohort study of 491 infants, similar results were found in children younger than two months (125). The nasogastric tubes were often inserted with only one attempt and parental satisfaction was equal for both fluid replacement strategies (126). A prospective pilot study comparing the IVH to NGH among moderately ill infants with bronchiolitis showed no differences in the need for oxygen administration or in the hospital LOS (124).

2.4.2 Pharmacological treatment

2.4.2.1 Saline inhalations

The theory of the beneficial effect of the hypertonic saline (HS) solution arose from the discovery that the obstruction of small airways does not result from bronchoconstriction but from oedema, mucus, and inflammatory exudate in the airways, contributing to ciliary dysfunction (3,20). In cystic fibrosis and other diseases with production of excessive amounts of mucus and dysfunction of ciliary clearance, the HS have had a beneficial effect by making the exudate more elastic and viscose (128). In the management of bronchiolitis, HS inhalations were first introduced in early 2000's and, since then, their efficacy has been evaluated in several RCT studies in combination with another therapies, such as terbutaline, salbutamol, or adrenaline, and compared to normal saline (NS) inhalations or standard care without any inhalations (129). These studies have had different outcomes in terms of clinical scoring, symptoms, duration of supplementary oxygen, admission rate, and the LOS. Additionally, several meta-analyses have been published (130–133).

A Cochrane meta-analysis published in 2013 concluded that the nebulised HS may reduce the LOS, as the mean of the LOS in days of 15 trials shortened (mean difference [MD] -0.45, 95% CI -0.82 to -0.08). At the same, these studies had major clinical and methodological variabilities (131). Another meta-analysis published in 2017 showed a modest effect of the HS in bronchiolitis management, where the mean LOS is -0.41 days (95% CI -0.75 to -0.07) of 17 trials. Nevertheless, the heterogeneity was still high and the effect in post hoc analyses was greater if the LOS was longer than three days, if the virologic results were available, if inhaled adrenaline was used additionally, and if the study was carried out prior to 2013 (130).

Additionally, a cumulative meta-analysis with 18 RCTs concluded that the mean cumulative MD in the LOS for infants with bronchiolitis treated with HS versus NS was -0.481 days (95% CI -0.750 to -0.212) (133). While the LOS is often considered a reliable outcome and the most meaningful one for families, the discharge criteria may vary considerably due to different oxygen saturation and feeding limits (129). Therefore, with the aim to reduce the heterogeneity, the studies with the longest LOS in hospital were excluded and the reduction in LOS end up to be only modest (132). A subgroup analysis showed that the cumulative MD in the LOS was -0.408 days (95% CI -0.733 to -0.083) without a significant heterogeneity (133). Furthermore, the largest and most recent RCTs do not establish any benefits of HS in the management of bronchiolitis (129,134–136). In the Cochrane meta-analysis, the admission rate due to bronchiolitis was reduced by 14% with the use of the HS compared to NS (relative risk [RR] 0.86, 95% CI 0.76 to 0.98). However, the cumulative risk ratio for the admission to hospital was 0.771 (95% CI 0.619 to 0.959) (130). Therefore, the HS has a minor impact on the hospital admission rate and on the LOS in the treatment of bronchiolitis.

2.4.2.2 Inhaled bronchodilators

Bronchodilators are divided into the beta- and alpha-receptor agonists. A beta-agonist, such as salbutamol, induces the relaxation of smooth muscles through the potassium channels and increases the diameter of the bronchus, while further vasodilation increases the blood flow through the lungs and may activate the ciliary function in the lungs. As an adverse effect, beta-agonists increase the heart rate and blood pressure. They offer well-established benefits in the treatment of acute asthma exacerbation (137). On the other hand, the adrenergic agents, such as racemic adrenaline and levo-adrenaline, affect the upper airways more by reducing the oedema in the submucosa and inducing vasoconstriction (13). They are actively used in the treatment of larynx spasms and laryngitis. Furthermore, these bronchodilators have been actively used in the management of bronchiolitis, even though their effects have been questioned in experimental studies since the 1970's (138). The beta-agonists (mostly salbutamol) and the adrenergic agents (mostly adrenaline) have been used and studied in bronchiolitis management for the past three decades. Several systematic reviews and meta-analysis have been published on this topic (13,14,139,140).

The RCTs of bronchodilators in bronchiolitis from 1990 to 2000 reported positive results in clinical findings (139,140). In contrast, a meta-analysis including

five outpatient RCTs with 251 patients compared the beta-agonists to placebos and found no effect on the admission rates. Even though the meta-analysis showed a statistically significant reduction in the respiratory rate and heart rate, the clinical impact of it was minor (140). Similarly, another meta-analysis with eight studies that combine bronchodilators showed improvement in the clinical scores (RR 0.76, 95% CI 0.60 to 0.95) but not in the admission rates (RR 0.85, 95% CI 0.47 to 1.53). The lack of a sufficient number of RCTs and the conflicting evidence presented piqued the interest of further studies (141).

An updated version of the Cochrane meta-analysis on adrenaline in bronchiolitis, published in 2011 (13) aimed to establish a more clinically relevant pooled data and used the admission rates and the LOS as outcomes, since the previous version primary focused on clinical findings. This meta-analysis, with 19 studies and a total of 2,256 children, compared the effects of adrenaline to those of a placebo or to other active components of treatment, such as corticosteroids (13). In comparison to a placebo, the adrenaline had a moderate effect on the admission rate at enrolment (RR 0.67 95% CI 0.5 to 0.89) but no effect on the overall admission rates for up to seven days (RR 0.81, 95% CI 0.63 to 1.03), and it had only a minor impact on the mean LOS (13). The subsequent subgroup analyses that compared adrenaline to a beta-agonist, did not have any influence on either admission at enrolment (RR 0.67, 95% CI 0.41 to 1.09) or overall admission rates (RR 1.05, 95% CI 0.71 to 1.54). However, one large multicentre RCT, involving 800 patients and combining adrenaline and corticosteroids, showed a reduction in the admission rates but solely in the overall admission rate for up to seven days (RR 0.64, 95% CI 0.44 to 0.95) (66). Following the publication of the Cochrane review, a large double-blind RCT of 404 infants that compared adrenaline and saline inhalations did not find any significant reduction in the LOS or improvement in clinical scores. The administration of adrenaline on demand, however, did shorten the mean LOS from 61.3 hours to 47.6 hours ($p = 0.01$) in this study (114). Furthermore, adrenaline inhalations are not shown to be beneficial, not even in infants who later developed atopic eczema, allergic sensation, or recurrent wheezing (142).

The most recent Cochrane meta-analysis used the measurement of pulse oximetry as a primary outcome and the admission rates, clinical scoring, and LOS as secondary outcomes (14). It concluded that in comparison to a placebo, the bronchodilators had neither a clinically nor a statistically beneficial effect on oxygen saturation (MD -0.43, 95% CI -0.92 to 0.06), admission rates (OR 0.75, 95% CI 0.46 to 1.21), or LOS (MD 0.06, 95% CI -0.27 to 0.39), but they did have a rather modest impact on clinical scoring (MD -0.30, 95% CI -0.54 to -0.05) (14). Furthermore, it found that

salbutamol had no significant impact on oxygen saturation, clinical scoring, or admission rates in subgroup analyses. Interestingly, the adverse effects, such as tachycardia, desaturation, hyperactivity, tremors, and prolonged cough, were reported solely in patients receiving bronchodilators (14).

2.4.2.3 Corticosteroids

In the treatment of asthma, including both chronic and acute therapies, corticosteroids are the established treatment choices with rare adverse effects (143,144). Corticosteroids have anti-inflammatory effects by stimulating the anti-inflammatory mediators, reducing the eosinophils and mast cells and inducing the neutrophils (144). The vasoconstrictive effects of corticosteroids also reduce oedema in the respiratory tract. In bronchiolitis, the immune response overreaction might have a detrimental effect. Therefore, corticosteroids are assumed to influence the inflammation in the airways of infants with bronchiolitis. Some studies suggest that glucocorticoids might only have a minor impact on inflammation in bronchiolitis in comparison to other wheezing phenotypes (145,146).

The Cochrane meta-analysis on the use of corticosteroids in infants with bronchiolitis with 17 RCT studies included 2,596 infants (111). The majority of the patients were treated as outpatients, mostly in the paediatric ED, and the two primary outcomes for them were the rate of admissions to the hospital in day one or admissions up to seven days. The pooled risk ratios for hospital admission did not achieve a statistical significance by day one (RR 0.92, 95% CI 0.78 to 1.08) nor by day seven (RR 0.86, 95% CI 0.7 to 1.06). Furthermore, no significant improvements in any secondary outcomes, such as clinical scores, respiratory rate, heart rate, or oxygen saturation, were found. In eight RCTs that included 633 infants admitted due to bronchiolitis, no significant decline in the LOS was seen in the glucocorticoid group in comparison to the placebo group (MD -0.18 days, 95% CI -0.39 to 0.04). Corticosteroids were not associated with a significant reduction in the readmissions rates one day after discharged (RR 0.92, 95% Cl 0.78 to 1.08) or seven days after discharge (RR 0.86, 95% Cl 0.7 to 1.06). However, one large double-blind RCT of 800 infants showed that a combination of adrenaline and oral dexamethasone in comparison to a placebo reduced the hospital admissions by the day seven (RR 0.65, 95% CI 0.44 to 0.95) (66). In this RCT, a high-dose of dexamethasone was given for six days (1 mg/kg, max 10 mg, followed by 0.6 mg/kg). The authors also found that in order to prevent one admission, 11 of the infants with bronchiolitis need to be treated with a high dose of steroids combined with adrenaline.

2.4.2.4 Other medication

A Cochrane meta-analysis on antibiotics in infants with bronchiolitis that included seven RCTs and 824 children did not found any decrease in the duration of the supplementary oxygen requirement (pooled MD -0.20 days, 95% CI -0.72 to 0.33) or in the LOS (MD -0.32 days, 95% CI -140 to 0.76) (147). The asthma medications, such as leukotriene inhibitors and ipratropium bromide, are believed to decrease inflammation and muscle constriction in the airways and to release the symptoms of bronchiolitis. Furthermore, the nebulised recombinant human deoxyribonuclease (rhDNA) is thought to reduce the thickness of the mucus by breaking down DNA. However, the leukotriene inhibitors (MD -0.95, 95% CI -3.08 to 1.19) or the nebulised rhDNase (MD 0.5, 95% CI 0.10 to 0.90), respectively, had no beneficial effect on the LOS in bronchiolitis in this meta-analyses that included 1,296 children and five studies, respectively (148). Furthermore, the ipratropium bromide did not yield a significant improvement in the course of bronchiolitis (113).

2.4.3 Supportive and pharmacological treatment in the paediatric intensive care unit (PICU)

There are several studies describing the management of critically ill infants with bronchiolitis (19,65,85,101), however, only a few clinical trials focused on their treatment in the PICU (149–152). The use of medication for bronchiolitis has been reported to be two-fold in comparison to its use on general ward (19). In the PICU, the recruitment of bronchiolitis patients for prospective studies may be difficult due to the small number of eligible cases. One multicentre double-blind RCT failed to recruit patients for a comparison study of aminophylline and placebo (152). The aminophylline is thought to increase the respiratory reflex. Another multicentre double-blind RCT aiming to determine the efficacy of dexamethasone in critically ill infants with RSV bronchiolitis was, like the aminophylline RCT, prematurely ended due a slow enrolment of appropriate cases (151). The authors' hypothesis was that those patients with only mild oxygenation problems would benefit from a corticosteroid the most. However, the duration of mechanical ventilation, the total LOS in the hospital, the PICU LOS, or the duration of oxygen supplementation did not have statistically or clinically significant connections with the severity of disease. On the other hand, even high doses of dexamethasone did not have any short-term side effects in the study (151). Furthermore, the Cochrane meta-analysis gathers three RCTs on the use of surfactant in intubated infants with bronchiolitis and the

pooled results did not show any reduction in the duration of ventilation (MD -63.04 hours, 95% CI -130,43 to 4.35). However, the mean LOS in the PICU was shortened by 3.31 days (95% CI -6.38 to -0.25) (149). Inhaled nitric oxide (NO) causes vasodilation and increases ventilation-perfusion matching, and is used therefore in adult respiratory distress syndrome and pulmonary hypertension in neonates. A double-blind pilot RCT on the NO in bronchiolitis showed that the NO is well tolerated and that its profile of adverse effects is similar to the placebo group (150). The intravenous magnesium, in an RCT with 162 infants with severe bronchiolitis, did not provide any benefits for patients (153). The magnesium infusion is used as a rescue therapy in severe asthma, but its mechanisms are still not fully understood (154).

The use of medication in the PICU is frequent. In the US, between 2007 and 2010, 60% of 342 critically ill infants received bronchodilators, 33% received corticosteroids and 63% received antibiotics (65). Another multicentre retrospective cohort study reported the use of salbutamol in 88% of intubated infants with RSV bronchiolitis and the use of corticosteroids in 35% (95). However, several studies have proven that less invasive ventilation, a decreased use of diagnostic tools and less medication have not been associated with prolonged LOS in the PICU or in the hospital for severe bronchiolitis patients (65,85,155). A multicentre prospective observational study of 342 infants with bronchiolitis younger than 24 months who required the nCPAP or PICU admission reported a wide variation in management without differences in disease severity (65). The higher use of medication was associated with higher respiratory distress severity scores (RDSS), but neither medication nor the RDSS was associated with more frequent use of respiratory support (65).

2.4.4 Respiratory support

In bronchiolitis, acute respiratory failure is treated with respiratory support which can be categorised as the NIV or invasive ventilation. Three types of NIV are used: continuous positive airway pressure (CPAP), used either with nasal prongs or with helmet, non-invasive positive pressure ventilation (NIPPV), and HFNC. Acute respiratory failure is the most common reason for paediatric patients admission to the ICU, with bronchiolitis being the leading cause of admission to the PICU for infants (156). There are several factors that expose neonates and infants to acute respiratory failure. The elastic components and collateral ventilation pores of the

lungs are underdeveloped in neonates and infants; therefore, their lung compliance is lower and peripheral airway resistance is higher in comparison to an adult. Furthermore, the chest wall of the neonates consists primarily cartilage and is thus extremely pliable, making the maintenance of the outward recoil of the chest wall difficult to retain. Additionally, the functional residual capacity, where gas exchange takes place, is only 10–15% of the total lung capacity in infants. The peripheral airways are responsible for over half of the total airway resistance, unlike in adults, for whom the peripheral airways contribute to about 30% of the total airway resistance. In fact, due to the structural changes of the chest wall and lung tissue development, the functional residual capacity increases throughout the first six years of life, over time reaching adult lung capacity to maximise the vital capacity. In bronchiolitis, the small airways collapse due to inflammation, secretion and airway constriction further leading to an increased airway resistance and a decreased lung volume (157). Additionally, premature infants' alveolar dead space is larger (158), therefore, the infants with bronchiolitis are at a higher risk of acute respiratory failure.

2.4.5 Non-invasive ventilation

2.4.5.1 High-flow nasal cannula (HFNC)

In the 1990s, a new technology for supplementary oxygen administration that delivers a humified and heated oxygen–air mixture through the HFNC was introduced to resolve the problem of low-flow oxygen administration (117). Furthermore, it was noted that the HFNC creates a distending pressure for neonates, even without the non-sealing prongs like those used in the nCPAP (159), improves the muco-ciliary clearance, increases the viscosity of the airway secretions and prevents energy and water loss (160). Since the inspired flow in neonates can be 5–10 L/min, the HFNC mimics this flow better than the low-flow methods and this high flow also washes out the increased dead space (161). For neonates, the indications for the use of the HFNCs are not just for providing supplementary oxygen but also to treat apnoea, to increase respiratory work, and to prevent extubation failure (160). In addition, the HFNC has become standard care for severe bronchiolitis (117,160,162); initially in the PICU and currently in both the paediatric ED and on the ward (163,164). Nevertheless, the evidence of the HFNC effectiveness in bronchiolitis is mostly based on descriptive retrospective studies,

even though two prospective RCTs are published (165,166). Recently the use of the HFNCs has been expanded to other patient groups: those with asthma, recurrent wheezing, obstructive sleep apnoea (167), and in post-operative treatment after cardiac surgery (168).

Several observational studies have found improvement in clinical findings with the use of the HFNC (54,169–172). Few descriptive retrospective studies reported improvement in the respiratory rate or the heart rate in the first 1–2 hours after beginning of the HFNC (171–177). Typically, treatment failure has happened during the first 12 hours (177–179). The predictors of HFNC failure included prior hypercapnia (aOR 1.34, 95% CI 1.08 to 1.67) and a low respiratory rate (aOR 0.96, 95% CI 0.92 to 0.99) in a retrospective chart review of 113 infants with bronchiolitis treated with the HFNC (171).

Previous retrospective studies have suggested that the HFNC could reduce the intubation rates and the need for intensive care (172,176). The abovementioned retrospective chart review showed that after the introduction of the HFNC, the intubation rates declined from 23% to 9% and, consequently, the LOS decreased by two days ($p = 0.0058$) (176). Interestingly, the nCPAP was used only prior to introducing the HFNC for 5.3% of the 57 infants with bronchiolitis (176). An Australian and New Zealand chart review from 2005 to 2009 showed that among the 298 infants younger than 24 months received HFNC, those with bronchiolitis tolerated the HFNC the best and benefitted the most from it—only 2% needed intubation in comparison the other disease groups, where the need for intubation was 50% (172). Ultimately, however, the introduction of the HFNC to the general ward has not decreased the intubation rate (164).

Recently, three RCTs on the HFNC were published: two comparing the HFNC to standard oxygen delivery (165,166) and one comparing the HFNC to nCPAP (178). One of these, a large RCT, failed to show significant differences between the weaning off of oxygen when comparing the low-flow supplementary oxygen treatment (24.0 h, 95% CI 18 to 20) to the HFNC (21.0, 95% CI 17 to 34). However, the HFNC group experienced treatment failure less often and 63% of those who failed in the low-flow oxygen group were treated successfully with the HFNC (166). Similarly, another multicentre RCT of 1,472 patients that compared the HFNC and standard oxygen delivery found that failures were more frequent in the standard oxygen delivery group (23% vs. 12%), while 61% of those who initially failed in the standard group responded to the HFNC treatment (165). On the other hand, the other multicentre RCT found that treatment failures occur more often in the HFNC group—51% in comparison to 31% in the CPAP group (178). The differences in

patient demographics and centres did not explain the outcomes in any of these studies (165,166,178). Even though previous retrospective chart reviews have shown that the HFNC is comparable to the nCPAP (180), the fact that several factors influence the positive end-expiratory pressure (PEEP) level, such as the size of the prongs in relation to the nostrils and an air leak via the mouth, it is difficult to draw conclusions on the equality of the HFNC and nCPAP. What these three recent RCTs did show, however, is that the HFNC may be a bridge between the general ward and the PICU, as well as between the standard low-flow treatment and nCPAP (165,166,178). As the benefits of the HFNC are well documented in neonates, for whom the anatomic dead space is larger, the real benefits might come from its dead space wash-out rather than from distending pressure. Its high flow generates continuous positive pressure, which prevents microatelectasis and keeps the alveoli open. Therefore, the HFNC is assumed to alleviate respiratory distress by also inducing the mucus clearance and a ventilation-perfusion match.

2.4.5.2 Continuous positive airway pressure (CPAP)

The use of the CPAP is well established in adults and neonates (181,182), as well as in the treatment of neuromuscular diseases and the obstructive sleep apnoea syndrome in children (183,184). The nCPAP was introduced for infant bronchiolitis in 1981 (185), and in recent decades, the use of NIV has increased tremendously and is now most often the first-line respiratory support in an intensive care setting (186,187). However, evidence for its use still relies mostly on descriptive studies and the research-based evidence of its benefits is lacking (188). It appears that nCPAP relieves respiratory distress (189,190), shortens the LOS and ventilation times (189,191) and can be used safely when transporting infants with severe bronchiolitis (192). A European cross-sectional electronic survey of the PICUs revealed that over 90% of those who answered it were willing to use the CPAP for bronchiolitis. The CPAP was delivered equally often through oronasal masks, total face masks, nasal masks, and the nasal cannulas, while the helmet was more frequently used in Southern Europe (187). A Canadian cross-sectional survey reached 13 out of 16 PICUs and offered a different scenario to describe the management practices in the PICUs (186). The doctors who answered favoured the NIV: 57% HFNC, 29% CPAP and 7% NIPPV (186).

Theoretically, the nCPAP has several advantages in bronchiolitis. The PEEP increases the lumen of the small airways and prevents microatelectasis, while further increases fractional residual capacity (118). The reduction in respiratory distress has

been reported in several observational studies (193,194), and in two RCT studies (190,195). Improvements in the respiratory effort were observed during the first hours of treatment (193,194). A prospective observational study of 12 infants younger than three months treated with the nCPAP reports decreased muscular respiratory effort (193). In a retrospective case review, 49 infants were treated successfully with the NIV, and improvements in the respiratory rate, oxygen saturation, blood gases were reported within two hours of administration, with the total hospital LOS and ventilation duration being shortened (194). As mentioned, two RCTs on the nCPAP are published (190,195), of which one compared the nCPAP to standard care, finding a reduction in carbon dioxide (195). The other RCT compared the nCPAP to standard oxygen delivery and reports statistically significant reductions in clinical scores and detection of improvement in the inspiratory muscle work by oesophageal pressure (190).

Several studies reported decreases in admission rates to the PICU, as well as in the need for invasive ventilation, in the duration of ventilation and in the reduction of the number of complications associated with invasive ventilation, which consequently also reduced costs (189,191,194,196,197). A descriptive study over a 10-year period reported an increase in the use of NIV by 2.8% annually, and a decline of 1.4% in intubations among infants with severe bronchiolitis who are treated in the tertiary PICU in Australia. Treatment failures in the NIV group are more common in infants with comorbidities (196). A retrospective two-centre cohort study of 135 infants younger than six months reported that while the LOS is shorter (74.1+/- 6.8 vs. 169.5 +/- 7.5 h, $p < 0.001$) and the rate of suspected bacterial infection is lower (3.4% vs. 45.7% , $p < 0.001$) in a group of 89 infants treated with the nCPAP, yet the patients themselves were less ill in comparison to the intubated infants ($n = 46$) (191).

2.4.6 Invasive ventilation

Although the NIV is now the primary respiratory support for bronchiolitis (85,197), invasive ventilation is needed in cases of severe acute respiratory failure. A retrospective chart review from Australia and New Zealand reports that 79% of infants admitted to the PICU due to bronchiolitis need respiratory support and 18% need intubation (38). Currently, there is no consensus on the best ventilation mode (198). With respect to the conventional ventilation modalities, the pressure control mode is most commonly used one (199).

More invasive types of respiratory support are associated with infection (197) and may be complicated by the baro- and volutrauma; in addition, more sedation is needed. Furthermore, the smaller the infants are the more vulnerable they are to complications (200). To prevent side effects, lung protective strategies, such as lowering the tidal volume to 6–8 ml/kg and limiting the pressure to 30 cm H2O are beginning to be used during mechanical ventilation (200).

