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REVIEW
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How Should Oxygen Supplementation Be Guided by Pulse Oximetry in Children: Do We Know the Level?

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Supplemental oxygen is one of the most commonly prescribed therapies to children in hospital, but one of the least studied therapeutics. This review considers oxygen from a range of perspectives; discovery and early use; estimation of oxygenation in the human body—both clinically and by medical device; the effects of illness on oxygen utilization; the cellular consequences of low oxygen; and finally, how clinical studies currently inform our approach to targeting supplementing oxygen in those with lower than normal oxygen saturation.

Keywords: oxygen, lower respiratory tract infection, oxygen saturation, hypoxia, hypoxemia

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Oxygen really is the elixir of life. It is vital for ATP production at the mitochondrial powerhouse of cellular function, a lack of oxygen spells cell injury and death. No wonder clinicians are so cautious of low oxygen states. But how cautious do we need to be? Is our physiological system able to manage low oxygen challenges? And what should be considered low from a clinical perspective?

This review will consider our understanding of oxygen: its history, physiological principles, monitoring in our bodies, the effects of low oxygen at a cellular level, and how much clinical studies inform our understanding of risks and benefits of supplementing oxygen.

OXYGEN—A BRIEF HISTORY

In the late 18th century, the Swedish pharmacist Karl Scheele and the English theologian–chemist Joseph Priestley did a series of independent combustion experiments with mercuric oxide and potassium nitrate inadvertently discovering a new "air" (Experiments and Observations on Different Kinds of Air, Vol. 1–6, 1775, London). After refinements by Antoine Lavoisier in 1778, the gas was named oxyge'ne (meaning acid former). The first recorded medicinal use was 5 years later by the French physician Caillens who treated a young woman suffering from tuberculosis.

The medicinal use of oxygen became popular by the end of the 18th century supported by the "Pneumatic Institution." Despite some medical studies throughout the 19th century (1) with advanced understanding of physical and chemical properties of oxygen (the Fick Principle in particular), it was not until 1917 when the Scottish physician/physiologist John Scott Haldane published a seminal paper on the proposed therapeutic administration of oxygen that sparked a revolution for the use of oxygen in medicine (2): continuous oxygen delivery was more beneficial than intermittent use. Though it would not be until the 1960s, his theory was proved correct (3). Recent novel approaches to oxygen delivery include high flow devices and non-invasive ventilation strategies.

PHYSIOLOGICAL PRINCIPLES OF OXYGEN

Oxygen is carried in the blood principally bound to hemoglobin (Hb), but also dissolved within plasma. The relationship between oxygen saturation and blood oxygen content can be estimated with reference to the oxygen dissociation curve (**Figure 1**). This relationship is stable during health, but can be affected by a number of factors that influence the ease (or affinity) with which oxygen is bound to and released from Hb, including temperature, partial pressure of carbon dioxide, 2,3-diphosphoglycerate, and pH. A right shift makes it more difficult for oxygen to bind to Hb, but easier for it to be released at the tissues. A left shift has the opposite, easier binding but less readily released. As Hb becomes fully saturated, additional oxygen must be dissolved within plasma, which has a limited capacity under normal circumstances (but can be enhanced by supplementing oxygen above FiO_2 0.21). Decrease in pH/increased H+ ion shifts the curve to right and to the left with alkalosis. This is known as the Bohr effect. Carbon dioxide affects the curve in two ways: first, it influences intracellular pH (the Bohr effect), and second, CO_2 accumulation generates high-level carb-amino compounds causing a right shift. 2,3-DPG is an organophosphate, generated in erythrocytes during glycolysis. The production of 2,3-DPG increases with respect to reduced peripheral tissue oxygen. High levels of 2,3-DPG shift the curve to the right. Low levels of 2,3-DPG is seen in states such as septic shock and hypophosphataemia and cause left shift. Hyperthermia causes a right shift, while hypothermia causes a left shift. Carbon monoxide binds Hb 240 times more readily than oxygen, and therefore interferes with Hb's acquisition of oxygen. It lowers the potential for Hb to bind to oxygen and shifts the curve to the left *via* formation of carboxyhaemaglobin. In the context of an increased level of carbon monoxide, a person can suffer from severe tissue hypoxia while maintaining normoxaemia/normal PaO_2 (4). Methemoglobinemia (a form of abnormal Hb) causes a left shift in the curve. Fetal hemoglobin (HbF) is structurally different from adult Hb. The fetal dissociation curve is shifted to the left relative to adults. Typically, the fetal arterial partial pressure of oxygen is low and hence the left shift enhances placental uptake of oxygen.

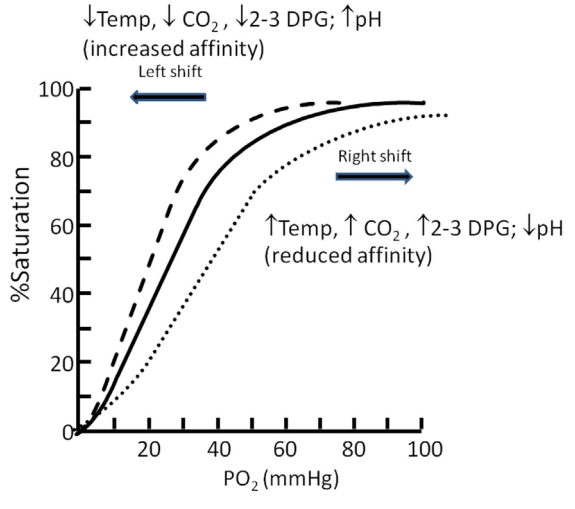

FIGURE 1 | **Oxygen in children – what level**. Oxyhemoglobin dissociation curve.

Normal values of oxygen saturation have been reported widely (5, 6) and at sea level (101 kPa/760 mmHg) oxygen saturation is within the normal range when reading between 94–100%. An oxygen saturation below 94% is hypoxemia. Oxygen saturations are lower in those living at altitude (estimated at a reduction of 5% per 1000 m altitude) (7). Once above an altitude of 6500 m, oxygen saturation stabilize at about 60–65% and do not drop further due to an increase in ventilation and the subsequent respiratory alkalosis shifting the oxyhemoglobin dissociation curve to the left (8).

ASSESSING OXYGEN

Clinical Determination of Low Oxygen States

Historically, and today in resource poor regions, low oxygen status is determined clinically by identifying cyanosis – a dark blue/purple discoloration of the skin or mucous membranes (typically the tongue or inner lip). Cyanosis is one of the earliest and critical signs a medical student will be taught (9). It is one of the cardinal signs of severe illness, and failure to recognize cyanosis can appropriately lead to increased patient morbidity (10). Cyanosis is therefore considered a critical test of clinical ability to be able to appropriately identify and, if present, treat with supplemental oxygen. It is, however, a difficult clinical sign to elicit visually and recognition can be complicated by a number of factors including room lighting, skin pigmentation, and anemia.

For most clinicians, the point at which they are confidently able to discriminate someone as demonstrating cyanosis equates to approximately 85% oxygen saturation. However, detection of clinical cyanosis in respiratory illness varies appreciably from clinician to clinician (11), and identifying hypoxemia is significantly improved by availability of oxygen saturation measurement (12).

Determination of Low Oxygen Using Medical Device

Arterial blood sampling for determination of arterial oxygenation is painful and invasive, and as a consequence of limited use in pediatrics outside intensive care. As a consequence, non-invasive surrogates for arterial oxygen, i.e., pulse oximetry, are extremely helpful in estimating oxygen saturation. Oxygen saturation monitoring is a relatively new technology, and although ubiquitous in developed healthcare settings, it is not available to the majority of people who require an estimate of oxygenation during ill health in developing healthcare settings (13). The principle of pulse oximetry is based on the red and infrared (IR) light absorption of oxygenated and deoxygenated Hb. Oxygenated Hb absorbs more IR light (wavelength 850–1000 nm) whereas deoxygenated/reduced Hb absorbs more red light (wave length 600–750 nm). Red (R) and IR light are emitted through an area of skin with good blood flow. A photodetector is sited opposite to the emitter and receives the wavelength of light passing through

the measuring site. Light is increasingly absorbed during a pulse "wave" and more accurately reflects arterial blood oxygen levels. The R/IR ratio is calculated following photodetection. Typically, an R/IR ratio of 0.5 equates to approximately 100% SpO_2, a ratio of 1.0 equates to approximately 82% SpO_2, while a ratio of 2.0 equates to 0% SpO_2. Measured values will be inaccurate if there is movement or extraneous light (particularly with incorrect sized clip in children) or if nail polish is *in situ*. Skin pigmentation should not affect accuracy. Oxygen saturation readings <70% are generally considered unreliable, as the monitors algorithms are imprecise below this level. Likewise, to improve accuracy, beat to beat measurements are not generally accepted due to artifactual influences; therefore, the SpO_2 value represents an average overtime (a period typically of 10–15 s).

The introduction of pulse oximetry in a widespread manner in the 1980s and 1990s provided a clearly presented, precise number that staff find authoritatively acceptable. The step difference from our previous understanding of clinically detected cyanosis (85% oxygen saturation) to achieving normoxia (94% oxygen saturation) has provided a whole new level of clinical concern – what exactly does an oxygen saturation in the range 85–94% mean in the context of disease. Is it necessary to have normal oxygen saturation during illness?

Before the widespread use of oxygen saturation monitoring, supplemental oxygen was used either blindly (at a set level for a set time) or to relieve clinical cyanosis (i.e., oxygen saturation below c85%). The widespread availability of supplemental oxygen and precise, reliable, ubiquitous methods of estimating arterial oxygen provide clinicians with a capability for meticulousness that requires supporting evidence for benefits and harm.

WHAT IS LOW OXYGEN?

Hypoxia is low tissue oxygen associated with tissue injury, whereas hypoxemia is low blood oxygen levels that may or may not be associated with hypoxia. The level of oxygen carried in the blood depends on the amount of oxygen bound to Hb and, to a lesser extent, dissolved in blood. In healthy humans breathing room air (21% oxygen) at sea level (101 kPa/760 mmHg), the partial pressure of arterial blood oxygen will be in the range 11–13 kPa (75–100 mmHg). At this level, intracellular oxygen is 2.7 kPa (20 mmHg) and mitochondrial oxygen is above 1.3 kPa (9.7 mmHg).

Tissues cannot store oxygen and therefore must be supplied with a constant and steady supply. The global amount of oxygen delivery per minute is termed DO_2. Reduction in DO_2 is associated with reduced renal blood flow (with consequent reduction in urine output), lethargy, metabolic acidosis, and (if measured) a lower venous oxygen saturation (14). Delivery at a tissue level may be further compromised in those who are affected by anemia, hypovolemia, poor cardiac output, or edema of tissues. The global amount of oxygen consumed each minute is termed VO_2. Global oxygen consumption (VO_2) at a cellular level is increased by pyrexia, physical activity (increased respiratory rate or seizures), catabolic states, and pain, whereas VO_2 is reduced by sedation, muscle paralysis, assisted ventilation and hypothermia. In normal health, oxygen consumption is supply independent; however, with illness, increased extraction and reduced delivery can compromise the DO_2 critical point leading to supply failure and hypoxia (**Figure 2**).

Although global oxygen delivery and consumption can be determined, the ability to identify specific dynamic organ level risk is limited in day to day practice. Different organs and tissue groups have varied blood flow and oxygen uptake each minute, receiving varied amounts of cardiac output (**Table 1**). In hypoxic states, preferential shunting of blood away from tissues with low oxygen demand (skin, intestinal tract) help to maintain oxygen delivery to vital organs such as heart and brain which have high oxygen extraction rates and a poorer ability to tolerate low oxygen delivery. At a cellular level, reduced oxygen carried within capillaries reduces intracellular and consequently mitochondrial PaO_2. Critical mitochondrial levels of oxygen lie in the range 0.01–0.10 kPa (16). Tissues particularly sensitive to low oxygen supply are renal tubular cells, cardiomyocytes, and neurons (17).

EFFECTS OF HYPOXIA ON CELLULAR LEVEL

Cells are vulnerable to both excessive and inadequate levels of oxygen. Protection from hypoxic/hyperoxic insults is achieved by complex homeostatic responses which influence cardiovascular, respiratory, and hematological parameters. The influence of

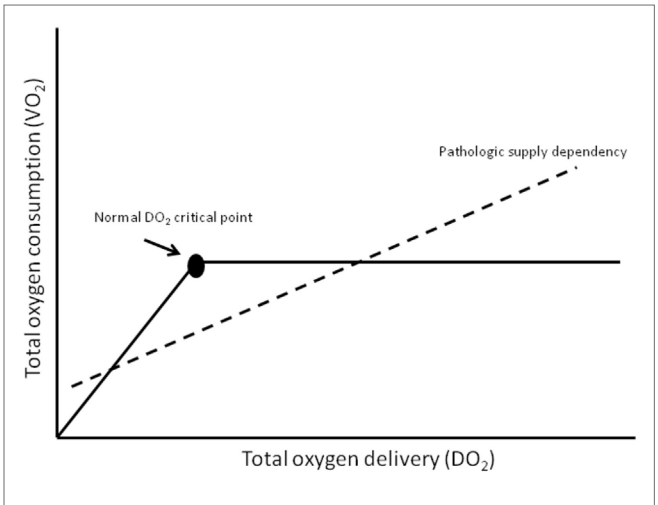

FIGURE 2 | Oxygen in children what level. Adapted from Gutierrez and Theodorou (15).

TABLE 1 | Oxygen in children – what level.

Organ	% of Cardiac output	Blood flow (ml/min)	Oxygen uptake (ml/min)
Brain	14	840	52
Heart	5	300	34
Splanchnic bed	28	1,680	83
Kidney	23	1,380	19
Skeletal muscle	16	960	57
Skin	8	480	12

Adapted from Ref. (18).

hypoxia over the longer term on cardiac output (CO = HR × SV), ventilatory rate, as well as hematocrit and cellular oxygen demand/consumption may limit the negative influence of hypoxia. Ventilatory control is achieved *via* peripheral and central chemoreceptors. The effect of hypoxia on hematocrit is mediated *via* renal erythropoietin regulation.

The cellular adaptive response to hypoxia is regulated *via* the hypoxia-inducible factor (HIF) family of transcription factors (19). HIF-1 is a heterodimeric protein comprising an oxygen-regulated subunit HIF-1 alpha and constitutively expressed HIF-1 beta subunit (aryl hydrocarbon receptor nuclear translocator) (20) (**Figure 3**). Under normoxic conditions, HIF-1 alpha is rapidly removed by polyubiquitylation and proteasome degradation. Under hypoxic conditions, specific enzyme activity is reduced, intracellular HIF-1 alpha accumulates and translocates to the nucleus. Subsequent dimerization with HIF-1 beta and binding to coactivators result in transcriptional activation of hypoxia-responsive genes involved in metabolism, cellular proliferation, vascular physiology, and erythropoiesis (**Figure 4**).

CLINICAL STUDIES OF OXYGEN THERAPY

The principle region of interest for studies of SpO_2 in human clinical studies is the effect within normoxia (≥94%) and clinical cyanosis (85%). This region of interest oxygen saturation (85–94%) would not generally be considered symptomatic during health and could still be associated with adequate mitochondrial oxygenation, and so the benefits and harms of supplementing oxygen within this range during disease are of interest.

Clinical Studies in Adults

There is physiological first principle evidence that low oxygen increases respiratory rate; however, supplemental oxygen as a therapy to provide symptomatic relief of dyspnea in adults is ineffective (22). A Cochrane review of oxygen supplementation in adults with respiratory disease demonstrates the lack of good quality evidence (23).

Clinical Studies in Children

In children, the sensitivity of the developing brain to hypoxemia is much debated, yet has limited supporting evidence of benefits or risks in the region of interests (85–94% SpO_2) (24). Hypoxemia is common in children who are unwell (25), in particular those with respiratory illness (26) and may often be undetected (27). The effects of hypoxia associated with newborn Hypoxic Ischemic Encephalopathy or out of hospital cardiac arrest are well described. Typically, such events are associated with a profound period of hypoxia often with marked acidosis and diminished cardiac output – though the ability of the young brain to withstand some episodes of prolonged hypoxemia can be impressive. Persisting hypoxia leads ultimately to cellular energy failure and cell death as the adapted mechanisms demonstrated above begin to fail. The boundary between hypoxemia and anoxia is termed dysoxia (28).

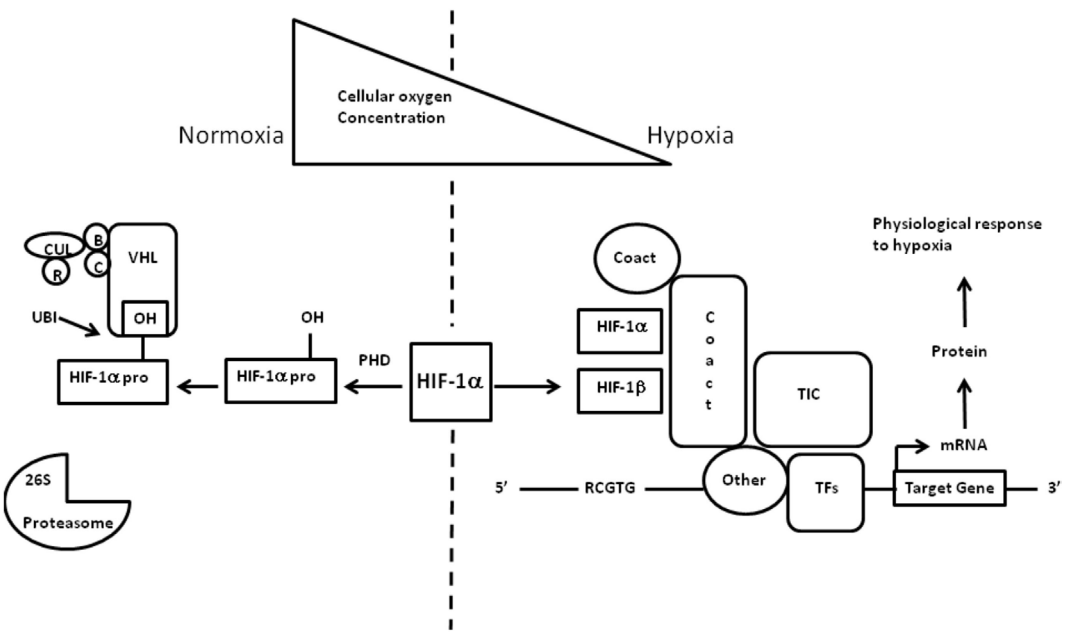

FIGURE 3 | **Regulation of hypoxia-inducible factor (HIF)-1 oxygen in children – what level**. Regulation of HIF-1 adapted from Imtiyaz and Simon (19) and Semenza (20). HIF transcription factors are heterodimers consisting of an oxygen-regulated alpha chain bound to the constitutive beta subunit (aryl hydrocarbon receptor nuclear translocator). Under normoxic conditions, the alpha chain hydroxylated by the HIF prolyl hydroxylases leading to recognition by the von Hippel–Lindau (VHL) E3 ubiquitin ligase complex VHL which recruits elongins B and C, Cullin 2, and RBX1 (R) to constitute a functional E3 ubiquitin-protein ligase complex. Polyubiquitylation occurs and the alpha chain is degraded by the proteasome. Under hypoxic conditions, the HIF alpha chains are maintained and target gene transcription is enhanced. HIF-1 dimerizes and escapes prolyl hydroxylation, ubiquitination, and degradation. The HIF-1 heterodimer binds to hypoxia response elements containing recognition sequence 5_-RCGTG-3_ and recruits coactivator molecules resulting in increased transcription initiation complex formation. mRNA synthesis production and translation of proteins to mediate physiologic responses to hypoxia. TF = transcription factors.

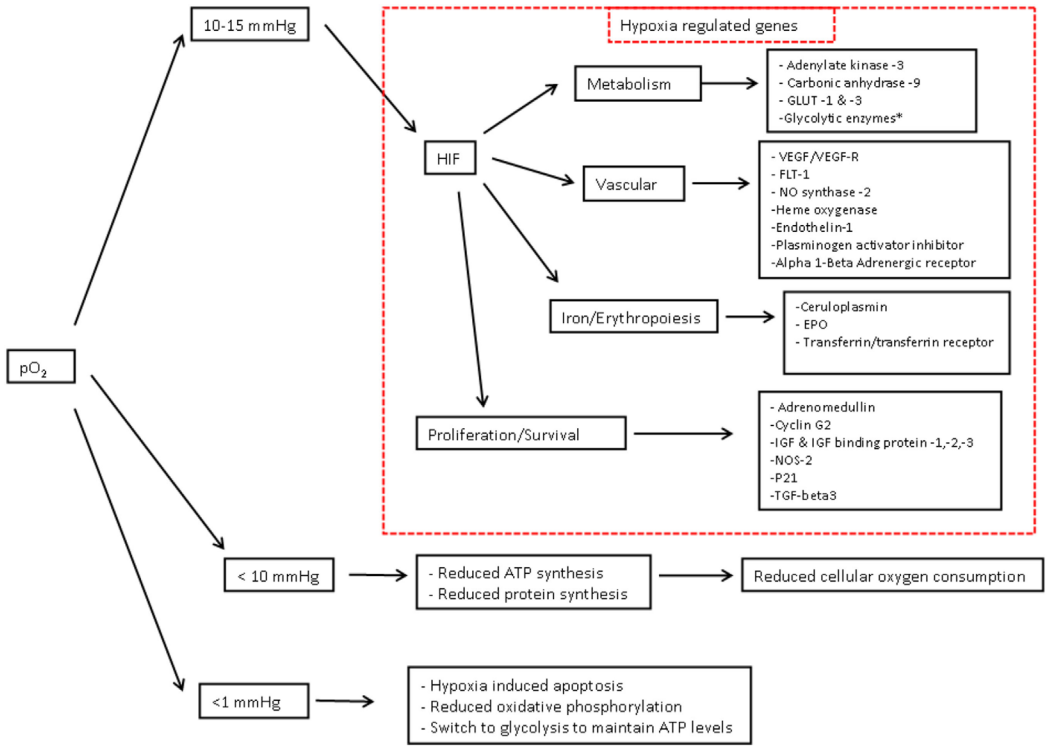

FIGURE 4 | **Cellular consequences of hypoxia – Oxygen in children what level**. Cellular consequences of hypoxia—adapted from Semenza (20) and Span and Bussink (21). As partial pressure of cellular O2 falls, there are a number of target genes involved in oxygen homestasis. Hypoxia-inducible factor-1-regulated genes include the 11 glycolytic enzymes aldolase A, aldolase C, enolase1, glyceraldehyde-3-phosphate dehydrogenase, hexokinase 1, hexokinase 2, lactate dehydrogenase A, phosphofructokinase L, phosphoglycerate. kinase 1, pyruvate kinase M, and triosephosphate isomerase. Abbreviations: EPO, erythropoietin; HO, heme oxygenase; IGF, insulin-like growth factor; IGFBP, IGF binding protein; NOS, nitric oxide synthase; PAI, plasminogen activator inhibitor; TGF, transforming growth factor; VEGF, vascular endothelial growth factor. 1 mmHg = 0.13 kPa, 10 mmHg = 1.3 kPa, 15 mmHg = 2 kPa.

There is sufficient evidence (as above) to identify from physiological and biochemical principles that those who have cardiorespiratory or biochemical instability are most likely to be hypoxically challenged at a cellular level. Patients include those with significant acidosis associated with sepsis, dehydration, or diabetic ketoacidosis or those with a high probability of acute sudden reductions in global oxygen delivery, i.e., acute severe asthma or pneumothorax. In such patients, supplementing oxygen to normoxic values provides a reliable buffer against shifts in the oxygen dissociation curve or sudden challenges to oxygen delivery.

From a clinical perspective, the more challenging questions are based around the clinical management of patients who are biochemically stable (or with only mild pyrexia/increased carbon dioxide) and have hypoxemia within the range 85–94%, particularly over the longer term of days, weeks, or months. These include children recovering from acute lower respiratory tract infection or chronic lung disease.

Chronic Oxygen Supplementation (Weeks or Months)

Preterm infants with lung disease often have hypoxemia and are provided with supplemental oxygen as a treatment. The early unrestricted use of oxygen for preterm infants in the 1950s was associated with a disastrous increase in the incidence of retinopathy of prematurity (29). The subsequent rebound restriction of supplemental oxygen reduced the incidence of ROP, but correspondingly increased death and brain injury (30, 31). In the 1970s and 1980s, the development and use of transcutaneous oxygen sensors enabled oxygen to be better titrated, controlling the risk of supplementing oxygen. Though ROP continued to be problematic even within transcutaneous oxygen target ranges (32). More recent studies in preterm infants have considered the risks and benefits of different target ranges for oxygen saturation. In a pre-planned international meta-analysis, a study was closed early when it became apparent that there were excess deaths in those infants managed within a lower oxygen saturation range (33). Of significant note was that the difference in the peak median oxygen saturation separating the two groups was just 3% SpO_2; 89% in the lower and 92% in the higher range. In this vulnerable population of preterm infants, small differences in oxygen saturation over prolonged periods of time within the range interest (85–94% SpO_2) has important effects on outcomes.

Children beyond the newborn period may also be considered a vulnerable population. The most studied population in this age group is children with obstructive sleep apnea (OSA). Children with reported OSA attain lower high school scores than contemporary peers without reported OSA (34, 35). When

tested in a randomized controlled trial however, the anticipated effect on learning was not identified (36), creating further debate (37), though recent studies continue to suggest that prolonged repeated episode of airway obstruction (and possibly the associated hypoxia) do have cognitive effects in developing brains (37). Random repeated episodic obstructive events over many months result in both sleep architecture arousals and recurrent hypoxemic events; teasing out which is most associated with potential cognitive deficits is difficult.

Acute Oxygen Supplementation in Respiratory Disease

Is it helpful to have a one size fits for oxygen saturation limits? Should our response to oxygen saturation be more responsive and intuitive to the patients' illness and symptoms? As one of the most commonly prescribed treatments, oxygen supplementation and its effects on illness is poorly studied.

In general, there is very little evidence, of poor quality, supporting the use of oxygen in children with acute lower respiratory tract infection (38). Acute LRTI is the leading cause of mortality among children in developing countries and is responsible for up to 30% of all mortality in children under 5 years of age (39), with an estimated 120 million cases of pneumonia each year (40).

Hypoxemia is common in children with LRTI (41) and SpO_2 <94% is present in 73% of children under one year of age admitted to hospital in a developed setting with acute bronchiolitis (42). In older children with pneumonia in a developing healthcare setting, hypoxemia (SpO_2 <90%) is present in 13% (25). Outcomes are poorer in those with nutritional deficit at the time of hypoxia (43). The World Health Organization recommends an oxygen saturation target of 90% for supplementing oxygen in stable children (44). This is generally considered a pragmatic proposal in resource poor countries where oxygen provision is challenging, but also takes account of the stability of the oxygen dissociation curve at oxygen saturation greater than 90%. In high and middle income healthcare settings, oxygen is generally provided to maintain oxygen saturation above 92%.

In a pilot trial for children with pneumonia, early use of supplemental oxygen did not prevent subsequent development of hypoxaemial (45). Children with pneumonia, provided with supplemental oxygen to maintain SpO_2 ≥90% had fewer deaths than those who did not receive supplemental oxygen (46).

There is just one randomized controlled trial of oxygen supplementation in acute respiratory disease in children. Bronchiolitis is the most common lower respiratory tract infection in children under one year of age. Most commonly caused by Respiratory Syncytial Virus the only effective management is maintenance of hydration and relief of hypoxemia. In 2005, a discrepancy arose between two guidelines for the management of bronchiolitis. With no evidence to support either position, a UK guideline recommending supplementing oxygen until normoxia was achieved (SpO_2 ≥94%) and a US guideline recommended, on the basis of oxygen dissociation characteristics, that oxygen supplementation could be limited to <90% if the child was stable and improving. In a double-blind randomized controlled equivalence trial testing, these two oxygen saturation targets, outcomes for key clinical parameters were equivalent or possibly better for infants managed to the lower oxygen saturation target (42). Neurodevelopmental outcomes were not assessed within this trial, as the brief and improving oxygen saturation of trial subjects was not considered to be sufficient of neurodevelopmental concern—though this position is not accepted by all (47).

So do we know the correct target for oxygen saturation in acute lower respiratory tract infection in children? And what is it worth to know? In developed economies, there may be little appetite to push boundaries where outcomes are generally good and significant risk of severe neurodisability or death would be unacceptable outcomes (48). But just as early use of oxygen demonstrated harm as well as good, so possibly is the case with use of supplemental oxygen in children. In the Bronchiolitis of Infancy Discharge Study, outcomes appeared better in those managed to a lower oxygen saturation (and so fewer received supplemental oxygen for a shorter duration) with more speedy recovery (from a parent perspective) and a faster ability to regain feeding. Oxygen toxicity was postulated as possible for these effects (42). In developing healthcare, the ability to most effectively distribute scarce supplemental oxygen as a resource does support further evaluation of target oxygen saturation. These are proposed to be tested in an MRC trial in Africa (the COAST trial).

Do we know the level at which we should supplement oxygen? Not yet.

AUTHOR CONTRIBUTIONS

All authors listed have made substantial, direct, and intellectual contribution to the work and approved it for publication. Both authors revised the manuscript sections and completed editing.

REFERENCES

1. Birch SB. Some remarks on the exhibition of oxygen as a therapeutic. *Lancet* (1869) 93(2380):492–3. doi:10.1016/S0140-6736(02)66126-4
2. Haldane JS. The therapeutic administration of oxygen. *BMJ* (1917) 1(2928):181–3. doi:10.1136/bmj.1.2928.181
3. Petty TL, Finigan MM. Clinical evaluation of prolonged ambulatory oxygen therapy in chronic airway obstruction. *Am J Med* (1968) 45(2):242–52. doi:10.1016/0002-9343(68)90042-9
4. Morgan TJ. The oxyhaemoglobin dissociation curve in critical illness. *Crit Care Resusc* (1999) 1(1):93–100.
5. Balasubramanian S, Suresh N, Ravichandran C, Dinesh Chand GH. Reference values for oxygen saturation by pulse oximetry in healthy children at sea level in Chennai. *Ann Trop Paediatr* (2006) 26(2):95–9. doi:10.1179/146532806X107421
6. Mau MK, Yamasato KS, Yamamoto LG. Normal oxygen saturation values in pediatric patients. *Hawaii Med J* (2005) 64(2):44–5.
7. Subhi R, Smith K, Duke T. When should oxygen be given to children at high altitude? A systematic review to define altitude-specific hypoxaemia. *Arch Dis Child* (2009) 94(1):6–10. doi:10.1136/adc.2008.138362
8. Hackett PH, Roach RC. High altitude medicine. In: Auerbach PS, editor. *Wilderness Medicine*. St Louis, MO: Mosby (1995). p. 1–37.
9. Medd WE, French EB, Wyllie VMcA. Cyanosis as a guide to arterial oxygen desaturation. *Thorax* (1959) 14:247–50.
10. Stadie WC. The oxygen of the arterial and venous blood in pneumonia and its relation to cyanosis. *J Exp Med* (1919) 30(3):215–40. doi:10.1084/jem.30.3.215

11. Comroe JH Jr, Botelho S. The unreliability of cyanosis in the recognition of arterial anoxemia. *Am J Med Sci* (1947) 124(1):1–6. doi:10.1097/00000441-194707000-00001
12. Smyth A, Carty H, Hart CA. Clinical predictors of hypoxaemia in children with pneumonia. *Ann Trop Paediatr* (1998) 18(1):31–40. doi:10.1080/02724936.1998.11747923
13. Enoch AJ, English M, Shepperd S. Does pulse oximeter use impact health outcomes? A systematic review. *Arch Dis Child* (2015) 101:694–700. doi:10.1136/archdischild-2015-309638
14. Leach RM, Treacher DF. The pulmonary physician in critical care * 2: oxygen delivery and consumption in the critically ill. *Thorax* (2002) 57(2):170–7. doi:10.1136/thorax.57.2.170
15. Gutierrez JA, Theodorou AA. Chapter 2: Oxygen delivery and oxygen consumption in pediatric critical care. In: Lucking SE, Maffei FA, Tamburro RF, Thomas NJ, editors. *Pediatric Critical Care Study Guide*. New York: Springer (2012). p. 19–38.
16. Scandurra FM, Gnaiger E. Cell respiration under hypoxia: facts and artefacts in mitochondrial oxygen kinetics. *Adv Exp Med Biol* (2010) 662:7–25. doi:10.1007/978-1-4419-1241-1_2
17. Carreau A, El Hafny-Rahbi B, Matejuk A, Grillon C, Kieda C. Why is the partial oxygen pressure of human tissues a crucial parameter? Small molecules and hypoxia. *J Cell Mol Med* (2011) 15(6):1239–53. doi:10.1111/j.1582-4934.2011.01258.x
18. Crocetti J, Krachman S. Chapter 22: Oxygen content, delivery, and uptake. In: Criner GJ, D'Alonzo GE, editors. *Critical Care Study Guide; Text and Review*. New York: Springer (2002). p. 355–68.
19. Imtiyaz HZ, Simon MC. Hypoxia-inducible factors as essential regulators of inflammation. *Curr Top Microbiol Immunol* (2010) 345:105–20. doi:10.1007/82_2010_74
20. Semenza GL. HIF-1, O(2), and the 3 PHDs: how animal cells signal hypoxia to the nucleus. *Cell* (2001) 107(1):1–3. doi:10.1016/S0092-8674(01)00518-9
21. Span PN, Bussink J. Biology of hypoxia. *Semin Nucl Med* (2015) 45(2):101–9. doi:10.1053/j.semnuclmed.2014.10.002
22. Abernethy AP, McDonald CF, Frith PA, Clark K, Herndon JE II, Marcello J, et al. Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. *Lancet* (2010) 376(9743):784–93. doi:10.1016/S0140-6736(10)61115-4
23. Cranston JM, Crockett A, Currow D. Oxygen therapy for dyspnoea in adults. *Cochrane Database Syst Rev* (2008) (3):CD004769. doi:10.1002/14651858.CD004769.pub2
24. Bass JL, Gozal D. Oxygen therapy for bronchiolitis. *Pediatrics* (2007) 119(3):611. doi:10.1542/peds.2006-3002
25. Subhi R, Adamson M, Campbell H, Weber M, Smith K, Duke T, et al. The prevalence of hypoxaemia among ill children in developing countries: a systematic review. *Lancet Infect Dis* (2009) 9(4):219–27. doi:10.1016/S1473-3099(09)70071-4
26. Duke T, Blaschke AJ, Sialis S, Bonkowsky JL. Hypoxaemia in acute respiratory and non-respiratory illnesses in neonates and children in a developing country. *Arch Dis Child* (2002) 86(2):108–12. doi:10.1136/adc.86.2.108
27. Wong JYW, Moon S, O'Callaghan C. Arterial oxygen desaturation in infants recovering from acute bronchiolitis: hypoxic infants coughed more. *Am J Respir Crit Care Med* (2003) 167(7):A387.
28. Robin ED. Special report: dysoxia. Abnormal tissue oxygen utilization. *Arch Intern Med* (1977) 137(7):905–10. doi:10.1001/archinte.1977.03630190059015
29. Patz A, Hoeck LE, De La Cruz E. Studies on the effect of high oxygen administration in retrolental fibroplasia. I. Nursery observations. *Am J Ophthalmol* (1952) 35(9):1248–53. doi:10.1016/0002-9394(52)91140-9
30. James S, Lanman JT. History of oxygen therapy and retrolental fibroplasia. Prepared by the American Academy of Pediatrics, Committee on Fetus and Newborn with the collaboration of special consultants. *Pediatrics* (1976) 57(Suppl 2):591–642.
31. Cross KW. Cost of preventing retrolental fibroplasia? *Lancet* (1973) 2(7835):954–6. doi:10.1016/S0140-6736(73)92610-X
32. Cunningham S, Fleck BW, Elton RA, McIntosh N. Transcutaneous oxygen levels in retinopathy of prematurity. *Lancet* (1995) 346(8988):1464–5. doi:10.1016/S0140-6736(95)92475-2
33. BOOST II United Kingdom Collaborative Group, BOOST II Australia Collaborative Group, BOOST II New Zealand Collaborative Group; Stenson BJ, Tarnow-Mordi WO, Darlow BA, et al. Oxygen saturation and outcomes in preterm infants. *N Engl J Med* (2013) 368(22):2094–104. doi:10.1056/NEJMoa1302298
34. Gozal D, Pope DW Jr. Snoring during early childhood and academic performance at ages thirteen to fourteen years. *Pediatrics* (2001) 107(6):1394–9. doi:10.1542/peds.107.6.1394
35. Bass JL, Corwin M, Gozal D, Moore C, Nishida H, Parker S, et al. The effect of chronic or intermittent hypoxia on cognition in childhood: a review of the evidence. *Pediatrics* (2004) 114(3):805–16. doi:10.1542/peds.2004-0227
36. Marcus CL, Moore RH, Rosen CL, Giordani B, Garetz SL, Taylor HG, et al. A randomized trial of adenotonsillectomy for childhood sleep apnea. *N Engl J Med* (2013) 368(25):2366–76. doi:10.1056/NEJMoa1215881
37. Hunter SJ, Gozal D, Smith DL, Philby MF, Kaylegian J, Kheirandish-Gozal L. Effect of sleep-disordered breathing severity on cognitive performance measures in a large community cohort of young school-aged children. *Am J Respir Crit Care Med* (2016) 194(6):739–47. doi:10.1164/rccm.201510-2099OC
38. Rojas-Reyes MX, Granados Rugeles C, Charry-Anzola LP. Oxygen therapy for lower respiratory tract infections in children between 3 months and 15 years of age. *Cochrane Database Syst Rev* (2014) 12:CD005975. doi:10.1002/14651858.CD005975.pub3
39. Bryce J, Boschi-Pinto C, Shibuya K, Black RE; Group WHOCHER. WHO estimates of the causes of death in children. *Lancet* (2005) 365(9465):1147–52. doi:10.1016/S0140-6736(05)71877-8
40. Walker CL, Rudan I, Liu L, Nair H, Theodoratou E, Bhutta ZA, et al. Global burden of childhood pneumonia and diarrhoea. *Lancet* (2013) 381(9875):1405–16. doi:10.1016/S0140-6736(13)60222-6
41. Scott JA, Brooks WA, Peiris JS, Holtzman D, Mulholland EK. Pneumonia research to reduce childhood mortality in the developing world. *J Clin Invest* (2008) 118(4):1291–300. doi:10.1172/JCI33947
42. Cunningham S, Rodriguez A, Adams T, Boyd KA, Butcher I, Enderby B, et al. Oxygen saturation targets in infants with bronchiolitis (BIDS): a double-blind, randomised, equivalence trial. *Lancet* (2015) 386(9998):1041–8. doi:10.1016/S0140-6736(15)00163-4
43. West TE, Goetghebuer T, Milligan P, Mulholland EK, Weber MW. Long-term morbidity and mortality following hypoxaemic lower respiratory tract infection in Gambian children. *Bull World Health Organ* (1999) 77(2):144–8.
44. World Health Organisation. *Oxygen Therapy for Children: A Manual for Healthcare Workers*. Geneva: WHO Publications (2015).
45. Singhi SC, Baranwal AK; Guruprasad, Bharti B. Potential risk of hypoxaemia in patients with severe pneumonia but no hypoxaemia on initial assessment: a prospective pilot trial. *Paediatr Int Child Health* (2012) 32(1):22–6. doi:10.1179/2046905511Y.0000000001
46. Duke T, Wandi F, Jonathan M, Matai S, Kaupa M, Saavu M, et al. Improved oxygen systems for childhood pneumonia: a multihospital effectiveness study in Papua New Guinea. *Lancet* (2008) 372(9646):1328–33. doi:10.1016/S0140-6736(08)61164-2
47. Wainwright CE, Kapur N. Oxygen saturation targets in infants with bronchiolitis. *Lancet* (2015) 386(9998):1016–8. doi:10.1016/S0140-6736(15)00155-5
48. Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT. *N Engl J Med* (2013) 368(20):1929–31. doi:10.1056/NEJMe1304996

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Feasibility of a Peer-Led Asthma and Smoking Prevention Project in Australian Schools with High Indigenous Youth

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Background: The high global burden of asthma and tobacco smoking among Indigenous people may potentially be reduced by appropriate interventions that target prevention of tobacco smoke uptake and improved asthma management. The latter includes targeted treatment based on airway inflammation. We undertook a feasibility study in two Darwin schools with a high proportion of Indigenous youth to determine the feasibility of an innovative, peer-led, school-based education program called the Asthma and Smoking Prevention Project (ASPP). A subset of children with reported persistent respiratory symptoms were also clinically evaluated to determine the lower airway inflammatory profile and optimize asthma management.

Methods: The ASPP is founded on an evidence-based three-step program and targets improving asthma management and preventing the uptake of tobacco smoking. The program uses a student-centered approach in which senior students (peer leaders) deliver the ASPP to Grade 7 students using activities, videos, and games. Students completed questionnaires related to asthma and smoking at baseline and 3 months after program delivery. Students with respiratory symptoms at 3 months were invited for a comprehensive clinical evaluation and tests including sputum induction.

Results: The ASPP was well received. Of the 203 students involved, 56 (28%) were Indigenous and 70% completed baseline and follow-up questionnaires. Self-reported asthma was high (19%), 10% of students reported smoking and 63% reported exposure to tobacco at home. Of the 22 students who were clinically evaluated, 41% were Indigenous. Clinically important airway inflammation was high; 23% had Fractional Exhaled Nitric Oxide Levels ≥35 ppb, 88% had airway neutrophilia (>15%), and 29% had airway eosinophilia (>2.5%). Optimization of medication and management was required in 59% of students.

Abbreviations: ASPP, Asthma and Smoking Prevention Project; ACT, Asthma Control Test; eCO, exhaled carbon monoxide test; CO, carbon monoxide in breath; IQR, interquartile range; NT, Northern Territory; QoL, quality of life; Triple A, adolescent asthma action.

Conclusion: Our study has demonstrated the implementation of the ASPP was well received by the schools as well as by the students. The high prevalence of clinically important airway inflammation and suboptimal asthma management highlights the need for a community-based study on persistent respiratory symptoms in adolescents to reduce the burden of chronic lung disease particularly for Indigenous Australians.

Keywords: asthma, adolescent, Indigenous, airway inflammation, tobacco smoking, school-based service

INTRODUCTION

Respiratory health is poorer in Indigenous populations globally (compared to their non-Indigenous counterparts) including in Australia (1). Asthma and tobacco smoking are arguably the most important public health issues of all the respiratory health problems relevant to Indigenous populations (2, 3). Tobacco smoking is a major risk factor for adverse asthma-related outcomes (4). Further, despite declining rates of daily smoking in Australia (5), the prevalence of smoking among Indigenous people, with and without asthma remains disproportionately higher than other Australians (2). The prevalence of asthma is also higher in Indigenous Australians (17.5%) compared with non-Indigenous Australians (10.1%) (6), with poorer asthma outcomes more likely in Indigenous Australians (e.g., they are three times more likely to die from asthma) (7). However, both these respiratory health problems (tobacco smoking and asthma outcomes) can be improved by targeted effective programs that are culture specific (8, 9).

The various effective programs for tobacco control include legal, community, and individual approaches (10, 11). At the individual level, preventing the uptake of tobacco smoking is arguably superior to methods for quitting smoking as smoking behaviors are often established in youth and are a strong predictor of later daily smoking and poorer long-term outcomes (12, 13). In Australia, more than two-thirds of Indigenous smokers and ex-smokers began smoking regularly before the age of 18 years (6). Thus, to tackle the high prevalence of tobacco smoking in at-risk groups such as Indigenous people, prevention strategies in adolescence is important and needed.

However, there are few preventative programs targeting at-risk groups such as Indigenous populations (14). In non-Indigenous settings, current evidence suggests that school-based smoking prevention programs can have substantial positive effects in both the short and long term (11). Schools are an ideal place for initiating health promotion programs as they provide easy access to the target group and complement health and well-being. They also encourage young people to assume leadership roles and take responsibility for their health. Peer-led education also provides a unique opportunity to disseminate hard to deliver messages. At this age, peers have a greater influence on health behaviors than do parents or health personnel (15).

A peer-led program, the "Adolescent Asthma Action Program" (Triple A), was developed as a response to concerns about high rates of asthma attacks, school absenteeism and smoking in schools (15). Triple A was efficacious in non-Indigenous settings in Australia (16) and Jordan (17), but has not been available in schools with at-risk groups such as Indigenous youth. We, therefore, conducted a feasibility study based on the Triple A program (15, 16) with an added smoking prevention module, called the "Asthma and Smoking Prevention Project" (ASPP).

Other strategies to improving respiratory health (e.g., asthma outcomes) include targeted therapies based on airway inflammation (18). Non-eosinophilic airway inflammation, measured by sputum cellularity (19), is an important cause of severe asthma (20) and is associated with smoking (21). While eosinophilic asthma responds to corticosteroids, non-eosinophilic asthma has a poor response to corticosteroids and is related to increased asthma severity (22). An important association with non-eosinophilic airway inflammation includes systemic inflammatory markers (e.g., C-reactive protein and interleukin-6) (23). These drivers of inflammation are modifiable (23) and have the potential to improve detection and management of respiratory health. None of these factors, however, have been examined in adolescents with persistent respiratory symptoms.

Thus, in our feasibility study, our primary aim was to determine whether the ASPP was acceptable and relevant for schools in Northern Territory (NT) schools with high proportion of Indigenous students. Our secondary aim was to clinically evaluate a subset of students with self-reported respiratory symptoms to (i) examine the type of lower airway inflammation profile and (ii) optimize asthma management.

MATERIALS AND METHODS

Study Design and Setting

We conducted this feasibility study (during March to June 2014) in two schools with a high number of Indigenous students in Darwin, the capital of the NT of Australia. A third school with more than 170 Grade 7 students withdrew prior to implementing ASPP due to logistical issues at the school level unrelated to the study. One school was a middle school (Grades 7–9) and the second a high school (Grade 7–12). This study was approved by the local Human Research Ethics Committee (HREC-2012-1900) and the NT Department of Education and Children's Services (DET2013/138). One school used the opt-out format for consent, whereas the second requested the opt-in approach where written informed consent was obtained from caregivers. Indigenous ethnicity was self-reported (Aboriginal and/or Torres Strait

Islander). Participants in our study were minors, thus consent was required to be obtained from caregivers.

Implementation of the ASPP

High-level negotiation was undertaken with the NT Department of Education and Children's Services to support the implementation of the ASPP into the nominated schools, and with school principals to embed the ASPP into the Health and Physical Education curriculum. The principals also identified key teachers to help drive the implementation into Grade 7 classes. ASPP staff presented the program to key teaching staff prior to roll out of the ASPP.

Participants

The ASPP participants consisted of two groups (i) Peer Leaders (15–17 years) and (ii) Grade 7 (12–14 years) students (the target intervention group). Peer Leaders were students in either Grade 9 or 11 (depending which school they attended). The number of Peer Leaders was dependent on the size of the school. Selection of Peer Leaders was undertaken by teachers, based on assessment of student leadership qualities. All Grade 7 students completed the program, but the exhaled carbon monoxide (eCO) test and questionnaires were obtained only in those with a completed consent form.

Details of the ASPP

We briefly describe the Triple A (15, 16) methods as they have previously been published (15, 17, 24). The ASPP is based on the Triple A program (15, 16) enriched with experience from existing tobacco education programs for Indigenous Australians, including normative education, training and social consequences of smoking, parental influences, and self-efficacy to resist smoking (25). The ASPP uses a student-centered strength-based approach to increase knowledge of asthma at a school level, create a supportive environment for students with asthma, and to promote a non-smoking culture in schools.

The theoretical basis of ASPP is embedded in social cognitive theory (15), which proposes a reciprocal interaction between a person, a targeted behavior, and a particular social context. It emphasizes that people learn not only from their own experiences but also by observing the actions of others. Adolescents are encouraged to (i) observe and imitate the positive behaviors of others, (ii) see positive behaviors modeled and practiced, (iii) empower and increase their own capability and confidence to implement new skills, (iv) adopt positive attitudes about implementing new skills, and (v) experience a supportive environment in order to use their new skills. The ASPP has been shown to encourage a sense of personal responsibility and improved quality of life for students with asthma, with fewer asthma attacks and reduced school absenteeism (17).

Educator Workshop and Steps of the ASPP

Before implementation of the ASPP in schools, educators were trained in an interactive 1-day workshop using standardized program manuals. The educators included Asthma Foundation NT staff, school nurses, university students (e.g., pharmacy students) (26), and research nurses. Following the educators' workshop, the school component was undertaken and consisted of three steps (**Figure 1**) (16).

Step 1

Involved the ASPP educators' training volunteer students were involved as peer leaders in an interactive 1-day workshop. The process was based on empowerment education, using a variety of strategies (e.g., videos, games, role plays, and quiz shows) during school lessons. Peer leaders learnt about asthma and smoking refusal skills and strategies to lead and teach their younger peers using standardized program manuals, detailed lesson plans, and materials (15).

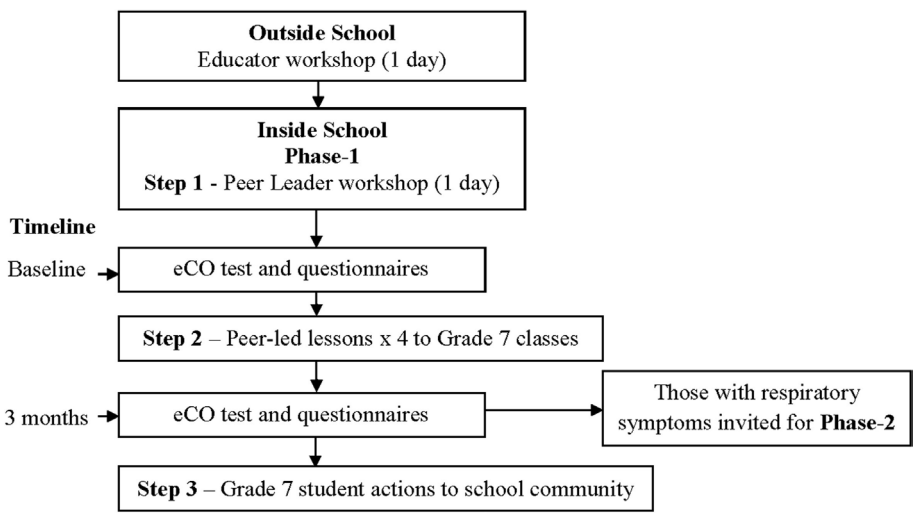

FIGURE 1 | Asthma and Smoking Prevention Project flow diagram.

Step 2

The peer leaders worked in groups of four (with support from class teachers) and delivered the four lessons of the ASPP to Grade 7 classes (target group) using standardized program manuals and materials (15). Sessions focused on asthma (how to avoid triggers, prevent exercise induced asthma, and what to do during an asthma attack) and peer pressure resistance training (e.g., how to say "no" to smoking; taking a smoke-free pledge). Learning was through videos, interactive games, and quiz shows, while furthering their skills in group leadership (15).

