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WILEY PEDIATRIC PULMONOLOGY

ABSTRACT

Post-Graduate Courses

#1. PEDIATRIC LONG-TERM NON-INVASIVE VENTILATION DEFINITION AND SITUATION

PLTNIV: Definition and Situation

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Definition

Respiratory support can be distinguished as "invasive" and "non-invasive". The distinction depends on the interface used for patient-ventilator connection. For non-invasive ventilation (NIV), gases are conducted into the airways via an external interface. For invasive ventilation (IMV), gases are conducted into the airways through an endotracheal tube or tracheostomy [1,2].

Indications for and Goals of NIV

Non-invasive ventilation in children is indicated essentially for: 1) Diseases due to increased respiratory load (intrinsic cardiopulmonary disorders, abnormalities of the upper airways, chest wall deformities); 2) Disorders characterized by weakness of the respiratory muscles (neuromuscular diseases, spinal cord injuries); 3) Abnormal neurological control of ventilation (congenital or acquired alveolar hypoventilation syndrome) [1,2].

Non-invasive ventilation can alleviate chronic respiratory failure through the correction of hypoventilation, the improvement of respiratory muscle function and reducing the workload of the respiratory system [1,2]. Goals of NIV are the relief from symptoms, reduction of the work of breathing, improvement and stabilization of gas exchanges, patient-ventilator synchrony, improvement of duration and quality of sleep, improvement of the quality of life and functional status, and prolongation of survival [3].

Patients and Interface Selection

Long-term NIV is applicable to cooperative and stable patients with a certain degree of respiratory autonomy [1,2]. Usually, NIV is applied at night and/or during daytime naps [1–3].

The choice of interface depends on the characteristics of the patient (age, facial characteristics, degree of cooperation, and severity of respiratory impairment). In children, interface acceptance is the first step for a successful NIV program [1,2]. Nasal masks are the most often used interfaces, although there are promising experiences with the use of oro-nasal and full-face masks, nasal pillows and mouthpieces [1,2].

Ventilation Mode

Pressure-targeted ventilation is the modality most often used for non-invasive ventilation [1–3].

Continuous positive airway pressure (CPAP) support is based on the delivery to the airways of a constant pressure for the whole respiratory cycle. With CPAP, the work of breathing is entirely up to the patient [1–3]. CPAP acts by elevating the intraluminal pressure of the upper airway at levels higher than those of the critical transmural pressure that determines the collapse of the upper airway. This pressure keeps the airways open, promotes relaxing of the upper airway dilator muscles, and reduces inspiratory muscle activity of the upper airways and diaphragm [1–3]. CPAP prevents alveolar collapse favoring alveolar recruitments and the increase in functional residual capacity. Through this mechanism, CPAP improves oxygenation and downloading the inspiratory muscles reduces the work of breathing.

Bi-level positive airway pressure (Bi-level PAP) provides respiratory support at two different levels. Using bi-level PAP is possible, therefore, to separately adjust a lower expiratory positive airway pressure (EPAP, CPAP) and a higher inspiratory positive airway pressure (IPAP, PIP). The inspiratory pressure enhances the patient's spontaneous inspiratory act [1–3]. The expiratory pressure allows eliminating more easily exhaled air and CO_2. The EPAP plays the same role discussed above for CPAP [1–3]. The tidal volume will be generated as the result of the delta between the inspiratory and expiratory pressures [1–3].

In Pressure Support Ventilation (PSV) mode, the ventilator ensures a maximum value of inspiratory pressure in the airways equal to that set by the operator. This pressure support allows the patient to achieve more effective breaths. The patient determines respiratory rate, inspiratory flow and inspiratory time by determining the onset of inspiration, muscle strength applied during the inspiration and the passage to expiration [1]. The use of the PSV mode allows preserving the patient's spontaneous breathing while ensuring the reduction of excessive work of breathing undergone by the patient. This mode is preferable in patients capable of spontaneous breathing and able to activate the ventilator cycles.

In Pressure Control Ventilation (PCV) mode, the operator sets the maximum level of pressure that is delivered by the ventilator during the inspiratory act, the respiratory rate and the inspiratory:expiratory ratio (I:E), in the absence of respiratory effort. Breaths delivered by the ventilator are determined by a pressure, duration of inspiration and

expiration default. This mode is preferable in severely ill patients with significant impairment of the muscle pump efficiency or ventilatory drive [1].

Training Program and Discharge Plan for Long-Term Use

If NIV can be established gradually, an accurate clinical training session aimed at the introduction of the patient and family to its practice must be planned [1,2]. Training should start by using very low pressures and when the patient tolerates pressures throughout the night, the pressures can be gradually increased [1,2].

The choice of pressures is the process by which the clinician searches for a compromise between defect correction (through the increase in pressures), and the limitation of the side effects (with the use of a pressure as low as possible, although still effective) [1,2]. Pressure requests depend on the individual patient's current clinical condition and must be obtained from the evaluation of its monitoring [1–3].

Before discharge, the patient's respiratory status should be stable on the same ventilator, circuit and interfaces that the child will use at home. A personalized follow-up plan must always be provided [1,2].

The optimal frequency for follow-up evaluations has not yet been readily determined. These evaluations should generally be scheduled more frequently in infants and younger children [1,2]. On such occasions, the history and a complete clinical and instrumental assessment (ventilator, circuits, humidification, interfaces) must be performed [1,2].

Compliance should be systematically evaluated through the internal memory of the instrument to verify the actual time of ventilator use. This check also allows assessing air leakages, pressures delivered and nocturnal SpO_2 values [1,2].

Polysomnographic evaluations are recommended before initiating NIV and discharging with the ventilator, and during each in-hospital follow-up admission [1–3].

Pulmonary function tests, blood gas analysis, chest x-ray and lateral projection of the skull, echocardiography should be periodically repeated [1,2].

Situation

An increasing number of children with chronic hypercapnic respiratory failure are currently treated with NIV [1,2]. Non-invasive ventilation allows preserving functions such as swallowing, feeding, speaking, coughing, heating/humidification of the inspired air [1].

The introduction of NIV has reduced the number of emergency room visits per year, tracheostomies, intubations and the length of stay in the pediatric intensive care units. Non-invasive ventilation has allowed early weaning from IMV and extubations. Non-invasive ventilation has also enabled preventing vocal cord or trachea damages, and reduce the risk of lower respiratory tract infections [1].