Extubation failure occurs in 9–20% of intubated infants (156,201,202). A prospective observational study on the weaning off of mechanical ventilation in infants with bronchiolitis showed that 15% of them do undergo reintubation and weaning failure within 48 hours, but no risk factors for extubation failure were identified (203).

2.5 Guidelines

The Thoracic Society of Australia and New Zealand published its first bronchiolitis guidelines in 1993, setting the age limit for bronchiolitis at six months (204). These guidelines highlighted the importance of minimal handling by minimizing the risks of hypoxia and dehydrations. A 1998 multicentre study on the management of bronchiolitis in Europe, Australia, and the US found that treatment practices vary substantially between countries and even between hospitals within the same country with a minor impact on patients' clinical status (205). Similarly, several other studies at the time remarked on the major use of unproven medications and diagnostic tools (32,103,206–210). Consequently, this sparked a growing interest in setting guidelines.

The purpose of the guidelines is to reduce the variability of care (which is associated with higher costs) and to link the care to evidence-based practices. Different kinds of guidelines aiming to work on different levels have been published in recent decades: local clinical practice guidelines and national evidence-based guidelines. Some of these local guidelines have showed that it is possible to unify practices and decrease the use of unproven therapies (211–213). A multifaceted approach and systematic implementation has been also suggested for increasing the impact (214).

In addition to the local guidelines, several national guidelines on the treatment of bronchiolitis have been published (16,17,48–51,215) (Table 1). Both AAP (12) and the National Collaborating Centre for Women's and Children's Health (NICE) (17) have updated their evidence-based guidelines on the diagnosis and management of

bronchiolitis in children. The differences between these guidelines are summarised in Table 1 and Table 3.

The Finnish Current Care Guidelines for the treatment of lower respiratory tract infections in children, including bronchiolitis in infants, were published in 2014 (16). The guidelines are based on the available literature but, in addition to the evidence-based approach, they are applied to the Finnish health care system context (16,216). They belong to a group of clinical practice guidelines and are referred to as the Current Care Guidelines, created by the Finnish Medical Society Duodecim (217)

Table 3. National guidelines on the management of bronchiolitis

	Finland, 2016 (16)	NICE, 2015 (17)	AAP, 2014 (12)	Canada, 2014 (48)	Italy, 2014 (49)	Australia, 2008 (50)	SIGN, 2006 (51)
Fluid support	Not mentioned	NGH or IVH, isotonic fluids	NGH or IVH	NGH or IVH	NGH or IVH	NGH or IVH	Preferred NGH
Suction	Not mentioned	Not recommended	Not recommended routinely, no deep suctions	No deep suctions	Nasal suctions, no deep suctions	May be tried	Nasal suction
Saline inhalation	Not recommended	Not recommended	Not recommended for outpatients, may be used for inpatients	Not recommended for outpatients, may be used for inpatients	Recommended	Not mentioned	Not mentioned
Beta-agonist	Not recommended	Not recommended	Not recommended	Not recommended	Not routinely, trials with careful monitoring	Not routinely, trial with careful monitoring may be tried for older infants (> 9 months)	Not recommended
Adrenaline	Not routinely recommended	Not recommended	Not recommended	Not routinely, trial with careful monitoring	Not recommended	Not routinely, trial with careful monitoring	Not recommended
Corticosteroids	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended

AAP, American Academy of Pediatrics; NICE, the National Institute for Health and Care Excellence; SIGN, Scottish Intercollegiate Guidelines Network; NGH, nasogastric hydration; IVH, intravenous hydration.

3 AIMS OF THE STUDY

The aims of this thesis were to describe the management of bronchiolitis and to evaluate changes in the management of severe bronchiolitis, with a special focus on the influence of guidelines. In addition, this thesis considered the risk factors for intensive care and respiratory support in infant bronchiolitis.

The specific aims of the thesis are:

- To describe the definitions and treatment strategies of bronchiolitis in two countries, Finland and Sweden, at the time when national guidelines were not available (I).

- To evaluate the risk factors for and incidence of patients with severe bronchiolitis admitted to the PICU, with or without the need for respiratory support (II).

- To investigate the changes in the management of severe bronchiolitis in the PICU in relation to the publication of evidence-based guidelines (III).

- To assess the impact of the Current Care Guidelines on prescribing adrenaline inhalations in four Finnish university hospitals (IV).

4 MATERIALS AND METHODS

4.1 Study design

Three separate materials were analysed in this thesis. The management practice of bronchiolitis in Finland and Sweden was investigated through a structured questionnaire that was sent to all paediatric hospitals in both countries (I). The data for a case-control study on the risk factors for and treatment of bronchiolitis in the PICU were collected retrospectively from the electronic patient files of the Tampere University Hospital from the 2000–2012 period and supplemented with an identical data collection from the 2013–2015 period (II and III). Finally, all infants younger than 12 months who were treated in the PICU from 2000 to 2015 due to bronchiolitis were identified. The infants with bronchiolitis who were treated in the ED just prior and subsequent to the cases needing treatment in the PICU and who were not admitted to the PICU were considered to be the controls. The prescription of racemic adrenaline was estimated based on the numbers of doses delivered by the four university hospitals' pharmacies to the paediatric departments before (2012–2013) and after (2015–2016) the publication of the Finnish Current Care Guidelines for bronchiolitis management. The numbers of doses were registered separately for different paediatric units, such as the ED, the paediatric ward, and the PICU (IV).

4.1.1 Questionnaire on treatment strategies (I)

A questionnaire on the current bronchiolitis practice was sent to all the paediatric hospitals in Finland and Sweden. The paediatricians responsible for the treatment of bronchiolitis in the hospitals were asked to complete the questionnaire on the diagnostic criteria and the current bronchiolitis practice. All of the 22 Finnish paediatric hospitals and 21 out of 37 (57%) Swedish paediatric hospitals completed the questionnaire. At the end of 2011, there were 61,000 infants less than 12 months of age in Finland and 96,000 in Sweden. The questionnaire covered 70,000 of 96,000 (74%) infants younger than 12 months in Sweden and 100% of them in Finland. For each hospital's catchment area, the number of infants aged less than 12 months at

the end of 2011 was obtained from the Official Statistics of Finland and Sweden. The numbers were used to create a weighted index to reflect the size of each paediatric hospital.

The questionnaire included questions on the age limits and the clinical findings for the definition of bronchiolitis. It comprised questions on practices for measuring the oxygen saturation and respiratory rate on admission, including indications and doses of medication, such as salbutamol, adrenaline, and inhaled or systemic corticosteroids. Indications for beginning additional oxygen or nCPAP treatment were recorded.

The questions were planned to reflect the clinical problems encountered almost daily when treating infants with severe bronchiolitis. The attending doctors were asked to list, using their own words in Finnish, Swedish or English, the five most important clinical findings of bronchiolitis. The words were grouped into laboured breathing, chest retractions, audible wheezing, prolonged expiration, fine crackles, cough, air trapping, eating problems, apnoea, fatigue, and mucus in the airways.

The questionnaire also included questions on the indications for hospital treatment, on the use of laboratory tests and viral diagnostic tests, and on the use of chest radiography.

4.1.2 Clinical data collection (II, III)

The clinical data were collected retrospectively from the electronic patient files of the Tampere University Hospital, in Tampere, Finland, from the 2000–2012 period and supplemented with an identical data collection for the 2013–2015 period. All infants younger than 12 months, with the International Classification of Diseases - 10th edition (ICD-10) codes of J10*–18*, J20*–22*, J45*or J46* during the 2000–2015 period, who were treated in the PICU were identified (Figure 1). All of these patient files were manually reviewed and the diagnoses were re-evaluated to meet our definition of bronchiolitis—the first episode of expiratory breathing difficulty, with or without audible wheezing, associated with a lower respiratory tract infection. Among 179 eligible infants, 105 met the criteria of bronchiolitis, for whom bronchiolitis was a primary reason for their PICU stay (Figure 1). Eighty-three of those bronchiolitis patients were from Pirkanmaa (Tampere) Hospital District. Of the 105 cases, 34 were first treated on the paediatric ward and 71 were admitted directly to the PICU, including 22 patients from other surrounding hospitals. The indications for PICU admission were an acute worsening of breathing such as

exhaustion, hypercapnia or recurrent apnoea. The indications were similar for the infants transferred from the surrounding hospitals and for those transferred from the ED or another ward of the University Hospital.

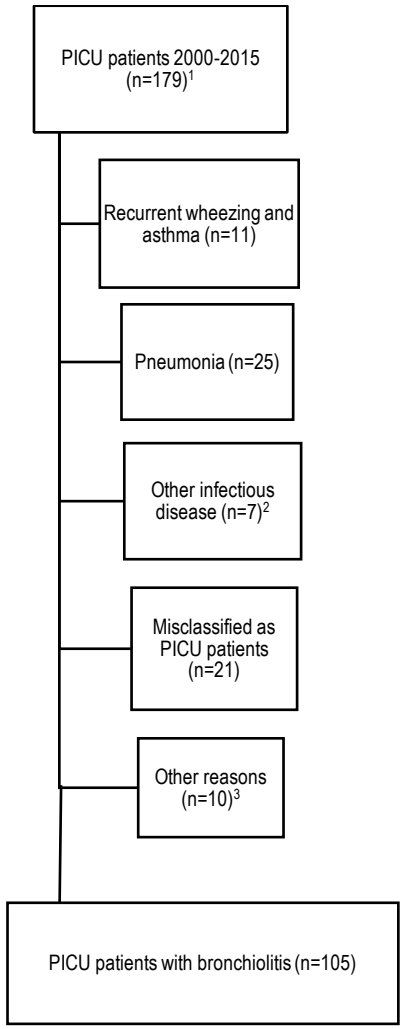

Figure 1. Infants with bronchiolitis treated in the PICU.

[1]Patients with ICD-10 codes of J10*–18*, J20*–22*, J45*or J46*. [2]Laryngitis (n = 3), influenza (n = 1), fever at age less than three months (n = 1), tuberculosis (n=1), sepsis (n=1).[3]Ventricoperitoneal shunt (n = 1), epileptic seizure (n = 1), bronchoscopy (n = 2), apnoea (n = 1), heart disease (n = 1), polyarthritis nodosa (n = 1), unknown reason (n=3).

For all 105 cases, two controls were selected. The controls were admitted to the ED for bronchiolitis with the ICD-10 codes J21* just prior and subsequently to the case, and the same re-evaluation to meet our definition of bronchiolitis was applied to all of them. The controls were not admitted to the PICU; instead, 146 of them were treated as inpatients on the ward and 64 as outpatients discharged from the ED.

The hospital records of all 315 patients were reviewed and the same structured form was completed separately for the findings and treatments in the ED, on the ward, and in the PICU. The form comprised of information on gender, gestational age (classified with the cut-off points of 28, 32 and 37 gestational weeks), birth weight, age and weight on admission for bronchiolitis, previous medical history, such as presence of respiratory distress syndrome (RDS), BPD, CHD, and of treatment with surfactant as a neonate.

In addition, previous hospital admissions were recorded, including treatment periods in the neonatal intensive care unit (NICU), presence of atopy such as doctor-diagnosed atopic dermatitis or food allergy, family histories of atopy or asthma, and the use of inhaled corticosteroids. Clinical findings, such as audible wheezing, fine or coarse crackles on auscultation and signs of dehydration at admission, were recorded. Viral antigen test results, if available, were also collected.

Secondary infections like otitis media, conjunctivitis and pneumonia, during the hospitalisation were recorded. The information on the administered treatments was recorded separately for the ED, the ward, and the PICU. The need for supplementary oxygen and fluid replacement therapy either intravenously or through nasogastric tubes was collected. Saline inhalation and its concentrations, if given, were recorded and the bronchodilators of inhaled salbutamol and racemic adrenaline, if administered, were registered separately. The use of other medications, such as inhaled or systemic corticosteroids, theophylline, magnesium sulphate or antibiotics, were collected.

Respiratory support with the HFNC and nCPAP was considered as the NIV and respiratory support with intubation as invasive ventilation. Apnoea was defined as a breathing pause with or without bradycardia or desaturation, detected and recorded by the medical staff.

The total LOS in the hospital and the LOS in the PICU were reported in days. To evaluate the changes in the management of bronchiolitis, the data were split into three periods: years 2000–2005, 2006–2010, and 2011–2015. The period from 2000–2005 represented the era before and the 2006–2010 and 2011–2015 periods represented the era after the AAP guidelines on the management of bronchiolitis were published (215).

4.1.3 Consumption of racemic adrenaline (IV)

The consumption of racemic adrenaline was examined in the four Finnish University Hospitals—Kuopio, Oulu, Tampere, and Turku—from 2012 to 2016. The consumption estimation was based on the numbers of doses of racemic adrenaline (Racepinephrine 2.25% 0.5 ml) delivered by the hospital pharmacies to the paediatric units: the ED, the paediatric infectious disease ward, and the PICU. The national Current Care Guidelines on the management of lower respiratory tract infections including bronchiolitis was published in 2014, and it recommended racemic adrenaline for bronchiolitis as an on-demand rescue therapy. The consumption of adrenaline was studied both before and after the publication of the guideline.

The actual cost of the treatment with racemic adrenaline was obtained from the Tampere University Hospital pharmacy, and the cost data were evaluated by using the 2017 prices, which were reported in euros. One dose of racemic adrenaline costs €2.30 at the 2017 level. It was estimated that the administration of one inhalation, including the preparation of the drug and the solution, takes 10 minutes. The total time of extra work was evaluated in hours. The nurses' salaries were not included in the cost data.

The exact numbers of infants with bronchiolitis admitted to the included paediatric departments were not available. However, the numbers of infants less than 12 months of age who were admitted for bronchiolitis to the paediatric department were available from the Tampere University Hospital for the years 2013–2015, and the comparable diagnoses were confirmed by revisiting the patients records. The number of patients were 238 in 2013, 213 in 2014, and 172 in 2015. The total numbers of laboratory-confirmed RSV infections were obtained from the National Infectious Disease Register and these numbers were 1991 in 2013, 2868 in 2014, 2436 in 2015 and 4947 in 2016 (National Infectious Disease Register, National Institute for Health and Welfare, Finland).

The consumption of racemic adrenaline was expressed in crude numbers of consumed doses and as the numbers of consumed doses per 10,000 children younger than 16 years in the overall population. The number of children younger than 16 years of age was obtained from the government data for each university hospital district: Tampere (91,010), Oulu (88,094), Kuopio (26,518) and Turku (78,641) (National Institute for Health and Welfare).

4.2 Statistical methods (I–IV)

The data were analysed either by using the SPSS package version 20 (SPSS Inc. Chicago, IL, USA) or the SPSS 23 software (SPSS Inc., Chicago, IL, USA). The t-test was applied for normally distributed continuous data, and the results were expressed as means and 95% CI. The Mann–Whitney U test or the Kruskal–Wallis test was used to analysed the non-normally distributed continuous data and the results were expressed as medians and interquartile ranges (IQR). The Chi squared test or Fisher´s exact test, when appropriate, was used to analysed the categorised data and the results were expressed as numbers and percentages. The two-sided p-value below 0.05 was considered statistically significant. The Bonferroni correction by multiplying the p-values by two was applied in paired comparisons.

The odds ratio (OR) and their 95% Cls were calculated first as non-adjusted, and thereafter by using the multivariable logistic regression to obtain the aOR for age, gender, and risk factors that were significant in the non-adjusted analyses.

For the Finnish and Swedish questionnaire data, the results are expressed as mean weighted proportions and their standard deviations (SD). The weighted proportions are based on the numbers of children younger than 12 months in the area for which the hospital primarily provides inpatient care—the number of children younger than 12 months old in the area, divided by either 61,000 (in the case of a Finnish hospital) or by 70,000 (in the case of a Swedish hospital).

The population-based incidence of bronchiolitis treated in the PICU was calculated for the Tampere University Hospital district. At the time of the study, the hospital provided inpatient care for a population of about 90,000 children younger than 16 years and a population of infants younger than 12 months ranging from 4,761 to 5,880. In addition, the hospital provided paediatric intensive care for the population of about 10,000 infants aged less than 12 months from four surrounding central hospitals.

4.3 Ethics

The studies of the current thesis were carried out with the permission of the chief physician of the attending university hospitals. Since the study was based on register data only and the patients were not contacted, the parents' permission was not needed.

5 RESULTS

5.1 Diagnosis of bronchiolitis (I)

In the two Nordic countries, Finland and Sweden, the upper age limit for the definition of bronchiolitis varied from three to 24 months. The mean upper age limit for the definition of bronchiolitis was 12.7 months (SD 5.0) in Finnish children's hospitals and 12.5 months (SD 7.8) in Swedish children's hospitals. Responding paediatricians were asked to list the five most characteristic symptoms and signs of bronchiolitis (Table 4). Laboured breathing, chest retractions, and fine crackles were the characteristics assessed as most important in both countries, followed by prolonged expiration and audible wheezing.

Table 4. Symptoms and signs assessed by doctors as characteristics of bronchiolitis in Finnish and Swedish children´s hospitals.

Children´s hospitals in Finland	Children´s hospitals in Sweden
Laboured breathing 98% (0.13)	Laboured breathing 88% (0.33)
Chest retractions 65% (0.48)	Chest retractions 74% (0.44)
Fine crackles 56% (0.50)	Fine crackles 70% (0.46)
Audible wheezing 54% (0.50)	Prolonged expiration 45% (0.50)
Prolonged expiration 53% (0.50)	Cough 39% (0.49)
Cough 37% (0.48)	Air trapping 25% (0.43)
Air trapping 31% (0.46)	Audible wheezing 21% (0.41)

Weighted percentages based on the number of children <12 months of age in the area in which the hospital primarily provides inpatient care, expressed as a mean and standard deviation.

5.2 Characteristics of infants treated in the paediatric intensive care unit (PICU) (II, III)

The 105 infants treated in the PICU were younger in comparison to the 210 controls who were treated on the ward (n = 146) or in the ED (n = 64). The median age was 1.7 months (IQR 0.9–3.5) in the cases and 4.0 months (IQR 2.1–6.1) in the controls ($p < 0.001$). The infants treated in the PICU, when compared to the controls, had lower birth weight, were more frequently born premature, presented comorbidities more frequently and had been previously treated in the hospital more often (Table 5). In the univariate comparisons, the risk factors for admission to the PICU were age younger than two months, premature birth at <37 gestational weeks, a birth weight under 2,500 g (Table 5).

Table 5. Basic and clinical data presented separately for 105 infants treated for bronchiolitis in the PICU (cases) and for 210 controls treated for bronchiolitis in the ED or on the ward.

Characteristic	Cases n = 105 (%)	Controls n = 210 (%)	OR	95% CI	p-value
Gender (males)	61 (58)	108 (51)	1.3	0.82-2.10	0.263
Age < 2 months	60 (57)	44 (21)	5.0	3.00-8.38	< 0.001
Premature birth (< 37 weeks)	45/97 (46)	22/204 (11)	7.2	3.95-12.99	< 0.001
Birth weight < 2,500 g	40/99 (40)	9/203 (4)	14.6	6.70–31.87	< 0.001
Previous hospitalisation	57/100 (57)	34/209 (16)	6.8	3.98–11.71	< 0.001
NICU	35/78 (45)	8/183 (4)	17.8	7.71–41.14	< 0.001
Paediatric ward	22/65 (34)	26 (13)	3.4	1.78–6.65	< 0.001
Underlying disease	27 (26)	12 (6)	5.6	2.74–11.78	< 0.001
CHD[b]	13/89 (15)[c]	7/204 (3)	4.8	1.85–12.53	0.001a
BPD/RDS[b]	8/88 (9)	1/198 (1)	19.7	2.42–160.08	0.001a
Other relevant disease[b]	12/91 (13)	6/203 (3)	5.0	1.81–13.75	0.002a
Atopy	3/102 (3)	8 (4)	0.7	0.20–2.95	0.696
Asthma in family	10/103 (10)	26 (16)	0.8	0.35–1.65	0.486
Current or earlier inhaled corticosteroids	9/104 (9)	2 (1)	9.9	2.09–46.48	<0.001
Respiratory syncytial virus	59/92 (64)	66/127 (51)	1.7	0.98–2.96	0.056

[a] Bonferroni correction with multiplying the p-value by 2.[b] Compared to patients without underlying disease. [c] Seven cases with hemodynamically significant CHD. PICU, paediatric intensive care unit; ED, emergency department; NICU, neonatal intensive care unit; CHD, congenital heart disease; BPD, bronchopulmonary dysplasia; RDS, respiratory distress syndrome.

Similar risk factors were seen in the univariate analysis for respiratory support: age younger than two months (OR 3.8, 95% Cl 2.0 to 7.2), prematurity <37 weeks (OR 6.7, 95% Cl 3.3 to 13.5), a birth weight under 2,500 g (OR 8.7, 95% Cl 4.2 to 18.1), and CHD (OR 5.0, 95% Cl 1.9 to 15.1) (Supplementary table in II).

Wheezing and coarse crackles were associated with a diminished risk for PICU admission (Table 6) and wheezing was associated with a lower need for respiratory support in those admitted. Apnoea, fine crackles and dehydration were associated with the need for PICU admission (Table 6). Additionally, apnoea was associated with the need for respiratory support (OR 6.7, 95% Cl 3.0-15.0) (Supplementary table in II).

Table 6. Clinical findings presented separately for 105 infants treated for bronchiolitis in the PICU (cases) and for 210 controls treated for bronchiolitis in the ED or on the ward.

Characteristic	Cases n = 105 (%)	Controls n = 210 (%)	OR	95% CI	p-value
Apnoea	29 (27)	2 (1)	39.7	9.25–170.33	< 0.001
Tachypnoea (> 50/min)	36 (34)	52 (25)	1.6	0.95–2.64	0.076
Audible wheezing	39 (37)	143 (68)	0.3	0.17–0.45	< 0.001
Fine crackles	26 (25)	27 (13)	2.2	1.23–4.06	0.008
Coarse crackles	33 (31)	97 (46)	0.5	0.33–0.87	0.012
Dehydration	10 (10)	8 (4)	2.7	1.91–6.95	0.022

PICU, paediatric intensive care unit; ED, emergency department.

The data for the case-control study were divided into three periods: 2000–2005, 2006–2010 and 2011–2015. Approximately equal thirds of the infants needing admission to the PICU were treated during each time period. For them, the LOS in the hospital or the LOS in the PICU was unchanged (Table 7). There were no differences in infant birth weight, presence of apnoea, previous hospitalisation or in amount in RSV positive infections between the three time periods. There was a difference in infant age between the three time periods, but only in those treated in the ED (Table 7). In the infants treated in the PICU, there was a difference in CHD (Table 7).

Table 7. Characteristics of 105 infants treated in the PICU, 146 infants treated at the ward and 64 infants treated in the ED, presented separately in three periods: 2000–2005, 2006–2010 and 2011–2015.

