Oxygen treatment of acute bronchiolitis

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Abstract

Acute bronchiolitis is the most common lower respiratory tract infection in children under two years of age. Treatment of acute bronchiolitis is supportive, i.e. application of oxygen to children with hypoxaemia and care for proper hydration. The value obtained by pulse oximetry is merely an indirect measurement of the actual oxygen level in the blood and does not reflect the severity of the disease. By the application of oxygen we only correct hypoxaemia, but do not treat the underlying cause. Nevertheless, as there is no clinical sign that would precisely define children with hypoxaemia, pulse oximetry remains the decisive investigation in decision-making about oxygen application. Studies have shown that when assessing the severity of the disease, pediatricians trust the values of oxygen saturation (SpO_2) rather than the clinical assessment. Since pulse oximetry has been in use, the percentage of hospitalised patients due to acute bronchiolitis has increased by about 250 %. Guidelines for treating children with acute bronchiolitis are not consistent in terms of specifying a SpO_2 cut-off value that requires oxygen therapy. In this review we have critically evaluated these guidelines and presented our own experience regarding oxygen treatment of acute bronchiolitis.

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1 Introduction

Acute bronchiolitis is the most common lower respiratory tract infection in children younger than two years. Although it is usually a self-limited disease treated in the outpatient paediatric setting, it represents the leading cause of hospitalisation in infants below one year of age (1). Over the past 30 years the number of hospital admissions related to acute bronchiolitis has dramatically increased. There are various causes for this situation, yet the two most important ones seem to be the use of pulse oximetry and absence of clear definition for clinically important hypoxemia (2,3)

Because of the great burden of disease affecting children, numerous studies have been undertaken with the aim to improve the treatment of acute bronchiolitis. They showed that there is currently no medication that would shorten or affect the course of the disease. Therefore, supplemental oxygen administration and care for proper hydration remain the only treatment option available in these children (2,3)

This survey paper presents mechanisms underlying the development of hypoxaemia in children with acute bronchiolitis, provides guidance on when and how oxygen therapy should be initiated, discusses advantages and limitations of pulse oximetry, and gives recommendations for the management of these children using oxygen therapy.

2 Pathophysiological basis of the disease

Acute bronchiolitis is a viral lower respiratory tract infection affecting children younger than two years. The disease is spread through droplets in the air. After the incubation period and previous signs of upper respiratory tract infection, approximately one-third of children develop inflammation of small air passages, called bronchioles. Based on the history and clinical assessment, and according to the degree of the disease severity, acute bronchiolitis in children is divided into mild, moderate and severe disease (Table 1).

Bronchiole blocking occurs as a result of apoptosis of bronchiolar epithelial cells, accumulation of inflammatory cells, oedema and increased mucus production. Air trapping behind the blocked bronchiole leads to lung hyperinflation. After absorption of the trapped air, localised atelectasis form distal to the blocking. Insufficiently ventilated atelectatic area and presence of unchanged perfusion lead to a ventilation/perfusion (V/Q) mismatch, the main mechanism behind the development of hypoxaemia in children with acute bronchiolitis.

Hypoxaemia is caused by important V/Q mismatch, and to a lesser degree, by reduced rate of gas diffusion across the alveolar-capillary membrane. According to the Fick's law of diffusion, gas diffusion rate is directly proportional to the diffusion surface area and the difference in partial gas pressures, and inversely proportional to the diffusion distance. In acute bronchiolitis, the above mentioned pathological and physiological mechanisms are responsible for an increase in the diffusion distance, leading to a decreased oxygen diffusion rate (4,5). Under normal physiological conditions, partial pressure of gas in alveolar capillaries (PaO_2) becomes practically

	Mild bronchiolitis	Moderate bronchiolitis	Severe bronchiolitis
Behaviour	Normal	Irritation	Exhaustion
Respiratory rate	Normal – slightly increased for the patient's age	Increased	Significantly increased or reduced
Work of breathing	Normal to slightly increased	Moderately increased	Strongly increased
SpO_2 (without oxygen supplement)	> 92%	90–92%	< 90%
Nutrition/Hydration	Normal	Worse than usual > 50% normal	Worse than usual < 50% normal

Table 1: Assessment of the severity of acute bronchiolitis. Based on Øymar K et.al. (1).