Convincing data have been reported from national surveys on long-term experiences with NIV performed especially in Western countries [4–7]. In the last years, new data have come out from developing and Eastern countries [8–10].

Neuromuscular disease such as Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA), and diseases of the central nervous system such as the congenital central alveolar hypoventilation syndrome represent two main indications for NIV [4–7]. Among respiratory diseases, airway malacia and obstructive sleep apnea have been the most frequently treated with CPAP/NIV [4–7]. Children with severe physical and cognitive disabilities are also increasingly offered long-term ventilation to prolong life [4,6].

The survival is longer in patients treated with NIV than in those undergoing IMV [4–7]. Usually, the median age at the beginning of IVM ventilation is significantly lower than in those treated with NIV [4]. Non-invasive ventilation has been successfully started even in children under 1 year of age [6]. Data are available on the possible weaning from long-term NIV, as well as on deaths during NIV (for example in children in whom a palliative approach was taken) [4–10]. Children with neuromuscular and neurological disease are least likely to wean off from NIV. Children most likely to discontinue long-term NIV are those with chronic lung disease of prematurity, airway malacia, and upper-airways abnormalities [4–10]. Non-invasive ventilation failures and consequently tracheostomy and IVM have been reported for example in children with Cerebral Palsy [4–10]. A significant number of patients with NIV have transitioned to adult care [7].

Compliance with NIV is a major issue. Data downloaded from built-in software showed a wide range on mean nightly use [2]. Parental assessment of PAP use may overestimate actual home ventilator use. In this latter study, patients with greater improvement in apnea-hypopnea index were more likely to be adherent. Clinical parameters and nighttime and daytime symptoms improved after PAP therapy regardless of age or adherence. Treatment adherence was not correlated with age, type of underlying disease, interfaces used, nocturnal gas exchanges, and duration of PAP treatment. Children who attempted to use CPAP at least 6 nights a week were treated with CPAP for a longer time on the nights of use. Usage in the first week of treatment predicted longer term use over 2 to 3 months. A predictor of PAP use was maternal education. Adherence was demonstrated lower in African American children. Adherence did not correlate with severity of apnea, pressure levels, or psychosocial parameters other than a correlation between family social support and nights of PAP use in month-3 [2].

Complications and Contraindications

Serious complications with the use of NIV are not reported in children and adverse effects described are minor [1,2].

Mid-facial hypoplasia has been described mainly in patients who started NIV earlier in life. Monitoring of maxillo-mandibular growth is necessary in infants and younger children receiving long-term NIV [1,2].

Swallowing disorders, personal history of inhalation from gastro-esophageal reflux, paralysis of the vocal cords and absent tolerance to NIV will contraindicate its use. Failure of NIV or a high level of daily dependence from mechanical ventilation (≥ 16–20 hours) are indications for IVM [1,2].

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Management of Complex OSA in Children.

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Sleep-disordered breathing (SDB) is a prevalent disease in pediatrics. It is not a distinct disease, but rather a syndrome of upper airway dysfunction during sleep characterized by snoring and/or increased respiratory effort secondary to increased upper airway resistance and pharyngeal collapsibility[1,2]. SDB includes a spectrum of clinical entities with variable severity of intermittent upper airway obstruction ranging from habitual snoring to severe obstructive sleep apnea (OSA)[3,4]. In 2016, the results of a European Respiratory Society Task Force on the diagnosis and management of pediatric OSA were published[5]. The main recommendations of this paper concerning severe OSA will be presented in this summary.

In a first step, it is important to recognize the child with possible severe OSA. Certain symptoms such as frequent loud snoring, witnessed apneas, restless sleep and oral breathing are associated with the presence of SDB. Young children and children with underlying syndromes are especially at risk of severe OSA and its possible complications. In the context of SDB symptoms and underlying syndromes with an inherent risk of OSA, the presence of failure to thrive and pulmonary hypertension are certainly indicative for the presence of OSA. Polygraphy or polysomnography, which is still the gold standard for the diagnosis of OSA, should be performed to document the presence and severity of OSA. Polygraphy and polysomnography provides us with the number of obstructive events per hour of sleep (the obstructive apnea hypopnea index, oAHI). Moderate-to-severe OSA is defined as an oAHI>5. To date, there are no other screening tools that can substitute polysomnography. However, some of these tools, for instance nocturnal oximetry, have their value considering their inherent limitations.

Moderate-to-severe OSA is an indication for treatment irrespective of the presence of morbidity. Especially in patients with underlying syndromes, treatment is a priority because these children have a higher risk of developing serious complications including pulmonary hypertension. In the Task Force document, an algorithm is presented guiding treatment from the least invasive (pharmacological treatment) to the most invasive (tracheostomy). Especially in children with underlying conditions, it is important to identify the site(s) of upper airway obstruction. These children might benefit from adenotonsillectomy, although residual disease is highly prevalent with the need for additional treatment including orthodontics, maxillofacial surgery and non-invasive ventilation. Because of increasingly available devices and especially interfaces for non-invasive ventilation in children, this option is being increasingly used in specialized centers. It is important after each treatment and with increasing age to follow the child with moderate-to-severe OSA to objectify if OSA is still present.

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PLTNIV in Children with Neuromuscular Diseases

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Neuromuscular diseases (NMD) affect the muscle, the nerve or the neuromuscular junction.

Respiratory complications are frequent in children with neuromuscular diseases (NMD). The incidence, age of onset and severity depend on which disease we are talking about.

The respiratory "pump" includes the chest wall, respiratory muscles and respiratory control center. Although there is sometimes parenchymal disease, caused by frequent aspirations or infection, it is the failure of this pump that most commonly causes respiratory problems in NM patients[1].

Respiratory efficiency is dependent on the balance between respiratory load and respiratory muscle capacity, under the control of the respiratory center. In NM patients, as respiratory load overwhelms muscular strength, an imbalance occurs causing alveolar hypoventilation[2]. Ineffective cough and reduction of ventilation leads to respiratory infections, atelectasis and acute and chronic respiratory failure, causing frequent hospital admissions and limited survival[1]. Weakness of pharyngeal muscles can also contribute to sleep disordered breathing (SDB)[1,3].

