


GUIDELINES



Clinical practice guidelines: management of severe bronchiolitis in infants under 12 months old admitted to a pediatric critical care unit

Christophe Milési^{1*} , Florent Baudin², Philippe Durand³, Guillaume Emeriaud⁴, Sandrine Essouri⁵, Robin Pouyau², Julien Baleine¹, Sophie Beldjilali⁶, Alice Bordessoule⁷, Sophie Breinig⁸, Pierre Demaret⁹, Philippe Desprez¹⁰, Bénédicte Gaillard-Leroux¹¹, Julie Guichoux¹², Anne-Sophie Guilbert¹³, Camille Guillot¹⁴, Sandrine Jean¹⁵, Michael Levy¹⁶, Odile Noizet-Yverneau¹⁷, Jérôme Rambaud¹⁵, Morgan Recher¹⁴, Stéphanie Reynaud², Frédéric Valla², Karim Radoui¹⁸, Marie-Agnes Faure¹⁹, Guillaume Ferraro²⁰ and Guillaume Mortamet²¹ on behalf of the French Speaking Group for Pediatric Intensive and Emergency Care

© 2022 Springer-Verlag GmbH Germany, part of Springer Nature

Abstract

Purpose: We present guidelines for the management of infants under 12 months of age with severe bronchiolitis with the aim of creating a series of pragmatic recommendations for a patient subgroup that is poorly individualized in national and international guidelines.

Methods: Twenty-five French-speaking experts, all members of the Groupe Francophone de Réanimation et Urgence Pédiatriques (French-speaking group of paediatric intensive and emergency care; GFRUP) (Algeria, Belgium, Canada, France, Switzerland), collaborated from 2021 to 2022 through teleconferences and face-to-face meetings. The guidelines cover five areas: (1) criteria for admission to a pediatric critical care unit, (2) environment and monitoring, (3) feeding and hydration, (4) ventilatory support and (5) adjuvant therapies. The questions were written in the Patient-Intervention-Comparison-Outcome (PICO) format. An extensive Anglophone and Francophone literature search indexed in the MEDLINE database via PubMed, Web of Science, Cochrane and Embase was performed using pre-established keywords. The texts were analyzed and classified according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. When this method did not apply, an expert opinion was given. Each of these recommendations was voted on by all the experts according to the Delphi methodology.

Results: This group proposes 40 recommendations. The GRADE methodology could be applied for 17 of them (3 strong, 14 conditional) and an expert opinion was given for the remaining 23. All received strong approval during the first round of voting.

*Correspondence: c-milesi@chu-montpellier.fr

¹ Pediatric Intensive Care Unit, Montpellier University Hospital, Montpellier, France

Full author information is available at the end of the article

Conclusion: These guidelines cover the different aspects in the management of severe bronchiolitis in infants admitted to pediatric critical care units. Compared to the different ways to manage patients with severe bronchiolitis described in the literature, our original work proposes an overall less invasive approach in terms of monitoring and treatment.

Keywords: Bronchiolitis, Guidelines, Recommendation, Noninvasive ventilation, High-flow nasal cannula, Pediatric intensive care

Introduction

Bronchiolitis is a common lung infection in young children and infants. Every year, a large proportion of infants is affected [1–3]. Approximately one-tenth of these children is admitted [3], and between 2 and 6% of them present a severe form and are referred to pediatric intensive care units (PICUs) [1, 2, 4, 5]. In contrast to the mild to moderate forms, the management of this subgroup of patients is poorly codified by national [6] and international [7, 8] recommendations.

The definition of severe acute bronchiolitis is mainly clinical and based on low levels of evidence. In this work, we chose severity criteria from the English, Canadian and Australasian recommendations [7–9] remodeled in the French recommendations from the Haute Autorité de Santé (HAS) 2019 [6]. The presence of at least one of the following criteria defines severe bronchiolitis: poor general appearance, heart rate $>180/\text{min}$ or $<80/\text{min}$, respiratory rate $>70/\text{min}$ or $<30/\text{min}$ or apneas, chest recessions and/or nasal flaring, poor food intake ($<50\%$ in the previous 12 h), and $\text{SpO}_2 < 90\%$ on room air.

Many of the patients who meet the criteria for severe illness are admitted to intensive care units. The purpose of this work is to provide a set of recommendations for the population of infants under 12 months of age who are admitted to these units. This initial management proposal should be adapted according to the infant's condition and evolution, as flexibility is a key feature of the working method used by the experts involved in developing the recommendations. In general, the paucity of high-quality studies in this field suggested the need to proceed with great humility in drafting them. It should also be noted that when a patient meets the diagnostic criteria for acute respiratory distress syndrome, readers should follow those specific recommendations [10, 11].

In this context, the Groupe Francophone de Réanimation et Urgence Pédiatriques (French-speaking group of paediatric intensive and emergency care; GFRUP) has formalized expert recommendations on the management of acute severe bronchiolitis in infants under 12 months of age admitted to a PICU (Table 1). They are based on the analysis of the literature that targets this population and on the recommendations of expert representatives

Take-home message

The GFRUP group presents a guideline of 40 recommendations regarding the management of infants under 12 months of age with severe bronchiolitis. Compared to the different ways to manage patients with severe bronchiolitis described in the literature, our original work proposes an overall less invasive approach in terms of monitoring and treatment.

of the diversity of French-speaking ICUs. As no experts come from low-income countries, the implementation of these recommendations should be discussed and adapted to the particular conditions of these countries.

Methods





































These guidelines were drawn up by a group of experts convened by the GFRUP. The work has been registered on PROSPERO (number CRD42021236932). The group's agenda was defined beforehand. The organizing committee first identified five domains of expertise (1) intensive care admission criteria, (2) environment and monitoring, (3) feeding and hydration, (4) ventilatory support, and (5) adjuvant therapies) and designated five expert-leaders (FB, RP, PD, SE, and GE). Within each expert group, the questions to be addressed were defined and validated by the experts. The questions were formulated according to a Patient-Intervention-Comparison-Outcome (PICO) format. The literature was analyzed, and the guidelines were formulated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology [12]. SJ served as methodologist. A level of evidence was defined for each bibliographic reference cited according to the type of study, and this level of evidence could be reassessed in light of the methodological quality of the study. An overall level of proof was determined for each criterion, taking into account the level of evidence of each bibliographic reference, the between-study consistency of the results, the direct or indirect nature of the results, and cost analysis.

A high overall level of proof led to a “strong” recommendation (should be done: GRADE 1+, should not be done: GRADE 1–). A moderate, low, or very low overall level of proof led to a “conditional” recommendation (should probably be done: GRADE 2+, should probably

Table 1 2022: Table of recommendations

		R01 The experts suggest that the following severity factors be considered when deciding on PICU admission: - Presence of apneas - Hypercapnic acidosis with venous $p\text{CO}_2 > 60$ mmHg and/or $\text{pH} < 7.30$ if blood gas testing is available - Altered alertness and/or hypotonia - Hypoxemia with $\text{SpO}_2 < 92\%$ under standard oxygen therapy (i.e., nasal cannulas at low-flow up to 2 L/min) - Significant increase in clinical work of breathing or respiratory fatigue For patients already hospitalized, dynamic assessment of these parameters is important to consider		EXPERT OPINION
		R02 When available, additional factors that should probably be considered as risk factors for intensive care admission are: - History of prematurity especially if < 32 weeks of amenorrhea - Age below 6 weeks - Identification of respiratory syncytial virus (RSV) as opposed to other viruses - Evidence of viral or bacterial co-infection - Presence of atelectasis or consolidation on radiography (if performed, see R6 recommendation) or lung ultrasound (posterior consolidation > 1 cm and/or high lung ultrasound score)		NO RECOMMENDATION
		R03 The experts suggest the use of clinical scores for the initial patient assessment and follow-up		GRADE 1-
		R04 Virological identification tests should probably not be performed		GRADE 1
		R05 The experts suggest that serum sodium level should not be systematically checked. However, the test should be performed if there are clinical signs suggestive of hyponatremia (e.g., altered alertness)		GRADE 1+
		R06 The experts suggest that chest radiography should not be routinely performed, but should be reserved for patients with clinical signs of ventilatory complications or for the search for differential diagnosis		GRADE 2-
		R07 The experts suggest that lung ultrasound be performed as an alternative to chest radiography		GRADE 2
		R08 The experts cannot comment on the place given to blood gas testing in the initial assessment, although it is widely performed in practice. The experts suggest that clinical assessment should be the preferred method for judging the severity of the patient's condition		GRADE 2+
		R09 The experts suggest not systematically inserting a peripheral venous line		WEAK AGREEMENT
		R10 Patients should probably be placed in the supine position (except for patients supported by invasive ventilation). Studies on prone positioning are needed		STRONG AGREEMENT
		R11 The experts suggest monitoring the trend of respiratory parameters and/or clinical scores to assess disease evolution		
		R12 The experts suggest that $p\text{CO}_2$ (and PtcCO_2) should not be systematically monitored		
		R13 The experts suggest that gastric enteral nutrition (or oral nutrition when possible) should be preferred to intravenous hydration, regardless of the type of ventilatory support		
		R14 There is no evidence to support continuous enteral nutrition over discontinuous nutrition		
		R15 The experts suggest that oral or enteral nutrition should not be thickened		

Table 1 (continued)

		R16 The experts suggest that the recommendations for energy and protein intake in the critically ill infant be implemented
		R17 When enteral feeding is not possible, the experts suggest using an isotonic rather than a hypotonic solution. There is no evidence for choosing a balanced isotonic solution over an unbalanced solution
		R18 The experts suggest monitoring the fluid balance (input/output balance and/or weight) on a daily basis to avoid fluid overload
		R19 The experts suggest the use of a noninvasive ventilatory support protocol
		R20 Noninvasive ventilatory support is effective to reduce the work of breathing and improve clinical respiratory parameters
		R21 The experts suggest noninvasive ventilatory support as a first-line treatment rather than invasive ventilation
		R22 For the most severe form, continuous positive airway pressure should probably be used as the first-line treatment rather than high-flow nasal cannula
		R23 Continuous positive airway pressure should probably be initiated at a positive pressure level of 7 cmH ₂ O
		R24 The experts suggest the use of noninvasive ventilation with two pressure levels in cases of failure of continuous positive pressure and in the absence of intubation criteria
		R25 The choice of interface should take into account the ventilator being used and the expertise of the medical team. The experts are not in a position to suggest a specific type of interface for patients ventilated with continuous positive airway pressure. In cases of failure, the experts suggest the use of a face mask to improve patient-ventilator synchronization
		R26 The high-flow nasal cannula should not be used prophylactically to reduce the risk of admission to the PICU
		R27 A flow rate of 1.5–2 L/kg/min should probably be initiated with high-flow nasal cannula and should not exceed 2 L/kg/min
		R28 The experts are not able to make a recommendation regarding the choice of invasive ventilation mode
		R29 Noninvasive ventilatory support (continuous positive airway pressure or nasal high flow) should probably be used during patient transport. If a high-flow nasal cannula is used, a humidification heating system should be used. The experts do not recommend routine intubation for transport.
		R30 The experts suggest that non-medicinal measures (parental presence, installation, optimization of the interface and ventilation, feeding) should be preferred to improve the infant's comfort. If these measures fail, drug sedation may be used
		R31 Corticosteroids, whether inhaled or systemic, should probably not be used
		R32 Inhaled beta2-agonists and/or inhaled epinephrine should probably not be used routinely. In some cases, a therapeutic test could be considered to avoid intubation
		R33 The experts suggest that intravenous beta2-agonists should not be used



































	EXPERT OPINION
	NO RECOMMENDATION
	GRADE 1-
	GRADE 1
	GRADE 1+
	GRADE 2-
	GRADE 2
	GRADE 2+
	WEAK AGREEMENT
	STRONG AGREEMENT

Table 1 (continued)

