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

Minna Mecklin¹ · Paula Heikkilä¹ · Matti Korppi¹

Received: 7 November 2017 / Revised: 19 March 2018 / Accepted: 16 April 2018 / Published online: 15 May 2018
© Springer-Verlag GmbH Germany, part of Springer Nature 2018

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 days (4–8) and 8 days (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.

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.

Keywords Bronchiolitis · Management · Infant · Intensive care · Respiratory support · High-flow nasal cannula

Communicated by Piet Leroy

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s00431-018-3156-4>) contains supplementary material, which is available to authorized users.

✉ Minna Mecklin
minna.mecklin@fimnet.fi

Paula Heikkilä
paula.heikkila@uta.fi

Matti Korppi
matti.korppi@uta.fi

¹ Tampere Center for Child Health Research, University of Tampere and Tampere University Hospital, Arvo Building, FI-33014 Tampere, Finland

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 sulfate 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 3% 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, and 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 the Tampere University Hospital, Tampere, Finland, for the years 2000–2012 [19], 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 authors (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 [19]. 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 sulfate, each separately for treatments in the PICU, at the ward and in the ED. In addition, data was collected whether chest radiographs were taken and antibiotics were used. In the case of PICU patients, the use of nasal continuous positive airway pressure (nCPAP) and intubation was 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 was 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 was 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 Fisher's exact test when appropriate was 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. 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%, Supplementary Tables 2 and 3). Nearly 90% 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% 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 and 2015. Similar changes in the use of bronchodilator and saline inhalations were seen at the ward and in the ED (Supplementary Tables 2 and 3).

During 2011–2015, less than 5% 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

(Supplementary Tables 2 and 3). Inhaled corticosteroids were not given to any of the patients during hospitalization.

Chest radiograph and antibiotics

Chest radiograph was obtained from over 60% of infants treated in the PICU (Table 2), but the respective figure was only less than 10% at the ward and in the ED (Supplementary Tables 2 and 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 (Supplementary 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%): 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 days (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

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

	Years 2000–2005, <i>N</i> = 41 (%)	Years 2006–2010, <i>N</i> = 27 (%)	Years 2011–2015, <i>N</i> = 37 (%)	<i>p</i> 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* interquartile range (25th–75th 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

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 adrenaline 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

Fig. 1 Respiratory support of infants with bronchiolitis admitted to the PICU

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 adrenaline 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%, and decreased 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% 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 is 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, has been reported in both outpatient and inpatient 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 to 74% of infants admitted to the PICU due to bronchiolitis, but, in the ED and at the ward, they were only taken from 10%. In the USA, the number after launching of the AAP bronchiolitis guideline have been less than 50% in infants hospitalized for bronchiolitis [35], but as high as 87% 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% 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.

Authors' contributions Minna Mecklin was responsible on analysis, interpretation of data, and writing the article and took part in study design. Paula Heikkilä collected and reviewed patients records and made contribution on study design, interpretation of data, and writing. Matti Korppi was responsible on study design and interpretation of data and had substantial contribution on writing the article.

Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent The study was carried out with the permission of the Chief Physician of the University Hospital.