Every child with neuromuscular disorders must have a respiratory assessment investigating for infection risk, cough capacity, sleep quality and the presence of SDB, the presence or progression of scoliosis, swallowing difficulties and somatic growth[4].

Lung function should be obtained in all patients that can cooperate, including determination of breathing patterns and respiratory rate, lung volumes such as vital capacity (VC), total lung capacity (TLC) and residual volume (RV), measurement of maximal inspiratory (MIP) and expiratory pressures MEP), cough peak flow (CPF) and sniff nasal inspiratory pressure (SNIP)[2]. In some centers, invasive tests which require esophageal or gastric pressure transducers, are also used.

Assessment of sleep disruption should be carried out regularly in NM children since sleep disordered breathing and sleep fragmentation are frequent. Patients with muscle weakness, moderate to severe limitation of lung function (VC<60%), non-ambulant, with significant scoliosis, suspected diaphragmatic weakness or with nocturnal or daytime symptoms of sleep disturbance should have a polysomnography (PSG) if it is available in adequate time. If it is not possible, a nocturnal oximetry and capnography should be obtained at least annually[4]. When there are doubts regarding oximetry or capnography results, a PSG must be obtained.[4,5]

Diurnal hypercapnia or SDB are clear indications to initiate ventilation, non-invasive (NIV) being the indicated modality. It can be continuous (CPAP) or bilevel positive airway pressure, according to the clinical situation. NIV reduces symptoms of SDB and morning headaches and improves appetite, concentration and quality of life and improves survival.[7,8]

Ventilation should be initiated in patients in whom SDB is suspected or diagnosed or in an acute setting, during an infectious or atelectasis episode.[6] In children with spinal muscular atrophy (SMA), NIV may be used prophylactically, even in small daytime periods, to increase lung growth and prevent chest wall deformities.[7] NIV may also have a role in palliative care as it reduces respiratory distress and anguish.[6,7]

In children with great dependence on NIV, when this is not tolerated or if there is bulbar compromise, a tracheostomy and invasive ventilation may be considered but it should be carefully discussed with the family and the children, and their preferences taken into account.[6,7]

Facial side-effects of masks, such as facial flattening, skin injury and air leaks, are particularly frequent in NMD children and may compromise the adherence to NIV[9]. It has to be promptly managed by changing masks, skin protection and considering alternative ventilation modes.

Airway clearance assessment is very important in the management of NM children. Whenever possible, it should be quantified by CPF. Manual cough assist, air-stacking maneuvers or mechanical assisted cough can be prescribed according to child and family preferences and disease stage.[4] In children with recurrent atelectasis or great difficulty in mobilizing secretions, oscillatory techniques may be useful.[4]

Swallowing dysfunction and nutritional status evaluation are essential in the management of NM children. Caloric supplements or feeding by nasogastric tube or gastrostomy have to be considered in order to improve somatic growth and respiratory performance.[4,7] In some diseases, such as Duchenne Muscular Dystrophy, overweight may also be a problem and specialized support by a nutritionist ought to be provided.[10]

Scoliosis and other orthopedic abnormalities are frequent and may compromise respiratory performance. Surgery may improve quality of life although respiratory function and SDB should be assessed beforehand.[4,10]

As part of a global management, chronic and acute pain, social inclusion and school attendance are relevant aspects when considering these children's quality of life and management.

Technological evolution of ventilators, masks and cough equipment has eased respiratory management in increasingly younger children, in a more comfortable manner and with a better quality of life, significantly changing the prognosis of neuromuscular disorders, and allowing many patients to reach adulthood. Transition to adult care is now a reality in childhood NMD and has to be considered in each adolescent patient.[8]

The complexity of these patients justifies their referral and follow-up in specialized centers, where multidisciplinary support is optimized for the overall development and quality of life of the child and family.

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Central Congenital Hypoventilation Syndrome (CCHS) and Rapid-onset Obesity with Hypothalamic Dysregulation, Hypoventilation, and Autonomic Dysregulation (ROHHAD syndrome)

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Introduction

Central congenital hypoventilation syndrome (CCHS) is not an uncommon reason for long-term pediatric home ventilation. Although invasive mechanical ventilation through tracheostomy has commonly been recommended in patients younger than five years for safety issues, non-invasive ventilation (NIV) has also been reported as a safe approach in small infants (1). Nevertheless, attempting non-invasive ventilation in neonates and infants should be performed cautiously, especially in patients having severe breath-holding spells (2).

Increasing knowledge in genetics, specifically the phenotype/genotype relationship, enables identification of patients with milder respiratory hypoventilation who can potentially benefit from a less invasive approach from the neonatal period without life-threatening episodes. There is a confirmed correlation between the size of the PHOX2B expanded allele and the severity of both the respiratory phenotype and associated symptoms (3, 4).

The incidence of dependency on continuous ventilation is lower than 40% in patients with polyalanine repeat expansion mutations (PARMs) and continuous ventilation is rarely indicated in individuals with the 20/25 genotype. Only 10% of patients with a CCHS phenotype will be heterozygous for a non-polyalanine repeat expansion mutation (NPARM) in the PHOX2B gene. Continuous ventilatory dependence is commonly observed in patients with genotypes from 20/27 to 20/33 and also in individuals with NPARMs, approximately 70–80% of them (3, 5).

Rapid-onset obesity, with hypothalamic dysregulation, hypoventilation and autonomic dysregulation (ROHHAD syndrome) is a rare cause of respiratory failure. Often reported as healthy prior to the appearance of symptoms, patients with ROHHAD syndrome usually present with hyperphagia and significant weight gain at around 3 years of age (15 kg or more in a single year). Months and years later, hypothalamic dysfunction disorders can be diagnosed: antidiuretic hormone secretion abnormalities, central hypothyroidism, growth hormone deficiency, autonomic dysfunction, etc. All children with ROHHAD develop alveolar hypoventilation with a shallow breathing pattern during sleep. An abnormal response to hypoxemia and hypercapnia occurs during wakefulness as well as sleep, with half of the children demonstrating abnormal breathing patterns when awake. Ventilatory needs may vary over time. On initial screening for ROHHAD, only 2/6 (33.3%) children had nocturnal hypoventilation (NH). All children had NH at follow-up and required non-invasive positive pressure ventilation (6).

