Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 08/24/2019
Approved on: 11/09/2019

ORIGINAL ARTICLE

Treatment of acute viral bronchiolitis

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Keywords:
Bronchiolitis,
Bronchiolitis,
Viral,
Infant,
Drug Therapy.

Abstract

Introduction: Acute viral bronchiolitis (AVB) is one of the main respiratory infections in infants. Available information on the treatment of AVB in children under 2 years is reported, based on the most recent scientific evidence published in the literature. **Methods:** Simple non-systematic review was performed on PubMed and Cochrane sites using the terms "bronchiolitis", "viral bronchiolitis", "infant" and "treatment" in Portuguese. In the English language, the terms were "bronchiolitis", "viral bronchiolitis", "infant", and "drug therapy". The search period was 15 years, from 2004 to 2019. The materials obtained had the title and abstract read; when the documents reported more recent evidence on the subject, they were read in full. **Results:** In the databases cited there were 1,091 non-systematic reviews, 113 clinical protocols, 3 editorials, 243 articles. The currently most accepted treatments for AVB are oxygen supplementation in the presence of hypoxemia and noninvasive or invasive ventilatory support, according to the severity of respiratory failure. **Discussion:** Increased knowledge about the pathophysiology of AVB has allowed us to review the treatments used in the past and now. The treatment of AVB deserves reflection and new intervention proposals, since current scientific evidence levels do not support the use of corticosteroids and beta 2 adrenergic, routine practices of pediatricians. Clinical stabilization of the patient, oxygen therapy and ventilatory support are recommended.

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Residência Pediátrica; 2021: Ahead of Print.
DOI: 10.25060/residpediatr-2021.v11n3-186

INTRODUCTION

Acute viral bronchiolitis (AVB) is one of the main respiratory infections that affect children under 2 years of age and the main cause of hospitalization of healthy children under three months of age worldwide. AVB causes social and financial impacts on health systems and influences morbidity and mortality in groups most vulnerable to severe AVB: premature infants, low birth weight, patients with pulmonary, cardiac and neuromuscular diseases and immunosuppressed individuals who are more likely to be hospitalized[1].Up to 2 years of age, 95% of infants will be infected with RSV[2].

Symptoms start in the upper airway: nasal congestion and runny nose for 2 to 4 days, in addition to fever, which may be absent in up to 50% of cases. Lower respiratory tract infection evolves in 6 to 8 days with tachypnea and respiratory distress. Pulmonary auscultation may or may not have bullous rales and/or expiratory wheezes[3].

The definition of BVA is controversial between European and American academies. European guidelines define the presence of respiratory effort in children under 1 year of age and Americans as the first wheezing event in children under 2 years of age preceded by symptoms of runny nose and sneezing, which is the most used classification[4].

Apnea may be the initial manifestation of AVB in preterm infants and children younger than two months of age, and these are risk factors for severe AVB[3].

AVB is caused by Respiratory Syncytial Virus (RSV) in up to 80% of cases in the first year of life, followed by Human Rhinovirus (RV) in 5 to 15%[3,4]. Other viral agents together do not reach 5% of expression: Parainfluenza, Metapneumovirus, Bocavirus, Coronavirus, Adenovirus, Influenza. Atypical bacteria may account for 1% to 3% of cases. In those older than 1 year, VR becomes more prevalent[1,3].

The RSV initiates replication in the mucosa of the nasal epithelium and the inflammatory lesion will spread to the terminal bronchiole, determining AVB. The inflammatory lesion is interalveolar and everything indicates that each virus has a different profile of lesion[4]. The inflammation is secondary to the action of chemokines (IL1, IL6, IL8, RANTES, macrophage-binding PTN 1) and damages the mucosa, submucosa and adventitia of the lower respiratory epithelium, causing local edema and debris. Cytokines recruit and activate lymphocytes, neutrophils, macrophages, eosinophils and NK cells (natural killers) that lead to increased local mucus production and will cause hyperreactivity in the lower airway[5].

RV could be a trigger for future asthma, but its prevalence in AVB is lower[4].

In AVB caused by Rhinoviruses with a family history of atopy, there could be a low risk of progression to asthma, but there is still a lack of studies validating this statement[4-8].

It is currently possible to quickly identify the viral pathogen that may one day direct the management, there are clinical differences determined by the inflammation of RSV and Rhinovirus. VRS causes less wheezing and more secretion, while inflammation and wheezing are more present in Rhinovirus infection[4].

AVB has three serious acute complications: apnea (in young infants), acute respiratory failure, and dehydration.