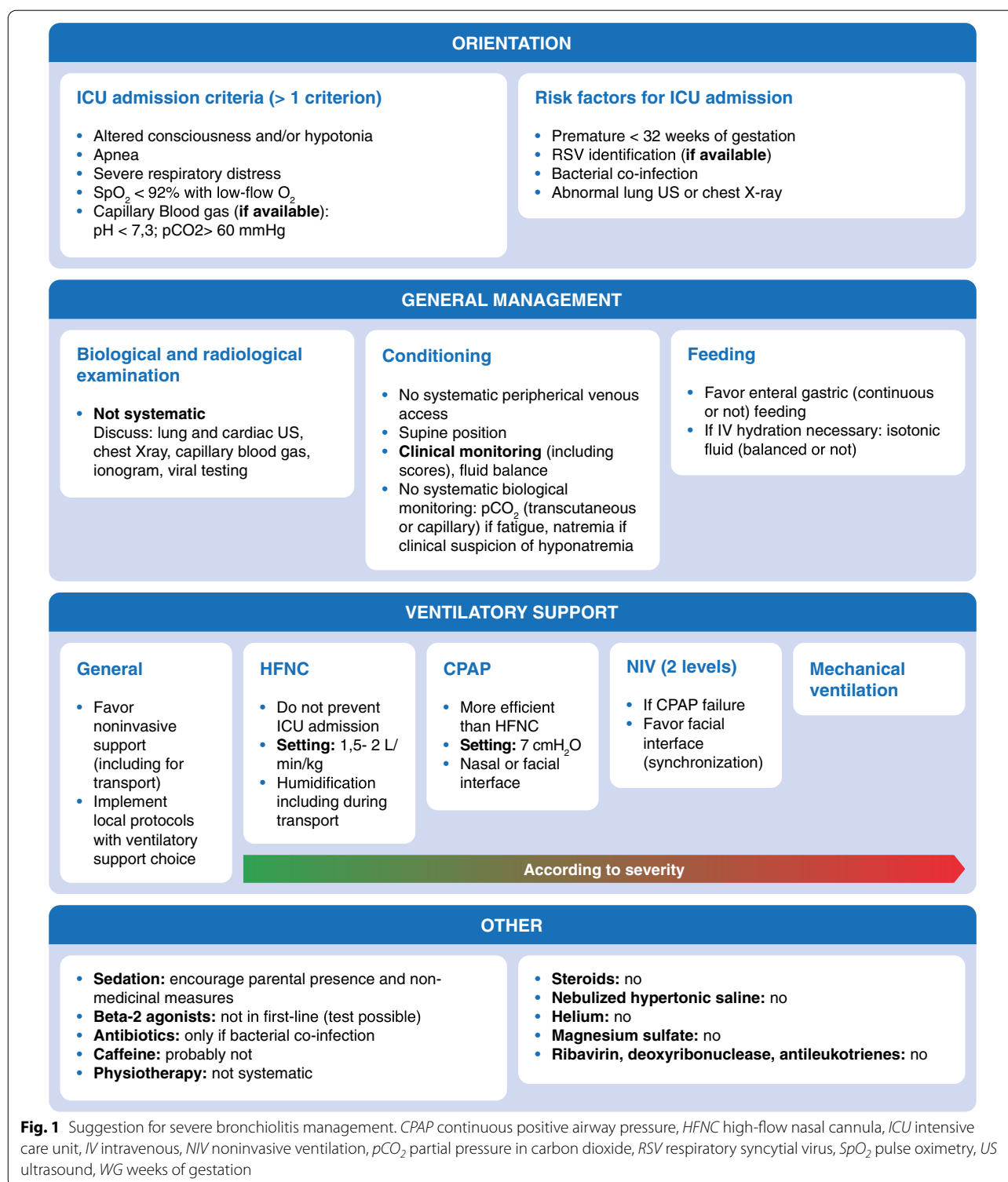
		R34	Intravenous theophylline should not be used
		R35	The experts suggest that antibiotic therapy should not be systematically used but should be reserved for suspected pulmonary superinfection or bacterial co-infection
		R36	Caffeine should probably not be used routinely in patients presenting with apnea
		R37	Helium should probably not be used. Despite the beneficial effects on the work of breathing, feasibility makes it difficult to implement
		R38	Nebulization of hypertonic saline should probably not be used routinely
		R39	Respiratory physiotherapy should probably not be systematically performed
		R40	Ribavirin, deoxyribonuclease (DNase), antileukotrienes, magnesium sulfate, and inhaled nitric oxide should probably not be used

 EXPERT OPINION
 NO RECOMMENDATION
 GRADE 1-
 GRADE 1
 GRADE 1+
 GRADE 2-
 GRADE 2
 GRADE 2+

 WEAK AGREEMENT
 STRONG AGREEMENT

not be done: GRADE 2— When the literature was inconsistent or insufficient, the response to a question was a recommendation in the form of an expert opinion (the

experts recommend...). The proposed recommendations were presented and discussed one-by-one by all the experts. Each expert then reviewed and anonymously



rated each recommendation using a scale of 1 (complete disagreement) to 9 (complete agreement). The collective rating was established using a GRADE grid. To approve a recommendation, at least 50% of the experts had to be in agreement and less than 20% in disagreement. For an

agreement to be strong, at least 70% of the experts had to be in agreement. In the absence of strong agreement, the recommendations were reformulated and rated again, with a view to reaching a consensus. Only expert opinions that elicited strong agreement were kept.

Literature search

A literature search was independently performed from MEDLINE databases via PubMed, Web of Science, Cochrane, and Embase. To be included in the analysis, publications had to be written in English or French and published after 2000. The main search terms used were bronchiolitis and infant/child/pediatric. The detailed search strategy, including terms and the algorithm, is available in Supplementary Material 1. In the absence of data published after 2000, older references were checked and added exceptionally.

Results

These guidelines encompass 40 recommendations (3 strong, 14 conditional, 23 expert opinions). For two questions, no recommendation could be applied. After one round of scoring and amendments, strong agreement was reached for all recommendations, which are summarized in Fig. 1 and Table 1.

Recommendations

Intensive care admission criteria

Recommendation

R1—The experts suggest that the following severity factors be considered when deciding on PICU admission:

- Presence of apneas
- Hypercapnic acidosis with venous $p\text{CO}_2 > 60$ mmHg and/or $\text{pH} < 7.30$ if blood gas testing is available
- Altered alertness and/or hypotonia
- Hypoxemia with $\text{SpO}_2 < 92\%$ under standard oxygen therapy (i.e., nasal cannulas at low-flow up to 2 L/min)
- Significant increase in clinical work of breathing or respiratory fatigue

For patients already hospitalized, dynamic assessment of these parameters is important to consider (**expert opinion, strong agreement**)

Rationale

The literature mainly comprises retrospective data whose interpretations have been impacted by the significant changes in the management of severe bronchiolitis in recent years.

The clinical elements that seem to indicate the need for intensive care admission are the presence of apneas, hypoxemia and/or hypercapnia [13–18]. On the other hand, $p\text{CO}_2$ thresholds to indicate PICU admission or ventilatory support initiation remain heterogeneous. According to the main studies conducted in this population [19–31], the mean venous or capillary $p\text{CO}_2$ on admission is 59.6 mmHg for pH values < 7.30 . For the other clinical parameters (respiratory rate, heart rate, SpO_2), no threshold can be proposed.

Recommendation

R2—When available, additional factors that should probably be considered as risk factors for intensive care admission are:

- History of prematurity especially if < 32 weeks of amenorrhea
- Age below 6 weeks
- Identification of respiratory syncytial virus (RSV) as opposed to other viruses
- Evidence of viral or bacterial co-infection
- Presence of atelectasis or consolidation on radiography (if performed, see R6 recommendation) or lung ultrasound (posterior consolidation > 1 cm and/or high lung ultrasound score) (**GRADE 2+, strong agreement**)

Rationale

For the most part, the factors of vulnerability are similar to those in patients admitted to wards [6].

The factors that appear to be more specifically associated with PICU admission are a history of prematurity [16, 32–38], identification of respiratory syncytial virus (RSV) as opposed to other viruses [38, 39], evidence of viral or bacterial co-infection [39–41], and the presence of atelectasis or consolidation on chest radiography (only if available according to recommendation R6) [13, 14, 36]. Lung ultrasound has demonstrated its utility as a bedside tool to stratify risk, and a dedicated score (LUSBRO) based on previous findings in bronchiolitis and the neonate was created [42]. Posterior or paravertebral consolidation > 1 cm or lung derecruitment assessment using different ultrasound scores was associated with PICU admission [13, 14, 36, 43–46].

The international guidelines emphasize the fragility linked to certain pathologies such as bronchopulmonary dysplasia, congenital heart disease with hemodynamic effects (shunt), neuromuscular pathologies, and immune deficiencies [7–9].

Recommendation

R3—The experts suggest the use of clinical scores for the initial patient assessment and follow-up (**Expert opinion, strong agreement**)

Rationale

The multiplicity of parameters to be considered when deciding on PICU admission justifies the use of scores. Although most of the scores are not specific to severe bronchiolitis and cannot predict the need for or the duration of ventilatory support, they are widely used as outcome or inclusion criteria in studies because they may provide a more objective evaluation (and follow-up) by decreasing inter-individual subjectivity [20, 22, 47–50]. Among the scores identified, the modified Wood's

Clinical Asthma Score (mWCAS) [51] and the Wang score [52] appeared to be the most cited in the bronchiolitis studies, and the recent critical bronchiolitis score (CBS) [53] may be promising because it was developed specifically for severe bronchiolitis in the PICU.

Environment and monitoring

Paraclinical tests at the initial phase and during hospitalization

Recommendation

R4—Virological identification tests should probably not be performed (**GRADE 2—, strong agreement**)

Rationale

Although this criterion may be considered a risk factor for PICU admission, there is no evidence that virus identification provides an individual benefit regarding the disease course of RSV or other respiratory virus. There is also no evidence of a collective benefit of virological screening that would allow zoning of patients to avoid viral spread [54, 55]. Nevertheless, the identification of a virus can sometimes rule out differential diagnoses. It can also have epidemiological significance.

Recommendation

R5—The experts suggest that serum sodium level should not be systematically checked. However, the test should be performed if there are clinical signs suggestive of hyponatremia (e.g., altered alertness) (**Expert opinion, strong agreement**)

Rationale

Although hyponatremia is common in patients admitted with acute bronchiolitis [56, 57], there are no studies in this area. This recommendation is consistent with the Australian and American recommendations [8, 55].

Recommendation

R6—The experts suggest that chest radiography should not be routinely performed, but should be reserved for patients with clinical signs of ventilatory complications or for the search for differential diagnosis (**Expert opinion, strong agreement**)

Rationale

Although many children have radiographic chest abnormalities, these do not correlate with disease severity, although one retrospective study suggested an association between initial atelectasis and severity [58]. Fever was shown to be a good predictor of radiographic abnormalities [59]. On the other hand, it seems that the abnormalities identified on radiography are associated with a

greater prescription of antibiotics without improving the course of the disease [60].

Recommendation

R7—The experts suggest that lung ultrasound be performed as an alternative to chest radiography (**Expert opinion, strong agreement**)

Rationale

Regarding lung ultrasound as a diagnostic tool, several clinical studies—recently quoted in the evidence-based guidelines from the POCUS Working Group of the European Society of Pediatric and Neonatal Critical Care (ESPNIC)—strongly suggested that the lung ultrasound score is helpful for descriptive purposes in viral bronchiolitis, with good concordance between operators [44, 61]. Two prospective observational studies strongly suggested that, unlike the chest X-ray, a high value of the lung ultrasound score recruitment score might well predict PICU admission and/or the need for respiratory support [42, 43].

Recommendation

R8—The experts cannot comment on the place given to blood gas testing in the initial assessment, although it is widely performed in practice. The experts suggest that clinical assessment should be the preferred method for judging the severity of the patient's condition (**Expert opinion, strong agreement**)

Rationale

However, if blood gas testing is performed, we suggest capillary sampling, which is easier to perform and less painful than arterial sampling, given that the measurement of pH and pCO₂ is reliable and well correlated with arterial sampling [62].

Patient conditioning and installation

Recommendation

R9—The experts suggest not systematically inserting a peripheral venous line (**Expert opinion, strong agreement**)

Rationale

Practice studies show a rate of peripheral venous line placement in 38–93% of the patients admitted to PICUs [55, 63, 64]. However, no comparative study has examined the management of severe bronchiolitis with and without peripheral venous access. The randomized trial published by Oakley et al. considered all forms of bronchiolitis regardless of severity [65].

The use of a peripheral venous line could be considered in cases of severe bronchiolitis with a probable need for hydration and/or intravenous drug therapy or in cases of emergency.