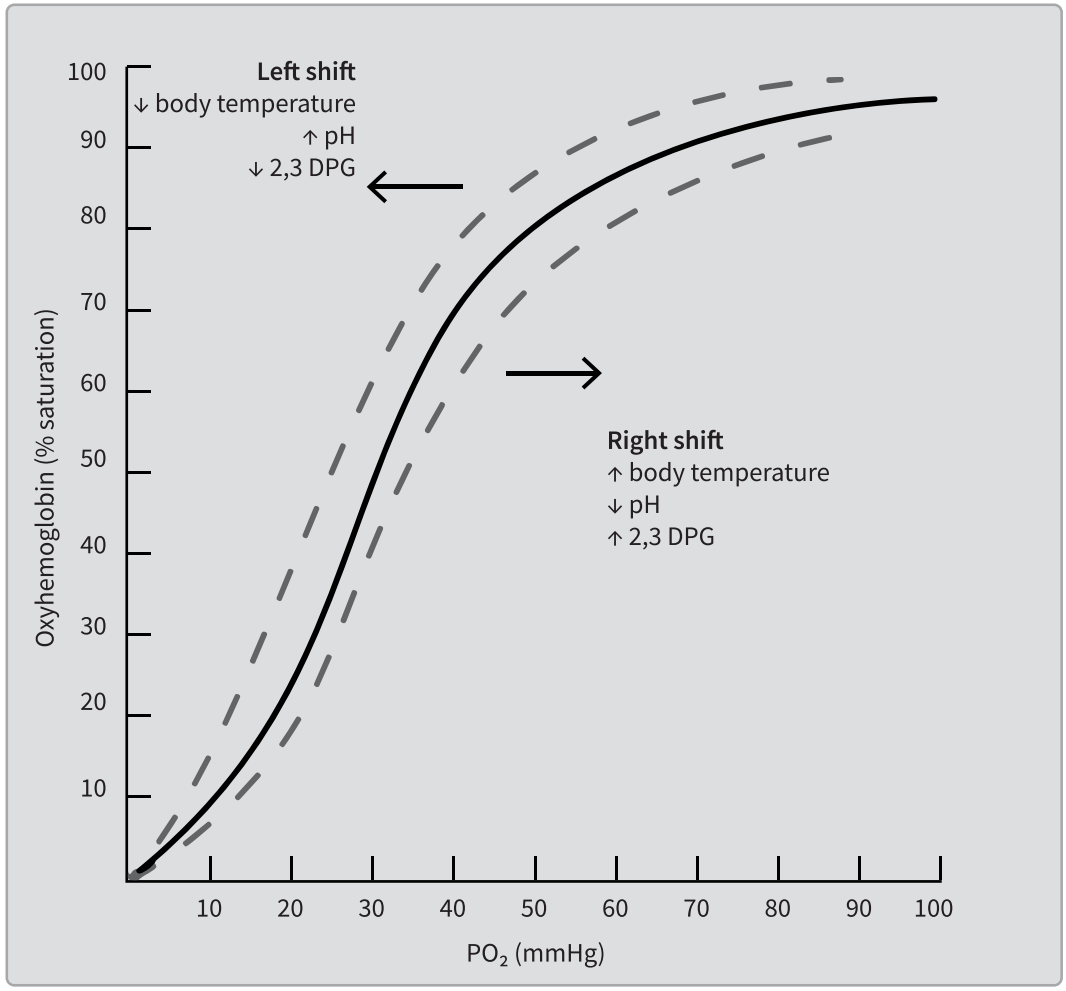

Figure 1: Oxygen-haemoglobin dissociation curve and curve shifts in particular conditions (based on West JB (6), 2,3-diphosphoglycerate.

equal to alveolar gas pressure (PAO_2), when blood reaches about one-third of the distance along capillaries. In acute bronchiolitis, however, this values are attained later or not at all, as indicated by increased difference between PaO_2 and PAO_2 (4).

