

## REVIEW

## RESPIRATORY SYNCYTIAL VIRUS IN INFANTS

## Bronchiolitis clinics and medical treatment

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## ABSTRACT

Bronchiolitis is the most common acute lower respiratory tract infection in infants and the first cause of hospitalization in this age group. Despite it has been studied for over 70 years, its management remains controversial and nowadays the treatment is only supportive. Pediatricians should be well acquainted with the clinical course of the disease. In particular, they should know that the severity of respiratory symptoms peaks between days 3-7 of the disease and dehydration is a key sign to consider for the management. In this review, we will discuss the most controversial points in the management of bronchiolitis according to six evidence-based guidelines, six clinical practice guidelines and five consensus-based reviews.

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Acute bronchiolitis is the most common cause of hospitalization in infants.<sup>1-3</sup> It is a viral lower respiratory infection and every year it is estimated that about 100,000 children are hospitalized due to bronchiolitis in the USA with a high social and economic burden.<sup>4-6</sup>

In this review, we will discuss the most controversial points in the management of bronchiolitis according to six evidence-based guidelines (EBG),<sup>7-12</sup> 6 clinical practice guidelines (CPG)<sup>13-18</sup> and 5 consensus-based reviews (CBR).<sup>19-23</sup> Although guidelines have addressed bronchiolitis treatment worldwide, several knowledge gaps and controversies still exist. Not is it clear how acute viral bronchiolitis should be most appropriately defined, which diagnostic examinations are needed in managing these patients, when the child with bronchiolitis should be admitted, which is the most appropriate treatment and when infants can be safely discharged.

## Definition

Despite ample evidence that bronchiolitis represents a continuum, including different diseases that may have in common similar phenotypes, bronchiolitis remains a diagnosis based on clinical signs and symptoms.<sup>24, 25</sup> Nobody has yet tried to define bronchiolitis according to clinical, pathological or biological heterogeneity.

The main differences in the clinical definition of bronchiolitis are age at presentation, and lung auscultatory findings. Most definitions have considered the age limit of 12 and 24 months,<sup>10, 17</sup> but others recommended 6 months<sup>26</sup> or even more than 24 months.<sup>27, 28</sup> The immune response, the lung anatomy and physiology differ with age, and these differences may influence the different phenotypic appearances of bronchiolitis. In older children, bronchiolitis can be confused with an episode of viral-induced wheezing bronchitis.<sup>29-31</sup>

Another important controversy about definition of bronchiolitis concerns the characteristic lung sounds observed during chest auscultation: predominant wheeze, or predominant presence of bilateral crackles. Wheezing is a high-pitched, musical, adventitious lung sound produced by turbulent airflow that passes through narrowed airways, and it reflects a bronchial disease such as asthma. Conversely, crackles are caused by small airways popping open and alveoli collapsed by fluid, thus possibly reflecting two different entities affecting two different lung structures.<sup>32,33</sup> No evidence yet shows whether bronchodilator responses depend from the infant's auscultatory sounds and/or age.

Specific studies in infants with a homogeneous definition of bronchiolitis should evaluate whether responses to medical treatment and long-lasting respiratory sequelae differ after the disease.

### VRS and bronchiolitis

Bronchiolitis is a viral lower respiratory infection. Respiratory syncytial virus (VRS) is the most frequently detected virus in infants with bronchiolitis and it represents the major etiological agent in this disease. Over 10 consecutive epidemic seasons of bronchiolitis, enrolling 723 previously healthy term hospitalized infants, a virus was detected from nasopharyngeal aspirates in 351 infants and RSV was found in 234 (32.4%), human Rhinovirus in 44 (6.1%), human Bocavirus in 11 (1.5%), human Metapneumovirus in 12 (1.6%).<sup>34</sup> RSV has been recognized to cause a more severe form of bronchiolitis and to affect more frequently younger infants,<sup>35</sup> while Rhinovirus, the second more frequent virus in this disease, usually affects older infants with a higher predisposition to atopy.<sup>36</sup> Co-infections can also be found in about 10% of infants hospitalized with bronchiolitis, but it seems not to affect the clinical severity.<sup>37</sup> Etiologic diagnosis is particularly useful for cohorting patients and for infection control in both hospitalized patients and outpatients and it has a role in research. There are not convincing data suggesting the virology testing to be routinely done in all patients presenting at the ED as it seems not to impact the management decisions.<sup>38</sup>