Therefore, sooner or later all children with ROHHAD will require at least nocturnal respiratory support. Approximately half of the children with ROHHAD require round-the-clock mechanical ventilation, some of them via tracheostomy (5).

Ventilatory Support in Central Hypoventilation Syndromes

Invasive ventilation

The main objective of ventilator support for patients with central hypoventilation syndromes is adequate ventilation and oxygenation in order to prevent adverse events due to hypoxemia/hypercapnia, mainly during sleep. The ventilatory assistance required in central hypoventilation syndromes has tremendous variability. In CCHS, for example, although infants usually require continuous mechanical ventilation, there are several experiences published using NIV in patients with milder hypoventilation. Positive pressure ventilation via tracheostomy is the most effective means to ensure adequate ventilation when continuous ventilation is required. Other candidates for invasive ventilation are normally children who cannot tolerate or be properly fitted with a mask (such as young infants). Additionally, patients requiring very high ventilatory pressures, not very common in these patients except for episodes of acute deterioration, should be invasively ventilated. Difficulties with invasive ventilation are mainly related to the requirement for a constant presence of trained caregivers and the risk of death due to tracheostomy obstruction/decannulation, thus there is an increasing demand from parents to use non-invasive support in this population.

Transition from invasive to non-invasive

A few articles have reported recommendations on how to switch from invasive to non-invasive ventilation in patients with central hypoventilation syndromes (1, 7, 8).

These are some reasonable recommended preliminary steps: previous review of upper airway and removal of hypertrophic lymphoid tissue if present, close supervision with several polysomnographic studies during a one-month period on the non-invasive support ventilator and the tracheostomy corked to ensure adequate titration for the patient. The ventilation parameters for normal sleep architecture should be set to achieve a minimum hemoglobin saturation (SpO_2) of 96% and a maximum transcutaneous carbon dioxide ($PtcCO_2$) of 40 mmHg.

Obviously, ensuring patient collaboration is crucial as removal of the interface during nocturnal ventilation could lead to severe consequences. This tends to happen after puberty when the interests of teenagers center on social relationships.

Non-invasive ventilation

- Non-invasive positive pressure ventilation (NIPPV) allows ventilatory support to be delivered via interfaces/masks, avoids tracheostomy, and is especially appropriate for those who require only nocturnal ventilation.

Modes and Settings

Many children with central hypoventilation syndromes are not capable of triggering the ventilator adequately during sleep, hence the selected mode should guarantee a respiratory rate. A pressure-controlled mode is commonly used because it fulfills the aforementioned criteria. Unfortunately, if lung conditions change, the tidal volume delivered could no longer be appropriate, so minute volume alarms should be tightly set.

New modes which offer volume guarantee are available. Average Volume-Assured Pressure Support (AVAPS) (Philips Respironics®) and iVAPS (intelligent VAPS) (ResMed®) adjust the pressure support (PS) in order to maintain a target average ventilation over several breaths. AVAPS calculates the average PS provided to the patient during the preceding 2 minutes in order to achieve a particular tidal volume. During AVAPS titration in a CCHS patient, the inspiratory positive airway pressure (IPAP) level ranged between the expiratory positive airway pressure (EPAP) and 19cmH2O to ensure adequate tidal volume, calculated around 8 mL per kilogram of predicted body weight under a constant rate of 16 breaths per minute (7). We also have an unpublished experience with the iVAPS mode in a 12-year-old teenager who successfully transitioned from invasive ventilation to this mode. Theoretically, the advantage of iVAPS is the setting of alveolar ventilation related to the patient's height, such that its value is adjusted and modified according to the patient's respiratory rate to compensate for anatomic dead space.

Nevertheless, these modes should be used cautiously because the algorithms to provide pressure and respond to leaks vary greatly between different types of devices. It has been shown that a 21–40% decrease in tidal volume is delivered when random leaks appear (9).

- Non-invasive negative pressure ventilation (NPV) generates a negative inspiratory pressure around the chest to support inspiratory effort. The use of NPV has been limited by obstructive sleep apnea due to the asynchrony between the opening of vocal cords and inspiratory efforts. NPV is used infrequently since NIPPV is available. Nevertheless, a few Ondine's patients have been successfully switched from invasive ventilation to NPV to remove their tracheostomy or from NIPPV to treat midfacial hypoplasia (1).
- Diaphragmatic pacing electrically stimulates the phrenic nerve, generating breathing using the patient's own diaphragm. These pacers can be used for approximately 12 hours a day and offer day-time freedom from the ventilator. Diaphragmatic pacers are not free of complications which include equipment failure, infection and obstructive apnea. Usually, patients are on day-time diaphragmatic pacemaker and use NIPPV at night, although endotracheal intubation could be occasionally required during respiratory tract infections (10).

In summary, teams managing patients with central hypoventilation syndromes should be able to offer non-invasive ventilation support in those patients fulfilling the clinical criteria for safety from the beginning or during their evolution. Knowing the patient's genotype could help to make decisions regarding the respiratory support required. Finally, negative pressure ventilation and diaphragmatic pacing, in spite of not being available worldwide, should be considered as alternative options when facing complications with NIPPV or tracheostomy weaning.

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#2. PORTUGUESE-BRAZILIAN SESSION

Genetics of Tuberculosis

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Pulmonary tuberculosis develops through a complex interrelationship of environmental, immunological and socioeconomic factors and genetic susceptibility. The fact that nearly one-third of the world's population is believed to be affected with latent tuberculosis infection although only a small fraction of the population develops active TB disease during their lifetime, suggests that most individuals possess an immune response able to contain or eliminate the bacteria, even after exposure to *M. tuberculosis*.

The role of genetic factors in the susceptibility to tuberculosis has been suggested by several epidemiological studies, such as high inter-ethnic differences, showing in particular a higher prevalence of disease in populations of African origin than in those of Caucasian origin. In addition, studies of twins highlighted the importance of genetic factors by showing a higher rate of concordance for the disease in monozygotic (~ 60%) than in dizygotic (~ 35%) twins. Moreover, after a first association reported in a Gambian population, a meta-analysis showed that several polymorphisms of the NRAMP1 gene were associated with pulmonary tuberculosis in African and Asian populations but not in European populations.