PICU patients	2000–2005	2006–2010	2011–2015	p-value
n = 105	n = 41 (%)	n = 27 (%)	n = 37 (%)	
Age, months, median, (IQR)	1.8 (0.9–1.8)	1.7 (0.9–1.7)	1.6 (0.8–3.2)	0.961
Sex (male)	23 (56)	15 (56)	21 (57)	0.995
Premature birth	18 (44)	13 (48)	14 (38)	0.520
Birth weight under 2,000 g	11 (27)	9 (33)	7 (19)	0.462
CHD	2 (5)	10 (37)	1 (3)	< 0.001
RSV	25 (61)	11 (41)	23 (62)	0.171
LOS (PICU) days, median (IQR)	3 (1–6.5)	2 (1–5)	4 (2–7.5)	0.244
LOS (hospital) days, median (IQR)	7 (5–12)	5 (4–8)	8 (4–12.5)	0.127
Ward patients	2000–2005	2006–2010	2011–2015	p-value
n = 146	n = 61	n = 24	n = 6	
Age, months, median (IQR)	3.5 (2.1–6.6)	4.3 (1.4–6.0)	3.0 (2.0–4.5)	0.696
Sex, male (%)	31 (51)	14 (58)	24 (39)	0.220
LOS (hospital) days, median (IQR)	2.0 (1–4)	2.0 (1–3.75)	2.0 (1–4)	0.697
ED patients	2000–2005	2006–2010	2011–2015	p-value
n = 64	n = 23	n = 28	n = 13	
Age, months, median (IQR)	6.7 (5.0–9.3)	5.0 (2.4–6.2)	3.7 (1.9–6.0)	0.010[a]
Sex (male) (%)	14 (61)	16 (57)	9 (69)	0.761

CHD, congenital heart disease; RSV, respiratory syncytial virus; PICU, paediatric intensive care unit; ED, emergency department; IQR, interquartile range; LOS, length of stay.

5.3 Diagnostic testing and clinical findings (I, III)

Pulse oximetry was in use in nearly all Finnish and Swedish children's hospitals. The oxygen saturation was therefore measured at admission in almost all hospitals in Finland and Sweden (Table 8). The weighted mean of the lowest acceptable oxygen saturation in the room air was 94% (range 85–95, SD 1.7) in Finnish and 93% (90–95, SD 1.3) in Swedish hospitals. The respective figures for the highest acceptable respiratory rates were 51/min (range 40–70, SD 6.2) and 50/min (30–60, SD 8.5).

Table 8. Measurements of respiratory distress and supportive treatment in Finnish and Swedish paediatric hospitals during hospital stay.

	Finland			Sweden		
	Always	Often	Rarely	Always	Often	Rarely
Oxygen saturation	95	5	0	89	8	0
Respiratory rate	63	28	9	71	12	17
Supplementary oxygen[1]	13	76	10	23	75	3
Suction	39	61	0	57	33	10
IVH	0	55	45	0	38	62
NGH	0	24	76	8	73	19

Weighted percentages based on the number of children <12 months of age in the area in which the hospital primarily provides inpatient care. IVH, intravenous hydration; NGH, nasogastric hydration. 1 Data missing from 3 % of Swedish hospitals.

Tests for an RSV identification were performed in all bronchiolitis cases by 49% of the Finnish and by 17% of the Swedish responding paediatricians. On the other hand, only 3% of the Swedish and 0% of the Finnish doctors responded that the RSV was never studied. Tests were performed in the laboratory, using either antigen or genome detection methods but bedside tests were rarely used (data not shown).

In the PICU, the use of chest radiographs did not change between years 2000 and 2015 ($p = 0.633$). For the three time periods the figures were: 63% in 2000–2005, 74% in 2006–2010, and 65% in 2011–2015. The chest radiographs were taken from 12% of infants with bronchiolitis discharged from the ED or admitted to the ward.

5.4 Management of bronchiolitis in inpatient settings (I, III)

5.4.1 Supportive treatment (I,III)

The questionnaire data revealed that supplementary oxygen was given by 89% and 98% (always–often) of Finnish and of Swedish paediatric departments, respectively (Table 8). IVH was given (always–often) by 55% of the Finnish responding paediatricians, while the NGH was primarily used by 24%. These figures in the Swedish responses were 38% and 81%, respectively (Table 8) (I).

In the PICU, the administration of supplementary oxygen remained rather stable during the three surveillance periods (p = 0.199, Table 9). Similarly, no significant changes were seen in the use of supplementary oxygen on the ward (20% vs. 17% vs. 26%, p = 0.541) or in the ED (2% vs. 2% vs. 0%, p = 0.427). Nearly 90% of infants treated in the PICU needed supplementary fluids and the use of NGH and IVH was equally common (Table 9). In the ED, the NGH was little used (2% vs. 2% vs. 7%, p = 0.256). On the ward, the NGH (26% vs. 17% vs. 23%, p = 0.641) was more common than intravenous hydration (5% vs. 4% vs. 7%, p = 0.881), with no significant changes over time (III).

Table 9. Supportive treatment of 105 infants with bronchiolitis in the PICU presented separately for three time periods between 2000–2015.

	2000–2005 n = 41 (%)	2006–2010 n = 27 (%)	2011–2015 n = 37 (%)	p-value	p-value 2000–2005 vs. 2006–2010[a]	p-value 2006–2010 vs. 2011–2015[a]
Oxygen support	35 (85)	26 (96)	30 (81)	0.199	0.294	0.138
NGH[b]	25 (61)	17 (63)	26 (70)	0.674	1.0	1.0
IVH	24 (59)	21 (78)	29 (78)	0.100	0.202	1.0

a Bonferroni correction by multiplying the p-value by two. NGH, nasogastric hydration; IVH, intravenous hydration. b The figures for use of NGH solely for rehydration were 9 (22), 5 (2) and 4 (11), respectively.

5.4.2 Pharmacological treatment (I, III)

The beta-agonists were given (always–often) by 47% of the Finnish and 38% of the Swedish responding paediatricians. Inhalations of racemic adrenaline were given (always–often) by 79% of the Finnish responding paediatricians and in Sweden, by 86% of the responding paediatricians were given (always-often) inhalations of levo-adrenaline. Anticholinergics, inhaled corticosteroids, and intramuscular adrenaline were rarely given (if at all). Nebulised saline inhalations were given (always–often) in 45% of the Finnish responding paediatricians' cases and in 92% of the Swedish responding paediatricians' cases—when used, they were given as isotonic (0.9%) saline for half of the time and as hypertonic (3%) saline for the other half in both countries. Both these countries employed different strategies for the first-line medication. In Finland, the first-line medication was racemic adrenaline combined with either salbutamol or with hypertonic saline in 87% of the children's hospitals (Table 10). By contrast, the Swedish responding paediatricians most often used inhaled levo-adrenaline with hypertonic saline as their first-line medication.

Table 10. First-line inhalation therapy in two Nordic countries: Finland and Sweden

	Finnish hospitals, %	Swedish hospitals, %
Racemic adrenaline and salbutamol	44 (0.50)	9 (0.28)
Salbutamol alone	0	5 (0.22)
Racemic adrenaline and 3% saline	43 (0.50)	1 (0.08)
Racemic adrenaline alone	12 (0.32)	0
Levo-adrenaline and 3% saline	0	83 (0.38)

Weighted percentages based on the number of children < 12 months of age in the area in which the hospital primarily provides inpatient care, expressed as mean and standard deviation.

Corticosteroids were not recommended in any form for bronchiolitis patients by 37% of the Finnish and 48% of the Swedish responding paediatricians. The main reasons for the use of inhaled corticosteroids (ICS) were a history of wheezing, or a prolonged obstruction on the ward, or a history of previous ICS use. The most common reason in Swedish hospitals to continue with the ICS was that the medication was started on the ward. Additionally, 37% of Finnish hospitals used the ICS for prematurely born babies. The mean recommended duration of post-discharge ICS treatment was 48.2 days in Finland (14–90 days, SD 23.5) and 51.8 days (1–150, SD 59.0) in Sweden. The routine control visits subsequent to the admission for bronchiolitis was not recommended, however, 17% of the Finnish and 31% of the Swedish responding paediatricians recommended the control visit if medication had been prescribed. If the symptoms were severe, the respective figures were 34% and 27%.

In the PICU, inhaled bronchodilators were used in over 80% of infants (Table 11). The use of bronchodilators was similar by time on the ward (92% vs. 88% vs. 74%, $p = 0.023$) and in the ED (85% vs. 71% vs. 78%, $p = 0.174$). In critically ill infants, the use of salbutamol decreased over time ($p = 0.019$), while the use of racemic adrenaline increased over time ($p = 0.035$, Table 11). Similar changes were observed for both the ward and the ED.

The hypertonic saline inhalations were given to half of the infants treated in the PICU between 2011–2015 (Table 11). The treatment was introduced in 2013 and, therefore, was not used from prior to 2010. The increase in HS use was seen on the ward and in the ED, in which the use of HS inhalations in 2011–2015 was 69% and 22%, respectively.

Table 11. Management of 105 infants with bronchiolitis in the PICU presented separately for the three time periods during 2000–2015

	2000–2005 n = 41 (%)	2006–2010 n = 27 (%)	2011–2015 n = 37 (%)	P-value	P value 2000–2005 vs. 2006–2010[a]	P value 2006–2010 vs. 2011-2015[a]
Inhaled saline	2 (5)	6 (22)	21 (57)	<0.001	0.060	0.012
0.9%	2 (5)	6 (22)	2/18 (11)	0.092	0.060	0.680
3%	0/39 (0)	0/21	19/35 (54)	<0.001	-	<0.001
Inhaled bronchodilators	34 (83)	23 (85)	34 (92)	0.491	1.0	0.792
Adrenaline	24 (59)	21 (78)	31 (84)	0.035	0.202	1.0
Salbutamol	28 (68)	12 (44)	14 (38)	0.019	0.102	1.0
Anticholinergic	6 (15)	2 (7)	0 (0)	0.052	0.730	0.18
Theophylline	4 (10)	1/26 (4)	3 (8)	0.648	0.698	0.944
Systemic steroids	12 (29)	4 (15)	2 (5)	0.019	0.338	0.404
Antibiotics	14 (34)	5 (19)	16 (43)	0.116	0.320	0.074

a Bonferroni correction by multiplying the p-value by two.

The use of systematic corticosteroids decreased during the three study periods in the PICU (p = 0.019), on the ward (18% vs. 17% vs. 2%, p = 0.009), and in the ED (8% vs. 8% vs. 0%, p = 0.042). Inhaled corticosteroids were not given to any of the patients during hospitalisation. At the same time, the use of antibiotics did not change significantly in the PICU, on the ward or in the ED. In critically ill infants, the antibiotics were most often used for pneumonia.

5.4.3 Respiratory support (I, III)

All hospitals could provide the nCPAP—and of the responding paediatricians 81% had used the nCPAP in Finland and 73% in Sweden. In both countries, the nCPAP therapy occurred more often on the ward (Finland 56%, Sweden 81%) than in the PICU.

During the 2000 to 2015 period, 53 patients needed respiratory support (Figure 2). Most often, the primary form of respiratory support was nCPAP. A total of 21 infants needed invasive ventilation (Figure 2) and, for them, the duration of the treatment as intubated varied from one to 11 days (median 4.5, IQR 3–7.75). The infants treated with mechanical ventilation had the longest median LOS in the PICU and in the hospital. During the entire 2000–2015 time-frame, the use of non-invasive

respiratory support, such as the HFNC and nCPAP, increased; despite this, the need for mechanical ventilation remained constant (Table 12).

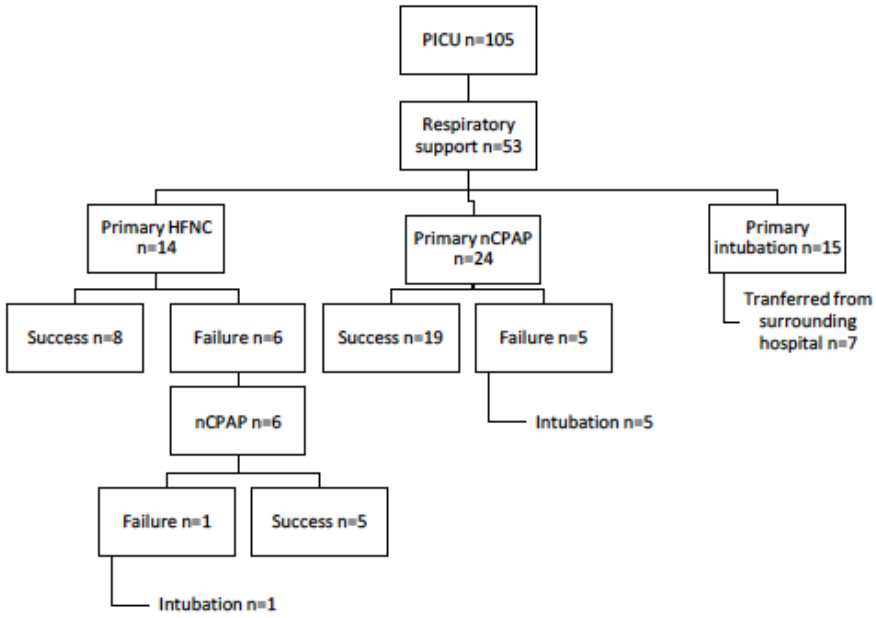

Figure 2. Respiratory support of infants with bronchiolitis admitted to the PICU.

PICU, paediatric intensive care unit; HFNC, high-flow nasal cannula; nCPAP nasal continuous positive airway pressure.

Table 12. Respiratory support of 105 infants with bronchiolitis in the PICU presented separately for three time periods from 2000–2015.

	2000–2005 n = 41 (%)	2006–2010 n = 27 (%)	2011–2015 n = 37 (%)	p-value	p-value 2000–2005 vs. 2006–2010[a]	p-value 2006–2010 vs. 2011–2015[a]
HFNC	0	1 (4)	26 (70)	< 0.001	0.430	< 0.001
nCPAP	5 (12)	12 (44)	21 (57)	< 0.001	0.006	0.660
Intubation	7 (17)	7 (26)	7 (19)	0.657	1.0	1.0

[a] Bonferroni correction by multiplying the p-value by two. PICU, paediatric intensive care unit; HFNC, high-flow nasal cannula; nCPAP, nasal continuous positive airway pressure

HFNC therapy was introduced in autumn 2011 and 70% of PICU patients were treated with HFNC between 2011 and 2015 (Table 11). Fourteen infants received

HFNC as a primary respiratory support (26%), but in half of them, the HFNC treatment was not successful, and they needed nCPAP. Eight infants were treated with HFNC alone and 24 infants with nCPAP with or without HFNC, without a need for mechanical ventilation (Figure 2).

5.5 Risk factors for severe bronchiolitis (II)

The multivariable logistic regression was adjusted for age, gender and risk factors, which were significant in the non-adjusted analyses. Previous hospitalisation and previous use of corticosteroids were related to prematurity and to low birth weight and, therefore, they were excluded from the final multivariable analyses. Even though several clinical findings were statistically significant in the non-adjusted analyses, we decided to include only the wheezing sound in the final multivariable analyses due to its clear definition in the Finnish clinical practice.

The independent significant risk factors for PICU admission were age younger than two months of age, having a low birth weight of < 2,000 g, and the presence of CHD. Reported apnoea and the absence of wheezing retained the statistical significance. Premature birth was a significant risk factor for the PICU admission in non-adjusted analyses but it lost its significance in the multivariable analyses (Table 13).

Table 13. Multivariable logistic regression: Risk factors for the intensive care need among 315 infants admitted for bronchiolitis in 2000–2015.

Risk factor	aOR	95% CI	p-value
Age < 2 months	11.50	5.12–25.80	< 0.001
Gender (male)	1.81	0.88–3.74	0.107
Premature birth	2.19	0.85–5.62	0.105
Birth weight under 2,000 g	15.93	2.36–107.27	0.004
CHD	15.85	4.15–60.50	< 0.001
Apnoea	7.22	1.44–36.10	0.016
Absence of wheezing	2.19	1.08–4.47	0.031

Area under the curve for predicted probability: 0.882. Hosmer–Lemeshow test: 1.80, p 0.937. aOR, adjusted odds ratio; CI, confidence interval; CHD, congenital heart disease.

For needing respiratory support, the independent significant risk factors were being less than two months of age, having a low birth weight of < 2,000 g and the presence of CHD, but apnoea, preterm birth, and the absence of wheezing were significant only in non-adjusted analyses (Table 14).

Supplementary analysis was performed without birth weight being included in the model, since almost half of the PICU admissions were associated with premature birth. In this this analysis, premature birth was an independent significant risk factor for PICU admissions (aOR 4.4, 95% CI 1.2 to 9.8) and use of respiratory support (aOR 3.8, 95% CI 1.7 to 8.9).

Table 14. Multivariable logistic regression: Risk factors for the respiratory support need among 315 infants admitted for bronchiolitis in 2000–2015.

Risk factor	aOR	95% CI	p-value
Age < 2 months	10.15	3.04–33.83	< 0.001
Gender (male)	1.29	0.55–3.07	0.560
Premature birth	2.32	0.82–6.53	0.111
Birth weight under 2,000 g	4.87	1.11–21.42	0.036
CHD	12.99	2.77–60.86	0.001
Apnoea	1.62	0.51–5.14	0.416
Absence of wheezing	1.44	0.57–3.65	0.440

Area under the curve for predicted probability: 0.864. Hosmer–Lemeshow test: 2.03, p 0.917. aOR, adjusted odds ratio; CI, confidence interval; CHD, congenital heart disease.

5.6 Incidence of paediatric intensive care unit (PICU) admission (II)

Between the years 2000 and 2015, the annual number of infants treated in the PICU varied from one to 14. The mean population of infants younger than 12 months was 5,335 in the catchment area of the hospital and varied between 4,761 and 5,880. The mean age-specific annual incidence was 1.5/1,000/year, varying between 0.18 and 2.59 (Figure 3).

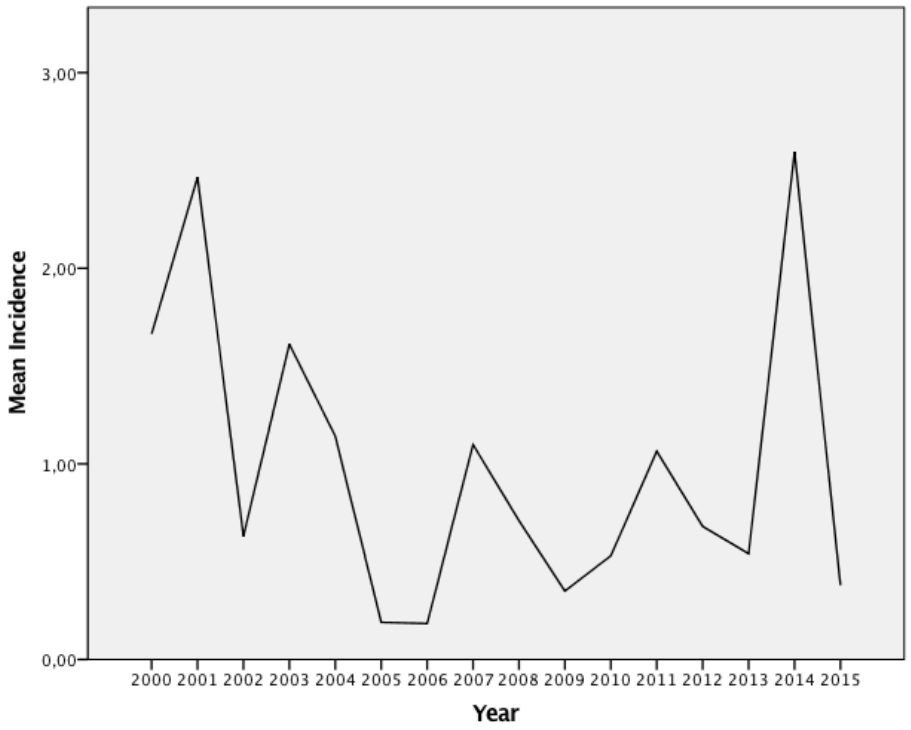

Figure 3. Annual age-specific incidence in bronchiolitis infants treated in intensive care during the study period from 2000–2015.

5.7 Consumption of racemic adrenaline in four university hospitals (IV)

The consumption of racemic adrenaline varied in the four attending university hospitals (Figure 4). In Oulu and Turku, the consumption was less frequent during the years from 2012–2016. The total consumption in relation to the child population of the primary hospital district was 56 doses/10,000 children and 74 doses/10,000 in the years 2012 and 2016, respectively. However, in three other university hospitals the use of racemic adrenaline was high in 2012 but decreased by the year 2016. In Kuopio, where the population-related consumption was highest (846 doses/10,000 in 2012), the consumption decreased but, in 2016, was still more common (532/10,000) than in other areas (Figure 5). This decrease of consumption occurred subsequent to the publication of the national Current Care Guidelines on

bronchiolitis, yet substantial differences persisted between the four attending university hospitals.

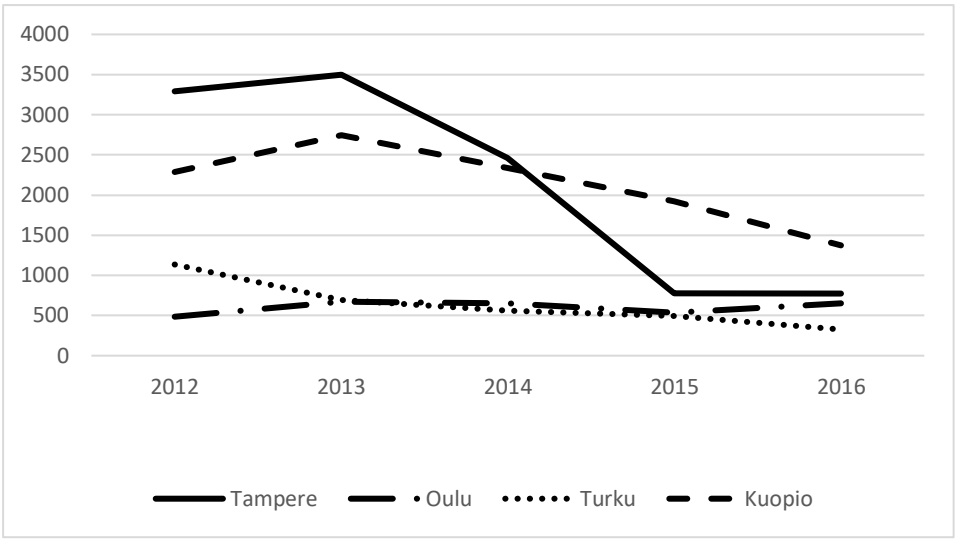

Figure 4. The consumption of racemic adrenaline in four university hospitals in Finland in years 2012–2016 (Racepinephrine (S2) 2.25% 0.5 ml inhalation solution).