Oxygen supplementation corrects hypoxaemia to some degree, but cannot eliminate it because it does not address its underlying cause. Oxygen therapy increases PAO_2 and improves the alveolar-arterial oxygen gradient and diffusion of oxygen, but fails to improve V/Q mismatch (5).

A specific feature of oxygen carried in the blood is its capacity to bind to haemoglobin: 98 % of oxygen is bound to haemoglobin and only 2 % is dissolved in the blood. Haemoglobin affinity for oxygen is not linear, therefore the oxygen-haemoglobin dissociation curve has a specific sigmoid shape (Figure 1). The curve flattens off as haemoglobin molecules approach full oxygen saturation. In this segment of the curve only minimal changes in blood oxygen saturation (SpO_2) levels occur despite significant changes in PaO_2 levels (6).

Since SpO_2 90 % lies on the end plateau portion of the oxygen-haemoglobin

dissociation curve, a further decrease in oxygen saturation causes a sharp drop in PaO_2 levels. There is some controversy over the exact cut-off value below which clinically relevant hypoxaemia ensues, yet some investigators believe that a SpO_2 of 90 % does not represent an arbitrary but rather a physiological, i.e. clinically relevant cut-off value of important hypoxaemia. In the absence of the leftward shift, an oxygen saturation over 90 % is regarded as an indicator of appropriate blood oxygen saturation (7).

Patients with acute bronchiolitis often have concomitant conditions, such as increased body temperature, decreased pH in the blood and increased PCO_2 and 2,3-diphosphoglycerate, which shift the oxygen-haemoglobin dissociation curve to the right. This physiological right shift reduces haemoglobin affinity for oxygen. It enhances transport of oxygen to peripheral tissues, but decreases oxygen uptake by pulmonary capillaries. This should always be borne in mind when treating children with acute bronchiolitis (6).

Children younger than two years often have anaemia, which tends to worsen with infection. As a result of reduced blood oxiform capacity, the shape of haemoglobin-oxygen dissociation curve changes, which means that blood oxygen levels can be decreased despite appropriate PaO_2 and SpO_2 levels (6).

The term hypoxaemia denotes decreased PaO_2 levels while tissue hypoxia refers to insufficient oxygen supply at the tissue level. The latter leads to impaired function of an organ or the whole organism, and is potentially life-threatening. It is important to know that the terms are not interchangeable. Oxygen diffusion gradient at the capillary level is very low (= 4 kPa), which suggests that peripheral tissues can tolerate very low oxygen levels. Studies *in vitro* have shown normal utilisation of oxygen by tissues even with PaO2 levels of 0.7 kPa (4).

3 Pulse oximetry

Pulse oximetry began to be used in medicine in the 1980s. SpO_2 determined using pulse oximetry is only an indirect measurement of PaO_2, which can be measured directly by arterial blood gas analysis. SpO_2 levels do not delineate the severity of the illness (8). The measured SpO_2 value reflects the level of oxygenation but provides no information on ventilation or acid-base balance. Moreover, normal SpO_2 values do not rule out a possible increase in partial pressure of carbon dioxide (PCO_2) in infants.

Nevertheless, pulse oximetry readings remain an important factor in the decision to use oxygen therapy in infants with lower respiratory tract infection as there is no clinical sign or symptom that would accurately define hypoxaemia in these patients (9).

It should be noted that pulse oximetry has several limitations. As shown by a prospective observational study of mechanically ventilated children carried out in the USA, the reliability of the investigation is lowest in the hypoxaemic SpO_2 range of 76 % to 90 % (10). In this SpO_2 range, arterial oxygen saturation is overestimated by 3 % – 5 %. There is a need for better algorithms to assess oxygen saturation in this hypoxaemic range. On the other hand a SpO_2 level of > 91 % is considered to represent a good approximation to true blood oxygen levels (10).