References

- 1 American Academy of Pediatrics Subcommittee on Diagnosis and Management of Bronchiolitis S on D and M of (2006) Diagnosis and management of bronchiolitis. *Pediatrics* 118:1774–1793. <https://doi.org/10.1542/peds.2006-2223>
- 2 Baraldi E, Lanari M, Manzoni P et al (2014) Inter-society consensus document on treatment and prevention of bronchiolitis in newborns and infants. *Ital J Pediatr* 40:65. <https://doi.org/10.1186/1824-7288-40-65>
- 3 Beggs S, Wong ZH, Kaul S et al (2014) High-flow nasal cannula therapy for infants with bronchiolitis. *Cochrane Database Syst Rev* 1:CD009609. <https://doi.org/10.1002/14651858.CD009609.pub2>
- 4 Bradshaw ML, Déragon A, Puligandla P, Emeriaud G, Canakis AM, Fontela PS (2018) Treatment of severe bronchiolitis: a survey of Canadian pediatric intensivists. *Pediatr Pulmonol* doi: <https://doi.org/10.1002/ppul.23974>
- 5 Brooks CG, Harrison WN, Ralston SL (2016) Association between hypertonic saline and hospital length of stay in acute viral bronchiolitis: a reanalysis of 2 meta-analyses. *JAMA Pediatr* 170:577–584. <https://doi.org/10.1001/jamapediatrics.2016.0079>
- 6 Davison C, Ventre KM, Luchetti M, Randolph AG (2004) Efficacy of interventions for bronchiolitis in critically ill infants: a systematic review and meta-analysis. *Pediatr Crit Care Med* 5:482–489
- 7 Donlan M, Fontela PS, Puligandla PS (2011) Use of continuous positive airway pressure (CPAP) in acute viral bronchiolitis: a systematic review. *Pediatr Pulmonol* 46:736–746. <https://doi.org/10.1002/ppul.21483>
- 8 Elenius V, Bergroth E, Koponen P et al (2017) Marked variability observed in inpatient management of bronchiolitis in three Finnish hospitals. *Acta Paediatr Int J Paediatr* 106:1512–1518. <https://doi.org/10.1111/apa.13931>
- 9 Essouri S, Baudin F, Chevret L, Vincent M, Emeriaud G, Juvet P (2017) Variability of care in infants with severe bronchiolitis: less-invasive respiratory management leads to similar outcomes. *J Pediatr* 188:156–162.e1. <https://doi.org/10.1016/j.jpeds.2017.05.033>
- 10 Everard ML, Bara A, Kurian M, et al (2005) Anticholinergic drugs for wheeze in children under the age of two years. *Cochrane database Syst Rev* (3):CD001279. doi: <https://doi.org/10.1002/14651858.CD001279.pub2>
- 11 Everard ML, Hind D, Ugona K et al (2014) SABRE: a multicentre randomised control trial of nebulised hypertonic saline in infants hospitalised with acute bronchiolitis. *Thorax* 69:1105–1112. <https://doi.org/10.1136/thoraxjnl-2014-205953>
- 12 Fernandes RM, Bialy LM, Vandermeer B et al (2013) Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database Syst Rev* 6:CD004878. <https://doi.org/10.1002/14651858.CD004878.pub4> [doi]
- 13 Florin TA, Byczkowski T, Ruddy RM et al (2014) Variation in the management of infants hospitalized for bronchiolitis persists after the 2006 American Academy of Pediatrics bronchiolitis guidelines. *J Pediatr* 165:92.e1. <https://doi.org/10.1016/j.jpeds.2014.05.057>
- 14 Friedman JN, Rieder MJ, Walton JM, Canadian Paediatric Society, Acute Care Committee, Drug Therapy and Hazardous Substances Committee (2014) Bronchiolitis: recommendations for diagnosis, monitoring and management of children one to 24 months of age. *Paediatr Child Health* 19:485–498
- 15 Gadomski AM, Scribani MB (2014) Bronchodilators for bronchiolitis. *Cochrane Database Syst Rev* 6:CD001266. <https://doi.org/10.1002/14651858.CD001266.pub4> [doi]
- 16 Ganu SS, Gautam A, Wilkins B, Egan J (2012) Increase in use of non-invasive ventilation for infants with severe bronchiolitis is associated with decline in intubation rates over a decade. *Intensive Care Med* 38:1177–1183. <https://doi.org/10.1007/s00134-012-2566-4>
- 17 Hartling L, Bialy LM, Vandemeer B, et al (2011) Epinephrine for bronchiolitis. *Cochrane database Syst Rev* (6):CD0031:CD003123. doi: <https://doi.org/10.1002/14651858.CD003123.pub3>
- 18 Hasegawa K, Tsugawa Y, Brown DF et al (2013) Trends in bronchiolitis hospitalizations in the United States, 2000–2009. *Pediatrics* 132:28–36. <https://doi.org/10.1542/peds.2012-3877> [doi]
- 19 Heikkilä P, Forma L, Korppi M (2015) Hospitalisation costs for infant bronchiolitis are up to 20 times higher if intensive care is needed. *Acta Paediatr* 104:269–273. <https://doi.org/10.1111/apa.12881>
- 20 Jat KR, Mathew JL (2015) Continuous positive airway pressure (CPAP) for acute bronchiolitis in children. *Cochrane Database*