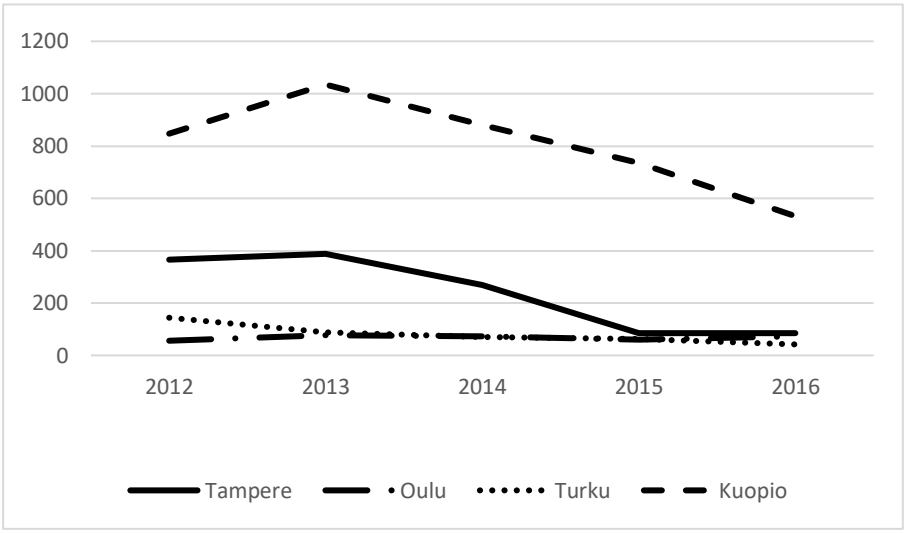

Figure 5. The consumption of racemic adrenaline in four university hospitals in Finland in years 2012–2016 (Racepinephrine (S2) 2.25% 0.5 ml inhalation solution) adjusted to doses per 10,000 children under the age of 16 years.

In the two university hospitals, where the consumption of racemic adrenaline was most common, two-thirds of the consumption took place on the ward (IV, Table 1). Among the diseases for which racemic adrenaline is used, the bronchiolitis is the most common. Thus, it may be assumed that the consumption of racemic adrenaline on the ward was mainly for the purpose of treating bronchiolitis. The numbers of children admitted to the ED in Tampere for bronchiolitis were available for the years 2013–2015 and the average numbers of the doses delivered by the hospital pharmacy per child admitted were 14.7 in 2013, 11.5 in 2014, and 4.5 in 2015. As the RSV epidemic was severe in 2016 in Finland and the total numbers of laboratory-confirmed RSV infections were 2.5, 1.7, and 2.0 times higher than in 2013, 2014, or 2015, respectively, it can be concluded that the consumption of racemic adrenaline per bronchiolitis patients was lower in 2016 than previously.

The annual cost of racemic adrenaline reflected its consumption (Figure 6). In Turku and in Oulu the costs were stable. The total repeated costs, including needles, syringes, and saline solutions, were €2.46 per one dose of racemic adrenaline. Another notable expense was the time that the staff took to prepare and administering the medication. In 2012, it took up to 1263 hours to prepare the medicines and solutions ready for use and to administer the nebulised medicines to the infants (Figure 7). In Tampere, the decrease amounted to 967 hours, which represents the equivalent of 25.3 working weeks for one nurse.

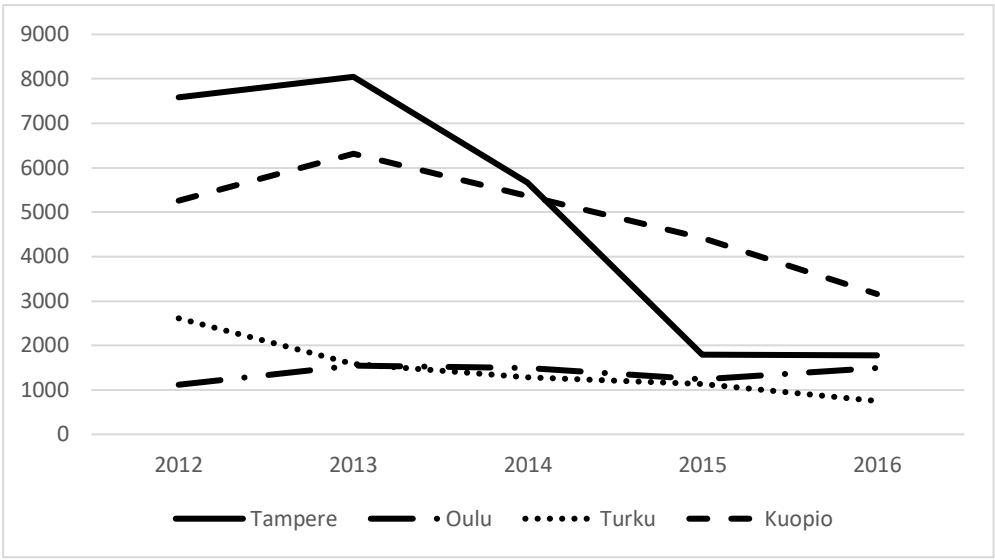

Figure 6. The costs (€) of racemic adrenaline (Racepinephrine (S2) 2.25% 0.5 ml inhalation solution) used for giving the nebulisation in four university hospitals in Finland during the years 2012–2016.

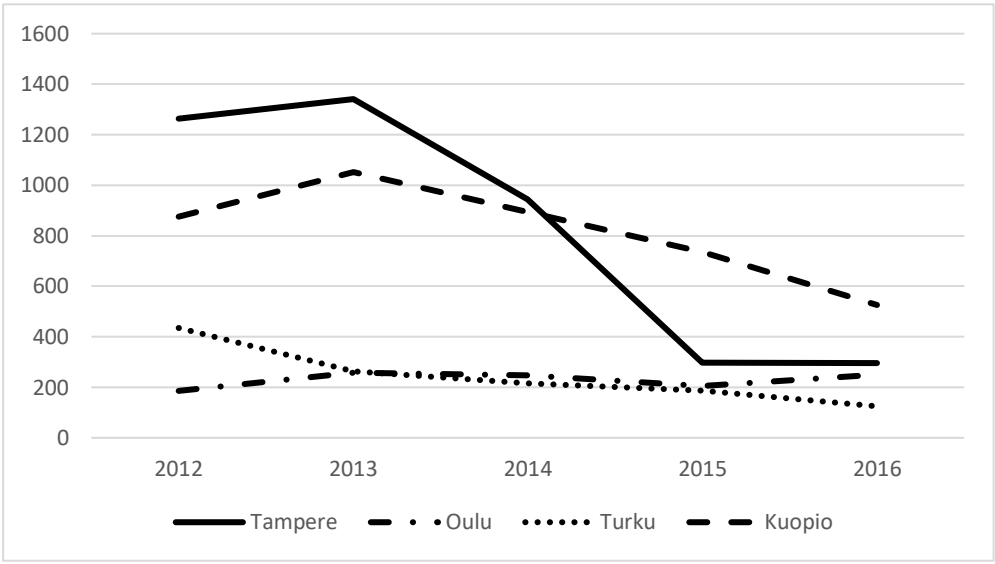

Figure 7. The working time of nurses (in hours) for administration the nebulised racemic adrenaline (Racepinephrine (S2) 2.25% 0.5 ml inhalation solution) in four university hospitals in Finland during the years 2012–2016.

6 DISCUSSION

6.1 Definition and diagnosis of bronchiolitis

The definition of bronchiolitis varies greatly around the world (12,16,17,48–51). However, this thesis confirmed that the definition of bronchiolitis used in Finland and Sweden is rather similar, and follows the European upper age limit for the definition of bronchiolitis, which is 12 months of age. Since the incidence of bronchiolitis is highest in infants ranging in age from three to six months (17), and patients who are older than 12 months form a heterogeneous group, including asthma cases, one can argue that the upper age limit for the definition of bronchiolitis should be 12 months or as low as six months. In the current thesis, one-third of the responding Swedish paediatricians considered the upper age limit to be six months. A corresponding survey from the United Kingdom (UK) showed that one-third of the respondents set 12 months as the upper age limit for bronchiolitis, and one-third set it to 24 months (218). However, the disease was not considered to be bronchiolitis when a child's age approached two years and if a child wheezed. In the future, the upper age limit for the definition of bronchiolitis should be standardised to decrease heterogeneity within the group and to increase comparability between studies.

The diagnosis of bronchiolitis is clinical; thus, it poses a challenge to paediatricians and other physicians when attempting to recognise the signs and symptoms of this disease and to differentiate it from other clinical entities, such as wheezing bronchitis and a first asthma attack. For this thesis, the data obtained from the questionnaire showed that both Finnish and Swedish doctors considered the most important symptoms to be signs of laboured breathing, chest retractions, prolonged expiration and wheezing or fine crackles. All current guidelines have emphasised the typical clinical course of bronchiolitis; in the first days, symptoms in the upper airways progress to symptoms and signs of lower respiratory tract infection (12,16,17,48–51). However, different guidelines highlight different signs of lower respiratory tract infections; some consider wheezing mandatory for bronchiolitis, while, for others, wheezing means bronchial reactivity that is typical for recurrent wheezing and asthma (12,16,17). Moreover, the validity and reliability of the

auscultatory findings are questioned, especially in infants (44). It is clinically impossible to make an accurate assessment of the site—that is, the small or large airways—or determine the nature of the obstruction—that is, mucus, swelling, or bronchial constriction. Since the reliability of the clinical findings are questioned, they are seldom considered in trials. However, in real life, clinicians base their treatment decisions on the clinical findings. Thus, more precise and reliable tools are needed to differentiate the different phenotypes of infants with breathing difficulties.

All of the Finnish and Swedish paediatricians who participated in the study conducted for this thesis stated that they always or often used pulse oximetry, but only two-thirds reported measuring respiratory rates at admission or even during their patients' hospital stays. Many uncertainties have been associated with the use of pulse oximetry (60). Therefore, pulse oximetry is a poor predictor of severe bronchiolitis, the duration of hospital stays or the need for intensive care (3,74,75,80). Furthermore, the increased use of pulse oximetry has been associated with increased hospitalisation rates, prolonged hospital stays for bronchiolitis and an increase in health care expenses (37,75,77–79). However, for patients with severe hypoxia —that is, oxygen saturation < 85%—the need for respiratory support has increased three-fold in comparison to patients with oxygen saturation > 94% (2). Measuring oxygen saturation is a useful tool and a practical part of clinical assessment; however, a high respiratory rate may be a better prediction of the severity of disease (18,219). Therefore, measuring the respiratory rate should be part of the clinical assessment of every infant with bronchiolitis.

In addition to misinterpretations related to pulse oximetry, other inconveniences are related to using it to detect hypoxia. No research-based evidence exists for normal values of oxygen saturation for infants; moreover, the guidelines vary in terms of recommended level for starting or discontinuing supplementary oxygen or for the discharging patients (12,17). Since lowering the saturation limit from 94% to 92% has decreased the hospitalisation rate by 50% (74) without worsening the outcomes, most guidelines favour the saturation limit of 92% as the threshold for the administration of supplementary oxygen and for hospital admission (17,49,51). Additionally, RCTs have found no significant disadvantages when the oxygen supplementation level is decreased to 90% of oxygen saturation (75,80,81). Thus, the threshold level of oxygen supplementation is 90% in the US and Canada (12,48). In the current thesis, Finnish and Swedish paediatricians used a saturation limit > 92%. The Finnish Current Care Guidelines do not specify the lower limit for acceptable saturation for room air. The recommendation to lower the saturation limit to 90% would be safe and would decrease hospitalisation rates and LOS as well as health

care expenses. However, small changes in oxygen saturation may cause substantial changes in partial oxygen tension within the 90–95% oxygen saturation range. Therefore, the clinical decisions should not be based solely on oxygen saturation levels; they should also consider the information obtained from the clinical examination.

Nearly half of the responding Finnish paediatricians, but only one-fifth of the Swedish respondents, reported that RSV testing was routinely done for infants with bronchiolitis. Because RSV testing does not influence the outcome (2,220), routine testing for respiratory viruses is not recommended (12,48,152). However, the Finnish Current Care Guidelines concluded that testing may be done to detect the onset of an epidemic and to cohort the patients treated on the ward (16,17).

The guidelines recommend using chest radiographs only if the course of the disease is atypical (51), if signs of respiratory complication occur (12), or if patients are at a high risk of severe disease (50). The use of chest radiographs has led to more frequent use of antibiotics, probably due to the fact that typical radiographic findings of bronchiolitis may be misinterpreted as pneumonia (19,221). The 16-year bronchiolitis cohort revealed that chest radiographs were taken from 67% of the infants in the PICU, but radiographs were rarely taken on the ward or in the ED. A prospective multicentre cohort study from three Finnish tertiary hospitals showed significant variability (15% to 95%) in obtaining chest radiographs between facilities for hospitalised infants with bronchiolitis. The findings reported in a small observational study on critically ill infants with bronchiolitis suggested that even in invasively ventilated patients, less frequent use of laboratory tests and chest radiographs did not lead to worse outcomes (85). As the use of NIV continues to increase, and complications related to NIV are rare, it might be assumed that the use of chest radiographs would decrease. However, introducing new respiratory supports without precise indications and weaning-off protocols might have an opposite effect. Therefore, monitoring of real-life clinical strategies must be continued.

6.2 Risk factors for severe bronchiolitis

In the current study, the age of the infants treated in the PICU was significantly younger than those treated on the ward or discharged from the ED. Age younger than two months was an independent significant risk factor for the need for intensive care and the need for respiratory support. Even though several bronchiolitis studies

have included children up to the age of 24 months (2,100,101,222), almost all of the critically ill patients admitted to the PICU have been younger than 12 months (223). Previously, the median age of infants with bronchiolitis treated in the PICU has been reported to vary between 60 days and 71 days (41,101,155,223). Many studies have found that a young age is associated with a more severe form of the disease (2,22,41,99,100,102). A large multicentre cohort study with 379 infants diagnosed with bronchiolitis reported greater than four-fold risk for respiratory support among infants younger than two months; moreover, young age (up to six months) was an independent significant risk factor in comparison to children that were older than 12 months (2). Furthermore, the risk for PICU admission or death within 14 days after discharge increased by 60% for every decrease in month of age (41).

In this thesis, low birth weight was the strongest predictor of admission to the PICU. In a prospective cohort study including 16 centres, a birth weight < 2.3 kg and tachypnoea >70 breaths/min on admission independently predicted later transfer to the PICU from the ward (18). In the same cohort, the risk of needing respiratory support was nearly two-fold in infants with a birth weight < 2.3 kg (2). In the present thesis, having a low birth weight of < 2 kg was an independent significant risk factor for PICU admission and for respiratory support.

In a recent large population-based cohort study from Canada, 102 of 34,270 infants with bronchiolitis were admitted to the PICU or died within two weeks after being discharged from hospital. The study confirmed that comorbidities were the most significant predictors for these severe outcomes; if two or more risk factors were present, the risk increased up to seven-fold (41). Although comorbidities have been reported in 10% to 33% of infants with bronchiolitis treated in the PICU (2,18,41,100,155), not all studies have found them to be independent significant predictors for PICU admissions (2,18,100). In this thesis, the presence of CHD was an independent predictor for PICU admission and for respiratory support, even though, less than 25% of the CHD cases where hemodynamically significant. The presence of CHD has been associated with prolonged LOS in hospital and in the PICU, as well as, prolonged respiratory support (145). In this thesis, all of the infants with CHD were older than two months. CHD is associated with maternal diabetes, maternal drug use, chemical exposures, air pollution and tobacco smoke exposure (224), but none of these variables were controlled in the present analyses. Therefore, the association between CHD and the need for respiratory support may reflect an association of maternal health with the infants' respiratory health. In particular, tobacco smoke exposure impairs lung development (225). Previously, maternal

smoking during pregnancy was identified as an independent significant risk factor for need of respiratory support in bronchiolitis in infants (2).

A large cohort study from Canada confirmed the association between prematurity and admission to the PICU, and a one-week decrease in gestational age increased the odds by 15% (41). In this thesis, the effect of multicollinearity was seen in the model where premature birth and birth weight were combined. In the multivariable analysis, premature birth lost significance, although, almost half of the infants admitted to the PICU were born preterm. However, in the model without birth weight, premature birth was found to be an independent predictor for both PICU admission and for respiratory support.

In this thesis, apnoea was found to be an independent predictor for admission to the PICU; however, it was not statistically significant as a risk factor for respiratory support. In a large prospective cohort study, the multivariable logistic regression showed that the presence of apnoea at admission was an independent risk factor for respiratory support at admission (2).

6.3 Management of bronchiolitis and the impact of guidelines

The cornerstones of treatment for infant bronchiolitis are fluid intake and oxygen supplementation, when necessary (9). The responding Swedish paediatricians favoured NGH and the great majority of them reported using it always or often. The Finnish respondents reported that they primarily used IVH. Although, both replacement therapies can have side effects, they have been established as safe option for treating bronchiolitis (124–127). Since NGH provides more physiological hydration, and even feeding, without any substantial risk of aspiration, it might be considered to be superior to IVH (124–126). In the current thesis, the single centre 16-year cohort study revealed a hydration strategy that was opposite to other hospitals in Finland: NGH was more common than IVH on the ward. Because the use of NGH is safe, even with NIV, it should be favoured in hospitalised infants with bronchiolitis if rehydration is needed.

The Cochrane meta-analysis on saline inhalation published in 2008 found a reduction of almost a day in the mean LOS (226). Perhaps the influence of the Cochrane review can be observed in Finnish and in Swedish hospitals. In both countries, the children's hospitals used either isotonic or hypertonic saline inhalations. A similar increase in the use of hypertonic saline was seen in the PICU, on the ward, and in the ED at Tampere University Hospital after 2013 when

hypertonic saline inhalations were introduced as an option. However, when the number of published RCTs increased, the pooled impact of hypertonic saline inhalation decreased. In 2015, a meta-analysis concluded that the mean LOS decreased by 0.45 days when hypertonic saline was given (227). Another cumulative meta-analysis showed that the benefits of hypertonic saline inhalations decreased by the time (133). Thus, the use of hypertonic saline inhalation is no longer recommended in any cases (12,16,17,48–50).

The responding Finnish and Swedish paediatricians reported the frequent use of bronchodilator inhalations. In Finland, paediatricians used racemic adrenaline with or without salbutamol; in Sweden, they used levo-adrenaline. Both, racemic and levo-adrenaline have equal availability and are expedient medications for use in hospitals. In Finland, it is advised that racemic adrenaline to be used to avoid confusions in dosing because levo-adrenaline has several concentrations. When the questionnaire was sent out in 2011, no clinical practice guidelines for bronchiolitis were available in Finland or in Sweden. However, the AAP guidelines on the management of bronchiolitis, published in 2006, recommended that inhaled bronchodilators should only be continued only if a positive response was observed, otherwise, they should be discontinued (215). The recommendation was based on a meta-analysis of eight RCTs, involving 394 infants, which found no effect on admission rates, but slight improvements in clinical scores (228). The AAP guidelines preferred the use of an alpha-adrenergic agent, adrenaline, based on the short-term benefits documented in the RCTs, which were superior to the effects of beta-agonists (13,229). The impact of the guidelines was seen in the use of bronchodilators in Finland and Sweden; at that time the alpha-adrenergic agents were more commonly used. Although, none of the updated guidelines, including the Finnish Current Care Guidelines, recommends the use of bronchodilators to treat bronchiolitis (12,17), they are actively used. The incidence of future asthma increases by the age at which bronchiolitis is diagnosed: < 3 months, 8.5%, < 6 months, 13%, < 12 months, 31% and 12–24 months, 55% (230,231). Perhaps, the physicians base their decision on clinical evaluation, and they prescribe bronchodilators for infants that have a greater likelihood of experiencing bronchial reactivity that is older age and a history of wheezing (232). Finally, young infants experiencing their first expiratory breathing difficulty episode should be the only patients included under the diagnosis of bronchiolitis. Asthma medications, such as bronchodilators, should not be given to them.

None of the guidelines recommend the use of corticosteroids (12,16,17,48–51). Still, only one-third of Finnish and Swedish paediatricians did not recommend the use of corticosteroids for any infants with bronchiolitis; moreover, they considered

their use in special cases, such as patients with a previous history of wheezing, when there were signs of bronchial obstruction, or in infants that were born prematurely. If the diagnosis of bronchiolitis is restricted to the first episode of expiratory breathing difficulty in infants without a previous history of bronchial obstructions, one could argue that the infants mentioned above did not have bronchiolitis. In three Finnish university hospitals, when diagnosis of bronchiolitis was restricted to infants younger than 12 months without previous wheezing, the use of corticosteroids was rare, but it increased up to 60% in infants ranging in age between 12–24 months or with a history of wheezing (232). There is also a tendency to use asthma medications, including bronchodilators and corticosteroids, for patients with greater likelihood of having bronchial obstruction. As documented in several studies, the total use of corticosteroids decreased after the implementation of the 2006 AAP guidelines. (233–235). In the current thesis, the influence of the guidelines was not seen in the 16-year cohort study, probably due the fact that the use of corticosteroids was rare; they were used in <20% and <10% of the infants hospitalised due to bronchiolitis or treated as outpatients, respectively.

The use of racemic adrenaline to treat infant bronchiolitis in four university hospitals in 2012–2016 was determined by evaluating how many 0.5 ml doses of racemic adrenaline the hospital pharmacies delivered to the paediatric units. The Finnish Current Care Guidelines published in 2014 recommend that inhalations of racemic adrenaline should not be given routinely; they should only be administered as a clinical trial in selected cases. The data obtained by the pharmacies are exact and reliable, and the results assume that most of racemic adrenaline doses were given to infants with bronchiolitis. However, patient-specific and disease-specific data were not available. Both clinical experience and clinical studies have shown that laryngitis, laryngeal obstruction or asthma seldom need to be treated using racemic adrenaline or hospitalisation (236).

6.4 Management of severe bronchiolitis

Recently, the management of bronchiolitis has changed significantly, since most therapeutic options have proven to be ineffective. Therefore, the role of supportive management is highlighted in the current guidelines, and new methods for respiratory support have been developed. These changes are seen in the results of the current thesis' results for 2000 to 2015. However, the meta-analyses and the guidelines only focus on hospitalised infants with bronchiolitis; they exclude those

with the most severe disease. Furthermore, there is lack of robust studies focusing on critically ill infants with bronchiolitis.

In the current thesis, half of the infants needed respiratory support and nCPAP was most often used. A recent prospective multicentre study on 342 infants treated for bronchiolitis in the PICU reported a wide variation (7% to 100%) in the use of respiratory support between different hospitals (65). This reflects a variation in the admission criteria, since, in some hospitals, the use of any respiratory support is an indication of PICU admission (127). However, respiratory strategies have changed over time, especially since the introduction of HFNC therapy (85). Between 2011 and 2015, 70% of the infants in the PICU were treated with HFNC. Currently, HFNC treatments are given on the ward (237), which might decrease the number of transfers to the PICU.