In addition, research has shown that paediatricians assessing the severity of illness in infants rely on SpO_2 levels to a greater extent than on actual clinical assessment (11). Since the introduction of pulse oximetry, there has been a 250 % increase in the hospitalisation rate of infants with acute bronchiolitis (1). In a

randomised double-blind study, Schuh et al. showed that a minimal change in SpO_2 levels (of only a few percent) can have a decisive influence on the paediatrician's decision about acute bronchiolitis management. The study involved children with mild to moderate acute bronchiolitis and true SpO_2 levels above 87 %. It was found that hospitalisation rates were by nearly 20 % lower (41 % vs. 25 %, $p = 0.005$) in children whose SpO_2 levels determined by a pulse oximeter with a modified algorithm were by 3 % higher than their true SpO_2 levels (11).

Moreover, hospitalisations tend to be prolonged, not because of clinical deteriorations, but as a result of monitoring SpO_2 by pulse oximetry. In their retrospective study and review of hospital records of children hospitalised for acute bronchiolitis, Schroeder at al. determined the extent to which hospital stay was prolonged on the basis of SpO_2 readings, provided that all other criteria for discharge, including adequate food and fluid intake, were met. The length of hospital stay was prolonged on average for 1.6 day in one-fourth of children (26 %) (12).

4 Normal SpO_2

In order to determine a SpO_2 cut-off level indicating hypoxaemia, the reference range of SpO_2 values for a normal and healthy children population had to be defined. Studies have shown a very wide range of normal SpO_2 values (13). In addition, transient desaturation (SpO_2 of < 90 %) episodes, occuring particularly during sleep, are common in children (14), and have no impact on their further development (15). Yet, transient hypoxaemia episodes occuring over several months or even years in children with sleep-related breathing disorders, and long-term high-altitude hypoxaemia or hypoxaemia associated with congenital heart disease may have adverse effects on neurocognitive functioning (16).

Transient and clinically insignificant desaturations (SpO_2 < 90 %) are common in children suffering from acute bronchiolitis. McCulloh et al., who used continuous pulse oximetry in children with acute bronchiolitis, found that they had frequent transient desaturations, which, however, required no initiation or escalation of oxygen therapy (17). In Slovene hospitals, these desaturation episodes probably tend to be overlooked because of the use of intermittent pulse oximetry monitoring.

A prospective cohort study by Principi et al. showed that desaturations with a SpO_2 below 90 % occur frequently in children with acute bronchiolitis during the recovery period, i.e. after discharge home. Desaturation was defined as a SpO_2 below 90 %, sustained for at least one minute. At least one such desaturation episode was recorded in 64 % of children within 72 hours after discharge home, the longest episode lasting nearly nine minutes. There was no difference between children with oxygen desaturation and those without it in terms of illness deterioration, i.e. rate of hospital readmissions. Usually, children had desaturation episodes while sleeping or eating (18).

There is a lack of studies on potential long-term effects of mild hypoxaemia associated with bronchiolitis on neurocognitive development in children. Given that completely normal, healthy children may show occasional transient desaturations with a SpO_2 below 90 % (14), it can be assumed that mild acute hypoxaemia associated with bronchiolitis has no significant impact on brain development in these children.

5 Risks of oxygen therapy

Children are given supplemental oxygen to improve organ oxygenation and prevent tissue hypoxia. Yet, careful titration of oxygen therapy is required because of the risk of tissue hyperoxaemia. While the consequences of tissue hypoxia leading to cell death are well known, recent studies have shown that hyperoxaemia exerts harmful effects, too. Numerous studies in animals and healthy volunteers have demonstrated that breathing high-concentration oxygen may lead to lung tissue damage (19). The degree of this damage is directly associated with the concentration of the inhaled oxygen and the exposure time. It rarely occurs with FiO_2 levels below 0.5, i.e. when the child is breathing oxygen-enriched air with an oxygen saturation of 50 % (19).

Investigations, conducted mainly in mechanically ventilated patients, showed that excessive oxygen leads to increased production of oxygen free radicals. High oxygen intake causes oxidative stress and the resulting cell death and inflammatory response (20).

Under normal conditions, arterial PCO_2 plays a key role in the control of breathing. In patients with severe lung disease and chronic hypercapnia, hypoxaemia is the main factor addressed to improve breathing. High-concentration oxygen may impair respiratory centre function and worsen hypercapnia. In these group of patients appropriate assessment of ventilation status should therefore be based on arterial blood gas analysis and PCO_2 determination (21).