The imbalance in the production of cytokines responsible for the activation and deactivation of macrophages may be one of the possible mechanisms for this phenomenon. For instance, the presence of IL-10 at the site of infection by *M. tuberculosis* appears to facilitate the evolution to active disease, probably by the suppression of protective mechanisms against the development of tuberculosis. Furthermore, cases of active pulmonary tuberculosis showed significantly higher levels of mediators that impair the Th1 and innate immunity, including intracellular mediators, such as the suppressor of cytokine signaling (SOCS1) and interleukin-1 receptor-associated kinase M (IRAK-M) as well as extracellular mediators (IL-10, TGF-β RII, IL-1RN) and enzymes (indoleamine 2,3-dioxygenase).

Studies carried out in Brazilian populations showed that 1) the −871A>G and −336A>G single nucleotide polymorphisms (SNPs) were associated, the first with protection to both pulmonary and extra-pulmonary TB, the latter only with the pulmonary form; 2) an association between GGAG haplotypes showed protection to tuberculosis infection; 3) the 139G>A and −939G>A SNPs were associated with susceptibility to tuberculosis, and in particular with pulmonary and extra-pulmonary forms respectively, and 4) the −871A>G and −336A>G SNPs were associated, the first with protection to both pulmonary and extra-pulmonary TB, the latter only with the pulmonary form. Moreover, CD209 and CD209L polymorphisms were associated with tuberculosis infection in a Northeastern Brazilian population, also suggesting that variations in these genes may influence the protection and susceptibility to infection caused by *M. tuberculosis*.

The polymorphisms of the HLA system have also been the subject of numerous studies, the most interesting results having been obtained with certain class II antigens. Polymorphisms related to HLA-DRB1, HLA-DQB1, HLA-DQB and HLA-DQA1 genes were associated with higher susceptibility to pulmonary TB. Conversely, the presence of HLA-DRB1, HLA-DQB1, HLADQB1, HLA-DQA1 and HLA-DQA1 genes demonstrated protection against PTB.

The above-mentioned findings suggest that the human genetics of TB involves a continuous spectrum from Mendelian to complex predisposition with intermediate major gene involvement.

The understanding of the molecular genetic basis of TB will have fundamental immunological and medical implications, in particular for the development of new vaccines and treatments. For instance, recent advances showed that patients with IFN-γ production defects could benefit from treatment with recombinant IFN-γ.

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Difficult-to-Control Asthma: Diagnosis and Treatment.

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Asthma in children presents high prevalence in many countries, with important repercussions in school performance, leisure and emotional aspects. It is estimated that approximately 5–10% of children with

asthma have severe disease. Some children with severe asthma are difficult-to-control, and some are insensitive to conventional pharmacological therapy (corticosteroids, long-acting beta-2 agonists, and leukotriene receptor antagonists), representing one of the major challenges in the clinical management of severe asthma. This group of patients is classified as severe resistant-therapy asthma (STRA). Severe asthma in children is strongly associated with the atopic phenotype. Not all STRA children have a history of hospitalizations, although their daily life is severely compromised by continuous disabling symptoms. Specific questions with regard to disease control (GINA or ACT criteria) are essential for correct detection of disease control. Any child with uncontrolled asthma using high-dose inhaled corticosteroid, and long-acting beta-2 agonist (LABA), deserves to be carefully evaluated, with clinical follow-up of at least 6 months by a specialist in the area for adequate diagnosis and management. A systematic clinical evaluation to exclude the following causes is essential: 1) another disease; 2) inadequate inhalation technique; 3) adherence-to-treatment problems; 4) relevant environmental factors; 5) or treatable comorbidities (allergic rhinitis, obesity, severe gastroesophageal reflux, among others). In patients with the final diagnosis of STRA, the first choice for treatment (Step 5 of GINA), associated with inhaled corticosteroid and LABA, is anti-IgE (omalizumab). The second option, usually not effective in many children, would be the use of daily systemic corticosteroids, although many children have shown to be clinically resistant to this therapy in the diagnostic approach and their use is also associated with a number of serious adverse events. Omalizumab emerged a little over a decade ago as an alternative for this group of patients, showing reduced exacerbations and hospitalizations for asthma. However, all therapies for complex diseases such as asthma may present distinct clinical responses, and each patient should be evaluated individually. Although omalizumab is a high-cost medication, one recent real-life study has shown a greater impact on prevention of exacerbations and hospitalizations. In conclusion, difficult-to-control asthma in children requires a careful systematic clinical evaluation by well-trained multidisciplinary teams for reducing the burden of disease in this group of patients.

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Early CF Lung Disease: The Brazilian Experience

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Cystic fibrosis (CF) is a well-known genetic disease caused by CFTR (Cystic Fibrosis Transmembrane conductance Regulator) protein dysfunction [1]. Previously recognized mainly as a pediatric entity, it is switching progressively to a substantial condition for adult pulmonologists, since many patients are living longer and becoming adults [2]. The consequences of CFTR dysfunction to the respiratory tract include disturbances in mucocilliary clearance, and increased susceptibility to acute and chronic respiratory infections, resulting in neutrophilic inflammation and airway damage (bronchiectasis) [1]. These events may occur very early in life, which means that early therapeutic interventions have potential impact for long term prognosis.

Cystic fibrosis used to be relatively unknown by health professionals in Brazil, a situation that is changing rapidly in the last years. One of the reasons for this change is the dissemination of newborn screening (NBS) for several Brazilian States, which has resulted in earlier diagnosis. The increasing contribution of newborn screening to the diagnosis of CF in Brazil can be seen in Figure 1. From 2009 to 2014, 1,341 cases of CF were diagnosed, 602 (44.9%) through newborn screening. The increasing percentage of cases diagnosed through newborn screening every year is noticeable, reaching almost 70% of all cases diagnosed in 2014 (Figure 1).

While we observed this impressive impact of NBS in diagnosis, many caveats remain regarding adequate follow-up and treatment of CF in the country. Many CF Centers do not have adequate resources for CF care, and our National public health model (SUS) does not recognize many of the needs of CF patients. Therefore, access to drugs and resources is delegated to States, resulting in substantial heterogeneity throughout the country.