### Clinical evaluation

The clinical course includes an incubation period of about 5 days followed by the onset of coryza that usually lasts 3 days. Although infants can present fever the very first days of runny nose, they are usually feverless when symptoms of an acute lower respiratory infection appear. As presenting symptom, apnea is always considered a risk factor for severe bronchiolitis.<sup>39,40</sup> In evaluating an infant with bronchiolitis, it is important to know that the risk of reduction in food intake with possible dehydration and of severe respiratory symptoms usually peaks between 3 to 7 days after the onset of rhinitis and cough.<sup>2</sup> Equally important, during these days the child's clinical status can undergo a sudden worsening probably secondary to mucus plugs that may occlude respiratory and terminal bronchioles.

High fever during respiratory distress period is rare and is reported in only 30% of the patients.<sup>2</sup> In the presence of high fever, the child should be carefully evaluated to rule out other causes of fever. Several studies have reported that a proven secondary bacterial infection is present in only 1.2% of the infants with bronchiolitis,<sup>41,42</sup> and should be suspected if the child presents a new fever and the clinical status worsens. A urine tract infection is reported in 1-7% of the febrile infants with bronchiolitis.<sup>43</sup> Particular attention should be paid to infants younger than 30 days of age with high fever (>39 °C) and localized fine crackles at lung auscultation may indicate a possible bacterial pneumonia.

A key point to evaluate when considering a child with bronchiolitis is the food intake. In fact it is well known that it is the first clinical sign predicting the worsening of respiratory effort and it is a good marker of hypoxia.<sup>44</sup>

### Diagnostic examinations

There is no agreement in literature on which are the most appropriate diagnostic examinations of bronchiolitis. The results of six EBG, six CPG, and five CBR (Table I, II, III) on the management of bronchiolitis show how opinions have remained unchanged or have developed over the past 20 years. All the guidelines and reviews

TABLE I.—*Diagnostic tests in infants for bronchiolitis according to the six evidence-based guidelines.*

Parameters	Scotland 2006 <sup>7</sup>	Hong Kong 2006 <sup>8</sup>	Mexico 2015 <sup>9</sup>	NICE 2015 <sup>10</sup>	Finland 2015 <sup>11</sup>	Australasia 2016 <sup>12</sup>
Oxygen saturation						
Pulse oximetry at admission	Yes	Yes	–	Yes	–	Yes
SaO <sub>2</sub> a/a cut off for admission	≤92%	–	<90%	–	–	<92%
SaO <sub>2</sub> a/a cut off for discharge	>94%	–	>94%	>92%	–	>92%
Blood gas assessment only in severe forms	Yes	Yes	–	–	–	–
Chest X-ray						
Recommended as a routine	No	No	No	No	–	No
Blood tests						
Recommended as a routine	No	No	No	No	–	No
Viral tests						
Recommended as a routine	No	–	No	–	–	–
For cohorting	Yes	–	Yes	–	–	–
Clinical variables						
Presence of fever	Yes	Yes	Yes	Yes	–	–
Severe respiratory symptoms peak	72 hours	–	–	3-5 days	–	–
Microbiological tests						
Recommended as a routine	No	–	Yes	Yes	No	No
Urine culture	No	–	–	–	Yes	No

TABLE II.—*Diagnostic tests for infants with bronchiolitis according to the six clinical practice guidelines.*