Careful titration of oxygen therapy as with other medications is required to prevent unintended adverse effects of hypo- or hyperoxia (20,22).

6 Guidelines of acute bronchiolitis management

Cut-off values of clinically important hypoxaemia have not yet been defined. Therefore, there is some discrepancy between the established guidelines for the management of children with acute bronchiolitis in terms of SpO_2 cut-off levels requiring oxygen therapy. The clinical practice guideline published by the American Academy of Pediatrics recommends that clinicians inititate oxygen therapy only when SpO_2 is less than 90 %, because transient hypoxaemic episodes are not associated with complications (23).

The NICE (National Institute for Health and Care Excellence) guideline, however, recommends that children receive oxygen supplementation when they have oxygen saturation of less than 92 %, and that during treatment SpO_2 should be maintained at > 94 % (24).

A randomised controlled study by Cunningham et al. compared two groups of children, in whom oxygen therapy was initiated at SpO_2 of < 90 % and < 94 %, respectively (25). This multicentre study was conducted in eight hospitals in Great Britain between 2012 and 2013 and involved 615 children, between six weeks and 12 months of age. The infants were randomly allocated to two groups: in one group, oxygen saturation was measured with a standard pulse oximeter (n = 308) and in another with a modified pulse oximeter (n = 307) with an adjusted algorithm. The measured SpO_2 levels in the latter group were higher than their true levels, i.e. 94 % instead of 90 %. SpO_2 levels between 85 % and 100 % were adjusted accordingly. It was agreed that in both groups oxygen supplementation was started when the oxygen saturation reading on the pulse oximeter monitor was less than 94 %. As

expected, oxygen was administered to fewer children monitored with a modified pulse oximeter as compared to those monitored with a standard device (56 % vs. 73 %). In addition, the duration of oxygen supplementation was shorter in the modified pulse oximetry group than in the group monitored with a standard pulse oximeter (6 hrs vs. 28 hrs) and so was the length of hospital stay (30 hrs vs. 44 hrs). Surprisingly, children in whom oxygen therapy was started at oxygen saturation levels of < 90 % showed even a more favourable course of illness. In these children, appropriate feeding was started three hours earlier, as reported by their parents they were free of symptoms one day earlier, and they had a lower rate of readmissions for exacerbation of the disease within 28 days of discharge. The groups had comparable rates of unfavourable outcomes. The investigators concluded that oxygen therapy initiated at an oxygen saturation of 90 % is as safe as that started at an oxygen saturation of less than 94 %. Although the study shows with great reliability that short-term oxygen supplementation at SpO_2 levels of < 90 % is safe, its long-term effects on neurocognitive and personality development are not yet fully understood.

All current guidelines favour the use of intermittent over continuous pulse oximetry for SpO_2 determination in children hospitalised for acute bronchiolitis.

According to the NICE guidelines, children are ready for discharge when their oxygen saturation is > 92 %, and after they had been without supplemental oxygen for at least four hours, including sleep episode (24), or as recommended by the American Academy of Pediatrics, when their SpO_2 is ≥ 90 % and their food and fluid intake is adequate (23). After re-establishement of normal eating patterns, deterioration of respiratory function occurs very rarely (26).

Cunningham et al. compared two guideline recommendations for discharge, i.e. stable oxygen saturation of ≥ 90 %, or SpO_2 of ≥ 94 % for at least four hours (27).

They studied 68 infants aged up to 18 months, treated with oxygen supplementation for acute bronchiolitis. Normal feeding (meeting > 75 % of normal nutritional requirements for their age and weight) was re-established at a median of 11 hours, SpO_2 ≥ 90 % at 17 hours and SpO_2 ≥ 94 % at 63 hours. The infants resumed normal eating and achieved a stable SpO_2 of ≥ 90 % 22 hours sooner than a stable SpO_2 of ≥ 94 %. Accepting lower SpO_2 levels at discharge would significantly reduce the length of hospital stay for children with acute bronchiolitis requiring oxygen therapy (average - 3 days) (27), but it would require potential negative clinical effects to be studied beforehand (25).