Step 3

The Grade 7 students disseminated what they had learnt in the ASPP to members of the school community and family through creative performances, e.g., drama, dance, and rap activities.

Data Collection

At baseline (before the ASPP was delivered), students (who consented) undertook an eCO test and questionnaire. The eCO test was done using the PiCO+ Smokerlyzer® device [Bedfont Scientific, England, UK measuring in parts per million (ppm)]. In our study, the cut off point for adolescent smokers was defined as elevated levels of carbon monoxide in breath (CO) >4 ppm (27). Student questionnaires included: the International Study of Asthma and Allergies in Childhood Questionnaire (28) with modified questions for chronic respiratory disease from the St. George's Respiratory Questionnaire, questions on cough (29), the asthma control test (ACT) was a composite score (ranging from 0 to 12) and smoking-related questions. eCO and questionnaires were repeated at the 3-month follow-up.

At the end of their workshop, Peer Leaders completed a feedback questionnaire. Teaching staff also provided informal feedback about the ASPP.

Clinical Evaluation

Students reporting current respiratory symptoms or self-reported asthma on the 3-month follow-up questionnaire were invited to have a clinical evaluation by a respiratory specialist. Demographic, medical history, and clinical data were recorded on standardized data collection forms for students whose caregiver provided written consent.

Participants were clinically evaluated and undertook additional tests: Fractional Exhaled Nitric Oxide (FE_{NO}) using the Niox Mino (Aerocrine, Sweden) (30), spirometry (easy on-PC, ndd, Zurich, Switzerland), airway hyper-responsiveness (AHR) using hypertonic saline and sputum induction. The standardized 4.5% hypertonic saline challenge was used and sputum was processed using standard methods as previously done and (31) venipuncture (for full blood count and C-reactive protein) was also undertaken in those who had provided consent.

Definitions

An AHR positive result was defined as a fall in forced expiratory volume during the first second (FEV_1) of ≥15% from baseline (31). FeNO values ≥35 ppb (30) were considered abnormal. Airway eosinophilia and neutrophilia were considered present when the percentage of sputum eosinophils and neutrophilia were >3 and >15%, respectively (32, 33). Optimization of clinical management and classification of asthma was in accordance with the Australian Asthma Handbook. Management and classification for cough was based on an evidence-based cough guideline (34).

Analyses

Data were entered on an Access database and analyzed using Stata version 14 (StataCorp, College Station, TX, USA). Data are presented as numbers and percentages, median and interquartile range (IQR) 25–75%, mean and SD or range, depending on data distribution. As this was a feasibility pilot study, before and after statistical comparison and a sample size calculation were not undertaken. However, we aimed to recruit 200 Grade 7 students as our target group. Qualitative data from Peer Leaders were thematically described.

RESULTS

Schools/Demographics

Of the total number of Grade 7s (School 1: $n = 190$ and School 2: $n = 77$), consent was obtained from 49% from School 1 and 98% from School 2. A total of 203 students from the two schools participated in this study (e.g., completed questionnaires and eCO). The number of participating students per school is summarized in **Table 1**. Over half the students were female (55%) and 56 (28%) were Indigenous. Due to small numbers in this study, data were combined and results presented as a total.

Questionnaires

Questionnaires were completed by 173 students at baseline and a further 156 at 3 months. Students completed baseline questionnaires unsupervised. As these were poorly completed (e.g., inconsistent and incomplete answers), ASPP staff supervised the completion of the follow-up questionnaires at 3 months (ASPP staff were in the classroom and helped when requested). At baseline, self-reported asthma was high ($n = 33$, 19%) with 20% of students reporting wheezing in the previous 12 months. Previous smoking was reported in 18 (10%) students, with first time smoking in 14 (8%) students aged less than 12 years. More than 24% reported that their friends were current smokers.

TABLE 1 | School demographics of participating students.

	School 1	School 2	Total
	$n = 130$ (%)	$n = 73$ (%)	$n = 203$ (%)
Male/female	61/69	30/43	91/112
Indigenous	19 (15)	37 (51)	56 (28)
Number of Grade 7s	93 (72)	66 (90)	159 (78)
Number of peer leaders	37 (28)	7 (10)	44 (22)
Completed baseline questionnaire[a]	108 (83)	68 (93)	176 (87)
Completed follow-up questionnaire[b]	107 (82)	49 (67)	156 (77)
Completed both questionnaires	98 (75)	44 (60)	142 (70)

[a]*n = 27 did not complete questionnaire.*
[b]*n = 47 did not complete questionnaire.*

Exposure to tobacco smoke at home was very high, with more than 99 (63%) students living in a house with >1 smoker (range 1–20 smokers). The smoking pledge was signed by 87 (49%) students, with 48 (27%) students leaving the question empty. Results of baseline and 3-month questionnaires are summarized in **Table 2**.

Of those students who completed both questionnaires ($n = 142$, 70%), results were paired. Fifteen students completed the ACT; there was no change in the median ACT score from baseline (IQR 8.5, 6–10) to 3 months (IQR 8.5, 7–10). Only three students (2%) reported being current smokers at baseline with none at follow-up. Students' exposure to tobacco smokers at home was high (range 1–20 smokers).

The eCO test was well received by students and was obtained for 91 (45%) students at baseline and 77 (34%) at 3 months. At baseline, elevated CO levels were found in three (3%) students compared with four (5%) at 3 months. Of the three students who reported being current smokers at baseline, only one had elevated CO levels consistent with that of a smoker (>4 ppm) (27).

Feedback of the ASPP

The students' feedback was overwhelmingly positive, with the most common responses described in **Table 3**. While we did not formally evaluate the ASPP for teaching staff, teachers were also receptive to the program as described: "*I am glad you let us trial this at our school. It has been a character building event for a lot of the Year 9's that participated. We have noticed more engagement and involvement with other students and many have kept their connections to their Year 7 peers too. A great program, we hope you will consider us again.*" Further, both schools provided support for further implementation of the ASPP and have invited us to run the program again in the future.

TABLE 2 | Baseline and follow-up questionnaire results.[d]

	Baseline	Follow-up
	***n* = 176**	***n* = 156**
ISAAC questionnaire		
Wheezing in last 12 months	36 (20%)	34 (22%)
Wheezing during exercise in the last 12 months	41 (23%)	34 (22%)
Ever diagnosed with asthma by doctor	33 (19%)	21 (13%)
Asthma control test (ACT)[a]		
ACT score (0–12)[b]	9 (6–10)	9 (7–9)
Cough		
Any cough present	56 (32%)	30 (19%)
Acute cough (≤14 days)	32 (18%)	20 (13%)
Chronic cough (≥28 days)	11 (6%)	7 (4.5%)
Smoking questions		
Number of students ever tried smoking?	18 (10%)	15 (10%)
How old when tried smoking		
≤12 years	14 (8%)	13 (8%)
>12 years	7 (4%)	5 (3%)
Family/household smoking		
How many people smoke cigarettes at home? (range)	1–20	1–15
Who smokes in your family?		
Mum	48 (27%)	46 (29%)
Dad	63 (36%)	51 (33%)
Siblings (brother/sister)	31 (18%)	22 (14%)
Aunt/uncle(s)	33 (19%)	25 (16%)
Grandparent(s)	28 (16%)	24 (15%)
Other	24 (14%)	21 (13%)
Are there rule about smoking cigarettes at home?[c]		
No rules	27 (15%)	22 (14%)
No one is allowed to smoke in my home	62 (35%)	60 (38%)
Only special guests are allowed to smoke in my home	7 (4%)	2 (1%)
People are allowed to smoke in certain areas in my home	9 (5%)	16 (10%)
People are allowed to smoke anywhere in my home	7 (4%)	2 (1%)
People are allowed to smoke outside only	86 (49%)	75 (48%)
Smoking and friends		
How many of your closest friends smoke?		
None	102 (58%)	88 (56%)
1 or 2	24 (14%)	25 (16%)
3 or more	19 (11%)	14 (9%)
Unsure	19 (11%)	24 (15%)
Would you smoke a cigarette, if friend offered it?		
Yes	1 (1%)	2 (1%)
No	160 (91%)	143 (92%)
Maybe	8 (5%)	7 (4.5%)

[a]*Only students who self-reported asthma on questionnaires.*

[b]*Interquartile range (IQR) (25, 75).*

[c]*Some responses have more than one answer.*

[d]*The numbers reported in the table do not match up (e.g., response to "ever tried smoking" was reported as no and response to "how old when smoking" an age was reported). We have, therefore, reported what was transcribed by the students and recognized as a limitation as described in the discussion.*

Missing data at baseline: wheezing in last 12 months; n = 1 (0.5%), wheezing when exercising; n = 1 (1%), doctor confirmed asthma; n = 2 (1%), how bad is asthma today; n = 6 (3%), is asthma a problem when exercising; n = 6 (3%), cough because of asthma; n = 7 (4%), wake at night because of cough; n = 6 (3%), current cough; n = 6 (3%), ever tried smoking; n = 6 (3%), age tried smoking; n = 2 (1%), current smokers; n = 5 (3%), last cigarette; n = 5 (3%), how often smoke; n = 11 (6%), mum smoke; n = 9 (5%), dad smoke; n = 9 (5%), brother/sister smoke; n = 9 (5%), aunt/uncle; n = 9 (5%), grandparent; n = 9 (5%), other; n = 9 (5%), rules for smoking; n = 14 (8%), no smoking at home; n = 15 (9%), guests smoke' n = 15 (9%), smoke in certain areas; n = 15 (9%), smoke anywhere; n = 15 (9%), smoke outside only; n = 15 (9%), friends smoke; n = 9 (5%), offered smoke; n = 7 (4%).

Missing data at follow-up: wheezing in last 12 months; n = 1 (1%), wheezing when exercising; n = 1 (1%), doctor confirmed asthma; n = 1 (1%), how bad is asthma today; n = 1 (1%), is asthma a problem when exercising; n = 1 (1%), cough because of asthma; n = 1 (1%), wake at night because of cough; n = 1 (1%), current cough; n = 2 (2%), ever tried smoking; n = 3 (2%), age tried smoking; n = 1 (1%), current smokers; n = 3 (2%), last cigarette; n = 4 (3%), how often smoke; n = 8 (5%), mum smoke; n = 6 (4%), dad smoke; n = 6 (5%), brother/sister smoke; n = 6 (4%), aunt/uncle; n = 6 (4%), grandparent; n = 6 (4%), other; n = 7 (4.5%), rules for smoking; n = 10 (6%), no smoking at home; n = 10 (6%), guests smoke' n = 10 (6%), smoke in certain areas; n = 10 (6%), smoke anywhere; n = 10 (6%), smoke outside only; n = 10 (6%), friends smoke; n = 5 (3%), offered smoke; n = 4 (3%).

Clinical Evaluation

Of the 37 students who reported current respiratory symptoms on the 3-month questionnaire, consent was obtained for 24 (65%). The clinical evaluation took place within 3 weeks of the 3-month questionnaire. Two students were away at the time leaving 22 students who undertook this component. **Table 4** provides the demographic and clinical characteristics of these students.

Over 20% of students reported current symptoms of breathlessness, wheeze, chest pain, and tiredness/lethargy (**Table 4**). Cough was reported in all students, with a dry cough 19 (86%) being most common.

Clinical diagnosis of asthma (intermittent or persistent) was higher 12 (54%) than student self-reported asthma 10 (46%). Eight of the eleven students with known asthma pre-evaluation had persistent asthma (**Table 4**). Optimization of asthma medications and change of management was required in 59% of students. Importantly, one student was suspected to have bronchiectasis and was referred for further investigation.

Tests Results

All students completed FE_{NO}, spirometry, and AHR challenge. Induced sputum was successfully collected from 17 (77%) students. Clinically important high FE_{NO} levels (≥35 ppb) were documented in five (23%) students. Fifteen (88%) students had clinically important airway neutrophillia (>15% neutrophils) and 6 (35%) had airway eosinophilia (>2.5%). Of the five with FeNO levels ≥35 ppb, the median FeNO was 47 (max = 109), three were known to have asthma pre-evaluation, and airway eosinophilia was present in one. Of the 15 students with airway neutrophilia, five were known to have asthma pre-evaluation. Four (18%) students had abnormal spirometry results, but AHR was not present in any student.

A blood sample was collected from 14 (64%) students, and all results were within the normal ranges for cell counts. Absolute counts are as follows: Neutrophils: median 4 (IQR 3, 5); Eosinophils: median 0.4 (IQR 0.2, 0.7); and C-reactive protein: mean 1.3 (SD 0.7). The median peripheral eosinophil count in those with airway eosinophilia was 0.55 (IQR 0.3, 0.7).

TABLE 3 | Peer leader feedback.

Questions	Most common responses
What are the most important points gained from Asthma and Smoking Prevention Project?	How important asthma awareness is (9%) How to treat someone who is having an asthma emergency (53%) How to teach others about asthma (9%) Asthma can kill you (2%) Asthma is important and serious (24%) Smoking makes asthma worse (4%) Ways to say no to smoking (9%) Go get check-ups often (2%) What causes asthma attacks (triggers) and how to deal with them (44%) What happens to your lungs when you have an asthma attack (4%) Asthma won't prevent you from living your life (4%) Fun and teamwork (20%) Gaining confidence to speak in public (20%) How to say "no" to smoking (4%) Working together as a team (4%)
What did you like in particular?	The fun of the workshop (13%) Hands on activities/games (42%) How the presenters did the workshop—it was not boring/they had games (11%) Sit down and talk and then break the day into activities (2%) Role playing (2%) The videos about asthma (4%) Doing first aid presentations (6%) The safe environment for learning (4%) The straw game—it helped understand what it feels like to have asthma (4%) Learning about smoking (4%)
What can be improved?	Nothing (64%) More standing or more activities outside (7%) Structure of questionnaires could be improved (2%)

DISCUSSION

Our study involving 203 students from two schools with a high percentage of Indigenous students showed that the ASPP was a

TABLE 4 | Demographic and clinical characteristics of 22 students with current respiratory symptoms.

	n = 22 (%)
Male/female	4/18
Age (years)[a]	13 (1.4)
Indigenous	9 (41%)
Gestational age (weeks)	40 (38–41)
Birth weight (kg)	3.2 (2.8, 3.6)
Special care nursery admission	1 (6%)
Previous respiratory hospitalization	3 (14%)
Mother smoked during pregnancy	7 (32%)
Exposed to household smoke	8 (36%)
Symptoms	
Current symptoms	
Breathless	6 (27%)
Wheeze	5 (23%)
Hemoptysis	0 (0%)
Chest pain	5 (23%)
Tiredness/lethargy	6 (27%)
Ever symptoms	
Breathless	15 (68%)
Wheeze	15 (68%)
Hemoptysis	1 (5%)
Chest pain	15 (68%)
Tiredness/lethargy	17 (77%)
Clinical examination	
Dry/wet cough	19/3
Chest wall hyperinflation	2 (9%)
Wheeze present	1 (5%)
Crackles present	0 (0%)
Chronic suppurative otitis media	1 (5%)
Classification of persistent asthma	
Mild	6 (27%)
Moderate	2 (9%)
Severe	1 (5%)

(Continued)

TABLE 4 | Continued

	n = 22 (%)
Spirometry and FeNO (*n* = 22)	
FEV_1[b]	90 (82, 100)
Forced vital capacity[b]	95 (83, 102)
FE_{NO} <20 ppb	13 (59%)
FE_{NO} 20–<35 ppb	4 (18%)
FE_{NO} ≥35 ppb	5 (23%)
Sputum characteristics (*n* = 17)	
Mucoid	3 (18%)
Mucopurulent	1 (6%)
Purulent	2 (12%)
Airway inflammation	
Eosinophilia (>2.5%)	6 (35%)
Airway neutrophilia (>15%)	15 (88%)
Clinical classification and management (*n* = 22)	
Self-identified asthma (on follow-up Q)	10 (46%)
Asthma diagnosed at clinical review	
Intermittent asthma	4 (18%)
Persistent asthma	8 (36%)
Optimization of medication and change of management plans	13 (59%)

[a]*Mean (SD).*

[b]*% predicted and IQR (25, 75).*

n = 1 child away for clinical examination. n = 1 child excluded as did not have medical records. Results are for only those children who completed clinical review missing (ever breathless, n = 1 (4%), ever wheeze, n = 1 (4%); ever hemoptysis, n = 1 (4%); ever tired/lethargic, n = 2 (9%), ever breathless 12 months, n = 2 (9%), ever wheeze 12 months, n = 2 (9%); ever hemoptysis 12-months, n = 2 (9%); ever chest pain, n = 2 (9%), ever tired/lethargic 12 months, n = 2 (9%), ever breathless 12 months, n = 2 (9%), ever wheeze 12 months, n = 2 (9%); ever hemoptysis 12 months, n = 2 (9%); ever chest pain, n = 2 (9%), ever tired/lethargic 12 months, n = 2 (9%), breathless now, n = 3 (13%), wheeze now, n = 3 (13%); hemoptysis now, n = 3 (13%); chest pain now, n = 3(13%), tired/lethargic now, n = 3 (13%), mum smoked(not stated, n = 10 (44%), exposed to household smoke, n = 7 (30%), previous respiratory hospitalization, n = 1 (4%), birth weight, n = 5 (23%), ICU admission, n = 1 (4%). mucoid (n = 13 (59%), sputum type; n = 13 (59%).

feasible program for implementation into schools in the NT. For the clinical evaluation component, we found that students with respiratory symptoms had clinically important airway inflammation (35% airway eosinophilia and 88% neutrophilia) and clinically important elevated FE_{NO} levels (23% with values ≥35 ppb). Most students (59%) also required optimization of medication and management.

Our feasibility study established that the ASPP was well received in the urban NT schools. This was evidenced by (i) support from the NT Department of Education, (ii) successful implementation of the ASPP within school's curriculum with minimal disruptions to existing curricula, (iii) positive feedback from Peer Leaders of the acceptability of the ASPP, (iv) teacher endorsement and willingness to be involved in future implementation of the program, and (v) obtaining a 70% response rate for follow-up questionnaires at 3 months. This study illustrates the potential for further school-based health interventions in at-risk groups.

Previous smoking was reported by 10% of students, with first time smoking when aged less than 12 years in 8% of students. These data are consistent with anecdotal evidence from several remote NT Indigenous communities, reporting that smoking is initiated among children aged less than 13 years. Students in our study reported high exposure to tobacco smoke at home (63%), far exceeding nationally reported data (7.8%) (2). This is consistent with our previous study on children hospitalized for asthma, which reported high exposure to tobacco smoke at home (Indigenous 95.2% and non-Indigenous 45.7%) (35). Our results highlight the importance of integrating interventions during adolescence to target social norms, behaviors, and attitudes (36) to prevent the uptake of tobacco smoking and prevent poorer long-term outcomes [e.g., chronic respiratory diseases such as bronchiectasis (35) and cardiovascular disease] (37).

Our sample was too small to examine for differences for improved asthma control and reduced uptake of tobacco smoking, and our study was not designed to replicate the results of previous studies (16, 17). However, we identified several important findings, including high self-reported asthma (19%) compared to the national average of 10.2% (2). Of those students with asthma, more than 20% reported being symptomatic in the previous 12 months, which is consistent with data reported from the Australian National Young People and Asthma Survey (38). Thus, our study that is focused on individuals, confirms the need to improve the diagnosis and management of respiratory symptoms in this age group.

Of students who underwent clinical evaluation, those with asthma had either poorly controlled asthma and/or were incorrectly diagnosed with asthma. Although no one had elevated systemic inflammatory markers, a majority had clinically important airway inflammation [88% had clinically important airway neutrophillia (>15%) and 35% had airway eosinophilia (>3%) (32, 33)]. Our findings of the lack of systemic makers in the presence of clinically important lower airway inflammation is in contrast to data in adults but consistent with pediatric studies (39, 40). We (41, 42) and others (39, 40) have shown the discordance between local (i.e., airways) and systemic inflammation in children with chronic lower airway infection and asthma, respectively. The possible reasons for this discordance include the lack of spill over effect in children (compared to adults) and the cross-sectional study design. However, these remain speculative and an in-depth discussion is beyond the scope of this paper. The reason for our findings of a very high proportion with airway neutrophilia is unknown, but possibly related to various factors, including tobacco smoke exposure, acute, and/or chronic persistent lower airway infection (1–3). Tobacco smoking in people with asthma is a known risk factor for poor asthma control and non-eosinophilic airway inflammation (21, 43). Eosinophilic inflammation identified in both FE_{NO} and sputum was very high, in particular, for those with previously diagnosed asthma, resulting in over two-thirds requiring optimization of medication and change of management. These data suggest that better individualized clinical evaluation is required and a larger community-based study is needed to ascertain objective diagnoses in a setting of high

prevalence of chronic disease (e.g., bronchiectasis) to improve clinical outcomes particularly for Indigenous Australians. Our cohort study on children referred to respiratory specialists for chronic cough found that 70% were previously diagnosed incorrectly with asthma before referral (44). Also, Indigenous children were significantly more likely to have radiologically proven bronchiectasis (odds ratio = 4.4, 95% CI 1.9, 10) than non-Indigenous children on further evaluation. As respiratory issues account for the most common reason why Indigenous Australians present to doctors and the second most common self-reported chronic illness (45), it is imperative that better individualized management is required.

Our results are also consistent with national data describing 91% of Australian youth with asthma reporting poor control, with 63% reporting being short of breath on a weekly basis (38). In addition, 11.6% reported being current smokers (38). Plausible factors for suboptimal management in this group may include independent decision making of adolescents, reduced role of caregivers, less medical supervision, decreased adherence to therapy, and peer pressure (46). Further, individuals from low socioeconomic backgrounds are at particular risk for poorer outcomes, as found by a recent study evaluating risk factors for asthma-related deaths in children (47). Earlier studies have shown that the proportion of Indigenous children with poorly controlled asthma is higher than Australia-wide data, and that management was generally suboptimal (48).

Our study has several limitations. Firstly, the numbers of students were lower than anticipated. We had planned to include 200 Grade 7 students; however, with the withdrawal of a large school shortly before commencing the ASPP, we had limited time to find another school, which was much smaller. Secondly, one school required parental consent for objective measurements (e.g., eCO test and questionnaires). Thirdly, the smoking pledge was inconsistently done with Peer Leaders in the fourth lesson of the program. Nevertheless, valuable lessons were learnt that will support future implementation of the ASPP include (i) while we received high level school support, earlier involvement with class teachers is needed to encourage support of Peer Leaders during lessons, (ii) negotiating opt-out consent will provide more robust data to further strengthen findings from previous studies (16, 17), and (iii) questionnaires were not suitable for this population and further modification is required to make them more literacy and language appropriate. Using electronic devices such as tablets to complete questionnaires will restrict the possibility of conflicting responses, in addition to having a more reliable dataset to compare against objective measurements such as eCO levels. It could be argued that the withdrawal of the third school meant that the ASPP program may not feasible in the NT. However, we do not believe this is the case and would not have impacted the outcomes of this feasibility pilot study for several reasons. First, we were planning to undertake the study in two schools only, however, when one school was unable participate in the study due to logistical reasons at the school level, which were not related to the study, we had to recruit another smaller school in the vicinity, which also had high proportions of Indigenous students. Second, we have shown the feasibility of the ASPP in two diverse schools in Darwin as discussed above. Importantly, the implementation of the program model has shown to be effective in other geographically diverse populations in rural and metropolitan regions in Australia and in Jordan (15, 17, 24).

In conclusion, implementation of the ASPP in two urban-based NT schools was feasible and well received by the NT Department of Education and Children's Services and schools. Of the students reporting current respiratory symptoms, most were found to have clinically significant airway inflammation and suboptimal management. Therefore, better community-based data, improving asthma management and preventing uptake of tobacco smoking of adolescents through innovative programs such as the ASPP in schools could potentially improve lung health particularly of Indigenous Australians.

AUTHOR CONTRIBUTIONS

GM setup and managed the study, recruited participants, cleaned the data, performed the data analysis, and wrote the manuscript. AC and SS conceptualized the study. AC, SS, and JS obtained the grant and edited the manuscript. CW recruited participants, schools, contributed to data collection, and edited the manuscript. HP and SP contributed to data collection, processing sputum samples, and edited the manuscript. AC and SCS undertook the clinical evaluation.

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REFERENCES

1. Morgan J. Indigenous Australians and the struggle for health equality. *Lancet Respir Med* (2015) 3:188–9. doi:10.1016/S2213-2600(15)00045-4
2. Australian Centre for Asthma Monitoring. *Asthma in Australia 2011: With a Focus Chapter on Chronic Obstructive Pulmonary Disease*. Canberra, ACT: AIHW (2011).
3. Kovesi T. Respiratory disease in Canadian First Nations and Inuit children. *Paediatr Child Health* (2012) 17:376–80.
4. Ferrante G, Antona R, Malizia V, Montalbano L, Corsello G, La Grutta S. Smoke exposure as a risk factor for asthma in childhood: a review of current evidence. *Allergy Asthma Proc* (2014) 35:454–61. doi:10.2500/aap.2014.35.3789
5. Thomas DP. Smoking prevalence trends in Indigenous Australians, 1994-2004: a typical rather than an exceptional epidemic. *In J Equity Health* (2009) 8:37. doi:10.1186/1475-9276-8-37
6. ABS. *Australian Aboriginal and Torres Strait Islander Health Survey: First Results, Australia, 2012-13*. Canberra: Australian Bureau of Statistics (2012).
7. Jenkins CR, Chang AB, Poulos LM, Marks GB. Asthma in Indigenous Australians: so much yet to do for Indigenous lung health. *Med J Aust* (2009) 190:530–1.
8. Chang AB, Taylor B, Masters IB, Laifoo Y, Brown AD. Indigenous health-care worker involvement for Indigenous adults and children with asthma. In: Cates C, editors. *Cochrane Database Syst Rev* (2010) 12:CD006344. doi:10.1002/14651858.CD006344.pub3
9. McCallum GB, Morris PS, Brown N, Chang AB. Culture-specific programs for children and adults from minority groups who have asthma. *Cochrane Database Syst Rev* (2016) (In press).
10. Minichiello A, Lefkowitz AR, Firestone M, Smylie JK, Schwartz R. Effective strategies to reduce commercial tobacco use in Indigenous communities globally: a systematic review. *BMC Public Health* (2016) 16:21. doi:10.1186/s12889-015-2645-x
11. Thomas RE, McLellan J, Perera R. School-based programmes for preventing smoking. *Cochrane Database Syst Rev* (2013) 4:CD001293. doi:10.1002/14651858.CD001293.pub3
12. Joffer J, Burell G, Bergström E, Stenlund H, Sjörs L, Jerdén L. Predictors of smoking among Swedish adolescents. *BMC Public Health* (2014) 14:1296. doi:10.1186/1471-2458-14-1296
13. Johnston V, Westphal DW, Earnshaw C, Thomas DP. Starting to smoke: a qualitative study of the experiences of Australian Indigenous youth. *BMC Public Health* (2012) 12:963. doi:10.1186/1471-2458-12-963
14. Carson KV, Brinn MP, Labiszewski NA, Peters M, Chang AB, Veale A, et al. Interventions for tobacco use prevention in Indigenous youth. *Cochrane Database Syst Rev* (2012) 8:CD009325. doi:10.1002/14651858.CD009325.pub2
15. Shah S, Mamoon HA, Gibson PG. Peer-led asthma education for adolescents: development and formative evaluation. *Health Promot J Austr* (1998) 8:177–82.
16. Shah S, Peat JK, Mazurski EJ, Wang H, Sindhusake D, Bruce C, et al. Effect of peer led programme for asthma education in adolescents: cluster randomised controlled trial. *BMJ* (2001) 322:583–5.
17. Al-sheyab N, Gallagher R, Crisp J, Shah S. Peer-led education for adolescents with asthma in Jordan: a cluster-randomized controlled trial. *Pediatrics* (2012) 129:e106–12. doi:10.1542/peds.2011-0346
18. Hargreave FE. Quantitative sputum cell counts as a marker of airway inflammation in clinical practice. *Curr Opin Allergy Clin Immunol* (2007) 7:102–6.
19. Petsky HL, Cates CJ, Lasserson TJ, Li AM, Turner C, Kynaston JA, et al. A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax* (2012) 67:199–208. doi:10.1136/thx.2010.135574
20. Gibson PG. What do non-eosinophilic asthma and airway remodelling tell us about persistent asthma? *Thorax* (2007) 62:1034–6. doi:10.1136/thx.2007.079061
21. Thomson NC, Chaudhuri R. Asthma in smokers: challenges and opportunities. *Curr Opin Pulm Med* (2009) 15:39–45. doi:10.1097/MCP.0b013e32831da894
22. Gibson PG. Tackling asthma phenotypes in community studies. *Thorax* (2009) 64:369–70. doi:10.1136/thx.2008.109710
23. Wood LG, Scott HA, Garg ML, Gibson PG. Innate immune mechanisms linking non-esterified fatty acids and respiratory disease. *Prog Lipid Res* (2009) 48:27–43. doi:10.1016/j.plipres.2008.10.001
24. Gibson PG, Shah S, Mamoon HA. Peer-led asthma education for adolescents: impact evaluation. *J Adolesc Health* (1998) 22:66–72.
25. Flay BR. School-based smoking prevention programs with the promise of long-term effects. *Tob Induc Dis* (2009) 5:6. doi:10.1186/1617-9625-5-6
26. Shah S, Roydhouse JK, Sawyer SM, Gallagher R. Medical students go back to school-the Triple A journey. *Aust Fam Physician* (2008) 37:952–4.
27. Al-sheyab N, Kheirallah KA, Mangnall LJ, Gallagher R. Agreement between exhaled breath carbon monoxide threshold levels and self-reported cigarette smoking in a sample of male adolescents in Jordan. *Int J Environ Res Public Health* (2015) 12:841–54. doi:10.3390/ijerph120100841
28. Gibson PG, Henry R, Shah S, Toneguzzi R, Francis JL, Norzila MZ, et al. Validation of the ISAAC video questionnaire (AVQ3.0) in adolescents from a mixed ethnic background. *Clin Exp Allergy* (2000) 30:1181–7.
29. Chang AB, Newman RG, Carlin JB, Phelan PD, Robertson CF. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. *Eur Respir J* (1998) 11:462–6.
30. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* (2011) 184:602–15. doi:10.1164/rccm.9120-11ST
31. Chang AB, Harrhy VA, Simpson J, Masters IB, Gibson PG. Cough, airway inflammation and mild asthma exacerbation. *Arch Dis Child* (2002) 86:270–5.
32. Cai Y, Carty K, Henry RL, Gibson PG. Persistence of sputum eosinophilia in children with controlled asthma when compared with healthy children. *Eur Respir J* (1998) 11:848–53.
33. Gibson PG, Grootendor DC, Henry RL, Pin I, Rytila PH, Wark P, et al. Sputum induction in children. *Eur Respir J Suppl* (2002) 37:44s–6s.
34. Chang AB, Robertson CF, Van Asperen PP, Glasgow NJ, Masters IB, Teoh L, et al. A cough algorithm for chronic cough in children: a multicenter, randomized controlled study. *Pediatrics* (2013) 131:e1576–83. doi:10.1542/peds.2012-3318
35. Giarola BF, McCallum GB, Bailey EJ, Morris PS, Maclennan C, Chang AB. Retrospective review of 200 children hospitalised with acute asthma. Identification of intervention points: a single centre study. *J Paediatr Child Health* (2014) 50:286–90. doi:10.1111/jpc.12470
36. Cremers HP, Mercken L, de Vries H, Oenema A. A longitudinal study on determinants of the intention to start smoking among non-smoking boys and girls of high and low socioeconomic status. *BMC Public Health* (2015) 15:648. doi:10.1186/s12889-015-1917-9
37. Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Symptoms of chronic bronchitis and the risk of coronary disease. *Lancet* (1996) 348:567–72.
38. Blanchard M, Morris J, Birrell E, Stephens-Reicher J, Third A, Burns J. *National Young People and Asthma Survey: Issues and Opportunities in Supporting the Health and Wellbeing of Young People Living with Asthma*. (2014). Available from: https://www.pharmacynews.com.au/getmedia/d78362d2-b5c4-44bc-8aea-b0297bbebca4/National-Young-People-and-Asthma-Survey.aspx
39. Jensen ME, Gibson PG, Collins CE, Wood LG. Airway and systemic inflammation in obese children with asthma. *Eur Respir J* (2013) 42:1012–9. doi:10.1183/09031936.00124912
40. Ullmann N, Bossley CJ, Fleming L, Silvestri M, Bush A, Saglani S. Blood eosinophil counts rarely reflect airway eosinophilia in children with severe asthma. *Allergy* (2013) 68:402–6. doi:10.1111/all.12101
41. Pizzutto SJ, Upham JW, Yerkovich ST, Chang AB. High pulmonary levels of IL-6 and IL-1beta in children with chronic suppurative lung disease are associated with low systemic IFN-gamma production in response to non-typeable *Haemophilus influenzae*. *PLoS One* (2015) 10:e0129517. doi:10.1371/journal.pone.0129517
42. Wurzel DF, Marchant JM, Yerkovich ST, Upham JW, Mackay IM, Masters IB, et al. Prospective characterization of protracted bacterial bronchitis in children. *Chest* (2014) 145:1271–8. doi:10.1378/chest.13-2442
43. Gulsvik A, Refvem OK. A scoring system on respiratory symptoms. *Eur Respir J* (1988) 1:428–32.
44. Chang AB, Robertson CF, Van Asperen PP, Glasgow NJ, Mellis CM, Masters IB, et al. A multicenter study on chronic cough in children: burden and etiologies based on a standardized management pathway. *Chest* (2012) 142:943–50.

45. ABS. *The Health and Welfare of Australia's Aboriginal and Torres Strait Islander People, an Overview 2011*. Canberra: Australian Bureau of Statistics (2011).
46. Jamrozik K. Population strategies to prevent smoking. *BMJ* (2004) 328:759–62. doi:10.1136/bmj.328.7442.759
47. Van Asperen P. Deaths from childhood asthma, 2004-2013: what lessons can we learn? *Med J Aust* (2015) 202:125–6.
48. Chang AB, Shannon C, O'Neil MC, Tiemann AM, Valery PC, Craig D, et al. Asthma management in Indigenous children of a remote community using an Indigenous health model. *J Paediatr Child Health* (2000) 36:249–51.

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The Incidence and Short-term Outcomes of Acute Respiratory Illness with Cough in Children from a Socioeconomically Disadvantaged Urban Community in Australia: A Community-Based Prospective Cohort Study

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Background: Acute respiratory illnesses with cough (ARIwC) are predominant causes of morbidity in Australian Indigenous children; however, data on disease burden in urban communities are scarce. This study aimed to determine the incidence of ARIwC, the predictors of recurrent (≥4 episodes) ARIwC, and development of chronic cough following an ARIwC in urban, predominantly Indigenous, children aged <5 years from northern Brisbane, Australia.

Methods: Prospective cohort study of children aged <5 years registered with a primary healthcare center. ARIwC episodes and outcomes were collected for 12 months. Recurrent ARIwC was defined as ≥4 episodes in 12 months. Chronic cough was defined as cough lasting >4 weeks. Children who developed chronic cough were reviewed by a pediatric pulmonologist. Incidence densities per child-month of observation were calculated and predictors of recurrent ARIwC and chronic cough were evaluated in logistic regression models.

Results: Between February 2013 and November 2015, 200 children were enrolled; median age of 18.1 months, range (0.7–59.7 months) and 90% identified as Indigenous. A total of 1,722 child-months of observation were analyzed (mean/child = 8.58, 95% CI 8.18–9.0). The incidence of ARIwC was 24.8/100 child-months at risk (95% CI 22.3–27.5). Twenty-one children (10.5%) experienced recurrent ARIwC. Chronic cough was identified in 70/272 (25.7%) episodes of ARIwC. Predictors of recurrent ARIwC were presence of eczema, mold in the house, parent/carer employment status, and having an Aboriginal and Torres Strait Islander mother/non-Aboriginal and Torres Strait

Islander father (compared to both parents being Aboriginal and Torres Strait Islander). Predictors of chronic cough included being aged <12 months, eczema, childcare attendance, previous history of cough of >4 weeks duration, having an Aboriginal and Torres Strait Islander mother/non-Aboriginal and Torres Strait Islander father (compared to both parents being Aboriginal and Torres Strait Islander), and a low income. Of those with chronic cough reviewed by a pediatric pulmonologist, a significant underlying disorder was found in 14 children (obstructive sleep apnea = 1, bronchiectasis = 2, pneumonia = 2, asthma = 3, tracheomalacia = 6).

Discussion: This community of predominantly Aboriginal and Torres Strait Islander and socially disadvantaged children bear a considerable burden of ARIwC. One in 10 children will experience more than three episodes over a 12-month period and 1 in five children will develop chronic cough post ARIwC, some with a serious underlying disorder. Further larger studies that include a broader population base are needed.

Keywords: acute respiratory illness, cough, incidence, predictors, clinical outcomes, Aboriginal and Torres Strait Islander, cohort study

INTRODUCTION

Acute respiratory illnesses (ARIs) are leading causes of childhood mortality and morbidity in developed and developing countries alike. Indigenous children in developed countries have high ARI hospitalization rates similar to that of children in developing countries (1–3). Cough (particularly if wet), when present, likely reflects lower airway diseases, is a key symptom of chronic lung disease (4) and represents a significant burden to families (5). Recurrent episodes of ARI, particularly lower respiratory tract infections (LRTIs) can lead to the development of chronic suppurative lung disease and bronchiectasis (6). These conditions cause substantial respiratory morbidity and mortality in developing countries (7) and vulnerable populations in developed countries (8). Thus prevention, early identification, and management of ARI with cough (ARIwC) are important public health and clinical goals.

The burden of ARI in Australia's Aboriginal and Torres Strait Islander population is disproportionate to population size (9) and, in some regions of Australia, higher than that reported in developing countries (3). Although over half of Australia's Aboriginal and Torres Strait Islander population live in urban or regional areas, the majority of health research is conducted in remote communities and this impacts on the ability to "close the gap" (10, 11). Studies on ARI in Aboriginal and Torres Strait Islander children have largely focused on remote communities with substantial social disadvantage. In contrast, there are no cohort studies that have comprehensively investigated ARIwC and its predictors and outcomes in urban Aboriginal and Torres Strait Islander children who can access several types of primary care services such as Aboriginal Community Controlled Health Organizations (ACCHOs), Aboriginal and Torres Strait Islander friendly general practices (GPs), mainstream GPs, and emergency departments (EDs) for acute care. Availability of such data may inform future targeted interventions. Data from Aboriginal and/or Torres Strait Islander-focused primary care, collected by an Aboriginal researcher in a setting that is culturally appropriate, are likely more reflective of factors important to Aboriginal and Torres Strait Islander people compared to other settings (e.g., from EDs).

Thus, we determined the incidence of ARIwC and the predictors of recurrent (≥4 episodes) ARIwC and chronic cough (>4 weeks duration) over a 12-month period in urban, predominantly Aboriginal and Torres Strait Islander, children aged <5 years from a socioeconomically disadvantaged community in northern Brisbane, Australia. Our specific primary objectives in this cohort of children were to (a) determine the incidence ARIwC and the recurrence of ARIwC (≥4 episodes/year) over a 12-month period and (b) determine the proportion of children who develop chronic cough (≥4 weeks duration) and their etiology following an ARIwC. Our secondary objectives were to (a) determine the demographic, clinical, environmental, socioeconomic, and cultural predictors of recurrent ARIwC and chronic cough post ARIwC and (b) describe health service utilization and medication use for ARIwC.

MATERIALS AND METHODS

Setting

The study was conducted in a primary health care center [Caboolture Community Medical (CCM)] in an outer suburb of Brisbane, Australia. The district's population approximates 378,045 and 2.24% are Indigenous. Since 2011 CCM has provided services to over 11,300 residents of the region; 59% are Aboriginal and Torres Strait Islander. Thus, CCM has provided at least one service to approximately 78% of the district's Aboriginal and Torres Strait Islander population.

Design

We undertook a prospective cohort study of children aged <5 years registered with CCM that serves a socially disadvantaged

urban community with a high proportion of Aboriginal and Torres Strait Islander patients. The full study protocol has been previously published (12). Briefly, children were enrolled at the time of presentation to the clinic for any reason (including accompanying another person) and followed up monthly via phone or face-to-face contacts for 12 months.

Participants and Recruitment

Children were eligible for inclusion if (a) they were aged <5 years at the time of enrollment; (b) parents were willing and able to complete the study requirements; and (c) the family was not intending to move from the study area in 12 months following enrollment. No exclusion criteria applied. An Aboriginal research officer undertook all recruitment and follow-up procedures. Written informed consent was obtained from parents/legal guardians following provision of a detailed information statement.

Case Definitions

1. ARIwC was defined as an acute illness (i.e., <14-day duration) with cough as a symptom (13) and the presence of one or more other local or systemic symptoms consistent with a respiratory illness (e.g., runny nose, fever, shortness of breath, and wheeze).
2. Recurrent ARIwC was defined as ≧4 episodes of ARIwC in a 12-month period (14). A greater than 3 day and night break in cough was required to classify an episode as a new illness.
3. Chronic cough was defined a cough lasting >4 weeks (13) with no more than a 3-day break in cough in the preceding month.

Data Collection

Data were collected at enrollment and then monthly for 12 months via detailed questionnaires administered by an Aboriginal research officer to parents/carers and review of medical records at CCM. Data collected included demographic, epidemiological, cultural, socioeconomic, and clinical data at baseline and at each monthly follow-up. At parent report of the onset of an ARIwC, a detailed illness report was completed and the child was placed on weekly follow-up, consisting of a questionnaire completed by telephone and/or face-to-face contact, for four weeks to determine cough persistence, health service utilization, and medication use during the illness. Children who had had no more than a three-day break in cough over the four weeks were classified as chronic cough at day 28 and reviewed by a pediatric pulmonologist within two weeks. Loss to follow-up was defined as two consecutive months without successful contact with the family; loss to follow-up during an ARIwC episode was defined as two consecutive weeks without contact.

Data Analyses

The incidence density of ARIwC over a 12-month period was calculated by dividing the number of events by the person time at risk and presented as incidence per 100 child-months at risk with the corresponding 95% confidence intervals (CIs); the latter calculation assumed a Poisson distribution. The duration of ARIs (days or weeks) was subtracted from total child-months of observation to obtain child-months at risk. Incidence densities were calculated for the study cohort as a whole and by gender, age, and Indigenous status. Incidence densities by age group are presented as age at the month of observation, not by age at enrollment in order to more accurately reflect the age at which illness occurred. The proportion of children who developed recurrent ARIwC and those who developed chronic cough following ARIwC were calculated and presented with their respective 95% CIs.

Univariate analyses were performed to compare child characteristics between children who did and did not have recurrent ARIwC and children who did and did not develop chronic cough. This was undertaken for the cohort as a whole and then for Indigenous children only. Children aged 36 months and older were chosen as the reference group for outcomes by age group given the risk for ARI is highest in younger infants (15, 16). For the chronic cough analyses, only the first episode of chronic cough over the 12-month follow-up period was included in the analysis. Chi-square tests were performed on binary variables and the logistic command was used in Stata for variables with more than two categories.

To identify the predictors of chronic cough and recurrent ARIwC, we initially planned to use variables satisfying an *a priori* significance of <0.2 at a univariate level. From here a backwards, stepwise logistic regression was to be used to assess each variable individually. However, there were too many variables satisfying these criteria to validly include in modeling given the sample size, and this was the same for variables satisfying an *a priori* significance of <0.1. Hence only those variables with significance of <0.05 were included in the models.

Ethics and Cultural Oversight

The study was approved by Human Research Ethics Committees of the Queensland Children's Health Services (HREC/12/QRCH/169), University of Queensland (2012001395), and Queensland University of Technology (1300000741). The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12614001214628). Cultural oversight was provided by an Indigenous Research Reference Group. This group consisted of Aboriginal Elders, clinicians, researchers, health service providers, and community members. Community approval for the study was also obtained.

RESULTS

Study Cohort

Between February 2013 and November 2015, 403 children were screened and 200 were enrolled in the study. The median age of the children enrolled was 18.1 months (range, 0.7–59.7 months); 55% were male and 90% identified as Aboriginal and Torres Strait Islander. Detailed analyses of the characteristics of the Aboriginal and Torres Strait Islander children enrolled in the study have been previously published (17). Of those not enrolled, 44 (21.6%) were ineligible, 72 (35.4%) refused, and 87 (42.8%) were not enrolled for other reasons such as homelessness or not with a primary carer/legal guardian at the time they were approached about

the study and therefore not able to obtain valid consent. There were no significant differences in age and gender between those enrolled and not enrolled.

At the 12-month time point, 52 (26%) children had incomplete data and 11 parents withdrew consent at various time points. Of the children lost to follow up, there were 10 children with no follow-up data, the remaining 53 children had 172 months of observation for analysis [mean = 3.24 child-months of observation (95% CI 2.77–3.76)]. Hence there were a total of 1,722 child-months of observation available for analysis [mean = 8.58 (95% CI 8.18–9.00) child-months of observation] and 1,479 child-months at risk as the denominator for incidence densities.

Overall Incidence of ARIwC

There were 367 reported ARIwC episodes in 200 children; median of one episode per child (range 0–8) and 45 children had none. Of those with no ARIwC episodes, the total months of observation were 244 (5.4 months per child, 95% CI 4.76–6.14) and 27 (60%) of these children were withdrawn or lost to follow-up during the study period. Of these, 20 (44%) were male, 40 (88.8%) were Aboriginal and Torres Strait Islander and 19 (42.2%) were aged less than 2 years.

The overall incidence density of ARIwC for the whole cohort was 24.9 cases per 100 child-months at risk (95% CI 22.3–27.5). The rates were 23.1 (95% CI 19.9–26.6) for males and 27.0 (95% CI 23.2–31.3) for females. Incidence density of ARIwC was 23.7 (95% CI 21.2–26.5) in the Aboriginal and Torres Strait Islander children and 34.3 (95% CI 25.7–45.3) in the non-Aboriginal and Torres Strait Islander children. The higher rates in the non-Aboriginal and Torres Strait Islander children were predominantly due to three children with multiple, prolonged illnesses, one of whom were subsequently diagnosed with bronchiectasis. The incidence densities by age group are presented in **Table 1**.

Health Service Utilization, Medication Use, and Parent Knowledge

Complete data on health service utilization and medication use were available for 330 (89.9%) episodes of ARIwC. A health professional was consulted in 210 episodes (63.6%) and of these 160 (76.2%) were GP attendances and 34 were ED presentations (16.2%). There were 25 hospitalizations for ARIwC for 15 children (hospitalization rate of 1.5 per 100 child-months of observation); two children were hospitalized on three occasions, six children were hospitalized twice, and the remainder had one each. The median length of hospital stay was 2 days (range 1–11). Four admissions resulted from specialist reviews of children with chronic cough as part of the study, and chest CT scans and bronchoscopies were performed; two children were subsequently diagnosed with bronchiectasis.

Antibiotics were prescribed in 105 (31.8%) episodes. This included 7/49 (14.3%) episodes in which the symptom was dry cough only (i.e., no fever or wet cough), 87/251 (34.7%) episodes in which wet cough was present, and 54/118 (45.8%) episodes in which both wet cough and fever were present. Oral steroids were prescribed in 16 (4.9%) episodes, inhaled corticosteroids in 9 (2.7%), bronchodilators in 22 (6.7%), and use of over-the-counter cough medicines were reported in four episodes (1.2%). Investigations were performed in 24 (7.3%) episodes.

Data on parental cough knowledge and antibiotic data were available from 152 parents (76%). Cough lasting more than 4 weeks and a wet cough were considered abnormal by 144 (95%) parents. Fifty-two parents (34.2%) thought a child should be prescribed antibiotics for cough, 63 (41.4%) did not think antibiotics should be prescribed for cough and 37 (24.3%) were undecided. One hundred twenty-nine parents (84.8%) stated that if your child was prescribed antibiotics that they should finish the course, 20 (13.1%) said they should be taken until no symptoms were present.

TABLE 1 | Incidence of ARIwC over 12 months in children aged less than 5 years from an urban, disadvantaged community, by age-group for time at risk.

Age group (months)	Events	Months at risk	Incidence/100 child-months at risk	95% CI
<6	22	83.68	26.2	16.1–40.1
6 to <12	75	231.84	32.3	26.4–38.9
12 to <24	133	477.87	27.8	23.9–32.1
24 to <36	45	277.59	16.2	12.1–21.1
36 to <60	66	346.03	19.0	15.0–23.6
≧60	26	56.69	45.8	32.9–60.2
Total	367	1,473.74	24.9	22.7–27.2

Recurrent ARIwC

Twenty-one children (10.5%) experienced recurrent ARIwC during the follow-up period. Of these, 13 (61.9%) were male, 16 (76.2%) were Aboriginal and Torres Strait Islander and 15 (71.4%) were aged <2 years (**Table 2**). Of the 21 children identified with recurrent ARIwC, there were 105 illnesses recorded, with a mean of 5 (95% CI 4.0–6.0) illnesses per child, and a mean of 7.5 (95% CI 6.3–8.7) health care visits over the observation period. There were 158 health professional consultations; 124 (78.4%) were GP visits, 17 (10.7%) ED visits, and eight hospitalizations in eight children. Of the children with recurrent ARIwC, antibiotics were prescribed in 35% of all illnesses.

Based on the univariate analyses presented in Tables S1–S4 in Supplementary Material, a logistic regression model was constructed to evaluate the association between child, parental, household, and environmental characteristics and recurrent ARIwC. These were performed firstly including all children and then for Aboriginal and Torres Strait Islander children only; the latter model included cultural characteristics. Age and gender were retained irrespective of final statistical significance. The model results are presented in **Table 2**. We found that a history of eczema, having mold in the house, households in which only the mother identified as Aboriginal and Torres Strait Islander (compared to both parents identifying as such), and the employment status of the mother were associated with recurrent ARIwC.

Duration of Cough and Occurrence of Chronic Cough

Of the 367 ARIwC episodes, weekly follow-up data over a 4-week period were available for 272 episodes in 147 children. Lack of

TABLE 2 | Predictors of recurrent acute respiratory illness with cough in children aged less than 5 years from a disadvantaged urban community.

All children (n = 191)	aRR	95% CI	P value	Indigenous children only (n = 174)	aRR	95% CI	P value
Male gender	1.37	0.44–4.23	0.98	Male gender	1.16	0.33–4.00	0.92
Age group in months				**Age group in months**			
36 to >60			Ref	36 to >60			Ref
24 to <36 months	1.29	0.17–9.47	0.051	24 to <36 months	1.72	0.23–12.8	0.35
12 to <24 months	2.15	0.37–12.34	0.24	12 to <24 months	2.01	0.34–11.8	0.22
6 to <12 months	1.70	0.30–9.72	0.66	6 to <12 months	1.55	0.26–9.22	0.51
<6 months	1.15	0.20–6.46	0.49	<6 months	0.85	0.12–5.70	0.71
Eczema ever	13.10	2.78–61.5	0.001	Eczema ever	12.6	2.69–59.5	0.002
Mold in house	0.07	0.012–0.44	0.005	Mold in house	0.06	0.007–0.62	0.01
Parent Indigenous status				**Parent Indigenous status**			
Both parents Indigenous			Ref	Both parents Indigenous			Ref
Indigenous father/non-Indigenous mother	3.60	0.42–30.85	0.16	Indigenous father/non-Indigenous mother	3.16	0.39–25.1	0.25
Indigenous mother/non-Indigenous father	10.42	1.27–85.39	0.03	Indigenous mother/non-Indigenous father	8.94	1.16–68.4	0.07
Both parents non-Indigenous[a]				Both parents non-Indigenous	NA	NA	NA
Mothers employment status				**Mothers employment status**			
Full time			Ref	Full time[a]			Ref
Casual/part time	0.12	0.01–1.23	0.04	Casual/part time	0.0.28	0.02–2.83	0.19
Unemployed	0.07	0.01–0.38	0.004	Unemployed	0.09	0.01–0.56	0.01

[a]*Omitted due to collinearity.*

TABLE 3 | Weekly cough persistence[a] and cough type over 28 days in 272 episodes of ARIwC.

