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Recent advances in the management of acute bronchiolitis

Claudia Ravaglia and Venerino Poletti*

Address: Pulmonology Unit, Department of Thoracic Diseases, GB Pierantoni - L Morgagni Hospital, via C. Forlanini 34, 47100 Forlì, Italy

* Corresponding author: Venerino Poletti (venerino.poletti@gmail.com)

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Abstract

Acute bronchiolitis is characterized by acute wheezing in infants or children and is associated with signs or symptoms of respiratory infection; it is rarely symptomatic in adults and the most common etiologic agent is respiratory syncytial virus (RSV). Usually it does not require investigation, treatment is merely supportive and a conservative approach seems adequate in the majority of children, especially for the youngest ones (<3 months); however, clinical scoring systems have been proposed and admission in hospital should be arranged in case of severe disease or a very young age or important comorbidities. Apnea is a very important aspect of the management of young infants with bronchiolitis. This review focuses on the clinical, radiographic, and pathologic characteristics, as well as the recent advances in management of acute bronchiolitis.

Introduction

Bronchiolitis is a general term used to describe a non-specific inflammatory injury that primarily affects the small airways (less than 2 mm in diameter). The term can describe a clinical syndrome or a constellation of histological abnormalities that may occur in a variety of disorders [1–3]. Primary bronchiolitis can develop into acute bronchiolitis, but also into constrictive bronchiolitis, respiratory bronchiolitis, follicular bronchiolitis, mineral dust airway disease and diffuse panbronchiolitis (Table 1); not all of them are associated with airflow limitation.

Definition and etiology

Acute bronchiolitis is rarely symptomatic in adults because total pulmonary resistance is influenced to a lesser extent by small airways. Inhalation injury, infections, drug-induced processes or known exposure to a predisposing factor before the onset of the disease are associated with acute bronchiolitis [4–9]. Examples of predisposing factors include inhalation of nitrogen oxides, ammonia, welding fumes, or food flavoring fumes (e.g. diacetyl) – infection with RSV, adenovirus, or *Mycoplasma pneumoniae* – and ingestion of busulfan, gold, or penicillamine. Other potential causes could be aspiration, lung and bone marrow transplantation, connective tissue diseases and Stevens–Johnson syndrome [10]. However, the term acute bronchiolitis generally refers to a disease characterized by acute wheezing in infants or children, associated with signs or symptoms of respiratory infection [11–13]. Bronchiolitis is a clinical diagnosis described as "a constellation of clinical symptoms and signs including a viral upper respiratory prodrome followed by increased respiratory effort, wheezing and diffuse bilateral crackles in children less than 12 months of age" by the European Respiratory Society (ERS) and in children no less than 24 months by the American Academy of Pediatrics (AAP) [14]. Common viruses, such as rhinoviruses, which are typically limited to the upper respiratory tract, can trigger recurrent wheezing [15]. Approximately 20% of children develop acute bronchiolitis in the first year of life [16–19], mostly in winter, and 2–3% of them are hospitalized as a result [14,20–23]. The most common etiologic agent is RSV (60–80% of cases) [13,24,25] but adenoviruses, rhinoviruses, enteroviruses, influenza and parainfluenza viruses, and human metapneumovirus (HMPV) can also be responsible [14,26–28]; in particular, rhinovirus is the second most common virus inducing acute bronchiolitis, and HMPV seems to account for 3–19% of bronchiolitis cases [29,30]. Other pathogens are mycoplasma and

Table 1. Classification of bronchiolar disorders Adapted from [1]

- Acute bronchiolitis
- Constrictive bronchiolitis
- Respiratory bronchiolitis
- Diffuse panbronchiolitis
- Follicular bronchiolitis
- Mineral dust airway disease
- Interstitial lung diseases with bronchiolar involvement (RB-ILD/DIP, HP, COP, pulmonary Langerhans' cell histiocytosis, sarcoidosis, bronchiolocentric interstitial pneumonia)
- Large airway diseases with bronchiolar involvement (chronic bronchitis, bronchiectasis, asthma)
- Other bronchiolar disorders (e.g., diffuse aspiration bronchiolitis, lymphocytic bronchiolitis)