There is no specific treatment for AVB and this article reviewed the most used approaches in the last 15 years, according to the literature.

METHODS

We performed a simple and non-systematic review of the literature with a comprehensive search for articles, consensus, reviews and meta-analyses. The bases used were PubMed and Cochrane with the terms bronchiolitis, viral bronchiolitis, infant and treatment in Portuguese and in English terms bronchiolitis, viral bronchiolitis, infant and drug therapy. The search period was 15 years - 2004 to 2019. The materials obtained had the title and abstract read; when documents reported more recent evidence on the matter, they were read in full. In addition, guidelines and guidelines from the American Academy of Pediatrics (AAP), European Consensus of Pediatrics and Australian Consensus of Pediatrics were consulted on the BVA theme of the last 5 years.

RESULTS

The therapeutic approach of AVB has changed over the years and the most frequent treatment options according to their levels of scientific evidence are described below.

The quality levels of scientific evidence are described in table 1.

Nostril cleaning

Nasal lavage can improve nasal obstruction in mild cases. Maintaining a clear airway is important in young infants for optimal breastfeeding performance and efficient ventilation. Physiological saline solution can be instilled in the nostrils before the oral diet and when there is nasal obstruction. The

Table 1. Quality level of scientific evidence and application in clinical practice.

Quality Level	What does it mean for clinical practice?
A	Reliable evidence to guide clinical practice.
B	Evidence is reliable for part of clinical situations.
C	Less reliable evidence that can be recommended, but requires more discretion in application.
D	Weak evidence should be applied with caution.

Source: Adaptation of the authors Dall´Olio CC, Sant´Anna MF, Sant´Anna CC. Based on Ralston SL, Lieberthal . AS, Meissner HC. Clinical Practice Guideline: the diagnosis , Management, and prevention of Bronchiolitis.. Pediatrics. Oct 2015; 136 (4) 782.

ideal position for the maneuver is the infant sitting on the caregiver's lap, with the head straight and never lying down[6].

Vigorous and deep nasal aspiration can irritate the mucosa more and worsen local edema, being contraindicated in AVB . Superficial aspiration can be used to try to improve suction capacity when impaired[8-10]. Level D of evidence.

Corticosteroids

There is agreement between guidelines and consensus that there is no indication for the use of oral, intravenous or inhaled corticosteroids in AVB caused by RSV. There are no clinical benefits or scientific evidence to support its use. As AVB is not asthma, although wheezing can be present in both diseases, their etiologies and pathophysiology are different.

In AVB by RV, there is no evidence for the prescription of corticosteroids, even if the patient has a positive bronchodilator response[4,10]. Level D of evidence.

Although systemic and oral corticosteroids have an anti-inflammatory action, they help to reduce the edema of the respiratory mucosa and improve bronchoconstriction, they do not change the course of AVB and also prolong viremia, making their use unnecessary[1-4,8,10-13].

Non-use of corticosteroids in AVB has level B of evidence.

Bronchodilators

Nebulization with adrenergic B2 such as fenoterol or salbutamol is very common in AVB[10]. Although wheezing may be present, the cause of bronchospasm in AVB seems to be related to the presence of debris in the bronchiole. According to the consensus, there are no benefits in terms of length of stay, clinical improvement, pulmonary function tests when compared to nebulization with placebo such as B2 adrenergics, and their use is unnecessary. Level A of evidence[7,8,10].

The use of B2 can cause adverse effects such as tachycardia, tremors, in addition to generating costs[8].

However, patients with a family or personal history of atopy may perhaps respond to the bronchodilator when Rhinovirus (RV) is the etiologic agent of AVB. Level D of evidence.

This should not generalize the conduct, since in about 80% of the events there is RSV infection, and another 5% include the sum of the prevalence of other less prevalent viruses[1,4].

viral etiological identification , a bronchodilator test can be performed, if there is an improvement in RR and auscultation after nebulizing or using spray with B2, it is possible to choose to maintain the prescription. Level D of evidence.

Oxygen therapy

In the last 5 years, the oxygen saturation cut-off point (O_2sat) has been changed to start O_2 supplementation. The AAP recommendation is to indicate if O_2sat is below 90%, whereas before it was below 96%; in the Australian consensus, the oxygen supply starts below 92% of O2sat[8,10].

Tolerating saturation up to 90% is only applicable in patients with non-severe AVB, in good general condition, who accept diets and have non-severe respiratory distress[9,10].