N = 272 episodes	Cough has not stopped	Cough type	Cough has stopped	Unknown
Day 7	194 (71.3)	Wet 49 (25.6) Dry 47 (24.2) Variable 81 (41.8) N/A* 17 (8.8)	40 (14.7)	38 (14.0)
Day 14	150 (55.2)	Wet 36 (24.0) Dry 42 (28.0) Variable 45 (30.0) N/A 27 (18.0)	78 (28.7)	44 (16.2)
Day 21	111 (40.8)	Wet 25 (22.5) Dry 31 (27.9) Variable 36 (32.4)	114 (41.9)	47 (17.4)
Day 28	70 (25.7)	Wet 18 (25.7) Dry 20 (28.6) Variable 26 (37.1) N/A 6 (25.7)	152 (55.9)	50 (18.4)

[a]*There has been no break in cough of >3 days in the week prior to each contact timepoint. At each weekly contact parents were asked whether the child's cough had stopped for >3 days in the preceding week, as any break in cough of that duration at any time during the 28 days of follow-up meant the child did not meet the study definition of chronic cough at day 28.*

**N/A, Not applicable.*

follow-up data was a result of some ARIwC being identified too late to validly commence follow-up from the reported onset date. Failure to contact the parent/guardian at any timepoint over the 4-weeks led to the outcome of chronic cough being unknown. If it was known the cough had stopped prior to LTFU, the presence of persistent cough (i.e., no break in cough during the 28-day follow-up period) at all subsequent timepoints was classified as "no." The presence of cough at each weekly timepoint together with cough type is presented in **Table 3**.

Chronic cough at the day-28 follow-up was identified in 70/272 (25.7%) episodes in 43/147 (29.2%) children with follow-up or 21.5% (43/200) of the entire study cohort; cough status was unknown at day-28 in 59 (21.7%) episodes for 53 children. Prior to their first episode of chronic cough identified in the study, 53.4% (23/43) children had no prior ARIwC reported in the period of observation before the chronic cough episode, 11 children had one prior episode, seven had two, one had three, and one child had six episodes. Seventeen children had one episode of chronic cough only; 14 children had 2, seven had three episodes and three children had four episodes over the follow-up period. Cough status and type at each time-point of follow-up for the 272 episodes are presented in **Table 3**.

The baseline characteristics of children who did and did not have an episode of chronic cough are presented in Tables S5–S8 in Supplementary Material. Based on the univariate analyses, a logistic regression model was constructed to evaluate the association between child, parental, household and environmental characteristics, and parental knowledge with the development of chronic cough. These were performed first including all children and then for Indigenous children only; the latter model included cultural characteristics. Age and gender were retained irrespective of final statistical significance. The model results are presented in **Table 4**.

Diagnostic Outcomes of Children with Chronic Cough

Of the 43 children who developed at least one episode of chronic cough, 26 (60.4%) were reviewed by a pediatric respiratory physician who used a standardized approach and all had a spirometry (when able) and CXR as per guidelines (18). The remainder of the children (n = 17) were not reviewed as parents declined to attend as the child's cough had resolved by time of review appointment (n = 2) or did not attend for other reasons (n = 15).

Of the 26 children reviewed, 14 (53.8%) children had an underlying chronic lung disease diagnosed for the first time as direct result of the study. Among the primary diagnoses, protracted bacterial bronchitis (PBB) was the most common diagnosis n = 19 (73%) (**Table 5**). Nineteen (73.0%) children

TABLE 4 | Predictors of chronic cough following ARIwC in children aged less than 5 years from an urban disadvantaged community.

All children (n = 194)	aRR	95% CI	P value	Indigenous Children only (n = 176)	aRR	95% CI	P value
Male gender	0.77	0.34–1.75	0.53	Male gender	0.51	0.21–1.26	0.14
Age group in months				**Age group in months**			
36 to >60			Ref	36 to >60			Ref
<24 to <36 months	0.33	0.05–2.11	0.24	<24 to <36 months	0.38	0.05–2.49	0.31
>12 to <24 months	2.83	0.81–9.91	0.10	>12 to <24 months	2.43	0.66–8.85	0.17
6 to <12 months	7.32	1.62–33.0	0.01	6 to <12 months	6.41	1.32–31.0	0.02
<6 months	4.74	1.12–20.0	0.03	<6 months	4.39	0.98–19.5	0.05
Eczema ever	3.76	1.14–12.3	0.02	Eczema ever	3.99	1.21–13.1	0.02
Childcare attendance	3.56	1.28–9.92	0.01	Childcare attendance	3.04	1.02–9.06	0.04
Previous chronic cough	3.39	1.29–8.89	0.01	Previous chronic cough	2.45	0.88–6.82	0.10
Parent Indigenous status				**Parent Indigenous status**			
Both parents Indigenous			Ref	Both parents Indigenous			Ref
Indigenous father/non-Indigenous mother	3.06	0.898–10.4	0.06	Indigenous father/non-Indigenous mother	2.73	0.81–9.11	0.09
Indigenous mother/non-Indigenous father	6.23	1.82–21.2	0.003	Indigenous mother/non-Indigenous father	5.41	1.63–17.9	0.005
Both parents non-Indigenous[a]				Both parents non-Indigenous	NA	NA	NA
Household income				**Household income**			
$52,000 to <$78,000	0.46	0.098–2.22	0.33	$52,000 to <$78,000	0.30	0.06–1.57	0.14
$26, 000 to <$52,000	0.19	0.050–0.759	0.01	$26, 000 to <$52,000	0.18	0.04–0.73	0.01
<$26,000	0.43	0.123–1.56	0.18	<$26,000	0.35	0.09–1.33	0.11

[a]*Omitted due to collinearity.*

TABLE 5 | Final and secondary diagnoses of 26 children with chronic cough who presented for specialist review.

Final primary diagnosis	Secondary diagnoses
Asthma, n = 1	Allergies/hay fever, n = 1
Pneumonia, n = 2	Obstructive sleep apnea, n = 1 Recurrent childhood cough, n = 1 Otitis media, n = 1
Protracted bacterial bronchitis, n = 19	Allergic rhinitis, n = 3 Eczema, n = 1 Pharyngomalacia, n = 1 Obstructive sleep apnea, n = 3 Tracheomalacia, n = 5 Allergic Rhinitis, n = 3 Bilateral Glue Ear, n = 1 Failure to Thrive, n = 1 Tonsillitis, n = 3 Excess environmental tobacco smoke exposure, n = 1
Non-specific cough, n = 2	Nil
Bronchiectasis, n = 2	Tracheomalacia, n = 1 Excess environmental tobacco smoke exposure, n = 1

who presented for review had more than one diagnosis (**Table 5**). Of the three children with either asthma or bronchiectasis, all had recurrent ARIwC.

DISCUSSION

This is one of the few studies to investigate ARIwC incidence at a community level in Australia. Our study represents children from predominantly low socioeconomic backgrounds, with high levels of environmental tobacco smoke (ETS) exposure and 90% of families are welfare recipients (17). We focused on ARIwC rather than any ARI alone as cough is the most common reason for presentation to GPs in Australia (19); more likely associated with lower airway diseases (particularly if wet); a key symptom in chronic lung disease (4) and represents a significant burden to families (5), including Aboriginal and Torres Strait Islander families (20).

Overall one in five children will experience an ARIwC each month; one in 10 will have four or more episodes per year and one in five will have at least one episode of chronic cough. A history of eczema, having an Aboriginal and Torres Strait Islander mother/non-Aboriginal and Torres Strait Islander father (compared to both parents identifying as Aboriginal and Torres Strait Islander), and mother not in paid employment were independently associated with development of recurrent ARIwC. Health service utilization for ARIwC is high, as is the use of antibiotics. Variables independently associated with the development of chronic cough were being aged <12 months, eczema, childcare attendance, previous history of cough >4 weeks duration, and having Aboriginal and Torres Strait Islander mother/non-Aboriginal and Torres Strait Islander father (compared to both parents identifying as Aboriginal and Torres Strait Islander); having a low income was protective. A significant new underlying chronic lung disease was diagnosed in 14 children. PBB was the most common cause of chronic cough, diagnosed in 73% of children reviewed by the specialist. The lack of association with ETS, an unusual finding in studies of ARI, is likely due to the very high prevalence of smoking in the study cohort.

ARIwC: Incidence and Risk Factors

Currently, the majority of information on ARI incidence is based on hospitalizations and ED presentations, with most studies focusing on LRTI and hospitalization rates (21). There are no urban studies that have a predominantly Aboriginal and Torres Strait Islander cohort.

Sarna and colleagues' (22) Brisbane-based study of 154 infants followed from birth until 24 months of age reported an incidence of any ARI of 0.56/child-month, with URTI and LRTI accounting

for 83% and 17% of ARI episodes per month (mean incidence of 0.47/month and 0.10/month, respectively). These rates differed from ours (average of 0.29 per child-month). This is not surprising as, although they utilized daily cards (22), cough was not a prerequisite in either definition of URTI or LRTI. However, if reported, a dry cough was considered an URTI and moist cough an LRTI. In our study, wet cough predominated suggesting that the incidence of LRTI was higher if we used the same definition. Sarna and colleagues (22) also reported that GP consultations occurred in 47.6% of episodes and antibiotics were prescribed in 21.9% of ARI episodes, lower than in our study. A Perth study (21) (1996–1998) followed 263 infants from birth until 5 years of age and utilized daily symptom diary and fortnightly phone calls. Children aged <2 years averaged four episodes of ARI/year, reducing to 2–3 episodes/year between ages 2 and 5 years (21). Forty-five percent resulted in GP visits and antibiotics were prescribed in 23.6%, similar to the Brisbane cohort (22). In the Perth study (21), ARI episodes with runny/blocked nose or dry cough were considered an URTI and episodes associated with wheeze, or cough (not further defined) and "rattly" chest were considered LRTI. To meet inclusion, infants had to be at high risk of atopy (at least one parent had doctor diagnosed atopy). A cohort study in healthy children conducted in Melbourne between July 2001 and December 2001 followed 121 children aged 12–71 months for 12 weeks utilizing a parent-completed daily symptom diary to identify episodes of influenza-like illness (ILI) (15). The authors reported an incidence of 0.53 episodes/child-month, 46.7% resulted in GP visits and antibiotics were prescribed in 17.5%. The difference between these three urban Australian studies and ours reflect not only differences in design and case definitions but marked differences in socioeconomic status. The cohorts were comprised of predominantly first-born children, high-income families, high use of childcare, low levels of ETS exposure, and small numbers of Aboriginal and Torres Strait Islander children.

Aboriginal and/or Torres Strait Islander children have higher rates of ED presentation and hospitalizations for ARI than non-Aboriginal and Torres Strait islander children (16, 23). Despite this, little is known about the community incidence of ARI in this population. A Northern Territory (NT) study reviewed clinic presentations for Aboriginal infants during the first year of life in five remote communities (24). The median number of presentations per child for any reason was 21 (IQR 15–29), with the most common reasons being URTI [median six visits per child (IQR 3–10)] and LRTI [median of three visits per children for LRTI (IQR 2–5)] (24). Another NT retrospective review of clinic records in two remote communities of children reported a median of 16 (IQR 10–22) presentations per child per year. The most common reasons for presentation were URTI (32%) and LRTI (10.7%) (25). Direct comparisons between these NT studies and ours are not possible given the different demographic and geographical profiles of the communities involved, differences in study design and differences in access to health care (single clinics in NT communities versus multiple health care services for urban children).

Recurrent ARIwC: Rates and Risk Factors

Longitudinal studies have shown that recurrent respiratory infections in early childhood can be associated with long-term poorer respiratory health (e.g., COPD) including impaired lung function (26, 27). Despite this, the burden of recurrent ARI in childhood is unclear particularly for ARIwC. Of 21 children identified in our study with recurrent ARIwC, 105 illnesses were recorded (mean of five episodes per child, 95% CI 4.0–6.0). There were 158 health professional consultations; of these 124 (78.4%) were GP visits, 17 (10.7%) ED visits, seven (4.4%) respiratory specialist reviews, and eight (5.0%) hospitalizations. Among children with recurrent ARIwC, antibiotics were prescribed in 35% of all illnesses. Eczema, having an Aboriginal and Torres Strait Islander mother/non-Aboriginal and Torres Strait Islander father and having a mother not in paid employment were independently associated with recurrent ARIwC in our cohort with the latter being protective. The high rate of recurrent ARIwC in non-Aboriginal and Torres Strait Islander children, despite the small numbers of those children enrolled, reflects the experience of one non-Aboriginal child who was diagnosed with bronchiectasis during the study.

There are few comparable studies on recurrent ARIwC. A Finnish (28) cross-sectional analysis of data from an intervention study in children aged 1–6 years attending day care centers used the same classification of recurrent ARI as ours but did not require cough in the case definition. They reported that 44% of children aged 1–3 years had recurrent ARI in the preceding 12 months. Risk factors were mother's education, parental history of atopy, and day care attendance while having older siblings, and furry pets reduced the risk of recurrent ARI (28). In another prospective birth cohort study, with children followed to 2 years of age (14), that defined recurrent ARI as >98 respiratory illness days per year, 10% of children experienced recurrent ARI; similar to our study but again did not require cough. The median number of illnesses in children with recurrent ARI was 9.6 (IQR 7.6–11.1) episodes per year. The only risk factor for recurrent ARI was having older siblings (adjusted OR 3.03, 95% CI 1.94–4.74); however, the factors they examined were limited in comparison to our study. Due to several differences between this study and ours, any direct comparison is problematic.

Our finding of an increased risk of recurrent ARIwC in those with atopy is not surprising as the association is well documented (29, 30). Having an Aboriginal and Torres Strait Islander mother/non-Aboriginal and Torres Strait Islander father increased the risk of recurrent ARIwC compared to both parents identifying as Aboriginal and Torres Strait Islander; the reverse combination was trending toward significance. However, this finding is likely confounded as further examination of the data indicated that those parent structures were more common in single-parent households than dual-parent households. Hence the increased risk of ARIwC may be a factor of parent structures rather than Aboriginal and Torres Strait Islander status *per se*.

Our findings of having an unemployed mother and mold present in the house as being protective factors for ARIwC are difficult to explain. We had low levels of childcare use, a known risk for ARI (31–33), in the study children and this may be related to the employment status of mothers. Our measure of mold was parent-reported and not evaluated objectively. Mold has been associated as being a risk factor for ARI in several studies (34, 35) and it is unclear why we have a reverse association. It

could also be related to the amount of time children spend inside the house and use (or not) of air-conditioning; however, we did not collect those data.

Post ARIwC: Occurrence of Chronic Cough and Risk Factors

As there are currently no published data on the occurrence and etiologies of chronic cough post ARI in Aboriginal and Torres Strait Islander children in an urban setting, we examined these factors. This is important in the context that chronic respiratory illnesses, most manifested by chronic cough, are prevalent among this population group (36). Early recognition and appropriate management may prevent the development of CSLD and bronchiectasis (37). We identified chronic cough in 70/272 (25.7%) of episodes with completed weekly follow-up and recurrent episodes were not uncommon.

There are few community-based studies of the duration and outcome of ARIwC in children. A British prospective cohort study in preschool children presenting to eight GPs with cough ≤28 days duration at time of enrollment reported that 90% children had stopped coughing at 25 days (38). These findings were supported by a systematic review of 10 studies (39). However, none of the studies involved examining the children at the point of chronic cough occurrence. Our previous prospective cohort study of 879 children aged <15 years presenting to a Brisbane tertiary pediatric ED with ARIwC identified that 20% (95% CI 17–23) of children had a persistent cough at day 28 (40); that study utilized the same methods.

We identified eczema, young age, childcare attendance, having a previous episode of chronic cough and having an Aboriginal and Torres Strait Islander mother/non-Aboriginal and Torres Strait Islander father as being associated with increased risk of developing chronic cough. Atopy, young age, and childcare attendance are well-documented risk factors for ARI, including recurrent episodes as described above (29, 30, 32, 33, 38). The association with Indigenous status of the parent is again likely to be the same as for recurrent ARIwC described above. This association suggests that assessment of parent support in the home should be an important component in the management of children with recurrent ARIwC and those with chronic cough.

Post ARIwC: Etiologies of the Children's Chronic Cough

On clinical review using a standardized pathway, we found that 14 children who had chronic cough had a previously undiagnosed chronic underlying lung disease. This included two children with bronchiectasis (prevalence of 7.7% of cohort reviewed by a physician). Both children had long histories of recurrent episodes of wet cough that had not been investigated. This prevalence of 8% is similar to that found (9%) in a national multicenter study involving 346 children presenting for the first time to a pediatric respiratory physician (20). One major difference in the national study was that the median duration of cough was 16 weeks (IQR 8–32) at the time of enrollment. In the aforementioned study (20), Aboriginal and Torres Strait Islander children (10 of 34) were significantly ($P = 0.001$) more likely to have bronchiectasis than non-Aboriginal and Torres Strait Islander children (21 of 312). The prevalence of newly diagnosed bronchiectasis in our ED study described above was 3.4% (4/117), none of whom were of Aboriginal and Torres Strait Islander origin (41).

Thus, given the implications of earlier diagnosis and subsequent management of children with an underlying lung disease (e.g., bronchiectasis), the review of children with persistent cough four weeks following an ARIwC at the transitional stage from sub-acute to chronic cough is warranted, particularly in those with known risk factors or recurrent ARIwC. This review should follow evidence-based guidelines (42) for the management of cough in children with early referral to tertiary care if the cough is not resolving.

Parental Knowledge of Cough and Antibiotic Use

Parent knowledge of symptoms, illness duration, and medication use is important for clinicians to understand. This enables tailored advice and assistance with the management of the child's illness. As far as we are aware, this is the first study to report parent knowledge of cough and antibiotic use in Aboriginal and Torres Strait Islander families. We found a high proportion of parents knew that a cough lasting more than 4 weeks and wet cough were abnormal (94.7 and 93.4%). However, a high proportion thought antibiotics should be given for cough (34%) or were unsure (24.3%) and 13% thought antibiotics should be stopped when symptoms had resolved rather than completing the full course.

It is encouraging that most parents could recognize abnormal cough and, while this may differ in other settings and/or in the parents of children who were not enrolled, it may partially explain the high health service use for ARIwC in our study. There appears to be a dearth of literature specifically addressing parent knowledge of chronic cough and wet cough. A qualitative study involving 60 parents of children aged 5 months to 17 years from a range of socioeconomic backgrounds found that a wide range of perceptions will initiate parents seeking help for a child with cough that were similar across socioeconomic groups (43). These perceptions were influenced by parent experiences with ARI (particularly other children with ARI illnesses) and their confidence and efficacy in managing illness (43).

The use of antibiotics in community managed ARI in children is an important problem globally. A systematic review of qualitative studies of parent consulting and clinician antibiotic prescribing decisions in pediatric ARI reported important influences were the perception of a threat or uncertainty with respect to the child's illness and illness outcomes (44). They concluded that interventions aimed at improving both parent and clinician management of illness need to "fit" with social norms and ensure concerns of safety are addressed. A systematic review of interventions to influence consulting and antibiotic use for ARI in children reported that using materials that engaged the child, as well as the parent, modified parental knowledge and behavior thus reducing consultation rates (45).

Strengths and Limitations

The strengths of this study are the comprehensiveness of the data collected and that Aboriginal researchers undertook all

study procedures. The clinic was actively engaged in study design and implementation and was supported by the members of our Indigenous Research Reference Group ensuring the cultural applicability of the study. The relationships built between researchers and study parents were important in keeping families engaged during the study. These relationships allowed the parents to be heard when their child presented with ARI, especially given cough is at times considered trivial to some health professionals (4, 46). The longitudinal design with intensiveness of follow-up when ARIwC was reported allowed a comprehensive assessment of the outcomes of ARIwC in these children. The review of children with persistent cough by a pediatric respiratory physician in accordance with cough management guidelines (42) enabled the identification of underlying lung disease that would not otherwise have been detected. Our focus on ARIwC rather than any ARI provides a more specific measure of a type of ARI that is likely to be of greater burden to families.

Our study had several limitations. Firstly, being a single center study limits the generalizability of the study findings to other urban communities. However, CCM has provided a service to over 70% of the Moreton Bay's Aboriginal and Torres Strait Islander population, despite five other Aboriginal Community Controlled Health Organizations in the region as well as two hospitals and multiple mainstream GPs. Our findings are within the ranges of incidence and health service use of other community-based studies as is the prevalence of recurrent ARIwC and chronic cough post ARIwC.

Second, we identified a large numbers of predictors associated with ARIwC in our study, however, due to small numbers in some of the variables we were unable to include them in the analysis models to further explore their relationship with study outcomes. The number of non-Aboriginal and Torres Strait Islander children in our study was small 20 (10%), and they had similar socioeconomic and social disadvantage as the Aboriginal and Torres Strait Islander children, which may explain the high rates of ARIwC in the former group. Further, larger studies are needed to confirm whether the disease burden does indeed differ between groups within the region.

Third, there are likely differences between children who were and were not enrolled; parents of children who experience frequent ARI episodes may be more inclined to enroll their child and remain in the study introducing selection bias. The extent to which this has influenced our study findings is unknown at this stage.

Also, there is also the potential of bias in our outcome estimates derived from loss-to-follow-up, particularly as those who complete the study may differ from those who do not. Loss to follow up during the weekly follow up could reflect that the child had stopped coughing or child had recovered and the parent decided that the cough was no longer of concern. In the ED cough study, loss to follow-up was associated with a milder illness and in our study, incomplete weekly follow-up data were also associated with parents not continuing after the child had stopped coughing. Missing data at monthly time points reflected parents who either withdrew from the study or had more than one missed contact attempt. However, that our overall loss to follow-up was 31.5% of children by the end of 12 months. We consider a retention rate of 68.5% as relatively successful given the characteristics of the study population (17) and the challenges associated with retaining those families in a longitudinal study. Of note is that a particular period during the study in which loss-to-follow-up was highly coincided with a 3-month period in which the Aboriginal staff were not available due to illness and other personal matters. Retention was high when they returned to duty. This highlights the importance of Aboriginal and Torres Strait Islander people being a major part of studies in this population. The resources available for the study also limited the capacity to implement measures that would have improved participant retention. Home visiting would likely have facilitated ongoing engagement of families and hence further studies should consider including sufficient resources to make this possible.

Lastly, although we restricted recruitment of children to those aged <5 years, this is not a birth cohort study. Thus, we are unable to evaluate precursors to the development of recurrent ARIwC and chronic lung disease that have occurred pre- and post-birth, particularly the changes in those exposures over time as children age.

Possible Future Intervention Points

The etiology and development of recurrent ARIwC and chronic lung disease are complex and interventions beyond a biomedical focus are required over the long term, particularly those that address socioeconomic disadvantage. Based on our study's findings, possible intervention points to improve respiratory health include the transitional phase from acute to chronic cough, the point at which recurrent episodes within a 12-month period are identified and, generally, enhancing the uptake and impact of the available public health interventions.

There is currently limited evidence for interventions to prevent recurrent ARI and exacerbations of chronic lung disease in children (47). Hence focusing on strategies to minimize the risk of disease and optimize early recognition and management of chronic cough are likely important, as is ongoing, high-quality research. There is good evidence that cough management pathways in children with chronic cough are effective in improving clinical outcomes (48). An algorithm previously successfully evaluated in children with chronic cough (20) is now the subject of a clinical trial in children at the transitional phase from acute to chronic cough, including children from this study's community (49). Given recurrent ARIs in early childhood, particularly LRTIs, are known precursors to chronic lung disease, further investigation and monitoring of children when they reach the "recurrent" threshold may be warranted. At the primary care level, clinicians need ongoing education with respect to the early recognition and management of persistent cough and recurrent ARIwC and parents need to be provided with sufficient information to know when to seek care. Clinical management needs to be coupled with preventative measures such as supporting the uptake and timeliness of maternal and childhood immunizations through mechanisms that account for socioeconomic disadvantage and marginalization; exploring innovative methods to reduce environmental tobacco smoke exposure in populations

that current programs do not appear to be reaching; and wider access to early childhood support programs for parents, particularly single parent families and the unemployed.

CONCLUSION

This study is the most comprehensive assessment of ARIwC at the community level in a predominantly Aboriginal and Torres Strait Islander cohort of young children. Our estimated disease incidence over a 12-month period of 24.8 cases per 100 child-months and prevalence of the occurrence of chronic cough (21%) were relatively high indicating the considerable burden of disease in this community. Further, the common finding (32.6%) of an underlying chronic lung disease in these children who would otherwise not have been identified suggests that children with chronic cough should be comprehensively followed up.

AVAILABILITY OF DATA AND MATERIAL

Study data and materials may be made available on request with appropriate human research ethics committee approval and with the consent of the participating community as required by Australian criteria for research with Indigenous communities.

ETHICS STATEMENT

The study was approved by Human Research Ethics Committees of the Queensland Children's Health Services (HREC/12/QRCH/169), University of Queensland (2012001395) and Queensland University of Technology (1300000741). The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN 12614001214628). Cultural oversight was provided by an Indigenous Research Reference Group. This group consisted of Aboriginal Elders, clinicians, researchers, health service providers, and community members. Community approval for the study was also obtained.

AUTHOR CONTRIBUTIONS

KH contributed to study design, had primary responsibility for recruitment and data collection, and wrote the first draft of the manuscript. AC contributed to study design and implementation and provided significant input to the drafting of the manuscript. JA contributed to study design, managed the study at CCM and contributed to the manuscript. DA assisted with data management and analysis and contributed to the manuscript. VG undertook respiratory physician reviews, contributed to the design of data collection at these reviews and to the final manuscript. MD assisted with recruitment, data collection, and participant follow-up. MO contributed to study design and the final manuscript. KO conceptualized the study, had overall responsibility for study conduct and completed and contributed to the manuscript. All authors approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/article/10.3389/fped.2017.00228/full#supplementary-material.

REFERENCES

1. Nair H, Simões EAF, Rudan I, Gessner BD, Azziz-Baumgartner E, Zhang J, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet* (2013) 381(9875):1380–90. doi:10.1016/S0140-6736(12)61901-1
2. O'Grady KF, Revell A, Maguire G, Millonig R, Newman M, Reid D, et al. *Lung Health Services for Aboriginal and Torres Strait Islander Peoples in Queensland*. Brisbane: Queensland Government (2010).
3. O'Grady KA, Torzillo PJ, Chang AB. Hospitalisation of indigenous children in the Northern Territory for lower respiratory illness in the first year of life. *Med J Aust* (2010) 192(10):586–90.
4. Chang AB, Redding GJ, Everard ML. Chronic wet cough: protracted bronchitis, chronic suppurative lung disease and bronchiectasis. *Pediatr Pulmonol* (2008) 43(6):519–31. doi:10.1002/ppul.20821
5. Marchant JM, Newcombe PA, Juniper EF, Sheffield JK, Stathis SL, Chang AB. What is the burden of chronic cough for families? *Chest* (2008) 134(2):303–9. doi:10.1378/chest.07-2236
6. Singleton RJ, Valery PC, Morris P, Byrnes CA, Grimwood K, Redding G, et al. Indigenous children from three countries with non-cystic fibrosis chronic suppurative lung disease/bronchiectasis. *Pediatr Pulmonol* (2014) 49(2):189–200. doi:10.1002/ppul.22763
7. McCallum GB, Binks MJ. The epidemiology of chronic suppurative lung disease and bronchiectasis in children and adolescents. *Front Pediatr* (2017) 5:27. doi:10.3389/fped.2017.00027

8. Redding GJ, Singleton RJ, Valery PC, Williams H, Grimwood K, Morris PS, et al. Respiratory exacerbations in indigenous children from two countries with non-cystic fibrosis chronic suppurative lung disease/bronchiectasis. *Chest* (2014) 146(3):762–74. doi:10.1378/chest.14-0126
9. Chang AB, Chang CC, O'Grady KF, Torzillo PJ. Lower respiratory tract infections. *Pediatr Clin North Am* (2009) 56(6):1303–21. doi:10.1016/j.pcl.2009.09.003
10. Pyett P, Waples-Crowe P, Van Der Sterren A. Engaging with Aboriginal communities in an urban context: some practical suggestions for public health researchers. *Aust N Z J Public Health* (2009) 33(1):51–4. doi:10.1111/j.1753-6405.2009.00338.x
11. Eades SJ, Taylor B, Bailey S, Williamson AB, Craig JC, Redman S, et al. The health of urban Aboriginal people: insufficient data to close the gap. *Med J Aust* (2010) 193(9):521.
12. Hall KK, Chang AB, Sloots TP, Anderson J, Kemp A, Hammill J, et al. The respiratory health of urban indigenous children aged less than 5 years: study protocol for a prospective cohort study. *BMC Pediatr* (2015) 15(1):56. doi:10.1186/s12887-015-0375-y
13. Chang AB, Landau LI, Van Asperen PP, Glasgow NJ, Robertson CF, Marchant JM, et al. Cough in children: definitions and clinical evaluation – position statement of the thoracic society of Australia and New Zealand. *Med J Aust* (2006) 184(8):398–403.
14. Toivonen L, Karppinen S, Schuez-Havupalo L, Teros-Jaakkola T, Vuononvirta J, Mertsola J, et al. Burden of recurrent respiratory tract infections in children: a prospective cohort study. *Pediatr Infect Dis J* (2016) 35(12):e362–9. doi:10.1097/INF.0000000000001304
15. Lambert SB, O'Grady KF, Gabriel SH, Nolan TM. Respiratory illness during winter: a cohort study of urban children from temperate Australia. *J Paediatr Child Health* (2005) 41(3):125–9. doi:10.1111/j.1440-1754.2005.00561.x
16. Moore HC, de Klerk N, Jacoby P, Richmond P, Lehmann D. Can linked emergency department data help assess the out-of-hospital burden of acute lower respiratory infections? A population-based cohort study. *BMC Public Health* (2012) 12:703. doi:10.1186/1471-2458-12-703
17. Hall KK, Chang AB, Anderson J, Dunbar M, Arnold D, O'Grady KF. Characteristics and respiratory risk profile of children aged less than 5 years presenting to an urban, Aboriginal-friendly, comprehensive primary health practice in Australia. *J Paediatr Child Health* (2017) 53(7):636–43. doi:10.1111/jpc.13536
18. Howie PW, Forsyth JS, Ogston SA, Clark A, Florey CD. Protective effect of breast feeding against infection. *BMJ* (1990) 300(6716):11–6. doi:10.1136/bmj.300.6716.11
19. Kotsimbos T, Armstrong D, Buckmaster N, de Looze F, Hart D, Holmes P, et al. *Respiratory Infectious Disease Burden in Australia*. Queensland: The Australian Lung Foundation (2007).
20. Chang AB, Robertson CF, Van Asperen PP, Glasgow NJ, Mellis CM, Masters IB, et al. A multicenter study on chronic cough in children: burden and etiologies based on a standardized management pathway. *Chest* (2012) 142(4):943–50. doi:10.1378/chest.11-2725
21. Kusel MM, de Klerk N, Holt PG, Landau LI, Sly PD. Occurrence and management of acute respiratory illnesses in early childhood. *J Paediatr Child Health* (2007) 43(3):139–46. doi:10.1111/j.1440-1754.2007.01033.x
22. Sarna M, Ware RS, Sloots TP, Nissen MD, Grimwood K, Lambert SB. The burden of community, managed acute respiratory infections in the first 2, years of life. *Pediatr Pulmonol* (2016) 51:1336–46. doi:10.1002/ppul.23480
23. O'Grady KA, Chang AB. Lower respiratory infections in Australian Indigenous children. *J Paediatr Child Health* (2010) 46(9):461–5. doi:10.1111/j.1440-1754.2010.01845.x
24. Kearns T, Clucas D, Connors C, Currie BJ, Carapetis JR, Andrews RM. Clinic attendances during the first 12 months of life for Aboriginal children in five remote communities of Northern Australia. *PLoS One* (2013) 8(3):e58231. doi:10.1371/journal.pone.0058231
25. Clucas DB, Carville KS, Connors C, Currie BJ, Carapetis JR, Andrews RM. Disease burden and health-care clinic attendances for young children in remote aboriginal communities of northern Australia. *Bull World Health Organ* (2008) 86(4):275–81. doi:10.2471/BLT.07.043034
26. Duijts L, Reiss IK, Brusselle G, de Jongste JC. Early origins of chronic obstructive lung diseases across the life course. *Eur J Epidemiol* (2014) 29(12):871–85. doi:10.1007/s10654-014-9981-5
27. Lopez Bernal JA, Upton MN, Henderson AJ, Dedman D, McCarthy A, Davey Smith G, et al. Lower respiratory tract infection in the first year of life is associated with worse lung function in adult life: prospective results from the Barry Caerphilly Growth study. *Ann Epidemiol* (2013) 23:422–7. doi:10.1016/j.annepidem.2013.05.006
28. Hatakka K, Piirainen L, Pohjavuori S, Poussa T, Savilahti E, Korpela R. Factors associated with acute respiratory illness in day care children. *Scand J Infect Dis* (2010) 42(9):704–11. doi:10.3109/00365548.2010.483476
29. O'Connell EJ. The burden of atopy and asthma in children. *Allergy* (2004) 59(Suppl 78):7–11. doi:10.1111/j.1398-9995.2004.00563.x
30. Stensballe LG, Kristensen K, Simoes EAF, Jensen H, Nielsen J, Benn CS, et al. Atopic disposition, wheezing, and subsequent respiratory syncytial virus hospitalization in Danish children younger than 18 months: a nested case-control study. *Pediatrics* (2006) 118(5):e1360–8. doi:10.1542/peds.2006-0907
31. Wald ER, Dashefsky B, Byers C, Guerra N, Taylor F. Frequency and severity of infections in day care. *J Pediatr* (1988) 112(4):540–6. doi:10.1016/S0022-3476(88)80164-1
32. Yin JK, Lahra MM, Iskander M, Lambert SB, Heron L, Nissen MD, et al. Pilot study of influenza vaccine effectiveness in urban Australian children attending childcare. *J Paediatr Child Health* (2011) 47(12):857–62. doi:10.1111/j.1440-1754.2011.02098.x
33. Louhiala PJ, Jaakkola N, Ruotsalainen R, Jaakkola JJ. Form of day care and respiratory infections among Finnish children. *Am J Public Health* (1995) 85(8 Pt 1):1109–12. doi:10.2105/AJPH.85.8_Pt_1.1109
34. Fisk WJ, Eliseeva EA, Mendell MJ. Association of residential dampness and mold with respiratory tract infections and bronchitis: a meta-analysis. *Environ Health* (2010) 9:72. doi:10.1186/1476-069x-9-72
35. Polyzois D, Polyzoi E, Wells JA, Koulis T. Poor indoor air quality, mold exposure, and upper respiratory tract infections – are we placing our children at risk? *J Environ Health* (2016) 78(7):20–7.
36. Australian Institute of Health and Welfare. *The Health and Welfare of Australia's Aboriginal and Torres Strait Islander Peoples: 2015*. Canberra: Australian Institute of Health and Welfare (2015).
37. Chang AB, Bell SC, Torzillo PJ, King PT, Maguire GP, Byrnes CA, et al. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand Thoracic Society of Australia and New Zealand guidelines. *Med J Aust* (2015) 202(3):130. doi:10.5694/mjac14.00287
38. Hay AD, Wilson A, Fahey T, Peters TJ. The duration of acute cough in preschool children presenting to primary care: a prospective cohort study. *Fam Pract* (2003) 20(6):696–705. doi:10.1093/fampra/cmg613
39. Thompson M, Vodicka TA, Blair PS, Buckley DI, Heneghan C, Hay AD, et al. Duration of symptoms of respiratory tract infections in children: systematic review. *BMJ* (2013) 347:f7027. doi:10.1136/bmj.f7027
40. O'Grady KF, Grimwood K, Sloots TP, Whiley DM, Acworth JP, Phillips N, et al. Prevalence, codetection and seasonal distribution of upper airway viruses and bacteria in children with acute respiratory illnesses with cough as a symptom. *Clin Microbiol Infect* (2016) 22(6):527–34. doi:10.1016/j.cmi.2016.02.004
41. O'Grady KF, Drescher BJ, Goyal V, Phillips N, Acworth J, Marchant JM, et al. Chronic cough postacute respiratory illness in children: a cohort study. *Arch Dis Child* (2017) 102(11):1044–8. doi:10.1136/archdischild-2017-312848
42. Chang AB, Glomb WB. Guidelines for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. *Chest* (2006) 129(1 Suppl):260S–83S. doi:10.1378/chest.129.1_suppl.260S
43. Ingram J, Cabral C, Hay AD, Lucas PJ, Horwood J. Parents' information needs, self-efficacy and influences on consulting for childhood respiratory tract infections: a qualitative study. *BMC Fam Pract* (2013) 14(1):106. doi:10.1186/1471-2296-14-106
44. Lucas PJ, Cabral C, Hay AD, Horwood J. A systematic review of parent and clinician views and perceptions that influence prescribing decisions in relation to acute childhood infections in primary care. *Scand J Prim Health Care* (2015) 33(1):11–20. doi:10.3109/02813432.2015.1001942
45. Andrews T, Thompson M, Buckley DI, Heneghan C, Deyo R, Redmond N, et al. Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis. *PLoS One* (2012) 7(1):e30334. doi:10.1371/journal.pone.0030334
46. Faniran A, Peat J, Woolcock A. Persistent cough: is it asthma? *Arch Dis Child* (1998) 79(5):411–4. doi:10.1136/adc.79.5.411

47. O'Grady KF, Grimwood K. The likelihood of preventing respiratory exacerbations in children and adolescents with either chronic suppurative lung disease or bronchiectasis. *Front Pediatr* (2017) 5:58. doi:10.3389/fped.2017.00058
48. Chang AB, Oppenheimer JJ, Weinberger M, Weir K, Rubin BK, Irwin RS. Use of management pathways or algorithms in children with chronic cough: systematic reviews. *Chest* (2016) 149(1):106–19. doi:10.1378/chest.15-1403
49. O'Grady KF, Grimwood K, Toombs M, Sloots TP, Otim M, Whiley D, et al. Effectiveness of a cough management algorithm at the transitional phase from acute to chronic cough in Australian children aged <15 years: protocol for a randomised controlled trial. *BMJ Open* (2017) 7(3):e013796. doi:10.1136/bmjopen-2016-013796

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Persistent Bacterial Bronchitis: Time to Venture beyond the Umbrella

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Chronic cough in children is common and frequently mismanaged. In the past, cough was diagnosed as asthma and inappropriate asthma therapies prescribed and escalated. It has been realized that persistent bacterial bronchitis (PBB) is a common cause of wet cough and responds to oral antibiotics. The initial definition comprised a history of chronic wet cough, positive bronchoalveolar (BAL) cultures for a respiratory pathogen and response to a 2-week course of oral amoxicillin–clavulanic acid. This is now termed PBB-micro; PBB-clinical eliminates the need for BAL. PBB-extended is PBB-micro or PBB-clinical but resolution necessitating 4 weeks of antibiotics; and recurrent PBB is >3 attacks of PBB-micro or-clinical/year. However, the airway has only a limited range of responses to chronic inflammation and infection, and neutrophilic airway disease is seen in many other conditions, such as cystic fibrosis and primary ciliary dyskinesia, both chronic suppurative lung disease endotypes, whose recognition has led to huge scientific and clinical advances. There is an urgent need to extend endotyping into PBB, especially PBB-recurrent. We need to move from associative studies and, in particular, deploy sophisticated modern –omics technologies and systems biology, rather as has been done in the context of asthma in U-BIOPRED. In summary, the use of the term PBB has done signal service in pointing us away from prescribing asthma therapies to children with infected airways, but we now need to move beyond a simple description to teasing out underlying endotypes.

Keywords: cystic fibrosis, primary ciliary dyskinesia, endotype, airway infection, airway inflammation, bronchoalveolar lavage

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The history of our understanding and management of chronic cough in children is a litany of wrong diagnosis, inappropriate therapy, and muddled thinking. Cough was initially attributed to bronchitis, and treated with antibiotics; next it was appreciated that some children who coughed also had asthma, and responded to asthma therapy. This led to the catastrophic explosion of asthma mis-diagnoses (1–3), when normal children coughing with viral colds were diagnosed as asthmatic, and treatment escalated every time they coughed with another cold, despite ample evidence that escalating asthma therapy above low-dose inhaled corticosteroids is subject to the law of very rapidly diminishing returns (4). Subsequently, systematic studies (5) showed that the commonest cause of chronic wet cough was what was termed "persistent bacterial bronchitis" (PBB), many cases of which responded to a relatively short course of oral antibiotics. Noteworthy in this paper was that around 50% of these coughers were given an initial diagnosis of asthma, which was proven correct in less than 10%. The response to antibiotics was confirmed in a relatively small randomized controlled trial (6), which although a commendable attempt to secure an evidence base, used a cough score (7) as an end-point, rather than any more scientific biomarker or objective cough counting. The next

consideration became the relationship between PBB and future bronchiectasis—would untreated PBB lead to bronchiectasis eventually, and would we, with this new paradigm of early and aggressive use of antibiotics prevent long term lung damage? I return to this important question below.

So, by going back to the future, have we made any progress? Of course, it is good that children with chronic airway infection are not treated with inhaled corticosteroids, which will likely worsen, not improve airway defenses (8–11), and to that extent the term PBB has served us very well. But it is now time to move beyond this, and this will only happen if weak thinking and general complacency about airway disease, and a culture where the so-called clinical diagnoses and assessments are deemed acceptable instead of making objective measurements is filtered out of the bloodstream of pediatric pulmonology where it is currently so strong. At present, there is little sign that this change is happening. Here, I advance the proposition that PBB is a description, not a diagnosis; and, in 2017, it is an umbrella term of exclusion. Failure to appreciate this will lead to scientific bankruptcy; PBB should be the start of thinking, not the finish. Elsewhere it has been argued that asthma is no more a useful diagnosis than arthritis or anemia (12), and I would argue the same is true for PBB. Chronic suppurative lung disease (CSLD) is well ahead of asthma in terms of defining airway endotypes, but still has a long way to go, as exemplified by PBB.

The aim of this annotation is to critically review our concepts of PBB, and where we should go next, especially in light of the recent ERS statement (13). The aim is to be provocative; so many airway diseases are stuck in thought-free ruts, and we need to lift our eyes to the towering achievements in those CSLDs which have moved out of the rut.

WHAT IS PBB?

The initial definition was (i) a history of chronic wet cough, (ii) positive bronchoalveolar (BAL) cultures for a respiratory pathogen, and (iii) response to a 2-week course of oral amoxicillin–clavulanic acid (5). The definition has been modified, in part rightly reflecting the inappropriateness of bronchoscopy in many of these children (14). The original definition is now termed PBB-micro; PBB-clinical eliminates the need for BAL, and overtly acknowledges the need to exclude other causes of chronic wet cough, which is implied but not stated in PBB-micro. Unfortunately, there is no requirement to try to define infection non-bronchoscopically, with either cough swabs or better, induced sputum which is feasible even in very resource poor settings (15) and very young children (15, 16) and gives results comparable to BAL. This is a sad exemplar of the current "don't measure" culture of pediatric pulmonology, which is a significant omission, as is the absence of any requirement to test if infection has resolved with antibiotics. The ERS statement (13) effectively defines PBB-clinical as PBB, but allows up to 4 weeks of antibiotics to resolve symptoms; again, there is no requirement for positive bacteriology. PBB-extended is PBB-micro or PBB-clinical but resolution necessitating 4 weeks of antibiotics; and recurrent PBB is >3 episodes of PBB/year. As to what investigations should be performed to exclude other causes of chronic wet cough, this is left to such energy and enthusiasm as may be possessed by the treating physician. It is perfectly clear that the infected airway signals a problem in stereotypic fashion—wet cough, respiratory distress, wheeze related to secretion retention—whether the cause be, for example, anatomical airway obstruction, a local or systemic immunodeficiency, or any one of many aspiration syndromes.

WHAT ARE CSLD AIRWAY ENDOTYPES?

An endotype is a subtype of a condition defined by a distinct pathophysiological mechanism (17). The march to CSLD endotypes started in 1938, when Dorothy Anderson first identified the pancreatic disease of cystic fibrosis (CF) (18), thus beginning the pathway to the differentiation of CF from other causes of chronic wet cough and bronchiectasis. A series of brilliant discoveries has led to the determination of the underlying gene defect (19–21) and the development of specific diagnostic tests [sweat test (22), genotyping (23), transepithelial potential differences (24, 25)] which make a diagnosis certain in all but the most difficult cases; and finally to diagnosis after newborn screening (26). The treatment has gone from non-specific therapies directed at the downstream consequences of *CFTR* dysfunction to designer molecules correcting the basic defect (27–29), and evidence for benefit has come from huge randomized, double-blind controlled trials. Finally, the age of personalized medicine in CF is dawning with the use of rectal spheroids (30) to determine *in vitro* the likely response to designer molecules *in vivo*.

Another obvious CSLD endotype is primary ciliary dyskinesia (PCD). From Kartagener's original description (31) *via* Afzelius' brilliant linking of electron microscopic abnormalities in sperm tails of infertile men with the syndrome (32), thus implicating ciliary dysfunction as the primary abnormality, the modern age has witnessed an explosion of diagnostic tests (33), including ciliary motility, electron microscopy [including electron microscopic tomography (34)], genotyping (35), and immunofluorescence of ciliary proteins (36). The intricacies of ciliary assembly are being unraveled, which has brought the realization that PCD can result not just from mutations in ciliary proteins but also in mutations in proteins responsible for ciliary assembly (37, 38). As yet therapeutic progress has lagged behind, although it is clear that some therapies which work well for CF (rhDNase) are useless or harmful in most PCD patients (39). The systemic immunodeficiencies are also being unraveled, with many specific genetic defects emerging from the umbrellas of antibody deficiency and common variable immunodeficiency (40).

In summary, the overwhelming message is that the discrimination of specific CSLD endotypes has led to an explosion of progress in the understanding of disease pathophysiology, and is likely to lead to novel and highly specific treatments, and which will not be possible unless endotypes are defined. Indeed, without defining endotypes, progress will not be made and valuable therapies discarded. So in asthma, if Brown had not shown that oral prednisolone only worked in wheezy patients with sputum eosinophilia, we would have lost that most efficacious of respiratory treatments (41). In later years, the anti-interleukin 5 monoclonal mepolizumab would have been discarded as ineffective (42) were

it not to have been trialed in a specific group of asthmatics, with persistent airway eosinophilia and recurrent acute asthma lung attacks (43, 44). Also of note, without appreciating the different molecular subclasses of CF, the new molecules would probably have been discarded as useless if prescribed for all comers with the disease, let alone all those with a wet cough. So endotype-based therapy must be the target; where does this leave PBB?

PBB ENDOTYPES?

The broadening of the spectrum of PBB beyond a single episode (above) certainly implies different endotypes, and there are tantalizing hints from the literature that not all "PBB" is equal. A bad outcome (bronchiectasis) is associated with poor response to antibiotics (45), recurrent PBB, and isolation of *Haemophilus Influenzae* (46). Clearly a child with a single episode of chronic wet cough which responds to a single 2-week course of co-amoxyclav and never relapses requires no clinical investigation, although such children may be a useful control group to compare with those requiring multiple antibiotic courses and those who progress to bronchiectasis. The child needing prolonged and recurrent courses of antibiotics is not merely a diagnostic puzzle but also a scientific conundrum; what is the pathophysiology? The important question has been raised as to whether PBB is a precursor of bronchiectasis. The concept of a pre-bronchiectatic state has been proposed (47), and there is much robust evidence in favor of it. It is biologically inconceivable that airways can pass virtually instantaneously from normal caliber to fixed and irreversible dilatation. Indeed, it is clear both from immunodeficiency (48) and CF (49) that there is a phase of airway dilatation demonstrable on HRCT and which is reversible. It is also clinical experience that the progression of chronic airway infection to bronchiectasis can be halted if the underlying cause is remedied, for example, an endobronchial foreign body removed or chronic aspiration prevented. Hence, clearly for some patients with bronchiectasis, there will be a phase indistinguishable from PBB preceding airway dilatation, which likely (but unproven) may be reversed by intensive treatment.

It is clear that it would be unethical to do true natural history studies of chronic productive cough, to see who if untreated will progress to bronchiectasis and who eventually resolve their symptoms spontaneously. However, children who have had a prolonged, undiagnosed productive cough which eventually recovered undoubtedly exist in the community, never having been referred to secondary care, and should actively be sought as a control group. There are important questions we should start trying to address. First, does an episode of PBB-clin or -micro which responds to a 2-week course of antibiotics and never relapses represent a transient immunological insult, for example, a viral infection, which when overcome never recurs? Alternatively, are there genetic and epigenetic pathways which determine a benign, easily treated course despite an underlying mucosal immunodeficiency? If such a pathway existed and we understood it, might this open up new therapies for the more severe forms of the disease? Hypothetically, PBB could arise from infection with unusually virulent organisms (for which there is currently no evidence, but of course does not exclude the possibility that such evidence can be obtained) or an abnormal host response to common pathogens, and we need better to understand normal and pathological mucosal defenses. There are some such studies in the literature already (50–52), but we need to move from associative studies and, in particular, deploy sophisticated modern –omics technologies and systems biology, rather as has been done in the context of asthma in U-BIOPRED (53, 54). How can we predict who will progress to bronchiectasis? One approach would be to determine the immunological, molecular, and –omics signatures of established idiopathic bronchiectasis, and see if there is a group within the PBB umbrella in whom these signatures can be detected, implying they are the true pre-bronchiectatic PBBs. What are the biomarkers of progression, and conversely, of a response to treatment?

It could be questioned whether invasive approaches are ethical and appropriate in very young children. However, it should be noted that bronchoscopy, BAL lavage, endobronchial biopsy, and bronchial brushings are all acceptable diagnostic procedures in young children. I would argue that it is rather unethical to give prolonged and recurrent courses of antibiotics to young children without making every effort to establish the underlying diagnosis. Clearly, a single episode of PBB responding to a 2-week treatment course of oral antibiotics and never recurring does not merit invasive investigation, but how many courses, and for how long, would the pediatric community feel happy to administer "blind"? I would argue that currently we are too ready to sleep walk into more and more antibiotics without looking for specific diagnoses much more intensely.