RB-ILD/DIP, respiratory bronchiolitis–associated interstitial lung disease/desquamative interstitial pneumonia; HP, hypersensitivity pneumonitis; COP, cryptogenic organizing pneumonia

chlamydia, and other fungal and mycobacterial infections [11,12,31–33]. Dual infections are reported in 20–30% of children, most commonly with RSV and either HMPV or rhinovirus [34], but whether concomitant infection modifies the severity of bronchiolitis is not known [18,34–39]. Pathological changes of the airways of children with bronchiolitis can explain symptoms of the disease and help in finding appropriate treatment [11,40]. The infection starts in the upper airways and spreads to the lower airways within a few days, with subsequent bronchial inflammation and invasion of white blood cells (mostly mononuclear cells), edema of the submucosa and adventitia [18,22]. Airways can be partially or totally obstructed by plugs of necrotic epithelium and fibrin [1,15,40], sometimes with a "ball-valve" mechanism, resulting in trapping of air distal to obstructed areas, atelectasis and mismatch of pulmonary ventilation and perfusion [21,22]. Smooth-muscle constriction seems to be much less important in the pathological process [15,22]. Epithelium damage may be caused directly by viruses [18] or indirectly by several chemokines, including macrophage inflammatory protein-1, interleukin (IL)-8, IL-6, IL-1, and Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES) [41,42]. These cytokines can recruit and activate neutrophils, lymphocytes, macrophages, eosinophils, and natural killer cells [41,42], and can also increase mucus production and airway hyper-reactivity [43].

Clinical picture and diagnosis

The most common clinical signs of bronchiolitis in children are tachypnea, tachycardia, and prolonged expiration [10,11]. Usually, a 2–6 month old infant presents with worsening respiratory symptoms, preceded by a 2–3 days history of rhinorrhea [44,45]. Fever is uncommon and rarely ≥40 degrees centigrade [46,47]. Cyanosis may be observed in severe cases [45], particularly in infants who were premature, with episodes of apnea at presentation [48] as well as feeding problems [18,22]. On examination, there are typically fine inspiratory crackles and/or expiratory wheeze [13], nasal flaring, high respiratory rate and chest retractions [10,11]; an alternative diagnosis should be sought if the infant is drowsy, lethargic, irritable, pale or mottled [45]. Risk factors for bronchiolitis, or a poor outcome, include prematurity, young age, male gender, period of birth, underlying lung disease (such as bronchopulmonary dysplasia), neuromuscular disease, heart disease, exposure to tobacco smoke, young maternal age, short duration/no breastfeeding, maternal asthma and poor socioeconomic factors [18,19,44,48]. Individual clinical findings on physical examination have limited value in predicting outcomes, because of the minute-to-minute variability [15,49]. Recently, specific gene polymorphisms have been identified [50,51], for example, vitamin D receptor gene may reveal neonatal vitamin D levels, associated with wheezing in infants [52,53]. In adults, bronchiolitis should be considered in patients who present with cough and dyspnea, especially when the symptoms do not follow a typical pattern for asthma or chronic obstructive pulmonary disease. The clinical setting may alert the clinician to suspect bronchiolitis; for example, recent toxic fume exposure, symptoms of viral infection, history of organ transplantation, or concomitant connective tissue disease [1]. Acute bronchiolitis usually does not require investigations [11,14,22,54,55]. Viral antigen tests usually have only a small predictive value [56]; the identification of specific agents can be limited to the hospital setting, where it can reduce use of antibiotics, number of investigations and length of hospitalization [18,57–59]. RSV infection should be confirmed by a nasopharyngeal aspirate and can be useful for infection control purposes [14,45]; however, this has been questioned by others [27]. A positive viral test could be useful to exclude bacterial infections in infants with bronchiolitis and fever during the first few months of life; some authors have shown that bacterial infections can accompany RSV infection, mostly in the urinary tract [60]. However, a prospective study of 218 patients excluded serious bacterial infections in young infants with fever [61]. Again, in the majority of cases, the diagnosis of bronchiolitis is clinical. Oxygen saturation should be measured [14,22], while blood gas measurement to detect hypercapnia is indicated only in critical cases [18,62]. Mansbach *et al.* demonstrated that a pulse oximetry level of 94% could be related to an increased likelihood of hospitalization [63]; Shaw *et al.* had previously revealed that mild hypoxia could correlate with a more severe disease course, reflecting a pulmonary ventilation-to-perfusion mismatch [64]. Blood and urine cultures [62], urea and electrolytes should be measured only in particular conditions [48], but all the admitted infants should receive barrier nursing, to avoid nosocomial spread of infection [45]. Chest radiography is not usually recommended as a routine test [14,45,54,65], but it can be more useful in children with high or prolonged fever, low oxygen saturation, underlying cardiopulmonary disease or mechanical ventilation [54,66]. Differential diagnosis may include gastroesophageal reflux, laryngotracheobronchomalacia, pertussis, foreign body aspiration, vascular ring and other mediastinal obstructions or other congenital lung diseases [18,22], but it is very seldom necessary to think about a differential diagnosis. Asthma should also be considered in infants older than 12 months of age with recurrent episodes of wheezing [18]. When bronchiolitis is suspected in adults, the most helpful tests are chest imaging, usually a high resolution computerised tomography (HRCT) scan, and pulmonary function testing with diffusing capacity and ambulatory oximetry. The most consistent abnormalities on HRCT are expiratory air trapping (mosaic or diffuse) and bronchial wall thickening (e.g. centrilobular nodules and "v" or "y" shaped branching linear opacities) [66,67]. In addition, a pattern of diffuse ground glass opacity and a mosaic pattern of attenuation are seen in some patients [68,69]. Other than a mosaic pattern of attenuation, which is highly suggestive of bronchiolitis obliterans, it is often difficult to distinguish severe asthma from bronchiolitis [70,71]. Cylindric bronchial dilation or bronchiectasis can be seen with constrictive bronchiolitis, particularly in cases related to transplantation, collagen vascular disease, inhalation of toxic fumes, and previous infection [72]. Subpleural distribution of patchy consolidation or ground glass density is a characteristic finding of proliferative bronchiolitis on HRCT. Well or poorly-defined nodules on CT scans may correlate with areas of organizing pneumonia [73].