Parameters	Spain 2010 <sup>13</sup>	South Africa 2010 <sup>14</sup>	Australia 2012 <sup>15</sup>	Australia 2013 <sup>16</sup>	USA 2014 <sup>17</sup>	Colombia 2014 <sup>18</sup>
Oxygen saturation						
Pulse oximetry at admission	Yes	–	Yes	Yes	Yes	Yes
SaO <sub>2</sub> a/a cut off for admission	<92%	<90-92%	<90%	<93%	<90%	≤92%
SaO <sub>2</sub> a/a cut off for discharge	>94%	–	>92%	≥93%	–	–
Blood gas assessment only in severe forms	Yes	–	Yes	Yes	–	–
Chest X-ray						
Recommended as a routine	No	–	No	No	No	No
Blood tests						
Recommended as a routine	No	–	No	No	No	No
Viral tests						
Recommended as a routine	No	No	No	No	–	–
For cohorting	Yes	Yes	Yes	Yes	–	–
Clinical variables						
Presence of fever	–	–	Yes	–	–	–
Severe respiratory symptoms peak	>72 hours	–	1-3 days	4-5 days	–	–
Microbiological tests						
Recommended as a routine	No	No	–	Yes	No	–
Urine culture	No	–	–	–	Yes	–

agree that all infants who come to the emergency room for bronchiolitis should have oxygen saturation (SaO<sub>2</sub>) measured. SaO<sub>2</sub> should be considered in combination with other clinical signs and it should be measured after the infant stabilization and upper airways gentle cleaning.<sup>45, 46</sup>

Two EBG, 3 CPG and 1 CBR agree that arterial gas monitoring should be limited to infants with severe respiratory distress and those needing intensive care unit admission (Table I, II, III).

Regarding the role of laboratory findings in infants with bronchiolitis, all the guidelines and reviews agree that blood tests such as white-blood-cell counts and C reactive protein do not need to be measured routinely, whereas 2 clinical practice guidelines recommended that electrolytes should be measured only in children with severe dehydration needing intravenous (IV) fluid replacement (Table I, II, III).

Chest X-ray is not recommended in infants

TABLE III.—*Diagnostic tests for infants with bronchiolitis according to the five consensus-based methods.*

Parameters	Switzerland 2003 <sup>19</sup>	Brazil 2011 <sup>20</sup>	Italy 2014 <sup>21</sup>	Canada 2014 <sup>22</sup>	Argentina 2015 <sup>23</sup>
Oxygen saturation					
Pulse oximetry at admission	Yes	Yes	Yes	Yes	Yes
SaO <sub>2</sub> a/a cut off for admission	<92%	<92%	<90-92%	<90%	<94%
SaO <sub>2</sub> a/a cut off for discharge	>92%	>94%	>93%	>90%	>94%
Blood gas assessment only in severe forms	—	—	—	—	Yes
Chest X-ray					
Recommended as a routine	No	No	No	No	No
Blood tests					
Recommended as a routine	No	No	No	No	No
Viral tests					
Recommended as a routine	No	No	No	No	No
For cohorting	Yes	Yes	Yes	Yes	Yes
Clinical variables					
Presence of fever	—	—	—	—	—
Severe respiratory symptoms peak	—	—	—	>4 days	4-6 days
Microbiological tests					
Recommended as a routine	No	No	—	No	—
Urine culture	—	—	—	Yes	—

with mild or moderate bronchiolitis and should be performed only in infants with severe bronchiolitis, or in those suspected of having a complication or bacterial pneumonia (Table I, II, III).

Bronchiolitis is viral disease and viral testing can be important to reduce the inappropriate use of antibiotics. Most of the guidelines and reviews recommend viral testing but only for clustering patients to reduce infection spreading in the department (Table I, II, III).

### Admission to the hospital

Physicians sometimes find it difficult to decide when an infant with bronchiolitis should be admitted to the hospital. In making this decision, they should consider the presence of one or more risk factors for more severe disease, disease timing, the infants' clinical signs and symptoms, and family reliability.