Cohort studies of CF patients diagnosed by newborn screening have shown that early diagnosis may impact nutrition [3,4], and may also facilitate the identification of lung disease signs such as bronchiectasis, air trapping, and airflow obstruction very early in life [5,6]. However, there are few studies assessing therapeutic interventions in this setting, as well as indication and timing for radiological and functional assessments in infants and toddlers with CF remain highly controversial [7].

Since 2010, NBS was started regularly for all newborns in the Brazilian State of São Paulo. A new outpatient clinic (ALAFIC) was created in our Center to follow these patients, adopting a specific protocol of clinical and laboratory procedures to maintain them as healthy as possible. The first encounter occurred usually at 2 months of age, and we found many patients presenting with significant nutritional deficits: 44% with a Weight/Height Z score lower than −1, 26% with hypoalbuminemia.

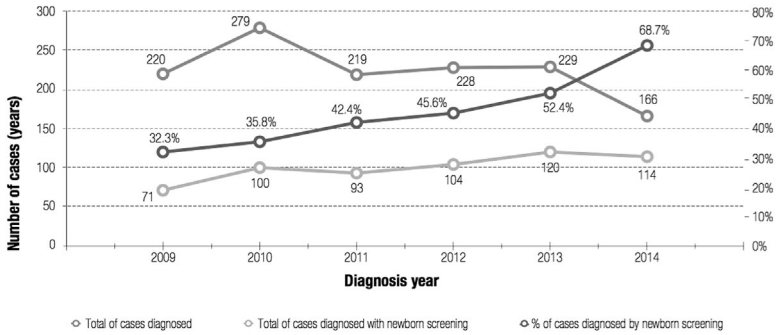

FIGURE 1 New cases diagnosed and the participation of newborn screening in the diagnosis of cystic fibrosis in Brazil, 2009–2014 [8].

While significant improvements in nutrition have been observed after pancreatic enzyme replacement and nutritional supplementation, many patients manifested respiratory symptoms very early, with significant clinical impact. At the first encounter, 20% of the patients attending our Center presented clinical respiratory manifestations such as cough or tachypnea. During the follow-up of the first five years, 80% had at least one hospital admission, mainly due to respiratory causes such as acute viral bronchiolitis. The mean age of the first acquisition of *Pseudomonas aeruginosa* was 11 months, and 54% of the patients had their first positive culture before their first anniversary.

The protocol for radiological examination in our Institution is an annual plain radiograph, and a chest CT scan is indicated when persistent radiographic abnormalities are identified, or when patients remain with persistent respiratory symptoms such as tachypnea or wet cough. A total of 60% of the patients had their first chest CT scan performed at three years of age (only one patient before one year of age), and this procedure resulted in the introduction of dornase alfa in 75% of instances. Therefore, a significant and very strong correlation was observed between the ages of the first chest CT scan and the introduction of dornase alfa ($r = 0.849$, $p<0.001$). The need for at least one hospital admission due to a respiratory cause was associated with introduction of dornase alfa before the age of three years old ($p = 0.026$).

Expanding the view to the Brazilian CF Patient Registry data, it is possible to realize that the scenario for CF patients in the country has much to improve. The 2014 Annual Report[8] depicts a proportion of 30% of children and adolescents (up to 17 years old) with signs of obstruction in lung function tests (forced expiratory volume at the first second – FEV1 – lower than 70% of predicted). Examining data only from patients younger than 12 years old show 22% of them in the same situation (FEV1 < 70%), illustrating a significant respiratory compromise very early in life. The mean FEV1 value of Brazilian patients in this age group was 86%, in contrast to the 2014 Cystic Fibrosis Foundation (CFF) Patient Registry Data (United States) that reports 96% [9]. Another marker of CF lung disease, pulmonary infection/colonization by **mucoid** *P. aeruginosa*, is reported for 10% of children up to 12 years old. While this report is based only on annual identification of this particular microorganism, it may be considered as a surrogate marker of chronic *P. aeruginosa* infection, representing an elevated rate in the current era of routine *P. aeruginosa* eradication.

Fortunately, there are also some good news for the upcoming future. The Brazilian CF Patient Registry (REBRAFC) is expanding every year, and it now comprises more than 4,000 registered CF patients in the country, a condition that may help to improve knowledge about the disease among healthcare providers. The Brazilian Cystic Fibrosis Study Group (GBEFC), a non-profit organization composed of healthcare professionals involved in CF care and owner/manager of the REBRAFC, is also working hard to improve CF diagnosis through better sweat chloride testing (with financial aid from the CFF), and also by supporting the most extensive genotyping initiative ever carried out in the country for CF patients – aiming to sequence the CFTR gene of 3,000 patients without defined genotype (with a grant from Vertex Inc.).

In addition, the GBEFC is directing significant efforts to improve CF care, by organizing the first Brazilian Guidelines for the Diagnosis and Treatment of Cystic Fibrosis, a publication produced by more than 80 healthcare professionals involved in CF care, from several Centers throughout the country. These guidelines may help clinicians to standardize CF treatment in different Brazilian States, and possibly contribute to convince health authorities to expand treatment options available for CF in the country, aiming at a better quality of life and prognosis for Brazilian CF patients.

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Early CF Lung Disease – the Portuguese Experience

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In Portugal, cystic fibrosis was included in the newborn screening program in November 2013, enabling an early diagnosis and treatment, attempting to prevent/postpone its complications, thus improving the prognosis.

From this moment onward, the manner in which we looked at the children arriving at our CF clinic changed dramatically. The new patients are no longer very sick children with families desperately looking for a diagnosis and treatment, but generally healthy newborn babies and confused parents who, until that moment, had not thought that something was wrong with their children.

Health teams meet these "healthy" newborn babies and their goal is that they remain "healthy" as long as possible. Generally, during the following months, the main concerns are centered around pancreatic enzyme supplementation and nutrition whose adjustments turn out to be the major problem.

However, lung disease starts very early in the life of a CF patient and I will present our experience with the infants that we followed from the start of the newborn screening program.

From November 2013, 14 newborn patients started their follow-up at our CF Center, 12 identified by the screening program and 2 following a diagnosis of meconium ileus. Almost all patients have been diagnosed under the age of three weeks.