Recommendation

R10—Patients should probably be placed in the supine position (except for patients supported by invasive ventilation). Studies on prone positioning are needed (**GRADE 2—, strong agreement**)

Rationale

Given the recommendations for the prevention of unexpected infant death and in the absence of data on the potential benefit of prone positioning, HAS 2019 recommends that infants with bronchiolitis be placed in bed flat on their back [6]. There is no evidence to justify a different recommendation for infants with severe bronchiolitis, apart from patients on invasive ventilation who should be positioned on their back with 30°–60° inclination, which is similar to the adult recommendations [66].

A physiological study compared prone versus supine positioning in children with severe bronchiolitis with noninvasive ventilatory support [67]. This study concluded that there is a probable benefit of the prone position, as it significantly improves the work of breathing. An ongoing study should identify a potential benefit of prone position in terms of ventilation time and hospital length of stay (NCT 03976895).

Patient follow-up and monitoring

Recommendation

R11—The experts suggest monitoring the trend of respiratory parameters and/or clinical scores to assess disease evolution (**Expert opinion, strong agreement**)

Rationale

Management of infants with acute severe bronchiolitis requires monitoring of respiratory (SpO₂, respiratory rate) and hemodynamic (heart rate, blood pressure) parameters [53, 55, 68]. Studies performed on patients with severe bronchiolitis use these parameters as criteria of judgment and the evolution of these parameters as a factor of the failure or success of a treatment, suggesting their consideration for the clinical monitoring of patients [69, 70]. Similarly, clinical scores are used to assess the evolution of the disease and the effectiveness of management and/or therapy [69, 71, 72].

Recommendation

R12—The experts suggest that pCO₂ (and PtcCO₂) should not be systematically monitored (**Expert opinion, strong agreement**)

Rationale

Increased pCO₂ appears to be a risk factor for transfer to the PICU and also helps assess disease progression [69, 73]. Notably, pCO₂ has been shown to be a factor associated

with high-flow nasal cannula (HFNC) failure [28, 74, 75]. However, no studies have compared routine pCO₂ monitoring versus no monitoring on patient outcome improvement.

Transcutaneous CO₂ measurement (PtcCO₂) is feasible in clinical practice with good correlation with venous pCO₂, although it requires at least one blood gas [76]. In a prospective double-blind study, it was shown that PtcCO₂ did not have a significant predictive value for respiratory deterioration in patients [72].

The experts, therefore, suggest that pCO₂ should not be systematically monitored, but that its measurement should be reserved for cases of clinical deterioration.

Feeding and hydration

Nutrition

Recommendation

R13—The experts suggest that gastric enteral nutrition (or oral nutrition when possible) should be preferred to intravenous hydration, regardless of the type of ventilatory support (**Expert opinion, strong agreement**)

Rationale

Several studies have shown that enteral feeding compared with intravenous hydration during a fasting period does not increase the risk of gastric distension, vomiting, or aspiration, regardless of the type of ventilation [32, 65, 77–83]. A cohort study in children with noninvasive ventilatory support (with and without bronchiolitis) showed a very low incidence of inhalation pneumonitis (1.5%) [84]. Oral or enteral feeding compared with fasting or interrupted feeding is also associated with a reduction in the hospital length of stay [65, 78, 79, 85], which is in line with recent European recommendations (ESPNIC) [86]. Despite the lack of data, oral nutrition may be associated with a higher risk of inhalation than gastric nutrition, especially for patients with an increased work of breathing.

However, it should be noted that most studies did not distinguish between hydration and oral/enteric nutrition *versus* intravenous hydration, which may make it difficult to interpret their results.

Recommendation

R14—There is no evidence to support continuous enteral nutrition over discontinuous nutrition (**No recommendation, strong agreement**)

Rationale

No studies have evaluated the superiority of continuous gastric administration over the discontinuous mode. The

comparison is only valid for the gastric route because the choice of the transpyloric route requires a continuous flow [87–89]. Practices remain heterogeneous in this area [83, 87, 90].

Recommendation

R15—The experts suggest that oral or enteral nutrition should not be thickened (**Expert opinion, strong agreement**)

Rationale

No clinical studies have evaluated the effect of routine thickening of oral nutrition in infants with bronchiolitis. In patients supported by noninvasive or invasive ventilation, no studies have evaluated the thickening of enteral nutrition. The increased viscosity and osmolarity of thickened nutrition could potentially increase the risk of tube obstruction and affect gastric emptying time, which is already impaired in critically ill children.

Recommendation

R16—The experts suggest that the recommendations for energy and protein intake in the critically ill infant be implemented (**Expert opinion, strong agreement**)

Rationale

Fortified nutrition has been shown to achieve significantly higher energy and protein targets, but at the same time it increases the risk of overnutrition [88, 91]. A retrospective study showed a positive association between protein intake and hospital length of stay and ventilation [92]. Nevertheless, these results need to be kept in perspective because of numerous biases, and they are also at odds with the results of larger studies conducted in general intensive care populations [93, 94].

Thus, to date, in the absence of strong scientific evidence, the nutritional strategy proposed to patients with severe bronchiolitis may be identical to that recommended for critically ill children [86]. Pragmatically, intubated and sedated infants could be fed through a gastric tube with their usual milk (breast milk or formula adapted to the age and possible history), aiming at about 65% of the nutritional references for the population, i.e., about 65 kcal/kg/day, as the Schofield equations are unreliable for this weight range. If water restriction is necessary, fortification of breast milk or the use of infant formula pre-enriched in energy and protein would help limit enteral water intake without compromising nutritional objectives. No studies have assessed the energy requirements of infants but, based on expert opinion, continuous enteral nutrition on a gastric tube could be proposed for infants supported by noninvasive ventilation, with a target of

85–100 kcal/kg/day (or 120–130 mL/kg/day of formula). The total energy expenditure is probably less reduced in these infants compared to those on invasive ventilation support. Intakes could be increased later during the recovery phase according to the observed weight loss.

Hydration

Recommendation

R17—When enteral feeding is not possible, the experts suggest using an isotonic rather than a hypotonic solution. There is no evidence for choosing a balanced isotonic solution over an unbalanced solution (**Expert opinion, strong agreement**)

Rationale

Infants with bronchiolitis are at risk of hyponatremia [57], which may be increased by administration of hypotonic solution [56, 95].

In patients admitted for bronchiolitis, hyponatremia is associated with a poorer outcome, including longer hospital stay and increased risk of mechanical ventilation [96].

For this reason, and although no randomized controlled trials have compared the two types of intravenous fluids in infants admitted to the PICU for bronchiolitis, it seems reasonable to use isotonic intravenous fluids as a maintenance infusion in children for whom enteral nutrition is not possible or has been delayed, in accordance with American and British recommendations [7, 97].

Furthermore, the superiority of a balanced crystalloid solution over an unbalanced solution has not been evaluated. The potentially deleterious effects of isotonic saline put forward as a reason for preferring balanced solutions relate primarily to their use as a vascular filling solution in the perioperative period or in states of shock, and not as a maintenance solution.

Recommendation

R18—The experts suggest monitoring the fluid balance (input/output balance and/or weight) on a daily basis to avoid fluid overload (**Expert opinion, strong agreement**)

Rationale

In patients with bronchiolitis, fluid overload at 24 h of admission is associated with increased duration of mechanical ventilation, as well as longer ICU and hospital length of stay, regardless of the route of fluid administration (enteral or intravenous) [31].

Children admitted to intensive care are also at risk of energy and protein deficits, particularly because of a deficit in nutritional intake that is exacerbated by the associated fluid restriction [98]. However, in a pilot study

including 23 children ventilated for respiratory infection, a strategy of restricted fluid intake was feasible without limiting protein and caloric intake compared to a more liberal strategy [99].

To our knowledge, no randomized controlled trial has evaluated the value of monitoring fluid balance in children admitted to a PICU for bronchiolitis.

Ventilatory support

Recommendation

R19—The experts suggest the use of a noninvasive ventilatory support protocol (**Expert opinion, strong agreement**)

Rationale

Four “before-and-after” studies specifically evaluated the value of implementing a protocol for HFNC use in the PICU [26, 28, 100, 101]. The results are homogeneous and these studies, although retrospective, confirm the positive impact of using the protocol on patient outcome [102, 103].

Noninvasive ventilation

Recommendation

R20—Noninvasive ventilatory support is effective to reduce the work of breathing and improve clinical respiratory parameters (**GRADE 1 + , strong agreement**)

Rationale

Data from eight studies (four on continuous positive airway pressure, CPAP [19, 21, 25, 104] and four on high-flow nasal cannula, HFNC [105–108]) are convergent and show a significant and lasting reduction in the markers of respiratory failure (respiratory frequency, $p\text{CO}_2$) and work of breathing (esophageal pressure–time product) with noninvasive ventilatory support.

A physiological study [25] evaluated different levels of positive airway pressure and showed greater effectiveness in terms of reduction in the work of breathing with a CPAP setting of 7 cmH_2O . With regard to HFNC, the work by Milési et al. and Weiler et al. showed that the physiological impact was greater when the flow was close to 2 L/kg/min [105, 108].

Recommendation

R21—The experts suggest noninvasive ventilatory support as a first-line treatment rather than invasive ventilation (**Expert opinion, strong agreement**)

Rationale

The widespread use of noninvasive ventilatory support as the first-line therapy for managing bronchiolitis reinforces this recommendation despite the lack of strong data [30]. Nowadays, randomized studies comparing noninvasive support versus intubation at the outset are no longer ethically conceivable in view of the good tolerance of CPAP, noninvasive ventilation (NIV) and HFNC described in the literature. It is probably for this reason that there are no randomized prospective studies comparing noninvasive support versus intubation.

One retrospective study showed that management was less invasive and ICU length of stay was shorter in children supported by CPAP compared with intubated patients [109], which has been supported by the results from other studies [110–112]. Two other studies, retrospective and with a limited number of patients, did not show a more rapid clinical improvement in patients who received CPAP or NIV compared with patients who were initially intubated [29, 113].

There are no studies comparing the use of HFNC with invasive ventilation.

Recommendation

R22—For the most severe form, continuous positive airway pressure should probably be used as the first-line treatment rather than high-flow nasal cannula (**GRADE 2 + , strong agreement**)

Rationale

Four randomized controlled trials in the literature compared the efficacy and safety of HFNC versus CPAP. In the largest one, Milési et al. found a higher failure rate of HFNC (51 versus 31%) in a multicenter study [20]. In this work, it is important to note that a large majority of the CPAP failures was explained by poor tolerance of the device, whereas in the HFNC group, support failure was mainly due to respiratory deterioration.

The other three studies, of small size and with variable criteria of judgment, did not confirm these results [71, 114, 115], which explains the conclusions of a recent meta-analysis on this question [116].

Recommendation

R23—Continuous positive airway pressure should probably be initiated at a positive pressure level of 7 cmH₂O (**GRADE 2+, strong agreement**)

Rationale

Only one physiological study evaluating different levels of positive pressure demonstrated greater efficacy for a CPAP setting of 7 cmH₂O [25]. But most data on bronchiolitis in the PICU were based on levels of pressure support close to 7 cmH₂O, with significant efficiency and a low adverse effect rate.

Recommendation

R24—The experts suggest the use of noninvasive ventilation with two pressure levels in cases of failure of continuous positive pressure and in the absence of intubation criteria (**Expert opinion, strong agreement**)

Rationale

There are no studies in the literature that randomly compare two levels of pressure in NIV to another noninvasive ventilation modality. The data are limited to three retrospective studies evaluating the risk factors for failure using this mode [27, 117, 118]. These studies highlight that this technique can be used as initial support or as rescue, with greater efficiency in terms of the reduction in oxygen requirements compared to CPAP [117]. However, we cannot specifically recommend two pressure levels of ventilation. Delacroix et al. suggested that the use of NIV at two pressure levels could be associated with unfavorable outcomes, but the retrospective design of the study makes the interpretation of these results difficult [27].

Recommendation

R25—The choice of interface should take into account the ventilator being used and the expertise of the medical team. The experts are not in a position to suggest a specific type of interface for patients ventilated with continuous positive airway pressure. In cases of failure, the experts suggest the use of a face mask to improve patient-ventilator synchronization (**Expert opinion, strong agreement**)

Rationale

A European survey of practice showed that the face mask was widely used [119]. However, only two small single-center randomized controlled trials [120, 121] compared two types of CPAP interfaces. The first compared the helmet versus the face mask, the second the helmet versus nasal cannulas. In both trials, there was no difference in terms of respiratory physiological parameters or failure, but there seemed to be more discomfort with a face mask.