Current guidelines reach a good consensus that infants without risk factors but with severe retractions, nasal flaring, SaO<sub>2</sub> <90%, respiratory rate >70 breaths/minute, apnea episodes and <75% food intake should be hospitalized for monitoring and treatment.

Several risks factors exist for a severe course of bronchiolitis and infants with one of these risk factors should be carefully considered for hospital admission even in the absence of severe respi-

ratory symptoms. An important risk factor is the infant's age.<sup>47</sup> Many studies have reported that bronchiolitis is more severe in infants younger than 3 months of age. This age-related difference probably reflects the smaller bronchial tree and the immunological system immaturity in younger infants. Comorbidities such as severe prematurity, immunodeficiency, neurological diseases, chronic lung diseases, and congenital heart diseases are all associated with severe bronchiolitis. Finally, in deciding hospital admission, independently from the clinical severity, important features to consider are the parents' ability to manage the child at home and to recognize the signs of disease worsening. Passive smoke and low social economic status has been associated with an increased risk to develop bronchiolitis.<sup>48-51</sup> The only protective factor for bronchiolitis is breastfeeding, a practice that should always be encouraged.<sup>51</sup>

Bronchiolitis is an evolving disease, and the clinical signs usually worsen between 3 and 7 days after the onset of coryza. Therefore infants, particularly if younger than 3 months of age, even if in general conditions, should be carefully monitored during disease progression because bronchiolitis can worsen.

Many clinical severity scores for bronchiolitis, based on feeding capacity, SaO<sub>2</sub>, retractions, nasal flaring, tachypnea and infant behavior have

been published and should be used in evaluating the disease's severity and infant management.<sup>36, 52, 53</sup>

## Management

### Supportive management

Nowadays the treatment of bronchiolitis is mainly supportive. Bronchiolitis infant should undergo minimum handling and should be kept in the supine position at 45° degrees and with the head slightly hyperextended.<sup>54</sup> Intravenous or *via* nasogastric tube hydration should be provided when the child is not able to feed, and/or he/she manifests severe tachypnea (respiratory rate higher than 70 beats/minute).<sup>55</sup>

A pivotal point in managing the child with bronchiolitis is oxygen administration. Most guidelines recommend oxygen when SaO<sub>2</sub> is either lower than 92% or lower than 90% (Table IV, V, VI). Given that hemoglobin affinity for oxygen describes a sigmoid shape, a little difference in the blood oxygen partial tension occurs between SaO<sub>2</sub> of 98% or 90%. For this reason, oxygen can be administered safely even using the 90% threshold.

### Pharmacological management

Although bronchiolitis has a well-known pathogenesis, no effective medical treatment is yet available for this disease. The various medications used so far have allowed scarce clinical

TABLE IV.—Support therapy in infants with bronchiolitis according to the six evidence-based guidelines.

Parameters	Scotland 2006 <sup>7</sup>	Hong Kong 2006 <sup>8</sup>	Mexico 2015 <sup>9</sup>	NICE 2015 <sup>10</sup>	Finland 2015 <sup>11</sup>	Australasia 2016 <sup>12</sup>
Physio-kinesiotherapy	No	No	—	No	—	No
Nasal suction						
Recommended as a routine	Yes	No	—	No	—	No
Gently	—	—	—	—	—	Yes
Frequently	—	—	—	—	—	—
Fluid maintenance						
Nasogastric	Yes	—	—	Yes	—	Yes
Intravenous	—	Yes	—	Only in PICU	—	Yes
Nasogastric equivalent to intravenous	—	—	—	—	—	Yes
Oxygen administration						
When to start	≤92%	—	<90%	<92%	—	<92%
When to suspend	>94%	—	>94%	>92%	—	>92%

PICU: pediatric intensive care unit.