TWENTY-FIRST CENTURY TREATMENT OF PBB?

There is much scope for improvement of the current management of PBB, assuming that other underlying causes have been excluded. The presence of a wet cough and palpable secretions within the airway can be established clinically. However, whether this is due to bacterial infection cannot be, and every effort should be made to obtain lower airway cultures non-invasively. Second, cough and its frequency are poorly appreciated by parents and children (55) and we should surely objectively measure cough frequency over 24 h with one of a number of counters (56, 57). Validated questionnaires (7) are of course a step forward, but should not be a substitute for direct measurement. If antibiotics are prescribed, these steps should be repeated to ensure that infection has cleared. If there is relapse, it is essential to re-evaluate the diagnosis, as well as repeating the basic measurements (above). The point at which more detailed investigation, including bronchoscopy should be performed, and the role of airway clearance and mucolytics, particularly in preventing recurrence, needs to be explored. The pervasive "no-measurement" culture needs to be tackled firmly in PBB as elsewhere.

SUMMARY AND CONCLUSION

It is clear that in the past, the umbrella term PBB has done signal service, not least in preventing the over-use of inhaled

corticosteroids in children with a chronic wet cough. But it is also clear that it is only a staging post, and that we need to define PBB endotypes and move to specific treatments in particular in those who have PBB-extended and PBB-recurrent, including defining those at high risk of progressing to bronchiectasis. The time is right for a much more detailed and sophisticated assault on the underlying pathophysiology. Finally, we must avoid the treatment of PBB repeating the mistakes of history. Children were (and are) treated with inhaled corticosteroids for eosinophilic airway inflammation with no attempt to demonstrate that airway inflammation was actually present, and with bronchodilators without seeing if there was true reversible airway obstruction due to constriction of airway smooth muscle; too often we have given these treatments and believed the patient's subjective impressions. This is akin to prescribing insulin without making any attempt to make measurements of blood glucose homeostasis. And yet all of the current PBB definitions include treatment with antibiotics, without mandating attempts to determine that (a) infection is present in the first place, (b) that infection has resolved, and (c) that cough frequency has returned to normal. This is not a tolerable standard of care in the twenty-first century. We should be looking at the dizzy heights reached in CF and move to emulate them in PBB.

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REFERENCES

1. Bush A, Fleming L. Is asthma overdiagnosed? *Arch Dis Child* (2016) 101:688–9. doi:10.1136/archdischild-2015-309053
2. Looijmans-van den Akker I, van Luijn K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. *Br J Gen Pract* (2016) 66:e152–7. doi:10.3399/bjgp16X683965
3. Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemière C, et al. Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA* (2017) 317:269–79. doi:10.1001/jama.2016.19627
4. Lemanske RF Jr, Mauger DT, Sorkness CA, Jackson DJ, Boehmer SJ, Martinez FD, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* (2010) 362:975–85. doi:10.1056/NEJMoa1001278
5. Marchant JM, Masters IB, Taylor SM, Cox NC, Seymour GJ, Chang AB. Evaluation and outcome of young children with chronic cough. *Chest* (2006) 129:1132–41. doi:10.1378/chest.129.5.1132
6. Marchant J, Masters IB, Champion A, Petsky H, Chang AB. Randomised controlled trial of amoxycillin clavulanate in children with chronic wet cough. *Thorax* (2012) 67:689–93. doi:10.1136/thoraxjnl-2011-201506
7. Chang AB, Newman RG, Carlin JB, Phelan PD, Robertson CF. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. *Eur Respir J* (1998) 11:462–6. doi:10.1183/09031936.98.11020462
8. Sabroe I, Postma D, Heijink I, Dockrell DH. The yin and the yang of immunosuppression with inhaled corticosteroids. *Thorax* (2013) 68:1085–7. doi:10.1136/thoraxjnl-2013-203773
9. Lee CH, Kim K, Hyun MK, Jang EJ, Lee NR, Yim JJ. Use of inhaled corticosteroids and the risk of tuberculosis. *Thorax* (2013) 68:1105–13. doi:10.1136/thoraxjnl-2012-203175
10. Ernst P, Gonzalez AV, Brassard P, Suissa S. Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. *Am J Respir Crit Care Med* (2007) 176:162–6. doi:10.1164/rccm.200611-1630OC
11. Andréjak C, Nielsen R, Thomsen VØ, Duhaut P, Sørensen HT, Thomsen RW. Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. *Thorax* (2013) 68:256–62. doi:10.1136/thoraxjnl-2012-201772
12. Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al. After asthma – redefining airways diseases. A *Lancet* commission. *Lancet* (2017). doi:10.1016/S0140-6736(17)30879-6
13. Kantar A, Chang AB, Shields MD, Marchant JM, Grimwood K, Grigg J, et al. ERS statement on protracted bacterial bronchitis in children. *Eur Respir J* (2017) 50(2):1602139. doi:10.1183/13993003.02139-2016
14. Chang AB, Upham JW, Masters B, Redding GR, Gibson PG, Marchant JM, et al. Protracted bacterial bronchitis: the last decade and the road ahead. *Pediatr Pulmonol* (2016) 51:225–42. doi:10.1002/ppul.23351
15. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet* (2005) 365:130–4. doi:10.1016/S0140-6736(05)17702-2
16. Jochmann A, Artusio L, Robson K, Nagakumar P, Collins N, Fleming L, et al. Infection and inflammation in induced sputum from preschool children with chronic airways diseases. *Pediatr Pulmonol* (2016) 51:778–86. doi:10.1002/ppul.23366
17. Lötvall J, Akdis CA, Bacharier LB, Bjermer L, Casale TB, Custovic A, et al. Asthma endotypes: a new approach to classification of disease entities within the asthma syndrome. *J Allergy Clin Immunol* (2011) 127:355–60. doi:10.1016/j.jaci.2010.11.037
18. Andersen DH. Cystic fibrosis of the pancreas and its relation to celiac disease. *Am J Dis Child* (1938) 56:344–99. doi:10.1001/archpedi.1938.01980140114013
19. Rommens JM, Iannuzzi MC, Kerem B, Drumm ML, Melmer G, Dean M, et al. Identification of the cystic fibrosis gene: chromosome walking and jumping. *Science* (1989) 245:1059–65. doi:10.1126/science.2772657
20. Kerem B, Rommens JM, Buchanan JA, Markiewicz D, Cox TK, Chakravarti A, et al. Identification of the cystic fibrosis gene: genetic analysis. *Science* (1989) 245:1073–80. doi:10.1126/science.2570460
21. Riordan JR, Rommens JM, Kerem B, Alon N, Rozmahel R, Grzelczak Z, et al. Identification of the cystic fibrosis gene: cloning and characterization of complementary DNA. *Science* (1989) 245:1066–7. doi:10.1126/science.2475911
22. Gibson LE, di Sant'Agnese PA. A note on studies of salt excretion in sweat: relationships between rate, conductivity, and electrolyte composition of sweat from patients with cystic fibrosis and from control subjects. *J Pediatr* (1963) 62:855–67. doi:10.1016/S0022-3476(63)80099-2
23. Sosnay PS, Siklosi KR, Van Goor F, Kaniecki K, Yu H, Sharma N, et al. Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. *Nat Genet* (2013) 45:1160–7. doi:10.1038/ng.2745
24. Rowe SM, Clancy JP, Wilschanski M. Nasal potential difference measurements to assess CFTR ion channel activity. *Methods Mol Biol* (2011) 741:69–86. doi:10.1007/978-1-61779-117-8_6
25. Hug MJ, Derichs N, Bronsveld I, Clancy JP. Measurement of ion transport function in rectal biopsies. *Methods Mol Biol* (2011) 741:87–107. doi:10.1007/978-1-61779-117-8_7
26. Barben J, Castellani C, Dankert-Roelse J, Gartner S, Kashirskaya N, Linnane B, et al. The expansion and performance of national newborn screening programmes for cystic fibrosis in Europe. *J Cyst Fibros* (2017) 16:207–13. doi:10.1016/j.jcf.2016.12.012

27. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* (2011) 365:1663–72. doi:10.1056/NEJMoa1105185
28. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* (2015) 373:220–31. doi:10.1056/NEJMoa1409547
29. Donaldson SH, Pilewski JM, Griese M, Cooke J, Viswanathan L, Tullis E, et al. Tezacaftor/ivacaftor in subjects with cystic fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR. *Am J Respir Crit Care Med* (2017). doi:10.1164/rccm.201704-0717OC
30. Dekkers JF, Berkers G, Kruisselbrink E, Vonk A, de Jonge HR, Janssens HM, et al. Characterizing responses to CFTR-modulating drugs using rectal organoids derived from subjects with cystic fibrosis. *Sci Transl Med* (2016) 8:344ra84. doi:10.1126/scitranslmed.aad8278
31. Kartagener M. Zur Pathogenese der Bronchiektasien. I. Mitteilung: Bronchiektasien bei Situs viscerum inversus. *Beiträge zur Klinik und Erforschung der Tuberkulose und der Lungenkrankenheiten*. (Vol. 83), (1933). p. 489–501.
32. Afzelius BA. A human syndrome caused by immotile cilia. *Science* (1976) 193:317–9. doi:10.1126/science.1084576
33. Lucas JS, Barbato A, Collins SA, Goutaki M, Behan L, Caudri D, et al. European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia. *Eur Respir J* (2017):49:1601090. doi:10.1183/13993003.01090-2016
34. Shoemark A, Hogg C. Electron tomography of respiratory cilia. *Thorax* (2013) 68:190–1. doi:10.1136/thoraxjnl-2012-202938
35. Collins SA, Walker WT, Lucas JS. Genetic testing in the diagnosis of primary ciliary dyskinesia: state-of-the-Art and future perspectives. *J Clin Med* (2014) 3:491–503. doi:10.3390/jcm3020491
36. Shoemark A, Frost E, Dixon M, Ollosson S, Kilpin K, Patel M, et al. Accuracy of immunofluorescence in the diagnosis of primary ciliary dyskinesia. *Am J Respir Crit Care Med* (2017) 196:94–101. doi:10.1164/rccm.201607-1351OC
37. Marshall CB, Mays DJ, Beeler JS, Rosenbluth JM, Boyd KL, Santos Guasch GL, et al. p73 is required for multiciliogenesis and regulates the Foxj1-associated gene network. *Cell Rep* (2016) 14:2289–300. doi:10.1016/j.celrep.2016.02.035
38. Olcese C, Patel MP, Shoemark A, Kiviluoto S, Legendre M, Williams HJ, et al. X-linked primary ciliary dyskinesia due to mutations in the cytoplasmic axonemal dynein assembly factor PIH1D3. *Nat Commun* (2017) 8:14279. doi:10.1038/ncomms14279
39. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. *Chest* (1998) 113:1329–34. doi:10.1378/chest.113.5.1329
40. Yazdani R, Hakemi MG, Sherkat R, Homayouni V, Farahani R. Genetic defects and the role of helper T-cells in the pathogenesis of common variable immunodeficiency. *Adv Biomed Res* (2014) 3:2. doi:10.4103/2277-9175.124627
41. Brown HM. Treatment of chronic asthma with prednisolone; significance of eosinophils in the sputum. *Lancet* (1958) 2(7059):1245–7. doi:10.1016/S0140-6736(58)91385-0
42. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* (2000) 356:2144–8. doi:10.1016/S0140-6736(00)03496-6
43. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* (2009) 360:985–93. doi:10.1056/NEJMoa0805435
44. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* (2009) 360:973–84. doi:10.1056/NEJMoa0808991
45. Goyal V, Grimwood K, Marchant J, Masters IB, Chang AB. Does failed chronic wet cough response to antibiotics predict bronchiectasis? *Arch Dis Child* (2014) 99:522–5. doi:10.1136/archdischild-2013-304793
46. Wurzel DF, Marchant JM, Yerkovich ST, Upham JW, Petsky HL, Smith-Vaughan H, et al. Protracted bacterial bronchitis in children: natural history and risk factors for bronchiectasis. *Chest* (2016) 150:1101. doi:10.1016/j.chest.2016.06.030
47. Eastham KM, Fall AJ, Mitchell L, Spencer DA. The need to redefine non-cystic fibrosis bronchiectasis in childhood. *Thorax* (2004) 59:324–7. doi:10.1136/thx.2003.011577
48. Gaillard EA, Carty H, Heaf D, Smyth RL. Reversible bronchial dilatation in children: comparison of serial high-resolution computer tomography scans of the lungs. *Eur J Radiol* (2003) 47:215–20. doi:10.1016/S0720-048X(02)00122-5
49. Sly PD, Gangell CL, Chen L, Ware RS, Ranganathan S, Mott LS, et al. Risk factors for bronchiectasis in children with cystic fibrosis. *N Engl J Med* (2013) 368:1963–70. doi:10.1056/NEJMoa1301725
50. Marchant JM, Gibson PG, Grissell TV, Timmins NL, Masters IB, Chang AB. Prospective assessment of protracted bacterial bronchitis: airway inflammation and innate immune activation. *Pediatr Pulmonol* (2008) 43:1092–9. doi:10.1002/ppul.20906
51. Chang AB, Yerkovich ST, Gibson PG, Anderson-James S, Petsky HL, Carroll ML, et al. Pulmonary innate immunity in children with protracted bacterial bronchitis. *J Pediatr* (2012) 161:621–5. doi:10.1016/j.jpeds.2012.03.049
52. Baines KJ, Upham JW, Yerkovich ST, Chang AB, Marchant JM, Carroll M, et al. Mediators of neutrophil function in children with protracted bacterial bronchitis. *Chest* (2014) 146:1013–20. doi:10.1378/chest.14-0131
53. Kuo CS, Pavlidis S, Loza M, Baribaud F, Rowe A, Pandis I, et al. A transcriptome-driven analysis of epithelial brushings and bronchial biopsies to define asthma phenotypes in U-BIOPRED. *Am J Respir Crit Care Med* (2017) 195:443–55. doi:10.1164/rccm.201512-2452OC
54. Auffray C, Adcock IM, Chung KF, Djukanovic R, Pison C, Sterk PJ. An integrative systems biology approach to understanding pulmonary diseases. *Chest* (2010) 137:1410–6. doi:10.1378/chest.09-1850
55. Hamutcu R, Francis J, Karakoc F, Bush A. Objective monitoring of cough in children with cystic fibrosis. *Pediatr Pulmonol* (2002) 34:331–5. doi:10.1002/ppul.10174
56. Birring SS, Fleming T, Matos S, Raj AA, Evans DH, Pavord ID. The Leicester Cough Monitor: preliminary validation of an automated cough detection system in chronic cough. *Eur Respir J* (2008) 31:1013–8. doi:10.1183/09031936.00057407
57. Kelsall A, Houghton LA, Jones H, Decalmer S, McGuinness K, Smith JA. A novel approach to studying the relationship between subjective and objective measures of cough. *Chest* (2011) 139:569–75. doi:10.1378/chest.10-0438

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Long-term Non-Invasive Ventilation in Infants: A Systematic Review and Meta-Analysis

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Background: The use of long-term non-invasive ventilation (NIV) to treat sleep and breathing disorders in children has increased substantially in the last decade; however, less data exist about its use in infants. Given that infants have distinct sleep and breathing patterns when compared to older children, the outcomes of infants on long-term NIV may differ as well. The aim of this study is to systematically review the use and outcomes of long-term NIV in infants.

Methods: Ovid Medline, Ovid Embase, CINAHL (via EbscoHOST), PubMed, and Wiley Cochrane Library were systematically searched from January 1990 to July 2017. Studies on infants using long-term NIV outside of an acute care setting were included. Data were extracted on study design, population characteristics, and NIV outcomes.

Results: A total of 327 studies were full-text reviewed, with final inclusion of 60. Studies were distributed across airway (40%), neuromuscular (28%), central nervous system (10%), cardio-respiratory (2%), and multiple (20%) disease categories. Of the 18 airway studies reporting on NIV outcomes, 13 (72%) reported improvements in respiratory parameters. Of the 12 neuromuscular studies exclusively on spinal muscular atrophy type 1 (SMA1), six (50%) reported decreased hospitalizations and nine (75%) reported on mortality outcomes. Risk of bias was moderate to serious, and quality of the evidence was low to very low for all studies. Most studies had an observational design with no control group, limiting the potential for a meta-analysis.

Conclusion: The outcomes reported in studies differed by the disease category being studied. Studies on airway conditions showed improvements in respiratory parameters for infants using NIV. Studies on neuromuscular disorder, which were almost exclusively on SMA1, reported decreased hospitalizations and prolonged survival. Overall, it appears that NIV is an effective long-term therapy for infants. However, the high risk of bias and low quality of the available evidence limited strong conclusions.

Keywords: continuous positive airway pressure, bi-level positive airway pressure, obstructive sleep apnea, Pierre Robin sequence, laryngo-tracheomalacia, spinal muscular atrophy type 1, central hypoventilation syndrome

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INTRODUCTION

Rationale

Long-term non-invasive ventilation (NIV), defined as respiratory support delivered through an interface outside the airway, has become the treatment of choice for a number of chronic conditions resulting in respiratory insufficiency or sleep and breathing disorders in infants and children (1–3). These conditions include airway disorders, neuromuscular disorders (NMDs), and disorders of the central nervous system (CNS) (3–6). The shift toward NIV therapies may have been driven by improvements in NIV technology, a greater emphasis on home-based care, and a growing acceptance of NIV as a viable long-term respiratory support (1, 6, 7). With the increasing number of infants and children living at home using NIV, understanding the benefits and risks of NIV is becoming important not only for specialists involved in starting this therapy but also for pediatricians and primary care physicians providing care to these children within the community and policy makers responsible for decisions about provision of healthcare resources.

While there is a considerable body of work describing the use of long-term NIV, including continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BPAP), in a broad range of pediatric populations, less is known about its use in infants (8–10). Without sufficient data to suggest otherwise, similar NIV treatment approaches are likely followed in both infants and older children, despite key physiological differences in sleep and breathing patterns in infancy. Both sleep and breathing processes are immature at birth and continue to develop through infancy, resulting in change in sleep patterns and breathing control that continue through early life (11). Sleep occupies a greater proportion of time in infants compared to older children (12), which makes infants more vulnerable to respiratory disorders that disrupt sleep. Immaturity of central respiratory centers in infants contributes to increased respiratory events and a greater variability in oxygen saturation, both of which may be important for the normal development of respiratory control (11, 13). Since sleep and breathing processes differ by age, especially in early life, the type of respiratory and sleep disorders treated with NIV, the response to NIV treatment, and the outcomes for NIV may also differ in infants as compared to older children.

Most data available on long-term NIV use in infants is limited to single-center observational studies with relatively small sample sizes (8). Aggregation of the available data for combined data analysis will improve our understanding of the risks and benefits of NIV therapy in the infant population.

Abbreviations: ALTE, acute life-threatening events; BPAP, bi-level positive airway pressure; CHS, central hypoventilation syndrome; CNS, central nervous system; CPAP, continuous positive airway pressure; GRADE, Grading of Recommendations Assessment, Development and Evaluation; LTM, laryngo-tracheomalacia; NIV, non-invasive ventilation; NMD, neuromuscular disorder; OSA, obstructive sleep apnea; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRS, Pierre Robin sequence; ROBINS-I, Risk of Bias in Non-Randomized Studies of Interventions; SIDS, sudden infant death syndrome; SMA1, spinal muscular atrophy type 1.

Objective

The objective of this systematic review is to summarize the available evidence on the use of long-term NIV for infants and to estimate effect sizes for specific sub-populations and clinical outcomes compared to alternative respiratory care strategies.

Research Question

Does the use of NIV, compared to supportive care, or invasive ventilation, improve clinical outcomes for infants under the age of 2 years with chronic conditions resulting in respiratory insufficiency or sleep and breathing disorders?

METHODS

Study Design

This review was conducted using systematic review methodology.

Participants

The inclusion criteria for this systematic review were as follows: (1) infants, defined by the Public Health Agency of Canada as ages 0–24 months inclusive (14); (2) NIV use, defined as breathing support delivered from outside the airway; and (3) long-term NIV use, defined as greater than three months outside of an acute care setting. For studies that examined a broader age range, the mean age of NIV initiation had to be less than 24 months in order to be included in this review, or data had to be presented separately for infants. We did not place any restrictions on study design or outcome eligibility.

Systematic Review Protocol

The protocol for this systematic review was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (15). The full protocol has been registered in the PROSPERO database for international prospective reviews (16).

Search Strategy

This systematic review is an extension of a prior scoping review on long-term NIV in children (8). The scoping review search strategy, using Medical Subject Headings (MeSH) and free-text terms for "child" and "non-invasive ventilation," was developed for MEDLINE (Ovid) and adapted for subsequent electronic databases with the full protocol published elsewhere (17) [see **Table 1** for original MEDLINE (Ovid) search strategy]. Human studies published from 1990 onward were searched in MEDLINE (Ovid), Embase (Ovid), CINAHL (Ebsco), Cochrane Library (Wiley), and PubMed between November 17 and 28, 2014, with no restriction on study design. Gray literature, in the form of conference abstracts on respiratory and sleep medicine, was identified from 2012 to 2014. The literature search was re-run on April 29, 2016, and July 12, 2017, using the same search strategy in Ovid MEDLINE, Ovid Embase, CINAHL, and Wiley Cochrane Library to identify additional studies.

TABLE 1 | Search strategy used in the Ovid Medline database for the scoping review to identify literature on the use of long-term non-invasive ventilation in children.

Ovid MEDLINE(R) In-Process and other non-indexed citations and Ovid Medline(R): 1946 to November Week 1, 2014
Original search date: 17 November 2014
Update search dates: 29 April 2016 and 12 July 2017

1. Continuous Positive Airway Pressure/
2. Noninvasive Ventilation/
3. Intermittent Positive-Pressure Breathing/
4. Ventilators, Negative-Pressure/
5. AVAPS.tw.
6. [(auto* or adaptive) adj2 (servoventilation or ventilation)].tw.
7. AutoSet*.tw.
8. ((bi level or bi-level) adj2 (airway* or air way* or assist* or breath* or positive pressure* or respirat* or ventilat* or support* or therap*)).tw.
9. BIPAP*.tw.
10. BPAP*.tw.
11. c flex.tw.
12. CNEP.tw.
13. (continuous negative adj2 pressure).tw.
14. (continuous positive airway* or continuous positive air way*).tw.
15. (continuous positive adj2 pressure).tw.
16. CPAP*.tw.
17. ((domicil* or home*) adj5 ventilat*).tw.
18. intermittent positive pressure breathing.tw.
19. IPPB*.tw.
20. ((long term or longterm) adj5 ventilat*).tw.
21. ((nasal* or mask*) adj2 (positive adj2 pressure)).tw.
22. ((nasal* or mask*) adj2 ventilat*).tw.
23. nCPAP*.tw.
24. ((negative pressure) adj2 (respirat* or ventilat*)).tw.
25. ((night* or nocturnal* or sleep*) adj5 ventilat*).tw.
26. NIPPV*.tw.
27. ((noninvasive adj5 ventilat*) or (non invasive adj5 ventilat*)).tw.
28. (noninvasive respiratory support* or non invasive respiratory support*).tw.
29. NPPV*.tw.
30. (positive pressure adj2 respirat*).tw.
31. REMstar*.tw.
32. (tank adj (respirat* or ventilat*)).tw.
33. VPAP*.tw.
34. or/1–33
35. Hypoventilation/pc, rh, th [Prevention & Control, Rehabilitation, Therapy]
36. Interactive Ventilatory Support/
37. Intermittent Positive-Pressure Ventilation/
38. Positive-Pressure Respiration/
39. Respiration, Artificial/
40. Respiratory Insufficiency/pc, rh, th [Prevention & Control, Rehabilitation, Therapy]
41. exp Sleep Apnea Syndromes/pc, rh, th [Prevention & Control, Rehabilitation, Therapy]
42. Ventilators, Mechanical/
43. ((airway* or air way* or breath* or inspirat* or respirat* or ventilat*) and (positive adj2 pressure)).tw.
44. intermittent positive pressure.tw.
45. IPPV*.tw.
46. (mechanical adj (respirat* or ventilat*)).tw.
47. (positive adj2 pressure adj (assist* or support* or therap*)).tw.
48. positive airway pressure.tw.
49. pulmonary ventilator*.tw.
50. respiratory support*.tw.
51. or/35–50
52. (noninvasive or non invasive or spontaneous*).mp.
53. 51 and 52
54. 34 or 53
55. exp Adolescent/
56. exp Child/
57. exp Infant/
58. exp Minors/
59. exp Pediatrics/
60. exp Puberty/
61. exp Schools/
62. adoles*.mp.
63. (baby* or babies or infant* or infancy or neonat* or newborn* or postmatur* or prematur* or preterm*).mp.
64. (boy* or girl* or teen*).mp.
65. (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).mp.
66. (elementary school* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school*).mp.
67. minors*.mp.
68. (pediatric* or peadiatric* or pediatric*).mp.
69. (prepubescen* or pubescen* or pubert*).mp.
70. or/55–69
71. 54 and 70
72. (case reports or comment or editorial or letter).pt.
73. 71 not 72
74. exp animals/not humans.sh.
75. 73 not 74
76. limit 75 to yr = "1990-Current"
77. remove duplicates from 76

The search strategy also included infant keywords to help identify studies on infants.

Data sources, Study Selection, and Data Extraction

The titles and abstracts of studies identified by the literature search were screened by two reviewers (JEM and MCC) to determine eligibility for full-text retrieval. English, French, Spanish, and Portuguese studies that were considered eligible were full-text reviewed for inclusion by two reviewers (JEM and MCC). The final included studies pertaining to children 0–18 years were then full-text screened by two reviewers (PKB and MMA) to identify studies relevant to infants for inclusion in this systematic review. Any disagreement at the screening, eligibility, and inclusion levels were discussed until a consensus was reached. The reference lists of studies meeting inclusion were also reviewed to identify any additional relevant literature.

Data were entered into a pre-established data collection form in Microsoft Excel (version 14.0.4760, Microsoft Corporation, 2010). These data included author's name, year of publication, country of publication, study design, sample size, age of NIV initiation, NIV type, primary underlying disease conditions, co-morbidities, and primary and secondary outcome measures. One reviewer (PKB) extracted the data, and 20% of data extraction was verified by a second reviewer (MCC).

Risk of Bias

The Cochrane Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool (18) was used to assess the risk

of bias in individual studies. The tool measured confounding, selection, measurement, missing data, and reporting bias. Bias was ranked as low, moderate, severe, critical, or no information. Risk of bias in individual studies was independently assessed by two reviewers (PKB and MMA), with disagreements resolved by discussion and consensus.

Quality Assessment

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool (19) was used to determine the quality of studies at an outcome level. Two reviewers (PKB and MMA) independently assessed the quality of studies, with disagreements being resolved through discussion and consensus. Meta-analysis was performed to calculate risk ratios for appropriate outcomes using Review Manager (version 5.3., Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

Synthesis of Results

Studies were grouped by disease category (airway, NMD, CNS, cardio-respiratory or multiple disorders) after the data collection stage, to allow for adequate pathophysiological comparisons. Within each disease category, studies were grouped based on primary disease conditions. We included studies with infants who had multiple disease conditions under one disease heading if >75% of the infant cohort had the same disease condition; otherwise these studies were included in the multiple disorders category.

Primary and secondary outcomes were established after data collection, during synthesis of the data, based on the most common and clinically relevant outcomes reported in studies with the same disease condition. Primary outcomes were as follows: (1) objective changes in respiratory parameters, (2) discontinuation of NIV, (3) hospitalizations, and (4) mortality. Secondary outcomes were as follows: (1) improvements in underlying disease conditions, (2) improvements in growth parameters, (3) NIV facilitation of extubation, (4) predictors of NIV requirement, (5) NIV success/failure, (6) adherence to respiratory support, and (7) mask complications. Studies were included in the synthesis if they reported on at least one primary or secondary outcome. Continuous data were presented as a weighted mean (standard deviation) or median (interquartile range) where appropriate. Results were grouped and reported based on the primary underlying disease category being studied. Primary outcomes were reported in both tabular and narrative format, while secondary outcomes were only reported narratively.

RESULTS

Study Selection and Characteristics

The search strategy, after removal of duplicates, identified 12,594 studies and additional records (**Figure 1**). After screening of the titles and abstracts, and with the addition of records from additional sources, 1046 studies met eligibility for review. After full-text review, 327 studies on children ages 0–18 years met the inclusion criteria for the scoping review. Full-text review of these 327 articles identified 64 studies meeting the infant inclusion criteria. Four conference proceedings met inclusion criteria but were excluded because of insufficient data reporting, leaving 60 articles reporting on a total of 977 infants for inclusion in this systematic review (**Table 2**) (3, 7, 9, 10, 20–75).

The majority of studies were retrospective (41/60, 68%), quantitative (59/60, 98%), and single-center studies (54/60, 90%). The most common study design was observational, which included cohort studies (31/60, 52%), case series (13/60, 25%), and cross-sectional studies (8/60, 13%). Forty-eight percent of studies were exclusively on the infant population. Based on primary underlying disease categories, the studies were distributed across airway disorders (24/60, 40%), NMD (17/60, 28%), CNS (6/60, 10%), cardio-respiratory diseases (1/60, 2%), and multiple disease categories (12/60, 20%; **Table 2**). Thirteen studies did not report NIV outcomes, only the number of infants using NIV, and were excluded from further analysis (7, 25, 26, 32, 33, 37, 47, 52, 57, 59, 72, 74, 75).

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) was the most common airway disorder studied in the infant population, with 12 studies (12/60, 20%) reporting on this condition (**Table 2**). Of these, 10 studies reported on infant NIV outcomes and were synthesized in the review (10, 20–24, 27–30). These studies included infants with multiple underlying conditions, the most common being a history of acute life-threatening events (ALTE), family history of sudden infant death syndrome (SIDS), and craniofacial malformations. Eight studies (8/10, 80%) reported on changes in respiratory parameters, with seven of these studies (7/10, 70%) showing improvements in central, obstructive, and/or mixed apneas from a diagnostic to titration polysomnography (**Table 3**) (10, 20, 22, 23, 27–29) Only one study (1/10, 10%) included diagnostic polysomnography results after long-term NIV use (weighted mean of 12 months), which showed an overall decrease in respiratory events, normalization of respiratory gases, and increased arousals during REM sleep (29). Five studies (5/10, 50%) reported discontinuation of NIV in infants because of improvements in respiratory parameters, with discontinuation rates ranging from 14 to 100% (weighted mean 70 ± 26%) (20, 21, 27, 29, 30). No studies reported on hospitalization outcomes (**Table 4**). One study (1/10, 10%) of five infants using NIV reported mortality outcomes, with all infants alive at the time of study publication (27).

Pierre Robin Sequence

Seven studies (7/60, 12%) reported on infants with Pierre Robin sequence (PRS) using long-term NIV (**Table 2**). Four studies (4/7, 57%) reported on primary or secondary outcomes and were synthesized for this review (31, 34–36). A cohort study reported normalization of polygraphy parameters and gas exchange post-NIV initiation (**Table 3**) (31). A case series reported a decrease in respiratory rates, statistically significant improvements in respiratory effort, and normalization of respiratory gases after administration of NIV therapy in infants with PRS (36). Two studies on 16 infants with PRS reported discontinuation from NIV in 11 (69%) infants because of improvements in respiratory parameters (31, 36). Two studies comparing infants on NIV and invasive mechanical ventilation showed that the length of hospitalization were shorter for infants on NIV than for those receiving invasive mechanical ventilation via a tracheostomy (**Table 4**) (31,

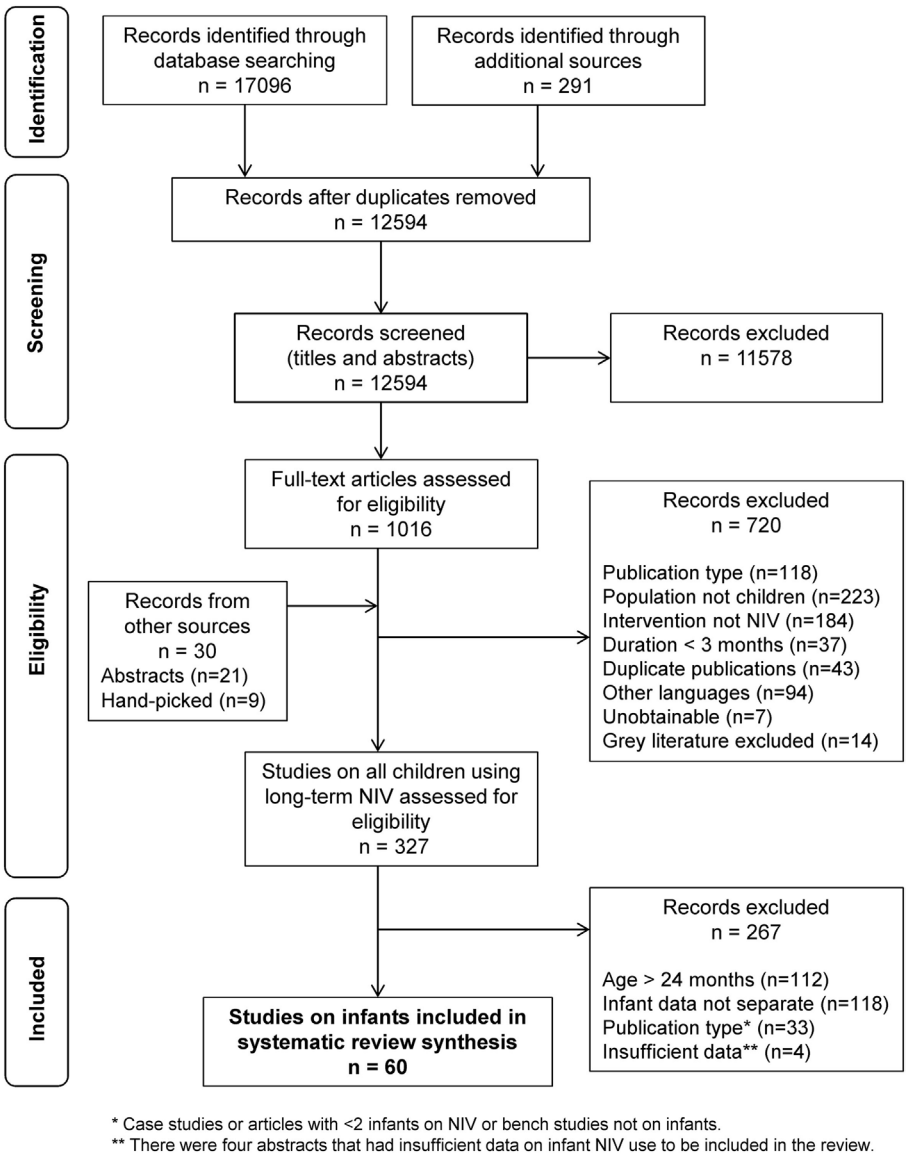

FIGURE 1 | Flow diagram outlining the study selection process for the systematic review, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (15).

35). No studies addressed survival outcomes in infants with PRS using long-term NIV. Adherence of infants to NIV was reported as excellent, showing more than 8 hours of NIV use per day in two studies (31, 36), with only a 1–2 week period required to adjust to the mask ventilation (31, 35). An additional cohort study demonstrated that infants with PRS using NIV were 10.43 times more likely to progress to a surgical airway compared to infants who required less advanced respiratory supports such as prone positioning and a nasopharyngeal airway (34).

Laryngo-Tracheomalacia

All four studies (4/60, 7%) on infants with laryngo-tracheomalacia (LTM) using long-term NIV reported on primary or secondary outcomes and were synthesized in the review (**Table 2**) (38–41). Three studies (3/4, 75%) reported on changes in respiratory parameters (**Table 3**) (38, 39, 41). A case–control study of 10 infants with LTM showed improvements in respiratory frequency and respiratory effort in infants using CPAP or BPAP compared to spontaneous breathing (38). Normalization of arterial oxygen saturations after NIV use was seen in two studies (39, 41). NIV discontinuation was reported in two studies, with a combined discontinuation due to improvement rate of 81% (13/16 infants) (39, 40). No studies examined hospitalization or mortality outcomes. Improvement in chest wall deformity after NIV use in three patients and normalization of weight in four patients was reported in one case–control study (39). The same study

TABLE 2 | Characteristics and outcomes of 60 studies included in the systematic review on infants using long-term NIV.

First author, year, country	Study design	Study duration	Total *n*(M/F)	Infants on NIV	Age [mean ± SD or median (range) unless otherwise stated]	Interventions	Infant NIV outcomes	
							Primary	Secondary
Articles on airway disorders: obstructive sleep apnea								
Downey (20), 2000, USA	Quantitative: observational (cohort)	7 years	18 (n/a)	$n = 10$[a]	Overall: <2 years	CPAP ($n = 14$) IMV ($n = 4$)	• Changes in respiratory parameters • Discontinuation of NIV	• Number of subjects on NIV
Guilleminault (21), 1995, USA	Quantitative: observational (cohort)	n/a	74 (35/39)	$n = 74$	24 ± 9 weeks	CPAP ($n = 74$)	• Discontinuation of NIV	• Number of subjects on NIV
Harrington (22), 2003, Australia, Finland	Quantitative: observational (case–control)	n/a	18 (11/7)	$n = 6$	13 ± 4 weeks	CPAP ($n = 6$)	• Changes in respiratory parameters	• Number of subjects on NIV
Leonardis (23), 2013, USA	Quantitative: observational (cross-sectional)	4 years	126 (86/40)	$n = 18$	NIV group: 16 months	None ($n = 33$) NIV ($n = 18$) IMV ($n = 7$)[b]	• Changes in respiratory parameters	• Number of subjects on NIV
Liu (24), 2012, China	Quantitative: observational (case series)	n/a	3 (2/1)	$n = 2$	Overall: 1 month to 5 years Infants: 1–7 months	CPAP ($n = 2$) BPAP ($n = 2$)	• Changes in respiratory parameters	• Number of subjects on NIV • Benefit of NIV (growth parameters)
Marcus (25), 1995, USA	Quantitative: observational (cross-sectional)	n/a	94 (60/34)	$n = 3$[c]	Overall: <1–19 years Infants: <1 year ($n = 3$)	CPAP ($n = 94$)		• Number of subjects on NIV*
Massa (26), 2002, UK	Quantitative: observational (cohort)	5 years	66 (39/27)	$n = 9$[c]	Overall: 5.9 ± 5.1 years Infants: <1 year ($n = 18$)	CPAP ($n = 66$)		• Number of subjects on NIV*
McNamara (27), 1995, Australia	Quantitative: control before–after	0.5 years	5 (2/3)	$n = 5$	8–12 weeks	CPAP ($n = 5$)	• Changes in respiratory parameters • Discontinuation of NIV • Survival/mortality	• Number of subjects on NIV
McNamara (28), 1999, Australia	Quantitative: observational (case–control)	n/a	24 (13/11)	$n = 8$	CPAP group: 10.8 ± 1.3 weeks	CPAP ($n = 8$)	• Changes in respiratory parameters • Discontinuation of NIV	• Number of subjects on NIV
McNamara (29), 1999, Australia	Quantitative: observational (cohort)	n/a	24 (15/9)	$n = 24$	1–51 weeks	CPAP ($n = 24$)	• Changes in respiratory parameters	• Number of subjects on NIV

(*Continued*)

TABLE 2 | Continued

First author, year, country	Study design	Study duration	Total *n*(M/F)	Infants on NIV	Age [mean ± SD or median (range) unless otherwise stated]	Interventions	Infant NIV outcomes	
							Primary	**Secondary**
Robison (10), 2013, USA	Quantitative: observational (cross-sectional)	4 years	295 (196/99)	*n* = 18	CPAP/bi-level group: 15.6 months (3–29 months)	None (*n* = 76) NIV (*n* = 18) T&A (*n* = 116) IMV (*n* = 6)[b]	• Changes in respiratory parameters	• Number of subjects on NIV
Rosen (30), 2010, USA	Quantitative: observational (case series)	5.5 years	16 (n/a)	*n* = 6	Overall: <2 years	CPAP (*n* = 6)	• Discontinuation of NIV	• Number of subjects on NIV
Articles on airway disorders: Pierre Robin sequence								
Amaddeo (31), 2016, France	Quantitative: observational (cohort)	1 year	44 (n/a)	*n* = 9	Infants: 0–2 months	CPAP (*n* = 9)	• Changes in respiratory parameters • Discontinuation of NIV • Hospitalizations	• Number of subjects on NIV • Adherence to NIV
Cheng (32), 2011, Australia	Quantitative: observational (case series)	5 years	6 (n/a)	*n* = 6	26 days to 11 months	CPAP (*n* = 6)		• Number of subjects on NIV*
Daniel (33), 2013, Australia	Quantitative: observational (cross-sectional)	12 years	39 (16/23)	*n* = 18	n/a	CPAP (*n* = 18)		• Number of subjects on NIV*
Goudy (34), 2017, USA	Quantitative: observational (cohort)	9 years	38 (18/20)	*n* = 9	n/a (neonates)	NIV (*n* = 9) NPA (*n* = 14) IMV (*n* = 8) MDO (*n* = 5)		• Number of subjects on NIV • NIV success/failure
Kam (35), 2015, Canada	Quantitative: observational (cohort)	11 years	139 (72/67)	*n* = 20[d]	23 months (5 days to 8 years)	None (*n* = 61) CPAP (*n* = 20) IMV (*n* = 19)[b]	• Hospitalizations	• Number of subjects on NIV
Leboulanger (36), 2010, France	Quantitative: observational (case series)	10 years	7 (3/4)	*n* = 7	1–10 months	CPAP (*n* = 5) BPAP (*n* = 2)	• Changes in respiratory parameters • Discontinuation of NIV	• Number of subjects on NIV • Adherence to NIV
Müller-Hagedorn (37), 2017, Germany	Quantitative: observational (cohort)	7 years	68 (n/a)	*n* = 5	n/a	CPAP (*n* = 5)		• Number of subjects on NIV*
Articles on upper airway disorders: Laryngo-tracheomalacia								
Essouri (38), 2005, France	Quantitative: control before–after	n/a	10 (5/5)	*n* = 10	9.5 months (3–18 months)	None (*n* = 10) CPAP (*n* = 10) BPAP (*n* = 10)	• Changes in respiratory parameters	• Number of subjects on NIV

(*Continued*)

TABLE 2 | Continued

First author, year, country	Study design	Study duration	Total *n*(M/F)	Infants on NIV	Age [mean ± SD or median (range) unless otherwise stated]	Interventions	Infant NIV outcomes	
							Primary	**Secondary**
Fauroux (39), 2001, France, UK	Quantitative: control before–after	n/a	12 (10/2)	*n* = 5	Overall: 32.9 ± 25.8 months Infants: 8–19 months	None (*n* = 12) BPAP (*n* = 12)	• Changes in respiratory parameters • Discontinuation of NIV	• Number of subjects on NIV • Adherence to NIV • Benefit of NIV (growth parameters)
Shatz (40), 2004, Israel	Quantitative: observational (cohort)	3 years	50 (36/14)	*n* = 50	6.5 ± 3.5 months (1–18 months)	CPAP (*n* = 5) BPAP (*n* = 9)	• Discontinuation of NIV	• Number of subjects on NIV • Improvement in underlying disease
Zwacka (41), 1997, Germany	Quantitative: observational (case series)	n/a	10 (5/5)	*n* = 10	3 weeks to 5 months	CPAP (*n* = 7)	• Changes in respiratory parameters	• Number of subjects on NIV • Benefit of NIV (growth parameters)
Articles on airway disorders: breath holding spells								
Guilleminault (42), 2007, USA, Taiwan	Quantitative: observational (case–control)	2.5 years	19 (11/8)	*n* = 14	31 ± 3 weeks	CPAP (*n* = 14)	• Changes in respiratory parameters	• Number of subjects on NIV • NIV success/failure
Articles on neuromuscular disease: spinal muscular atrophy type 1								
Bach (43), 2000, USA	Quantitative: observational (case series)	n/a	11 (6/5)	*n* = 8	3–28 months	BPAP (*n* = 11)	• Hospitalizations • Survival/Mortality	• Number of subjects on NIV • Benefit of NIV (extubation) • Benefit of NIV (growth parameters)
Bach (44), 2002, USA	Quantitative: observational (cohort)	5 years	56 (n/a)	*n* = 33	Overall for patient groups: NIV: 11.2 ± 5.7 months IMV: 10.8 ± 5.0months supportive: 6.0 ± 1.3 months	NIV (*n* = 33) IMV (*n* = 16) None (*n* = 7)	• Hospitalizations • Survival/mortality	• Number of subjects on NIV
Bach (45), 2003, USA	Quantitative: observational (case series)	n/a	3 (2/1)	*n* = 3	4–11 months	NIV (*n* = 3)		• Number of subjects on NIV • Benefit of NIV (growth parameters)

(*Continued*)

TABLE 2 | Continued

First author, year, country	Study design	Study duration	Total *n*(M/F)	Infants on NIV	Age [mean ± SD or median (range) unless otherwise stated]	Interventions	Infant NIV outcomes	
							Primary	**Secondary**
Bach (46), 2007, USA	Quantitative: observational (cohort)	13	92 (n/a)	*n* = 92[d]	Therapy group: none: 6.6 ± 4.1 months bi-level: 10.6 ± 5.7 months IMV: 14.8 ± 15.2 months	None (*n* = 18) BPAP (*n* = 47) IMV (*n* = 27)	• Hospitalizations • Survival/mortality	• Number of subjects on NIV
Barnerias (47), 2014, France	Quantitative: observational (cross-sectional)	20 years	222 (n/a)	*n* = 8	Overall: 3 months (0.5–8 months)	NIV (*n* = 8)		• Number of subjects on NIV*
Birnkrant (48), 1998, USA	Quantitative: observational (case series)	2 years	4 (3/1)	*n* = 3	4–9 months	BPAP (*n* = 4)	• Survival/mortality	• Number of subjects on NIV • Benefit of NIV (extubation)
Chatwin (49), 2011, UK	Quantitative: observational (cohort)	19 years	13 (8/5)	*n* = 13	4–24 months	BPAP (*n* = 13)	• Survival/mortality	• Number of subjects on NIV • Benefit of NIV (growth parameters)
Ednick (50), 2008, USA	Quantitative: observational (cohort)	3.5 years	7 (1/6)	*n* = 7	8.3 ± 3.7 months	BPAP (*n* = 7)		• Number of subjects on NIV • Benefit of NIV (extubation)
Gregoretti (51), 2013, Italy	Quantitative: observational (case series)	18 years	194 (103/91)	*n* = 31	NIV group: 12.6 ± 14.4 months (0–42 months) IMV group: 6.9 ± 4.3 months	None (*n* = 121) NIV (*n* = 31) IMV (*n* = 42)	• Hospitalizations • Survival/mortality	• Number of subjects on NIV
Ioos (52), 2004, France	Quantitative: observational (cohort)	n/a	180 (n/a)	*n* = 33	19 ± 17 months	n/a		• Number of subjects on NIV*
Lemoine (53), 2012, USA	Quantitative: observational (cohort)	7 years	49 (31/18)	*n* = 49	Groups: NIV: 136 days (34–196 days) Supportive care: 69 days (38–145 days)	None (*n* = 23) BPAP (*n* = 26)	• Hospitalizations • Survival/mortality	• Number of subjects on NIV
Ottonello (54), 2011, Italy	Quantitative: observational (cohort)	4 years	16 (n/a)	*n* = 14[e]	Overall: <3 years Infants: 10.4 ± 6.2 months	NIV (*n* = 16)	• Hospitalizations • Survival/mortality	• Number of subjects on NIV • Benefit of NIV

(*Continued*)

TABLE 2 | Continued

First author, year, country	Study design	Study duration	Total *n*(M/F)	Infants on NIV	Age [mean ± SD or median (range) unless otherwise stated]	Interventions	Infant NIV outcomes	
							Primary	**Secondary**
Petrone (55), 2007, Italy	Quantitative: control before–after	n/a	9 (7/2)	*n* = 9[d]	7 months (2–33 months)	BPAP (*n* = 9)	• Changes in respiratory parameters	• Number of subjects on NIV
Vasconcelos (56), 2005, Portugal	Quantitative: observational (cohort)	11 years	22 (16/6)	*n* = 7[d]	Overall: 5.5 years (6 months to 26 years) SMA type 1 group: 13 months (3 months to 3 years)	None (*n* = 5) BPAP (*n* = 17)	• Hospitalizations • Survival/mortality	• Number of subjects on NIV • Benefit of NIV (growth parameters)
Articles on neuromuscular disease: achondroplasia								
Afsharpaiman (57), 2011, Iran, Australia	Quantitative: observational (cohort)	15 years	46 (22/24)	*n* = 7	Overall: 3.9 years Infants: <2 years (*n* = 7)	CPAP (*n* = 9) AT (*n* = 13)		• Number of subjects on NIV*
Articles on neuromuscular disease: multiple (spinal muscular atrophy type 1 and congenital myopathy)								
Han (58), 2015, Korea	Quantitative: observational (cohort)	13.4 years	57 (n/a)	n/a	Overall: 7.7 months (2–158 months) Infants with SMA type 1: 6.6 months (2–26) CM: 7.8 months (3–121)	NIV (*n* = 8) IMV (*n* = 46)	• Survival/mortality	• Number of subjects on NIV • NIV success/failure
Articles on neuromuscular disease: myotonic dystrophy								
Wood (59), 2017, UK, Germany	Quantitative: observational (cross-sectional)	4 years	610 (272/338)	*n* = 2	41.1 years (8 months to 78 years)	NIV (*n* = 35)		• Number of subjects on NIV*
Articles on central nervous system disease: congenital hypoventilation syndrome								
Garcia Teresa (60), 2017, Spain	Quantitative: observational (cross-sectional)	3.75 years	38 (17/21)	*n* = 8[d]	11.35 (5 months to 28.6 years)	NIV (*n* = 8)	• Hospitalizations • Survival/mortality	• Number of subjects on NIV • NIV failure/success
Hartmann (61), 1994, UK	Quantitative: observational (case series)	n/a	9 (3/6)	*n* = 6	22 days to 52 months	VNEP (*n* = 9)[f] CPAP (*n* = 3)[g]	• Discontinuation of NIV	• Number of subjects on NIV • Benefit of NIV (growth parameters) • NIV success/failure • Quality of life

(*Continued*)

TABLE 2 | Continued

First author, year, country	Study design	Study duration	Total *n*(M/F)	Infants on NIV	Age [mean ± SD or median (range) unless otherwise stated]	Interventions	Infant NIV outcomes	
							Primary	Secondary
Khayat (62), 2017, Canada, USA	Quanitative: observational (control before–after)	2.7 years	8 (4/4)	*n* = 2	Overall: 10.0 years (8.4–11.6 years) infants: 1.1 years	BPAP (*n* = 8)[h]		• Number of subjects on NIV • NIV modality
Noyes (63), 1999, UK, Germany	Qualitative: content analysis	n/a	7 (3/4)	*n* = 5	66 days to 59 months	VNEP (*n* = 5) CPAP (*n* = 1)[g] IMV (*n* = 2)	• Discontinuation of NIV	• Number of subjects on NIV • Benefit of NIV (growth parameters) • Quality of life
Ramesh (64), 2008, UK	Quantitative: observational (cross-sectional)	n/a	15 (5/10)	*n* = 7	Early start: 8 weeks (5–26 weeks) Late start: 8 years (1.5–11 years)	NIV (*n* = 15)		• Number of subjects on NIV • Benefit of NIV (extubation) • Mask complications
Tibballs (65), 2003, Australia	Quantitative: observational (case series)	n/a	4 (2/2)	*n* = 2	6 weeks to 9 years	BPAP (*n* = 4)	• Changes in respiratory parameters	• Number of subjects on NIV • Benefit of NIV (extubation) • Mask complications
Articles on cardio-respiratory disease: congenital heart disease								
Bunn (66), 2004, UK	Quantitative: observational (case series)	n/a	4 (0/4)	*n* = 3	5–34 months	NIV (*n* = 4)	• Changes in respiratory parameters • Discontinuation of NIV	• Number of subjects on NIV
Articles on multiple underlying disease conditions								
Adeleye (67), 2016, Canada	Quantitative: observational (cohort)	5 years	92 (54/38)	*n* = 49	208.5 ± 101.2 days	NIV (*n* = 49)		• Number of subjects on NIV • Adherence to NIV
Amaddeo (3), 2016, France	Quantitative: observational (cohort)	1 year	76 (39/37)	n/a	Overall for patient groups: acute: 0.3 year (0.1–13.5) Sub-acute: 0.6 year (0.2–18.2) Chronic: 1.6 years (0.1–19.5)	CPAP (*n* = 64) BPAP (*n* = 12)		• Number of subjects on NIV • Predictors of NIV requirement

(*Continued*)

TABLE 2 | Continued

First author, year, country	Study design	Study duration	Total *n*(M/F)	Infants on NIV	Age [mean ± SD or median (range) unless otherwise stated]	Interventions	Infant NIV outcomes	
							Primary	**Secondary**
Bertrand (68), 2006, Chile	Quantitative: observational (cohort)	10.5 years	35 (18/17)	*n* = 9[d]	12 months (5 months to 14 years)	CPAP (*n* = 1) BPAP (*n* = 8) IMV (*n* = 26)	• Hospitalizations • Discontinuation of NIV • Survival/Mortality	• Number of subjects on NIV
Chatwin (7), 2015, UK	Quantitative: observational (cohort)	18 years	449 (281/168)	*n* = 59[c]	Overall: 10 years (3–15 years) Infants: <1 year (*n* = 59)	CPAP (*n* = 57) BPAP (*n* = 392)		• Number of subjects on NIV*
Fauroux (69), 2005, France	Quantitative: observational (cross-sectional)	0.5 year	40 (22/18)	*n* = 16	Overall: 10.0 years (0.6–18 years) Infant: 1.8 years (0.2–15.3 years)[i]	NIV (*n* = 40)		• Number of subjects on NIV • Adherence to NIV • Mask complications
Kherani (70), 2016, Canada	Quantitative: observational (cohort)	23 years	51 (30/21)	*n* = 25	NIPPV: 0.6 year (0.4–0.7 year) IMV: 0.4 year (0.1–0.7 year)	NIV (*n* = 25) IMV (*n* = 26)	• Changes in respiratory parameters • Discontinuation of NIV • Survival/mortality	• Number of subjects on NIV
Koontz (71), 2003, USA	Quantitative: observational (cohort)	n/a	20 (n/a)	*n* = 6	1–2 years	BPAP (*n* = 6)		• Number of subjects on NIV • Adherence to NIV
Machaalani (72), 2016, Australia	Quantitative: observational (cohort)	2 years	99 (63/36)	*n* = 22	n/a	CPAP (*n* = 55) BPAP (*n* = 44)		• Number of subjects on NIV*
Markstrom (9), 2008, Sweden	Quantitative: observational (cohort)	7 years	18 (11/7)	*n* = 18	4 months (1–12 months)	BPAP (*n* = 18)	• Changes in respiratory parameters • Discontinuation of NIV	• Number of subjects on NIV
Nathan (73), 2017, Malaysia	Quantitative: observational (cohort)	13 years	70 (40/30)	*n* = 51	Overall: 12 months CPAP: 6 months (3–12 months) BPAP: 12 months (5–33 months) IMV: 30 (12–57 months)	CPAP (*n* = 30) BPAP (*n* = 30) IMV (*n* = 10)	• Discontinuation of NIV • Hospitalizations • Survival/mortality	• Number of subjects on NIV • Predictors of NIV • NIV modality
Ramirez (74), 2012, France	Quantitative: observational (case series)	18 months	97 (n/a)	*n* = 18	Infants: <2 years (*n* = 18)	CPAP and BPAP (n/a)		• Number of subjects on NIV*

(*Continued*)

TABLE 2 | Continued

First author, year, country	Study design	Study duration	Total *n*(M/F)	Infants on NIV	Age [mean ± SD or median (range) unless otherwise stated]	Interventions	Infant NIV outcomes	
							Primary	Secondary
Zhou (75), 2012, China	Quantitative: observational (cohort)	2 years	14 (12/2)	$n = 6^{c}$	Overall: 50 days to 12 years Infants: <1 year ($n = 6$)	CPAP ($n = 1$) BPAP ($n = 13$)		• Number of subjects on NIV*

Studies have been classified according to the primary disease category and disease condition reported. Studies with multiple disease categories have been included at the end of the table.
AT, adenotonsillectomy; CPAP, continuous positive airway pressure; BPAP, bi-level positive airway pressure; IMV, invasive mechanical ventilation; n/a, data not available/reported; MDO, mandibular distraction osteogenesis; NIV, non-invasive ventilation; NPA, nasopharyngeal airway; SMA, spinal muscular atrophy; VNEP, negative extra-thoracic pressure ventilation.
**Articles reporting only on the number of subjects using NIV were excluded from synthesis.*
[a]Four patients did not tolerate CPAP.
[b]Full list of non-surgical and surgical interventions are in the full text of article.
[c]Number of patients less than 1 year of age.
[d]Determined by the mean/median age of the population during NIV initiation.
[e]Determined by age at first respiratory decompensation.
[f]VNEP failed in two patients.
[g]CPAP used in conjunction with VNEP.
[h]Compared intelligent volume-assured pressured support BPAP to traditional BPAP.
[i]Only includes infants in the obstructive sleep apnea group.