7 Management of acute bronchiolitis with high-flow oxygen delivery

Hypoxaemic infants with bronchiolitis receive oxygen through a nasal cannula or face mask. High-flow nasal cannula (HFNC) oxygen therapy involves delivery of humidified heated high-flow gas mixture through an adjusted two-prong nasal cannula. As compared to a standard nasal cannula, this cannula allows titration of oxygen percentage and gas flow rate, and appropriate oxygene supplementation in patients with profound hypoxaemia. In addition, HFNC oxygen therapy provides a higher level of respiratory support: under proper conditions in the upper respiratory tract it creates positive end-expiratory pressure (28). This treatment modality was first established in the field of neonatol-

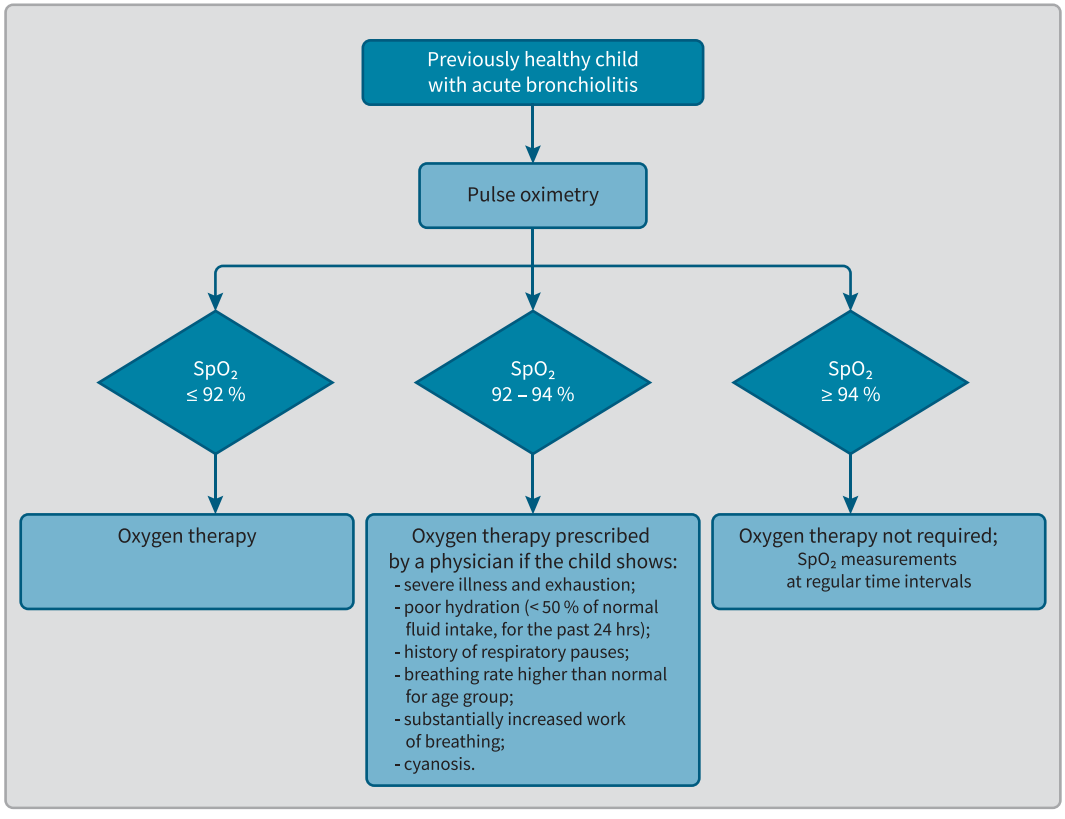

Figure 2: Protocol for the management of acute bronchiolitis with oxygen supplementation proposed by the Unit of Pulmonary Diseases, Division of Paediatrics, Ljubljana.