Last, two retrospective studies evaluated the feasibility and predictors of failure of the cannula interface and nasopharyngeal tubes in different noninvasive ventilatory modes [122, 123], but these two studies did not compare these interfaces to others. Patient comfort and tolerance should be important factors in the choice of the interface.

High-flow nasal cannula

Recommendation

R26—The high-flow nasal cannula should not be used prophylactically to reduce the risk of admission to the PICU (**GRADE 1-, strong agreement**)

Rationale

Two large randomized control studies failed to demonstrate the benefit of prophylactic HNFC to avoid admission in PICU [124, 125]. This was confirmed by a recent meta-analysis that evaluated the impact of using HFNC to manage bronchiolitis outside of the PICU on short-term patient outcomes [116]. On the admission to PICU outcome, they reported 1127 patients in the HFNC group and 1096 patients in the standard oxygen therapy group and no significant difference in PICU admissions (OR=1.1 [0.81–1.42]). Despite some superiority of HFNC in terms of treatment failure on the wards, most data suggest that prophylactic use of HNFC does not modify the underlying disease process in moderately severe bronchiolitis [116, 126].

Recommendation

R27—A flow rate of 1.5–2 L/kg/min should probably be initiated with high-flow nasal cannula and should not exceed 2 L/kg/min (**GRADE 2+, strong agreement**)

Rationale

Physiological studies have demonstrated that the efficiency of HNFC to improve the work of breathing increases with a flow rate close to 2 L/kg/min [105–108]. A higher flow rate (3 L/kg/min versus 2L/kg/min) failed to demonstrate better efficiency and was associated with greater discomfort [22].

Invasive ventilation

Recommendation

R28—The experts are not able to make a recommendation regarding the choice of invasive ventilation mode (**No recommendation, strong agreement**)

Rationale

No randomized trials have evaluated the short-term outcome of infants intubated for bronchiolitis based on

ventilation mode, particularly for neurally adjusted ventilatory assist (NAVA) mode.

Transport and ventilator support

Recommendation

R29—Noninvasive ventilatory support (continuous positive airway pressure or nasal high flow) should probably be used during patient transport.
If a high-flow nasal cannula is used, a humidification heating system should be used.
The experts do not recommend routine intubation for transport (**GRADE 2+, strong agreement**).

Rationale

Several teams have reported their experience using non-invasive ventilatory support for transport of patients with bronchiolitis [127–132]. All the studies agreed on the safety of the technique during transport and a decreased use of invasive ventilation after PICU admission. Schlappbach et al. showed a significant reduction in the use of intubation for transport using HFNC without affecting intensive care management [130]. A review of the literature on the adverse effects of noninvasive ventilatory support for transport reported the need for intubation during transport in only 0.4% of cases and the use of invasive ventilation within 24 h of transport in 10% of cases ($n=63/650$). Other adverse events were anecdotal in this study [133].

Adjuvant therapies

Sedation

Recommendation

R30—The experts suggest that non-medicinal measures (parental presence, installation, optimization of the interface and ventilation, feeding) should be preferred to improve the infant's comfort. If these measures fail, drug sedation may be used (**Expert opinion, strong agreement**).

Rationale

The discomfort associated with noninvasive ventilatory support in infants with bronchiolitis is common [20, 22, 120, 121] and is the leading cause of ventilation failure [20, 120]. The presence and empowerment of the parents is encouraged in the PICU [134]. No randomized study has investigated the value of sedation in improving the efficacy and tolerance of noninvasive support in this population. The use of hydroxyzine [20, 22] and midazolam [120, 121] has been reported with good tolerance. In two pediatric cohorts (including 30% of patients with bronchiolitis), dexmedetomidine improved the tolerance of noninvasive ventilatory support at the cost of

mild side effects such as bradycardia and hypo/hypertension, which resolved when the dosage was reduced [135, 136]. Mild sedation that does not impair airway patency, respiratory drive or muscle strength could, therefore, be of interest to optimize the efficacy of noninvasive ventilatory support in cases of failure of non-drug measures.

Place of corticosteroids

Recommendation

R31—Corticosteroids, whether inhaled or systemic, should probably not be used (**GRADE 2, strong agreement**).

Rationale

In 2013, a Cochrane review showed that there was no benefit to the use of corticosteroids regarding hospital length of stay [137]. Importantly, the data did not include patients admitted to the PICU.

In our specific population, two studies were performed. The first, including 22 patients and comparing dexamethasone with placebo, showed no difference in cytokine concentration between the two groups, which would potentially explain the lack of a clinical benefit of corticosteroids [138]. The second study, evaluating the same molecule with a higher dose, was stopped prematurely because of a recruitment problem. It did not find any beneficial effect of corticosteroids in terms of duration of invasive ventilation or duration of hospitalization in intensive care [139].

Place of bronchodilators

Recommendation

R32—Inhaled beta2-agonists and/or inhaled epinephrine should probably not be used routinely. In some cases, a therapeutic test could be considered to avoid intubation (**GRADE 2–, strong agreement**).

Rationale

Only one study looked at patients admitted to the PICU [140]. In this small randomized controlled trial, the authors compared adrenaline, salbutamol and norepinephrine aerosols. The primary endpoint was the rate of hospitalization at day 7. No difference was found in any group compared with placebo.

Five randomized controlled studies compared nebulized epinephrine or beta2-agonists versus placebo [141–144]. No effect of these treatments was found on hospital length of stay, hospitalization rate, or clinical signs of respiratory distress.

Similarly, in a study comparing inhaled epinephrine with dexamethasone versus placebo, no significant effect on admission rate was found [145]. This was confirmed by the work by Kua et al. [146].

In two studies by the same team comparing adrenaline aerosol combined with 3% saline versus placebo combined with 3% saline, the results were contradictory for the main outcome, which was hospital length of stay [147, 148].

Recommendation

R33—The experts suggest that intravenous beta2-agonists should not be used (**Expert opinion, strong agreement**)

Rationale

We did not identify any studies evaluating the place of this therapy in our population.

Recommendation

R34—Intravenous theophylline should not be used (**GRADE 1–, strong agreement**)

Rationale

Only one randomized study on this issue was identified, by Turner et al. [149]. The authors compared continuous infusion of theophylline *versus* placebo in a population with bronchiolitis requiring ventilatory support. The trial was stopped early because of insufficient enrollment. However, the results obtained did not show a positive effect of theophylline in terms of the duration of ventilation required. It should also be noted that the adverse effects of this molecule are not negligible and that the therapeutic index is narrow.

Place of antibiotics

Recommendation

R35—The experts suggest that antibiotic therapy should not be systematically used but should be reserved for suspected pulmonary superinfection or bacterial co-infection (**Expert opinion, strong agreement**)

Rationale

Apart from severe forms of bronchiolitis, the use of antibiotics has not been shown to be of interest [150–153]. Bacterial infections are less frequent in infants with bronchiolitis than in infants with fever without bronchiolitis, but their incidence can reach 10–25% depending on the severity status [154–156]. Risk factors of bacterial infection in this population include the severity of the respiratory distress, higher general severity scores, and the need for invasive ventilation

and vasoactive agents [155, 157, 158], which explains the wide use of this class of drugs in this population [159]. However, the use of antibiotics is not without consequences [160] and should, therefore, be reserved for suspected pulmonary superinfection or bacterial co-infection.

If antibiotic therapy is warranted for suspected pulmonary superinfection, it is recommended that amoxicillin (100 mg/kg/day every 8 h) be used as the first-line therapy in the absence of microbiological documentation, taking into account the child's clinical data.

Place of caffeine in bronchiolitis with apnea

Recommendation

R36—Caffeine should probably not be used routinely in patients presenting with apnea (**GRADE 2–, strong agreement**)

Rationale

Apneas are frequent in this population [161], and caffeine has sometimes been used, by analogy with apneas in preterm infants, although the pathophysiological mechanism of apneas in viral bronchiolitis is different. The biological plausibility of this intervention is not clear, and the data in the literature are limited. Of the four studies reviewed, the study of Alansari et al., with about 90 patients under four months of age, was the only one that was prospective and randomized [162]. This study did not find a beneficial effect of a single dose of 25 mg/kg of caffeine on the occurrence of apneas, the need for ventilatory support, or the duration of hospitalization. However, this study was criticized for the randomization technique and the subjective method of apnea detection.

The other three observational studies [163–165] involved small numbers of patients under three to 12 months of age, with doses ranging from 10 to 25 mg/kg of caffeine. These studies also concluded that there was no beneficial effect on the prevention of mechanical ventilation or the hospital length of stay.

In the absence of a prospective randomized multicenter study targeting the population under 2 months of age with a protocol including maintenance doses, it is nevertheless difficult to affirm the non-effectiveness of caffeine for the prevention or treatment of apneas in this population.

Place of helium

Recommendation

R37—Helium should probably not be used. Despite the beneficial effects on the work of breathing, feasibility makes it difficult to implement (**GRADE 2–, strong agreement**)

Rationale

In 2015, a Cochrane systematic review with meta-analysis evaluated the value of a helium–oxygen mixture (heliox) in severe bronchiolitis [166]. Seven randomized controlled trials were included in the systematic review, with a total of 447 infants with acute bronchiolitis. No beneficial effect was found in terms of use of ventilation (invasive or not), intubation rate, or PICU length of stay. On the other hand, a significant effect on clinical signs of respiratory work was observed. Subsequently, a single additional randomized trial was published [167], without modifying the conclusions of the meta-analysis. The clinical benefit observed at two hours was no longer observed at 24 h.

It should also be noted that the use of this therapy is complicated by its low availability in routine practice and its cost.

Place of inhaled hypertonic saline

Recommendation

R38—Nebulization of hypertonic saline should probably not be used routinely (**GRADE 2–, strong agreement**)

Rationale

Hypertonic serum nebulization has been studied in bronchiolitis because it can decrease epithelial edema and improve mucociliary transport. A Cochrane review [168] and a meta-analysis [169] compared hypertonic saline nebulization *versus* isotonic saline, with a beneficial effect of the hypertonic saline in a population of children with non-severe forms. Nevertheless, the level of evidence remains low due to a high level of statistical heterogeneity and a risk of selection bias for some of the included studies. The very heterogeneous results can be explained in part by differences in the frequency of administration and the concentration of hypertonic saline (3, 6 or 7%) that was tested.

These findings are in contrast to those of two randomized trials, which also excluded severe forms and found no benefit [170, 171].

Only one retrospective study focused on patients with a severe form [172]. The authors showed a trend toward a reduction in the duration of ventilatory support for patients ventilated on CPAP, but comparability of the groups was limited and the analyses were conducted in very small subgroups.

Place of respiratory physiotherapy

Recommendation

R39—Respiratory physiotherapy should probably not be systematically performed (**GRADE 2–, strong agreement**)

Rationale

Despite a potential benefit of respiratory physical therapy on tidal volume and oxygen requirements [173], a meta-analysis published in 2016 and including 12 prospective randomized studies concluded that none of the respiratory physical therapy techniques were efficacious regarding vital parameters or hospital length of stay [174].

The prospective randomized study by Gajdos et al. confirmed this finding in a population of 496 infants [175]. As some patients may respond to this therapy, a therapeutic trial may be acceptable (e.g., in cases with severe atelectasis or when nasopharyngeal de-obstruction is difficult). A prospective study, underway since 2020, is investigating the impact of individualized respiratory physiotherapy that may involve external vibratory devices on infants hospitalized for bronchiolitis (NCT04553822).

Place of ribavirin, DNase, antileukotrienes, magnesium sulfate, and inhaled nitric oxide

Recommendation

R40—Ribavirin, deoxyribonuclease (DNase), antileukotrienes, magnesium sulfate, and inhaled nitric oxide should probably not be used (**GRADE 2–, strong agreement**)

Rationale

Three randomized trials evaluating ribavirin were identified in the literature. The first suggested a reduction in the duration of ventilation, but with a particularly long ventilation time in the control group (10 days), which received potentially deleterious water aerosols as placebo [176]. The other two low-powered studies did not show any significant difference in ventilation and length of stay [177, 178]. It should be noted that ribavirin aerosols may cause complications, in particular obstruction of intubation tubes.