- Syst Rev 1:CD010473. <https://doi.org/10.1002/14651858.CD010473.pub2>
- 21 Johnson LW, Robles J, Hudgins A et al (2013) Management of bronchiolitis in the emergency department: impact of evidence-based guidelines? *Pediatrics* 131(Suppl):103. <https://doi.org/10.1542/peds.2012-1427m>
 - 22 Kepreotes E, Whitehead B, Attia J et al (2017) High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. *Lancet* (London, England) 389:930–939. [https://doi.org/10.1016/S0140-6736\(17\)30061-2](https://doi.org/10.1016/S0140-6736(17)30061-2)
 - 23 Liu F, Ouyang J, Sharma AN, et al (2015) Leukotriene inhibitors for bronchiolitis in infants and young children. *Cochrane database Syst Rev* (3):CD010636. doi: <https://doi.org/10.1002/14651858.CD010636.pub2>
 - 24 Macias CG, Mansbach JM, Fisher ES, Riederer M, Piedra PA, Sullivan AF, Espinola JA, Camargo CA Jr (2015) Variability in inpatient management of children hospitalized with bronchiolitis. *Acad Pediatr* 15:69–76. <https://doi.org/10.1016/j.acap.2014.07.005>
 - 25 Maguire C, Cantrill H, Hind D, et al (2015) Hypertonic saline (HS) for acute bronchiolitis: systematic review and meta-analysis. *BMC Pulm Med* 15:x. doi: <https://doi.org/10.1186/s12890-015-0140-x>
 - 26 McCulloh RJ, Smitherman SE, Koehn KL, Alverson BK (2014) Assessing the impact of national guidelines on the management of children hospitalized for acute bronchiolitis. *Pediatr Pulmonol* 49: 688–694. <https://doi.org/10.1002/ppul.22835> [doi]
 - 27 Mecklin M, Hesselmar B, Qvist E, Wennergren G, Korppi M (2014) Diagnosis and treatment of bronchiolitis in Finnish and Swedish children's hospitals. *Acta Paediatr* 103:946–950. <https://doi.org/10.1111/apa.12671>
 - 28 Mecklin M, Heikkilä P, Korppi M (2017) Low age, low birthweight and congenital heart disease are risk factors for intensive care in infants with bronchiolitis. *Acta Paediatr* 106:2004–2010. <https://doi.org/10.1111/apa.14021>
 - 29 Milési C, Matecki S, Jaber S et al. (2013) 6 cmH₂O continuous positive airway pressure versus conventional oxygen therapy in severe viral bronchiolitis: a randomized trial. *Pediatr Pulmonol* 48:45–51. <https://doi.org/10.1002/ppul.22533>
 - 30 Milési C, Essouri S, Pouyau R et al (2017) High flow nasal cannula (HFNC) versus nasal continuous positive airway pressure (nCPAP) for the initial respiratory management of acute viral bronchiolitis in young infants: a multicenter randomized controlled trial (TRAMONTANE study). *Intensive Care Med* 43:209–216. <https://doi.org/10.1007/s00134-016-4617-8>
 - 31 National Institute for Health and Care Excellence (2015) Bronchiolitis: diagnosis and management of bronchiolitis in children. <http://www.NiceOrgUk/Guidance/Ng9> 1–301
 - 32 Parikh K, Hall M, Teach SJ (2014) Bronchiolitis management before and after the AAP guidelines. *Pediatrics* 133:1. <https://doi.org/10.1542/peds.2013-2005>
 - 33 Pierce HC, Mansbach JM, Fisher ES et al (2015) Variability of intensive care management for children with bronchiolitis. *Hosp Pediatr* 5:175–184. <https://doi.org/10.1542/hpeds.2014-0125>