TABLE 3 | Studies on infants using long-term NIV reporting change in respiratory parameters and discontinuation outcomes.

First author, year, country	Study design	Primary diagnosis	Infants using NIV	Age mean ± SD or med (range)	NIV type	Total apneas (mean ± SD events/hour)		Obstructive apneas (mean ± SD events/hour)		Central apneas (mean ± SD events/hour)		Infants who discontinued (%)
						Pre-NIV	Post-NIV	Pre-NIV	Post-NIV	Pre-NIV	Post-NIV	
Harrington (22), 2003, Australia, Finland	P, Obs: case–control	OSA	$n = 6$	13 ± 4 weeks	CPAP			17 ± 6	1 ± 1*			
Downey (20), 2000, USA	R, Obs: cohort	OSA	$n = 18$	<2 years	CPAP	12.8 ± 20.0	4.5 ± 13.4[†]	4.7 ± 13.4	2.0 ± 7.3[†]			90
McNamara (27), 1995, Australia	P, control before–after	OSA	$n = 5$	8–12 weeks	CPAP	[a]65.6 ± 14.6 [b]106.1 ± 13.9	10.5 ± 14.6** 26.6 ± 13.9**	[a]29.3 ± 9.4 [b]80.8 ± 16.8	[a]0.3 ± 9.4** [b]2.0 ± 16.8**	36.5 ± 6.6 25.6 ± 4.5	10.3 ± 6.6** 24.6 ± 4.5	100
McNamara (28), 1999, Australia	P, Obs: cohort	OSA	$n = 24$	1–51 weeks	CPAP	44.4 ± 9.3 68.6 ± 8.9	9.5 ± 1.2* 22.7 ± 2.3*	14.6 ± 3.9 43.6 ± 8.3	0.1 ± 0.1* 0.4 ± 0.1*	29.8 ± 7.6 25.0 ± 4.3	9.4 ± 1.2* 22.3 ± 2.2	72

(*Continued*)

TABLE 3 | Continued

McNamara (29), 1999, Australia	P, Obs: case–control	OSA	*n* = 8	10.8 ± 1.3 weeks	CPAP		22.2 ± 8.8 54.8 ± 16.3	10.6 ± 2.6* 25.7 ± 7.2*	36.1 ± 8.6 32.9 ± 8.1	26.3 ± 7.4 38.2 ± 8.2	
Leonardis (23), 2013, USA	R, Obs: cohort	OSA	*n* = 18	16.0 mo	CPAP BPAP	% decrease in AHI: 67.2*					
Robison (10), 2013, USA	R, Obs: cohort	OSA	*n* = 18	15.6 months (3–29 months)	CPAP BPAP	% decrease in AHI: 84.1*					
Guilleminault (21), 1995, USA	P, Obs: case–control	OSA	*n* = 72	24 ± 9 weeks (4–43 months)	CPAP						14
Rosen (30), 2010, United States	R, Obs: cohort	OSA	*n* = 6	<2 years	CPAP						50

First author, year, country	Study design	Primary Diagnosis	Infants using NIV	Age, mean ± SD or med (range)	NIV type	Change in respiratory parameters			Infants who discontinued (%)
						Variables	Pre-NIV, mean ± SD	Post-NIV, mean ± SD	
Leboulanger (36), 2010, France	P; Obs: case series	PRS	*n* = 7	2 months (1–10 months)	CPAP (*n* = 5) BPAP (*n* = 2)	RR (breaths/minute) T_I/T_{TOT} (%) P_{es} swing (cm H_2O) P_{di} swing (cm H_2O) Total sleep time with S_pO_2 < 90% (%) Total sleep time with P_aCO_2 > 50 mm Hg (%)	55 ± 9 59 ± 9 29 ± 13 31 ± 12 14 ± 10 88 ± 12	37 ± 7 40 ± 7* 9 ± 4* 12 ± 5* 1 ± 2* 0 ± 0†	71
Amaddeo (31), 2016, France	R; Obs: cohort	PRS	*n* = 9	0–2 months	CPAP	Apnea–hypopnea index (events/hour) Oxygen desaturation index (events/hour) Minimum S_pO_2 (%) % time S_pO_2 < 90% Maximum P_aCO_2 (%)	19–42 18–137 78–90 0–16 41–55	Normal PG and/or gas exchange (reported narratively)	66

First author, year, country	Study design	Primary diagnosis	Infants using NIV	Age, mean ± SD or med (range)	NIV type	Variables	Supportive care	CPAP	BPAP	Infants who discontinued (%)
Essouri (38), 2005, France	P; Obs: case–control	LTM	*n* = 10	9.5 months (3–18 months)	CPAP (*n* = 10) BPAP (*n* = 10)	RR (breaths/minute) T_I/T_{TOT} (%) P_{es} swing (cm H_2O) P_{di} swing (cm H_2O) PTP_{es}/minute (cm H_2O/second/minute) PTP_{di}/minute (cm H_2O/second/minute)	45 (24–84) 63 (35–86) 28 (13–76) 30 (16–75) 695 (364–1417) 845 (159–1183)	29 (18–60) 41 (34–60)** 10 (7–28)** 12 (8–32)** 143 (98–469)** 195 (115–434)**	25 (14–50)*c 48 (28–55)** 13 (6–33)** 14 (7–33)** 211 (73–588)** 248 (45–784)**	

(*Continued*)

TABLE 3 | Continued

Fauroux (39), 2001, France, UK	P; Obs: case–control	LTM	*n* = 5	8–19 months	CPAP	S_pO_2 (%) S_pO_2 nadir (%) % sleep with S_pO_2 < 90%	91.7 ± 2.3 74.7 ± 7.5 29.5 ± 19.6	96.2 ± 2.0* 88.0 ± 2.5* 0.5 ± 0.8*	60
Zwacka (41), 1997, Germany	R: Obs: cohort	LTM	*n* = 7	3 weeks to 3 months	CPAP	HR (beats/minute) RR (breaths/minute) S_aO_2 in REM sleep (%) S_aO_2 in NREM sleep (%)	135–160 34–42 60–95 85–98	110–130 22–28 88–100 92–100	
Shatz (40), 2004, Israel	R; Obs: cohort	LTM	*n* = 14	6.5 ± 3.5 months (1–18 months)	CPAP (*n* = 5) BPAP (*n* = 9)				100

First author, year, country	**Study design**	**Primary diagnosis**	**Infants using NIV**	**Age, mean ± SD or med (range)**	**NIV type**	**Change in respiratory parameters**	**Infants who discontinued (%)**
Tibballs (65), 2003, Australia	R; Obs: case series	CHS	*n* = 2	6 weeks and 9 months	BPAP (*n* = 2) VNEP (*n* = 2)	Decrease in P_aCO_2 to 40–50 mm Hg in one infant	
Hartmann (61), 1994, U	P; Obs: case series	CHS	*n* = 6	22 days to 5 months	VNEP (*n* = 6) CPAP (*n* = 2)	Improvements in hypoventilation in three patients (reported narratively)	33
Noyes (63), 1999, UK	P; Obs: cross-sectional	CHS	*n* = 5	66 days to 59 months	VNEP (*n* = 5) CPAP (*n* = 1)		33
Ramesh (64), 2008, UK	P; Obs: cross-section	CHS	*n* = 6	8 weeks (5–26 weeks)			0

AHI, apnea–hypopnea index (events/hour); BPAP, bi-level positive airway pressure; CHS, congenital hypoventilation syndrome; CPAP, continuous positive airway pressure; HR, heart rate; LTM, laryngo-tracheomalacia; NIV, non-invasive ventilation; Obs, observational study; OSA, obstructive sleep apnea; P, prospective; P_aCO_2, partial pressure of carbon dioxide; P_{di}, diaphragmatic pressure; P_{es}, esophageal pressure; PG, polygraphy; PRS, Pierre Robin sequence; R, retrospective; RR, respiratory rate; S_aO_2, oxygen saturation; SpO_2, pulse oximetry; T_I/T_{TOT}, inspiratory time/total respiratory cycle time; VNEP, negative extra-thoracic pressure ventilation.

**p < 0.05.*

***p < 0.01.*

†*p < 0.001.*

[a]*Apneas seen in non-rapid eye movement (NREM) sleep.*

[b]*Apneas seen in rapid eye movement (REM) sleep.*

also reported an average NIV use per day of 10.2 hours/day in seven infants (50).

Spinal Muscular Atrophy Type 1

There were 14 studies (14/60, 23%) of infants with spinal muscular atrophy type 1 (SMA1) using long-term NIV (**Table 2**). Twelve of these studies reported on primary or secondary outcomes and were synthesized (43–46, 48–51, 53–56). Only one study (1/12, 8%) reported on changes in respiratory parameters and showed improvements in respiratory effort and normalization of respiratory gases in SMA1 patients using NIV therapy (**Table 3**) (55). Six studies (6/12, 50%) reported on hospitalization outcomes (**Table 4**) (43, 44, 46, 51, 53, 54). Of these, two studies reported that hospitalizations per patient per year were significantly higher in infants on NIV than infants with a tracheostomy until after three years of age (44, 46). Nine studies (9/12, 75%) reported on mortality outcomes (43, 44, 46, 48, 49, 51, 53, 54, 56); four of these studies compared infants on supportive care with those using NIV, showing prolonged survival in the NIV group (44, 46, 51, 53). Three studies (3/12, 25%) reported improvements in growth parameters, seen by resolution of chest wall deformity (pectus excavatum) after the initiation of NIV therapy (43, 45, 49). An additional three studies showed that NIV helped facilitate extubation in infants with SMA1 (43, 48, 50).

Central Hypoventilation Syndrome

There were six studies (6/60, 10%) on NIV use for infants with central hypoventilation syndrome (CHS) that reported primary or secondary outcomes, and all six were summarized (**Table 2**) (60–65). The diagnosis of CHS was confirmed clinically in two studies (61, 65), via PHOX2B gene mutation analysis in three studies (60, 62, 64), and unreported in one study (63). NIV was used in conjunction with negative extra-thoracic pressure ventilation (VNEP) therapy in two studies: in one study, it was used as the primary therapy (65) and, in the second study, CPAP was used to relieve upper airway obstruction not resolved with VNEP (61). Improvements in respiratory parameters were reported in two studies: one showed the normalization of the partial pressure of carbon dioxide and resolution of pulmonary hypertension following the use of NIV (65) and the other study showed improvements in hypoventilation for 50% (3/6) of infants (**Table 3**) (61). One study with six infants reported NIV discontinuation in two infants (33%) because of improvements in respiratory parameters; the remaining four infants were using NIV only during sleep (61). One cohort study reported mortality outcomes and a higher hospitalization time for infants using invasive mechanical ventilation compared to NIV (**Table 4**) (60). Two studies showed parent-reported improvements in growth and development after NIV initiation using the results of a parent questionnaire (61, 63). An additional two studies reported pressure-related effects of mask use, which were predominantly skin breakdown and mid-face hypoplasia (64, 65). One cross-sectional study showed that it took less than a week for five of the six infants to adjust to NIV (61). A control before-after study of infants using two BPAP ventilators showed comparable sleep and respiratory parameters with both ventilators, with the exception of a greater decrease in the maximum transcutaneous carbon dioxide with the intelligent volume-assured pressured support compared to a traditional BPAP ventilator (62).

Synthesized Findings

After examining studies for all disease categories and respective outcomes, only three studies on infants with SMA1 reporting mortality outcomes were eligible for meta-analysis (44, 46, 51). The results of meta-analysis showed that there was a statistically significant decrease in the relative risk of mortality in the NIV group compared to the supportive care group (**Figure 2**).

Risk of Bias and Quality Assessment of Outcomes

Risk of bias ranged from moderate to severe in all studies synthesized in this review (**Table 5**). Study design was the main contributor to the low quality assessment of the studies. Almost all the included studies had an observational study design, which contributed to confounding bias in participant selection and selected reporting of results. Grading of the quality of the evidence for outcomes such as changes in respiratory parameters, discontinuation of NIV, hospitalizations, and mortality showed that the quality of evidence ranged from low to very low for all studies (**Table 6**).

DISCUSSION

Summary of Main Findings

To our knowledge, this is the first systematic review on the use of long-term NIV in infants. We identified studies on a diverse range of airway conditions in which NIV therapy improved the results of polysomnographic and respiratory parameters. With data available for NMD and CNS disorders limited to SMA1 and CHS, extrapolation of NIV benefits to other NMD and CNS disorders in infants is challenging. Not all outcomes were studied in all disease categories; length of hospitalization was the focus in studies of PRS, while hospitalizations and mortality were the focus in studies of SMA, and respiratory events and NIV discontinuation in the remaining groups. The overall quality of evidence to support appropriate conclusions was low to very low for all studies included in this review.

There is a diverse range of airway disorders that may benefit from NIV therapy. Previous studies have identified many conditions that can predispose infants to upper airway obstruction, including craniofacial disorders, laryngeal disorders, and nasal obstruction (76). Similarly, in this review, we identified NIV use in a wide variety of diseases associated with compromised airway function, the most common being OSA, PRS, ALTE, infants at risk for SIDS, and LTM. The improvement in respiratory parameters reported in infants with airway disorders reflects an overall benefit from NIV therapy. In addition, the underlying airway conditions have potential for improvement, as seen with the infants discontinuing due to underlying improvements, so there may be less risk with NIV compared to invasive mechanical ventilation. Extrapolating these results to conditions with a similar pathophysiology, but for which there is no evidence for NIV use in the literature, may be reasonable given the diversity of disorders represented in the available evidence.

TABLE 4 | Studies on infants using long-term NIV reporting hospitalization and mortality outcomes.

First author, year, country	Study design	Primary diagnosis	Infants using NIV	Age, mean ± SD or med (range)	NIV type	Hospitalization (per infant/year unless otherwise stated)			Mortality (% of total infants unless otherwise stated)		
						Supportive care	NIV	IMV	Supportive care	NIV	IMV
Bach (46), 2007, USA	R; Obs: cohort	SMA1	*n* = 47	10.6 ± 5.7 months	BPAP		1.58	0.37†	100	17	19
Bach (44), 2002, USA	R; Obs: case series	SMA1	*n* = 33	11.2 ± 5.7 months	BPAP		1.53	0.58*	100	6	6
Gregoretti (51), 2013, Italy	R; Obs: case series	SMA1	*n* = 31	12.6 ± 14.4 months	BPAP		0.023	0.006	93	45	17
Ottonello (54), 2011, Italy	R; Obs: cohort	SMA1	*n* = 16	10.4 ± 6.2 months	BPAP		0.15			13	
Bach (43), 2000, USA	R; Obs: case series	SMA1	*n* = 8	3–28 months	BPAP					13	
Birnkrant (48), 1998, USA	R; Obs: case series	SMA1	*n* = 3	4–9 months	BPAP					100	
Chatwin (49), 2011, UK	R; Obs: cohort	SMA1	*n* = 13	11 months (4–24 months)	BPAP					38	
Vasconcelos (56), 2005, Portugal	R; Obs: cohort	SMA1	*n* = 7	13 months (3 months to 3 years)	BPAP					71	
Lemoine (53), 2012, USA	R; Obs: cohort	SMA1	*n* = 26	136 days (54–196)	BPAP	46%	83%		NIV group had a significantly longer survival than supportive care group ($p = 0.047$, reported narratively)		

First author, year, country	Study design	Primary diagnosis	Infants using NIV	Age, mean ± SD or med (range)	NIV type	Length of hospital stay [mean ± SD or med (range)]			Mortality (% of total infants)
						No ventilation	NIV	IMV	
Leboulanger (36), 2010, France	P; Obs: case Series	PRS	*n* = 7	2 months (1–10 months)	CPAP (*n* = 5) BPAP (*n* = 2)				

(*Continued*)

TABLE 4 | Continued

First author, year, country	Study design	Primary diagnosis	Infants using NIV	Age, mean ± SD or med (range)	NIV type	Hospitalization (per infant/year unless otherwise stated)			Mortality (% of total infants unless otherwise stated)		
						Supportive care	NIV	IMV	Supportive care	NIV	IMV
Amaddeo (31), 2016, France	R; Obs: cohort	PRS	*n* = 9	0–2 months	CPAP		1 month (20–40 days)	2 months (6 weeks to 4 months)			
Kam (35), 2015, Canada	R; Obs: cohort	PRS	*n* = 20	23 months (5 days to 8 years)	CPAP	28 ± 24 days	66 ± 46 days	138 ± 76 days†	NR		
First author, year, country	**Study design**	**Primary diagnosis**	**Infants using NIV**	**Age, mean ± SD or med (range)**	**NIV type**	**Hospitalization (per infant/year or % of total)**			**Mortality (% of total infants)**		
McNamara (27), 1995, Australia	P, Obs: cohort	OSA	*n* = 5	8–12 weeks	CPAP	–			0%		
First author, year, country	**Study design**	**Primary diagnosis**	**Infants using NIV**	**Age, mean ± SD or med (range)**	**NIV type**	**Length of hospital stay [mean ± SD or med (range)]**			**Mortality**		
						No ventilation	**NIV**	**IMV**			
Garcia Teresa (60), 2017, Spain	P, Obs: cross-sectional	CHS	n/a	11.35 (5 months to 28.6 years)	NIV		91 ± 51 days	319 ± 336 days**	*n* = 2 infants		

BPAP, bi-level positive airway pressure; IMV, invasive mechanical ventilation; NIV, non-invasive ventilation; Obs, observational study; OSA, obstructive sleep apnea; P, prospective; PRS, Pierre Robin sequence; R, retrospective; SMA1, spinal muscular atrophy type 1.

**p < 0.05.*

***p < 0.01.*

†p < 0.001.

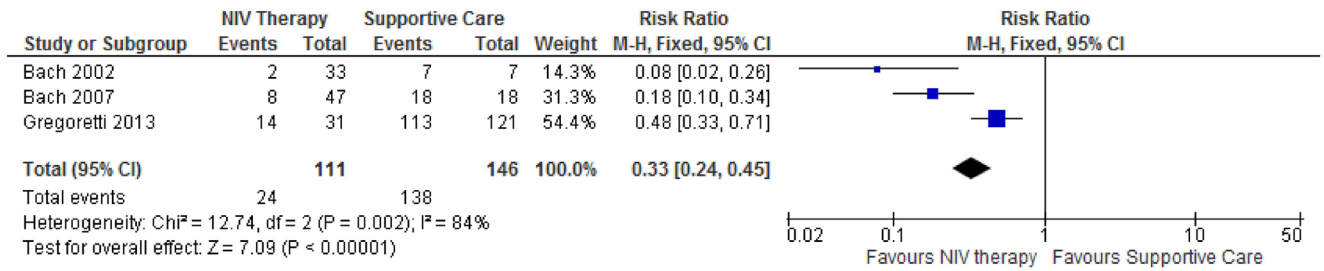

FIGURE 2 | A meta-analysis on the effect of non-invasive ventilation (NIV) on the relative risk of mortality in infants with spinal muscular atrophy. The meta-analysis shows that the relative risk of mortality is significantly lower in infants using NIV compared to infants on supportive care. This decrease may be attributed to prolonged survival in infants using long-term NIV compared to supportive care.

By contrast, extrapolation of outcomes for long-term NIV use in NMD and CNS disorders may be more challenging. The data relevant to long-term NIV use for NMD and CNS disorders are almost exclusively from two conditions: SMA1 and CHS. SMA1 is a progressively deteriorating disorder that is usually fatal during infancy. This contrasts with other NMD disorders presenting in infancy, such as congenital myopathy and congenital muscular dystrophy, which may have a better prognosis or steadier course (7, 58). The difference in prognoses of these conditions makes generalizing outcomes for NIV use in SMA1 to other NMD less appropriate. Similarly, CHS was the only CNS disorder for which data on long-term NIV use was available. NIV may be useful for other CNS disorders with accompanying respiratory compromise, such as congenital or acquired brain injury. Given the potentially unique physiology of CHS extrapolating the outcomes of NIV use for infants with CHS to other CNS conditions with different underlying respiratory pathophysiology may not be appropriate. Creation of national disease registries for infants and children using NIV will provide the opportunity to aggregate data on rare or minimally studied diseases and examine the use and outcomes of long-term NIV in these populations.

The outcomes that were reported in studies differed depending on the primary underlying disease category that was being examined. Studies of airway conditions predominantly reported on changes in respiratory parameters reported via polysomnography results and discontinuation of NIV. In addition, most studies reported short-term overnight polysomnography results; only one study had data on polysomnography results after long-term follow-up periods of NIV use in infants (29). Only one study on upper airway disorders reported on mortality outcomes (27) and none on hospitalization outcomes. Long-term outcomes, such as hospitalizations, intercurrent illness, growth and development, and quality of life warrant further study. Interestingly, studies on SMA1 predominantly reported on mortality and hospitalization outcomes, with only one study reporting on changes in respiratory parameters.

While the overall quality of the evidence available for the use of long-term NIV in infants is low to very low, there is a body of evidence that may help guide clinical practice. The reason for the low quality of the evidence included the study design and a high risk of bias due to the lack of blinding and randomization, and control for confounding variables. While these findings highlight the need for future studies of strong design and lower risk of bias, the available data still provide important information to inform treatment decisions for conditions where long-term NIV is being considered.

Limitations of the Included Studies

We identified a number of research gaps present in the studies included within this review. There was only one study that compared the efficacy of CPAP and BPAP ventilation in a cohort of infants (38). Similarly, while some studies reported mask complications (9, 21), only one compared the efficacy and practicality of different infant NIV masks (74). Only single studies were identified on the use of long-term NIV for infants with breath holding (42) and cardiac disease (66). Additionally, there were no studies on the clinical supports necessary for infants to be placed on NIV. It is important to know whether infants receive consultation and support from physicians, registered nurses, home care support, or a combination thereof, to determine whether a multidisciplinary NIV care plan is necessary for this population. The lack of comparison groups and/or homogeneity of outcomes reported precluded meta-analysis for most topics.

Additional issues relevant to long-term NIV use in infants that are not addressed in the current literature include: limitations in availability of masks and headgear; limitations in the availability of BPAP machines that are sufficiently sensitive to detect flow rates; the impact of NIV use on craniofacial growth and the impact of craniofacial growth on NIV use; comorbidities in infants using NIV; the impact of NIV on somatic growth and psychomotor development; and, most importantly, the impact of NIV use on quality of life for both infants and caregivers.

Limitations of the Review

Our review relied on the search methods and primary-level screening decisions of a scoping review on NIV in children with subsequent development of the research questions on NIV in infants. The methods to identify studies for the scoping review, however, were sufficiently inclusive to capture all relevant evidence on NIV in infants. We defined NIV for the scoping review on long-term NIV as breathing support outside the airway via an interface, consistent with the MeSH

TABLE 5 | Assessment of risk of bias in studies synthesized in the systematic review on long-term non-invasive ventilation in infants using the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool (18).

First author, year	Confounding	Selection	Measurement of intervention	Missing data	Measurement of outcomes	Selection of reported results	Overall risk of bias (RoB) assessment[a]
Obstructive sleep apnea							
Downey (20), 2000	Moderate	Moderate	Serious	Serious	Serious	Serious	Serious
Guilleminault (21), 1995	Serious	Serious	Serious	Serious	Serious	Moderate	Serious
Harrington (22), 2003	Moderate	Moderate	Serious	Moderate	Moderate	Moderate	Serious
Leonardis (23), 2013	Moderate	Serious	Moderate	Serious	Serious	Moderate	Serious
Liu (24), 2012	Serious	Serious	Moderate	Moderate	Moderate	Serious	Serious
McNamara (27), 1995	Moderate	Moderate	Moderate	Serious	Moderate	Moderate	Serious
McNamara (28), 1999a	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
McNamara (29), 1999b	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Robison (10), 2013	Moderate	Moderate	Serious	Serious	Serious	Moderate	Serious
Rosen (30), 2010	Moderate	Serious	Serious	Serious	Serious	Serious	Serious
Pierre Robin sequence							
Amaddeo (31), 2016	Serious	Serious	Serious	Moderate	Serious	Moderate	Serious
Kam (35), 2015	Moderate	Moderate	Serious	Serious	Moderate	Moderate	Serious
Leboulanger (36), 2010	Moderate	Moderate	Serious	Moderate	Moderate	Moderate	Serious
Goudy (34), 2017	Serious	Serious	Serious	Moderate	Serious	Moderate	Serious
Laryngo-tracheomalacia							
Essouri (38), 2005	Moderate	Moderate	Moderate	Moderate	Low	Low	Moderate
Fauroux (39), 2001	Moderate	Moderate	Moderate	Serious	Moderate	Moderate	Serious
Shatz (40), 2004	Moderate	Serious	Serious	Serious	Serious	Moderate	Serious
Zwacka (41), 1997	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Spinal muscular atrophy type 1							
Bach (43), 2000	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Bach (44), 2002	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Bach (46), 2007	Serious	Serious	Serious	Serious	Low	Moderate	Serious
Birnkrant (48), 1998	Serious	Serious	Serious	Moderate	Serious	Serious	Serious
Chatwin (49), 2011	Serious	Serious	Serious	Moderate	Moderate	Serious	Serious
Gregoretti (51), 2013	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Lemoine (53), 2012	Moderate	Serious	Serious	Moderate	Moderate	Moderate	Serious
Ottonello (54), 2011	Moderate	Serious	Serious	Moderate	Moderate	Moderate	Serious
Vasconcelos (56), 2005	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Congenital hypoventilation syndrome							
Hartmann (61), 1994	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Noyes (63), 1999	Serious	Serious	Serious	Serious	Serious	Serious	Serious
Ramesh (64), 2008	Moderate	Serious	Serious	Moderate	Serious	Serious	Serious
Tibballs (65), 2003	Moderate	Serious	Serious	Moderate	Serious	Serious	Serious
García Teresa (60), 2017	Serious	Serious	Serious	Moderate	Serious	Serious	Serious
Khayat (62), 2017	Serious	Serious	Serious	Moderate	Serious	Moderate	Serious

Low risk of bias—study is comparable to a well performed randomized trial within that domain. Moderate risk of bias—study is sound for a non-randomized study, but is not considered comparable to a well performed randomized trial within that domain. Serious risk of bias—study has some important problems within that domain. Critical risk of bias—the study is too problematic in this domain to provide any useful evidence on the effects of intervention. No information—no information on which to base a judgment about risk of bias within that domain.

[a]*Criteria set out by the ROBINS-I tool.*

terminology for NIV and, therefore, included CPAP as well as BPAP. Some investigators, however, do not consider CPAP as a mode of NIV because it requires spontaneous breathing from the patient (1, 77). To address this concern, we reported the different ventilation types used by infants in the tables included in this review. Finally, we defined infants as ages 0–2 years based on the Public Health Agency of Canada definition (14). Some investigators may not agree with this definition, as the Centre for Disease Control defines infants as less than one year of age (78). Regardless of the definition used, it is still unclear whether there are differences in the outcomes of pediatric NIV with respect to age. Future work should consider whether infants represent a distinct group within children using long-term NIV.

TABLE 6 | Quality assessment of outcomes of infants using long-term non-invasive ventilation using the Grading of Recommendations Assessment, Development and Evaluation criteria (19).

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias[a]	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
Obstructive sleep apnea												
Changes in respiratory parameters: respiratory gases pre-NIV to post-NIV												
5 (20, 22, 27–29)	Observational studies	Serious	Not serious	Not serious	Not serious	None	53	53			⊕⊕◯◯ low	Important
3 (10, 23, 24)	Observational studies	Serious	Not serious	Not serious	Not serious	None	–	–			⊕◯◯◯ very low	Important
Discontinuation of NIV												
5 (20, 21, 27, 28, 30)	Observational studies	Serious	Not serious	Not serious	Not serious	None	–	–			⊕⊕◯◯ low	Important
Pierre Robin sequence												
Changes in respiratory parameters: respiratory gases pre-NIV to post-NIV												
2 (31, 36)	Observational study	Serious	Not serious	Not serious	Not serious	None	–	–			⊕◯◯◯ very low	Important
Discontinuation of NIV												
2 (31, 36)	Observational studies	Serious	Not serious	Not serious	Not serious	None	–	–			⊕◯◯◯ very low	Important
Length of hospitalization												
2 (31, 35)	Observational studies	Serious	Not serious	Not serious	Not serious	None	–	–			⊕◯◯◯ very low	Important
Adherence												
2 (31, 36)	Observational studies	Serious	Not serious	Not serious	Not serious	None	–	–			⊕◯◯◯ very low	Important
Laryngo-tracheomalacia												
Changes in respiratory parameters: respiratory gases: supportive care vs. NIV												
3 (38, 39, 41)	Observational studies	Serious	Not serious	Not serious	Not serious	None	24	24			⊕⊕◯◯ low	Important
Discontinuation of NIV												
2 (39, 40)	Observational studies	Serious	Not serious	Not serious	Not serious	None	–	–			⊕◯◯◯ very low	Important
Benefit of NIV—improvement in growth parameter(s)												
1 (39)	Observational study	Serious	Not serious	Not serious	Not serious	None	–	–			⊕◯◯◯ very low	Important
Benefit of NIV—improvement in underlying condition(s)												
1 (40)	Observational study	Serious	Not serious	Not serious	Not serious	None	–	–			⊕◯◯◯ very low	Important

(*Continued*)

TABLE 6 | Continued

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Study design**	**Risk of bias[a]**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intervention**	**Control**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adherence												
1 (39)	Observational study	Serious	Not serious	Not serious	Not serious	None	–	–			⊕○○○ very low	Important
Spinal muscular atrophy type 1												
Mortality: NIV vs. supportive care												
3 (44, 46, 51)	Observational studies	Serious	Not serious	Not serious	Not serious	None	24/111 (21.6%)	138/146 (94.5%)	RR 0.37 (0.25–0.54) $z = 5.16$ $p < 0.0001$	595 fewer per 1000 (from 435 fewer to 709 fewer)	⊕⊕○○ low	Very important
6 (43, 48, 49, 53, 54, 56)	Observational studies	Serious	Not serious	Not serious	Not serious	None					⊕⊕○○ low	Very important
Hospitalization: per patient/per year												
3 (43, 46, 51)	Observational studies	Serious	Not serious	Not serious	Not serious	None	–	–			⊕⊕○○ low	Very important
3 (43, 53, 54)	Observational studies	Serious	Not serious	Not serious	Not serious	None					⊕○○○ very low	Important
Benefit of NIV—improvement in growth parameter(s)												
3 (44, 46, 54)	Observational studies	Serious	Not serious	Not serious	Not serious	None	–	–			⊕⊕○○ low	Important
Benefit of NIV—NIV facilitated extubation												
3 (43, 48, 50)	Observational study	Serious	Not serious	Not serious	Not serious	None	–	–			⊕○○○ very low	Important
Changes in respiratory parameters: respiratory gases												
1 (55)	Observational study	Moderate	Not serious	Not serious	Not serious	None	–	–			⊕⊕○○ low	Important
Congenital hypoventilation syndrome												
Changes in respiratory parameters: changes in respiratory gases post-NIV initiation												
2 (61, 65)	Observational study	Serious	Not serious	Not serious	Not serious	None	–	–			⊕⊕○○ very low	Important
Discontinuation of NIV												
2 (61, 64)	Observational studies	Serious	Not serious	Not serious	Not serious	None	–	–			⊕○○○ very low	Important
Benefit of NIV—improvement in growth parameter(s)												
2 (61, 63)	Observational studies	Serious	Not serious	Not serious	Not serious	None	–	–			⊕○○○ very low	Important

(*Continued*)

TABLE 6 | Continued

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias[a]	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute (95% CI)		
Mask complication(s)												
2 (64, 65)	Observational studies	Serious	Not serious	Not serious	Not serious	None	–	–			⊕OOO very low	Important
Adherence												
1 (61)	Observational study	Serious	Not serious	Not serious	Not serious	None	–	–			⊕OOO very low	Important

CI, confidence interval; n/a, data not available; NIV, non-invasive ventilation; RR, risk ratio.

CONCLUSION

This systematic review examines the use and outcomes of long-term NIV in infants across a range of respiratory and sleep disorders. Improvements in respiratory parameters and discontinuation from NIV due to improvement in underlying conditions have been shown for a broad range of upper airway disorders, such as OSA, PRS, and LTM, in infants. Long-term NIV use in infants with SMA1 decreased hospitalizations and prolonged survival compared to infants on supportive care. Infants with CHS may also show improvements in respiratory parameters after using NIV and potentially avoid tracheostomy. NIV appears to be a feasible method of providing long-term respiratory support for infants with a wide range of underlying conditions; however, several methodological weaknesses limit any strong categorical conclusions. The findings of this systematic review are relevant to a broad range of stakeholders and can be used to help guide clinicians on the use of long-term NIV in infants.

AUTHOR CONTRIBUTIONS

PB conceptualized and designed the review, assessed articles for inclusion, extracted and analyzed data, interpreted the data, drafted the initial manuscript, and completed all subsequent revisions until submission. MC conceptualized and designed the review, assessed articles for inclusion, verified data extraction, and critically reviewed the manuscript. RF developed the search strategy, carried out the literature searches, and critically reviewed the manuscript. MA and BA assessed articles for inclusion, and critically reviewed the manuscript. AK provided guidance on study design and critically reviewed the manuscript. CF provided guidance on study design and review methodology and critically reviewed the manuscript. JM conceptualized and designed the review, assessed articles for inclusion, verified data extraction, interpreted the data, and critically reviewed the manuscript. All authors reviewed the manuscript and approved the final manuscript for submission.

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REFERENCES

1. Amin R, Sayal P, Syed F, Chaves A, Moraes TJ, MacLusky I. Pediatric long-term home mechanical ventilation: twenty years of follow-up from one Canadian center. *Pediatr Pulmonol* (2014) 49(8):816–24. doi:10.1002/ppul.22868
2. McDougall CM, Adderley RJ, Wensley DF, Seear MD. Long-term ventilation in children: longitudinal trends and outcomes. *Arch Dis Child* (2013) 98(9):660–5. doi:10.1136/archdischild-2012-303062
3. Amaddeo A, Moreau J, Frapin A, Khirani S, Felix O, Fernandez-Bolanos M, et al. Long term continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) in children: initiation criteria in real life. *Pediatr Pulmonol* (2016) 51(9):968–74. doi:10.1002/ppul.23416
4. Katz S, Selvadurai H, Keilty K, Mitchell M, MacLusky I. Outcome of non-invasive positive pressure ventilation in paediatric neuromuscular disease. *Arch Dis Child* (2004) 89(2):121–4. doi:10.1136/adc.2002.018655
5. Simonds AK, Ward S, Heather S, Bush A, Muntoni F. Outcome of paediatric domiciliary mask ventilation in neuromuscular and skeletal disease. *Eur Respir J* (2000) 16(3):476–81. doi:10.1034/j.1399-3003.2000.016003476.x
6. Jardine E, O'Toole M, Paton JY, Wallis C. Current status of long term ventilation of children in the United Kingdom: questionnaire survey. *BMJ* (1999) 318(7179):295–9. doi:10.1136/bmj.318.7179.295
7. Chatwin M, Tan HL, Bush A, Rosenthal M, Simonds AK. Long term non-invasive ventilation in children: impact on survival and transition to adult care. *PLoS One* (2015) 10(5):e0125839. doi:10.1371/journal.pone.0125839
8. Castro-Codesal ML, Dehaan K, Featherstone R, Bedi PK, Martinez Carrasco C, Katz SL, et al. Long-term non-invasive ventilation therapies in children: a scoping review. *Sleep Med Rev* (2018) 37:148–58. doi:10.1016/j.smrv.2017.02.005
9. Markstrom A, Sundell K, Stenberg N, Katz-Salamon M. Long-term non-invasive positive airway pressure ventilation in infants. *Acta Paediatr* (2008) 97(12):1658–62. doi:10.1111/j.1651-2227.2008.00990.x
10. Robison JG, Wilson C, Otteson TD, Chakravorty SS, Mehta DK. Analysis of outcomes in treatment of obstructive sleep apnea in infants. *Laryngoscope* (2013) 123(9):2306–14. doi:10.1002/lary.23685
11. MacLean JE, Fitzgerald DA, Waters KA. Developmental changes in sleep and breathing across infancy and childhood. *Paediatr Respir Rev* (2015) 16(4):276–84. doi:10.1016/j.prrv.2015.08.002
12. Iglowstein I, Jenni OG, Molinari L, Largo RH. Sleep duration from infancy to adolescence: reference values and generational trends. *Pediatrics* (2003) 111(2):302–7. doi:10.1542/peds.111.2.302
13. Marcus CL. Sleep-disordered breathing in children. *Am J Respir Crit Care Med* (2001) 164(1):16–30. doi:10.1164/ajrccm.164.1.2008171
14. *Infancy (Birth – Two Years of Age)*. Public Health Agency of Canada (2016). Available from http://www.phac-aspc.gc.ca/hp-ps/dca-dea/stages-etapes/childhood-enfance_0-2/index-eng.php
15. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* (2009) 339:b2535. doi:10.1136/bmj.b2535
16. Bedi PK, Castro-Codesal ML, Featherstone R, AlBalawi MA, Alkhaledi B, Kozyrskyj A, et al. Long-term non-invasive ventilation in infants: a systematic review. *PROSPERO 2016:CRD42016051302*. (2016). Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016051302
17. Castro-Codesal ML, Featherstone R, Martinez Carrasco C, Katz SL, Chan EY, Bendiak GN, et al. Long-term non-invasive ventilation therapies in children: a scoping review protocol. *BMJ Open* (2015) 5(8):e008697. doi:10.1136/bmjopen-2015-008697
18. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* (2016) 355:i4919. doi:10.1136/bmj.i4919
19. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* (2008) 336(7650):924–6. doi:10.1136/bmj.39489.470347.AD
20. Downey R III, Perkin RM, MacQuarrie J. Nasal continuous positive airway pressure use in children with obstructive sleep apnea younger than 2 years of age. *Chest* (2000) 117(6):1608–12. doi:10.1378/chest.117.6.1608
21. Guilleminault C, Pelayo R, Clerk A, Leger D, Bocian RC. Home nasal continuous positive airway pressure in infants with sleep-disordered breathing. *J Pediatr* (1995) 127(6):905–12. doi:10.1016/S0022-3476(95)70026-9
22. Harrington C, Kirjavainen T, Teng A, Sullivan CE. nCPAP improves abnormal autonomic function in at-risk-for-SIDS infants with OSA. *J Appl Physiol* (2003) 95(4):1591–7. doi:10.1152/japplphysiol.00354.2002
23. Leonardis RL, Robison JG, Otteson TD. Evaluating the management of obstructive sleep apnea in neonates and infants. *JAMA Otolaryngol Head Neck Surg* (2013) 139(2):139–46. doi:10.1001/jamaoto.2013.1331
24. Liu D, Zhou J, Liang X, Huang Z, Tan Z, Zhong J. Remote monitoring of home-based noninvasive ventilation in children with obstructive sleep apnea-hypopnea syndrome. *Sleep Breath* (2012) 16(2):317–28. doi:10.1007/s11325-011-0516-y
25. Marcus CL, Ward SL, Mallory GB, Rosen CL, Beckerman RC, Weese-Mayer DE, et al. Use of nasal continuous positive airway pressure as treatment of childhood obstructive sleep apnea. *J Pediatr* (1995) 127(1):88–94. doi:10.1016/S0022-3476(95)70262-8
26. Massa F, Gonsalez S, Laverty A, Wallis C, Lane R. The use of nasal continuous positive airway pressure to treat obstructive sleep apnoea. *Arch Dis Child* (2002) 87(5):438–43. doi:10.1136/adc.87.5.438
27. McNamara F, Harris MA, Sullivan CE. Effects of nasal continuous positive airway pressure on apnoea index and sleep in infants. *J Paediatr Child Health* (1995) 31(2):88–94. doi:10.1111/j.1440-1754.1995.tb00753.x
28. McNamara F, Sullivan CE. Effects of nasal CPAP therapy on respiratory and spontaneous arousals in infants with OSA. *J Appl Physiol* (1999) 87(3):889–96. doi:10.1152/jappl.1999.87.3.889
29. McNamara F, Sullivan CE. Obstructive sleep apnea in infants and its management with nasal continuous positive airway pressure. *Chest* (1999) 116(1):10–6. doi:10.1378/chest.116.1.10
30. Rosen D. Some infants with Down syndrome spontaneously outgrow their obstructive sleep apnea. *Clin Pediatr (Phila)* (2010) 49(11):1068–71. doi:10.1177/0009922810378037
31. Amaddeo A, Abadie V, Chalouhi C, Kadlub N, Frapin A, Lapillonne A, et al. Continuous positive airway pressure for upper airway obstruction in infants with Pierre Robin sequence. *Plast Reconstr Surg* (2016) 137(2):609–12. doi:10.1097/01.prs.0000475799.07597.23
32. Cheng ATL, Corke M, Loughran-Fowlds A, Birman C, Hayward P, Waters KA. Distraction osteogenesis and glossopexy for Robin sequence with airway obstruction. *ANZ J Surg* (2011) 81(5):320–5. doi:10.1111/j.1445-2197.2010.05588.x
33. Daniel M, Bailey S, Walker K, Hensley R, Kol-Castro C, Badawi N, et al. Airway, feeding and growth in infants with Robin sequence and sleep apnoea. *Int J Pediatr Otorhinolaryngol* (2013) 77(4):499–503. doi:10.1016/j.ijporl.2012.12.019
34. Goudy S, Jiramongolchai P, Chinnadurai S. Logistic regression analysis of Pierre Robin sequence patients requiring surgical intervention. *Laryngoscope* (2017) 127(4):945–9. doi:10.1002/lary.26143
35. Kam K, McKay M, MacLean J, Witmans M, Spier S, Mitchell I. Surgical versus nonsurgical interventions to relieve upper airway obstruction in children with Pierre Robin sequence. *Can Respir J* (2015) 22(3):171–5. doi:10.1155/2015/798076
36. Leboulanger N, Picard A, Soupre V, Aubertin G, Denoyelle F, Galliani E, et al. Physiologic and clinical benefits of noninvasive ventilation in infants with Pierre Robin sequence. *Pediatrics* (2010) 126(5):e1056–63. doi:10.1542/peds.2010-0856
37. Muller-Hagedorn S, Buchenau W, Arand J, Bacher M, Poets CF. Treatment of infants with Syndromic Robin sequence with modified palatal plates: a minimally invasive treatment option. *Head Face Med* (2017) 13(1):4. doi:10.1186/s13005-017-0137-1
38. Essouri S, Nicot F, Clément A, Garabedian EN, Roger G, Lofaso F, et al. Noninvasive positive pressure ventilation in infants with upper airway obstruction: comparison of continuous and bilevel positive pressure. *Intensive Care Med* (2005) 31(4):574–80. doi:10.1007/s00134-005-2568-6
39. Fauroux B, Pigeot J, Polkey MI, Roger G, Boulé M, Clément A, et al. Chronic stridor caused by laryngomalacia in children: work of breathing and effects of noninvasive ventilatory assistance. *Am J Respir Crit Care Med* (2001) 164(10 Pt 1):1874–8. doi:10.1164/ajrccm.164.10.2012141
40. Shatz A, Goldberg S, Picard E, Kerem E. Pharyngeal wall collapse and multiple synchronous airway lesions. *Ann Otol Rhinol Laryngol* (2004) 113(6):483–7. doi:10.1177/000348940411300613
41. Zwacka G, Scholle S, Kemper G, Rieger B. Nasal CPAP therapy for infants with congenital stridor. *Sleep Breath* (1997) 2(4):85–97.