Management

A conservative approach to treatment seems adequate in the majority of children, especially for the youngest ones (<3 months) [21,22,72] and treatment is merely supportive. Clinical scoring systems have been proposed [62], but none have been formally accepted [44], although the New Zealand and Scotland guidelines have classified bronchiolitis into mild, moderate and severe (Table 2). Patients with uncomplicated bronchiolitis do not benefit from antibiotics [62]. Patients can deteriorate for 2–3 days after the onset of the disease but then start to improve [46], therefore hospital admission could be arranged after review if there is no improvement [46] and supplemental treatments should then be considered [31,74,75]. An important decision is whether to admit the patient to hospital and what are the indications for admission, candidates being severe disease, very young age, or important comorbidities (Table 3).

Apnea is a very important aspect of the management of young infants with bronchiolitis [15]. A retrospective study of 691 infants revealed that apnea can occur in 2.7% of cases [59], with young age and previous apneic episodes being the major risk factors [59]. Thresholds for oxygen therapy may influence outcomes: low values of oxygen saturation are representative of a higher risk of hospitalization [76] and, in these cases, hospitalization itself can be more prolonged [77]; administration of oxygen is therefore recommended for values of SpO2 <90% [14,77]. It is crucial to monitor oxygen saturation continuously during treatment [78], but monitoring can be slowed down or suspended as the child improves [14]. Recent studies have focused on indications and procedures of home oxygen therapy [79,80]. Adequate hydration is fundamental [1,21] as fever and tachypnoea may cause inadequate feeding and eventually poor hydration [81,82]. Oral feeding may be sustained and breastfeeding should be encouraged [44]. Enteral feeding by gastric tube, as boluses or continuously, should be started if the infant will not suck [78,82–87] as it can improve the nutritional status of infants and can be a direct route for breast milk administration [82,88]. However, it can interfere with breathing in compromised infants and intravenous fluids (IV) are preferred in these cases [21,22,45,82] to reduce the risk of aspiration [89,90].