During their first year of life, 3 patients have been admitted for gastrointestinal problems – the two patients with meconium ileus and one with distal intestinal obstruction syndrome (DIOS) at the age of 5 months, who has been operated – while 7 patients have been admitted for respiratory / lung infection problems – including, at a different period, the child with DIOS. Only five patients have never been admitted during their first year of life (nor have they later). Among the patients admitted for respiratory causes, all but one had respiratory symptoms, with or without troublesome infections, and only one was admitted strictly in an attempt to achieve MRSA eradication.

Excluding the two patients with meconium ileus who spend very long periods in the hospital including the first 3 months of their lives and could, because of this, have a different colonization pattern, we have reviewed all the respiratory cultures performed during the first 12 months of age:

A total of 114 sputum cultures were performed. The most frequently identified bacteria were *S. aureus* (10 patients, 31 samples), *E. coli* (7 patients, 23 samples), *P. aeruginosa* (5 patients, 7 samples) and *Haemophilus spp*. (5 patients, 17 samples). Of the 31 *S. aureus* isolates, 15 were methicillin-resistant (MRSA – 3 patients). Most *P. aeruginosa* isolates were sensitive to the antibiotics tested.

The first *S. aureus* isolate occurred in the first 3 months of life in 8 patients, while *P. aeruginosa* occurred in 2 patients.

No *S. maltophilia*, *A. xylosoxidans* or *B. cepacia* were identified.

At the present moment, 2 patients maintain MRSA colonization and one patient maintains *P. aeruginosa* colonization.

All of the patients are growing quite well and without major respiratory complaints. They follow physiotherapy programs continuously and antibiotic therapies according to infection. Dornase alfa is started only after three years of age.

Epidemiology, Clinical Features, Health Resources and Quality of Care for Community Acquired Pneumonia in Children

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Community-acquired pneumonia (CAP) is a leading cause of morbidity and mortality in children under five years of age. In low and middle income-countries (LMICs) pneumonia still accounts for the leading position as cause of mortality. In high-income countries, management guidelines and vaccination, including pneumococcal conjugate vaccines, have contributed to changes in epidemiology and clinical features, and pneumonia no longer accounts for relevant mortality. [1,2]

Nevertheless and despite a significant body of relevant literature and guidelines, day-to-day practice is influenced by factors related to the child (age and clinical presentation), the etiology, the sociodemographic features, environmental exposures and geographies. The expansion of vaccine programs including vaccines against measles, pertussis and influenza as well as *Haemophilus influenzae* type b and pneumococcal conjugate vaccines associated with social improvements (exclusive breastfeeding for the first 6 months of life and improved environmental hygiene), have all contributed to the reduction of risk factors for the severity of pneumonia. [3,4,5]

Pneumonia is also a leading indication for pediatric hospitalization where variation of management may account for ineffective care. [6]

The optimal management of community-acquired pneumonia (CAP) in children is controversial. Moreover, there is no single definition of pneumonia in childhood that is sensitive, specific, and can be widely implemented. [7]

Clinical practice guidelines (CPGs) are useful for summarizing evidence regarding a topic and for standardizing care, but assessing adherence to a CPG for a specific patient is often difficult, particularly if the guideline contains multiple branch points that depend on the results of clinical, laboratory, or radiographic data. [8] However there is a strong body of evidence expressed in geographically different guidelines, emphasizing the clinical criteria for the diagnosis and for establishing severity both for the tackling of procedures (general, microbiological and radiological investigations) and for treatment. At the end of the day, the conclusion is that current measures underpin the heterogeneous approach and management of CAP in children, with the strength of recommendations being generally low, reflecting the paucity of literature studies in this area of pediatric medicine. [5] Most of this heterogeneity is derived from differences in epidemiological data, prevalence of comorbidities, vaccination coverage, resource availability and health service accessibility.

Quality indicators (also referred to as quality measures or performance measures) are different from CPGs; they are specific measures that allow providers and external agencies to assess the quality of care provided for a given diagnosis. Achievement of these individual measures can easily be assessed for the management of a specific patient.[8]

As in other countries, Portugal has published a clinical orientation guideline for pneumonia in children and also a panel of evaluation criteria for CAP admitted to hospital, known as indicators that aim at assessing quality of care across the health system with the purpose of comparing results and providing access to informed health care.[9,10]

Whether most of CAP in children is managed in the community there is a broad of evidence coming mainly from hospitalized children explained by the fact that both the clinical severity and the resources used are more considerable.

Children with CAP may present with a range of symptoms and signs: fever, tachypnoea, breathlessness, difficulty in breathing, cough, wheeze, headache, abdominal pain and chest pain. The spectrum of severity of CAP can be mild to severe.

The most important decision in the management of CAP is whether to treat the child in the community or progress through the hierarchy of the healthcare system from primary to secondary or tertiary care and refer and admit for hospital-based care. This decision is best informed by an accurate assessment of severity of illness at presentation and an assessment of a likely prognosis. Severity assessment will influence microbiological investigations, initial antimicrobial therapy, route of administration, and duration of treatment and level of nursing and medical care. [7]

The prediction of CAP severity is the relevant question to be asked and includes possible microbial etiology, the possibility of benefit from specific or supportive therapy, possible benefit from experimental therapies (i.e., for enrollment in clinical trials), and the probability of morbidity or mortality.[11] Most commonly, the question of location of care (the major driver of the cost of treatment) has been the central problem of CAP severity. Moreover, prediction of severity may reduce broad-spectrum antibiotic use and decrease hospitalization among low-risk individuals.[3]

In many cases, the question of treatment or prognosis may depend more on chronic diseases, recent antibiotic exposures or individual susceptibility (respiratory risk factors or vaccination status) than acute physiology.

Although CAP is a well known entity, relevant questions such as quality of care and severity of disease remain to be answered mainly because of specific interaction with age and etiology of the acute lower respiratory infections in children.

The future should include targeting an approach of practice to the standards of care and to have precise indicators and models to predict etiology and severity and ultimately become relevant with regard to location of care and antibiotic selection.