42. Guilleminault C, Huang Y-S, Chan A, Hagen CC. Cyanotic breath-holding spells in children respond to adenotonsillectomy for sleep-disordered breathing. *J Sleep Res* (2007) 16(4):406–13. doi:10.1111/j.1365-2869.2007.00605.x
43. Bach JR, Niranjan V, Weaver B. Spinal muscular atrophy type 1: a noninvasive respiratory management approach. *Chest* (2000) 117(4):1100–5. doi:10.1378/chest.117.4.1100
44. Bach JR, Baird JS, Plosky D, Navado J, Weaver B. Spinal muscular atrophy type 1: management and outcomes. *Pediatr Pulmonol* (2002) 34(1):16–22. doi:10.1002/ppul.10110
45. Bach JR, Bianchi C. Prevention of pectus excavatum for children with spinal muscular atrophy type 1. *Am J Phys Med Rehabil* (2003) 82(10):815–9. doi:10.1097/01.PHM.0000083669.22483.04
46. Bach JR, Saltstein K, Sinquee D, Weaver B, Komaroff E. Long-term survival in Werdnig-Hoffmann disease. *Am J Phys Med Rehabil* (2007) 86(5):339–345; quiz 346–338, 379. doi:10.1097/PHM.0b013e31804a8505
47. Barnérias C, Quijano S, Mayer M, Estournet B, Cuisset JM, Sukno S, et al. [Multicentric study of medical care and practices in spinal muscular atrophy type 1 over two 10-year periods]. *Arch Pediatr* (2014) 21(4):347–54. doi:10.1016/j.arcped.2014.01.017
48. Birnkrant DJ, Pope JF, Martin JE, Repucci AH, Eiben RM. Treatment of type I spinal muscular atrophy with noninvasive ventilation and gastrostomy feeding. *Pediatr Neurol* (1998) 18(5):407–10. doi:10.1016/S0887-8994(97)00227-0
49. Chatwin M, Bush A, Simonds AK. Outcome of goal-directed non-invasive ventilation and mechanical insufflation/exsufflation in spinal muscular atrophy type I. *Arch Dis Child* (2011) 96(5):426–32. doi:10.1136/adc.2009.177832
50. Ednick M, Wong B, Inge T, Knue M, Kalra M. Post-operative respiratory outcomes using a standard extubation protocol after elective gastrostomy tube placement in pediatric patients with spinal muscular atrophy type 1. *J Pe1diatr Neurol* (2008) 6(3):249–52. doi:10.1055/s-0035-1557467
51. Gregoretti C, Ottonello G, Chiarini Testa MB, Mastella C, Ravà L, Bignamini E, et al. Survival of patients with spinal muscular atrophy type 1. *Pediatrics* (2013) 131(5):e1509–14. doi:10.1542/peds.2012-2278
52. Ioos C, Leclair-Richard D, Mrad S, Barois A, Estournet-Mathiaud B. Respiratory capacity course in patients with infantile spinal muscular atrophy. *Chest* (2004) 126(3):831–7. doi:10.1378/chest.126.3.831
53. Lemoine TJ, Swoboda KJ, Bratton SL, Holubkov R, Mundorff M, Srivastava R. Spinal muscular atrophy type 1: are proactive respiratory interventions associated with longer survival? *Pediatr Crit Care Med* (2012) 13(3):e161–5. doi:10.1097/PCC.0b013e3182388ad1
54. Ottonello G, Mastella C, Franceschi A, Bosticco D, Wolfler A, Pedemonte M, et al. Spinal muscular atrophy type 1: avoidance of hospitalization by respiratory muscle support. *Am J Phys Med Rehabil* (2011) 90(11):895–900. doi:10.1097/PHM.0b013e318232883a
55. Petrone A, Pavone M, Testa MBC, Petreschi F, Bertini E, Cutrera R. Noninvasive ventilation in children with spinal muscular atrophy types 1 and 2. *Am J Phys Med Rehabil* (2007) 86(3):216–21. doi:10.1097/PHM.0b013e31802ef774
56. Vasconcelos M, Fineza I, Felix M, Estevao MH. Spinal muscular atrophy – noninvasive ventilatory support in pediatrics. *Rev Port Pneumol* (2005) 11(5):443–55. doi:10.1016/S0873-2159(15)30520-1
57. Afsharpaiman S, Sillence DO, Sheikhvatan M, Ault JE, Waters K. Respiratory events and obstructive sleep apnea in children with achondroplasia: investigation and treatment outcomes. *Sleep Breath* (2011) 15(4):755–61. doi:10.1007/s11325-010-0432-6
58. Han YJ, Park JD, Lee B, Choi YH, Suh DI, Lim BC, et al. Home mechanical ventilation in childhood-onset hereditary neuromuscular diseases: 13 years' experience at a single center in Korea. *PLoS One* (2015) 10(3):e0122346. doi:10.1371/journal.pone.0122346
59. Wood L, Cordts I, Atalaia A, Marini-Bettolo C, Maddison P, Phillips M, et al. The UK myotonic dystrophy patient registry: facilitating and accelerating clinical research. *J Neurol* (2017) 264(5):979–88. doi:10.1007/s00415-017-8483-2
60. García Teresa MA, Porto Abal R, Rodríguez Torres S, García Urabayen D, García Martínez S, Trang H, et al. [Spanish patients with central hypoventilation syndrome included in the European Registry. The 2015 data]. *An Pediatr* (2017) 86(5):255–63. doi:10.1016/j.anpedi.2016.05.008
61. Hartmann H, Jawad MH, Noyes J, Samuels MP, Southall DP. Negative extrathoracic pressure ventilation in central hypoventilation syndrome. *Arch Dis Child* (1994) 70(5):418–23. doi:10.1136/adc.70.5.418
62. Khayat A, Medin D, Syed F, Moraes TJ, Bin-Hasan S, Narang I, et al. Intelligent volume-assured pressured support (iVAPS) for the treatment of congenital central hypoventilation syndrome. *Sleep Breath* (2017) 21(2):513–9. doi:10.1007/s11325-017-1478-5
63. Noyes J, Hartmann H, Samuels M, Southall D. The experiences and views of parents who care for ventilator-dependent children. *J Clin Nurs* (1999) 8(4):440–50. doi:10.1046/j.1365-2702.1999.00258.x
64. Ramesh P, Boit P, Samuels M. Mask ventilation in the early management of congenital central hypoventilation syndrome. *Arch Dis Child Fetal Neonatal Ed* (2008) 93(6):F400–3. doi:10.1136/adc.2008.139931
65. Tibballs J, Henning RD. Noninvasive ventilatory strategies in the management of a newborn infant and three children with congenital central, hypoventilation syndrome. *Pediatr Pulmonol* (2003) 36(6):544–8. doi:10.1002/ppul.10392
66. Bunn HJ, Roberts P, Thomson AH. Noninvasive ventilation for the management of pulmonary hypertension associated with congenital heart disease in children. *Pediatr Cardiol* (2004) 25(4):357–9. doi:10.1007/s00246-003-0501-8
67. Adeleye A, Ho A, Nettel-Aguirre A, Buchhalter J, Kirk V. Noninvasive positive airway pressure treatment in children less than 12 months of age. *Can Respir J* (2016) 2016:7654631. doi:10.1155/2016/7654631
68. Bertrand P, Fehlmann E, Lizama M, Holmgren N, Silva M, Sanchez I. [Home ventilatory assistance in Chilean children: 12 years' experience]. *Arch Bronconeumol* (2006) 42(4):165–70. doi:10.1157/13086621
69. Fauroux B, Lavis JF, Nicot F, Picard A, Boelle PY, Clément A, et al. Facial side effects during noninvasive positive pressure ventilation in children. *Intensive Care Med* (2005) 31(7):965–9. doi:10.1007/s00134-005-2669-2
70. Kherani T, Sayal A, Al-Saleh S, Sayal P, Amin R. A comparison of invasive and noninvasive ventilation in children less than 1 year of age: a long-term follow-up study. *Pediatr Pulmonol* (2016) 51(2):189–95. doi:10.1002/ppul.23229
71. Koontz KL, Slifer KJ, Cataldo MD, Marcus CL. Improving pediatric compliance with positive airway pressure therapy: the impact of behavioral intervention. *Sleep* (2003) 26(8):1010–5. doi:10.1093/sleep/26.8.1010
72. Machaalani R, Evans CA, Waters KA. Objective adherence to positive airway pressure therapy in an Australian paediatric cohort. *Sleep Breath* (2016) 20(4):1327–36. doi:10.1007/s11325-016-1400-6
73. Nathan AM, Loo HY, de Bruyne JA, Eg KP, Kee SY, Thavagnanam S, et al. Thirteen years of invasive and noninvasive home ventilation for children in a developing country: a retrospective study. *Pediatr Pulmonol* (2017) 52(4):500–7. doi:10.1002/ppul.23569
74. Ramirez A, Delord V, Khirani S, Leroux K, Cassier S, Kadlub N, et al. Interfaces for long-term noninvasive positive pressure ventilation in children. *Intensive Care Med* (2012) 38(4):655–62. doi:10.1007/s00134-012-2516-1
75. Zhou J, Liu DB, Zhong JW, Huang ZY, Qiu SY, Zhou YP, et al. Feasibility of a remote monitoring system for home-based non-invasive positive pressure ventilation of children and infants (Provisional abstract). *Int J Pediatr Otorhinolaryngol* (2012) 76(12):1737–40. doi:10.1016/j.ijporl.2012.08.012
76. Katz ES, Mitchell RB, D'Ambrosio CM. Obstructive sleep apnea in infants. *Am J Respir Crit Care Med* (2012) 185(8):805–16. doi:10.1164/rccm.201108-1455CI
77. Amaddeo A, Caldarelli V, Fernandez-Bolanos M, Moreau J, Ramirez A, Khirani S, et al. Polygraphic respiratory events during sleep in children treated with home continuous positive airway pressure: description and clinical consequences. *Sleep Med* (2015) 16(1):107–12. doi:10.1016/j.sleep.2014.07.030
78. Centres for Disease Control and Prevention. *Child Development: Infants (0-1 Year of Age)*. (2017). Available from: https://www.cdc.gov/ncbddd/childdevelopment/positiveparenting/infants.html

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Association of Asthma and Allergic Rhinitis With Sleep-Disordered Breathing in Childhood

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Objective: Asthma and allergic rhinitis (AR) are the most common chronic conditions in childhood and have previously been linked to sleep-related breathing disorder (SRBD). Aim of the study was to examine the association between SRBD risk and asthma control in children with asthma and with or without AR.

Methods: The assessment of FeNO and pulmonary function tests were performed in 140 children (65 with asthma, 57 with both asthma, and AR, 18 with only AR). Children with asthma completed the childhood Asthma Control Test (c-ACT), and the Sleep-Related Breathing Disorder scale, extracted from the Pediatric Sleep Questionnaire (PSQ). C-ACT scores $\leq$ 19 are indicative of poor asthma control whereas SRBD from PSQ scores $\geq$ 0.33 are suggestive of high risk for SRBD.

Results: Mean age $\pm$ SD was 7.8 $\pm$ 3.1 years. Mean PSQ $\pm$ SD and c-ACT $\pm$ SD scores were 0.17 $\pm$ 0.14 and 24.9 $\pm$ 3.2, respectively. High risk for SRBD was identified in 26 children. Children at high risk for SRBD had significantly decreased c-ACT score ($P = 0.048$), verified by a negative association between c-ACT and PSQ-SRBD scores ($r = -0.356$, $P < 0.001$). Additionally a difference in diagnosis distribution between children at high or low risk for SRBD was observed. More specifically, among children at high risk, 88.5% were diagnosed with both atopic conditions, while this percentage among children at low risk was 29.8%. Asthma was mainly diagnosed in the latter group ($P < 0.001$).

Conclusions: Poor asthma control is associated with SRBD. The presence of AR in children with asthma seems to increase the prevalence of SRBD in that particular population, requiring further investigation toward this direction.

Keywords: asthma, children, allergic rhinitis, sleep-related breathing disorder, pediatric sleep questionnaire

INTRODUCTION

Asthma is the most common chronic disease among children and has a significant financial impact in the Western world, especially in European countries (1), asserting that asthma control is of cardinal importance for public health. Management of symptoms and comorbidities are of fundamental importance for disease control (2). There is considerable evidence to support the interdependence of lower and upper airway; thus the umbrella term "united airway disease" is opportune. Epidemiological data indicate a correlation between allergic rhinitis (AR) and asthma (3, 4). Children with asthma and AR, exhibit poorer asthma control, reduced quality of life, increased risk for emergency visits, or hospitalizations, and higher health care burden (5, 6).

The link among asthma and sleep-related breathing disorder (SRBD) is bidirectional due to common risk contributors that, finally, induce airway inflammation (7, 8). SRBD in children with asthma may lead to difficult-to-control asthma. A recent study showed that SRBD is a robust risk factor for not-well-controlled asthma; through multivariate logistic regression analysis, the researchers have shown that the coexistence of SRBD and tonsillar hypertrophy were independent risk factors for not-well-controlled asthma after adjusting for other established factors to asthma control (9).

AR and SRBD in children are firmly related, and each medical condition can be detrimental to the other. Thusly, clinicians should be alert to the possibility of AR in patients with SRBD and vice versa. AR may influence sleep by several mechanisms. Nasal congestion due to the nasal mucosa allergic inflammatory procedure promotes increased airway resistance and may lead to oral breathing pattern, sleep fragmentation and excessive fatigue (10). Furthermore, inflammatory mediators of the allergic process could affect straightly the central nervous system by changing sleep circadian rhythm (10). It has been currently noticed, that the existence of AR in children with sleep disorders decreases Rapid Eye Movement (REM) sleep duration (11). In a recent study of children with moderate-to-severe persistent AR, even when submitted to treatment, demonstrated a higher prevalence of sleep disorders than the control group, principally night-time breathing disorders, daytime sleepiness, and parasomnias (12). In another, multicenter study, accomplished in various Latin-American centers, it was revealed that children with asthma and/or AR had a higher prevalence of sleep disorders in comparison to healthy controls (13).

Current asthma guidelines strongly emphasizes the importance of disease control assessment tools; yet, the monitoring of asthma control represents a major bottleneck for primary care physicians due to its multidimensional nature (14). Regarding children's, the childhood Asthma Control Test (c-ACT) is in alignment with asthma guidelines and represents one of the most extensively validated prognostic modality tools (15). FeNO is an important parameter of asthma management since many specialists have been using treatments applied in accordance to inflammatory markers, such as FeNO (16, 17). A recent meta-analysis suggests that using FeNO to guide treatment decisions may result in a lower rate of exacerbations, however it has trivial clinical advantage and the authors concluded that guideline-based asthma management and diagnosis constitute the optimal option (18).

Sleep disturbances occur frequently during childhood, affecting 15 to 30% of preschool children (19), and leading to a worldwide recognition as a crucial public health issue (20, 21). On top of that, the number of childhood sleep questionnaires has dramatically increased over the past few years (22). However, only a few have been validated by using standardized psychometric criteria, including the broadly used Pediatric Questionnaire for Sleep (PSQ) (23) and the SRBD-Scale, extracted from the PSQ (23).

The purpose of this preliminary study was to examine the association between SRBD risk and asthma control in children with asthma and with or without AR. As assessed by the following readout assays: (1) SRBD-Scale of PSQ, (2) levels of FeNO using the joint ATS/ERS guidelines (24).

METHODS

Patients

The participants were consecutive individuals, aged between 4 and nearly 12 years, who suffered from asthma, AR or both disease entities. All of them had visited the Asthma Outpatient Unit of a tertiary hospital in Greece, as part of their routine follow-up, within 11 months, during the period between February 2014 and January 2015.

Asthma was usually suspected based on a typical history taken from every child, followed by pre/post bronchodilator spirometry test. To diagnose asthma in school-aged children (5 years and older) we used the ATS/ERS recommendations (25). For the younger, preschool children, the diagnosis was suspected based on the NHLBI's asthma research networks instructions, considering a positive modified asthma predictive index (API) if the child had experienced at least 4 exacerbations of wheezing in the past year, each episode lasting more than 24 h, and the following major or minor criteria: one of the major criteria; parental physician diagnosed asthma, physician diagnosed atopic dermatitis, evidence of sensitization to one or more aeroallergen, (i.e., positive skin tests or blood tests to allergens such as grasses), or two minor criteria; wheezing apart from colds, peripheral blood eosinophils $\geq$4%, evidence of food allergies (26, 27). The diagnosis was also confirmed by treatment responses. The diagnosis of AR was performed according ARIA guidelines (28). Findings of AR were consistent with one or more of the following symptoms nasal congestion, runny nose, itchy nose, and sneezing, red and watery eyes.

Children with chronic conditions, other than atopic diseases, essentially craniofacial abnormalities, neuromuscular disorders and/or genetic syndromes and children on any regular medication, other than long term control or short term asthma and AR medications, were excluded. Similarly, children who either they or their parents had been unable to communicate in Greek, and who have expressed a reluctance to participate were also excluded from the study.

The study protocol has been approved by the institutional board of ethics, and parental consent has been obtained for

participation in the study, after being informed for the study goals.

Procedures

Comprehensive medical history was taken from all participants. Informations were collected on exacerbation frequency, night-time symptoms, use of inhaled bronchodilators or corticosteroids, and history of any previous inpatient hospitalization due to asthma. A physical examination was also been performed.

Additionally, anthropometric parameters were determined. The BMI z-score, according to the age and sex of each subject, was calculated (29). The respiratory function was evaluated by performing spirometry as previously recommended and described (2). Furthermore, FeNO was assessed using a conventional chemiluminescence FeNO analyser (ANALYZER CLD 88sp, ECO MEDICS, Switzerland) (24). All the above mentioned procedures have been adhered to standard biosecurity and institutional safety procedures.

Questionnaires

The 22-item SRBD subscale, extracted from the PSQ, was filled out by parents. We have used a Greek, non-validated version. The PSQ-SRBD questionnaire is assessing the presence of high risk for respiratory sleep disorders in children aged 2 to 18 years (30). The exported final score ranges from 0 to 1. Total scores ≥ 0.33 are considered positive and suggestive of high risk for pediatric SRBD (30).

A special version of ACT for children aged older than 4 and younger than 12 years, the c-ACT, complemented by parents and children with asthma (15). A list of c-ACT translations exists, but not all the listed questionnaires have undergone a full linguistic validation process. The Greek version of c-ACT is not validated. The c-ACT is divided into two separated parts; the first part is supplemented by the child and consists of four images. The gradation of the responses from the first part ranges from 0 to 3. The second part is answered by the escorting parent or guardian and consists of three other components ranging from 0 to 5. The total score of c-ACT is the sum of all responses, ranging from 0 which corresponds to the poorest asthma control, up to the value 27 which represents the optimal control of asthma (15). A value $\leq$19 indicates uncontrolled asthma.

Statistical Analysis

All data were checked for normality with the Kolmogorov-Smirnov test. For normally distributed variables, parametric statistics were used; conversely, nonparametric statistics were used when the distribution of data was not normal. All continuous variables are expressed as mean $\pm$ SD, at parametric statistics; and median and range (min, max) at nonparametric statistics. Correlations were investigated with Pearson or Spearman coefficient depending on the normality of the distribution. Significance was defined at the 5% level ($P < 0.05$). Analysis was performed using SPSS version 17 (IBM SPSS).

RESULTS

Out of a total consecutive 158 children who visited the Asthma Outpatient Unit of the University Pediatric Clinic during study, 140 met the inclusion criteria and, therefore, constituted the study sample. Among all participants, 65 had asthma alone, 57 had both asthma and AR, and 18 had AR alone. In particular, from the 18 excluded children; 3 were suffering from chronic conditions, other than atopic diseases, 5 had communication issues and 10 were excluded due to their parents' unwillingness to take part in the study.

Baseline characteristics of the studied population are listed in **Table 1**. The majority of subjects were boys ($n = 89$, 63.6%), and had the following characteristics: mean age $\pm$ SD 7.8 $\pm$ 3.1 years, mean PSQ result $\pm$ SD 0.17 $\pm$ 0.14, mean c-ACT score $\pm$ SD 24.9 $\pm$ 3.2, and a mean BMI z-score $\pm$ SD 0.97 $\pm$ 0.99. All children had normal lung function values.

Twenty six children were identified as high risk for SRBD group (mean PSQ $\pm$ SD 0.4 $\pm$ 0.08). Comparison between these 26 children and children with normal PSQ rating did not reveal statistically important differences in terms of age ($P = 0.858$), FeNO value ($P = 0{,}613$), or pulmonary function tests (**Table 2**).

We performed a statistical analysis (t-test), comparing children with poor asthma control (c-ACT$\leq$19; $n = 9$) with children with adequate/good control (c-ACT >19; $n = 113$) in terms of PSQ-SRBD scores. The results were the following: In children with poor asthma control (c-ACT score = 16.5 $\pm$ 2.46): PSQ-SRBD 0.308 $\pm$ 0.183; in children with good asthma control (c-ACT score = 25.4 $\pm$ 2.21): PSQ-SRBD 0.158 $\pm$ 0.136 ($P = 0.002$). Of note, total scores $\geq$ 0.33 are considered positive and suggestive of high risk for pediatric SRBD. This analysis indicated that in poor asthma control PSQ-SRBD values are higher and tend to show positive SRBD A limitation in this analysis was the very small number, only 9, of children with c-ACT $\leq$19.

TABLE 1 | General characteristics of the enrolled children.

Characteristics	Mean	Standard deviation
Age (years)	7.8	3.1
PSQ-SRBD result	0.17	0.14
ACT score	24.9	3.2
BMI (Kg/m^2)	19.1	3.3
BMI z-score	0.97	0.99
FVC (%pred)	93	12.3
FEV_1 (%pred)	101.8	14.2
PEF (%pred)	86.8	15.6
FEF25-75 (%pred)	103.9	23.5
FeNO50 (ppb.10^{-9})	50.4	70
NO alveolar	3.1	1.7
NO bronchial	3598.1	4780.9

BMI, Body Mass Index; c-ACT, childhood-Asthma Control Test; FEF25-75, Forced Expiratory Flow between 25 and 75% of vital capacity; FeNO50, Fractional Exhaled Nitric Oxide measured at a flow rate of 50 mL/s; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; NO, Nitric Oxide; PEF, Peak Expiratory Flow; PSQ, Pediatric Sleep Questionnaire; %pred, % predicted value; ppb, parts-per-billion, 10^{-9}.

TABLE 2 | Differences between children with high/low risk for SRBD.

Characteristics	High risk ($n = 26$)	Low risk ($n = 114$)	*P* value
Age (mean ± SD)	7.8 ± 3.3	7.9 ± 3.1	0.858
BMI (mean ± SD)	18.1 ± 2.4	19.3 ± 3.5	0.105
FVC (mean ± SD)	90.3 ± 12.4	93.7 ± 12.2	0.251
FEV_1 (mean ± SD)	99.9 ± 12.2	102.2 ± 14.6	0.487
PEF (mean ± SD)	86.6 ± 16.3	86.8 ± 15.5	0.961
FEF25-75 (mean ± SD)	105.9 ± 19.2	103.4 ± 24.6	0.655

BMI, Body Mass Index; FEF25-75, Forced Expiratory Flow between 25 and 75% of vital capacity; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; PEF, Peak Expiratory Flow.

A statistically significant difference was noticed in mean values of c-ACT between the two subgroups (25.1 ± 3.1 vs. 23.7 ± 3.5, $P = 0.048$), reporting a correlation between asthma control and less likelihood of SRBD. The difference between them is small, with a *P*-value of 0.048, which, although is statistically significant, is very close to 0.05. We have the impression, however, that this difference is indicative of a trend toward poorer asthma control in children with SRBD, which could be more powerfully verified by studies including larger samples. At the same time, a negative linear correlation was found between the c-ACT and PSQ-SRBD scores ($r = -0.356$, $r^2 = 0.127$, $P < 0.001$; **Figure 1**).

Finally, a statistically significant difference was found in the diagnosis distribution of either asthma or AR or simultaneous presence of the two conditions between the two subgroups of children with high or low risk for SRBD. Specifically, in the subgroup of children with high risk for SRBD, the majority ($n = 23$, 88.5%) were simultaneously diagnosed with asthma and AR, only two were suffering from asthma alone, while only one from AR alone. In contrast, the rate of coexistence of both atopic diseases among children with low PSQ-SRBD score was 29.8% ($P < 0.001$; **Figure 2**). The percentage of children in high risk for SRBD ($n = 26$) in the whole group of participants ($n = 140$) was 18.5%.

DISCUSSION

In the present study we have demonstrated that poor asthma control is associated with high risk for SRBD in children. Additionally, among the majority of children with high risk for SRBD both asthma and AR were observed, compared to children with low risk, where asthma without AR was more prevalent. To our best knowledge, this is the first study in European pediatric population showing that inadequate asthma control and concomitant presence of AR are associated with increased risk for SRBD.

Few former studies in this emerging scientific field, have reported that children with asthma and AR exhibit poorer asthma control and higher risk of exacerbations, impaired life quality and increased healthcare cost compared to individuals without AR (5, 31, 32). Of note, nearly 80% of children with asthma exhibit concomitant AR, and ∼40% with AR exhibit concomitant asthma (5, 6, 33). Previous studies have shown that appropriate quality and adequate quantity of sleep are crucial factors for many aspects of childhood health and development; however, more than 25% of children experience some type of sleep disorders (34). Accordingly, aggravation of the already impaired sleep quality is resulting in an increased night-time activity levels, leading to a vicious circle of further relapses of day-time sleepiness (34). Hence, a study shedding new light on the relationship between asthma control, AR and SRBD in children was sorely needed.

Our findings are in line with previous pediatric studies, showing a positive correlation between risk for Obstructive Sleep Apnea (OSA) and/or snoring and presence of asthma and/or wheezing (35–42). A random sample survey of 1234 children from Belgium, aged 6 to 14 years revealed a two-fold increased of OSA symptoms in children with wheezing (35). Similar findings have been reported in other countries (37, 38). Furthermore, in a group of African-American children with asthma, apnea-hypopnea index (AHI) was significantly higher in the subjects with inadequate asthma control (39). Additionally, a recent study enrolling Latin-American children from nine countries, with persistent asthma and/or AR as well as healthy controls, which filled the Children's Sleep Habits Questionnaire (CSHQ), concluded that especially uncontrolled asthma was leading to sleep impairment (13).

This study, though, was subjected to some limitations; therefore acknowledgment should be provided in order to allow interpretation of the described results. Firstly, as an observational, cross-sectional, pilot study with a small sample size, it cannot determine any causal relationship. Secondly, the risk of SRBD was assessed by a non-validated in Greek subjective instrument, such as SRBD subscale of the PSQ, and was not evaluated, thereafter, by a confirmatory objective tool, such as polysomnography. Thirdly, the evaluation of asthma control was based in c-ACT score, a non-validated in Greek composite control tool. However, although the idea of a score representing the overall asthma control seems attractive, it is universally accepted that asthma control represents a multidimensional process (14). The fact that both used questionnaires are non-validated in Greek, decreases the reliability of the study; the translation of both questionnaires into Greek and their reliability has to be determined by means of test-retest and internal consistency methods among a random sample of patients. Noteworthy, ACT is perhaps the most used subjective control tool in adults suffering with asthma and c-ACT represents one of the most extensively validated prognostic modality tools worldwide (15). C-ACT is beneficial in daily clinical practice based on its convenience to use, input from the child and caregiver, and alignment with asthma guidelines (15). SRBD subscale of the PSQ it can be valuable in clinical practice and research based on its ease of use and it can be useful for screening patients who require further medical evaluation, and for epidemiological reasons. Fourthly, we have only focused on asthma control and we did not examine the probable adverse effect of poor AR control on childhood SRBD. Nevertheless, this was the first European study underlining the importance of

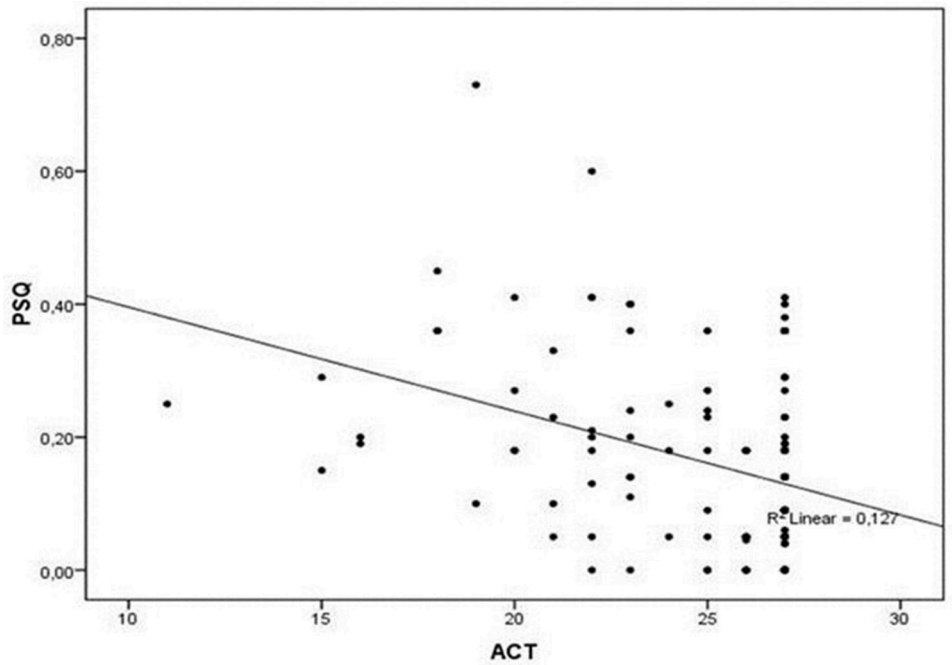

FIGURE 1 | Correlation between PSQ and ACT scores. A negative linear correlation was found between the c-ACT and PSQ-SRBD scores ($r = -0.356$, $r^2 = 0.127$, $P < 0.001$). ACT, Asthma Control Test; PSQ, Pediatric Sleep Questionnaire.

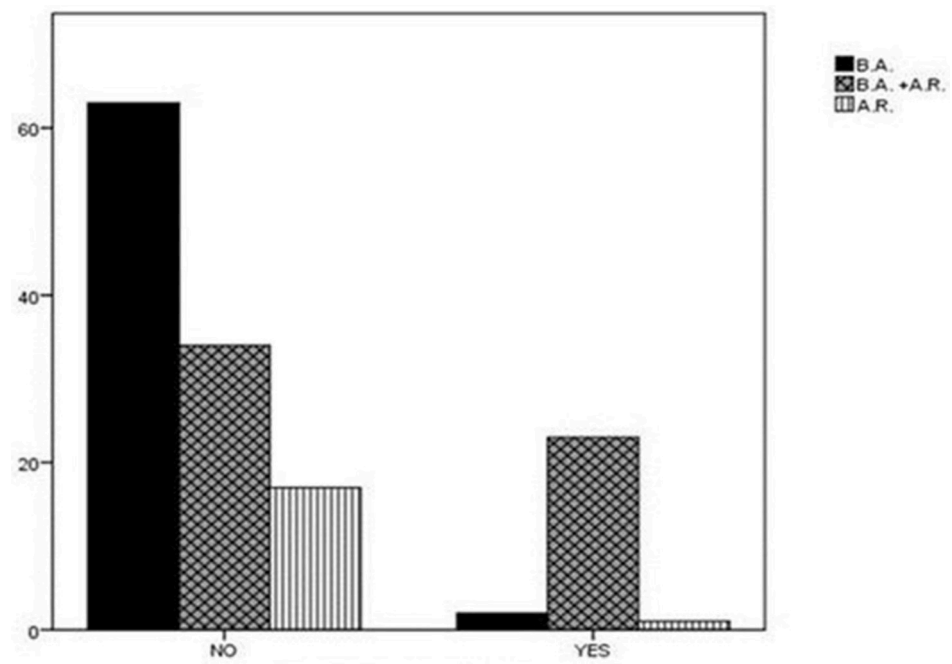

FIGURE 2 | Diagnosis distribution in children with high or low risk for SRBD. In the subgroup of children with high risk for SRBD, 88.5% of children were diagnosed with asthma and AR. In contrast, the rate of coexistence of asthma and AR among children with low PSQ-SRBD score was 29.8%. AR, Allergic Rhinitis; BA, Bronchial Asthma; SRBD, Sleep Related Breathing Disorder.

asthma control and, likewise, revealing the incremental role of AR in children with asthma, regarding the likelihood of SRBD. On the basis of the above-mentioned, more in depth knowledge about the need of multidisciplinary interventions integrating the co-management of asthma and AR, in order to diminish their impact on children's sleep is needed.

CONCLUSIONS

In the present study we have shown that inadequate asthma control is associated with SRBD and the coexistence of AR in children with asthma seems to increase further the burden of SRBD. Monitoring asthma control is an integral part of asthma treatment, endorsing the importance of adequate control. In this term, periodic objective assessments of lung function may be deemed necessary to achieve the therapeutic goals set for individual child; although this was not found in this first pilot study; since no difference in lung function was shown between the two groups of high risk and low risk for SRBD. The coexistence of SRBD and asthma may have a cumulative effect, in terms of morbidity, so both disturbances must be recognized and treated promptly.

There is an urgent need for further, large scale research, in order to better understand the mechanisms between allergic disease and sleep. Undoubtedly, a systematic screening process including large epidemiological studies due to identify children at risk for SRBD is crucial in order to improve quality of medical care.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of Ethics Committee of Democritus University of Thrace with written informed consent from parent/guardians of all subjects. All parents gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Ethics Committee of the Democritus University of Thrace.

AUTHOR CONTRIBUTIONS

EvP collected the data, contributed in designing and drafting the manuscript. PS contributed in the initial conception and critical revision. EN analyzed the data, contributed in the design and interpretation. MI collected the data, drafted the initial manuscript. AT revised the manuscript and critical revision. AC drafted the initial manuscript and approved the final manuscript as submitted. EmP analyzed the data, supervised drafting of the initial manuscript and supervised revision of the manuscript. All authors provide their approval for the final version to be published.

REFERENCES

1. Samolinski B, Fronczak A, Kuna P, Akdis CA, Anto JM, Bialoszewski AZ, et al. Council on the European Union. Prevention and control of childhood asthma and allergy in the EU from the public health point of view: Polish presidency of the European Union. *Allergy* (2012) 67:726–31. doi: 10.1111/j.1398-9995.2012.02822.x
2. Pijnenburg MW, Baraldi E, Brand PL, Carlsen KH, Eber E, Frischer T, et al. Monitoring asthma in children. *Eur Respir J.* (2015) 45:906–25. doi: 10.1183/09031936.00088814
3. Guerra S, Sherrill DL, Martinez FD, Barbee RA. Rhinitis as an independent risk factor for adult-onset asthma. *J Allergy Clin Immunol.* (2002) 109:419–25. doi: 10.1067/mai.2002.121701
4. Linneberg A, Henrik Nielsen N, Frølund L, Madsen F, Dirksen A, Jørgensen T. Copenhagen Allergy Study. The link between allergic rhinitis and allergic asthma: a prospective population-based study. The copenhagen allergy study. *Allergy* (2002) 57:1048–52. doi: 10.1034/j.1398-9995.2002.23664.x
5. de Groot EP, Nijkamp A, Duiverman EJ, Brand PL. Allergic rhinitis is associated with poor asthma control in children with asthma. *Thorax* (2012) 67:582–7. doi: 10.1136/thoraxjnl-2011-201168
6. Kiotseridis H, Cilio CM, Bjermer L, Aurivillius M, Jacobsson H, Dahl Å, et al. Quality of life in children and adolescents with respiratory allergy, assessed with a generic and disease-specific instrument. *Clin Respir J.* (2013) 7:168–75. doi: 10.1111/j.1752-699X.2012.00298.x
7. Brockmann PE, Bertrand P, Castro-Rodriguez JA. Influence of asthma on sleep disordered breathing in children: a systematic review. *Sleep Med Rev.* (2014) 18:393–7. doi: 10.1016/j.smrv.2014.01.005
8. Sánchez T, Castro-Rodríguez JA, Brockmann PE. Sleep-disordered breathing in children with asthma: a systematic review on the impact of treatment. *J Asthma Allergy* (2016) 9:83–91. doi: 10.2147/JAA.S85624
9. Ginis T, Akcan FA, Capanoglu M, Toyran M, Ersu R, Kocabas CN, et al. The frequency of sleep-disordered breathing in children with asthma and its effects on asthma control. *J Asthma* (2017) 54:403–10. doi: 10.1080/02770903.2016.1220012
10. Kimple AJ, Ishman SL. Allergy and sleep-disordered breathing. *Curr Opin Otolaryngol Head Neck Surg.* (2013) 21:277–81. doi: 10.1097/MOO.0b013e32835ff132
11. Di Francesco RC, Alvarez J. Allergic rhinitis affects the duration of rapid eye movement sleep in children with sleep-disordered breathing without sleep apnea. *Int Forum Allergy Rhinol.* (2016) 6:465–71. doi: 10.1002/alr.21689
12. Loekmanwidjaja J, Carneiro ACF, Nishinaka MLT, Munhoes DA, Benezoli G, Wandalsen GF et al. Sleep disorders in children with moderate to severe persistent allergic rhinitis. *Braz J Otorhinolaryngol.* (2018) 84:178–84. doi: 10.1016/j.bjorl.2017.01.008
13. Urrutia-Pereira M, Solé D, Chong Neto HJ, Acosta V, Cepeda AM, Álvarez-Castelló M, et al. Sleep disorders in Latin-American children with asthma and/or allergic rhinitis and normal controls. *Allergol Immunopathol.* (2017) 45:145–51. doi: 10.1016/j.aller.2016.05.005
14. Cloutier MM, Schatz M, Castro M, Clark N, Kelly HW, Mangione-Smith R, et al. Asthma outcomes: composite scores of asthma control. *J Allergy Clin Immun.* (2012) 129(Suppl. 3):S24–33. doi: 10.1016/j.jaci.2011.12.980
15. Liu AH, Zeiger R, Sorkness C, Mahr T, Ostrom N, Burgess S, et al. Development and cross-sectional validation of the childhood asthma control test. *J Allergy Clin Immun.* (2007) 119:817–25. doi: 10.1016/j.jaci.2006.12.662
16. Payne DN, Adcock IM, Wilson NM, Oates T, Scallan M, Bush A. Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone. *Am J Respir Crit Care Med.* (2001) 164:1376–81. doi: 10.1164/ajrccm.164.8.2101145
17. Barnes PJ, Dweik RA, Gelb AF, Gibson PG, George SC, Grasemann H, et al. Exhaled nitric oxide in pulmonary diseases: a comprehensive review. *Chest* (2010) 138:682–92. doi: 10.1378/chest.09-2090
18. Lu M, Wu B, Che D, Qiao R, Gu H. FeNO and asthma treatment in children: a systematic review and meta-analysis. *Medicine* (2015) 94:e347. doi: 10.1097/MD.0000000000000347
19. Mindell JA, Owens JA. Sleep problems in pediatric practice. Clinical issues for the pediatric nurse practitioner. *J Pediatr Health Care* (2003) 17:324–31. doi: 10.1016/mph.2003.92
20. Paraskakis E, Ntouros T, Ntokos M, Siavana O, Bitsori M, Galanakis E. Siesta and sleep patterns in a sample of adolescents in Greece. *Pediatr Int.* (2008) 50:690–3. doi: 10.1111/j.1442-200X.2008.02632.x
21. Singh GK, Kenney MK. Rising prevalence and neighborhood, social, and behavioral determinants of sleep problems in US children and adolescents, 2003–2012. *Sleep Disord.* (2013) 2013:394320. doi: 10.1155/2013/394320

22. Spruyt K, Gozal D. Development of pediatric sleep questionnaires as diagnostic or epidemiological tools: a brief review of dos and don'ts. *Sleep Med Rev.* (2011) 15:7–17. doi: 10.1016/j.smrv.2010.06.003
23. Spruyt K, Gozal D. Pediatric sleep questionnaires as diagnostic or epidemiological tools: a review of currently available instruments. *Sleep Med Rev.* (2011) 15:19–32. doi: 10.1016/j.smrv.2010.07.005
24. American Thoracic Society. European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med.* (2005) 171:912–30. doi: 10.1164/rccm.200406-710ST
25. Moeller A, Carlsen KH, Sly PD, Baraldi E, Piacentini G, Pavord I, et al. ERS task force monitoring asthma in children. monitoring asthma in childhood: lung function, bronchial responsiveness and inflammation. *Eur Respir Rev.* (2015) 24:204–15. doi: 10.1183/16000617.00003914
26. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med.* (2000) 162:1403–6. doi: 10.1164/ajrccm.162.4.9912111
27. Beigelman A, Bacharier LB. Management of preschool children with recurrent wheezing: lessons from the NHLBI's asthma research networks. *J Allergy Clin Immunol Pract.* (2016) 4:1–8 doi: 10.1016/j.jaip.2015.10.003
28. Bousquet J, Schünemann HJ, Samolinski B, Demoly P, Baena-Cagnani CE, Bachert C, et al. World Health Organization Collaborating Center for Asthma and Rhinitis. Allergic Rhinitis and its impact on asthma (ARIA): achievements in 10 years and future needs. *J Allergy Clin Immunol.* (2012) 130:1049–62. doi: 10.1016/j.jaci.2012.07.053
29. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, et al. Centers for disease control and prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics* (2002) 109:45–60
30. Chervin RD, Hedger K, Dillon JE, Pituch KJ. Pediatric Sleep Questionnaire (PSQ): validity and reliability of scales for sleep-disordered breathing, snoring, sleepiness, and behavioral problems. Sleep *Med.* (2000) 1:21–32. doi: 10.1016/S1389-9457(99)00009-X
31. Di Cara G, Carelli A, Latini A, Panfili E, Bizzarri I, Ciprandi G, et al. Severity of allergic rhinitis and asthma development in children. *World Allergy Organ J.* (2015) 8:13. doi: 10.1186/s40413-015-0061-4
32. Gabet S, Just J, Couderc R, Bousquet J, Seta N, Momas I. Early polysensitization is associated with allergic multimorbidity in PARIS birth cohort infants. *Pediatr Allergy Immunol.* (2016) 27:831–7. doi: 10.1111/pai.12622
33. Grossman J. One airway, one disease. *Chest* (1997) 111(Suppl. 2):11S—16S. doi: 10.1378/chest.111.2_Supplement.11S
34. Bathory E, Tomopoulos S. Sleep regulation, physiology and development, sleep duration and patterns, and sleep hygiene in infants, toddlers and preschool age children. *Curr Probl Pediatr Adolesc Health Care* (2017) 47:29–42. doi: 10.1016/j.cppeds.2016.12.001
35. Desager KN, Nelen V, Weyler JJ, De Backer WA. Sleep disturbance and daytime symptoms in wheezing school-aged children. *J Sleep Res.* (2005) 14:77–82. doi: 10.1111/j.1365-2869.2004.00432.x
36. Valery PC, Masters IB, Chang AB. Snoring and its association with asthma in Indigenous children living in the Torres Strait and Northern Peninsula Area. *J Paediatr Child Health* (2004) 40:461–5. doi: 10.1111/j.1440-1754.2004.00428.x
37. Ekici A, Ekici M, Kurtipek E, Keles H, Kara T, Tunckol M, et al. Association of asthma-related symptoms with snoring and apnea and effect on health-related quality of life. *Chest* (2005) 128:3358–63. doi: 10.1378/chest.128.5.3358
38. Chawes BL, Kreiner-Møller E, Bisgaard H. Upper and lower airway patency are associated in young children. *Chest* (2010) 137:1332–7. doi: 10.1378/chest.09-2601
39. Ramagopal M, Mehta A, Roberts DW, Wolf JS, Taylor RJ, Mudd KE, et al. Asthma as a predictor of obstructive sleep apnea in urban African-American children. *J Asthma* (2009) 46:895–9. doi: 10.3109/02770900903229636
40. Teculescu DB, Caillier I, Perrin P, Rebstock E, Rauch A. Snoring in French preschool children. *Pediatr Pulmonol.* (1992) 13:239–44. doi: 10.1002/ppul.1950130412
41. Ersu R, Arman AR, Save D, Karadag B, Karakoc F, Berkem M, et al. Prevalence of snoring and symptoms of sleep-disordered breathing in primary school children in Istanbul. *Chest* (2004) 126:19–24. doi: 10.1378/chest.126.1.19
42. Lu LR, Peat JK, Sullivan CE. Snoring in preschool children: prevalence and association with nocturnal cough and asthma. *Chest* (2003) 124:587–93. doi: 10.1378/chest.124.2.587

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REVIEW
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Congenital Lung Malformations: Unresolved Issues and Unanswered Questions

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Advances in prenatal and postnatal diagnosis, perioperative management, and postoperative care have dramatically increased the number of scientific reports on congenital thoracic malformations (CTM). Nearly all CTM are detected prior to birth, generally by antenatal ultrasound. After delivery, most infants do well and remain asymptomatic for a long time. However, complications may occur beyond infancy, including in adolescence and adulthood. Prenatal diagnosis is sometimes missed and detection may occur later, either by chance or because of unexplained recurrent or persistent respiratory symptoms or signs, with difficult implications for family counseling and substantial delay in surgical planning. Although landmark studies have been published, postnatal management of asymptomatic children is still controversial and needs a resolution. Our aim is to provide a focused overview on a number of unresolved issues arising from the lack of an evidence-based consensus on the management of patients with CTM. We summarized findings from current literature, with a particular emphasis on the vigorous controversies on the type and timing of diagnostic procedures, treatments and the still obscure relationship between CTM and malignancies, a matter of great concern for both families and physicians. We also present an algorithm for the assessment and follow-up of CTM detected either in the antenatal or postnatal period. A standardized approach across Europe, based on a multidisciplinary team, is urgently needed for achieving an evidence-based management protocol for CTM.

Keywords: lung malformations, pulmonary sequestration, congenital cystic adenomatoid malformation, bronchogenic cyst, postnatal management, surgery, children

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INTRODUCTION

The term congenital lung malformation is used as an umbrella term to cover a wide range of disorders, that include the entity formerly known as congenital cystic adenomatoid malformation (CCAM), intra- and extra-lobar pulmonary sequestration (PS), bronchogenic cysts, congenital large hyperlucent lobe (CLHL, also reported as congenital alveolar overdistension, formerly known as congenital lobar emphysema) and bronchial atresia. In the international literature the term "congenital thoracic malformations" (CTM) has been introduced as a term to describe the above entities clinically (1, 2). Clearly more sophisticated classifications should be used by pathologists examining excised CTM. We will use this terminology throughout the manuscript.

CTM account for 5–18% of all congenital abnormalities, have a cumulative incidence of 30–42 cases per 100,000 individuals (3), and thus are considered rare disorders (4). However, the prevalence may be underestimated as an unknown proportion of these lesions is detected postnatally by chance (5).

Complications of CTM were first reported in the 1970s (6). In the last two decades, antenatal diagnosis has been the rule, and improved postnatal imaging has detected missed cases (5). CTM are considered in the differential diagnosis of recurrent pneumonia occurring in the same location in children (7).

Despite multiple publications on the topic, there are actually no uniform management guidelines, and the postnatal management of CTM differs markedly among centers (8–16). This deficiency greatly hampers parental counseling, including pregnancy decisions and surgical planning.

Herein we review the existing literature on CTM. Our main objectives were (i) to summarize their etiology and classification, (ii) to describe their clinical presentation and associated complications, (iii) to review the evidence on the diagnostic approach and therapeutic strategies, and (iv) to highlight unanswered management questions. We carried out a literature search for English articles published on this topic since 1990 up to May 2019, in the Scopus, Web of Science, PubMed, and MEDLINE databases, using the search term "congenital lung malformations," "congenital thoracic malformations," "pulmonary sequestration," "congenital cystic adenomatoid malformation," "congenital pulmonary adenomatoid malformation," "congenital large hyperlucent lobe," "congenital alveolar overdistension," "congenital lobar emphysema," "bronchogenic cyst," combined with the following: "postnatal management," "surgery," "embolization." We excluded studies conducted exclusively in adults, but included those with a mixed study population of children (or adolescents) and adults. We have developed an algorithm for the evaluation and follow-up of cases of CTM detected either in the antenatal or postnatal period.

ETIOLOGY AND CLASSIFICATIONS OF CTM

Several hypotheses on the etiology of CTM have been proposed. It has been speculated that they are due to anomalies of airway embryogenesis, with both type and histopathology being related to the timing of the embryologic insult (17–22). This unifying theory might explain the overlapping features often seen in CTM; however, embryological speculations are often incorrect! An animal study suggested also that an exaggerated signaling of the fibroblast growth factor 10 (FGF10) may be responsible for the formation of abnormal cystic-like structures during early lung development (17). FGF10 contributes to lung morphogenesis through its receptor FGFR2, and its signaling is down-regulated by the Sonic Hedgehog (SHH) system. The deregulation of SHH-FGF10 signaling has been hypothesized to be the cause of CCAM (17). Moreover, a recent study showed that CTM consist of differentiated airway structures transcriptionally characterized by increased expression of airway epithelial markers as well as by dysregulated expression of genes related to the Ras and several kinases signaling pathways (23). A murine study showed that mutations in the *DICER1* gene leads to the formation of cystic airways, disruption of branching morphogenesis and mesenchymal expansion, features similar to pleuropulmonary blastoma (PPB) (24).

There is currently debate about the pathological classification of CTM. According to the 2002 Stocker classification, the term congenital pulmonary airway malformation (CPAM), that replaced the former CCAM, includes five types (1). Type 0 CPAM (bronchial type, formerly described as acinar dysplasia) is characterized by bronchial-type airways separated only by abundant mesenchymal tissue. Types 1 (the bronchial/bronchiolar type) and 2 CPAM (the bronchiolar type) are characterized by cysts >2 cm in diameter and multiple small cysts, respectively. In type 3 CPAM (the bronchiolar/alveolar type) the lesion is solid, and not cystic, because of the excess of bronchiolar structure separated by airspaces that resemble late fetal lung, while type 4 CPAM (the peripheral type) is characterized by peripheral thin-walled, often multiloculated cysts (2, 5, 8). However, the utility of classifications is different depending on whether obstetricians, pediatricians, radiologists, pathologists, or surgeons assess a CTM (1, 25–27). Although pathological classifications can be established only through histological examination, there is a great need to develop a uniform phenotypic description, particularly because pathological features of more than one lesion may be present in the same case and many diagnoses based on imaging have to be revised after pathological evaluation (2), hence the logic of the use of the umbrella term CTM.

Up to 6% of all CTM are PS (3), a malformation with no communication with the bronchial tree (8). Arterial blood supply is usually from the thoracic or abdominal aorta, or occasionally from other arteries (8). Extralobar PS, which has its own pleural lining, is usually situated below the left lower lobe (subdiaphragmatic site, 15% of the cases), and is less common than intralobar PS, which is mainly located within the left lower lobe. Mixed PS and CPAM is defined as a hybrid lesion, and is common in cases with extralobar PS (8, 28–30). Bronchogenic cysts, the most common isolated cyst reported in infancy, are situated in ∼50% of the cases in the mediastinum, close to the carina, and are characterized by closed respiratory-type epithelium-lined sacs containing cartilage in the wall developing from the primitive respiratory tract (2). CLHL most commonly affects the left upper or right middle lobes, and may show very few primitive alveoli or even a polyalveolar lobe. Mechanisms proposed to explain the air-trapping include dysplastic or deficient bronchial cartilage, thick mucus, extensive mucosal proliferation, bronchial torsion, bronchial atresia, and bronchial compression by cardiopulmonary vessels, lymph nodes, cysts, polyalveolar lung, or focal pulmonary hypoplasia (30). Overall, bronchogenic cysts, CLHL and other malformations (bronchial atresia, congenital small lung, and absent lung or trachea) have a significantly lower incidence than CPAM and PS (from 1:20.000 to <1 per 100.000 live births) (31–36).

Obviously, pathological classification of CTM is available only after surgery or at autopsy (1, 26, 27). Clinicians have to rely

on gray scale images, namely prenatal ultrasound (US) and possibly magnetic resonance imaging (MRI), the first postnatal lung imaging findings and any associated clinical features. Hence a clinical and imaging classification has been proposed which has the advantage of being derived from widely available investigations (25).

CLINICAL PRESENTATION AND COMPLICATIONS ASSOCIATED WITH CTM

Most CTM are detected prior to birth at prenatal US (37). The cystic and/or solid lesion may progressively enlarge, with eventual mediastinal shift, or also regress totally or partially before birth (38, 39). Antenatal complications of CTM include fetal hydrops, pleural effusion, or polyhydramnios secondary to failure of normal fetal swallowing because of esophageal compression. Hydrops, reported in 5–30% of all CTM, is the gravest complication, associated with high mortality (40, 41), and therefore requires prompt prenatal intervention and/or preterm delivery (10).