TABLE V.—Support therapy in infants with bronchiolitis according to the six clinical practice guidelines.

Parameters	Spain 2010 <sup>13</sup>	South Africa 2010 <sup>14</sup>	Australia 2012 <sup>15</sup>	Australia 2013 <sup>16</sup>	USA 2014 <sup>17</sup>	Colombia 2014 <sup>18</sup>
Physio-kinesiotherapy	No	No	No	No	No	—
Nasal suction						
Recommended as a routine	Yes	—	No	No	—	—
Gently	—	—	Yes	—	—	—
Frequently	—	—	Yes	—	—	—
Fluid maintenance						
Nasogastric	Yes	—	Yes	Yes	Yes	—
Intravenous	Only in PICU	—	Only in PICU	Only in PICU	Yes	—
Nasogastric equivalent to intravenous	—	—	Yes	—	Yes	—
Oxygen administration						
When to start	<90-92%	<90-92%	<95%	<93%	<90%	≤92%
When to suspend	>94%	—	>95%	≥93%	—	—

PICU: pediatric intensive care unit.

TABLE VI.—*Support therapy in infants with bronchiolitis according to the five consensus-based methods.*

Parameters	Switzerland 2003 <sup>19</sup>	Brazil 2011 <sup>20</sup>	Italy 2014 <sup>21</sup>	Canada 2014 <sup>22</sup>	Argentina 2015 <sup>23</sup>
Physio-kinesiotherapy	No	No	No	No	No
Nasal suction					
Recommended as a routine	Yes	Yes	Yes	Yes	—
Gently	—	—	Yes	Yes	—
Frequently	—	—	—	—	—
Fluid maintenance					
Nasogastric	Yes	Yes	Yes	Yes	—
Intravenous	—	Only in PICU	Yes	Yes	—
Nasogastric equivalent to intravenous	—	—	Yes	Yes	—
Oxygen administration					
When to start	≤92%	<92%	<90-92%	<90%	<94%
When to suspend	>94%	>94%	>93%	>90%	>94%

PICU: pediatric intensive care unit.

improvement and controversial results. Despite evidence reported by many guidelines published on bronchiolitis management, some therapeutic agents are still used worldwide in the treatment of infants hospitalized for this disease.<sup>56</sup> Specific studies in infants with a restrictive definition of bronchiolitis should evaluate responses to medical treatment.

### Bronchodilators

Bronchodilators used for managing infants with bronchiolitis include albuterol (beta-adrenergic agent), ipratropium bromide (anticholinergic agent) and epinephrine (adrenergic agent). A Cochrane review on albuterol reporting the results of 22 clinical trials enrolling 1428 infants with

bronchiolitis, showed no significant improvement in clinical score, in SaO<sub>2</sub>, in the rate of hospital admission, and in the length of hospitalization among infants treated with albuterol compared to those receiving placebo.<sup>57</sup> The results of these clinical trials should be also considered with caution because the controversial results observed in some patients reflect the various clinical definitions. A positive effect has possibly been shown in older patients possibly having recurrent wheezing episodes. All the guidelines analyzed reported that albuterol should not be used routinely in infants with bronchiolitis (Table VII, VIII, IX). Twelve guidelines reported that albuterol should be tried only in older infants with predominant wheezing at auscultation and

TABLE VII.—*Therapy in infants with bronchiolitis according to the six evidence-based guidelines.*

Parameters	Scotland 2006 <sup>7</sup>	Hong Kong 2006 <sup>8</sup>	Mexico 2015 <sup>9</sup>	NICE 2015 <sup>10</sup>	Finland 2015 <sup>11</sup>	Australasia 2016 <sup>12</sup>
Antibiotics						
Recommended as a routine	No	No	No	No	—	No
Used in the PICU	—	Yes	—	—	—	—
β <sub>2</sub> agonists						
Recommended as a routine	No	No	No	No	No	No
Trial	—	Yes	Yes	—	—	No
Anticholinergics	No	No	—	No	—	No
Epinephrine						
Recommended as a routine	No	No	No	No	No	No
Recommended as a routine in outpatients	—	Yes	—	—	No	No
Corticosteroids						
Inhaled	No	No	No	No	No	No
Oral	No	No	No	No	No	No
Used in the PICU	—	Yes	—	—	No	—
3% hypertonic saline	—	—	Yes	No	Yes	No

PICU: pediatric intensive care unit.