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Reviewing the Guidelines: Management of Acute Viral Bronchiolitis

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Acute viral bronchiolitis is one of the most common reasons for hospital admission in childhood, with increasing incidence in the last decades [1]. While the overall mortality is relatively low, its high incidence results in a very high burden, especially for low-income populations [2]. The main etiologic agent is respiratory syncytial virus (RSV), although several other viruses, such as rhinovirus, influenza, parainfluenza, adenovirus and metapneumovirus are identified in these patients [3]. Risk factors for severe bronchiolitis include preterm delivery or chronic diseases such as congenital heart disease, Down syndrome, chronic lung diseases and neuromuscular diseases – all of which are associated with a higher risk of hospitalization, need of mechanical ventilation and death [4].

Treatment of several diseases has changed dramatically in the last 50 years, but this is not the case for bronchiolitis. Although there have been hundreds of trials of drugs such as bronchodilators, steroids, antibiotics and other therapeutic strategies such as nebulized hypertonic saline and chest physiotherapy, they all lack evidence of significant benefit. Therefore, treatment of acute viral bronchiolitis remains mainly supportive [5].

Treatment guidelines are published periodically, with the most recent being the 2014 North American Clinical Practice Guideline from the American Academy of Pediatrics [6], and the 2015 British Clinical Guideline, commissioned by the National Institute for Health and Care Excellence (NICE) [7]. The AAP Guidelines designated recommendation levels to illustrate quality of evidence and balance for benefit and harm anticipated by its application in clinical practice. The NICE guidelines adopted the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, incorporating health economics for some topics. The wording used in the recommendations (for example, words such as 'offer' and 'consider') denoted the certainty with which the recommendation was made (the strength of the recommendation).

Both guidelines had several recommendations of treatments to avoid, in a genuine attempt to reduce unnecessary interventions administered to children with bronchiolitis. The basic principle of "Primum non nocere" is prevailing. The AAP guideline is significantly shorter and more objective, focusing also on immunoprophylaxis and prevention of viral contamination between patients and caregivers. The NICE guidelines are much more extensive and detailed, containing details of the trials used for evidence-based recommendations, resulting in a document of more than 300 pages.

Main Recommendations and Comments:

- The diagnosis and assessment of severity of bronchiolitis is made by history and physical examination – assessment of risk must also take into account age, history of prematurity or other underlying conditions such as cardiopulmonary disease, immunodeficiency or neuromuscular diseases.
- Consider the diagnosis in children younger than 2 years of age with a history of upper respiratory tract symptoms (coryza), that get worse and affect the lower respiratory tract (persistent cough, wheeze and/or crackles on chest auscultation and signs of increased work of breathing (tachypnea and/or chest retractions).
- Radiographic or other laboratory studies are not routinely indicated.
- Hospital admission must be considered for children presenting:
  - apnea (observed or reported).
  - persistent oxygen saturation of less than 92% when breathing air.*
  - inadequate oral fluid intake.
  - persisting severe respiratory distress (grunting, marked chest retractions, or a respiratory rate>70 breaths/minute.

*The AAP Guidelines recommend 90% as the cutoff value for pulse oximetry (see below).

- Continuous pulse oximetry is not indicated for patients admitted to the Hospital
- **Do not use** any of the following to treat bronchiolitis in children:
  - salbutamol
  - ipratropium bromide
  - systemic or inhaled corticosteroids
  - adrenaline (nebulized)
  - a combination of systemic corticosteroids and nebulized adrenaline
  - nebulized hypertonic saline (AAP guidelines state that it may be used for patients admitted to the Hospital)
  - oral montelukast
  - antibiotics
- Do not perform chest physiotherapy on children with bronchiolitis (NICE guidelines state that it may be indicated for children with comorbidities such as spinal muscular atrophy).
- Regarding nasal (upper airway suctioning), only the NICE guidelines recommend:
  - "Do not routinely perform upper airway suctioning in children with bronchiolitis."
  - "Consider upper airway suctioning in children who have respiratory distress or feeding difficulties because of upper airway secretions."

- "Perform upper airway suctioning in children with bronchiolitis presenting with apnea even if there are no obvious upper airway secretions."

- Oxygen supplementation is indicated for children with hypoxemia, but the consensus state different cutoff values for oxyhemoglobin saturation:
  - AAP guidelines: "Clinicians may choose **not to** administer supplemental oxygen if the oxyhemoglobin saturation exceeds 90% in infants and children with a diagnosis of bronchiolitis."
  - NICE guidelines: "**Give** oxygen supplementation to children with bronchiolitis if their oxygen saturation is persistently less than 92%."
- Nasogastric or intravenous fluids may be indicated for infants who cannot maintain hydration orally (less than 50–75% of the regular amount).
- Non-invasive ventilation (continuous positive airway pressure – CPAP) should be considered in children who have impending respiratory failure.

The inclusion of bronchodilators in the list of "Do not use drugs" was surprising and certainly very controversial among pediatricians and pediatric pulmonologists. The previous AAP guidelines published in 2006 [8] recommended a "carefully monitored trial" of bronchodilators for children with bronchiolitis, which seemed to be the breach for physicians to prescribe it. While bronchodilator use was definitely not associated with a reduction in hospital admission rates or length of stay, the belief that it could transiently improve respiratory mechanics may be the reason why it was prescribed to more than half of the admitted patients with bronchiolitis [9].

Regarding oxygen supplementation, which is undoubtedly helpful and indicated for hypoxemic children, the new cutoff value of 90% of oxyhemoglobin saturation and the possibility of avoiding continuous pulse oximetry monitoring proposed in the AAP guidelines are both very impactful. While a slightly different value was recommended in the NICE guidelines (pulse oximetry of at least 92%), both guidelines support the idea of reducing pulse oximetry role as a decision making indicator for admission or discharge of the hospital. A very interesting study carried out recently by Dr. Schuh and colleagues from Toronto [10] reinforces this view. They randomized children with moderate to severe bronchiolitis presenting to the emergency department to either having true oximetry values versus values that were artificially increased by 3 percentage points showed to the attending physician. Patients who had falsely elevated oximetry values were less likely to be hospitalized within 72 hours or receive active hospital care for more than 6 hours than those with unaltered oximetry readings. No difference was seen in the frequency of complications or unscheduled visits [10].

Implementing these guidelines will be challenging in several parts of the world, but they signal a new attitude of minimizing interventions and reducing the role of pulse oximetry as the main indicator of severity. This could be of significant impact for admission rates and length of stay, reducing costs and the burden of bronchiolitis for children and their families.

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