Several previous studies have suggested that the increased use of NIV may decrease the need for intubation, thus, lowering the complications associated with invasive ventilation; this further shortens the LOS in the hospital and in the PICU (189,191,194,196,197). In the current thesis, the use of NIV increased, as seen in use of both HFNC and nCPAP, but the need for intubation remained stable. As expected, infants treated with mechanical ventilation had the longest median LOS in the PICU and in the hospital. The increase in the use of NIV may be explained by the fact that NIV modalities were available and were started more easily than previously. Since the LOS in the PICU and the total LOS in hospital remain unchangeable in the 16-year study period, it is likely that the disease severity does not explain the increase in the use of NIV. A few RCTs have been published on NIV in bronchiolitis (165,166,178,190,195). The results have implied that nCPAP is superior to standard oxygen therapy (190,195). HFNC has been less often studied, but it seems to work well as a rescue therapy for those in whom standard low-flow oxygen delivery has failed (165,166).

The use of inhaled bronchodilators was frequent (90%) in infants treated for bronchiolitis in the PICU, and the total use of bronchodilators did not change over time during the 16-year follow-up. However, a decline in the use of salbutamol was observed, as was an increase in the use of adrenaline. A previous meta-analysis of 394 bronchiolitis patients younger than 24 months concluded that bronchodilators had an impact on clinical scores (228); it also found that adrenaline worked better than beta-agonist. Thus, the AAP 2006 bronchiolitis guidelines justified trials with bronchodilators and preferred the use of inhaled adrenaline over beta-agonists (215), which is seen in the current thesis in the treatment strategies for critical bronchiolitis. The meta-analyses published after 2006 have confirmed that the use of

bronchodilators have no impact on clinically significant outcomes, such as the hospital LOS or the hospital admission rates (14,229). Therefore, the updated guidelines currently available do not recommend the use of bronchodilators to treat bronchiolitis (12,16,17,48–50). Recent studies have reported that bronchodilators are used approximately in 60% to 90% of hospitalised infant with bronchiolitis (65,101,155). It is important to note that there are no guidelines for critically ill infants with bronchiolitis, and that all the RCTs included in the meta-analyses have been performed in moderately ill bronchiolitis patients. However, the use of bronchodilators has been reported to be two-times more common in PICU patients in comparison to other bronchiolitis cases (19). Therefore, more evidence on how to treat severe bronchiolitis is needed.

In a meta-analysis including eight RCTs and 633 infants hospitalised for bronchiolitis, the use of corticosteroids did not shorten the LOS in hospital (111). One multicentre double-blind RCT compared dexamethasone with a placebo, but it failed to recruit a sufficient number of patients. While the duration of mechanical ventilation, the LOS in hospital or in the PICU or the duration of supplementary oxygen were not shorter in the cases than in the controls, the analyses were under-powered (151). During the current 16-year survey, the use of systematic corticosteroids in the PICU decreased by almost 25%. The use of corticosteroids ranged from 20% to 30% in the US in hospitalised bronchiolitis patients (65,233). In line with the current results, the total use of corticosteroids decreased after the implementation of the AAP bronchiolitis guidelines (233–235).

Overall, the use of treatments without any research-based evidence for their effects has been decreased since the AAP 2006 guidelines on the management and prevention of bronchiolitis were implemented (65,233–235). The retrospective cohort study estimated a 20% decrease in unnecessary treatments, such as bronchodilators and corticosteroids, or unnecessary diagnostic tests, such as chest radiographs and complete blood cell count, after the implementation of the guidelines (235). Furthermore, the impact has been more significant for inpatients, including critically ill bronchiolitis patients admitted to the PICU, than for outpatients (65,233). However, the recommendations only focus on hospitalised infants with bronchiolitis; they do not address the severity of the disease. In real life, as the descriptive studies on treatment strategies shows, the use of medications is far more frequent, and it is influenced by the physician's clinical assessment and the severity of the disease. Therefore, evidence-based guidelines are needed for severe bronchiolitis.

6.5 Methodological aspects

This study's comparison of the Finnish and Swedish treatment strategies for infant bronchiolitis was based on the questionnaire responses obtained from paediatricians, who were responsible for bronchiolitis treatment in each of the studied hospitals. This is a clear limitation of the study, since the respondents' answers did not reveal how the infants were treated in real-time. However, this was the only way to cover both countries in their entirety. The questionnaire was sent to all hospitals that provided inpatient care to children; paediatricians at all of the Finnish hospitals and more than half of the Swedish hospitals returned the questionnaire. The comparison of Finland and Sweden is rationale, since these countries share many similar features, such as a similar climate, high living standard, good social conditions, and high-quality public health care.

The 16-year case-control study on the characteristics of infants treated in the PICU at younger than 12 months of age, and on the risk factors of intensive care for bronchiolitis was a retrospective chart review. The patients' data were collected from the electronic files of the Tampere University Hospital. One member of the study group reviewed all of the patient records and confirmed, based on identical criteria, whether the reason for intensive care was bronchiolitis. This systematic checking of the patient records was a clear strength of the retrospective study. The study used a case-control design. Two controls were selected for all of the PICU patients, one admitted to the ED before and one after the PICU-treated case.

The risk factors were first identified using univariable analyses, but the final conclusions were based on adjusted analyses. Since nearly half of the PICU patients were born preterm, the analyses were made separately with premature birth and without premature birth in the model, with the aim of controlling the effect of multicollinearity between the potential risk factors, such as gestational age and birth weight. Because of the retrospective approach, not all the information was available in the patients' medical records, such as maternal history related to health and the mother's social and economic situation.

The interventions used for infant bronchiolitis were studied separately for the years 2000–2005, 2006–2010, and 2011–2015. There were no differences in infant age, birth weight, presence of apnoea, hospital LOS or in LOS in the PICU between three periods. However, those infants treated in the PICU between 2006-2010 had more often CHD. This classification allowed us to analyse the changes in relation to the AAP bronchiolitis guidelines published in 2006. The time periods of 2006–2010 and 2011–2015 represent the time after the guidelines were implemented. The

updated AAP guidelines and the Finnish Current Care Guidelines were published in 2014; the guidelines did not influence the treatment practices. Currently, HFNC is actively being used, but it was not introduced before 2013 at Tampere University Hospital. The main limitation of the study is that is a single-centre study.

The impact of the Finnish Current Care Guidelines on the use of racemic adrenaline was studied separately, and the influence was substantial in those two university hospitals that actively used racemic adrenaline before the national guideline was implemented. The main limitation of the study is its descriptive nature and that the site variability was not statistically tested. The usage data given by the hospitals' pharmacies are exact, but not patient-specific. However, they can be considered to be reliable estimates to describe the changes in the use of racemic adrenaline for infant bronchiolitis.

6.6 Future considerations

The definition of bronchiolitis needs to be unified to limit the heterogeneity of this disease group and to increase the comparability of the findings reported in the literature. Therefore, in the future, these groups—infants younger than 12 months with first expiratory breathing difficulty and those with previous wheeze—should be considered separately in clinical studies and in guidelines. Since it is currently impossible to clinically evaluate the true nature of breathing difficulty in infants with first expiratory breathing difficulty, more clinical evaluation tools are needed for these patients. A vaccine against RSV is currently being developed; hopefully, it will be available on the market in the next decade. The vaccination would reduce the incidence of severe bronchiolitis. No other new pharmacological innovations are being developed. Probably, in a few years HFNC will become the established treatment for bronchiolitis. To achieve that, more research is required to identify precise indications and weaning-off protocols. Furthermore, there is an obvious need for robust studies on critical bronchiolitis; only a few are currently available. Guidelines that focus solely on strategies to treat critically ill infants with bronchiolitis are urgently needed in order to implement consistent and effective treatment in the PICU.

7 CONCLUSIONS

This thesis confirmed that the definitions of and treatment strategies for infant bronchiolitis are rather similar in Finland and Sweden. In both countries, bronchiolitis was defined as the first expiratory breathing difficulty in infancy, and the mean upper age limit was close to 12 months in both countries. Based on the published guidelines, the definition of bronchiolitis is similar in Europe and the group of patients is more homogeneous when older infants and those with previous wheezing episodes are excluded. Adrenaline inhalations were given in both countries, but the Swedish paediatricians used inhaled levo-adrenaline and the Finnish paediatricians used inhaled racemic adrenaline. Corticosteroids were rarely used.

The average annual incidence of bronchiolitis requiring admission to the PICU at the age of younger than 12 months was 1.5/1000/year during the 16-year follow-up, but the variation by year was considerable. Nearly half of the infants with bronchiolitis treated in the PICU were born prematurely. In the adjusted analyses, independent significant risk factors for PICU admission and respiratory support were being age younger than two months old, birth weight of < 2000 g, and the presence of CHD.

The interventions for bronchiolitis in the PICU were evaluated in relation to time during three periods: years 2000–2005, 2006–2010, and 2011–2015. By time, the use of inhaled beta-agonists halved and systemic corticosteroids decreased nearly 25%, but the use of racemic adrenaline increased by 25% and hypertonic saline inhalations was introduced and used in half of the cases between 2011 and 2015. The current literature and evidence-based guidelines had impact on practice.

There were differences in the yearly consumption of racemic adrenaline between the four participating university hospitals before and after the publication of the bronchiolitis guidelines in 2014. Its overall use more than halved during the study period, particularly in two hospitals where the baseline consumption was highest. The Current Care Guidelines for bronchiolitis had an essential impact on clinical practice.

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10 ORIGINAL PUBLICATIONS

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REGULAR ARTICLE

Diagnosis and treatment of bronchiolitis in Finnish and Swedish children's hospitals

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ABSTRACT

Aim: There is no widely accepted consensus on the diagnosis and treatment of bronchiolitis. This study describes current practices in Finnish and Swedish hospitals.

Methods: A questionnaire on the diagnosis and treatment of bronchiolitis in children below 2 years of age was sent to all Finnish and Swedish hospitals providing inpatient care for children. All 22 Finnish hospitals answered, covering 100% of the <12-month-old population and 21 of the 37 Swedish hospitals responded, covering 74%.

Results: The mean upper age limit for bronchiolitis was 12.7 months in Finnish hospitals and 12.5 months in Swedish hospitals. In both, laboured breathing, chest retractions and fine crackles were highlighted as the main clinical findings, followed by prolonged expiration. The mean value for the lowest acceptable saturation in room air was 94% in Finnish hospitals and 93% in Swedish hospitals. The most important factors influencing hospitalisation were young age, desaturation and inability to take oral fluids. Finnish doctors preferred intravenous routes, and Swedish doctors preferred nasogastric tubes for supplementary feeding. The first-line drug therapy was inhaled racemic adrenaline in Finland and inhaled levo-adrenaline in Sweden.

Conclusion: The diagnosis and treatment of bronchiolitis is fairly similar in Finnish and Swedish hospitals.

INTRODUCTION

Bronchiolitis is the most common infectious cause of hospitalisation in infancy, mainly caused by respiratory syncytial virus (RSV) (1). However, there is no universally accepted definition of acute viral bronchiolitis, which means that it is challenging to treat (2). The lack of research-based evidence relating to the most beneficial treatments has led to varying clinical practices in different countries and even between different areas or hospitals within the same country (3–5).

In 1995, the treatment of RSV bronchiolitis was charted in 88 European children's hospitals (6). Remarkable inconsistencies in diagnostic definitions and in antiviral (ribavirin), bronchodilatory and anti-inflammatory treatment strategies were found at both national and international levels. Later, the effect of inhaled ribavirin was shown to be marginal and that treatment is no longer used (7). In 2006, the American Academy of Pediatrics (2) and Scottish Intercollegiate Guideline Network (www.sign.ac.uk) published evidence-based guidelines for diagnosis and treatment of bronchiolitis. The upper age limit in both guidelines was 24 months, which means that the evidence behind the recommendations comes from studies heterogeneous for aetiological factors and clinical presentations.

The aim of this study was to describe the definitions of and treatment strategies for bronchiolitis in two Nordic countries, Finland and Sweden. In addition, we discussed the consistency of the definitions and treatment strategies with international guidelines. National guidelines are not available for bronchiolitis in either country.

Key notes

- There is no widely accepted consensus on treating bronchiolitis in infants, and this article explores current practices in Finnish and Swedish hospitals.
- The first-line inhalation therapy was racemic adrenaline, with or without salbutamol, in Finnish hospitals and levo-adrenaline without salbutamol in Swedish hospitals.
- Doctors in both countries provided blood oxygen saturation monitoring and oxygen therapy, and hydration via a nasogastric tube or intravenously, in cases with insufficient oral intake.

MATERIAL AND METHODS

A written questionnaire on the diagnostic criteria and treatment practices for bronchiolitis was sent to all hospitals in Finland and Sweden providing inpatient care for infants and young children. The doctors responsible for the treatment of bronchiolitis patients in the hospital were asked to complete the questionnaire. We received a completed questionnaire from all 22 Finnish hospitals and from 21 of 37 (57%) Swedish hospitals. The numbers of children <12 months of age, living in each hospital's catchment area at the time of the study, were obtained from Official Statistics of Finland and Sweden. At the end of 2011, the number of infants under 12 months of age was 61,000 in Finland and the completed Swedish questionnaires covered 70,000 of the 96,000 infants in this age group. Thus, the returned questionnaires covered 100% of the Finnish and 74% of the Swedish <12-month-old population. Each hospital was then given a weighted index depending on the number of <12-month-old infants living in the area.

The questionnaire comprised questions on the age limits for a bronchiolitis diagnosis, the practices for measuring oxygen saturation and respiratory rate on admission, including the limits for intervention, the indications for the administration of bronchodilators or corticosteroids, the practices for giving inhaled saline and, if given, the concentration, and the indications for starting additional oxygen and treatment with nasal continuous positive airway pressure. The questions reflected the clinical problems encountered nearly daily when treating infants with bronchiolitis. The indications for hospital treatment and the use of viral diagnostics on admission were charted. The attending doctors were asked to list, using their own words in Finnish, Swedish or English, the five most important clinical findings of bronchiolitis. The words were grouped into laboured breathing, chest retractions, audible wheezing, prolonged expiration, fine crackles, cough, air trapping, eating problems, apnoea, fatigue and mucus in the airways.

The data were analysed using SPSS package version 20 (SPSS Inc. Chicago, IL, USA), and the results were expressed as mean weighted proportions and their standard deviations (SD). The weighted proportions were based on the numbers of children aged <12 months in the area that the hospital primarily provided inpatient care for. The number of <12-month-old children in the area was divided by 61,000 in the case of a Finnish hospital and by 70,000 in the case of a Swedish hospital.

RESULTS

Diagnosis

The upper age limit for the use of bronchiolitis as a diagnostic label varied from 3 to 24 months between the hospitals. The mean value for the upper age limit was 12.7 months (SD 5.0) in the Finnish children's hospitals and 12.5 months (SD 7.8) in the Swedish children's hospitals.

The most characteristic symptoms and signs of bronchiolitis, when each respondent was asked to list the five most important ones, are presented separately for Finnish and Swedish hospitals as weighted proportions (Table 1). Laboured breathing (weighted percentages 88–98%), chest retractions (65–74%) and fine crackles (56–70%) were the characteristics assessed as most important in both countries, followed by prolonged expiration. Finnish doctors highlighted audible wheezing (54% versus 21% in Swedish hospitals), while Swedish doctors highlighted eating problems (37% versus 5% in Finnish hospitals).

In nearly all Finnish and Swedish hospitals, the doctors had been advised to measure oxygen saturation in all bronchiolitis patients (Table 2). Oxygen saturation level was therefore measured in almost all hospitals and the weighted proportions were 95% and 89% for the Finnish and Swedish hospitals, respectively (Table 2). The respective figures were lower for the measurement of respiratory rate, at 63% in Finland and 71% in Sweden (Table 2). The weighted mean of the lowest acceptable oxygen saturation in room air was 94% (range 85–95, SD 1.7) in Finnish hospitals and 93% (90–95, SD 1.3) in Swedish hospitals. The weighted mean of the highest acceptable respiratory rate was 51 per min (40–70, SD 6.2) in Finnish hospitals and 50 per min (30–60, SD 8.5) in Swedish hospitals.

Tests for RSV identification were performed in all bronchiolitis cases in 49% of the Finnish and in 17% of the Swedish hospitals. On the other hand, only 3% of the

Table 1 Symptoms and signs assessed by doctors as characteristics of bronchiolitis in Finnish and Swedish children's hospitals

Finnish children's hospitals	Swedish children's hospitals
Laboured breathing 98% (0.13)	Laboured breathing 88% (0.33)
Chest retractions 65% (0.48)	Chest retractions 74% (0.44)
Fine crackles 56% (0.50)	Fine crackles 70% (0.460)
Audible wheezing 54% (0.50)	Prolonged expiration 45% (0.50)
Prolonged expiration 53% (0.50)	Cough 39% (0.49)
Cough 37% (0.48)	Air trapping 25% (0.43)
Air trapping 31% (0.46)	Audible wheezing 21% (0.41)

Weighted percentages based on the number of children <12 months of age in the area in which the hospital primarily provides inpatient care, expressed as means (SD).

Table 2 Measurement of blood oxygen saturation and respiratory rate in children treated for bronchiolitis in Finnish and Swedish children's hospitals

	Always, %		Often, %		Rarely or never, %	
Measurements	Finland	Sweden	Finland	Sweden	Finland	Sweden
Oxygen saturation	95	89	5	8	0	0
Respiratory rate	63	71	28	12	9	17

Weighted percentages based on the number of children <12 months of age in the area in which the hospital primarily provides inpatient care. Data were missing for oxygen saturation monitoring in 3% of Swedish hospitals, while the corresponding figures for respiratory rate monitoring were 17% in Swedish hospitals and 9% in Finnish hospitals.

Table 3 Inhalation therapy for infants hospitalised for bronchiolitis: the first-line medicines used in Finnish and Swedish hospitals

First-line medicines administered as inhaled	Finnish children's hospitals	Swedish children's hospitals
Racemic adrenaline and salbutamol	44% (0.50)	9% (0.28)
Racemic adrenaline and 3% saline	43% (0.50)	1% (0.08)
Levo-adrenaline and 3% saline	0	83% (0.38)
Salbutamol alone	0	5% (0.22)
Racemic adrenaline alone	12% (0.32)	0

Weighted percentages based on the number of children <12 months of age in the area in which the hospital primarily provides inpatient care, expressed as means (SD).

Swedish doctors and none of the Finnish doctors answered that RSV was never studied. Tests were performed in the laboratory, using either antigen detection or DNA detection methods, but bedside tests were rarely used (data not shown).

In both countries, the most important factors influencing hospitalisation were young age, desaturation and inability to take oral fluids (Table S1).

Treatment

The treatment modalities in bronchiolitis as weighted percentages are presented in Table S2. Inhaled beta$_2$-agonists were (always-often) given in 47% of Finnish hospitals and 38% of Swedish hospitals. The respective figure for inhaled racemic adrenaline was 79% in Finnish hospitals and, for inhaled levo-adrenaline, 86% in Swedish hospitals. Other drugs, such as anticholinergics, corticosteroids or intramuscular adrenaline, were rarely given or not at all. Nebulised saline inhalations were given (always-often) in 45% of the Finnish hospitals and 92% of the Swedish hospitals and, when used, as isotonic (0.9%) saline in half of the hospitals and as hypertonic (3%) saline in the other half in both countries. Intravenous fluids were (always-often) given in 55% of Finnish hospitals and 38% of Swedish hospitals, while nasogastric feeding tubes were primarily used in 24% and 81% of the Finnish and Swedish hospitals, respectively.

The use of inhaled drugs was different in Finnish and Swedish hospitals (Table 3). Racemic adrenaline with salbutamol diluted in 0.9% saline (44%) or in 3% saline (43%) were the two most commonly administered bronchodilatory regimens in Finnish hospitals, whereas levo-adrenaline diluted in 3% saline (83%) was the most commonly used bronchodilator in Swedish hospitals.

In 37% of Finnish hospitals and 48% of Swedish hospitals, corticosteroids were not recommended in any form for any patient. The reasons for using inhaled corticosteroids (ICS) on the ward were prolonged airway obstruction, a history of previous wheezing or the previous use of inhaled corticosteroids. A third of Swedish hospitals recommended the continuation of ICS after discharge, if this treatment was given on the ward (36%). A third of Finnish hospitals recommended the use of ICS for prematurely born babies (37%). The mean recommended duration of postdischarge ICS treatment was 48.2 days in Finland (14–90 days, SD 23.5) and 51.8 days (1–150, SD 59.0) in Sweden. A control visit was recommended if medication had been prescribed (Finnish 17%, Swedish 31%), or if there were severe symptoms (Finnish 34%, Swedish 27%).

In Sweden, every hospital had the facility to use nasal CPAP for bronchiolitis and 73% had used it. In Finland, 81% of hospitals had used nasal CPAP for bronchiolitis. In both countries, nasal CPAP therapy took place more often on the ward (Finnish 56%, Swedish 81%) than in the intensive care unit.

DISCUSSION

The AAP and SIGN guidelines define bronchiolitis as an inflammation of the bronchioles caused by an acute viral infection in children <24 months of age (2). However, the assessment of the site of inflammation in the airways is clinically impossible. In addition, there are no widely accepted age limits for the use of bronchiolitis as a diagnostic label. In our study, the upper age limit for bronchiolitis varied from 3 to 24 months. In Finland, the majority (71%) of doctors considered 12 months as the upper limit, but in Sweden, 35% considered 6 months, 26% considered 12 months and 28% considered 24 months, respectively. In most guidelines, only the first infection-associated episodes with respiratory distress are accepted as bronchiolitis cases (2–6).

A systematic review of the diagnosis of bronchiolitis concluded that clinical findings usually required for a bronchiolitis diagnosis were tachypnoea and wheezing (8), but respiratory rate was not routinely measured and monitored in a third of Finnish (37%) and Swedish (29%) hospitals. Although the validity and reliability of chest auscultation has been questioned in infants (9), audible wheezing was regarded as one of the three most important findings by Finnish doctors. In both countries, laboured breathing and chest retractions, reflecting the increased work needed for respiration, were the two most important physical findings. Transcutaneous blood oxygen saturation was measured in almost all patients. In a recent study, blood oxygen saturation of <94% was the best predictor of hospitalisation and a long hospital stay for bronchiolitis (10).

The cornerstones of bronchiolitis treatment are fluid and oxygen administration, if needed (1,2,11). This was also stressed in the answers in the present study. According to recent studies, there is only marginal evidence that bronchodilators are beneficial in bronchiolitis (12–14). Our study revealed that inhaled adrenaline is widely used in both countries, racemic adrenaline in Finnish hospitals and levo-adrenaline in Swedish hospitals. In addition, salbutamol was used fairly frequently together with racemic

adrenaline in Finnish hospitals. It goes without saying that bronchodilators, such as inhaled adrenaline or racemic adrenaline in emergency situations or salbutamol in recurrent wheezing, may reduce symptoms, but their effect should be monitored and they should only be continued if they are effective (2). Cochrane reviews have concluded that the administration of bronchodilators has not reduced the hospitalisation rates or shortened the length of hospital stay (12,13). In the most recent Norwegian study comprising <12-month-old infants with bronchiolitis, inhaled racemic adrenaline using a fixed schedule was no more effective than inhaled saline, whereas the strategy of on-demand inhalations was superior to that of scheduled inhalations (14).