At birth, clinical presentation of CTM is variable. Delivery is usually uncomplicated. Most neonates (>75%) are asymptomatic, with only a minority requiring any respiratory support (12). Beyond the neonatal period, presentation relates to infections and chronic cough or recurrent wheeze, although most babies remain asymptomatic. Symptoms are reported at an average age of 7 months (10). However, many are non-specific childhood complaints and unlikely related to the CTM. In some cases, a CTM might be suspected because of the coexistence of extrapulmonary anomalies, especially in patients with PS who may have associated congenital diaphragmatic hernia or an additional CTM, as well as cardiovascular abnormalities (25, 42).

Potential postnatal complications of undetected or untreated CTM include infections (bacterial, and also fungal and mycobacterial), bleeding (which may lead to hemothorax), air embolism, high-output cardiac failure due to shunting through systemic collaterals, pneumothorax and malignant changes (7, 8, 25, 27). It has been reported that these complications occur in about 3.2% of non-operated patients (43, 44). Although some complications may be prevented by prophylactic surgery, even complete resection of the lesion cannot preclude malignancy arising in the remaining lung tissue (13, 39, 45, 46).

The relationship between CTM and the development of malignancies is debated. PPB, bronchioloalveolar carcinoma and lung adenocarcinoma have been associated with CTM (44, 46). PPB is rare in the general population, with an incidence of 1 in 250,000 live births, but the frequency rises up to 4% in children with CPAM, and its mortality rate is about 20% (47–49). It is unclear whether type 4 CPAM is a regressed PPB or rather PPB is a complication of type 4 CPAM. Cavitation may be secondary to tumor necrosis or, conversely, malignancies may develop within cysts. Indeed, PPB has been described as a distinct entity, with similarities in imaging if compared to CPAM, but with its own specific genetic and molecular markers (24). Factors favoring the diagnosis of PPB include some specific features such as the development of pneumothorax, the evidence of bilateral or multisegment involvement and of a complex cyst, and, finally, a germline mutation in the *DICER1* gene, whereas CPAM is more likely with prenatal diagnosis, and the presence of a systemic feeding vessel and hyperinflated lung (24). A recent study on gene expression in CPAM also including mucin-encoding genes, found that *K-RAS* mutations and *MUC5AC*, *CK20,* and *HER2* expression genes (involved in early lung adenocarcinoma development) were present in all CTM with mucinogenic proliferation, thus supporting the importance of complete surgical resection of CTM because of the possible neoplastic nature of at least type 1 CPAM (50). These data provide further insights into the hypothesis that intra-cystic mucinous proliferation, typically seen in type 1 CPAM, may be the precursor also of the bronchioloalveolar carcinoma (49, 51). There are also reports of PPB and bronchioloalveolar carcinoma in children and adults with resected bronchogenic cysts (14, 52), and, finally, a preexisting bronchogenic cyst has been frequently associated with the development of pulmonary adenocarcinoma in adulthood (53). In conclusion, there is still a lively debate on the relationship between malignancies and CTM, indicating that the issue needs to be further investigated before a definite conclusion is reached.

EVIDENCE ON THE DIAGNOSTIC APPROACH AND THERAPEUTIC STRATEGIES FOR CTM

Diagnostic Approach

Antenatally, close monitoring with serial fetal US is the only investigation usually performed to assess size, location, characteristics (i.e., macro- or micro-cystic, solid, or mixed lesions), and volume changes with growth, as well as blood supply (although small accessory vessels arising below the diaphragm can be missed), mediastinal shift, pleural effusion, or other signs of fetal hydrops. Currently, it is impossible to predict accurately the behavior of a CTM *in utero*. In many cases, the lesion may be invisible at term (25). Although regression of the lesion after the 30th week of pregnancy is common, postnatal assessment is always recommended (8). Antenatally, if the lesion progressively enlarges and/or there are no signs of regression in the last 10 weeks of pregnancy, or if hydrops develops, options for intervention should be considered (25). In addition to US, fetal MRI may also be useful both to detect a systemic arterial blood supply and any complications. Moreover, a lesion volume >24.0 cm^3 at MRI during the third trimester of pregnancy has a 100% sensitivity and 91% specificity in predicting neonatal respiratory distress (54).

For cystic lesions, the CTM volume ratio (CVR) is a useful prognostic tool (55). It measures the volume of the lung lesion, divided by the head circumference to normalize for gestational age. A CVR >1.6 predicts an 80% increased risk of fetal hydrops, while a ratio <1.6 is associated with a survival rate of 94% and risk of hydrops <3% (56). Recently, it was suggested that a CVR ≥0.84 is a good predictor of respiratory distress at birth, as well as other US findings including polyhydramnios and ascites (57). The mass-to-thorax ratio is an additional good predictor of

adverse events, with also a negative predictive value of the risk of developing hydrops if >0.96 (58, 59). Finally, the increase of the cardiomediastinal shift angle, a novel measure of mediastinal shift, has been significantly associated with an adverse perinatal outcome of CTM (60).

Prenatal imaging is not a reliable predictor of post-natal histology. For example, the prenatal demonstration of a systemic arterial supply to a CTM, although generally associated with PS, is also found in hybrid lesions (33). Moreover, failure to detect a systemic arterial supply does not exclude PS (5).

Although CTM are usually detected antenatally, the diagnosis may be missed until later in life. In those detected antenatally, a chest radiograph is performed in many centers shortly after birth, and this is often normal. However, chest radiography has low sensitivity for detecting CTM (11). Therefore, initial investigation should include a computed tomography (CT) scan within the first months of life to confirm that the suspected CTM is still present, and many would propose the use of contrast to delineate the arterial supply and venous drainage prior to surgery, especially if PS is suspected (10, 11, 13, 14) (**Figure 1**). However, the timing of the first HRCT is still controversial. MRI may be a good alternative to CT to avoid radiation exposure, though MRI currently has a long image acquisition time, and thus requires the patient to be cooperative or sedated/anesthetized (61). Furthermore, MRI may not detect thin-wall cysts and emphysematous changes as well as CT (8, 62). Finally, MRI is not universally available and requires expertise in interpretation. However, MRI may be better than CT in mapping vascular anatomy, especially if the vessel is small and the drainage is close to the cardiac cavity (8).

Therapeutic Strategies for CTM

Although most CTM have a favorable prognosis, with a survival rate >95% (40, 41, 63), there is a risk of antenatal and postnatal complications (7, 45). When antenatal complications occur, the possible therapeutic options include thoracocentesis, pleuro-amniotic shunt placement, percutaneous ultrasound-guided sclerotherapy, or radiofrequency/laser ablation, fetal bronchoscopy, and rarely open fetal surgery (8, 10, 25, 64, 65), none of which are evidence based, and all of which should be considered a last resort. Factors that should be taken into account are gestational age, the position of the fetus and placenta, whether macrocysts or a high-flow vascular component is present, and, most of all, whether there has been a referral to a center with qualified multidisciplinary team and expertise. When fetal lung maturity is felt sufficient to provide good chances of postnatal survival, preterm delivery may represent a reasonable choice (66). If prior to postnatal viability fetal demise appears likely, repeated cyst aspiration and thoraco-amniotic shunting are therapeutic options. It has been reported that fetal bronchoscopy may represent a therapeutic tool with good outcome, but only in specialized centers (65, 66). Maternal betamethasone administration during the second trimester of gestation has been demonstrated to induce regression of some CTM and reverse fetal hydrops, increasing survival rate (67, 68). Steroids decrease the production of lung fluid and increase its

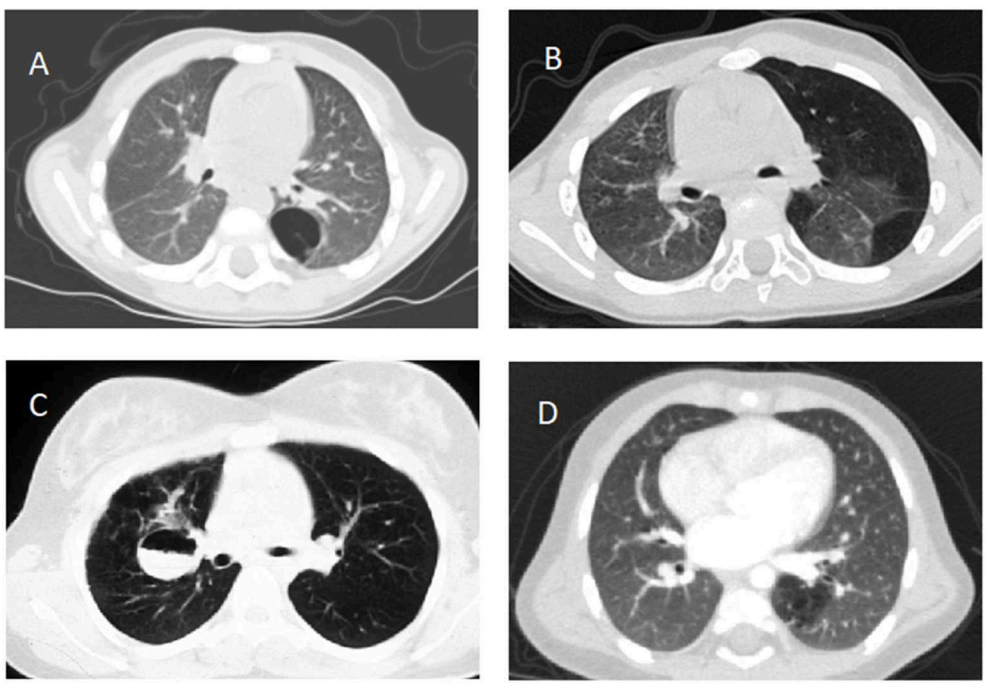

FIGURE 1 | Computed tomography scans documenting **(A)** type 1 congenital pulmonary airway malformation in the left lower lobe, **(B)** congenital lobar emphysema involving the left lung, **(C)** fluid filled bronchogenic cyst in the right lung, **(D)** intralobar pulmonary sequestration in the left lower lobe, all confirmed after lobectomy except **(B)**.

reabsorption within the CTM, thus mimicking the physiological third trimester changes (69). They are indicated for microcystic lesions, while it is unclear whether macrocytic CTM respond to this treatment (70, 71).

If symptoms and/or complications develop postnatally, the child should first be stabilized as far as possible and then therapeutic decisions taken. With the technological improvements in minimally invasive surgery, CTM are now usually removed by video-assisted thoracoscopy (VATS), a safe and feasible alternative to open thoracotomy (15, 72). VATS is usually uncomplicated, and allows the compressed surrounding lung to expand. Advantages of VATS over thoracotomy include smaller incisions with obvious cosmetic benefits, less pain, slightly lower complication rates, shorter hospital stays albeit with longer operative time, and more rapid return to normal activity (73–75). Moreover, the magnification provided by VATS allows for significantly improved discrimination between normal and affected lung and better visualization of fissures and vascular structures. Lobectomy is recommended for the majority of parenchymal CTM referred for surgery, in order to prevent postoperative air leaks, residual disease, and perhaps reduce the risk of some later malignancies (14). Conversely, lung-sparing strategies such as segmentectomy have been advocated for small, well-defined segmental lesions and in cases with bilateral or multilobar disease (75–77). Malignancy even after apparent complete resection of a CTM has been described in the same or also different lung areas (2, 78), but it cannot be excluded that the CTM was indeed neoplastic from the beginning (24).

If a systemic arterial blood supply is demonstrated by CT (**Figure 2**) or MRI, or PS is suspected, and embolization of the feeding vessel is contemplated, angiography should be performed to confirm the presence of abnormal vessels, assess their size and course, and guide transcatheter embolization (79) (**Figure 3**). Embolization leads to regression or complete involution of at least the solid components of CTM, as well as correcting high output cardiac failure if this is present (75), and thus is the preferred therapeutic option in this setting. Several embolization techniques have been proposed, and vascular plugs or microcoils are preferred to injection of alcohol, histoacryl, or gelatin sponge particles (80). Complications after percutaneous embolization are very rare, including migration of the occlusive device, infection, pain, and fever. Although embolization is an acceptable therapeutic strategy, there is still no clear consensus on which CTM are a good indication for first-line embolization. Moreover, cases referred for embolization should be carefully selected as secondary surgery was recently shown to be necessary in 13% of embolized children (81). Hybrid CTM with feeding vessels and other CTM and duplication cysts are at risk of infection or cancer, and should preferably undergo surgical resection (82). If there are large or multiple arteries, re-embolization may be necessary (81). Nevertheless, for carefully selected cases, embolization is a possible option, but long-term data are necessary to confirm clearly the indications for this procedure.

If imaging suggests a CLHL, postnatal management is conservative, unless there are symptoms. This lesion usually regresses over time, and there is no evidence that the development of the underlying lung is improved by surgery. However, if the enlarged lobe causes respiratory symptoms in the newborn period, lobectomy is indicated (8, 14).

While there is general consensus that any symptomatic CTM should be treated, the best management of asymptomatic children is controversial. The divergent opinions on type and

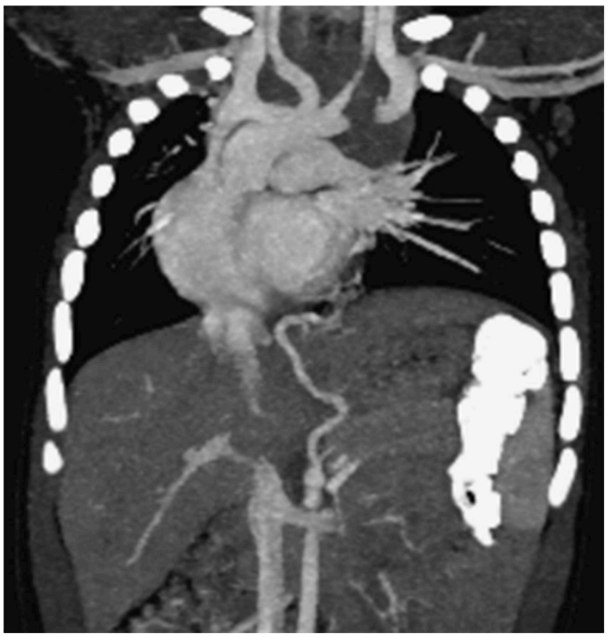

FIGURE 2 | Computed tomography scan documenting two aberrant vessels originating from the tripod celiac artery that lead to the left lower lobe representing intralobar pulmonary sequestration (coronal view).

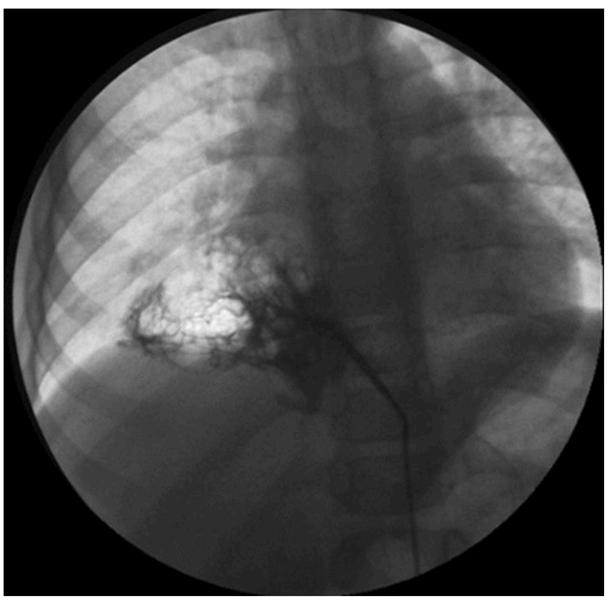

FIGURE 3 | Angiography showing an aberrant artery originating from the celiac trunk to the right lower lobe.

timing of any procedure for CTM reported in the literature are summarized in the **Table 1**. Treatment may be conservative or surgical. If an initial "wait and see" approach is adopted (13, 87), lung imaging may be repeated at 18 months of age, and if the CTM is confirmed, surgery should be planned around the 2nd birthday to allow the baby to grow (13). The rationale for this is to allow for possible spontaneous regression of the CTM, and thus a conservative approach is proposed until symptoms occur or when the cyst size changes on lung imaging (15, 16, 88, 89). Some authors follow-up asymptomatic patients by yearly physical examination and CT scans (16), but the radiation burden of this approach is not trivial. Moreover, the conservative approach has several issues including the risk of complications developing, of losing patients to follow-up while waiting, of increased surgical morbidity if the CTM becomes infected, or also of a substantial radiation exposure due to repeated CT (15, 91). However, the proportion of cases in whom, within the first year of life, the CTM become infected or regress spontaneously is variable (15, 16, 43, 92). The mean follow-up of patients treated conservatively is insufficient to confirm that this is the best option, as malignancies may occur much later, even in adulthood (16).

Other authors advocate elective surgery as the preferred option for a number of reasons, including prevention of late infection or cancer, less risk of emergency surgery, and more time for compensatory alveolar growth (11, 12, 22, 83, 84, 90). However, there are potential operative risks, albeit low in centers with expertise and experience, and cancer may develop elsewhere in the lungs despite the resection of the CTM (45). Also, there is no consensus on the age at surgery, with some preferring to operate in the neonatal period (93), and others waiting until after 4 weeks of age to reduce the risks of the anesthesia prior to that age (22). A recent retrospective study aimed to determine the optimal timing for CTM resection within the first year of life did not find significant differences in the complication rates, hospital re-admissions, or conversion from VATS to open surgery, suggesting that surgery is equally safe whenever made from the first month of life until the first birthday (85). Other authors concluded that morbidity associated with surgery is significantly higher in infants younger than 3 months,

TABLE 1 | Summary from the literature on the diagnostic work up and therapeutic strategies to antenatal suspicion of CPAM and PS in asymptomatic infants.

Diagnostic work up	**Therapeutic strategies**			
Procedure and timing	**Operative approach and timing**		**Conservative approach**	
	CPAM			
Chest X-ray, shortly after birth (11, 12, 14, 24)	Elective surgery in all cases, within the 1st year of life (11, 12, 22, 83–86) Or In cases with large and medium-sized cysts, within the 1st year of life (14, 87) Or In all cases up to 18 months of age when a 2nd HRCT is made for confirming the lesion (13)		Only in cases with small-sized cysts (87, 88) Or Until symptoms occur or changes in size are observed radiologically or parents/patients have concern (at which time surgery is due) (15, 16, 89)	
	PS			
HRCT, within the first months (11, 12, 14, 24) MRI, few weeks after birth (11) 2nd HRCT with contrast, at age 12–18 months (24) or at 5 years (89)	Elective surgery, within the 1st year of life (11) Or after the 1st year of life (81, 90) Or Only for intralobar PS, within the 1st year of life (14) Or In all cases up to 18 months of age when a 2nd HRCT is made for confirming the lesion (13) Or Elective embolization in case of CTM with no symptoms and no cysts (81)		Extralobar PS without significant shunting (14) Or Until symptoms occur or changes in size are observed radiologically or parents/patients have concern (at which time surgery is due) (89)	
	Advantages	**Disadvantages**	**Advantages**	**Disadvantages**
3rd HRCT, prior to transition (89)	Less risk of late complications Less risk of emergency surgery Prevention of cancer in the lesion itself More time for lung growth Short/long-term normal lung function	Potential operative morbidity and mortality No prevention of cancer in other areas of the lung	Avoidance of surgery if the lesion regresses spontaneously	Risk of complications during "wait and see" period Risk of developing high-flow heart failure Pulmonary Hypertension Abnormal lung growth Cumulative radiation risk Risk of losing patients to follow-up Greater morbidity of emergency surgery

CPAM, Congenital Pulmonary Adenomatoid Malformation; PS, Pulmonary Sequestration; HRCT, High Resolution Computed Tomography.

and suggested that the optimal timing is 3–9 months of life, as the surgical intervention duration significantly increases in older infants (86).

UNANSWERED QUESTIONS ABOUT THE MANAGEMENT OF CTM

CTM represent a heterogeneous group of abnormalities. Although the number of cases suspected or diagnosed early has been increasing (94), many management questions remain unanswered, and there are no universally accepted clinical recommendations or practice guidelines.

In terms of diagnosis, although prenatal US and postnatal CT scan are currently considered the gold standard tests, MRI is increasingly used for diagnosing CTM both antenatally and postnatally (5, 40, 95). Postnatal MRI has also been used as radiation-free technique to study any vascularization or re-vascularization after embolization of a systemic arterial supply (79). Nevertheless, the long scanning time and the scanner noise during the examination usually means that general anesthesia is required in infants older than 6 months of age, when the "feed and wrap" technique may be precluded. Future technological improvements will likely overcome these limitations. Widening the indications of chest MRI to suspected CTM would hopefully clarify whether or not MRI is a reliable tool for their diagnosis postnatally, thus reducing the extra radiation exposure associated with CT (15).

Whether conservative or active treatment of asymptomatic patients is best is still controversial, mainly because of the lack of knowledge on the natural history of CTM (8–16, 93). There is no reliable evidence on the optimal management of affected children. Indeed, most babies diagnosed with a CTM do well in the medium term, but an undefined proportion may develop malignancy. At present, this high-risk group cannot be

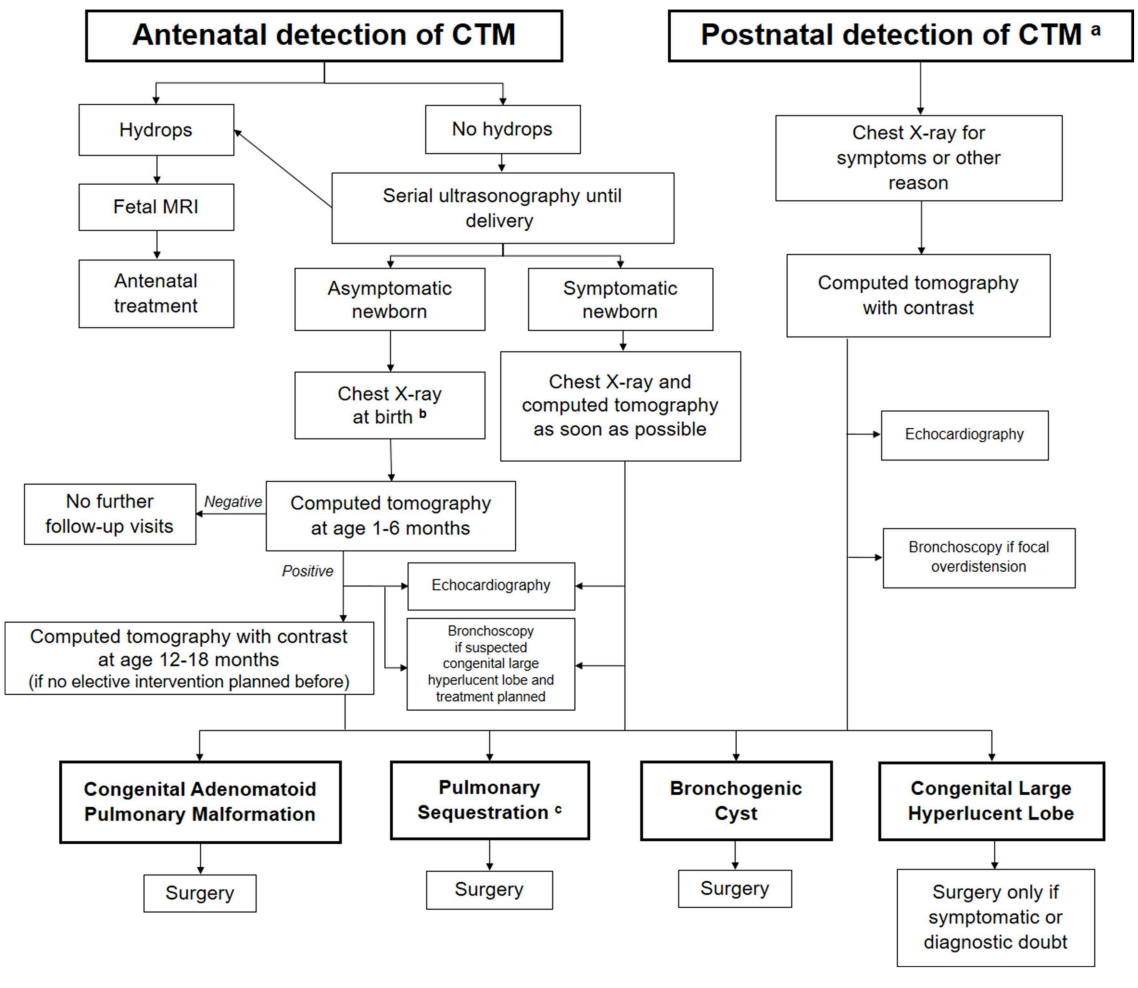

FIGURE 4 | Proposed algorithm for the assessment and follow-up of congenital thoracic malformations (CTM) detected either in the antenatal or postnatal period. [a]Postnatal detection may be suggestive of pleuropulmonary blastoma as well. [b]A Computed Tomography (CT) should be performed to detect a possible lesion at age 1–6 months in all asymptomatic cases, whatever is the chest X-ray finding (positive or negative) at birth. [c]Embolization considered only in asymptomatic cases without evidence of cysts.

identified, and therefore prospective studies gathering data to try to address this situation are urgently needed. A proposal to detect this high-risk group that includes radiological features and *DICER1* mutation analysis has been made (2). The indications for surgery and the timing in asymptomatic children with CTM is also controversial, highlighting the need for long-term outcome studies involving large numbers of patients. The risk of repeated radiological studies and the problem of losing patients at follow-up during a "wait and see" period must also be taken into account. Due to the divergent opinions on the management of CTM and its relevant impact on the family expectations and healthcare costs, we propose a diagnostic-therapeutic algorithm (**Figure 4**), which may be helpful for clinicians dealing with detection of CTM either in the antenatal or postnatal period. Like all algorithms, it is not meant to replace clinical judgment, but it should rather drive physicians to adopt a systematic approach to CTM.

Large-scale, prospective databases with data on clinical presentation, treatment and long-term course of CTM would be a good option to develop a shared clinical guideline. Although expert opinion should be kept in mind (8–16), the time has come to find answers to the unresolved issues of CTM by gathering evidence (96, 97). As controversies sill arise in this field, and many questions about proper management and follow-up are unanswered, a global CTM registry should be designed which would hopefully represent a new promising tool to advance the understanding of these rare disorders, to recruit candidates for research studies and ultimately to improve care of patients with an asymptomatic CTM.

AUTHOR CONTRIBUTIONS

FA, MP, and MB drafted the initial manuscript, searched for bibliography, and revised the final manuscript. FR, FB, and SM were involved in drafting the manuscript, critically revised the manuscript, and approved the final manuscript. AB and FS made substantial contributions to conception and design of the study and reviewed and approved the final manuscript. All authors read and approved the final manuscript as submitted.

REFERENCES

1. Stocker JT. Congenital pulmonary airway malformation - a new name for and an expanded classification of congenital cystic adenomatoid malformation of the lung. Symposium 24: non-neoplastic lung disease. *Histopathology*. (2002) 41(Suppl. 2):424–30.
2. Bush A, Abel RM, Chitty LS, Harcourt J, Hewitt R, Nicholson AG. Congenital lung disease. In: Wilmott RW, Deterding RR, Li A, Ratjen F, Sly P, Zar H, and Bush A, editors. *Kendig's Disorders of the Respiratory Tract in Children*. Philadelphia, PA: Elsevier (2019). p 289–337.
3. Andrade CF, Ferreira HP, Fischer GB. Congenital lung malformations. *J Bras Pneumol*. (2011) 37:259–71. doi: 10.1590/S1806-37132011000200017
4. Available online at: http://ern-lung.eu (accessed May 8, 2019).
5. Chowdhury MM, Chakraborty S. Imaging of congenital lung malformations. *Semin Pediatr Surg*. (2015) 24:168–75. doi: 10.1053/j.sempedsurg.2015.02.001
6. Heithoff KB, Sane SM, Williams HJ, Jarvis CJ, Carter J, Kane P, et al. Bronchopulmonary foregut malformations. A unifying etiological concept. *AJR Am J Roentgenol*. (1976) 126:46–55. doi: 10.2214/ajr.126.1.46
7. Montella S, Corcione A, Santamaria F. Recurrent pneumonia in children: a reasoned diagnostic approach and a single centre experience. *Int J Mol Sci*. (2017) 18:296. doi: 10.3390/ijms18020296
8. Durell J, Lakhoo K. Congenital cystic lesions of the lung. *Early Hum Dev*. (2014) 90:935–9. doi: 10.1016/j.earlhumdev.2014.09.014
9. Newman B, Caplan J. Cystic lung lesions in newborns and young children: differential considerations and imaging. *Semin Ultrasound CT MR*. (2014) 35:571–87. doi: 10.1053/j.sult.2014.07.001
10. Baird R, Puligandla PS, Laberge JM. Congenital lung malformations: informing best practice. *Semin Pediatr Surg*. (2014) 23:270–7. doi: 10.1053/j.sempedsurg.2014.09.007
11. Chen HW, Hsu WM, Lu FL, Chen PC, Jeng SF, Peng SS, et al. Management of congenital cystic adenomatoid malformation and bronchopulmonary sequestration in newborns. *Pediatr Neonatol*. (2010) 51:172–7. doi: 10.1016/S1875-9572(10)60032-0
12. Calvert JK, Lakhoo K. Antenatally suspected congenital cystic adenomatoid malformation of the lung: postnatal investigation and timing of surgery. *J Pediatr Surg*. (2007) 42:411–4. doi: 10.1016/j.jpedsurg.2006.10.015
13. Bush A. Prenatal presentation and postnatal management of congenital thoracic malformations. *Early Hum Dev*. (2009) 85:679–84. doi: 10.1016/j.earlhumdev.2009.08.056
14. Laberge JM, Puligandla P, Flageole H. Asymptomatic congenital lung malformations. *Semin Pediatr Surg*. (2005) 14:16–33. doi: 10.1053/j.sempedsurg.2004.10.022
15. Sueyoshi R, Okazaki T, Urushihara N, Fujiwara T, Tobayama S, Fukumoto K, et al. Managing prenatally diagnosed asymptomatic congenital cystic adenomatoid malformation. *Pediatr Surg Int*. (2008) 24:1111–5. doi: 10.1007/s00383-008-2227-4
16. Aziz D, Langer JC, Tuuha SE, Ryan G, Ein SH, Kim PC. Perinatally diagnosed asymptomatic congenital cystic adenomatoid malformation: to resect or not? *J Pediatr Surg*. (2004) 39:329–34. doi: 10.1016/j.jpedsurg.2003.11.021
17. Boucherat O, Jeannotte L, Hadchouel A, Delacourt C, Benachi A. Pathomechanisms of congenital cystic lung diseases: focus on congenital cystic adenomatoid malformation and pleuropulmonary blastoma. *Paediatr Respir Rev*. (2016) 19:62–8. doi: 10.1016/j.prrv.2015.11.011
18. Barnes NA, Pilling DW. Bronchopulmonary foregut malformations: embryology, radiology and quandary. *Eur Radiol*. (2003) 13:2659–73. doi: 10.1007/s00330-002-1812-5
19. Mendeloff EN. Sequestrations, congenital cystic adenomatoid malformations, and congenital lobar emphysema. *Semin Thorac Cardiovasc Surg*. (2004) 16:209–14. doi: 10.1053/j.semtcvs.2004.08.007
20. Keswani SG, Crombleholme TM, Pawel BR, Johnson MP, Flake AW, Hedrick HL, et al. Prenatal diagnosis and management of mainstem bronchial atresia. *Fetal Diagn Ther*. (2005) 20:74–8. doi: 10.1159/000081374
21. Kunisaki SM, Fauza DO, Nemes LP, Barnewolt CE, Estroff JA, Kozakewich HP, et al. Bronchial atresia: the hidden pathology within a spectrum of prenatally diagnosed lung masses. *J Pediatr Surg*. (2006) 41:61–5. doi: 10.1016/j.jpedsurg.2005.10.082
22. Azizkhan RG, Crombleholme TM. Congenital cystic lung disease: contemporary antenatal and postnatal management. *Pediatr Surg Int*. (2008) 24:643–57. doi: 10.1007/s00383-008-2139-3
23. Swarr DT, Peranteau WH, Pogoriler J, Frank DB, Adzick NS, Hedrick HL, et al. Novel molecular and phenotypic insights into congenital lung malformations. *Am J Respir Crit Care Med*. (2018) 197:1328–39. doi: 10.1164/rccm.201706-1243OC
24. Feinberg A, Hall NJ, Williams GM, Schultz KA, Miniati D, Hill DA, et al. Can congenital pulmonary airway malformation be distinguished from Type I pleuropulmonary blastoma based on clinical and radiological features? *J Pediatr Surg*. (2016) 51:33–7. doi: 10.1016/j.jpedsurg.2015.10.019
25. Bush A. Rare lung diseases: congenital malformations. *Indian J Pediatric*. (2015) 82:833–40. doi: 10.1007/s12098-015-1800-9

26. Langston C. New concepts in the pathology of congenital lung malformations. *Semin Pediatr Surg*. (2003) 12:17–37. doi: 10.1053/spsu.2003.00001
27. Seear M, Townsend J, Hoepker A, Jamieson D, McFadden D, Daigneault P, et al. A review of congenital lung malformations with a simplified classification system for clinical and research use. *Pediatr Surg Int*. (2017) 33:657–64. doi: 10.1007/s00383-017-4062-y
28. Hirose R, Suita S, Taguchi T, Koyanagi T, Nakano H. Extralobar pulmonary sequestration mimicking cystic adenomatoid malformation in prenatal sonographic appearance and histological findings. *J Pediatr Surg*. (1995) 30:1390–3. doi: 10.1016/0022-3468(95)90518-9
29. Winters WD, Effmann EL. Congenital masses of the lung: prenatal and postnatal imaging evaluation. *J Thorac Imaging*. (2001) 16:196–206. doi: 10.1097/00005382-200110000-00002
30. Conran RM, Stocker JT. Extralobar sequestration with frequently associated congenital adenomatoid malformation, type 2: report of 50 cases. *Pediatr Dev Pathol*. (1999) 2:454–63. doi: 10.1007/s100249900149
31. Olutoye OO, Coleman BG, Hubbard AM, Adzick NS. Prenatal diagnosis and management of congenital lobar emphysema. *J Pediatr Surg*. (2000) 35:792–5. doi: 10.1053/jpsu.2000.6084
32. Zamora IJ, Sheikh F, Olutoye OO, Cassady CI, Lee TC, Ruano R, et al. Mainstem bronchial atresia: a lethal anomaly amenable to fetal surgical treatment. *J Pediatr Surg*. (2014) 49:706–11. doi: 10.1016/j.jpedsurg.2014.02.051
33. Takeda S, Miyoshi S, Minami M, Ohta M, Masaoka A, Matsuda H. Clinical spectrum of mediastinal cysts. *Chest*. (2003) 124:125–32. doi: 10.1378/chest.124.1.125
34. Saini S, Prakash S, Rajeev M, Girdhar KK. Congenital lobar emphysema: anaesthetic challenges and review of literature. *J Clin Diagn Res*. (2017) 11:UD04–6. doi: 10.7860/JCDR/2017/26318.10617
35. Badiu I, Hiriscau A, Lupan I, Samasca G. CLE in infants. *Maedica*. (2017) 12:133–5.
36. Bonnefoy C, Blanc P, Coste K, Delabaere A, Dechelotte PJ, Laurichesse-Delmas H, et al. Prenatal diagnosis of lobar bronchial atresia. *Ultrasound Obstet Gynecol*. (2011) 37:110–2. doi: 10.1002/uog.8838
37. Mon RA, Johnson KN, Ladino-Torres M, Heider A, Mychaliska GB, Treadwell MC, et al. Diagnostic accuracy of imaging studies in congenital lung malformations. *Arch Dis Child Fetal Neonatal Ed*. (2018). doi: 10.1136/archdischild-2018-314979. [Epub ahead of print].
38. Laberge J, Flageole H, Pugash D, Khalife S, Blair G, Filiatrault D, et al. Outcome of the prenatally diagnosed congenital cystic adenomatoid lung malformation: a Canadian experience. *Fetal Diagn Ther*. (2001) 16:178–86. doi: 10.1159/000053905
39. Bush A, Hogg J, Chitty L. Cystic lung lesions – prenatal diagnosis and management. *Prenat Diagn*. (2008) 28:604–11. doi: 10.1002/pd.2039
40. Adzick NS. Management of fetal lung lesions. *Clin Perinatol*. (2009) 36:363–76. doi: 10.1016/j.clp.2009.03.001
41. Cavoretto P, Molina F, Poggi S, Davenport M, Nicolaides KH. Prenatal diagnosis and outcome of echogenic fetal lung lesions. *Ultrasound Obstet Gynecol*. (2008) 32:769–83. doi: 10.1002/uog.6218
42. Biyyam DR, Chapman T, Ferguson MR, Deutsch G, Dighe MK. Congenital lung abnormalities: embryologic features, prenatal diagnosis, and postnatal radiologic-pathologic correlation. *Radiographics*. (2010) 30:1721–38. doi: 10.1148/rg.306105508
43. Stanton M, Njere I, Ade-Ajayi N, Patel S, Davenport M. Systematic review and meta-analysis of the postnatal management of congenital cystic lung lesions. *J Pediatr Surg*. (2009) 44:1027–33. doi: 10.1016/j.jpedsurg.2008.10.118
44. Kotecha S, Barbato A, Bush A, Claus F, Davenport M, Delacourt C, et al. Antenatal and postnatal management of congenital cystic adenomatoid malformation. *Paediatr Respir Rev*. (2012) 13:162–70. doi: 10.1016/j.prrv.2012.01.002
45. Papagiannopoulos KA, Sheppard M, Bush A, Goldstraw P. Pleuropulmonary blastoma: is prophylactic resection of congenital lung cysts effective? *Ann Thorac Surg*. (2001) 72:604–5. doi: 10.1016/S0003-4975(00)02539-X
46. Lakhoo K. Management of congenital cystic adenomatous malformations of the lung. *Arch Dis Child Fetal Neonatal Ed*. (2009) 94:F73–6. doi: 10.1136/adc.2007.130542
47. Priest JR, Williams GM, Hill DA, Dehner LP, Jaffé A. Pulmonary cysts in early childhood and the risk of malignancy. *Pediatr Pulmonol*. (2009) 44:14–30. doi: 10.1002/ppul.20917
48. Nasr A, Himidan S, Pastor AC, Taylor G, Kim PCW. Is congenital cystic adenomatoid malformation a premalignant lesion for pleuropulmonary blastoma? *J Pediatr Surg*. (2010) 45:1086–9. doi: 10.1016/j.jpedsurg.2010.02.067
49. MacSweeney F, Papagiannopoulos K, Goldstraw P, Sheppard MN, Corrin B, Nicholson AG. An assessment of the expanded classification of congenital cystic adenomatoid malformations, and their relationship to malignant transformation. *Am J Surg Pathol*. (2003) 27:1139–46. doi: 10.1097/00000478-200308000-00012
50. Rossi G, Gasser B, Sartori G, Migaldi M, Costantini M, Mengoli MC, et al. MUC5AC, cytokeratin 20 and HER2 expression and K-RAS mutations within mucinogenic growth in congenital pulmonary airway malformations. *Histopathology*. (2012) 60:1133–43. doi: 10.1111/j.1365-2559.2011.04170.x
51. Lantuejoul S, Nicholson AG, Sartori G, Piolat C, Danel C, Brabencova E, et al. Mucinous cells in type 1 pulmonary congenital cystic adenomatoid malformation as mucinous bronchioloalveolar carcinoma precursors. *Am J Surg Pathol*. (2007) 31:961–9. doi: 10.1097/01.pas.0000249444.90594.27
52. Murphy JJ, Blair GK, Fraser GC, Ashmore PG, LeBlanc JG, Sett SS, et al. Rhabdomyosarcoma arising within congenital pulmonary cysts: report of three cases. *J Pediatr Surg*. (1992) 27:1364–67. doi: 10.1016/0022-3468(92)90299-M
53. Casagrande A, Pederiva F. Association between congenital lung malformations and lung tumors in children and adults: a systematic review. *J Thorac Oncol*. (2016) 11:1837–45. doi: 10.1016/j.jtho.2016.06.023
54. Girsen AI, Hintz SR, Sammour R, Naqvi A, El-Sayed YY, Sherwin K, et al. Prediction of neonatal respiratory distress in pregnancies complicated by fetal lung masses. *Prenat Diagn*. (2017) 37:266–72. doi: 10.1002/pd.5002
55. Yong PJ, Von Dadelszen P, Carpara D, Lim K, Kent N, Tessier F, et al. Prediction of pediatric outcome after prenatal diagnosis and expectant antenatal management of congenital cystic adenomatoid malformation. *Fetal Diagn Ther*. (2012) 31:94–102. doi: 10.1159/000331936
56. Crombleholme TM, Coleman B, Hedrick H, Liechty K, Howell L, Flake AW, et al. Cystic adenomatoid malformation volume ratio predicts outcome in prenatally diagnosed cystic adenomatoid malformation of the lung. *J Pediatr Surg*. (2002) 37:331–8. doi: 10.1053/jpsu.2002.30832
57. Ruchonnet-Metrailler I, Leroy-Terquem E, Stirnemann J, Cros P, Ducoin H, Hadchouel A, et al. Neonatal outcomes of prenatally diagnosed congenital pulmonary malformations. *Pediatrics*. (2014) 133:e1285–91. doi: 10.1542/peds.2013-2986
58. Wong KKY, Flake AW, Tibboel D, Rottier RJ, Tam PKH. Congenital pulmonary airway malformation: advances and controversies. *Lancet Child Adolesc Health*. (2018) 2:290–7. doi: 10.1016/S2352-4642(18)30035-X
59. Ehrenberg-Buchner S, Stapf AM, Berman DR, Drongowski RA, Mychaliska GB, Treadwell MC, et al. Fetal lung lesions: can we start to breathe easier? *Am J Obstet Gynecol*. (2013) 208:151. doi: 10.1016/j.ajog.2012.11.012
60. Shulman R, Sparks TN, Gosnell K, Blat C, Norton ME, Lee H, et al. Fetal congenital pulmonary airway malformation: the role of an objective measurement of cardiomediastinal shift. *Am J Perinatol*. (2018).
61. Baez JC, Seethamraju RT, Mulkern R, Ciet P, Lee EY. Pediatric chest MR imaging: sedation, techniques, and extracardiac vessels. *Magn Reson Imaging Clin N Am*. (2015) 23:321–5. doi: 10.1016/j.mric.2015.01.010
62. Corbett HJ, Humphrey GME. Pulmonary sequestration. *Paediatr Respir Rev*. (2004) 5:59–68. doi: 10.1016/j.prrv.2003.09.009
63. Hellmund A, Berg C, Geipel A, Bludau M, Heydweiller A, Bachour H, et al. Prenatal diagnosis and evaluation of sonographic predictors for intervention and adverse outcome in congenital pulmonary airway malformation. *PLoS ONE*. (2016) 11:e0150474. doi: 10.1371/journal.pone.0150474
64. Quintero RA, Kontopoulos E, Reiter J, Pedreira WL, Colin AA. Fetal bronchoscopy: its successful use in a case of extralobar pulmonary sequestration. *J Matern Fetal Neonatal Med*. (2012) 25:2354–2358. doi: 10.3109/14767058.2012.695826
65. Cruz-Martinez R, Méndez A, Perez-Garcilita O, Monroy A, Aguilar-Vidales K, Cruz-Martinez MA, et al. Fetal bronchoscopy as a useful procedure in a case with prenatal diagnosis of congenital microcystic adenomatoid

malformation. *Fetal Diagn Ther*. (2015) 37:75–80. doi: 10.1159/000361015
66. Gajewska-Knapik K, Impey L. Congenital lung lesions: prenatal diagnosis and intervention. *Semin Pediatr Surg*. (2015) 24:156–9. doi: 10.1053/j.sempedsurg.2015.01.012
67. Tsao K, Hawgood S, Vu L, Hirose S, Sydorak R, Albanese CT, et al. Resolution of hydrops fetalis in congenital cystic adenomatoid malformation after prenatal steroid therapy. *J Pediatr Surg*. (2003) 38:508–10. doi: 10.1053/jpsu.2003.50089
68. Curran PF, Jelin EB, Rand L, Hirose S, Feldstein VA, Goldstein RB, et al. Prenatal steroids for microcystic congenital cystic adenomatoid malformations. *J Pediatr Surg*. (2010) 45:145–50. doi: 10.1016/j.jpedsurg.2009.10.025
69. Jain L, Eaton DC. Physiology of fetal lung fluid clearance and the effect of labor. *Semin Perinatol*. (2006) 30:34–43. doi: 10.1053/j.semperi.2006.01.006
70. Morris LM, Lim FY, Livingston JC, Polzin WJ, Crombleholme TM. High-risk fetal congenital pulmonary airway malformations have a variable response to steroids. *J Pediatr Surg*. (2009) 44:60–5. doi: 10.1016/j.jpedsurg.2008.10.012
71. Loh KC, Jelin E, Hirose S, Feldstein V, Goldstein R, Lee H. Microcystic congenital pulmonary airway malformation with hydrops fetalis: steroids vs open fetal resection. *J Pediatr Surg*. (2012) 47:36–9. doi: 10.1016/j.jpedsurg.2011.10.015
72. Adams S, Jobson M, Sangnawakij P, Heetun A, Thaventhiran A, Johal N, et al. Does thoracoscopy have advantages over open surgery for asymptomatic congenital lung malformations? An analysis of 1626 resections. *J Pediatr Surg*. (2017) 52:247–51. doi: 10.1016/j.jpedsurg.2016.11.014
73. Engum SA. Minimal access thoracic surgery in the pediatric population. *Semin Pediatr Surg*. (2007) 16:14–26. doi: 10.1053/j.sempedsurg.2006.10.003
74. Mattioli G, Pio L, Disma NM, Torre M, Sacco O, Pistorio A, et al. Congenital lung malformations: shifting from open to thoracoscopic surgery. *Pediatr Neonatol*. (2016) 57:463–6. doi: 10.1016/j.pedneo.2015.10.009
75. Kim HK, Choi YS, Kim K, Shim YM, Ku GW, Ahn KM, et al. Treatment of congenital cystic adenomatoid malformation: should lobectomy always be performed? *Ann Thorac Surg*. (2008) 86:249–53. doi: 10.1016/j.athoracsur.2008.01.036
76. Johnson SM, Grace N, Edwards MJ, Woo R, Puapong D. Thoracoscopic segmentectomy for treatment of congenital lung malformations. *J Pediatr Surg*. (2011) 46:2265–9. doi: 10.1016/j.jpedsurg.2011.09.012
77. Rothenberg SS, Shipman K, Kay S, Kadenhe-Chiweshe A, Thirumoorthi A, Garcia A, et al. Thoracoscopic segmentectomy for congenital and acquired pulmonary disease: a case for lung-sparing surgery. *J Laparoendosc Adv Surg Tech A*. (2014) 24:50–4. doi: 10.1089/lap.2013.0337
78. Benjamin DR, Cahill JL. Bronchioloalveolar carcinoma of the lung and congenital cystic adenomatoid malformation. *Am J Clin Pathol*. (1991) 95:889–92. doi: 10.1093/ajcp/95.6.889
79. Borgia F, Santamaria F, Mollica C, Mongiello F, Esposito F, Palma G, et al. Clinical benefits, echocardiographic and MRI assessment after pulmonary sequestration treatment. *Int J Cardiol*. (2017) 240:165–71. doi: 10.1016/j.ijcard.2017.04.102
80. Lee BS, Kim JT, Kim EA, Kim KS, Pi SY, Sung KB, et al. Neonatal pulmonary sequestration: clinical experience with transumbilical arterial embolization. *Pediatr Pulmonol*. (2008) 43:404–13. doi: 10.1002/ppul.20799
81. Khen-Dunlop N, Farmakis K, Berteloot L, Gobbo F, Stirnemann J, De Blic J, et al. Bronchopulmonary sequestrations in a paediatric centre: ongoing practices and debated management. *Eur J Cardiothorac Surg*. (2018) 54:246–51. doi: 10.1093/ejcts/ezy049
82. Brown SC, De Laat M, Proesmans M, De Boeck K, Van Raemdonck D, et al. Treatment strategies for pulmonary sequestration in childhood: resection, embolization, observation? *Acta Cardiol*. (2012) 67:629–34. doi: 10.1080/AC.67.6.2184664
83. Laje P, Liechty KW. Postnatal management and outcome of prenatally diagnosed lung lesions. *Prenat Diagn*. (2008) 28:612–8. doi: 10.1002/pd.1966
84. Tsai AY, Liechty KW, Hedrick HL, Bebbington M, Wilson RD, Johnson MP, et al. Outcomes after postnatal resection of prenatally diagnosed asymptomatic cystic lung lesions. *J Pediatr Surg*. (2008) 43:513–7. doi: 10.1016/j.jpedsurg.2007.10.032
85. Jelin EB, O'Hare EM, Jancelewicz T, Nasr I, Boss E, Rhee DS. Optimal timing for elective resection of asymptomatic congenital pulmonary airway malformations. *J Pediatr Surg*. (2018) 53:1001–5. doi: 10.1016/j.jpedsurg.2018.02.032
86. Gulack BC, Leraas HJ, Ezekian B, Kim J, Reed C, Adibe OO, et al. Outcomes following elective resection of congenital pulmonary airway malformations are equivalent after 3 months of age and a weight of 5 kg. *J Pediatr Surg*. (2018) 53:60–6. doi: 10.1016/j.jpedsurg.2017.10.017
87. Makhijani AV, Wong FY. Conservative post-natal management of antenatally diagnosed congenital pulmonary airway malformations. *J Paediatr Child Health*. (2018) 54:267–71. doi: 10.1111/jpc.13727
88. Criss CN, Musili N, Matusko N, Baker S, Geiger JD, Kunisaki SM. Asymptomatic congenital lung malformations: is nonoperative management a viable alternative? *J Pediatr Surg*. (2018) 53:1092–7. doi: 10.1016/j.jpedsurg.2018.02.065
89. Cook J, Chitty LS, De Coppi P, Ashworth M, Wallis C. The natural history of prenatally diagnosed congenital cystic lung lesions: long-term follow-up of 119 cases. *Arch Dis Child*. (2017) 102:798–803. doi: 10.1136/archdischild-2016-311233
90. Cho MJ, Kim DY, Kim SC, Kim KS, Kim EA, Lee BS. Embolization versus surgical resection of pulmonary sequestration: clinical experiences with a thoracoscopic approach. *J Pediatr Surg*. (2012) 47:2228–33. doi: 10.1016/j.jpedsurg.2012.09.013
91. Kapralik J, Wayne C, Chan E, Nasr A. Surgical versus conservative management of congenital pulmonary airway malformation in children: a systematic review and meta-analysis. *J Pediatr Surg*. (2016) 51:508–12. doi: 10.1016/j.jpedsurg.2015.11.022
92. Gornall AS, Budd JL, Draper ES, Konje JC, Kurinczuk JJ. Congenital cystic adenomatoid malformation: accuracy of prenatal diagnosis, prevalence and outcome in a general population. *Prenat Diagn*. (2003) 23:997–1002. doi: 10.1002/pd.739
93. Adzick NS, Harrison MR, Crombleholme TM, Flake AW, Howell LJ. Fetal lung lesions: management and outcome. *Am J Obstet Gynecol*. (1998) 179:884–9. doi: 10.1016/S0002-9378(98)70183-8
94. Leith E, Aurora P, Wallis C. An infant with a persistent cough and an unusual course of the nasogastric tube. *Arch Dis Child*. (2018). doi: 10.1136/archdischild-2018-315524. [Epub ahead of print].
95. Alamo L, Gudinchet F, Reinberg O, Vial Y, Francini K, Osterheld MC, et al. Prenatal diagnosis of congenital lung malformations. *Pediatr Radiol*. (2012) 42:273–83. doi: 10.1007/s00247-011-2303-0
96. Morini F, Zani A, Conforti A, van Heurn E, Eaton S, Puri P, et al. Current management of congenital pulmonary airway malformations: a "European Pediatric Surgeons' Association" Survey. *Eur J Pediatr Surg*. (2018) 28:1–5. doi: 10.1055/s-0038-1660778
97. Hall NJ, Stanton MP. Long-term outcomes of congenital lung malformations. *Semin Pediatr Surg*. (2017) 26:311–6. doi: 10.1053/j.sempedsurg.2017.09.001

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Respiratory Morbidity and Lung Function Analysis During the First 36 Months of Life in Infants With Bronchopulmonary Dysplasia (BPD)

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Purpose: To explore the lung function of bronchopulmonary dysplasia (BPD) in premature infants to guide clinical prevention, early diagnosis and treatment.