Mild hypoxemia requires low FiO_2 of up to 30% and a nasal catheter with 1 to 2 liters of O_2\ min can be used. Continuous macro nebulization has no scientific validation study to support the BVA. Moderate conditions may require non-invasive ventilation (NIV), with nasal CPAP or high-flow nasal catheter, if available.

In severe AVB unresponsive to NIV, orotracheal intubation will be necessary[7]. Observational studies suggest that continuous pulse oximetry could lead to longer hospital stays in stable infants and lead to unnecessary clinical interventions due to inaccurate or false-positive oximetry readings. High-quality evidence is lacking to define the best strategy for this monitoring: whether intermittent or continuous[1]. Pulse oximetry would not need to be continuous in light, stable frames that saturate above 92% . Level C of evidence.

The oxygen therapy devices most used in acute ventilatory disorders and AVB are shown in Chart 1.

Chart 1. Oxygen Delivery Devices: flow, wire2, indications.

Oxygen delivery devices	Flow; FiO_2	Indications and comments
Macronebulization	Minimum 10L/min; up to 30%	Mild discomfort in a patient who cannot tolerate a catheter or mask. Not listed in the BVA
Nasal catheter	1 to 4 L/min; 25 to 40%	Ideal to have little coryza; Indicated in light BVA.
Simple Mask	5 L/min onwards; 30 to 50%	RR and mask shape affect the delivered O_2 concentration.
Mask with reservoir	10 to 12 L/min; 50 to 60%	Efficient in short-distance transport. Difficult adaptation in the non-collaborative patient.
non -rebreathing mask	10 to 15 L/min; 60 to 95%	Can be used for moderate to severe discomfort. It has 2 valves that reduce CO_2 retention.
High flow nasal cannula	4 to 20 L/min; 21 to 100%	It can be used in moderate discomfort with or without hypoxemia. Flow depends on age, greater than 15 L are difficult for infants to adapt to . Indicated in moderate or severe AVB.
ventilation with ambu	06 to 25 Liters; 21 to 100% FiO_2	I have reversed acute hypoxemia, but it is not a continuous support method. The flow depends on the age and size of the patient and whether or not the reservoir is used.

Legend: FiO_2: Inspired Oxygen Fraction. L/min: Liters per minute. RR: respiratory rate.

Nebulization with 3% hypertonic saline (SSH)

SSH appears to promote the breakdown of ionic bonds in mucus, making it more fluid and facilitating its removal through coughing. HSS without a bronchodilator can be used as a vehicle for nebulizations upon admission to the emergency department, and can reduce the length of hospital stay by up to 20% in non-severe AVB. Nebulization with SSH promotes reduction of airway edema, decreased secretion *plugging* , improves *clearance* mucociliary and airway hydration, from the nasal epithelium to the terminal bronchiole[12,13].

Hospitalized patients with moderate AVB using HSS may have a reduction in hospitalization time by 11 hours, when compared to those who did not use HSS. Adverse effects are infrequent: worsening cough and accentuation of bronchospasm[14].

The use of HSS before physical therapy, in mild cases, seems to reduce the rate of evolution to hospitalization by up to 16 %[14-19].

In the hospital environment, SSH is obtained with mixtures of saline solution or distilled water with 20% sodium chloride, so far the solution is not commercialized, so its use is somewhat restricted.

Usage is controversial and the works have construction biases. Level D of evidence[10].

Venous access and intravenous hydration

Nasogastric or enteral tube feeding is preferred when the moderate condition no longer allows the release of the oral diet and intravenous water support is indicated only in cases in which the oral route is not recommended due to tachydyspnea[8,10]. Level B of evidence.

Isotonic solution is preferred as there is a risk of water retention due to the release of antidiuretic hormone in severe AVB. There is no validation of this practice in the BVA, but it is routine for pediatric care practice.

Antibiotics

The use of antibiotics has no qualified evidence for the essentially viral etiology of AVB[3,8,10,14]. Level B of evidence[8,10]. Ditto for the prescription of macrolides for cough, which may persist for up to 3 weeks after AVB[15]. Although studies indicate that azithromycin could prevent recurrent wheezing after rhinovirus AVB, its use is not routinely supported[4,14].

The indiscriminate use of antibiotics can affect the airway microbiome and act as another factor pointed to the worsening of AVB[4].