Table 2. Assessment of the severity of bronchiolitis in infants <12 months Adapted from [41,55]

	Mild bronchiolitis	Moderate bronchiolitis	Severe bronchiolitis
Feeding	Normal	Less than usual >half the normal	Not interested <half the normal
Respiratory rate	<2 months >60/min >2 months >50/min	>60/min	>70/min
Chest wall recessions	Mild	Moderate	Severe
Nasal flare or grunting	Absent	Absent	Present
Sp02	>92%	88–92%	<88%
General behavior	Normal	Irritable	Lethargic

Table 3. Indications for hospital referral for acute bronchiolitis Adapted from [39]

Absolute indications	Relative indications	Indications for intensive care
− Cyanosis or very severe respiratory distress (RR >70 breaths/min, nasal flaring and/or grunting, severe chest wall recession) − Marked lethargy − Respiratory distress preventing feeding − Apneic episodes − Diagnostic uncertainty (toxic infant, temperature ≥40 degrees centigrade)	− Congenital heart disease − Any survivor of extreme prematurity − Any pre-existing lung disease or immunodeficiency − Down's syndrome − Social factors: isolated family	− Failure to maintain saturations >90% with increasing oxygen requirement − Deteriorating respiratory status and impending exhaustion − Worsening episodes of apnea

The current guidelines recommend that the amount of fluids administered to avoid dehydration should be at least 70–80% of the usual daily requirement, especially in infants with more severe disease [14,21,83], but should not exceed 100%, to avoid fluid overload or even electrolyte imbalances [14,81,82,90,91]. Monitoring of body weight, urine and serum osmolarity and electrolytes may therefore be useful in these cases [21,92]. Inhaled normal saline (0.9%) can be administered to increase clearing of mucous [44], although it is not suggested in current guidelines and reviews [14,18,21,22,93]. Hypertonic saline inhalations can determine an osmotic flow of water to the mucus layer [94], modifying the mucociliary clearance, but must include a bronchodilator as it can induce bronchospasm [44,95,96]. However, inhaled hypertonic saline is not recommended, and trials with hypertonic saline without bronchodilators are ongoing [21]. Several studies have focused on the role of bronchodilators in the treatment of bronchiolitis [15,97]. Although bronchodilators can produce an initial transient clinical improvement, especially because of their effect on the bronchial mucosa, a significant clinical benefit has never been demonstrated; therefore epinephrine, β2 agonists and anticholinergics are not recommended as routine therapy [44,62,97–99]. Inhaled adrenaline, for example, does not seem to reduce the duration of hospitalization in patients with moderate or severe bronchiolitis [98] and an "as needed" rather than a continuous administration may be more useful, as it could result in less inhalations per day (12 vs. 17), shorter hospitalization (47.6 vs. 61.3 hours), lower oxygen consumption (38.3 vs. 48.7%) and a reduced need for ventilatory support (4.0 vs. 10.8%) [74]. This effect is mainly observed in children aged less than 3 months, in whom a conservative approach would therefore be preferable. The use of corticosteroids in bronchiolitis is controversial [99]. On one hand, several clinical studies have excluded some benefits of systemic or inhaled steroids [100] in reducing both the rate of hospitalization [101] and the duration of hospitalization [102,103]. On the other hand, van Woensel *et al.* demonstrated that dexamethasone (0.15 mg/kg every 6 hours for 48 hours) may be useful in mechanically ventilated children or critically ill children in general [104]. The Pediatric Emergency Care Applied Research Network multicenter study found that a single oral dose of dexamethasone was not much more effective than placebo during treatment of the first episode of bronchiolitis in previously healthy children [105]. There are insufficient data to support the use of antibiotics in bronchiolitis in children in general [106], but it can be justified in the case of concomitant bacterial infections in infants with severe disease, especially in those who require mechanical ventilation [107]. Currently, there is no known role for antiviral therapy in bronchiolitis and therefore no indication for ribavirin, either nebulized or intravenous [108,109]. Surfactant also should not be recommended, as suggested in a recent Cochrane review [110]. Continuous positive airway pressure (CPAP) may improve respiratory failure and help avoid intubation of patients in the Intensive Care Unit [111]; CPAP can recruit alveoli, reduce airway resistance and improve lung emptying during expiration, resulting in improved gas exchange and decreased hyperinflation [112,113]. During mechanical ventilation with CPAP, pressure should generally be between 4 and 8 cmH2O, and a pressure of 7 cmH2O seems to be optimal to reduce respiratory distress [114]. The use of heated humidified high-flow nasal cannula (HFNC) can also increase pharyngeal pressure, thereby reducing respiratory efforts [115–117], and is better tolerated by the patient [118–120]. In cases where nasal CPAP is not sufficient, proper mechanical ventilation can be applied [120,121], both volume and pressure cycled, with different values of respiratory rate (10–60 per minute), maximum pressure (20–50 cmH2O) and tidal volume (6–20 ml/kg) [113]. The use of positive end expiratory pressure (PEEP) can also be considered in some cases (0–15 cmH2O) [113]. Finally, children with severe bronchiolitis (especially those with bronchopulmonary dysplasia), who do not improve despite mechanical ventilation, can benefit from extracorporeal membrane oxygenation [122,123]. Cochrane reviews do not recommend RSV immunoglobulin [124,125] or chest physiotherapy [126]. Gentle nasal suction to keep the air passages clear could be beneficial in infants with copious secretion [45]. In adults, treatment of the various forms of bronchiolitis depends upon the underlying cause or associated disorder. Inhaled bronchodilators and cough suppressants are often employed to control the cough that is frequently present. Macrolide antibiotics are being increasingly used in the management of bronchiolitis because of their success in improving symptoms, lung function, and mortality [127–130], mostly in bronchiolitis associated with mycoplasma infections. Glucocorticoids are commonly employed and are quite effective, particularly when bronchiolitis is associated with organizing pneumonia (e.g. cryptogenic organizing pneumonia) [131]; a dose of prednisone 0.5 to 1 mg/kg lean body weight per day to a maximum of 60 mg per day is usually recommended in the acute phase, then gradually tapered over three to six months. In bronchiolitis due to toxic inhalation injury, glucocorticoids are occasionally effective in the management of both the acute-phase illness (pulmonary edema) and the late-phase illness (bronchiolitis obliterans). Bronchiolitis in the setting of rheumatoid arthritis is sometimes related to medication (e.g. penicillamine, or gold), so any potential culprit medications should be discontinued. High dose systemic glucocorticoids have been used with variable success [132]. In patients with bronchiolitis obliterans following organ transplantation, intensification of immunosuppression is sometimes successful; gastroesophageal reflux disease (GERD) is prevalent in lung transplantation recipients, and non-acid reflux has been associated with the development of bronchiolitis obliterans syndrome. Aggressive therapy for GERD, possibly including surgery, has been proposed to prevent the progression of bronchiolitis obliterans syndrome, although additional studies are needed. Overall, the mortality rate of acute bronchiolitis is less than 1% [31,75] and varies from 2.9 (UK) to 5.3 (US) deaths per 100,000 for RSV bronchiolitis occurring in children aged less than 12 months [133,134]. The majority of deaths are observed in infants younger than 6 months and risk factors are premature birth, concomitant cardiopulmonary disease, immunodeficiency [14,133] or difficult socioeconomic conditions [44]. Wainwright evaluated children with bronchiolitis treated in outpatient clinics and described the resolution of symptoms in 40% of cases after 14 days and the persistence of symptoms in 10% after 4 weeks [18].