ogy: it was used for the management of respiratory distress and respiratory pauses in preterm infants (29). Many studies to date have shown HFNC oxygen therapy to be an efficient option for treating children with acute bronchiolitis (30). Acute bronchiolitis is characterised by nonhomogenous pulmonary ventilation leading to an increase in V/Q mismatch and hypoxaemia (3). Because of its beneficial effects on pathological changes this non-invasive modality is considered as one of treatment options in children with severe bronchiolitis (28). The introduction of HFNC oxygen therapy in ICUs has significantly reduced the need for invasive ventilatory support (31,32). HFNC oxygen therapy has been increasingly used also in hospital paediatric wards because of its beneficial effects in children with severe acute bronchiolitis. A recent multicentre randomised controlled study showed that as compared to standard oxygen therapy, the use of HFNC oxygen therapy outside ICU settings has significantly reduced ICU admissions (33).

8 Management of acute bronchiolitis by oxygen supplementation at the Unit of Pulmonary Diseases, Division of Paediatrics Ljubljana

According to the protocol of oxygen supplementation in children and adolescents, prepared by the Unit of Pulmonary Diseases, Division of Paediatrics, Ljubljana (34), oxygen therapy for acute bronchiolitis is started if a

child has an oxygen saturation of ≤ 92 % (Figure 2). Oxygen supplementation can be initiated at SpO_2 levels of 92 % to 94 % in severly ill children showing the following signs and symptoms: reduced hydration (< 50 % of normal fluid intake for the past 24 hours), history of respiratory pauses, respiratory rate higher than normal for the age group, substantially increased work of breathing, cyanosis and exhaustion.

Oxygen is considered to be a drug and requires a medical prescription in all but emergency situations, in which oxygen therapy should be initiated without delay. Target SpO_2 range should be included as part of the patient's oxygen prescription. The nurse who administers oxygen should achieve the prescribed target saturation range. After oxygen administration, SpO_2 levels should be measured at regular intervals together with other parameters of the work of breathing, i.e. respiratory rate and subjective assessment of respiratory effort. Regular measurements and monitoring of oxygen saturation in a child are required before starting oxygen therapy or after its discontinuation. If target SpO_2 levels of oxygen administered by an oxygen delivery device are exceeded, the nurse should gradually step down the inhaled oxygen concentration until oxygen therapy is finally discontinued (34).

HFNC oxygen therapy has been used at the Unit of Pulmonary Diseases, Division of Paediatrics since 2011. Its beneficial clinical effects were demonstrated by a prospective, observational study of infants less than 24 months of age suffering from hypoxaemic respiratory distress associated with acute bronchiolitis. This therapeutic intervention significantly reduced their respiratory and heart rates and improved their respiratory effort parameters. There was also a simultanous increase in pH values and a decrease in PCO_2 in the capillary blood (35).

9 Conclusion

Pulse oximetry is a very useful non-invasive procedure, yet the measured SpO_2 levels do not always reflect the true severity of the disease. Moreover, pulse oximetry provides the least accurate results for the oxygen saturation range of 76 % –90 %. Therefore, paediatricians treating children with acute bronchiolitis must not overrely on the measured oxygen saturation levels. The assessment of disease severity and the diagnosis should be based on accurate medical history and physical examination data. It has been shown that overreliance on SpO_2 levels leads to increased hospitalisation rates and prolonged length of hospital stay in children with acute bronchiolitis.

Oxygen should be treated as all other drugs. Prescription of oxygen therapy and appropriate oxygen administration and titration are required to prevent potential adverse effects of hypo- or hyperoxaemia. At the Unit of Pulmonary Diseases, Division of Paediatrics, Ljubljana, oxygen supplementation is started when a child has an oxygen saturation of ≤ 92 %. If risk factors for hypoxaemia are identified on the basis of medical history or clinical findings, oxygen therapy can be intitiated sooner, i.e. at an oxygen saturation rate of 92 %–94 %.

Research has shown that HFNC oxygen therapy is an effective respiratory support modality in children with acute bronchiolitis that can significantly decrease the number of children requiring invasive respiratory support. Since clearly defined guidelines for the use of HFNC oxygen therapy are not yet available, a decision to start oxygen therapy is made on the basis of clinical assessment and available equipment.

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