TABLE VIII.—*Therapy in infants with bronchiolitis according to the 6 clinical practice guidelines.*

Parameters	Spain 2010 <sup>13</sup>	South Africa 2010 <sup>14</sup>	Australia 2012 <sup>15</sup>	Australia 2013 <sup>16</sup>	USA 2014 <sup>17</sup>	Colombia 2014 <sup>18</sup>
Antibiotics						
Recommended as a routine	No	No	No	–	No	No
Used in the PICU	Yes	Yes	–	–	Yes	–
$\beta_2$ agonists						
Recommended as a routine	No	No	No	No	No	No
Trial	Yes	Yes	Yes	Yes	No	Yes
Anticholinergics	No	No	No	–	–	–
Epinephrine						
Recommended as a routine	No	No	–	–	No	No
Recommended as a routine in outpatients	Yes	Yes	–	–	No	No
Corticosteroids						
Inhaled	No	No	–	No	No	No
Oral	No	No	No	No	No	No
Used in the PICU	No	–	–	–	No	–
3% hypertonic saline	Yes	Yes	–	Yes	Yes	No

TABLE IX.—*Therapy in infants with bronchiolitis according to the 5 consensus-based methods.*

Parameters	Switzerland 2003 <sup>19</sup>	Brazil 2011 <sup>20</sup>	Italy 2014 <sup>21</sup>	Canada 2014 <sup>22</sup>	Argentina 2015 <sup>23</sup>
Antibiotics					
Recommended as a routine	No	No	No	No	No
Used in the PICU	–	Yes	–	–	–
$\beta_2$ agonists					
Recommended as a routine	No	No	No	No	No
Trial	Yes	Yes	Yes	Yes	Yes
Anticholinergics	–	No	No	–	–
Epinephrine					
Recommended as a routine	–	No	–	No	–
Recommended as a routine in outpatients	–	Yes	–	No	–
Corticosteroids					
Inhaled	No	No	No	No	No
Oral	No	No	No	No	No
Used in the PICU	–	No	–	–	–
3% hypertonic saline	–	Yes	No	Yes	–

PICU: pediatric intensive care unit.

with risk factors for atopy. Future studies may be needed to analyze the effect of albuterol by grouping infants with acute viral bronchiolitis according to age and auscultatory findings.

A Cochrane review on ipratropium bromide, reporting results of six clinical trials involving 321 infants, concluded that more evidence is needed before we can consider the use of this nebulized anticholinergic agent in the treatment of infants with bronchiolitis.<sup>58</sup> All the analyzed guidelines agree that nebulized ipratropium bromide should be avoided in infants with bronchiolitis.

Epinephrine is an adrenergic agent possessing both alpha and beta activities. Unlike albuterol,

the drug might also act by reducing edema in the bronchial mucosa. A Cochrane review reported the results of 19 studies enrolling 2,256 infants younger than 2 years with acute viral bronchiolitis and comparing epinephrine with placebo.<sup>59</sup> The study showed a reduction in the admission rate at day 1 but not at day 7 after an emergency department visits in those infants receiving epinephrine but found no differences in length of hospital stay for inpatients. When they analyzed studies comparing epinephrine *versus* albuterol they found no admission differences for outpatients, but inpatients receiving epinephrine had a shorter hospital stay than those receiving albuterol.