Many children complain of coughing and wheezing for several weeks after an episode of bronchiolitis (post-bronchiolitis syndrome) and intermittent symptoms may persist for several years [62]. Children hospitalized for bronchiolitis during infancy may have an increased risk of developing asthma or bronchial hyper-reactivity in the future [135,136]. The increased risk of bronchial asthma is more frequent in RSV-negative bronchiolitis or rhinovirus-bronchiolitis [137,138], whereas the association between RSV-bronchiolitis and respiratory disease seems to decrease with age [139,140]. In a small subgroup of patients, recovery from an episode of acute bronchiolitis can lead to chronic obstruction of the small airways resulting in expiratory airflow limitation, or so-called constrictive bronchiolitis [31,75]. This phenomenon is observed more frequently in adenovirus infections, measles, pertussis, mycoplasma, and influenza A [32]; unilateral hyperlucent lung and/or a combination of geographic hyperlucency, central bronchiectasis, and vascular attenuation (Swyer-James syndrome) has been observed [21,75].

Conclusion

Acute bronchiolitis in children is characterized by viral upper respiratory prodromes followed by increased respiratory effort, wheezing and diffuse bilateral crackles; the most common etiologic agent is RSV. The diagnosis of bronchiolitis is mostly clinical and usually does not require investigation. A conservative approach to treatment seems adequate in the majority of children, especially for the youngest ones, and the current management primarily consists of supportive care, including hydration, supplemental oxygen and mechanical ventilation when required.

Abbreviations

CPAP, continuous positive airway pressure; GERD, gastroesophageal reflux disease; HFNC, high-flow nasal cannula; HMPV, human metapneumovirus; HRCT, high resolution computerised tomography; RSV, respiratory syncytial virus.

Disclosures

The authors declare that they have no disclosures.

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