 - 34 Plint AC, Johnson DW, Patel H et al (2009) Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med* 360:2079–2089. <https://doi.org/10.1056/NEJMoa0900544>
 - 35 Ralston S, Garber M, Narang S et al (2013) Decreasing unnecessary utilization in acute bronchiolitis care: results from the value in inpatient pediatrics network. *J Hosp Med* 8:25–30. <https://doi.org/10.1002/jhm.1982>
 - 36 Ralston SL, Lieberthal AS, Meissner HC et al (2014) Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 134:1474. <https://doi.org/10.1542/peds.2014-2742> [doi]
 - 37 Sala KA, Moore A, Desai S, Welch K, Bhandari S, Carroll CL (2015) Factors associated with disease severity in children with bronchiolitis. *J Asthma* 52:268–272. <https://doi.org/10.3109/02770903.2014.956893>
 - 38 Schlapbach LJ, Straney L, Gelbart B et al (2017) Burden of disease and change in practice in critically ill infants with bronchiolitis. *Eur Respir J* 49:1601648. <https://doi.org/10.1183/13993003.01648-2016>
 - 39 Sharma BS, Gupta MK, Rafik SP (2013) Hypertonic (3%) saline vs 0.93% saline nebulization for acute viral bronchiolitis: a randomized controlled trial. *Indian Pediatr* 50:743–747
 - 40 Silver AH, Esteban-Cruciani N, Azzarone G et al (2015) 3% hypertonic saline versus normal saline in inpatient bronchiolitis: a randomized controlled trial. *Pediatrics* 136:1036–1043. <https://doi.org/10.1542/peds.2015-1037>
 - 41 Sokuri P, Heikkilä P, Korppi M (2017) National high-flow nasal cannula and bronchiolitis survey highlights need for further research and evidence-based guidelines. *Acta Paediatr Int J Paediatr* 106: 1998–2003. <https://doi.org/10.1111/apa.13964>
 - 42 Tapiainen T, Aittoniemi J, Immonen J et al. (2016) Finnish guidelines for the treatment of laryngitis, wheezing bronchitis and bronchiolitis in children. *Acta Paediatr* 105:44–49. <https://doi.org/10.1111/apa.13162>
 - 43 Teunissen J, Hochs AH, Vaessen-Verberne A et al (2014) The effect of 3% and 6% hypertonic saline in viral bronchiolitis: a randomised controlled trial. *Eur Respir J* 44:913–921. <https://doi.org/10.1183/09031936.00159613>
 - 44 Thia LP, McKenzie SA, Blyth TP et al (2008) Randomised controlled trial of nasal continuous positive airways pressure (CPAP) in bronchiolitis. *Arch Dis Child* 93:45–47
 - 45 Turner T, Wilkinson F, Harris C, Mazza D, Health for Kids Guideline Development Group (2008) Evidence based guideline for the management of bronchiolitis. *Aust Fam Physician* 37:6–13
 - 46 van Woensel JB, Vyas H, Group ST (2011) Dexamethasone in children mechanically ventilated for lower respiratory tract infection caused by respiratory syncytial virus: a randomized controlled trial. *Crit Care Med* 39:1779–1783. <https://doi.org/10.1097/CCM.0b013e318218a030>
 - 47 Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP (2013) Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane database Syst Rev* (7):CD006458. doi: <https://doi.org/10.1002/14651858.CD006458.pub3>