Viral swab research may support the non-prescription of antibiotics. The detection of RSV in the nasopharyngeal swab is done through the identification of the viral nucleic acid. The exam is easy and fast (20 minutes on average), sensitive and specific. There are isolated or group identification kits for viral strains. The nasal swab differentiates AVB from influenza A and B virus infection, and may direct the prescription of oseltamivir to groups at risk of influenza syndrome[16]. It is important to follow the kit manufacturer's technical collection standards for greater sensitivity and specificity of the result, which reaches 95%. However, there is no formal recommendation for this practice so far. Level C of evidence.

Decongestants and antitussives

The prescription of oral decongestant solutions, antihistamines and mucolytics such as acetylcysteine has no confirmed efficacy in cases of AVB. There is a risk of adverse effects especially in children under 6 months and are not supported by scientific evidence. Level A of evidence[8].

-Invasive Ventilation

The available material, age and clinical severity should be considered when choosing the ventilation method. It can be installed in hypoxemias (<92% saturation) or moderate tachydyspnea onwards. The use of intranasal CPAP with pressures of 4 to 8 cmH2O is an option for alveolar recruitment and reduction of airway resistance , it can improve alveolar hematosis and reduce stress especially in children younger than 2 months but the size of the nasal prong can be limiting use in older infants, as well as the presence of abundant nasal secretion[7].

High-flow nasal cannula therapy (HFNC: high-flow nasal cannula) is a mode of non-invasive ventilation that provides high-velocity and high-pressure intranasal flow in the pharynx only. The pressure will act on the terminal portion of the bronchiole, keeping its lumen patent, with a continuous and fast air flow. The goal is to reduce respiratory effort. In addition to humidifying the upper airway with heated air, the flow offered will vary according to the patient's respiratory rate and lung compliance. The management of HFNC is a separate chapter, it is indicated in AVB with saturation lower than 92% or in tachydyspnea even without hypoxia. It is an effective, safe therapy and can reduce orotracheal intubation when installed early in the emergency room. There is evidence of a greater chance of successful treatment with high-flow oxygen therapy already at hospital admission, which may reduce the outcome of ICU admission[7,20]. Level C of evidence[7,18-21].

Ribavarin

Ribavarin is an inhaled antiviral drug that acts by inhibiting RSV RNA synthesis. Although approved for use in adults with severe RSV infection by the FDA, the AAP does not indicate its use in pediatrics with severe AVB. The costs are high, the management technique difficult and the results were not effective in severe cases of AVB in the ICU when compared to placebo. Level C of evidence[2,4,22,23].

Respiratory Physiotherapy

To date, conventional chest physiotherapy (postural drainage plus percussion and chest vibration techniques) has not shown efficacy in the treatment of AVB and has been associated with adverse effects of worsening cough and bronchospasm. Level B of evidence[17,20].

Palivizumab

Palivizumab is passive immunization against RSV, a monoclonal antibody of the IgG1 type, released in 1998 by the FDA. The application is intramuscular, monthly for 5 months and should be started 1 month before the seasonality period of RSV at a dose of 15 mg/kg.

It is indicated for premature infants under 28 weeks, under 32 weeks if they have chronic pathologies and for term babies with lung diseases , neuropathies, heart diseases and immunosuppressed. It reduces hospitalizations for severe AVB[19]. Level B of evidence.

Heliox

The use of heliox gas, which is inert and comes from a mixture of oxygen and helium, was evaluated in a multicenter study in patients with severe AVB in the ICU. Its inhalation reduced the clinical severity score, even in the first hour of use, in patients before using mechanical ventilation. But it did not reduce the need for mechanical ventilation, intubation, or length of stay in the ICU. Heliox may be used in addition to care that is already used in the ICU for severe AVB[24-26]. Level D of evidence.

CONCLUSIONS

The treatment of AVB should not be like that of asthma because, despite wheezing, the pathophysiology is different. The fewer drugs prescribed without scientific validation, the fewer iatrogenic effects will affect patients. The etiological plurality of AVB makes it difficult to generalize its treatment[4].

There are few effective cures and immediate resolution of the disease and relapses are common. Currently, clinical and ventilatory support are recommended according to the severity of AVB. For oxygen therapy there are effective options that involve positive airway pressure: CPAP or high flow nasal therapy (HFNC). High flow treatment is promising and already available in Brazil. Its use in hospitalized patients with AVB should be early and started in the emergency department[7] There is consensus regarding the non-prescription of B2 adrenergics and corticosteroids[6,8,10].

Immunoglobulins, nucleoside analogues and hybrid inhibitors of viral replication, adhesion and gene transcription, aimed at the prevention and treatment of RSV are in clinical studies and promise to be effective in blocking the disease in the future[27].

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