A Cochrane systematic review of deoxyribonuclease (DNase) use in moderate forms of bronchiolitis was published in 2012 [179]. No benefit was found, and the control group even had a shorter hospital length of stay and a more favorable course of respiratory symptoms. Since no studies have been performed specifically in patients with

severe bronchiolitis, the effect of DNase remains to be determined in this population.

Antileukotriene therapy has not been shown to be effective in mild to moderate acute bronchiolitis [4]. No studies have been performed in patients with severe bronchiolitis.

Regarding magnesium sulfate, we identified four randomized controlled studies evaluating its efficacy in which no positive effect was found in terms of length of hospitalization [180–182], although Kose et al. observed an improvement in respiratory symptoms [183].

We identified two randomized controlled studies from the same team comparing the effect of nitric oxide “pulses” versus placebo [184, 185]. No beneficial effect was identified for any of the endpoints, although a post hoc analysis showed a shorter duration of hospitalization in patients hospitalized for more than 24 h.

Future directions

These guidelines highlight a lack of high-level evidence regarding certain crucial points in the management of severe bronchiolitis. Some topics that may seem obvious in daily practice are nevertheless not so obvious in the current literature.

We, therefore, felt it necessary to consider the following research topics to allow the scientific community to take ownership of them and provide new evidence for future revision of these guidelines:

1. Intensive care admission criteria: validation of a clinical score to facilitate and standardize the severity rating and the initial orientation of the patient and to follow the response to the ventilatory support;
2. Environment and monitoring: validation of lung ultrasound in relation to the prognosis and evolution of the disease; pCO₂ measurement in relation to the severity rating, ventilation strategy and follow-up; assessment of patient positioning, in particular the prone position;
3. Feeding and hydration: interest of continuous versus discontinuous enteral nutrition, natremia monitoring and management of dysnatremia;
4. Ventilatory support: benefit of indication for two pressure levels in NIV (including BiPAP or NAVA) compared to CPAP in patients requiring NIV, rapid identification of patients who are failing on NIV, and the best strategy to wean the patient from noninvasive ventilatory support;
5. Adjuvant therapies: comparison of sedative approaches.

Conclusion

These guidelines cover the different aspects in the management of severe bronchiolitis in infants admitted to pediatric critical care units. Given the low overall level of evidence, most recommendations are either conditional or expert opinion. Compared to the different ways to manage patients with severe bronchiolitis described in the literature, our original work proposes an overall less invasive approach in terms of monitoring and treatment. Importantly, these guidelines are not in contradiction with the ESPNIC guidelines on respiratory support [11] or with the other guidelines dealing with all forms of bronchiolitis regardless of severity. Finally, this work is the first step before working on the implementation of these recommendations in daily practice.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1007/s00134-022-06918-4>.

Author details

¹ Pediatric Intensive Care Unit, Montpellier University Hospital, Montpellier, France. ² Pediatric Intensive Care Unit, Lyon Hospital Femme-Mère-Enfants, Bron, France. ³ Pediatric Intensive Care Unit, Bicêtre Hospital, Assistance Publique des Hôpitaux de Paris, Kremlin-Bicêtre, France. ⁴ Pediatric Intensive Care Unit, Sainte-Justine University Hospital, Montreal, Canada. ⁵ Pediatric Department, Sainte-Justine University Hospital, Montreal, Canada. ⁶ Pediatric Intensive Care Unit, La Timone University Hospital, Assistance Publique des Hôpitaux de Marseille, Marseille, France. ⁷ Pediatric Intensive Care Unit, Geneva University Hospital, Geneva, Switzerland. ⁸ Pediatric Intensive Care Unit, Toulouse University Hospital, Toulouse, France. ⁹ Intensive Care Unit, Liège University Hospital, Liège, Belgium. ¹⁰ Pediatric Intensive Care Unit, Point-à-Pitre University Hospital, Point-à-Pitre, France. ¹¹ Pediatric Intensive Care Unit, Nantes University Hospital, Nantes, France. ¹² Pediatric Intensive Care Unit, Bordeaux University Hospital, Bordeaux, France. ¹³ Pediatric Intensive Care Unit, Strasbourg University Hospital, Strasbourg, France. ¹⁴ Pediatric Intensive Care Unit, Lille University Hospital, Lille, France. ¹⁵ Pediatric Intensive Care Unit, Trousseau Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France. ¹⁶ Pediatric Intensive Care Unit, Robert Debré Hospital, Assistance Publique des Hôpitaux de Paris, Paris, France. ¹⁷ Pediatric Intensive Care Unit, Reims University Hospital, Reims, France. ¹⁸ Pneumology EHS Pediatric Department, Faculté de Médecine d'Oran, Canastel, Oran, Algeria. ¹⁹ Esquirol Library Hospices Civils de Lyon, Lyon, France. ²⁰ Pediatric Emergency Department, Nice University Hospital, Nice, France. ²¹ Pediatric Intensive Care Unit, Grenoble-Alpes University Hospital, Grenoble, France.

Declarations

Conflicts of interest

GM reports personal fees from Aerogen, outside the submitted work. RP reports personal fees from Adene, Aerogen, Resmed and Fisher Paykel, outside the submitted work. BG-L reports personal fees from Baxter and Novartis, outside the submitted work. FV reports personal fees from Baxter and Nutricia, outside the submitted work. GE reports personal fees from Getinge, outside the submitted work.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of

this article is solely governed by the terms of such publishing agreement and applicable law.

Received: 9 August 2022 Accepted: 13 October 2022

Published: 2 January 2023

References

- Mahant S, Parkin PC, Thavam T, Imsirovic H, Tuna M, Knight B et al (2022) Rates in bronchiolitis hospitalization, intensive care unit use, mortality, and costs from 2004 to 2018. *JAMA Pediatr* 176(3):270–279
- Gupta P, Beam BW, Rettiganti M (2016) Temporal trends of respiratory syncytial virus-associated hospital and ICU admissions across the United States. *Pediatr Crit Care Med* 17(8):e343–e351
- France SP (2021) Bilan de la surveillance hivernale 2020–2021
- Deshpande SA, Northern V (2003) The clinical and health economic burden of respiratory syncytial virus disease among children under 2 years of age in a defined geographical area. *Arch Dis Child* 88(12):1065–1069
- Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA Jr (2013) Trends in bronchiolitis hospitalizations in the United States, 2000–2009. *Pediatrics* 132(1):28–36
- Santé Had (2018) Prise en charge du premier épisode de bronchiolite aiguë chez le nourrisson de moins de 12 mois
- Ricci V, Delgado Nunes V, Murphy MS, Cunningham S, Guideline Development G, Technical T (2015) Bronchiolitis in children: summary of NICE guidance. *BMJ* 350:h2305
- O'Brien S, Borland ML, Cotterell E, Armstrong D, Babl F, Bauert P et al (2019) Australasian bronchiolitis guideline. *J Paediatr Child Health* 55(1):42–53
- Friedman JN, Rieder MJ, Walton JM, Canadian Paediatric Society ACCDT (2014) Hazardous Substances C. Bronchiolitis: Recommendations for diagnosis, monitoring and management of children one to 24 months of age. *Paediatr Child Health* 19(9):485–498
- Khemani RG, Smith LS, Zimmerman JJ, Erickson S, Pediatric Acute Lung Injury Consensus Conference G (2015) Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 16(5 Suppl 1):S23–40
- Kneyber MCJ, de Luca D, Calderini E, Jarreau PH, Javouhey E, Lopez-Herce J et al (2017) Recommendations for mechanical ventilation of critically ill children from the Paediatric Mechanical Ventilation Consensus Conference (PEMVECC). *Intensive Care Med* 43(12):1764–1780
- Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S et al (2004) Grading quality of evidence and strength of recommendations. *BMJ* 328(7454):1490
- Coskun Y, Saglam F, Mamal-Torun M, Akman I (2017) Risk factors for intensive care need in children with bronchiolitis: a case-control study. *Turk J Pediatr* 59(5):520–523
- Wang EE, Law BJ, Stephens D (1995) Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr* 126(2):212–219
- Mansbach JM, Piedra PA, Stevenson MD, Sullivan AF, Forgey TF, Clark S et al (2012) Prospective multicenter study of children with bronchiolitis requiring mechanical ventilation. *Pediatrics* 130(3):e492–500
- 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(3):268–272
- Ramos-Fernandez JM, Moreno-Perez D, Gutierrez-Bedmar M, Hernandez-Yuste A, Cordon-Martinez AM, Milano-Manso G, et al (2017) [Prediction of Severe Course in Infants with RSV Bronchiolitis under 6 Months. Spain]. *Rev Esp Salud Publica* 91
- Bueno-Campana M, Sainz T, Alba M, Del Rosal T, Mendez-Echevarria A, Echevarria R et al (2019) Lung ultrasound for prediction of respiratory support in infants with acute bronchiolitis: a cohort study. *Pediatr Pulmonol* 54(6):873–880
- Cambonie G, Milesi C, Jaber S, Amsallem F, Barbotte E, Picaud JC et al (2008) Nasal continuous positive airway pressure decreases respiratory muscles overload in young infants with severe acute viral bronchiolitis. *Intensive Care Med* 34(10):1865–1872
- Milesi C, Essouri S, Pouyau R, Liet JM, Afanetti M, Portefaix A 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(2):209–216
- Milesi C, Matecki S, Jaber S, Mura T, Jacquot A, Pidoux O et al (2013) 6 cmH₂O continuous positive airway pressure versus conventional oxygen therapy in severe viral bronchiolitis: a randomized trial. *Pediatr Pulmonol* 48(1):45–51
- Milesi C, Pierre AF, Deho A, Pouyau R, Liet JM, Guillot C et al (2018) A multicenter randomized controlled trial of a 3-L/kg/min versus 2-L/kg/min high-flow nasal cannula flow rate in young infants with severe viral bronchiolitis (TRAMONTANE 2). *Intensive Care Med* 44(11):1870–1878
- Mayordomo-Colunga J, Medina A, Rey C, Concha A, Los Arcos M, Menendez S (2010) Helmet-delivered continuous positive airway pressure with heliox in respiratory syncytial virus bronchiolitis. *Acta Paediatr* 99(2):308–311
- Mayordomo-Colunga J, Medina A, Rey C, Los Arcos M, Concha A, Menendez S (2009) Success and failure predictors of non-invasive ventilation in acute bronchiolitis. *An Pediatr (Barc)* 70(1):34–39
- Essouri S, Durand P, Chevret L, Balu L, Devictor D, Fauroux B et al (2011) Optimal level of nasal continuous positive airway pressure in severe viral bronchiolitis. *Intensive Care Med* 37(12):2002–2007
- Metge P, Grimaldi C, Hassid S, Thomachot L, Loundou A, Martin C et al (2014) Comparison of a high-flow humidified nasal cannula to nasal continuous positive airway pressure in children with acute bronchiolitis: experience in a pediatric intensive care unit. *Eur J Pediatr* 173(7):953–958
- Delacroix E, Millet A, Pin I, Mortamet G (2020) Use of bilevel positive pressure ventilation in patients with bronchiolitis. *Pediatr Pulmonol* 55(11):3134–3138
- Guillot C, Le Reun C, Behal H, Labreuche J, Recher M, Duhamel A et al (2018) First-line treatment using high-flow nasal cannula for children with severe bronchiolitis: applicability and risk factors for failure. *Arch Pediatr* 25(3):213–218
- Nizarali Z, Cabral M, Silvestre C, Abadeso C, Nunes P, Loureiro H et al (2012) Noninvasive ventilation in acute respiratory failure from respiratory syncytial virus bronchiolitis. *Rev Bras Ter Intensiva* 24(4):375–380
- Clayton JA, McKee B, Slain KN, Rotta AT, Shein SL (2019) Outcomes of children with bronchiolitis treated with high-flow nasal cannula or noninvasive positive pressure ventilation. *Pediatr Crit Care Med* 20(2):128–135
- Flores-Gonzalez JC, Valladares CM, Yun Castilla C, Mayordomo-Colunga J, Quesada SP, Martin Delgado CM et al (2019) Association of fluid overload with clinical outcomes in critically ill children with bronchiolitis: Bronquirolitis en la Unidad de Cuidados Intensivos Pediatricos (BRUCIP) Study. *Pediatr Crit Care Med* 20(3):e130–e136
- Oakley E, Chong V, Borland M, Neutze J, Phillips N, Krieser D et al (2017) Intensive care unit admissions and ventilation support in infants with bronchiolitis. *Emerg Med Australas* 29(4):421–428
- Naja Z, Fayad D, Khafaja S, Chamseddine S, Dbaiibo G, Hanna-Wakim R (2019) Bronchiolitis admissions in a lebanese tertiary medical center: a 10 years' experience. *Front Pediatr* 7:189
- Richard N, Komurian-Pradel F, Javouhey E, Perret M, Rajoharison A, Bagnaud A et al (2008) The impact of dual viral infection in infants admitted to a pediatric intensive care unit associated with severe bronchiolitis. *Pediatr Infect Dis J* 27(3):213–217
- Evans J, Marlais M, Abrahamson E (2012) Clinical predictors of nasal continuous positive airway pressure requirement in acute bronchiolitis. *Pediatr Pulmonol* 47(4):381–385
- Hervas D, Reina J, Yanez A, del Valle JM, Figuerola J, Hervas JA (2012) Epidemiology of hospitalization for acute bronchiolitis in children: differences between RSV and non-RSV bronchiolitis. *Eur J Clin Microbiol Infect Dis* 31(8):1975–1981
- Grimaldi M, Cornet B, Milou C, Gouyon JB (2002) Prospective regional study of an epidemic of respiratory syncytial virus (RSV) bronchiolitis. *Arch Pediatr* 9(6):572–580