In the present study, inhaled corticosteroids were seen as an option in some hospitals in both countries, though not effective in bronchiolitis according to many studies and systematic reviews (15,16). On the other hand, the combined use of oral dexamethasone and inhaled adrenaline reduced the need for hospitalisation in two randomised controlled studies performed in paediatric emergency rooms (17,18), but the continuation of dexamethasone after the initial dose provided no additional benefits (19). One reason for the occasional use of corticosteroids in acute viral bronchiolitis could be that it is tried in severe cases just in case it works.

In Sweden, hypertonic saline inhalations were given to about half of the bronchiolitis patients. The question on saline inhalations did not distinguish the use of saline alone or combined with adrenaline. A recent Cochrane review comprising 11 trials confirmed that inhalations of 3% saline improve the clinical severity and reduce the length of hospital stay among infants with viral bronchiolitis (20). Hypertonic saline was combined with bronchodilators in eight studies and compared with isotonic 0.9% saline in three studies. A recent study revealed that a change of bronchiolitis treatment in infants <6 months of age to a more conservative regimen avoiding all routine therapies was not associated with a prolonged duration of hospital stay (21).

There is no consensus on the optimal fluid amounts and administration routes to treat feeding problems in bronchiolitis patients. In our study, intravenous administration was recommended more frequently in Finland, while nasogastric feeding tubes were used in Sweden. Both treatment modalities may be associated with potential complications: intravenous hydration with hypervolemia and electrolyte imbalance (1) and nasogastric tubes with obstruction of the upper airway (1) and an increased aspiration risk (22). Intravenous hydration has been widely used in the USA, Australia and New Zealand (23). A recent prospective pilot study concluded that hydration via nasogastric tubes was feasible for moderate bronchiolitis (24).

The rare use of virus identification, particularly in Sweden, should perhaps be re-evaluated in the light of current knowledge that bronchiolitis with rhinovirus has been associated with a higher risk of future wheezing and asthma in several studies (25). Furthermore, knowledge of virus type may influence the choice of treatment in the emergency ward.

The present study has some limitations. The coverage of Swedish hospitals was only 74% of the whole infant population in the country. In addition, it is difficult to say how well the answers given by the senior doctors who are responsible for bronchiolitis treatment in the hospital reflect real practice in the emergency rooms and emergency wards. As observed recently, there may be substantial variations in treatment modalities outside office hours (26).

The use of pharmacological interventions for infants with bronchiolitis, including bronchodilators or corticosteroids, has been surprisingly common in many countries (3–6,27–29). National evidence-based guidelines have therefore been published and they have influenced the management of bronchiolitis. For example, the use of corticosteroids has been decreased substantially in Australia and New Zealand (23), while the use of all nebulised treatments has been reduced in Ireland (4), the UK (21) and Switzerland (29). In the USA, the use of adrenaline or salbutamol inhalations and the use of corticosteroids decreased, but only modestly, after the implementation the bronchiolitis guidelines of the American Academy of Pediatrics in 2006 (30).

In conclusion, the diagnostic and hospitalisation criteria for bronchiolitis were fairly similar in Finnish and Swedish children's hospitals. In both countries, the doctors highlighted the monitoring of blood oxygen saturation and oxygen therapy, together with hydration via a nasogastric tube or an intravenous route, if needed.

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COMPETING INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Factors influencing hospitalisation for bronchiolitis in Finnish and Swedish paediatric emergency rooms.

Table S2 Treatment of children with bronchiolitis in Finnish and Swedish children's hospitals.

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REGULAR ARTICLE

Low age, low birthweight and congenital heart disease are risk factors for intensive care in infants with bronchiolitis

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Keywords
Bronchiolitis, Congenital heart disease, Infant, Intensive care, Respiratory support

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ABSTRACT

Aim: This study evaluated the incidence and risk factors for intensive care and respiratory support in infant bronchiolitis.

Methods: This retrospective descriptive case–control study focused on 105 patients treated in the paediatric intensive care unit (PICU) and 210 controls treated in the emergency department or on the paediatric ward in Tampere University Hospital in Finland between 2000 and 2015. Statistically significant risk factors in nonadjusted analyses were included in the adjusted logistic regression.

Results: The average age-specific annual incidence of bronchiolitis requiring PICU admission under the age of 12 months was 1.5/1000/year (range 0.18–2.59). Independently, significant risk factors for PICU admission were as follows: being less than two months old with an adjusted odds ratio (aOR) of 11.5, birthweight of <2000 g (aOR of 15.9), congenital heart disease (CHD) (aOR of 15.9), apnoea (aOR of 7.2) and the absence of wheezing (aOR of 2.2). Significant risk factors for needing respiratory support were a birthweight of <2000 g, an age of less than two months and CHD.

Conclusion: Less than 0.1% of infants under the age of 12 months were admitted to the PICU for bronchiolitis. Low age, low birthweight or prematurity and CHD were independently significant risk factors for both intensive care and respiratory support.

INTRODUCTION

Bronchiolitis is the most common infectious cause of hospitalisation in infants. Most bronchiolitis patients have an uneventful course treated at home, but about 3% of those under 24 months of age are hospitalised (1,2) and 2–3% of those hospitalised need mechanical ventilation (3). A Finnish study found that 37 per 1000 infants aged less than six months were admitted to the emergency department (ED) each year due to viral bronchiolitis and 70% of them were hospitalised, which was the equivalent of 2.6% of all infants. Furthermore, 6.1% needed treatment in the paediatric intensive care unit (PICU), which equated to an incidence of 2.3/1000/year in this age-specific population (4). Another Finnish study found that the rate of PICU treatment was 6.3% among those admitted to the ED due to bronchiolitis at less than 12 months of age (5).

Previous studies have identified several risk factors for severe bronchiolitis requiring hospitalisation, such as prematurity, young age, environmental factors like passive smoking and crowded households and underlying diseases like chronic lung disease, congenital heart disease (CHD) and some neurological syndromes (3,6). Likewise, previous studies have identified risk factors associated with severe bronchiolitis requiring mechanical ventilation, such as being under two months of age, maternal smoking during pregnancy, Caesarean section delivery, a birthweight of less than 2300 g, apnoea, inadequate oral intake, an oxygen saturation of less than 85% in room air and a respiratory rate of more than 70 breaths per minute (7–9). However, these previous prospective studies from the United States comprised infants who were over 12 months of age and

Abbreviations
95% CI, 95% confidence intervals; aOR, Adjusted odds ratio; CHD, Congenital heart disease; ED, Emergency department; HFNC, High-flow nasal cannula; IQR, Interquartile range; nCPAP, Nasal continuous positive airway pressure; OR, Odds ratio; PICU, Paediatric intensive care unit.

Key notes
- This study evaluated the incidence and risk factors for intensive care and respiratory support in 105 infants with bronchiolitis admitted to the paediatric intensive care unit (PICU).
- We found that less than 0.1% of infants under 12 months of age were admitted to the PICU for bronchiolitis.
- Low age, low birthweight or prematurity and congenital heart disease were independently significant risk factors for both intensive care and respiratory support.

those with recurrent wheeze (7,8,10), which do not fit the current European definition of bronchiolitis (11).

The aim of this retrospective case–control study was to evaluate the incidence of, and the risk factors for, intensive care and respiratory support in infants admitted to a Finnish hospital for bronchiolitis at less than 12 months of age in 2000–2015.

PATIENTS AND METHODS

This one-centre, case–control study was based on a retrospective review of the electronic patient files of Tampere University Hospital, Tampere, Finland, for the years 2000–2015 (12). It was carried out with the permission of the Chief Physician of the University Hospital. At the time of the study, the hospital provided inpatient care for a population of about 90 000 children aged less than 16 years and the population of infants aged less than 12 months ranged from 4761 to 5880. In addition, the hospital provided paediatric intensive care for a population of about 10 000 infants aged less than 12 months from four surrounding central hospitals (12). All the central hospitals surrounding the University Hospital had facilities to provide noninvasive ventilation support, such as nasal continuous positive airway pressure (nCPAP) during the surveillance period. High-flow nasal cannula (HFNC) treatment was introduced to the PICU at Tampere University Hospital in 2011 and to the paediatric ward in 2012.

We identified all patients treated in the PICU at less than 12 months of age with the International Classification of Diseases – 10th edition (ICD-10) codes of J10*-18*, J20*-22*, J45*or J46* during 2000–2015. One of the authors (PH) reviewed the 179 patient files that were identified, checked the established diagnoses and the registered clinical findings and assessed the final bronchiolitis diagnoses for this study. Bronchiolitis was defined as the first episode of expiratory breathing difficulty, with or without audible wheezing, associated with a lower respiratory tract infection (12). We excluded 11 infants with recurrent wheezing, one with blood culture-positive bacterial infections and 26 with tense alveolar infiltrates in chest radiographs on admission that suggested bacterial pneumonia. In addition, 36 infants were treated in the PICU for some other reason than bronchiolitis. The chart review showed that 105 infants had bronchiolitis as their main diagnosis or treating bronchiolitis was the main reason they received intensive care, and 83 bronchiolitis patients were from the Pirkanmaa (Tampere) Hospital District. Of the 105 cases, 34 infants were treated first on the paediatric ward and 71 were admitted directly to the PICU, including 22 patients from other surrounding hospitals. Infants were admitted to the PICU if they had acute worsening of their breathing, such as an increasing need of supplementary oxygen or increasing respiratory work, or recurrent apnoea. The indications for PICU admission were the same for infants transferred from the surrounding hospitals and for those transferred from the wards or the ED of the University Hospital.

We selected two controls for each of these 105 cases, who were admitted for bronchiolitis with ICD-10 codes J21* just before and after the case. The controls were not admitted to the PICU and 146 of them were treated as inpatients on the ward and 64 as outpatients in the ED. One of the authors (PH) reviewed the hospital records of the 105 cases and 210 controls and completed the same structural form to collect medical data on both groups. This was carried out separately for findings and treatments in the ED, on the ward, and in the PICU.

The data we collected comprised information on gender, gestational age classified with the cut-off points of 28, 32 and 37 weeks, birthweight and age and weight on admission for bronchiolitis. We also included the previous medical history, such as presence of respiratory distress syndrome, bronchopulmonary dysplasia, CHD, treatment with surfactant as a neonate and the use of inhaled corticosteroids at a later date. In addition, we looked at possible previous hospital admissions, including treatment periods in the neonatal intensive care unit, the presence of atopy – such as doctor-diagnosed atopic dermatitis or a food allergy – and family histories of atopy or asthma. Any presence of audible wheezing, fine or coarse crackles on auscultation and dehydration was recorded on admission. The results of any available viral antigen tests were collected. Secondary infections during hospitalisation, such as otitis media, conjunctivitis and pneumonia, were recorded. Any therapies with nCPAP and mechanical ventilation were also recorded and both were considered as respiratory support. Apnoea was defined as breathing pause, with or without bradycardia and desaturation, detected and recorded by the medical staff.

Statistical methods

IBM SPSS Statistics, version 23 (SPSS Inc., Chicago, IL, USA) was used to analyse the data. The chi-square test and the frequency and percentage distributions with 95% confidence intervals (95% Cl) were used in the univariate statistical calculations. Two-tailed $p < 0.05$ was considered statistically significant. We used the Bonferroni correction by multiplying p-values by two in paired comparisons. Continuous variables were presented as medians with interquartile ranges (IQR). Odds ratios (OR) and their 95% Cls were calculated first as nonadjusted and then in the multivariable logistic regression as adjusted ORs (aOR) for age, gender and risk factors that were significant in the nonadjusted analyses. Previous hospitalisation and the previous use of corticosteroids were related to prematurity, and therefore, they were excluded from the final multivariable analyses. Even though several clinical findings were statistically significant in the nonadjusted analyses, we decided to only add wheezing sound to the final multivariable analyses, due to its clear definition in Finnish clinical practice.

RESULTS

The median age was 1.7 months (IQR 0.9–3.5) in the 105 infants in the PICU bronchiolitis group and 4.0 months

(IQR 2.1–6.1) in the 210 infants in the control bronchiolitis group ($p < 0.001$). Their basic characteristics are presented in Table 1. Compared to the control group, infants treated in the PICU were younger and presented with higher comorbidities. They were also more likely to have been born premature, had lower birthweights and previously been treated more frequently in the hospital (Table 1). The risk of being admitted to the PICU was higher in infants aged less than two months (OR 5.0, 95% Cl: 3.0–8.4), born at <37 weeks (OR 7.2, 95% Cl: 4.0–13.0), with a birthweight under 2500 g (OR 14.6, 95% Cl: 6.7–31.9) and with apnoea (OR 39.7, 95% Cl: 9.3–170.3) (Table 1).

As expected, the same characteristics were associated with the need for respiratory support, including nCPAP and, or, mechanical ventilation during their PICU stay, as for PICU admission (Table S1). The risk for respiratory support was higher in infants aged less than two months (OR 3.8, 95% Cl: 2.0–7.2), those born preterm at less than 37 weeks (OR 6.7, 95% Cl: 3.3–13.5), with a birthweight under 2500 g (OR 8.7, 95% Cl: 4.2–18.1) and CHD (OR 5.0, 95% Cl: 1.9–15.1).

Wheezing was associated with a lower risk of PICU admission (OR 0.3, 95% CI: 0.2–0.5) and lower need for respiratory support (OR 0.4, 95% CI: 0.2–0.7) in those admitted (Tables 1 and S1).

Apnoea was strongly associated with admission to the PICU (OR 39.7, 95% Cl: 9.3–170.3) and with the need for respiratory support (OR 6.7, 95% Cl: 3.0–15.0; Tables 1 and S1). In fact, apnoeas were only reported in one patient in the control group. In all, 40 infants presented with apnoea during their hospital stay and 40% of them needed respiratory support in the PICU (Table S2). Statistically significant risk factors for apnoea in inpatients were being less than two months of age (OR 5.4, 95% Cl: 2.6–10.9), being

Table 1 Basic and clinical data presented separately for 105 infants treated due to bronchiolitis in the paediatric intensive care unit (cases) and for 210 controls treated due to bronchiolitis in the emergency department or at the ward

Characteristic	Cases n = 105 (%)	Controls n = 210 (%)	OR	95% Cl	p-Value
Gender (males)	61 (58)	108 (51)	1.3	0.82–2.10	0.263
Age <two months	60 (57)	44 (21)	5.0	3.00–8.38	<0.001
0-0.99 months	32 (31)	14 (7)	6.1	3.10–12.15	0.001
1–1.99 months	28 (38)	30 (15)	3.4	1.87–6.35	0.001*
2.0 months or more	45 (43)	166 (79)	–	–	–
Prematures (<37 weeks)	45/97 (46)	22/204 (11)	7.2	3.95–12.99	<0.001
<28 weeks	12 (12)	1 (1)	28.7	3.67–223.88	0.001
28–31 + 6 weeks	12 (14)	1 (1)	33.2	4.24–259.87	0.001*
32–36 + 6 weeks	21 (22)	20 (10)	3.7	1.85–7.29	0.001*
>37 weeks	52 (54)	182 (89)	–	–	–
Birthweight <2500 g	40/99 (40)	9/203 (4)	14.6	6.70–31.87	<0.001
<1000 g	12 (12)	1 (1)	27.9	3.57–217.61	0.001
1000–1499 g	8 (8)	1 (1)	20.4	2.50–165.40	0.001*
1500–1999 g	7 (7)	1 (1)	19.4	2.35–160.79	0.001*
2000–2499 g	13 (13)	6 (3)	7.1	2.59–19.57	0.001*
>2500 g	59 (60)	194 (96)	–	–	–
Previous hospitalisation	57/100 (57)	34/209 (16)	6.8	3.98–11.71	<0.001
NICU	35/78 (45)	8/183 (4)	17.8	7.71–41.14	<0.001
Paediatric ward	22/65 (34)	26 (13)	3.4	1.78–6.65	<0.001
Underlying disease	27 (26)	12 (6)	5.6	2.74–11.78	<0.001
CHD†	13/89 (15)‡	7/204 (3)	4.8	1.85–12.53	0.001*
BPD/RDS†	8/88 (9)	1/198 (1)	19.7	2.42–160.08	0.001*
Other relevant disease†	12/91 (13)	6/203 (3)	5.0	1.81–13.75	0.002*
Atopy	3/102 (3)	8 (4)	0.7	0.20–2.95	0.696
Asthma in family	10/103 (10)	26 (16)	0.8	0.35–1.65	0.486
Current or earlier inhaled corticosteroids	9/104 (9)	2 (1)	9.9	2.09–46.48	<0.001
Respiratory syncytial virus	59/92 (64)	66/127 (51)	1.7	0.98–2.96	0.056
Apnoea	29 (27)	2 (1)	39.7	9.25–170.33	<0.001
Tachypnoea (≥50/min)	36 (34)	52 (25)	1.6	0.95–2.64	0.076
Audible wheezing	39 (37)	143 (68)	0.3	0.17–0.45	<0.001
Fine crackles	26 (25)	27 (13)	2.2	1.23–4.06	0.008
Coarse crackles	33 (31)	97 (46)	0.5	0.33–0.87	0.012
Dehydration	10 (10)	8 (4)	2.7	1.91–6.95	0.022

NICU = neonatal intensive care unit; CHD = congenital heart disease; BPD = bronchopulmonary dysplasia; RDS = respiratory distress syndrome.
*Bonferroni correction with multiplying the p-value with 2.
†Compared with patient without underlying disease.
‡Seven cases with haemodynamically significant CHD.

born preterm at less than 37 weeks (OR 6.7, 95% Cl: 3.2–13.7) and having a birthweight under 2000 g (OR 10.3, 95% Cl: 4.5–23.7).

In the multivariable logistic regression, the independently significant risk factors for PICU admission were being under two months of age (aOR 11.5, 95% CI: 5.1–25.8), having a low birthweight under 2000 g (aOR 15.9, 95% CI: 2.4–107.3) and presenting with CHD (aOR 15.9, 95% CI: 4.2–60.5). Reported apnoeas (aOR 7.2, 95% CI: 1.4–36.1) and the absence of wheezing (aOR 2.2, 95% Cl: 1.1–4.5) retained their statistical significance, but premature birth lost its significance (Table 2).

In the multivariable logistic regression, the independently significant risk factors for needing respiratory support, namely mechanical ventilation or nCPAP, were being less than two months of age (aOR 10.2, 95% CI: 3.0–33.8), having a low birthweight of less than 2000 g (aOR 4.9, 95% CI: 1.1–21.4) and CHD (aOR 13.0, 95% CI: 2.8–60.9). Apnoea, preterm birth and the absence of wheezing lost their statistical significance (Table 3).

As 46% of the PICU admissions were associated with premature birth, we performed supplementary analyses by excluding birthweight from the model. In this model, premature birth was an independently significant risk factor for PICU admissions (aOR 4.4, 95% CI: 1.2–9.8) and respiratory support (aOR 3.8, 95% CI: 1.7–8.9).

The annual number of the patients with bronchiolitis varied between 1 and 14. The mean number of children aged less than 12 months in the population was 5335 and varied between 4761 and 5880. These figures allowed us to calculate the population-based incidences. The age-specific annual incidence varied considerably, from 0.18/1000/year to 2.59/1000/year, with a mean of 1.5 (Figure 1).

Table 3 Multivariate logistic regression: risk factors for the need of respiratory support among 315 infants admitted for bronchiolitis in 2000–2015

Risk factor	Adjusted odds ratio	95% CI	p-Value
Age <two months	10.15	3.04–33.83	<0.001
Gender (male)	1.29	0.55–3.07	0.560
Premature birth	2.32	0.82–6.53	0.111
Birthweight under 2000 g	4.87	1.11–21.42	0.036
CHD	12.99	2.77–60.86	0.001
Apnoea	1.62	0.51–5.14	0.416
Nonwheezing	1.44	0.57–3.65	0.440

CHD = congenital heart disease.
Area under the curve for predicted probability: 0.864. Hosmer–Lemeshow test: 2.03, p 0.917.

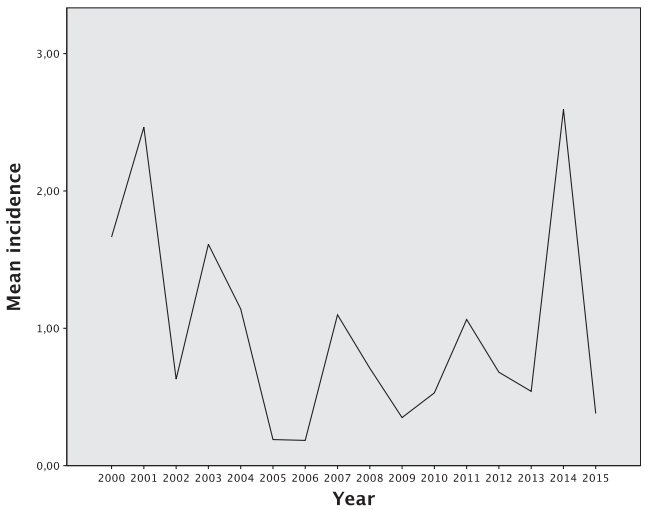

Figure 1 Annual age-specific incidence of bronchiolitis infant treated in intensive care during the study period 2000–2015.

DISCUSSION

There were four main results in this 16-year retrospective, one-centre, case–control study on the need for intensive care in infants with bronchiolitis at less than 12 months of age. First, the age-specific annual incidence varied considerably, from 0.18/1000/year to 2.59/1000/year. Second, an age of less than two months, birthweight under 2000 g or prematurity under 37 weeks of gestation and CHD were independently significant risk factors for PICU admissions and the need for respiratory support. Third, the presence of apnoea was associated with the need for intensive care. Fourth, audible wheezes and coarse crackles were, interestingly, more common in controls treated in the ED or on the ward than in cases treated in the PICU for bronchiolitis.

A Finnish study found that the incidence of bronchiolitis admissions to the ED at less than six months of age was 37/1000/year and the age-specific population-based incidence of bronchiolitis treated in the PICU was 2.3/1000/year in that age-specific population (4). The incidence was 1.5 times higher than the mean incidence of 1.5/1000/year in the present study, but the annual incidence varied considerably in our study. This variation was due to the low number of infants treated annually in the PICU and the variations in respiratory syncytial virus epidemics. The figures for the need of mechanical ventilation among those admitted to the PICU were 13% in the earlier study (4) and

Table 2 Multivariate logistic regression: risk factors for the need of intensive care among 315 infants admitted for bronchiolitis in 2000–2015

Risk factor	Adjusted odds ratio	95% CI	p-Value
Age <two months	11.50	5.12–25.80	<0.001
Gender (male)	1.81	0.88–3.74	0.107
Premature birth	2.19	0.85–5.62	0.105
Birthweight under 2000 g	15.93	2.36–107.27	0.004
CHD	15.85	4.15–60.50	<0.001
Apnoea	7.22	1.44–36.10	0.016
Nonwheezing	2.19	1.08–4.47	0.031

CHD = congenital heart disease.
Area under the curve for predicted probability: 0.882. Hosmer–Lemeshow test: 1.80, p 0.937.