A multicenter randomized double-blind trial conducted in 404 hospitalized infants with bronchiolitis has evaluated treatment with nebulized epinephrine at a fixed-schedule or on-demand versus placebo, using the length of hospital stay as primary outcome. No significant differences were observed in the length of hospital stay between the two groups (epinephrine vs placebo) when epinephrine was administered at a fixed time. Conversely, the hospital stay was 12 hours shorter in the group of infants who were treated with epinephrine on demand than in the infants receiving epinephrine at a fixed-schedule.<sup>60</sup>

All the guidelines recommend against using epinephrine routinely in inpatients. Only four guidelines recommend the use of epinephrine in outpatients in the emergency department with acute viral bronchiolitis (Table VII, VIII, IX).

### Corticosteroids

Systemic or inhaled corticosteroids are ineffective in infants with bronchiolitis. A Cochrane review reported the results of 17 trials on 2596 participants. The study provided no support for systemic or inhaled corticosteroids in infants with bronchiolitis because they do not change the admission rate and length of hospital.<sup>61</sup>

None of the analyzed guidelines support the use of corticosteroids in the treatment of infants with bronchiolitis (Table VII, VIII, IX). Only one guideline suggests using them in infants hospitalized in the intensive care unit.

### Hypertonic saline

A Cochrane review including seven studies on 581 infants has reported that 3% nebulized hypertonic reduces the length of hospital stay among infants hospitalized with mild-to-moderate bronchiolitis and improves the clinical severity score.<sup>62</sup> Conversely, two recent multicenter randomized double-blind studies performed in Europe and in Australia reported different results. They showed that 3% hypertonic saline did not change the length of hospital stay and duration of oxygen administration in hospitalized infants with bronchiolitis.<sup>63, 64</sup>

Recently, Zhang *et al.* published a Cochrane review including 28 trials involving 4195 infants

with bronchiolitis. 2222/4195 infants received hypertonic saline 3% and showed significant shorter length of hospital stay (GRADE quality of evidence: low), lower post-inhalation clinical score (GRADE quality of evidence: low) and lower risk of hospitalization (GRADE quality of evidence: moderate) than infants treated with normal saline.<sup>62</sup>

Discordant recommendations come also from the guidelines. Only eight guidelines recommend the use of nebulized 3% hypertonic saline in infants with bronchiolitis (Table VII, VIII, IX). Considering the last multicenter studies, we think that at the moment there is insufficient evidence to recommend the use of hypertonic saline in hospitalized infants with bronchiolitis.

### Antibiotics

Despite it is well recognize that bronchiolitis is a viral infection, the difficulties of the differential diagnosis with a bacterial infection induce many physicians to use antibiotics for its management. A Cochrane review reporting results of five studies with 543 infants showed minimal evidence to support the use of antibiotics for bronchiolitis.<sup>65</sup> Antibiotics should be used only in infants with severe respiratory symptoms who are at risk a secondary bacterial infection.

Macrolides have been tested in infants with bronchiolitis. A double-blind, placebo-controlled, randomized clinical trial with azithromycin in infants hospitalized for bronchiolitis demonstrated no difference in the length of hospital stay, duration of oxygen treatment and hospital readmission.<sup>66</sup> Conversely, in a small randomized double-blind clinical trial performed in 21 infants with bronchiolitis, clarithromycin seemed able to reduce the length of hospital stay and the duration of oxygen administration.<sup>67</sup> Yet the studies conducted so far on macrolides in infants with bronchiolitis cannot yet suggest the use of these antibiotics in infants with this disease.

All the guidelines agree on the fact that antibiotics should not be used routinely in infants with bronchiolitis unless they manifest signs of a secondary bacterial infection. Five guidelines recommend the use of antibiotics in the intensive care unit (Table VII, VIII, IX).