38. 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(12):2004–2010
39. Ghazaly M, Nadel S (2018) Characteristics of children admitted to intensive care with acute bronchiolitis. *Eur J Pediatr* 177(6):913–920
40. Shmueli E, Goldberg O, Mei-Zahav M, Stafler P, Bar-On O, Levine H et al (2021) Risk factors for respiratory syncytial virus bronchiolitis hospitalizations in children with chronic diseases. *Pediatr Pulmonol* 56(7):2204–2211
41. Tsou P, Vadivelan A, Kovvuri M, Garg N, Thangavelu M, Wang Y et al (2020) Association between multiple respiratory viral infections and pediatric intensive care unit admission among infants with bronchiolitis. *Arch Pediatr* 27(1):39–44
42. Bobillo-Perez S, Sorribes C, Gebelli P, Lledo N, Castilla M, Ramon M et al (2021) Lung ultrasound to predict pediatric intensive care admission in infants with bronchiolitis (LUSBRO study). *Eur J Pediatr* 180(7):2065–2072
43. Supino MC, Buonsenso D, Scateni S, Scialanga B, Mesturino MA, Bock C et al (2019) Point-of-care lung ultrasound in infants with bronchiolitis in the pediatric emergency department: a prospective study. *Eur J Pediatr* 178(5):623–632
44. Gori L, Amendolea A, Buonsenso D, Salvadori S, Supino MC, Musolino AM et al (2022) Prognostic role of lung ultrasound in children with bronchiolitis: multicentric prospective study. *J Clin Med* 11(14):4233
45. Mongodi S, De Luca D, Colombo A, Stella A, Santangelo E, Corradi F et al (2021) Quantitative lung ultrasound: technical aspects and clinical applications. *Anesthesiology* 134(6):949–965
46. Loi B, Vigo G, Baraldi E, Raimondi F, Carnielli VP, Mosca F et al (2021) Lung ultrasound to monitor extremely preterm infants and predict bronchopulmonary dysplasia. A multicenter longitudinal cohort study. *Am J Respir Crit Care Med* 203(11):1398–1409
47. McCallum GB, Morris PS, Wilson CC, Versteegh LA, Ward LM, Chatfield MD et al (2013) Severity scoring systems: are they internally valid, reliable and predictive of oxygen use in children with acute bronchiolitis? *Pediatr Pulmonol* 48(8):797–803
48. Luo G, Nkoy FL, Gesteland PH, Glasgow TS, Stone BL (2014) A systematic review of predictive modeling for bronchiolitis. *Int J Med Inform* 83(10):691–714
49. Kadafi KT, Yuliarto S, Monica C, Susanto WP (2022) Clinical review of high flow nasal cannula and continuous positive airway pressure in pediatric acute respiratory distress. *Ann Med Surg (Lond)* 73:103180
50. Beal G, Barbier C, Thoret S, Rubio A, Bonnet M, Mazet R et al (2019) Nebulized hypertonic saline 3% for 1 versus 3 days in hospitalized bronchiolitis: a blinded non-inferiority randomized controlled trial. *BMC Pediatr* 19(1):417
51. Wood DW, Downes JJ, Lecks HI (1972) A clinical scoring system for the diagnosis of respiratory failure. Preliminary report on childhood status asthmaticus. *Am J Dis Child* 123(3):227–228
52. Wang EE, Milner RA, Navas L, Maj H (1992) Observer agreement for respiratory signs and oximetry in infants hospitalized with lower respiratory infections. *Am Rev Respir Dis* 145(1):106–109
53. Mount MC, Ji X, Kattan MW, Slain KN, Clayton JA, Rotta AT et al (2022) **Derivation and Validation of the Critical Bronchiolitis Score for the PICU.** *Pediatr Crit Care Med* 23(1):e45–e54
54. Stollar F, Alcoba G, Gervais A, Argiroffo CB (2014) Virologic testing in bronchiolitis: does it change management decisions and predict outcomes? *Eur J Pediatr* 173(11):1429–1435
55. Ralston SL, Lieberthal AS, Meissner HC, Alverson BK, Baley JE, Gadomski AM et al (2014) Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. *Pediatrics* 134(5):e1474–e1502
56. Hanna S, Tibby SM, Durward A, Murdoch IA (2003) Incidence of hyponatraemia and hyponatraemic seizures in severe respiratory syncytial virus bronchiolitis. *Acta Paediatr* 92(4):430–434
57. Al Shibli A, Abukhatir D, Al Kuwaiti N, Nouredin MB, Al Harbi M, Al Kaabi A et al (2016) Hyponatraemia and neurological complications in children admitted with bronchiolitis. *Paediatr Int Child Health* 36(3):175–180
58. Shaw KN, Bell LM, Sherman NH (1991) Outpatient assessment of infants with bronchiolitis. *Am J Dis Child* 145(2):151–155
59. Ecochard-Dugelay E, Beliah M, Perreux F, de Laveaucoupet J, Bouyer J, Epaud R et al (2014) Clinical predictors of radiographic abnormalities among infants with bronchiolitis in a paediatric emergency department. *BMC Pediatr* 14:143
60. Schuh S, Lalani A, Allen U, Manson D, Babyn P, Stephens D et al (2007) Evaluation of the utility of radiography in acute bronchiolitis. *J Pediatr* 150(4):429–433
61. Singh Y, Tissot C, Fraga MV, Yousef N, Cortes RG, Lopez J et al (2020) International evidence-based guidelines on Point of Care Ultrasound (POCUS) for critically ill neonates and children issued by the POCUS Working Group of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC). *Crit Care* 24(1):65
62. Zavorsky GS, Cao J, Mayo NE, Gabbay R, Murias JM (2007) Arterial versus capillary blood gases: a meta-analysis. *Respir Physiol Neurobiol* 155(3):268–279
63. Caffrey Osvald E, Clarke JR (2016) NICE clinical guideline: bronchiolitis in children. *Arch Dis Child Educ Pract Ed* 101(1):46–48
64. Macias CG, Mansbach JM, Fisher ES, Riederer M, Piedra PA, Sullivan AF et al (2015) Variability in inpatient management of children hospitalized with bronchiolitis. *Acad Pediatr* 15(1):69–76
65. Oakley E, Borland M, Neutze J, Acworth J, Krieser D, Dalziel S et al (2013) Nasogastric hydration versus intravenous hydration for infants with bronchiolitis: a randomised trial. *Lancet Respir Med* 1(2):113–120
66. Wang L, Li X, Yang Z, Tang X, Yuan Q, Deng L et al (2016) Semi-recumbent position versus supine position for the prevention of ventilator-associated pneumonia in adults requiring mechanical ventilation. *Cochrane Database Syst Rev* 1:CD009946
67. Baudin F, Emeriaud G, Essouri S, Beck J, Portefaix A, Javouhey E et al (2019) Physiological effect of prone position in children with severe bronchiolitis: a randomized cross-over study (BRONCHIO-DV). *J Pediatr* 205(112–9):e4
68. Carande EJ, Galiza EP, Nickless A, Pollard AJ, Drysdale SB (2018) Viral bronchiolitis management in hospitals in the UK. *J Clin Virol* 104:29–33
69. **Cunningham S (2020) Critical care thresholds in children with bronchiolitis. *Am J Perinatol* 37(S 02):S42–S45**
70. Jat KR, Mathew JL (2019) Continuous positive airway pressure (CPAP) for acute bronchiolitis in children. *Cochrane Database Syst Rev* 1:CD010473
71. Vahlkvist S, Jørgensen L, la Cour A, Markoew S, Petersen TH, Kofoed PE (2020) High flow nasal cannula and continuous positive airway pressure therapy in treatment of viral bronchiolitis: a randomized clinical trial. *Eur J Pediatr* 179(3):513–518
72. Shaikh N, Tripathi S, Whelan A, Ford J, Kim M, Deshpande G (2021) Association of transcutaneous CO₂ with respiratory support: a prospective double blind observational study in children with bronchiolitis and reactive airway disease. *J Clin Monit Comput.* <https://doi.org/10.1007/s10877-021-00712-1>
73. Wrotek A, Kobińska M, Jackowska T (2021) Capillary blood gas predicts risk of intensive care in children with bronchiolitis. *Children (Basel)* 8(8):719
74. Abboud PA, Roth PJ, Skiles CL, Stolfi A, Rowin ME (2012) Predictors of failure in infants with viral bronchiolitis treated with high-flow, high-humidity nasal cannula therapy*. *Pediatr Crit Care Med* 13(6):e343–e349
75. Er A, Caglar A, Akgul F, Ulusoy E, Citlenbik H, Yilmaz D et al (2018) Early predictors of unresponsiveness to high-flow nasal cannula therapy in a pediatric emergency department. *Pediatr Pulmonol* 53(6):809–815
76. Gal S, Riskin A, Chistyakov I, Shifman N, Srugo I, Kugelman A (2015) Transcutaneous PCO₂ monitoring in infants hospitalized with viral bronchiolitis. *Eur J Pediatr* 174(3):319–324
77. Srinivasan M, Pruitt C, Casey E, Dhaliwal K, DeSanto C, Markus R et al (2017) Quality improvement initiative to increase the use of nasogastric hydration in infants with bronchiolitis. *Hosp Pediatr* 7(8):436–443
78. Slain KN, Martinez-Schlurmann N, Shein SL, Stormorken A (2017) Nutrition and high-flow nasal cannula respiratory support in children with bronchiolitis. *Hosp Pediatr* 7(5):256–262
79. Sochet AA, McGee JA, October TW (2017) Oral nutrition in children with bronchiolitis on high-flow nasal cannula is well tolerated. *Hosp Pediatr* 7(5):249–255
80. Yildirim S, Kaymaz N, Topaloglu N, Koksall Binnetoglu F, Tekin M, Aylanc H et al (2016) Do we really ponder about necessity of intravenous hydration in acute bronchiolitis? *Colomb Med (Cali)* 47(1):21–24