20% in our study. In a 2014 Finnish study, the PICU treatment rate was 6.3% among those hospitalised for bronchiolitis at less than 12 months of age (5), but population-based incidence figures could not be calculated in that study. In England, admission rates to the PICU ranged from 1.3 to 1.6 per 1000 infants at less than 12 months of age between 2004 and 2012 (13). These incidence figures were surprisingly similar to the mean incidence in the present study. In another study, based on the nationally representative database on paediatric hospitalisations in the United States, the need for mechanical ventilation increased between 2000 and 2009 (3). Although the annual incidences varied considerably in the present study, no such trends were seen.

Several studies have evaluated the clinical factors associated with cases of severe bronchiolitis using different outcomes, such as admission to the PICU (7,10,14–16), the need for mechanical ventilation (7–9) or the use of nCPAP (17). Five studies were carried out prospectively (7–10,15). However, none of the previous study groups were entirely comparable to our study group. Some studies included children over 12 months old (8,10,15,16) and some included children with episodes of previous wheezing (8,10,16, 17). In addition, some studies excluded children with an underlying disease and preterm birth (9,14,15).

In line with our findings, PICU admissions and, or, the need for respiratory support were predicted by young age (8–10,15,16) and low birthweight (7,8) in many studies. Two prospective multicentre studies highlighted that being less than two months old was a risk factor for PICU admission (10) and respiratory support (8). In the present adjusted analyses, infants who were less than two months old had an 11.5-fold risk for PICU admission and a 10.2-fold risk for needing respiratory support. Similarly, an Italian study that used adjusted analyses confirmed that an age of less than one month predicted admission to the PICU and the need for respiratory support in hospitalised infants with bronchiolitis under the age of 12 months (9). We found that a birthweight of less than 2000 g was an independently significant risk factor for PICU admission and respiratory support. Similar birthweights of less than 2300 g were the cut-off limits that increased the risk of both intensive care and respiratory support in two other studies (7,8).

Prematurity is a known risk factor for needing hospitalisation for severe bronchiolitis (18,19). Only a few studies have identified premature birth as a risk factor for PICU admission or the need for respiratory support (16). A retrospective hospital chart review published in 2015 concluded that premature birth was associated with PICU admission, but not to the length of PICU stay or treatment with mechanical ventilation (16). We found that those infants with bronchiolitis who were born preterm had a 7.2-fold risk of being admitted to the PICU and a 6.7-fold risk of needing respiratory support. Preterm birth was an independently significant risk factor if low birthweight was not in the multivariable model, but due to the interaction, it lost its significance if low birthweight was in the model.

Congenital heart disease has been associated with higher hospitalisation rates in infants with bronchiolitis (20), and haemodynamically significant CHD has been identified as a risk factor for severe bronchiolitis (18,21). Some earlier retrospective case–control studies focusing on complicated respiratory syncytial virus infections identified CHD as a risk factor for PICU admission, need of respiratory support, as well as a long duration of ventilation and PICU stay, in infants with bronchiolitis (22,23). In our present retrospective 16-year, case–control study, all the infants with CHD were more than two months of age. Finally, CHD was an independently significant risk factor for PICU admission and for respiratory support for infants older than two months, although, CHD was haemodynamically significant in less than 25% of CHD cases.

As expected, apnoea was an independently significant risk factor for PICU admission. A previous prospective multicentre study described apnoea as an independently significant risk factor for respiratory support (8), but we were not able to confirm that result, probably due to our retrospectively collected data on apnoea based on entries in hospital records. In a previous study, infants with apnoea were younger, more likely to be born preterm and had lower birthweights (24), in accordance with our current observations. A prospective multicentre cohort study showed that 56% of the 108 bronchiolitis patients with documented apnoeas during their inpatient stay required intensive care (24). In our study, 93% of infants with apnoeas during hospitalisation were admitted to the PICU and half of them required respiratory support.

In the present case–control study, audible wheezes and coarse crackles were more common among patients discharged from the ED or treated on the ward compared to those treated in the PICU. This was in line with a previous study on 583 children hospitalised for bronchiolitis at less than 24 months of age, which reported that wheezing was more common among those treated on the ward (80%) than in the PICU (60%) (10). It is possible that wheezing indicates a less invasive disease and more reactive airways and that bronchiolitis with wheezing may be the first sign of asthma (25). There is some indirect evidence for this assumption, as wheezing infants seem to be older (6) and to respond better to bronchodilators (26), have more subsequent wheezing (27) and are more likely to be associated with viruses other than respiratory syncytial virus (25), compared to nonwheezing infants with bronchiolitis. In particular, the first wheezing episode associated with a rhinovirus infection may the first sign of childhood asthma (28).

The strength of this study was the carefully registered clinical data on admission and during hospitalisation in infancy, even though they were collected retrospectively. However, there was some information that was insufficient, such as information about parental smoking or the nonsystematic examination of viral findings. One of the authors reviewed all the patient records after the cases were

identified from the electronic registers. This means that the established diagnoses were not accepted directly, but were always revisited based on the information registered in the patient records by the doctors and nurses.

The main shortcoming of this study was that the design was retrospective. On the other hand, organising prospective surveillance time that is long enough to include sufficient patients is laborious and expensive. The other shortcoming of this one-centre study was the small number of patients, even though the surveillance period was as long as 16 years.

CONCLUSION

The average age-specific annual incidence of bronchiolitis requiring intensive care at the age of less than 12 months was 1.5/1000/year, but varied considerably. The independently significant risk factors for PICU admission and respiratory support were being age less than two months, a birthweight under 2000 g or prematurity under 37 weeks and CHD.

FINANCE

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CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 Basic and clinical data presented separately for 45 infants with bronchiolitis requiring respiratory support (nasal CPAP and/or mechanical ventilation) treated and for 270 controls without need for respiratory support.

Table S2 Characteristics of infants with bronchiolitis presented separately for those 40 with apnoea and for those 275 without apnoea during hospital stay.

The change in management of bronchiolitis in the intensive care unit between 2000-2015

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Conflicts of interest: None

Abstract

This case-control study evaluated interventions for bronchiolitis in relation to time in the pediatric intensive care unit (PICU) during a 16-year surveillance period. Together, 105 infants aged <12 months were treated for bronchiolitis in the PICU, and for them, we selected 210 controls admitted for bronchiolitis closest to cases. We collected data on treatments in the PICU, at the ward and in the emergency department for three periods: years 2000-2005, 2006-2010 and 2011-2015. Median hospital length of stay for PICU patients were 7 days (interquartile range 5-12), 5 (4-8) and 8 (4-12.5, p=0.127), respectively. By time, the use of inhaled beta-agonist (68% vs. 44% vs. 38%, p=0.019) and systemic corticosteroids (29% vs. 15% vs. 5%, p=0.019) decreased, but that of racemic adrenaline (59% vs. 78% vs. 84%, p=0.035) and hypertonic saline (0% vs. 0% vs. 54%, p<0.001) inhalations increased in the PICU. Similar changes were seen at the ward. In the PICU, non-invasive ventilation therapies increased significantly, but intubation rates did not decline. *Conclusion:* Beta-agonists and systemic corticosteroids were used less by time in intensive care for infant bronchiolitis, but the use of hypertonic saline and racemic adrenaline increased, though their effectiveness has been questioned.

Keywords: Bronchiolitis, management, infant, intensive care, respiratory support, high-flow nasal cannula.

What is Known:

- Until now, studies have shown which treatments do not work in bronchiolitis, and so, there is no consensus how infants with bronchiolitis should be treated. In particular, there is no consensus on different interventions in intensive care for bronchiolitis.

What is New:

- During 2000-2015 treatments with inhaled beta-agonists and systemic corticosteroids decreased but treatments with racemic adrenaline and hypertonic saline inhalations increased in intensive care for bronchiolitis. Similar changes were seen at the ward. Though non-invasive ventilation therapies increased, the intubation rate did not decline.

Abbreviations: ED, emergency department; HFNC, high-flow nasal cannula; IQR, interquartile range; nCPAP, nasal continuous positive airway pressure; NIV, non-invasive ventilation; PICU, pediatric intensive care unit.

Introduction

Bronchiolitis is the most common infectious cause of hospitalization among infants. Nonetheless, there is no universally accepted definition for acute bronchiolitis, and no wide consensus how infants with bronchiolitis should be treated. The evidence for interventions such as inhalation of normal or hypertonic saline, inhalation of bronchodilators like adrenaline or salbutamol, inhalation of anticholinergics, inhaled or systemic steroids, or systemic theophylline or magnesium sulphate has been minor or absent [10, 12, 15, 23, 25]. Thus, the management of bronchiolitis is mostly supportive, by providing supplementary fluids and oxygen when needed. [36] About three per cent of hospitalized infants with bronchiolitis seem to need respiratory support [18]. The few studies on critical care of bronchiolitis have focused on the use of surfactant, ribavirin, corticosteroids, respiratory syncytial virus –specific monoclonal antibodies [6] or management of acute respiratory failure with non-invasive ventilation (NIV) or with invasive ventilation needing intubation [3, 7, 20] . However, research-based evidence still lacks for the effectiveness of all these interventions.

During the past decades several countries have published guidelines on management of bronchiolitis, but none of these were focusing on critically ill infants [1, 2, 14, 31, 42, 45]. Despite the guidelines, the use of unnecessary interventions in bronchiolitis treatment is frequent [13, 21, 24-26, 32], and the impact of these guidelines to clinical practice remains controversial [21]. Only a few recent studies have focused on the use of drug therapy in intensive care for bronchiolitis [9, 33, 37].

We have recently published our data on characteristics, costs and risk factors of infant bronchiolitis requiring hospitalization during a surveillance period of 16 years from 2000 to 2015 [19, 28]. The aim of this study is to evaluate the use of different interventions in the pediatric intensive care unit (PICU) and the change in them over time. A special focus was paid on the connection of the changes with the time-point when the American Academy of Pediatrics (AAP) guideline on management of bronchiolitis was published in 2006 [1, 19, 28].

Material and methods

This is a retrospective review of the electronic patient files of Tampere University Hospital, Tampere, Finland, for the years 2000-2012 [9], supplemented with an identical collection of the data for the years 2013-2015 [28]. The study was carried out with the permission of the Chief Physician of the University Hospital.

In short, patients treated with ICD-10 diagnoses J10*-18*, J20*-22*, J45*or J46* in the PICU at the age less than 12 months were identified by one of the author (PH). Altogether, 179 such patients were found, and after careful reviewing of the patient files, 57 patients did not have bronchiolitis and they were excluded. Finally, 105 infants had bronchiolitis as the main diagnosis, or the treatment of bronchiolitis was the primary reason for intensive care. We defined bronchiolitis as the first episode of expiratory breathing difficulty associated with lower respiratory tract infection with or without audible wheezing. Among 105 infants treated in the PICU, 34 infants were admitted from the pediatric ward, 71 were admitted directly from the emergency department (ED) and 22 infants were transferred from surrounding hospitals. The criteria for admission to the PICU were the same for the patients despite of admission site and time: exhaustion, hypercapnia or recurrent apnea. For each of these 105 infants treated for bronchiolitis in the PICU, two controls were selected: those who were admitted to the ED for bronchiolitis (ICD-10 codes J21*) just before and just next after the case, being treated as inpatients at the ward (n=146) or as outpatients in the ED (n=64).

The hospital recordings of all the 315 patients were reviewed, and the same structural form to collect medical data was completed [9]. Data on medical histories and interventions were collected; such as oxygen support, using either standard low-flow nasal administration or high-flow nasal cannula (HFNC) treatment, oral or intravenous fluid support, normal or hypertonic saline inhalations, inhaled adrenaline, salbutamol or anticholinergics, and systemic corticosteroids, theophylline or magnesium sulphate, each separately for treatments in the PICU, at the ward and in the ED. In addition, data was collected whether chest radiograph were taken and antibiotics were used. In the case of PICU patients, the use of nasal continuous positive airway pressure (nCPAP) and intubation were recorded if given. HFNC and nCPAP were considered as NIV and intubation was considered as invasive ventilation. Length of stay (LOS) in the PICU and in the hospital, were recorded in days.

We split the data into three groups: years 2000-2005, 2006-2010 and 2011-2015. The first 6-year time period represents the era before, and the second and third 5-year time periods after publishing of the AAP bronchiolitis guideline in 2006 [1].

Statistics

SPSS 23 software (SPSS Inc., Chicago, IL, USA) was used to analyze the data. Mann-Whitney U test or Kruskal-Wallis test were used for non-normally distributed continuous data, and the results are expressed as medians with interquartile ranges (IQR). The t-test was used for normally distributed continuous data, and the results are expressed as means with 95% confidential intervals (95% CI). Chi square test or Fishers exact test when appropriate, were used for categorized data, and the results are expressed as numbers and percentages. The two-sided p value below 0.05 was considered statistically significant. Bonferroni correction by multiplying p value with two was used in paired comparisons within the three groups.

Results

Basic data

During the three surveillance periods 105 infants aged <12 months were treated in the PICU: 41 in 2000-2005, 27 in 2006-2010 and 37 in 2011-2015 (Table 1). Characteristics of those 146 infants treated at the ward or in the ED are presented in the supplementary table 1 (Suppl. table 1). Infants treated in the PICU were younger than infants treated at the ward or in the ED; the figures were 1.7 months (IQR 0.9-3.5), 3.3 months (2.0-5.6) and 5.4 months (3.8-7.3) (p <0.001), respectively. Instead, the median ages of PICU patients did not change by the time (p 0.961, Table 1). Additionally, PICU patients had a longer median length of stay (LOS) in hospital than those who were treated at the ward (PICU 6 days, IQR 4-12, vs. ward 2 days, IQR 1-4, p <0.001) and the LOS of PICU patients remained constant during the 16-year study period (p 0.127, Table 1). Median LOS in the PICU was 3 days in the 105 patients treated in the PICU and did not change by the time (p 0.244, Table 1).

Supportive therapy

During the three surveillance periods, the need of supplementary oxygen remained stable in the PICU (85% vs. 96% vs. 81%, Table 2), at the ward (20% vs. 17% vs. 26%) and in the ED (2% vs. 2% vs. 0%, Suppl. Tables 2-3). Nearly 90 per cent of infants treated in the PICU needed supplementary fluids, and the nasogastric tube and intravenous hydration were used equally often (Table 2).

Drug therapy

Over 80 per cent of infants were treated with inhaled bronchodilators in the PICU (Table 2). The use of salbutamol decreased by the time (68% vs. 44% vs. 38%, p 0.019), and the use of racemic adrenaline increased by the time (59% vs. 78% vs. 84%, p 0.035). Hypertonic saline inhalations were not used during 2000-2010. Hypertonic (3%) saline inhalation therapy was introduced in 2013 and was given to half of the infants treated in the PICU between 2011-2015. Similar changes in the use of bronchodilator and saline inhalations were seen at the ward and in the ED (Suppl. tables 2-3).

During 2011-2015 less than 5 per cent of infants were treated with systemic corticosteroids in the PICU (Table 2). The use of corticosteroids decreased during the three study periods not only in the PICU (p 0.019, Table 2) but also at the

ward and in the ED (Suppl. tables 2-3). Inhaled corticosteroids were not given to any of the patients during hospitalization.

Chest radiograph and antibiotics

Chest radiograph was obtained from over 60 per cent of infants treated in the PICU (Table 2), but the respective figure was only less than 10 per cent at the ward and in the ED (Suppl. tables 2-3). A third of infants treated in the PICU received antibiotics during 2000-2005, and thereafter, the use of antibiotics first decreased and then increased (Table 2). Instead, the use of antibiotics declined constantly at the ward (Suppl. Table 2).

Respiratory support

The use of non-invasive respiratory support, such as HFNC and nCPAP, increased during 2000-2015, however the need of invasive ventilation remained constant (Table 2). HFNC therapy was introduced in autumn 2011, and thereafter, 70% of PICU patients were treated with HFNC. Fourteen infants received HFNC as primary respiratory support, and it was not successful in six (43%), and five infants were treated with nCPAP and one needed intubation (Fig. 1). Correspondingly, 24 (23%) infants were treated with nCPAP as primary respiratory support, and it was not successful in five (21%) and they were intubated (Fig. 1). Fifteen infants were treated primary with invasive ventilation (Fig. 1). Thus, altogether 21 (20%) bronchiolitis patients treated in the PICU needed invasive ventilation with the median duration of 4.5 days (IQR 3-7.75). In them, the median LOS in the PICU was 6 days (IQR 4-10) and in the hospital 12 days (6-16.5). In other infants treated for bronchiolitis in the PICU, the respective figures were 5 days (IQR 3-8) and 8 days (5-12.75) if respiratory support was given with NIV, and 2 (IQR 1-3) and 5 days (3.25-7) if no respiratory support was needed.

Discussion

The current case-control study on management of critically ill infants with bronchiolitis has four main findings. First, the use of many treatments with unproven effectiveness such as inhaled beta-agonists or systemic corticosteroids decreased in the PICU during 2000-2015, but at the same time, the use of racemic adrenaline and hypertonic saline inhalations increased. The changes at the ward were rather similar. Second, the use of non-invasive ventilation increased, but despite of this, the need of intubation did not decline. Third, the changes in the interventions took place in line with the published guidelines. The increase in the use of racemic adrenalin and hypertonic saline inhalations reflected the literature of that time, though currently their effectiveness is questioned and their use is not anymore recommended [5, 17]. Fourth, the changes had no significant influence on the LOS in hospital.

The AAP recommended in 2006 not to use routinely bronchodilators, but justified the clinical trial with bronchodilators and preferred the use of racemic adrenaline instead of beta-agonist inhalations [1]. The recommendation was based on meta-analyses on bronchodilators in bronchiolitis, which were not able to confirm any beneficial effects on hospitalization rates or the LOS in hospital [15, 17]. However, based on clinical experience in some bronchiolitis patients, most guidelines included a recommendation that bronchodilators can be tried but continued only if beneficial in the patient in question [1, 2, 31, 42]. A large randomized controlled trial published in 2009 on the combined use of racemic adrenalin with dexamethasone in the outpatient clinic, found a decline in the hospitalization rate [34]. Since the impact of adrenaline remains controversial, some guidelines still recommend the use of adrenaline as rescue therapy for selected cases [14, 45]. The use of bronchodilators was high in the current study, which is against the current Finnish guideline on treatment of bronchiolitis published in 2014 [42]. Earlier, there were no national guideline available, but the published studies, meta-analyses and AAP guideline concluded that salbutamol is not useful in bronchiolitis [15]. It seems that the decrease in the use of salbutamol inhalations in the current study led to an increase in the use of racemic adrenaline inhalations. Accordingly, inhaled adrenaline was reported to be the first line drug in both Finnish and Swedish hospitals in 2011: racemic adrenaline in Finland and levo-adrenaline in Sweden [27]. Other studies reported that the use of bronchodilators in the PICU ranged 60-73% [33, 37]. In a recent study from Finland covering the years 2009-2011, treatment of bronchiolitis varied a lot between three University Children`s hospitals, the main differences being particularly in the use of bronchodilators [8].

Meta-analyses published since 2009 showed that corticosteroids do not reduce hospitalization rates in the ED or the LOS in hospital [12]. However, a significant decline in hospital admissions was detected in one large randomized

control trial (RCT) which combined inhaled adrenaline and high-dose corticosteroids for bronchiolitis treatment [34]. Currently, none of the guidelines recommend the use of corticosteroids either systemically or as inhaled [2, 31, 36, 42, 45]. Despite this, the use of corticosteroids continues, though less actively than earlier [13,26, 32, 35]. In addition, corticosteroids have no substantial effect on the duration of mechanical ventilation [6, 46]. Recently, the use of corticosteroids was reported to be 33% in bronchiolitis patients treated in the PICU [33], and 16-18% in those treated at the ward or in the outpatient clinic [13, 26]. In the present study, the use of corticosteroids was rare, in the PICU less than 5 per cent, and deceased significantly from 2000 to 2015.

The Cochrane systematic review on hypertonic saline in bronchiolitis concluded in 2013 that hypertonic saline might shorten the LOS in hospital [47]. The 16 studies included in the meta-analysis showed significant heterogeneity, which makes the evidence of the reduced LOS in hospital less strong [25]. Furthermore, the four largest and most recent studies [11, 39, 40, 43] included in the meta-analysis did not find any LOS reduction [25]. The use of saline inhalations has not been studied in critically ill bronchiolitis patients, and the usefulness and indications of hypertonic saline inhalations are still open. At the moment, the evidence is not supporting a routine use on hypertonic saline inhalation. In the present study over 50 per cent of hospitalized bronchiolitis patients received inhaled hypertonic saline since 2011, at the time when product was available.

An early use of NIV may decrease the need of invasive ventilation [7]. NIV such as nCPAP and HFNC are widely used for severe bronchiolitis both at the wards and in the PICU [4, 16, 18, 41], even though, the evidence beyond these therapies in infant bronchiolitis is still scant [3, 20]. Until now, the studies on HFNC have been observational, and currently, there are two RCTs and both of them were published this year [22, 30]. HFNC was compared to standard oxygen delivery in 202 children who needed supplementary oxygen for moderate bronchiolitis at less than 24 months of age [22]. There was no significant difference between the groups in the primary outcome that was weaning off oxygen. However, treatment failures were more common in standard oxygen delivery group than in the HFNC group [22]. Another RCT compared HFNC with nCPAP in 142 infants with severe bronchiolitis at less than 6 months of age and reported more treatment failures in the HFNC group [30]. No serious events such as air leaks, bleeding or deaths occurred in either of these two studies [22, 30]. Only two RCTs have been conducted on nCPAP [29, 44], and both found some improvement in clinical signs of respiratory distress, nevertheless, no decline in intubation rates, LOS in the PICU or mortality. Even though, the studies have not confirmed the effectiveness of HFNC or nCPAP in bronchiolitis,

their use has increased dramatically [38]. In the present study, the use of NIV increased by the time, but the need of intubation and invasive ventilation did not decline. During the recent decade the admissions to the PICU have increased, maybe due to increased use of NIV [38]. As published recently, HFNC therapy can be given at the ward, but the use of nCPAP in infants with bronchiolitis requires the PICU or corresponding facilities [41].

An overuse of diagnostic tests, such as radiological and laboratory examinations, and medications as well, have been reported in both outpatients and inpatients settings [21, 32]. A recent observational care study on the PICU treatment in two countries and sites suggests, though with a small number of patients, that even concerning invasive ventilation, less use of laboratory test and chest radiographs did not lead to worse outcomes [9]. In the present study, chest radiographs were taken from 63-74 per cent of infants admitted to the PICU due to bronchiolitis, but, in the ED and at the ward the only from 10 per cent. In the USA, the number after launching of the AAP bronchiolitis guideline have been less than 50 per cent in infants hospitalized for bronchiolitis [35], but as high as 87 per cent in those admitted to the PICU [33]. A recent prospective multicenter cohort study from Finland compared three tertiary hospitals and found that chest radiographs were obtained in 15-95 per cent of bronchiolitis patients [8]. Severe bronchiolitis has been associated complication such as ventilator-associated bacterial pneumonia [9] and the use of antibiotics has been frequent [4]. In our study, the use of antibiotics decreased among infants treated at the ward during 2000-2015, but the use fluctuated between 19 and 34% in those treated in the PICU and their use was not associated with invasive ventilation.