### Other medications

A multicenter randomized double-blind controlled clinical trial in 225 oxygen-dependent infants hospitalized for bronchiolitis has shown that nebulized human deoxyribonucleases (DNase) failed to reduce the length of hospital stay.<sup>68</sup> Yet, nebulized DNase seems effective in infants with bronchiolitis complicated with a lobar collapse.<sup>69</sup> This observation awaits confirmation from other studies.

A Cochrane review including 5 studies with 1296 infants hospitalized for bronchiolitis showed that montelukast has no effect on the length of hospital stay and the clinical severity score.<sup>70</sup>

One study evaluated the effect of IV magnesium sulfate (MS) in infants with bronchiolitis.<sup>71</sup> No difference was observed in the readiness for discharge and bronchiolitis severity score between infants receiving IV MS or placebo.<sup>71</sup>

None of the analyzed guidelines recommends the use of DNase, montelukast and IV MS in the treatment of infants with bronchiolitis.

### Hospital discharge

Another important question relates to when an infant hospitalized with bronchiolitis can be safely discharged to home.<sup>72, 73</sup> In their prospective multiyear cohort study in 1,916 children admitted to the hospital for bronchiolitis, Mansbach *et al.*, found that in 88% of the infants the median number of days for clinical improvement was 4. The main risk factors for a longer hospital stay were: age <2 months, gestational age <37 weeks, severe retractions, inadequate oral intake and apnea.<sup>74</sup> The most important clinical variables to be considered for discharging an infant with bronchiolitis are food intake, respiratory status and SaO<sub>2</sub>. In a prospective observational study performed in 68 infants hospitalized for bronchiolitis, Cunningham *et al.*, have shown that the average time needed to resolve feeding difficulties was 22 hours. This time was shorter than the time needed to stabilize SaO<sub>2</sub>>94%. Food intake is therefore a highly sensitive criterion to take into consideration both when respiratory status worsens and when the child starts to recover from bronchiolitis.<sup>75</sup>

Another important point that can influence the length of hospital stay is the decision to monitor SaO<sub>2</sub> continuously or intermittently. When the child is hospitalized, continuous monitoring should be reserved to very severe hypoxemic cases, especially in the first 24 hours. Intermittent SaO<sub>2</sub> measurement is recommended in all other circumstances, as it was demonstrated in a randomized study on the use of intermittent vs continuous pulse oximetry for non-hypoxemic infants hospitalized for bronchiolitis.<sup>76</sup> All the guidelines analyzed agree that when SaO<sub>2</sub> is between 92-94% the child can be safely discharged from the hospital.

In conclusion, a child with bronchiolitis can be safely discharged from the hospital when oral fluid intake becomes adequate (>75% of the daily needs), the SaO<sub>2</sub> is >92% and the clinical conditions are stable.

### New therapeutics

Over the last decade, researchers have developed experimentations on new therapeutics for viral bronchiolitis with a particular focus on antivirals and vaccines. There are only two antivirals that has been approved by the Food and Drug Administration for treatment of RSV infection: inhaled ribavirin that it is no longer recommended because of insufficient proof of effectiveness, and Palivizumab, a humanized monoclonal antibody that targets the RSV F protein, administered for immunoprophylaxis in high-risk infants. Recently, there are under investigation in clinical trials 11 new antivirals for RSV that belong to four main therapeutic classes: immunoglobulins, siRNA-interference, fusion inhibitors, and small molecules.<sup>77</sup>

Regarding the development of a RSV vaccine, the landscape has recently expanded. Up to now there are 19 vaccine candidates using four approaches: particle-based, live-attenuated or chimeric, subunit and vector-based. Those prophylactic measures are designed to protect the population of young infants and children that are at high risk of severe forms and the older adults, an emerging target of at risk subjects.<sup>78</sup>

## Conclusions

Despite the many publications, bronchiolitis treatment does not significantly differ from what has been proposed almost 70 years ago.<sup>79</sup> Pediatricians taking care of infants with bronchiolitis should be well acquainted with its clinical symptoms and course.

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