81. Kugelman A, Raibin K, Dabbah H, Chistyakov I, Srugo I, Even L et al (2013) Intravenous fluids versus gastric-tube feeding in hospitalized infants with viral bronchiolitis: a randomized, prospective pilot study. *J Pediatr* 162(3):640–2 e1
82. Oakley E, Bata S, Rengasamy S, Krieser D, Cheek J, Jachno K et al (2016) Nasogastric hydration in infants with bronchiolitis less than 2 months of age. *J Pediatr* 178(241–5):e1
83. Babl FE, Franklin D, Dalziel S, Schibler A, Paediatric Research in Emergency Departments International C, Pediatric Critical Care Research G (2020) Enteral hydration in high flow therapy. *J Paediatr Child Health* 56(6):989
84. Tume LN, Eveleens RD, Mayordomo-Colunga J, Lopez J, Verbruggen S, Fricaudet M et al (2021) Enteral feeding of children on noninvasive respiratory support: a four-center european study. *Pediatr Crit Care Med* 22(3):e192–e202
85. Shadman KA, Kelly MM, Edmonson MB, Sklansky DJ, Nackers K, Allen A et al (2019) Feeding during high-flow nasal cannula for bronchiolitis: associations with time to discharge. *J Hosp Med* 14:E43–E48
86. Tume LN, Valla FV, Joosten K, Jotterand Chaparro C, Latten L, Marino LV et al (2020) Nutritional support for children during critical illness: European Society of Pediatric and Neonatal Intensive Care (ESPNIC) metabolism, endocrine and nutrition section position statement and clinical recommendations. *Intensive Care Med* 46(3):411–425
87. Leroue MK, Good RJ, Skillman HE, Czaja AS (2017) Enteral nutrition practices in critically ill children requiring noninvasive positive pressure ventilation. *Pediatr Crit Care Med* 18(12):1093–1098
88. van Waardenburg DA, de Betue CT, Goudoever JB, Zimmermann LJ, Joosten KF (2009) Critically ill infants benefit from early administration of protein and energy-enriched formula: a randomized controlled trial. *Clin Nutr* 28(3):249–255
89. Parlar-Chun R, Lafferty-Prather M, Gonzalez V, Pedroza C, Gourishankar A (2019) Protocol: randomised trial to compare nasoduodenal tube and nasogastric tube feeding in infants with bronchiolitis on high-flow nasal cannula; Bronchiolitis and High-flow nasal cannula with Enteral Tube feeding Randomised (BHETR) trial. *BMJ Open* 9(5):e025405
90. Valla FV, Baudin F, Demaret P, Rooze S, Moullet C, Cotting J et al (2019) Nutritional management of young infants presenting with acute bronchiolitis in Belgium, France and Switzerland: survey of current practices and documentary search of national guidelines worldwide. *Eur J Pediatr* 178(3):331–340
91. de Betue CT, van Waardenburg DA, Deutz NE, van Eijk HM, van Goudoever JB, Luiking YC et al (2011) Increased protein-energy intake promotes anabolism in critically ill infants with viral bronchiolitis: a double-blind randomised controlled trial. *Arch Dis Child* 96(9):817–822
92. Ng GYH, Ong C, Wong JMM, Teoh OH, Sultana R, Mok YH et al (2020) Nutritional status, intake, and outcomes in critically ill children with bronchiolitis. *Pediatr Pulmonol* 55(5):1199–1206
93. Mehta NM, Bechard LJ, Zurakowski D, Duggan CP, Heyland DK (2015) Adequate enteral protein intake is inversely associated with 60-d mortality in critically ill children: a multicenter, prospective, cohort study. *Am J Clin Nutr* 102(1):199–206
94. Bechard LJ, Staffa SJ, Zurakowski D, Mehta NM (2021) Time to achieve delivery of nutrition targets is associated with clinical outcomes in critically ill children. *Am J Clin Nutr* 114(5):1859–1867
95. Rodrigues RM, Schwartsman BG, Farhat SC, Schwartsman C (2014) Hypotonic solution decreases serum sodium in infants with moderate bronchiolitis. *Acta Paediatr* 103(3):e111–e115
96. Shein SL, Slain K, Martinez Schlurmann N, Speicher R, Rotta AT (2017) Hyponatremia and hypotonic intravenous fluids are associated with unfavorable outcomes of bronchiolitis admissions. *Hosp Pediatr* 7(5):263–270
97. Feld LG, Neuspiel DR, Foster BA, Leu MG, Garber MD, Austin K et al (2018) Clinical practice guideline: maintenance intravenous fluids in children. *Pediatrics*. <https://doi.org/10.1542/peds.2018-3083>
98. Hulst JM, Joosten KF, Tibboel D, van Goudoever JB (2006) Causes and consequences of inadequate substrate supply to pediatric ICU patients. *Curr Opin Clin Nutr Metab Care* 9(3):297–303
99. Ingelse SA, Geukens VG, Dijkshof ME, Lemson J, Bem RA, van Woensel JB (2019) Less is more? A feasibility study of fluid strategy in critically ill children with acute respiratory tract infection. *Front Pediatr* 7:496
100. Peterson RJ, Hassumani DO, Hole AJ, Slaven JE, Tori AJ, Abu-Sultaneh S (2021) Implementation of a high-flow nasal cannula management protocol in the pediatric ICU. *Respir Care* 66(4):591–599
101. Noelck M, Foster A, Kelly S, Arehart A, Rufener C, Wagner T et al (2021) SCRATCH trial: an initiative to reduce excess use of high-flow nasal cannula. *Hosp Pediatr* 11(4):319–326
102. Delacroix E, Millet A, Wroblewski I, Vilotitch A, Pin I, Ego A et al (2021) Has the introduction of high-flow nasal cannula modified the clinical characteristics and outcomes of infants with bronchiolitis admitted to pediatric intensive care units? A retrospective study. *Arch Pediatr* 28(2):141–146
103. Pedersen MB, Vahlkvist S (2017) Comparison of CPAP and HFNC in management of bronchiolitis in infants and young children. *Children (Basel)* 4(4)
104. Thia LP, McKenzie SA, Blyth TP, Minasian CC, Kozłowska WJ, Carr SB (2008) Randomised controlled trial of nasal continuous positive airways pressure (CPAP) in bronchiolitis. *Arch Dis Child* 93(1):45–47
105. Milesi C, Baleine J, Matecki S, Durand S, Combes C, Novais AR et al (2013) Is treatment with a high flow nasal cannula effective in acute viral bronchiolitis? A physiologic study. *Intensive Care Med* 39(6):1088–1094
106. Pham TM, O'Malley L, Mayfield S, Martin S, Schibler A (2015) The effect of high flow nasal cannula therapy on the work of breathing in infants with bronchiolitis. *Pediatr Pulmonol* 50(7):713–720
107. Hough JL, Pham TM, Schibler A (2014) Physiologic effect of high-flow nasal cannula in infants with bronchiolitis. *Pediatr Crit Care Med* 15(5):e214–e219
108. Weiler T, Kamekar A, Hotz J, Ross PA, Newth CJL, Khemani RG (2017) The relationship between high flow nasal cannula flow rate and effort of breathing in children. *J Pediatr* 189(66–71):e3
109. Essouri S, Laurent M, Chevret L, Durand P, Ecochard E, Gajdos V et al (2014) Improved clinical and economic outcomes in severe bronchiolitis with pre-emptive nCPAP ventilatory strategy. *Intensive Care Med* 40(1):84–91
110. Essouri S, Baudin F, Chevret L, Vincent M, Emeriaud G, Jouvett P (2017) Variability of care in infants with severe bronchiolitis: less-invasive respiratory management leads to similar outcomes. *J Pediatr* 188(156–62):e1
111. Soshnick SH, Carroll CL, Cowl AS (2019) Increased use of noninvasive ventilation associated with decreased use of invasive devices in children with bronchiolitis. *Crit Care Explor* 1(8):e0026
112. Cavari Y, Sofer S, Rozovski U, Lazar I (2012) Non invasive positive pressure ventilation in infants with respiratory failure. *Pediatr Pulmonol* 47(10):1019–1025
113. Wang C, Guo L, Chi C, Wang X, Guo L, Wang W et al (2015) Mechanical ventilation modes for respiratory distress syndrome in infants: a systematic review and network meta-analysis. *Crit Care* 19:108
114. Cesar RG, Bispo BRP, Felix P, Modolo MCC, Souza AAF, Horigoshi NK et al (2020) High-flow nasal cannula versus continuous positive airway pressure in critical bronchiolitis: a randomized controlled pilot. *J Pediatr Intensive Care* 9(4):248–255
115. Sarkar M, Sinha R, Roychowdhury S, Mukhopadhyay S, Ghosh P, Dutta K et al (2018) Comparative study between noninvasive continuous positive airway pressure and hot humidified high-flow nasal cannulae as a mode of respiratory support in infants with acute bronchiolitis in pediatric intensive care unit of a tertiary care hospital. *Indian J Crit Care Med* 22(2):85–90
116. Dafydd C, Saunders BJ, Kotecha SJ, Edwards MO (2021) Efficacy and safety of high flow nasal oxygen for children with bronchiolitis: systematic review and meta-analysis. *BMJ Open Respir Res* 8(1):e000844
117. Pons-Odena M, Fuente AE, Cambra Lasasa FJ, Matute SS, Rico AP, Modesto V (2012) Non-invasive ventilation in bronchiolitis: analysis according to a chronologic classification. *J Pediatr Intensive Care* 1(4):193–200
118. Wang BC, Pei T, Lin CB, Guo R, Elashoff D, Lin JA et al (2018) Clinical characteristics and outcomes associated with nasal intermittent mandatory ventilation in acute pediatric respiratory failure. *World J Crit Care Med* 7(4):46–51
119. Mayordomo-Colunga J, Pons-Odena M, Medina A, Rey C, Milesi C, Kallio M et al (2018) Non-invasive ventilation practices in children across Europe. *Pediatr Pulmonol* 53(8):1107–1114