This 16-year-long surveillance with carefully, though retrospectively, collected data, gives an overview how the management of severe bronchiolitis has been changed in relation to time. The study demonstrates that pediatric literature and evidence-based guidelines, probably both together, have influenced management strategies, even though the changes are slow. Still, obvious over-testing and over-treatment exist. This is a retrospective one-center study, and although long-term, the numbers of patients are rather small. This is not a register study but all patient files of the included bronchiolitis cases were separately reviewed for this study. Due the retrospective design and small number of patients, the results must be interpreted cautiously, and their generalization to other populations and health care systems needs carefulness.

In conclusion, beta-agonists and systemic corticosteroids were used less by time in intensive care for infant bronchiolitis, but the use of hypertonic saline and racemic adrenalin increased, though their effectiveness has been questioned. Still, we know a lot how severe bronchiolitis should not be treated, but less how it should be treated.

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Figure 1. Respiratory Support of infants with bronchiolitis admitted to the PICU.

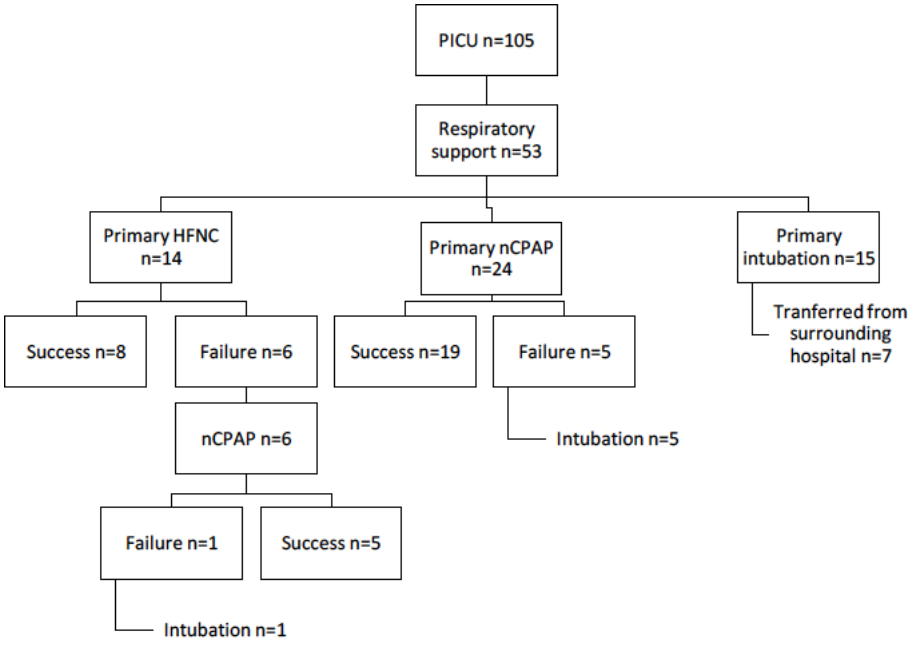

Table 1. Characteristics of 105 infants treated in the pediatric intensive care unit during 2000-2015.

	Years 2000-2005 **N=41 (%)**	**Years 2006-2010** **N=27 (%)**	**Years 2011-2015** **N=37 (%)**	**P value**
Age, months, median, (IQR)	1.8 (0.9-1.8)	1.7 (0.9-1.7)	1.6 (0.8-3.2)	0.961
Sex (male)	23 (56)	15 (56)	21 (57)	0.995
LOS (PICU) days, median (IQR)	3 (1-6.5)	2 (1-5)	4 (2-7.5)	0.244
LOS (hospital) days, median (IQR)	7 (5-12)	5 (4-8)	8 (4-12.5)	0.127

LOS (PICU), length of stay in the pediatric intensive care unit; LOS (hospital) length of stay in hospital; IQR inter-quartile range (25^{th} -75^{th} percentile).

Table 2. Management of 105 infants with bronchiolitis in the pediatric intensive care unit presented separately for three time periods during 2000-2015.

Treatment	Years 2000-2005 N=41 (%)	Years 2006-2010 N=27 (%)	Years 2011-2015 N=37 (%)	P value	P value 2000-2005 vs. 2006-2010[a]	P value 2006-2010 vs. 2011-2015[a]
Oxygen support	35 (85)	26 (96)	30 (81)	0.199	0.294	0.138
Fluid support (p.o.)	25 (61)	17 (63)	26 (70)	0.674	1.0	1.0
Fluid support (i.v.)	24 (59)	21 (78)	29 (78)	0.100	0.202	1.0
Inhaled saline	2 (5)	6 (22)	21 (57)	<0.001	0.060	0.012
0.9%	2 (5)	6 (22)	2/18 (11)	0.092	0.060	0.680
3%	0/39 (0)	0/21	19/35 (54)	<0.001	-	<0.001
Inhaled bronchodilators	34 (83)	23 (85)	34 (92)	0.491	1.0	0.792
Adrenaline	24 (59)	21 (78)	31 (84)	0.035	0.202	1.0
Salbutamol	28 (68)	12 (44)	14 (38)	0.019	0.102	1.0
Anticholinergic	6 (15)	2 (7)	0 (0)	0.052	0.730	0.18
Theophylline	4 (10)	1/26 (4)	3 (8)	0.648	0.698	0.944
Systemic steroids	12 (29)	4 (15)	2 (5)	0.019	0.338	0.404
Antibiotics	14 (34)	5 (19)	16 (43)	0.116	0.320	0.074
Chest radiograph	26 (63)	20 (74)	24 (65)	0.633	0.716	0.864
HFNC	0	1 (4)	26 (70)	<0.001	0.430	<0.001
nCPAP	5 (12)	12 (44)	21 (57)	<0.001	0.006	0.660
Intubation	7 (17)	7 (26)	7 (19)	0.657	1.0	1.0

[a] Bonferroni correction by multiplying p-value with two. HFNC, high flow nasal cannula; nCPAP, nasal continuous positive airway pressure.

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REGULAR ARTICLE

National treatment guidelines decreased the use of racemic adrenaline for bronchiolitis in four Finnish university hospitals

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Keywords
Bronchiolitis, Clinical guidelines, Prescribing patterns, Racemic adrenaline, Rescue therapy

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ABSTRACT

Aim: Inhaled racemic adrenaline was used for bronchiolitis in many hospitals in Finland prior to new national current care guidelines for bronchiolitis in 2014, which limited its recommendations to on-demand rescue therapy. We studied the drug's use before and after the new guidelines to gauge changes in prescribing habits.

Methods: This 2012–2016 study analysed how many 0.5 mL doses of racemic adrenaline were used for children by emergency rooms, paediatric wards and paediatric intensive care units at four university hospitals and estimated drug and staff costs.

Results: There were substantial differences in the yearly consumption of racemic adrenaline between the hospitals before and after the bronchiolitis guidelines were published, with reductions in drug costs and staff time. The overall use more than halved during the study period, particularly in two hospitals where baseline consumptions were highest, but not in a third where baseline consumption was already low. In the fourth, the baseline consumption was modest and there was a constant decrease during the study years.

Conclusion: The current care guidelines for bronchiolitis had some impact on clinical practice, as the overall use of racemic adrenaline more than halved, but considerable differences remained in the four study hospitals after their publication.

INTRODUCTION

Acute bronchiolitis is a common respiratory disease in infancy and in Nordic countries, it is defined as the first episode of respiratory distress, with or without wheezing, before the age of 12 months (1). In contrast, the guidelines issued by the American Academy of Pediatrics in 2006 (2) and the UK's National Institute for Health and Care Excellence in 2015 (3) are based on an upper age limit of 24 months. The incidence of bronchiolitis is high in children under the age of one, with one in three presenting with mild-to-moderate bronchiolitis and 1–3% with severe bronchiolitis being treated in hospital (2,4).

The treatment of acute bronchiolitis has included inhalations of hypertonic saline, racemic adrenaline or salbutamol, inhaled or systemic corticosteroids and repeated suctioning of the airways. However, none of these interventions have proved to be effective (5–7) and none of the current guidelines on managing bronchiolitis recommend routine use of bronchodilators or corticosteroids (2,3). Cleaning the airways with suctioning is only useful if there is much mucus in the respiratory tract and is not recommended when there is just mucosal swelling. Some research-based evidence has been published that suggests that inhaling racemic adrenaline may be useful in selected patients with bronchiolitis (8), but mainly as a rescue therapy (9). The cornerstones of the treatment for bronchiolitis are still monitoring breathing and feeding, and

Abbreviations
PICU, Paediatric intensive care unit; RSV, Respiratory syncytial virus.

Key notes

- We examined the use of racemic adrenaline in four Finnish university hospitals from 2012–2016, before and after 2014 when national current care guidelines on bronchiolitis limited its recommendations to on-demand rescue therapy.
- The overall use of racemic adrenaline more than halved, suggesting that the guidelines had an impact on clinical practice.
- However, we continued to find differences in its use between the hospitals before and after the guidelines were published.

supplementary oxygen and fluid and ventilator support if needed.

In the summer of 2014, national evidence-based current care guidelines for treating infant bronchiolitis and other lower respiratory tract infections in children were published in Finland (10). These guidelines did not recommend the use of racemic adrenaline for the routine treatment of acute bronchiolitis, but stated that it could be used as an on-demand rescue therapy.

In children's hospitals, the only common indication for the use of racemic adrenaline in recent years has been acute bronchiolitis (1). Other less common uses have included treating acute laryngitis, acute severe asthma and as a rescue therapy for laryngeal spasms during, or after, intubation.

Although different evidence-based guidelines are now being published more frequently in many countries, their effectiveness has been insufficiently studied (11). However, a 2017 study reported that the implementation of the UK bronchiolitis guidelines, which were published by the National Institute for Health and Care Excellence in 2015 and supported by a simple educational intervention, reduced the number of chest radiographs and antibiotics prescribed for bronchiolitis (12). In the United States, the publication of the 2006 American Academy of Pediatrics bronchiolitis guidelines was associated with reductions in the use of resources, including chest radiographies, bronchodilators and corticosteroids (13).

The aim of this study was to evaluate the impact of the 2014 Finnish evidence-based current care guidelines on the treatment of bronchiolitis in four university hospitals in Finland. The consumption of racemic adrenaline was assessed each year from 2012 to 2016, before and after publication of the national guideline on the treatment of bronchiolitis in 2014.

MATERIAL AND METHODS

This study evaluated the consumption of racemic adrenaline in the paediatric departments of four Finnish University Hospitals – Kuopio, Oulu, Tampere and Turku – using hospital pharmacy records. We estimated the consumption based on the numbers of doses of racemic adrenaline (racepinephrine 2.25% 0.5 mL) that the hospital pharmacies delivered to the paediatric departments of the hospitals. As well as analysing total consumption, we obtained detailed information on the amount used by the different paediatric units, such as the paediatric emergency room, the paediatric infectious disease ward and the paediatric intensive care unit (PICU).

Cost data on the actual drugs were obtained from the pharmacy at Tampere University Hospital and we used other data from the hospital on associated factors, such as staff time. All the costs were evaluated using 2017 prices and were reported as Euros. The doses of racemic adrenaline cost €2.30 each. The nurses' time was evaluated in hours and their salaries were not taken into account in the cost calculations. We estimated that it took 10 minutes to check the doctor's order, prepare the drug and solution ready for use and give the nebulised drug to the infant. This time was under-estimated rather than over-estimated and any time taken to reassure the infant was not included, although it was often needed.

The numbers of infants under the age of 12 months admitted for bronchiolitis to the paediatric emergency room of Tampere University Hospital were available from the hospital's electronic files for 2013–2015 and they were 238 in 2013, 213 in 2014 and 172 in 2015. The bronchiolitis diagnoses were confirmed by revisiting the patient records. According to the National Register for Infectious Diseases, the total number of laboratory-confirmed respiratory syncytial virus (RSV) infections in Finland was 4947 in 2016, compared to 1991 in 2013, 2868 in 2014 and 2436 in 2015 (14).

In addition, we retrieved Government data on the number of children under 16 years of age covered by the four hospital districts and these were: Tampere (91 010), Oulu (88 094), Kuopio (26 518) and Turku (78 641) (15).

The consumption of racemic adrenaline was expressed as crude numbers of consumed doses and as the number of consumed doses per 10 000 children aged less than 16 years in the population.

RESULTS

There were substantial differences in the yearly consumption of racemic adrenaline between the four university hospitals both before and after publishing of the bronchiolitis guideline (Table 1).

There was also a significant decrease in the annual use of racemic adrenaline between 2012–2013 and 2015–2016 in Kuopio and Tampere, but not in Oulu where the baseline consumption was already low (Table 1). In Turku, the baseline consumption was modest and there was a constant decrease during the study years (Fig. S1). The highest consumption in 2012 was in Tampere (3295), followed by Kuopio (2283), Turku (1135) and Oulu (468), but this had fallen by just over 54% in 2016 and the order had changed to Kuopio (1373), Tampere (773), Oulu (650) and Turku (326). When the rates were presented per 10 000 children under the age of 16 in 2012 and 2016, they were 846 and 734 in Kuopio, 366 and 85 in Tampere, 144 and 42 in Turku and 56 and 74 in Oulu. The overall reduction in the use of racemic adrenal across the four hospitals during the study period was just over 54%.

In 2012–2013, when the consumption of racemic adrenaline was common in Tampere and Kuopio, two-thirds of the consumption was in paediatric wards handling infection diseases. This was mainly due to the fact that the most common cause for hospitalisation was bronchiolitis and those patients were given racemic adrenaline inhalations. Although, the indications in the emergency room and PICU showed more variations, bronchiolitis was also the most common disease treated with racemic adrenaline.

The number of children admitted to the emergency room at Tampere for bronchiolitis was available and the average

Table 1 The number of doses of racemic adrenaline (2.25%, 0.5 mL inhalation solution) delivered from the pharmacies to the paediatric department in the four Finnish university hospitals. The data are presented separately for the emergency room (ER), paediatric infectious diseases ward (ward) and paediatric intensive care unit (PICU) of each hospital during 2012–2016

Hospital	Unit	2012		2013		2014		2015		2016	
Tampere	Total*	3295	366	3498	388	2460	270	780	85	773	85
	ER	870		738		630		210		293	
	Ward	2125		2400		1350		450		330	
	PICU	300		360		480		120		150	
Oulu	Total*	485	56	672	77	648	74	537	61	650	74
	ER†	–		–		–		–		–	
	Ward	230		291		240		248		325	
	PICU	155		251		270		185		210	
Turku	Total*	1135	144	689	88	560	71	490	63	326	42
	ER	280		417		110		30		146	
	Ward	290		120		330		310		145	
	PICU	270		150		60		116		30	
Kuopio	Total*	2283	846	2745	1035	2333	880	1919	734	1373	532
	ER	367		286		324		260		270	
	Ward	1625		1894		1709		1305		920	
	PICU	79		55		25		23		53	

*Total doses of racemic adrenaline (racepinephrine) and doses per 10 000 children aged less than 16 years.
†The ER costs were included in the ward costs and could not be obtained separately.

numbers of doses delivered from the hospital pharmacy for admitted children were 14.7 in 2013, 11.5 in 2014 and 4.5 in 2015. In 2016, when there was a severe RSV epidemic in Finland, the total numbers of laboratory-confirmed RSV infections were 2.5, 1.7 and 2.0 times higher than in 2013, 2014 or 2015, respectively.

The annual medication costs tended to be stable in Oulu and Kuopio and decreased in Tampere and Turku, reflecting changes in their use of racemic adrenaline. In 2012, the annual costs varied from €7579 to €1116 and in 2016, they varied from €3158 to €750 (Table 2). Another notable expense was the time that the nurses spent preparing the medicines and solutions ready for use and administering the nebulised medicines to the infants. In 2012, the annual working time varied from a total of 186 to 1263 hours for the four hospitals and in 2016, it varied from 125 to 526 hours (Table 2). The largest decrease, of 967 hours or 25.3 working weeks, occurred in Tampere. Other expenses that should be taken into account, apart from the cost of each drug dose (€2.30), were the two needles and two syringes required for one dose of racemic adrenaline (total €0.15), 2 mL of normal saline solution per dose (€0.03) and the pro-rata purchase price and servicing of the nebuliser (€2.38) for each dose. These repeated costs €2.48 per dose depended on the number of racemic adrenaline doses that were used. In 2012, the repeated costs ranged from €1193 to €8106 and in 2016, they ranged from €802 to €3378.

Table 2 The costs of racemic adrenaline (racepinephrine 2.25% 0.5 mL inhalation solution) and working time of nurses (in hours) used for administering nebulisation in four university hospitals in Finland during the years 2012–2016. In Finland, the regular working time of nurses is 38.25 hours per week

	2012	2013	2014	2015	2016
Tampere					
Costs (€)	7579	8045	5658	1794	1778
Working time (hour)	1263	1341	943	299	296
Oulu					
Costs (€)	1116	1546	1490	1235	1495
Working time (hour)	186	258	248	206	249
Turku					
Costs (€)	2611	1585	1288	1127	750
Working time (hour)	435	264	215	188	125
Kuopio					
Costs (€)	5251	6314	5366	4414	3158
Working time (hour)	875	1052	894	736	526

DISCUSSION

Racemic adrenaline inhalations have been widely used in the Nordic countries to treat bronchiolitis (1,9). The accumulating evidence against the routine use of adrenaline (2,9), meant that its use was not recommended for clinical practice when the Finnish evidence-based current care guidelines were published in 2014 (10). This study was conducted to evaluate the impact of these guidelines on clinical practice comparing the two years before and after their introduction.

There were three key results that emerged from our study. First, the use of racemic adrenaline decreased substantially after the Finnish guidelines were published, based on the number of doses delivered by pharmacies to the departments in the four university hospitals. Second, although the use of racemic adrenaline fell after the guidelines were published, its use continued to vary considerably between the hospitals, especially with regard to the population-based analyses. Third, the medication costs were relatively

modest, but time that the nurses spent administering racemic adrenaline showed a notable decrease. These results suggest that the evidence-based current care guidelines contributed to real-life treatment practice.

In the present study, the greatest decrease in the consumption of racemic adrenaline was mainly seen, as expected, in the hospitals that used the greatest quantities before the guidelines were issued. In the United States, the overall consumption of bronchodilators in bronchiolitis decreased modestly, from 70% to 58% in 2008–2012, after the 2006 American Academy of Pediatrics guidelines on the management of bronchiolitis were published. However, the figures for racemic adrenaline were not given separately (16). In hospitalised children in the United States, the use of racemic adrenaline for bronchiolitis decreased from 17.8% in 2004–2005 to 12.2% in 2007–2008 (17). On the other hand, some reports concluded that the use of bronchodilators remained stable after implementation of the 2006 guidelines, both in ambulatory and hospital settings (18,19). A study published in 2017, reported that following the publication of the 2015 guidelines on managing bronchiolitis by the UK's National Institute for Health and Care Excellence, a secondary paediatric unit in England performed an educational intervention and the use of salbutamol decreased from 36% to 24%. However, the authors pointed out that racemic adrenaline was not used by this hospital, either before or after 2015 (12).

The use of racemic adrenaline varied a lot between the four university hospitals in our study. A study of three of the four Finnish university hospitals featured in the current study was carried out in 2008–2010, and substantial variation was observed in terms of other diagnostic and treatment practices for bronchiolitis, such as the use of salbutamol inhalations, systemic corticosteroids or intravenous versus oral fluid therapies (20). Notable variations that cannot be explained by disease severity or readmission rates have been reported from the United States and Spain (19,21,22). Furthermore, the use of unnecessary treatment, such as bronchodilators, antibiotics and corticosteroids, has been associated with longer stays in hospital in the United States (19).

A retrospective time series study from the United States revealed that, after the implementation of the American 2006 bronchiolitis guidelines, the average total costs per patient fell by $197 in the emergency room (23). This reduction was based on the decreased use of chest radiographs and tests for viruses, as well as reductions in the medication used. Our study identified reductions in the medication costs and the time spent by the nurses who prepared and gave the inhalations of racemic adrenaline. In Tampere, the nurses' annual total working time decreased by 967 hours from 2012 to 2016, which was the equivalent of six months for one nurse working full time. The reduction meant that nurses were free to carry out other duties in these busy departments.

The impact that evidence-based guidelines and clinical practice guidelines have on everyday practice remains unclear (11,24). A prospective closed-loop audit study performed in the UK reported significant improvement in clinical practice after treatment guidelines were issued on the treatment of pneumonia (25). Meanwhile, a multicentre voluntary collaboration of 21 American primarily community hospitals found that a web-based initiative that included data collection and feedback to doctors on bronchiolitis resulted in a 29% reduction in the use of bronchodilators, a 68% reduction in the use of corticosteroids and a 44% reduction in chest radiography (26). In Finland, a limited number of doctors treat infants with bronchiolitis, which means that the implementation of the guidelines in the study hospitals was probably easier than in the case of many other illnesses or in other settings than hospitals with specific paediatric expertise. Our study showed that a certain level of harmonisation can be achieved between hospitals when national guidelines are issued. However, educational or other interventions may be needed, because significant differences in the treatment of bronchiolitis still existed, even between the university hospitals in our study, after implementing the national guidelines.

The main strength of the study was that the results were based on real consumption figures at the different paediatric units of the four university hospitals and the figures were obtained from the hospital pharmacies. However, the study had two main limitations. Firstly, no data was available to indicate why the racemic adrenaline was given to the patients, namely specific diseases and indications. We only estimated that most of the inhalations on the paediatric infection wards were given to bronchiolitis patients. Croup very rarely needs in-patient treatment in hospital (27) and patients with asthma are hospitalised less than earlier and those hospitalised with severe asthma are usually treated in an intensive care unit (28). In any case, racemic adrenaline is only a rescue therapy for severe asthma, and it is needed very rarely. Secondly, the figures were only obtained from four university hospitals and the use of racemic adrenaline in secondary-level hospitals as well as in out-patient clinics remains unclear. However, the hospitals we studied covered more than 30% of the child population in Finland.

CONCLUSION

We found some evidence that the 2014 Finnish evidence-based clinical care guidelines on the treatment of bronchiolitis had an impact on the everyday clinical care of children with regard to reducing the use of racemic adrenaline. They also had some impact on the amount of nursing time spent preparing and administering this treatment and reduced the already modest drugs costs. Future studies should focus on the impact that evidence-based current care guidelines have on children, including assessing cost-effectiveness. Maybe such monitoring should be part of producing and updating any guidelines.

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CONFLICT OF INTERESTS

The authors have no conflict of interests to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Figure S1 The annual consumption of racemic adrenaline in four university hospitals in Finland in years 2012–2016 (racepinephrine 2.25% 0.5 mL doses). The lower graph shows the consumption adjusted to doses per 10 000 children under the age of 16 years.