120. Chidini G, Piastra M, Marchesi T, De Luca D, Napolitano L, Salvo I et al (2015) Continuous positive airway pressure with helmet versus mask in infants with bronchiolitis: an RCT. *Pediatrics* 135(4):e868–e875
121. Mayordomo-Colunga J, Rey C, Medina A, Martinez-Cambor P, Vivanco-Allende A, Concha A (2018) Helmet versus nasal-prong CPAP in infants with acute bronchiolitis. *Respir Care* 63(4):455–463
122. Maamari M, Nino G, Bost J, Cheng Y, Sochet A, Sharron M (2022) Predicting failure of non-invasive ventilation with RAM cannula in bronchiolitis. *J Intensive Care Med* 37(1):120–127
123. Velasco Arnaiz E, Cambra Lasaosa FJ, Hernandez Platero L, Millan Garcia Del Real N, Pons-Odena M (2014) Is a nasopharyngeal tube effective as interface to provide bi-level noninvasive ventilation? *Respir Care* 59(4):510–517
124. Franklin D, Babl FE, Schlapbach LJ, Oakley E, Craig S, Neutze J et al (2018) A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med* 378(12):1121–1131
125. Durand P, Guiddir T, Kyheng C, Blanc F, Vignaud O, Epaud R et al (2020) A randomised trial of high-flow nasal cannula in infants with moderate bronchiolitis. *Eur Respir J* 56(1):1901926
126. Kepreotes E, Whitehead B, Attia J, Oldmeadow C, Collison A, Searles A 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* 389(10072):930–939
127. Chabernaude JL, Jourdain G, Durand S (2009) Non invasive ventilation for severe infant bronchiolitis. *Arch Pediatr* 16(6):726–728
128. Lode N, Bacher M, Pinto Da Costa N, Maury I (2009) Non invasive ventilation and bronchiolitis: out-of-hospital practice. *Arch Pediatr* 16(6):723–725
129. Fleming PF, Richards S, Waterman K, Davis PG, Kamlin CO, Sokol J et al (2012) Use of continuous positive airway pressure during stabilisation and retrieval of infants with suspected bronchiolitis. *J Paediatr Child Health* 48(12):1071–1075
130. Schlapbach LJ, Schaefer J, Brady AM, Mayfield S, Schibler A (2014) High-flow nasal cannula (HFNC) support in interhospital transport of critically ill children. *Intensive Care Med* 40(4):592–599
131. Millan N, Alejandro C, Martinez-Planas A, Caritg J, Esteban E, Pons-Odena M (2017) Noninvasive respiratory support during pediatric ground transport: implementation of a safe and feasible procedure. *Respir Care* 62(5):558–565
132. Holbird S, Holt T, Shaw A, Hansen G (2020) Noninvasive ventilation for pediatric interfacility transports: a retrospective study. *World J Pediatr* 16(4):422–425
133. Cheema B, Welzel T, Rossouw B (2019) Noninvasive ventilation during pediatric and neonatal critical care transport: a systematic review. *Pediatr Crit Care Med* 20(1):9–18
134. Hill C, Knaf KA, Santacrose SJ (2018) Family-centered care from the perspective of parents of children cared for in a pediatric intensive care unit: an integrative review. *J Pediatr Nurs* 41:22–33
135. Venkatraman R, Hungerford JL, Hall MW, Moore-Clingenpeel M, Tobias JD (2017) Dexmedetomidine for sedation during noninvasive ventilation in pediatric patients. *Pediatr Crit Care Med* 18(9):831–837
136. Piastra M, Pizza A, Gaddi S, Luca E, Genovese O, Picconi E et al (2018) Dexmedetomidine is effective and safe during NIV in infants and young children with acute respiratory failure. *BMC Pediatr* 18(1):282
137. Fernandes RM, Bialy LM, Vandermeer B, Tjosvold L, Plint AC, Patel H et al (2013) Glucocorticoids for acute viral bronchiolitis in infants and young children. *Cochrane Database Syst Rev* 6:CD004878
138. Somers CC, Ahmad N, Mejias A, Buckingham SC, Carubelli C, Katz K et al (2009) Effect of dexamethasone on respiratory syncytial virus-induced lung inflammation in children: results of a randomized, placebo controlled clinical trial. *Pediatr Allergy Immunol* 20(5):477–485
139. 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(7):1779–1783
140. Levin DL, Garg A, Hall LJ, Slogic S, Jarvis JD, Leiter JC (2008) A prospective randomized controlled blinded study of three bronchodilators in infants with respiratory syncytial virus bronchiolitis on mechanical ventilation. *Pediatr Crit Care Med* 9(6):598–604
141. Ralston S, Hartenberger C, Anaya T, Qualls C, Kelly HW (2005) Randomized, placebo-controlled trial of albuterol and epinephrine at equipotent beta-2 agonist doses in acute bronchiolitis. *Pediatr Pulmonol* 40(4):292–299
142. Patel H, Platt RW, Pেকেles GS, Ducharme FM (2002) A randomized, controlled trial of the effectiveness of nebulized therapy with epinephrine compared with albuterol and saline in infants hospitalized for acute viral bronchiolitis. *J Pediatr* 141(6):818–824
143. Abul-Ainane A, Luyt D (2002) Short term effects of adrenaline in bronchiolitis: a randomised controlled trial. *Arch Dis Child* 86(4):276–279
144. Wainwright C, Altamirano L, Cheney M, Cheney J, Barber S, Price D et al (2003) A multicenter, randomized, double-blind, controlled trial of nebulized epinephrine in infants with acute bronchiolitis. *N Engl J Med* 349(1):27–35
145. Plint AC, Johnson DW, Patel H, Wiebe N, Correll R, Brant R et al (2009) Epinephrine and dexamethasone in children with bronchiolitis. *N Engl J Med* 360(20):2079–2089
146. Kua KP, Lee SWH (2017) Systematic review and meta-analysis of the efficacy and safety of combined epinephrine and corticosteroid therapy for acute bronchiolitis in infants. *Front Pharmacol* 8:396
147. Flores-González JC, Dominguez-Coronel MT, Matamala Morillo MA, Aragón Ramírez M, García Ortega RM, Dávila Corrales FJ et al (2016) Does nebulized epinephrine improve the efficacy of hypertonic saline solution in the treatment of hospitalized moderate acute bronchiolitis? A double blind, randomized clinical trial. *Minerva Pediatr* 68(2):81–88
148. Flores-Gonzalez JC, Matamala-Morillo MA, Rodriguez-Campoy P, Perez-Guerrero JJ, Serrano-Moyano B, Comino-Vazquez P et al (2015) Epinephrine improves the efficacy of nebulized hypertonic saline in moderate bronchiolitis: a randomised clinical trial. *PLoS ONE* 10(11):e0142847
149. Turner A, Shann F, Delzoppo C, Henning R, Slater A, Beca J et al (2014) A multicentre, randomised, double-blind, placebo-controlled trial of aminophylline for bronchiolitis in infants admitted to intensive care. *Crit Care Resusc* 16(3):220–224
150. Farley R, Spurling GK, Eriksson L, Del Mar CB (2014) Antibiotics for bronchiolitis in children under two years of age. *Cochrane Database Syst Rev* 10:CD005189
151. Field CM, Connolly JH, Murtagh G, Slattery CM, Turkington EE (1966) Antibiotic treatment of epidemic bronchiolitis—a double-blind trial. *Br Med J* 1(5479):83–85
152. Kabir AR, Mollah AH, Anwar KS, Rahman AK, Amin R, Rahman ME (2009) Management of bronchiolitis without antibiotics: a multicentre randomized control trial in Bangladesh. *Acta Paediatr* 98(10):1593–1599
153. Kneyber MC, van Woensel JB, Uijtendaal E, Uiterwaal CS, Kimpen JL, Dutch Antibiotics in RSVTRG (2008) Azithromycin does not improve disease course in hospitalized infants with respiratory syncytial virus (RSV) lower respiratory tract disease: a randomized equivalence trial. *Pediatr Pulmonol* 43(2):142–149
154. Bilavsky E, Shouval DS, Yarden-Bilavsky H, Fisch N, Ashkenazi S, Amir J (2008) A prospective study of the risk for serious bacterial infections in hospitalized febrile infants with or without bronchiolitis. *Pediatr Infect Dis J* 27(3):269–270
155. Guitart C, Alejandro C, Bobillo-Perez S, Girona-Alarcon M, Sole-Ribalta A, Cambra FJ et al (2022) Risk factors and incidence of invasive bacterial infection in severe bronchiolitis: the RICOIB prospective study. *BMC Pediatr* 22(1):140
156. Cebey-Lopez M, Pardo-Seco J, Gomez-Carbala A, Martinon-Torres N, Martinon-Sanchez JM, Justicia-Grande A et al (2016) Bacteremia in children hospitalized with respiratory syncytial virus infection. *PLoS ONE* 11(2):e0146599
157. Thorburn K, Harigopal S, Reddy V, Taylor N, van Saene HK (2006) High incidence of pulmonary bacterial co-infection in children with severe respiratory syncytial virus (RSV) bronchiolitis. *Thorax* 61(7):611–615
158. Levin D, Tribuzio M, Green-Wrzesinski T, Ames B, Radwan S, Jarvis JD et al (2010) Empiric antibiotics are justified for infants with respiratory syncytial virus lower respiratory tract infection presenting with respiratory failure: a prospective study and evidence review. *Pediatr Crit Care Med* 11(3):390–395
159. Kneyber MC, Blusse van Oud-Alblas H, van Vliet M, Uiterwaal CS, Kimpen JL, van Vught AJ (2005) Concurrent bacterial infection and prolonged mechanical ventilation in infants with respiratory syncytial virus lower respiratory tract disease. *Intensive Care Med* 31(5):680–685

160. Brook I (1998) Microbial factors leading to recurrent upper respiratory tract infections. *Pediatr Infect Dis J* 17(8 Suppl):S62–S67
161. Schroeder AR, Mansbach JM, Stevenson M, Macias CG, Fisher ES, Barcega B et al (2013) Apnea in children hospitalized with bronchiolitis. *Pediatrics* 132(5):e1194–e1201
162. Alansari K, Toaimah FH, Khalafalla H, El Tatawy LA, Davidson BL, Ahmed W (2016) Caffeine for the treatment of apnea in bronchiolitis: a randomized trial. *J Pediatr* 177:204–11.e3
163. Heuze N, Goyer I, Porcheret F, Denis M, Faucon C, Jokic M et al (2020) Caffeine treatment for bronchiolitis-related apnea in the pediatric intensive care unit. *Arch Pediatr* 27(1):18–23
164. Cesar K, Iolster T, White D, Latifi S (2012) Caffeine as treatment for bronchiolitis-related apnoea. *J Paediatr Child Health* 48(7):619
165. Duffett M, Liu DM, Deshpande A, Choong K (2012) Caffeine in bronchiolitis associated apnea: a retrospective cohort study. *J Pediatr Intensive Care* 1(2):95–98
166. Liet JM, Ducruet T, Gupta V, Cambonie G (2015) Heliox inhalation therapy for bronchiolitis in infants. *Cochrane Database Syst Rev* 9:CD006915
167. Sellem W, Sultan AM (2019) Does heliox administered by low-flow nasal cannula improve respiratory distress in infants with respiratory syncytial virus acute bronchiolitis? A randomized controlled trial. *An Pediatr (Engl Ed)* 90(1):3–9
168. Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP (2017) Nebulised hypertonic saline solution for acute bronchiolitis in infants. *Cochrane Database Syst Rev* 12:CD006458
169. Heikkilä P, Renko M, Korppi M (2018) Hypertonic saline inhalations in bronchiolitis—a cumulative meta-analysis. *Pediatr Pulmonol* 53(2):233–242
170. Everard ML, Hind D, Ugonna K, Freeman J, Bradburn M, Cooper CL et al (2014) SABRE: a multicentre randomised control trial of nebulised hypertonic saline in infants hospitalised with acute bronchiolitis. *Thorax* 69(12):1105–1112
171. Morikawa Y, Miura M, Furuhashi MY, Morino S, Omori T, Otsuka M et al (2018) Nebulized hypertonic saline in infants hospitalized with moderately severe bronchiolitis due to RSV infection: a multicenter randomized controlled trial. *Pediatr Pulmonol* 53(3):358–365
172. Stobbelaar K, Kool M, de Kruijf D, Van Hoorenbeeck K, Jorens P, De Dooy J et al (2019) Nebulised hypertonic saline in children with bronchiolitis admitted to the paediatric intensive care unit: a retrospective study. *J Paediatr Child Health* 55(9):1125–1132
173. Bernard-Narbonne F, Daoud P, Castaing H, Rousset A (2003) Effectiveness of chest physiotherapy in ventilated children with acute bronchiolitis. *Arch Pediatr* 10(12):1043–1047
174. Roque i Figuls M, Gine-Garriga M, Granados Rugeles C, Perrotta C, Vilaro J (2016) Chest physiotherapy for acute bronchiolitis in paediatric patients between 0 and 24 months old. *Cochrane Database Syst Rev* 2:CD004873
175. Gajdos V, Katsahian S, Beydon N, Abadie V, de Pontual L, Larrar S et al (2010) Effectiveness of chest physiotherapy in infants hospitalized with acute bronchiolitis: a multicenter, randomized, controlled trial. *PLoS Med* 7(9):e1000345
176. Smith DW, Frankel LR, Mathers LH, Tang AT, Ariagno RL, Prober CG (1991) A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. *N Engl J Med* 325(1):24–29
177. Meert KL, Sarnaik AP, Gelmini MJ, Lieh-Lai MW (1994) Aerosolized ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory tract disease: a prospective, double-blind, randomized trial. *Crit Care Med* 22(4):566–572
178. Guerguerian AM, Gauthier M, Lebel MH, Farrell CA, Lacroix J (1999) Ribavirin in ventilated respiratory syncytial virus bronchiolitis. A randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 160(3):829–834
179. Enriquez A, Chu IW, Mellis C, Lin WY (2012) Nebulised deoxyribonuclease for viral bronchiolitis in children younger than 24 months. *Cochrane Database Syst Rev* 11:CD008395
180. Alansari K, Sayyed R, Davidson BL, Al Jawala S, Ghadier M (2017) IV magnesium sulfate for bronchiolitis: a randomized trial. *Chest* 152(1):113–119
181. Modaresi MR, Faghihinia J, Kelishadi R, Reisi M, Mirlohi S, Pajhang F et al (2015) Nebulized magnesium sulfate in acute bronchiolitis: a randomized controlled trial. *Indian J Pediatr* 82(9):794–798
182. Debbarma R, Khera D, Singh S, Toteja N, Choudhary B, Singh K (2021) Nebulized magnesium sulphate in bronchiolitis: a randomized controlled trial. *Indian J Pediatr* 88(11):1080–1085
183. Kose M, Ozturk MA, Poyrazoglu H, Elmas T, Ekinci D, Tubas F et al (2014) The efficacy of nebulized salbutamol, magnesium sulfate, and salbutamol/magnesium sulfate combination in moderate bronchiolitis. *Eur J Pediatr* 173(9):1157–1160
184. Tal A, Greenberg D, Av-Gay Y, Golan-Tripto I, Feinstein Y, Ben-Shimol S et al (2018) Nitric oxide inhalations in bronchiolitis: a pilot, randomized, double-blinded, controlled trial. *Pediatr Pulmonol* 53(1):95–102
185. Goldbart A, Golan-Tripto I, Pillar G, Livnat-Levanon G, Efrati O, Spiegel R et al (2020) Inhaled nitric oxide therapy in acute bronchiolitis: a multicenter randomized clinical trial. *Sci Rep* 10(1):9605