Methods: Thirty infants with BPD at 4–36 months of corrected gestational age were enrolled and divided into mild BPD and moderate and severe BPD groups. Thirty full-term healthy infants, and 30 non-BPD infants at 4–36 months of corrected gestational age were included as controls. Clinical information, including respiratory infections and re-hospitalization, was compared among these groups. Furthermore, lung function analysis was performed in the infants.

Results: The upper respiratory tract infection rate and re-hospitalization rate were significantly higher in the infants with BPD than in the non-BPD infants. The tidal volume/kg, proportion of time to reach peak tidal expiratory flow/total expiratory time, tidal volume exhaled at peak tidal expiratory flow/total tidal volume in BPD group were significantly lower in the BPD group than those in non-BPD group. These values gradually decreased as the severity of BPD increased. The respiratory rate (RR) in BPD group was significantly higher than that in non-BPD group. As the severity of the BPD increased, slope of the descending branch of expiration of tidal breathing flow capacity ring (TBFVL) increased.

Conclusion: There is a correlation between the severity of BPD and a poor prognosis of respiratory system. TBFVL can directly reflect the characteristics of Tidal Pulmonary Function in children with different degrees of BPD.

Keywords: bronchopulmonary dysplasia (BPD), prognosis, pulmonary function, tidal breathing flow volume loop, respiratory morbidity

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is the most serious respiratory disorder that is observed in premature infants. The "old" and classic definition of BPD was first proposed by Northway et al. (1). According to this report, BPD is usually observed secondary to severe respiratory distress syndrome, and is characterized by oxygen poisoning, barotrauma, volumetric injury, and sustained oxygen for at least 28 days. Following the implementation of lung protective ventilation strategies,

including prenatal glucocorticoids and postnatal pulmonary surfactants, the incidence of classic BPD has significantly reduced. Currently, the term BPD more commonly refers to light BPD (also known as "new" BPD). This definition was adopted by the National Institute of Child Health and Human Development in June of 2001 (2). Light BPD mainly occurs in the immature lung of extremely premature babies without symptoms of respiratory distress syndrome (RDS) or with mild symptoms after birth. In these cases, oxygen delivery is not usually required, or there is only a need for a low concentration of oxygen and oxygen dependence gradually appears during hospitalization. The period of continuous oxygen supply usually exceeds 36 weeks of corrected gestational age (GA). The foremost features of new BPD are delays in lung development and simplified alveolar structure. Following the development of perinatal medicine and technologies of neonatal intensive care, the incidence and survival rate of very low birth weight infants (VLBWI) and extremely low birth weight infants (ELBWI) have increased. However, although there has been a decrease in the rate that other adverse outcomes are observed in preterm infants, the rate of respiratory diseases that are associated with preterm birth has not declined.

Many studies investigating the risk factors of BPD have been reported worldwide. However, few studies have investigated lung function in BPD. In this study, the clinical characteristics, follow-up data, and lung function of premature infants with BPD, as well as non-BPD premature infants and normal lungs of health babies, who were hospitalized in the neonatology department of the Children's Hospital of Soochow University over the same period, were compared and analyzed to explore the respiratory system prognoses. The purpose of this study is to enable early detection of respiratory diseases and pulmonary dysfunction, in order to enable early intervention and treatment, helping to reduce the use of medical resources, improve the disease treatment, and the quality of life of children.

METHODS

Subjects

Data of premature infants who were diagnosed with BPD and hospitalized in the Neonatology Department of The Children's Hospital of Soochow University between October 1st, 2013 and October 1st, 2017 were collected in this study. The long-term situation of these patients was then recorded between October 1, 2014 and October 2017. Some data of premature infants without BPD and full-term health babies, who were hospitalized over the same period, were collected to serve as controls. This study was approved by The Medical Ethics Committee of The Children's Hospital of Soochow University (ethical examination approval number: 2013LW001).

Abbreviations: AUC, area under the curve; BPD, bronchopulmonary dysplasia; BTT, blood transfusion times; BW, body weight; CI, confidence interval; ELBWI, extremely low birth weight infants; FiO_2, fraction of inspired oxygen; GA, gestational age; nCPAP, nasal continuous positive airway pressure; NEC, necrotizing enterocolitis; NRDS, neonatal respiratory distress syndrome; OIT, oxygen inhalation time; P50, 50% saturation; PCO_2, pressure carbon dioxide; PDA, patent ductus arteriosus; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure; PMA, post-menstrual gestational age; ROC, receiver operating characteristic; RF-II, type II respiratory failure; RR, respiratory rate; sd, standard deviation; TBFVL, tidal breathing flow capacity ring; TEF75, exhale flow rate at the remaining 75% tidal volume; TPTEF/Te, proportion of time to reach peak tidal expiratory flow to total expiratory time; VLBWI, very low birth weight infants; VPTEF/Ve, the fraction of tidal volume exhaled at peak tidal expiratory flow (PTEF) to total tidal volume; VT/Kg, tidal volume per kg.

Observation

This study is a retrospective analysis. The infants were divided into four groups: a full-term healthy control group, a non-BPD premature infant group, a mild BPD infant group, and a moderate-to-severe BPD infant group. All of the clinical data from the infants [including the conditions of their mothers during pregnancy, the birth situation of the children, the clinical information (manifestation, symptoms, and examinations, diagnosis, and complications), and treatment measures during hospitalization] were collected, compared, and analyzed. Lung function tests and questionnaires were performed at 4–36 months of GA in the premature infant group. These tests were performed at 4–36 months in the full-term infant groups. The lung function and prognosis of the respiratory system of the infants with BPD were analyzed.

Diagnosis of BPD and Clinical Grading

The diagnosis of BPD was based on the standard of the National Institute of Child Health and Human Development (NICHD). The diagnostic criteria according to the last post-menstrual GA (PMA) (2) were as follows: (1) preterm low birth weight infants, with or without history of mechanical ventilation therapy, oxygen therapy time ≥28 days (PMA ≥ 32 weeks) or 36 weeks of corrected GA (PMA < 32 weeks) who still require oxygen therapy; (2) persistent or progressive respiratory insufficiency; (3) typical X-ray or CT findings of the lungs (such as, both lungs with enhanced texture, reduced permeability, ground glass-like, localized emphysema, or cystic changes); (4) exclusion of congenital heart disease, pneumothorax, pleural effusion and sputum. The clinical grading (2) is based on the aerobic degree of the infants whose GA <32 weeks, the corrected GA of 36 weeks or at discharge, and whose GA ≥ 32 weeks, 56 days of post birth or at the time of discharge were as follows: (i) mild: no oxygen necessary; (ii) moderate: fraction of inspired oxygen (FiO_2) <30%; iii) severe: FiO2 ≥ 30% and/or continuous positive pressure ventilation or mechanical ventilation.

Exclusion Criteria

Infants with the following criteria were excluded from the study: (i) a hospitalization time <28 days, (ii) patients with central nervous system and respiratory system malformation, paralysis, or severe complex congenital heart disease (except atrial septal defect, ventricular septal defect, and patent ductus arteriosus), (iii) patients who were transferred to another hospital, died, or showed chromosomal abnormalities or hereditary metabolic diseases within 28 days after birth, due to surgical

diseases or other reasons or (iv) patients whose clinical data was incomplete.

Pulmonary Function Measurement

The measurement was performed by a MasterScreen PAED Lung Function Analyzer (CareFusion, Hoechberg, German) to obtain the flow signals by flow sensors, which were then integrated to obtain the volume data, thus depicting the flow-volume curve under the tidal breathing state. The indices of tidal volume per kg (VT/Kg), respiratory rate (RR), proportion of time to reach peak tidal expiratory flow to total expiratory time (TPTEF/Te), peak volume ratio (VPTEF/Ve), exhalation flow rate (TEF) at the remaining 75% tidal volume (TEF75), TEF50, and TEF25 were recorded.

Pulmonary Function Analysis

The pulmonary function test was based on the guidelines for tidal breathing and lung function produced by the Respiratory Group Pulmonary Function Cooperative Group of the Chinese Medical Association Pediatrics Branch (3). The test was performed by a designated, trained, and experienced respiratory nurse in a designated and relatively quiet lung function room. The children that were tested did not have respiratory infections in the 2 weeks prior to the analysis, were not taking oral bronchodilator drugs in the week prior to the analysis, and did not show significant abdominal distension 1–2 h after eating. Briefly, the children were sedated with 0.5 ml/kg chloral hydrate, administered orally (if necessary, an enema was used), and placed in the supine position. The necks of the children were then slightly stretched. An appropriate mask was selected to fit tightly around the nose and mouth, to ensure that there was no air leakage. The mask was then connected to the flow sensor. The flow and volume signals of the tidal breathing of the subjects were recorded in real time. Once the breath was stable, 5 consecutive recordings were made. Each recording included at least 20 tidal breathing flow-volume loops. The average value was automatically calculated as the final result by the instrument.

Statistical Analysis

Collected data were analyzed using SPSS (version 19.0) statistical software (SPSS, Chicago, IL, USA). The measurement data that met the normal distribution are presented as mean ± standard deviation (±s). Comparisons between two groups were examined using *t*-tests. Comparison among groups was analyzed by variance. Non-normal distribution data are expressed as 50% saturation (P50), P25, or P75. The rank sum test was employed for comparison between the two groups. The *K* test was applied for comparison between groups. Count data are presented as (%). *Chi-square test* or Fisher's exact probability method was used for comparison between the two groups (4). $P < 0.05$ was considered statistically significant.

RESULTS

Respiratory Infections and Re-hospitalization

The rate of respiratory infection and re-hospitalization in infants under 1 year of age were compared the between the BPD and non-BPD groups. The frequencies of upper respiratory tract infection, pneumonia, wheezing, and re-hospitalization were significantly higher in the BPD group than those in the non-BPD group ($p < 0.01$; **Table 1**). In addition, the frequency of upper respiratory tract infection, pneumonia, and wheezing were significantly higher in the moderate/severe BPD group than in the mild BPD group. Similarly, these rates were higher in the mild BPD group than in the non-BPD group. Furthermore, the frequency of these conditions was higher in the non-BPD group than in the full term healthy controls (**Table 2**).

Lung Function Analysis

Compared with the results in the non-BPD group, the lung function parameters, including VT/Kg, TPTEF/Te, and the fraction of tidal volume exhaled at peak tidal expiratory flow to total tidal volume (VPTEF/Ve), were lower in the BPD group ($p < 0.05$). However, RR was higher in the non-BPD group than in the BPD group ($p < 0.05$). There was no significant difference in the TEF75, TEF50, or TEF25 between the two groups ($p > 0.05$; **Table 3**). The lung function analysis among

TABLE 1 | Lung function analysis in the BPD and non-BPD groups.

Item	BPD ($n = 30$)	Non-BPD ($n = 30$)	t/U	P
VT/Kg (ml/kg)	6.52 ± 1.70	8.00 ± 1.24	−3.86	< 0.001
RR (times/min)	41.35 ± 8.46	33.63 ± 6.48	3.97	< 0.001
TPTEF/Te (%)	15.55 (12.08, 17.85)	21.00 (17.95, 22.23)	160.00	< 0.001
VPTEF/Ve (%)	19.60 (16.98, 22.33)	22.70 (19.70, 25.80)	271.00	0.008
TEF75 (ml/s)	120.43 ± 37.86	122.59 ± 35.57	−0.22	0.825
TEF50 (ml/s)	90.50 (66.75, 112.50)	107.00 (72.50, 118.00)	357.50	0.439
TEF25 (ml/s)	52.50 (42.25, 75.00)	66.00 (42.50, 80.50)	364.50	0.508

BPD, bronchopulmonary dysplasia; VT/Kg, tidal volume per kg; RR, respiratory rate; TPTEF/Te, proportion of time to reach peak tidal expiratory flow to total expiratory time; VPTEF/Ve, the fraction of tidal volume exhaled at peak tidal expiratory flow (PTEF) to total tidal volume; TEF75, exhale flow rate at the remaining 75% tidal volume; TEF50, exhale flow rate at the remaining 50% tidal volume; TEF25, exhale flow rate at the remaining 25% tidal volume.

TABLE 2 | Respiratory infections and re-hospitalization in the BPD and non-BPD groups.

Frequency (time)	BPD ($n = 30$)	Non-BPD ($n = 30$)	U	P
Up res infection	4.00 (3.75, 5.00)	2.50 (2.00, 3.00)	73.50	<0.001
Pneumonia	2.00 (1.75, 2.25)	1.00 (0.00, 1.00)	78.00	<0.001
Wheezing	2.00 (2.00, 3.00)	0.50 (0.00, 1.00)	60.00	<0.001
Re-hosp	1.50 (1.00, 2.00)	0.00 (0.00, 1.00)	60.00	<0.001

BPD, bronchopulmonary dysplasia; Up res infection, upper respiratory tract infection; Re-hosp, re-hospitalization.

the four groups indicated that the TPTEF/Te, VPTEF/Ve, and VT/Kg in the moderate and severe BPD group were lower than those in the mild BPD group ($p < 0.05$). These same parameters were lower in the mild BPD group than in the non-BPD group ($p < 0.05$). Furthermore, these parameters were lower in the non-BPD group than in the full-term healthy controls ($p < 0.05$; **Table 4**).

Lung Function Analysis in Different Age Groups

The lung function analysis in the different age groups indicated that the TEF75 and TEF50 in the 12–24 and 24–36 month groups were higher than those in the 6–12 and < 6 month groups ($p < 0.05$). The TEF75 and TEF50 in the 6–12 months below group were higher than those of the < 6-month group ($P < 0.05$). The TEF25 gradually increased with age (**Table 5**).

Tidal Breathing Flow Capacity Ring (TBFVL) Status

Taking the 4 months of corrected gestational age as an example, the inspiratory phase was relatively smooth, the peak of exhalation was advanced, and the expiratory phase was steeper in the BPD group than in the Non-BPD groups. The more severe the BPD, the steeper the descending branch and the more severe of the slope (**Figure 1**).

DISCUSSION

BPD is the most common pulmonary complication in preterm infants. This condition is associated with a variety of risk factors and multiple long-term effects (5). BPD can reduce lung function (6), physical activity, and cardiovascular function (7). These effects can be sustained into adulthood (8). Therefore, BPD has a serious impact on the public health system, due to the burden it places on medical resources. In the past decade, researchers have described the long-term sequelae of premature survivors. These studies have mainly focused on the lungs and the nervous system. However, in this field, few studies have been performed in China. Previous studies have indicated that infants with BPD have an increased risk of respiratory infections, higher rates of re-hospitalization (9) and are more prone to wheezing and recurrent wheezing (10). Abnormalities in persistent lung function are more common in infancy, and the extent of the abnormalities depends on the severity of BPD (11). The data in this study suggest that the infants with BPD had more respiratory infections, pneumonia, wheezing and a higher frequency of re-hospitalization than those in the non-BPD premature group. There was a correlation between the BPD severity and the number of infections, which is consistent with the above findings.

BPD-induced pulmonary dysfunction is a restrictive or obstructive disorder syndrome that changes over time. The

TABLE 3 | Respiratory infections and re-hospitalization in the four groups.

Frequency (time)	Full-term ($n = 30$)	Non-BPD ($n = 30$)	Mild-BPD ($n = 15$)	M/S BPD ($n = 15$)	H	*P*
Up res infection	1.00 (1.00, 2.00)^{bdf}	2.50 (2.00, 3.00)^{df}	3.50 (3.00, 4.00)^{e}	5.00 (4.00, 5.00)	62.12	<0.001
Pneumonia	0.00 (0.00, 1.00)^{df}	1.00 (0.00, 1.00)^{de}	1.50 (1.00, 2.000)^{e}	2.00 (2.00, 3.00)	52.29	<0.001
Wheezing	0.00 (0.00, 0.00)^{adf}	0.50 (0.00, 1.00)^{de}	2.00 (2.00, 3.000)^{e}	3.00 (2.00, 3.00)	57.48	<0.001
Re-hosp	0.00 (0.00, 1.00)^{df}	0.00 (0.00, 1.00)^{de}	1.00 (1.00, 2.00)^{e}	2.00 (1.00, 2.00)	62.14	<0.001

BPD, bronchopulmonary dysplasia; M/S BPD, moderate and severe BPD group; Up res infection, upper respiratory tract infection; Re-hosp, re-hospitalization; a, the frequency is higher in the Full-term group than in the Non-BPD group, P < 0.05; b, the frequency is higher in the Full-term group than in the Non-BPD group, P < 0.001; d, the frequency is higher in the Full-term group than in the Mild-BPD group, P < 0.001; e, the frequency is higher in the Full-term group than in the M/S BPD group, P < 0.05; f, the frequency is higher in the Full-term group than in the M/S BPD group; P < 0.001.

TABLE 4 | Lung function analysis in four groups.

Item	Full-term ($n = 30$)	Non-BPD ($n = 30$)	Mild BPD ($n = 15$)	M/S BPD ($n = 15$)	H	*P*
VT/Kg (ml/kg)	8.45 (6.35, 9.43)^{ace}	8.20 (6.98, 8.93)^{cf}	6.35 (5.75, 7.60)^{e}	6.00 (5.20, 7.60)	14.78	0.002
RR (times/min)	34.90 (27.08, 41.60)^{f}	34.00 (28.15, 38.95)^{f}	42.70 (33.95, 47.00)	45.00 (40.00, 47.00)	20.19	<0.001
TPTEF/Te (%)	26.40 (23.53, 27.80)^{bdf}	21.00 (17.95, 22.23)^{cf}	15.55 (12.08, 17.85)^{f}	12.10 (11.70, 17.00)	53.43	<0.001
VPTEF/Ve (%)	28.85 (26.60, 30.70)^{bdf}	22.70 (19.70, 25.80)^{cf}	19.60 (16.98, 22.33)^{f}	17.00 (15.10, 19.30)	51.06	<0.001
TEF75 (ml/s)	113.50 (86.75, 137.75)	117.70 (97.50, 137.50)	120.0 (93.50, 141.00)	121.50 (98.75, 162.50)	0.46	0.928
TEF50 (ml/s)	109.50 (81.75, 130.00)	90.50 (66.75, 112.50)	107.0 (72.50, 118.00)	101.00 (73.50, 120.00)	2.86	0.413
TEF25 (ml/s)	79.50 (60.50, 87.00)^{ace}	52.50 (42.25, 75.00)	66.00 (42.50, 80.50)	62.50 (40.00, 79.50)	7.37	0.041

BPD, bronchopulmonary dysplasia; VT/Kg, tidal volume per kg; RR, respiratory rate; TPTEF/Te, proportion of time to reach peak tidal expiratory flow to total expiratory time; VPTEF/Ve, the fraction of tidal volume exhaled at peak tidal expiratory flow (PTEF) to total tidal volume; TEF75, exhale flow rate at the remaining 75% tidal volume; TEF50, exhale flow rate at the remaining 50% tidal volume; TEF25, exhale flow rate at the remaining 25% tidal volume. $^{a,b}P < 0.05$ and 0.001, respectively, compared to the non-BPD group results; $^{c,d}P < 0.05$ and 0.001, respectively, compared to the mild BPD group results; $^{e,f}P < 0.05$ and 0.001, respectively, compared to the moderate and severe BPD group results.

restrictive dysfunction is more severe clinically. However, the obstructive dysfunction is more common (12). Due to alveolar and pulmonary microvascular developmental delay in BPD infants (13), the number of alveoli was lower than in non-BPD infants. Furthermore, BPD infants showed simplified alveolar structure, mild fibrosis of airway and surrounding tissue, and microvascular dysplasia, leading to increased pulmonary vascular resistance and pulmonary vascular remodeling (14). Colin et al. (15) reported that the high elasticity of the chest wall of the newborn resulted in a decrease in transpulmonary pressure and a reduction in the lung capacity during expiration and closed airway, resulting in a decreased flow rate. Because the elasticity of the chest wall was higher in premature infants, the decreased expiratory flow rate was more pronounced in this group. Friedrich et al. (16) believed that, due to the immature lung development in premature infants, even if the lung capacity is normal after birth, the respiratory flow rate would still be decreased. This suggests that the

TABLE 5 | Lung function analysis in different age groups.

Item	<6 M (n = 28)	6–12 M (n = 31)	12–24 M (n = 21)	24–36 M (n = 10)	*F*	*P*
VT/Kg (ml/kg)	7.24 ± 1.17	7.61 ± 2.11	8.15 ± 2.11	8.51 ± 2.11	1.03	0.382
RR (time/min)	40.80 ± 9.80^{c}	37.15 ± 8.32^{b}	37.05 ± 8.53	31.49 ± 7.86	4.56	0.005
TPTEF/Te (%)	20.53 ± 5.15	20.45 ± 6.39	20.76 ± 5.81	18.58 ± 7.55	1.24	0.299
VPTEF/Ve (%)	23.65 ± 4.91	23.70 ± 5.35	23.11 ± 5.36	22.21 ± 7.69	0.68	0.565
TEF75 (ml/s)	100.48 ± 26.28^{ace}	114.33 ± 25.88^{be}	138.65 ± 41.51	157.70 ± 41.50	10.47	< 0.001
TEF50 (ml/s)	80.00 ± 28.93^{ace}	96.43 ± 25.44^{be}	119.15 ± 31.06	141.00 ± 47.56	12.25	< 0.001
TEF25 (ml/s)	53.37 ± 20.62^{ace}	63.90 ± 22.68^{be}	79.50 ± 22.50^{d}	100.80 ± 41.41	10.89	< 0.001

M, months; VT/Kg, tidal volume per kg; RR, respiratory rate; TPTEF/Te, proportion of time to reach peak tidal expiratory flow to total expiratory time; VPTEF/Ve, the fraction of tidal volume exhaled at peak tidal expiratory flow (PTEF) to total tidal volume; TEF75, exhale flow rate at the remaining 75% tidal volume; TEF50, exhale flow rate at the remaining 50% tidal volume; TEF25, exhale flow rate at the remaining 25% tidal volume. $^{a}P < 0.05$, respectively, compared to the 6–12 month group results; $^{b,c}P < 0.05$ and 0.001, respectively, compared to the 12–24 month group results; $^{d,e}P < 0.05$ and 0.001, respectively, compared to the 24–36 month group results.

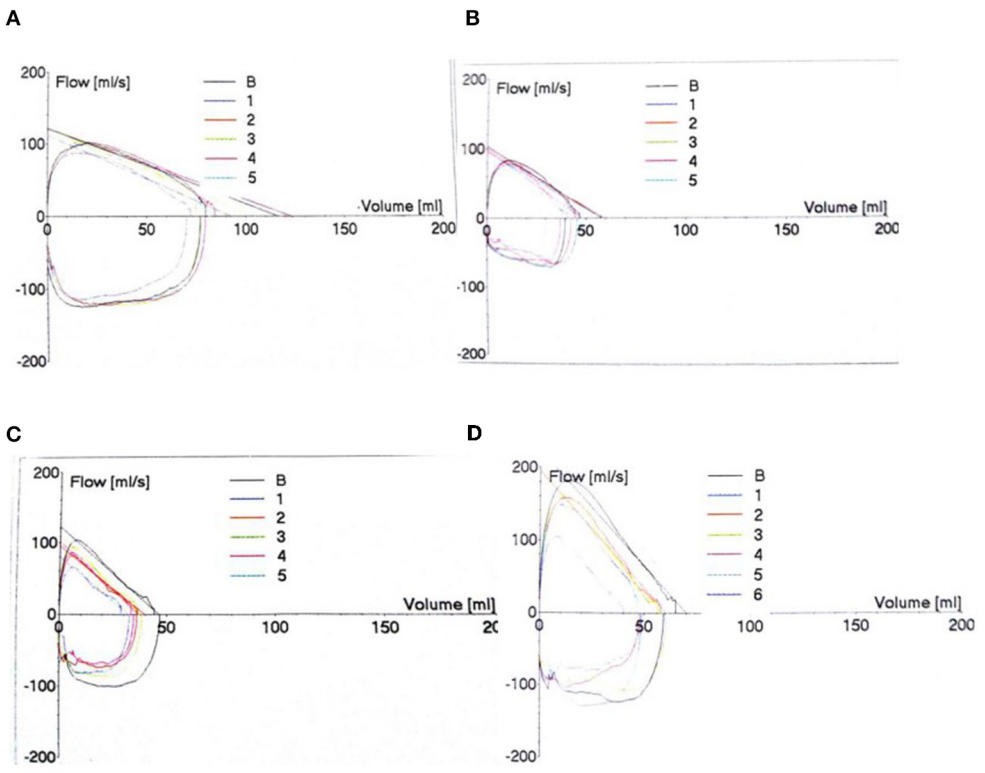

FIGURE 1 | Tidal Breathing Flow Capacity Ring (TBFVL) Status. The changes in TBFVL were recorded in the non-BPD **(A)**, mild **(B)**, moderate **(C)** and severe **(D)** BPD groups.

long-term development of the airway is delayed. Our study found that premature infants with BPD had small airway obstructions. The more severe the BPD disease, the more obvious the small airway obstruction was. Thus, in severe cases of BPD, oxygen supply would be more reliant on the increased respiratory rate for compensation to maintain normal ventilation function. The lung volume flow rate increased significantly after 1 year of age. However, the small airway obstruction was still observed. This suggests that the development of premature infants with lung dysplasia is dominated by the lung capacity development, while their airway development is delayed. All of these results are consistent with the above findings.

The tidal breathing flow volume loop can reflect the presence or absence of an obstruction in the airway, the degree and location of the obstruction, and the ventilatory function. This measurement assists in diagnosing the of nature of the pulmonary disease and the degree of lung damage, providing an objective indicator for clinical evaluation. Tidal pulmonary function is a new technology that reflects the lung function of infants and young children. The advantage of this method is that it is a safe, non-invasive, sensitive, and accurate reflection of changes in lung capacity and ventilation function. Our analysis indicates that the inspiratory phase of the BPD premature infants was relatively smooth and nearly a half elliptical shape. The exhalation curve, however, was not smooth. The peak of exhalation occurred sooner in BPD premature infants. The expiratory decline was steep. The more severe the BPD, the larger the slope of the descending branch. These findings support the work of Wei et al. (17).

This study was a small-sample study in a single center and external cohort verification was not performed. Because of time constraints, some parents did not aware the importance of early intervention, some patients with severe BPD died after they were discharged or transferred to other hospitals, resulting in fewer follow-up cases than expected. The larger the follow-up age span, the more discrete the observation indicators. In addition, we did not carry out dynamic follow-up assessment, thus, the results do not reflect the trend of dynamic alteration of the indices along with the age increase. Therefore, it would be valuable to perform further studies with a larger sample size, longer follow-up period, dynamic follow-up, and fully internal and external cohort verification.

In summary, the etiology of BPD is complex and diverse. BPD can cause abnormal lung function and seriously affect the prognosis. Therefore, clinicians should develop a preventive strategy for BPD, provide prenatal guidance, avoid the risk factors for BPD as much as possible, and establish follow-up management after discharge, systemically improving the long-term prognosis of children with BPD.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethics Committee of The Children's Hospital of Soochow University (ethical examination approval number: 2013LW001). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DC participated in study design and protocol development and writing of the manuscript. JC carried out the data analysis and interpretation of data. NC, MC, and XC participated in clinical data collection. XuZ participated in data analysis, interpretation of data and writing of the manuscript. XiZ participated in the design of the study and coordination. All authors read and approved the final manuscript.

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REFERENCES

1. Northway WH Jr, Rosan RC, Porter DY. Pulmonary disease following respirator therapy of hyaline-membrane disease. Bronchopulmonary dysplasia. *N Engl J Med.* (1967) 276:357–68. doi: 10.1056/NEJM196702162760701
2. Jobe AH, Bancalari E. Bronchopulmonary dysplasia. NICHD/NHLBI/ORD workshop summary. *Am J Respir Crit Care Med.* (2001) 163:1723–29. doi: 10.1164/ajrccm.163.7.2011060
3. Respiratory Lung Function Collaboration Group SoP, Chinese Medical Association. Children's lung function series guidelines (4th): tidal respiratory lung function. *Chin J Pract Pediatr.* (2016) 31:1617–21. doi: 10.3760/cma.j.issn.2095-428X.2016.21.005
4. Zhang Z. Univariate description and bivariate statistical inference: the first step delving into data. *Ann Transl Med.* (2016) 4:91. doi: 10.21037/atm.2016.02.11
5. Katz SL, Luu TM, Nuyt AM, Lacaze T, Adamo KB, Adatia I, et al. Long-term follow-up of cardiorespiratory outcomes in children born extremely preterm: recommendations from a Canadian consensus workshop. *Paediatr Child Health.* (2017) 22:75–9. doi: 10.1093/pch/pxx028
6. Kotecha SJ, Edwards MO, Watkins WJ, Henderson AJ, Paranjothy S, Dunstan FD, et al. Effect of preterm birth on later FEV1: a systematic review and meta-analysis. *Thorax.* (2013) 68:760–6. doi: 10.1136/thoraxjnl-2012-203079
7. Clemm H, Roksund O, Thorsen E, Eide GE, Markestad T, Halvorsen T. Aerobic capacity and exercise performance in young people born extremely preterm. *Pediatrics.* (2012) 129:e97–105. doi: 10.1542/peds.2011-0326

8. Landry JS, Chan T, Lands L, Menzies D. Long-term impact of bronchopulmonary dysplasia on pulmonary function. *Can Respir J.* (2011) 18:265–70. doi: 10.1155/2011/547948
9. Bhandari A, McGrath-Morrow S. Long-term pulmonary outcomes of patients with bronchopulmonary dysplasia. *Semin Perinatol.* (2013) 37:132–7. doi: 10.1053/j.semperi.2013.01.010
10. Fauroux B, Gouyon JB, Roze JC, Guillermet-Fromentin C, Glorieux I, Adamon L, et al. Respiratory morbidity of preterm infants of less than 33 weeks gestation without bronchopulmonary dysplasia: a 12-month follow-up of the CASTOR study cohort. *Epidemiol Infect.* (2014) 142:1362–74. doi: 10.1017/S0950268813001738
11. Doyle LW, Anderson PJ. Long-term outcomes of bronchopulmonary dysplasia. *Semin Fetal Neonatal Med.* (2009) 14:391–5. doi: 10.1016/j.siny.2009.08.004
12. Beverley R, Young-Jee K, Jaimee H, Jim K, Margaret T, Tepper RS, et al. Pulmonary function in bronchopulmonary dysplasia. *Pediatr Pulmonol.* (2010) 37:236–42. doi: 10.1002/ppul.10424
13. Copland I, Post M. Lung development and fetal lung growth. *Paediatr Respir Rev.* (2004) 5(Suppl. A):S259–64. doi: 10.1016/S1526-0542(04)90049-8
14. Mourani PM, Abman SH. Pulmonary vascular disease in bronchopulmonary dysplasia: pulmonary hypertension and beyond. *Curr Opin Pediatr.* (2013) 25:329–37. doi: 10.1097/MOP.0b013e328360a3f6
15. Colin AA. Infant pulmonary testing – techniques, physiological perspectives and clinical applications. *Paediatr Respir Rev.* (2004) 5(Suppl. A):S73–6. doi: 10.1016/S1526-0542(04)90014-0
16. Friedrich L, Pitrez PM, Stein RT, Goldani M, Tepper R, Jones MH. Growth rate of lung function in healthy preterm infants. *Am J Respir Crit Care Med.* (2007) 176:1269–73. doi: 10.1164/rccm.200703-476OC
17. Wei MC, Yu JL, Liu XH. Monitoring of lung function in children with bronchopulmonary dysplasia by tidal expiratory flow velocity-capacity loop. *J Chongqing Med Univ.* (2013) 10:1185–89.

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MINI REVIEW
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The Role of Vitamin D Deficiency in Children With Recurrent Wheezing—Clinical Significance

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Recurrent wheezing (RW) in infancy is one of the most frequent reasons for parents to consult health care providers and creates a significant global burden. Clinical course of RW is difficult to predict, also which infants will progress to asthma, since no valid biomarkers have been established. Identification of those infants with RW who are at risk of further recurrences and/or severe acute respiratory tract infection (ARTI) could help pediatricians to improve their therapeutic decisions. Increasing research interest is focused on the extra-skeletal actions of vitamin D (VD) and the clinical impact of VD insufficiency/deficiency. As VD deficiency could be a risk factor for causing RW in children, measurement of their serum level of 25-hydroxycholecalciferol [25(OH)D] is recommended. In the case of deficiency, VD administration is recommended in age-appropriate doses for at least 6 weeks, until achievement of normal blood 25(OH)D level, followed by supplementation as long as exposure to sun is inadequate. Higher doses of VD given in an attempt to prevent asthma development appear to be of no additional benefit. In children with severe ARTI, VD level is recommended to be assess.

Keywords: vitamin D, 25(OH)D, vitamin D receptor (VDR), recurrent wheezing, asthma, respiratory allergies

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KEY POINTS—QUESTIONS

Could vitamin D status be a biomarker for risk of ARTI in children with recurrent wheezing?
Does vitamin D supplementation affect the incidence and clinical course of ARTI?
Does vitamin D supplementation modify development of respiratory allergies (asthma)?

MEANING

- Children with recurrent wheezing may be vitamin D deficient, and their serum level of 25(OH)D would be useful for identifying those children who would benefit from vitamin D supplementation.
- Vitamin D supplementation may reduce the risk of respiratory infection and asthma exacerbation in some clinical contexts. In the case of deficiency, vitamin D should be administered in daily dose depending on age, for at least 6 weeks, until achievement of a normal serum 25(OH)D level, followed by supplementation when sun exposure is inadequate.
- In deficient children, higher doses of vitamin D appear to provide no extra benefit in modifying the clinical course of ARTIs or preventing asthma.

INTRODUCTION

Vitamin D (VD) research has been focused increasingly on its extra-skeletal actions and its possible role in immune system modulation, and on the clinical impact of VD insufficiency. Viral lower respiratory tract infection, acute viral bronchitis, acute bronchiolitis, viral pneumonia, viral wheeze, recurrent/transient/multi-trigger wheezing, and viral induced exacerbation of asthma are only a few of the vast range of terms used as diagnostic labels for respiratory illnesses cause by respiratory viruses in infancy and early childhood (1). Recurrent wheezing (RW) in infancy is one of the most frequent reasons for parents to consult health care providers and constitutes a huge global burden. This review analyzes the current evidence for the relationship between VD status and RW in infancy and childhood, including potential progress to asthma, and the effects of VD supplementation.

RECURRENT WHEEZING

Many different conditions can produce "wheezing," which is a musical sound caused by the passage of air through narrow respiratory tract airways, but this airway narrowing is caused most often by acute respiratory tract infection (ARTI) (2). RW in children aged ≤5 years is a heterogeneous condition, typically associated with recurrent upper respiratory tract infections (URTIs). As each patient may have 6–8 episodes of URTI per year, the question of whether a wheezing episode is an initial or a recurrent clinical event constitutes a challenge to the clinician, but RW is generally defined as 2 or more episodes of reported wheezing since birth. Wheezing phenotypes proposed by the European Respiratory Society (ERS) Task Force in 2008 differ, based on the criteria used for classification: episodic viral or multiple-trigger wheeze, according to symptom-based classification; transient, persistent and late-onset wheeze, according to time trend-based classification (3). Theoretically, this approach enables individual therapeutic decisions to be made based on the temporal pattern of symptoms (4). In clinical practice, so many infants and young children present wheezing with viral infections that early allocation to one of these phenotypes is unrealistic (5). Identification of those infants with RW at risk for future recurrence and/or severe evolution could help pediatricians to optimize their therapeutic decisions.

VITAMIN D

Sources and Metabolism

VD in the human organism comes from exposure to sunlight and from food and supplements. Ultraviolet B radiation converts 7-dehydrocholesterol to previtamin D_3 and subsequently to vitamin D_3 (6). Foods provide vitamins D_2 and D_3, supplements prescribed for treatment in the US contain D_2, while those for prevention, and all European supplements, contain D_3 (7). VD from all sources is metabolized in the liver to 25-hydroxyvitamin D [25(OH)D] which is further transformed in the kidneys by the enzyme 1α-hydroxylase [1α(OH)ase, CYP27B1] to its active form, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] (6). In addition, synthesis of the biologically active metabolite $1,25(OH)_2D$ takes place intracellularly (8). The effects of $1,25(OH)_2D$ are mediated through specific high-affinity vitamin D receptor (VDR) via upregulating or downregulating target genes (9).

Local Immunomodulatory and Antiviral Activity of Vitamin D

During a lower respiratory infection, various factors, virus-dependent and host-dependent, regulate the development and severity of infections. It has been suggested that host reactions to viral infection, rather than the direct viral injury, are responsible for the clinical and pathological manifestations (10) and contribute to the development of RW after repeated ARTI. Different respiratory viruses will produce an immune host response mediated by both T and B cells.

In addition to well-researched functions in calcium homeostasis, VD and VDR modulate both the innate and the adaptive immune response, and play a key role in the balance between T-helper 1 and T-helper 2 (Th1-Th2) cytokines (11, 12).

In vitro studies suggest that VD induces a shift in the balance between Th1-type and Th2-type cytokines toward Th2 dominance (2). It has been shown that VD decreases the proinflammatory type 1 cytokines: IL-12, interferon-gamma (IFN-γ), IL-6, IL-8, tumor necrosis factor alpha (TNFα) and IL-17 and increase anti-inflammatory IL-10 and Th2 cytokines: IL-4 and IL-5 (13–15). A few human studies demonstrated the shift toward Th2, while others do not confirm these results. The relationship between serum VD levels and asthma remains controversial, and a U-shaped association has been suggested, with both VD deficiency and high levels of VD leading to a risk of asthma and allergy (16).

VD modulates B cell activities, influencing production of immunoglobulin E (IgE), and decreasing cell proliferation and differentiation but increasing apoptosis (15). In a British birth cohort, at the age of 45 years, IgE concentrations were higher in both subjects with VD <25 nmol/l and those with VD >135 nmol/l, suggesting that both low and high VD levels are associated with elevated IgE levels, confirming the U-shaped relationship (17). A review of *in vitro* experiments investigating the immunomodulatory activity of VD revealed no influence on replication or clearance of respiratory viruses in human respiratory epithelial cells (15).

The respiratory viruses, rhinovirus (RV) and respiratory syncytial virus (RSV) are reported to downregulate VDR mRNA expression in primary bronchial epithelial cells (PBECs). RV replication and its capacity to infect epithelial cells were found reduced in VD treated PBECs, suggesting that this might contribute to the antiviral activity of vitamin D (18).

In vitro and animal studies have shown an inhibitory effect of VD on airway smooth muscle cells, suggesting implication of VD in airway remodeling, which may be a primary event in asthma pathogenesis (19, 20).

Despite lack of solid documentation, it is generally accepted that VD deficiency has effects not only on calcium homeostasis and bone health but also on non-skeletal diseases (21), as shown in **Figure 1** (22).

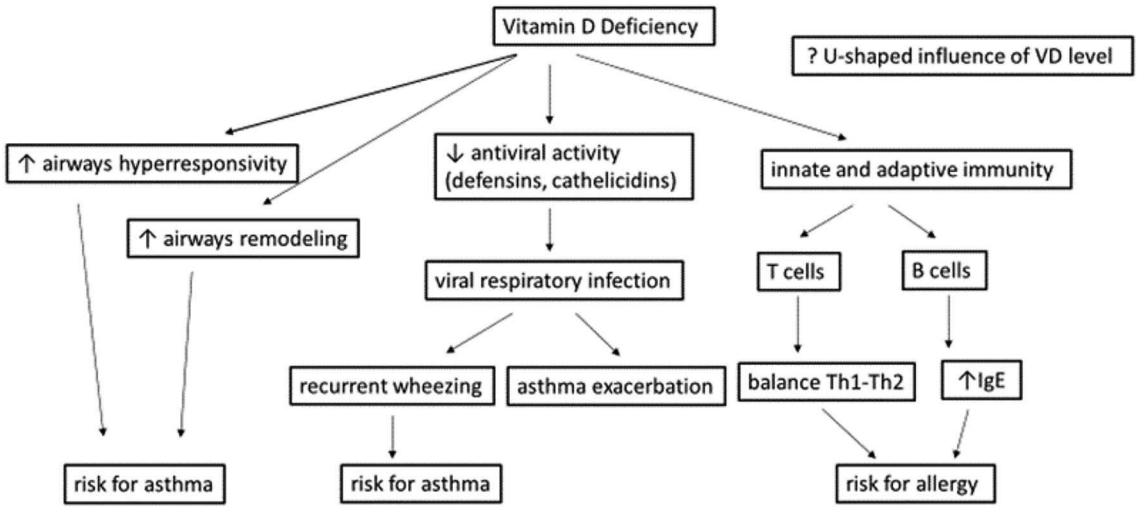

FIGURE 1 | Potential effects of vitamins D deficiency during a viral respiratory infection [adapted from Mirzakhani et al. (22)].

Vitamin D Requirements in Childhood

Needs for VD intake depend on latitude, season, ethnicity, age, body weight, health status, dress habits and use of sunscreen creams. Many experts suggest that both children and adults should take ≥800–1,000 IU vitamin D/day from dietary and supplemental sources when exposure to sunlight is unable to provide it (23). Sacheck and colleagues showed that children at risk for vitamin D deficiency achieved a higher mean 25(OH)D serum level after 3 months daily supplementation with 2,000 IU/day than with 600 and 1,000 IU/day, doses closer to the current recommended daily allowance (24). The Endocrine Society Practice Guidelines Committee (**Table 1**) and the European Academy of Pediatrics (EAP) recommend for prevention in infants (0–1 year) and children (1–18 years) at risk of vitamin D deficiency, 400–1,000 IU/day, and 600–1,000 IU/day, respectively (25).

For treatment of deficiency, 2,000 IU/day for at least 6 weeks, to achieve a serum 25(OH)D level >30 ng/ml has been suggested, followed by doses as for prevention (26). Administration of VD to patients with low baseline 25(OH)D levels should be in doses sufficient to achieve normal levels (i.e., treatment of deficiency not supplementation). Studies to date have produced conflicting findings of relative efficacy but both vitamin D_2 and D_3 are recommended (26).

Few pediatricians, however, apply these guidelines in practice. DelGiudice and colleagues report that although most primary care providers are aware that vitamin D deficiency is common, fewer than half currently recommend 600–1,000 IU supplementation for their pediatric patients (27).

Vitamin D Status: Deficiency—Insufficiency Definitions

Serum or plasma level of total 25(OH)D is currently used as the indicator of VD status (28). Almost all professional associations define VD status as sufficient when the level of 25(OH)D is at least 30 ng/mL, insufficient at 21–29 ng/mL and deficient at <20 ng/mL (7). The European Society for Pediatric Gastrenterology, Hepatology and Nutrition (ESPGAHN) characterizes as sufficient serum 25(OH)D concentrations >50 nmol/L (20 ng/ml), and <25 nmol/L (10 ng/ml) as severe deficiency (29). To convert 25(OH)D from ng/mL to nmol/L, multiply by 2.496 (28).

Current recommendations for VD screening concern only groups of children at risk for VD deficiency. Obesity, pigmented skin, inadequate diet intake, indoor lifestyle, lack of sunlight exposure (beyond a latitude of 35°), use of sun screen, liver disease, drugs (rifampicin, glucocorticoids, anticonvulsants) are all risk factors for VD deficiency and insufficiency in children (30). Following improved understanding of VD involvement in host reactions against infection and within the immune system, both innate and adaptive, the relevant guidelines have begun to include groups with recurrent RTI and asthma (31).

VITAMIN D STATUS AND RECURRENT WHEEZING/VIRAL RESPIRATORY INFECTION

Epidemiological and observational studies have demonstrated a clear association between VD deficiency and viral respiratory infections in certain contexts, while interventional studies on VD supplementation and/or VD status have had mixed findings.

Relationship Between Vitamin D Deficiency and Wheezing and/or Viral Respiratory Tract Infections

The most common viruses responsible for acute respiratory infections in infants and children are the influenza virus, RVs, RSV and metapneumovirus. Only few VD studies have identified the exact type of viral infection, but found no association of VD

TABLE 1 | Vitamin D requirements according to age; doses recommended by the Endocrine Society Practice Guidelines Committee, for prevention and treatment of vitamin D deficiency, and upper limits for administration without risk of adverse events (26).

Recommended daily dose (IU) of vitamin D	0–6 months	6–12 months	1–3 years	4–8 years	8–18 years
Prevention*	400–1,000			600–1,000	
Treatment of deficiency**	2,000			2,000	
Tolerated upper limit	2,000	2,000	4,000	4,000	4,000

25(OH)D = 25 hydroxy vitamin D.
**In patients at risk for vitamin D deficiency.*
***For at least 6 weeks, to achieve a blood level of 25(OH)D > 30 ng/ml.*

levels with the presence of a certain virus, except in patients with positive RSV, RV or coinfections (32).

Eroglu and colleagues recently showed that 25(OH)D_3 levels were significantly lower in children with RW than in a healthy control group, and had no relationship with hospitalization, oxygen, or steroid treatment (33). In an earlier study, a significantly lower mean 25(OH)D level was observed in patients with RW than in a healthy control group, and the level was negatively correlated with the duration of wheezing, number of wheezing episodes and systemic glucocorticoid need (34). Conversely, Pecanha and colleagues showed no association between 25(OH)D concentration and exacerbations, as assessed on the basis of hospitalizations, emergency department (ED) visits, and oral corticosteroid use in children with RW, but observed an association with onset of wheezing before the age of 1 year (35).

McNally and colleagues investigated 105 children aged <5 years with ARTI (bronchiolitis and pneumonia) requiring hospitalization, and 92 control children. Mean 25(OH)D level were not significantly different in the control and ARTI groups but were significantly lower in the 16 children with ARTI requiring PICU admission (15%) than in both the control subjects and children in the general pediatric ward. The authors concluded that deficient VD status may influence the severity of ARTI, but not the risk of hospitalization (36). Similarly, in a 17-center prospective cohort study of infants hospitalized with bronchiolitis, those with total 25(OH)D <20 ng/ml had an increased risk of intensive care and longer hospital length-of-stay (37). In a study comparing 64 infants hospitalized in a general pediatric ward for ARTI and 65 control subjects, all aged 1 month−2 years, mean 25(OH)D and prevalence of VD deficiency/insufficiency were similar in the two groups, and not associated with risk of hospitalization for ARTI (38). A review of 12 studies showed that the children with LRTI had significantly lower mean VD levels than the control subjects, and demonstrated a correlation between VD levels and the incidence and severity of LRTI (39).

Evidence generated from recent meta-analyses revealed that increased prenatal exposure to 25(OH)D (measured as cord blood or maternal venous blood) was inversely associated with risk for wheeze and/or RTI, in the offspring, while for asthma the evidence was mixed (40–42). The inverse association for wheeze was more pronounced and statistically significant in the studies that measured 25(OH)D levels in cord blood (43).

Role of Vitamin D Supplementation and Wheezing (Antenatal—Postnatal, Prevention –Treatment)

Almost all interventional studies support the value of VD supplementation in pregnancy in reducing the prevalence of RW in infants. The findings of efficacy studies of VD supplementation in infancy are contradictory regarding viral respiratory infection.

Antenatal Vitamin D Supplementation

The VD Antenatal Asthma Reduction Trial (VDAART) was a trial of prenatal VD supplementation, in which 440 women were randomized to receive 4,000 IU/day VD, and 436 women only 400 IU. The incidence of asthma and RW in their children at the age of 3 years was lower by 6.1% in the group with the higher intake, but this did difference was not statistically significant (28). Prenatal VD supplementation did not affect the development of asthma and RW at the age of 6 years (44). These results suggest that antenatal supplementation alone does not provide adequate protection, and postnatal supplementation is needed. In a meta-analysis of data from 16 birth cohorts, Feng showed that increased antenatal exposure to 25(OH)D is inversely related to the risk of asthma and wheeze in the offspring, but not respiratory tract infections (43).

Postnatal Vitamin D Supplementation

In 703 healthy children aged 1–5 years, administration of 2,000 IU, compared with 400 IU, of VD for a minimum of 4 months between September and May did not reduce the prevalence of upper ARTI during the winter (45). A secondary analysis of this multisite RCT assessing whether wintertime high-dose VD supplementation reduces URTI symptom severity and frequency of ED visits compared with low-dose found no differences; no data about the baseline VD levels are available (46). Even in children with a baseline serum 25(OH)D level <30 ng/mL, the incidence per person-year was no different (47). Laboratory confirmed ARTI was slightly more frequent

in the high-dose than the standard dose group, and the authors concluded that VD in doses >400 IU/day may not be indicated for preventing winter ARTIs in children (45). A 2017 meta-analysis of data from randomized controlled trials (RCTs) demonstrated that VD supplementation reduced the risk of at least one ARTI. Daily or weekly supplementation without additional bolus doses protected against ARTI, with the strongest effect in those with the lowest baseline 25(OH)D (48). Among 277 black infants born premature, 147 were consuming 200 IU/day from diet and 150 additional 400 IU/day from medical supplementation, which reduce the risk of RW by 12 months (49). Recently, 650 healthy children and adolescents were randomly assigned to taking 14,000 UI vitamin D weekly and 650 to taking placebo, for 8 months. No significant difference was observed between the vitamin D and placebo groups for influenza, but non-influenza respiratory viral infections were significantly reduced in the vitamin D group. When considering all respiratory virus infections, including influenza, the effect of vitamin D in reducing infection was also significant (50). In a recent prospective birth cohort study from China, infants receiving 400–600 IU of vitamin D from birth were divided into 4 groups, according to the average frequency of supplementation (0, 1–2, 3–4, and 5–7 days/week). Inverse trends were observed between supplementation and risk of ARTI, LRTI, and ARTI-related hospitalization (51).

Overall, the RCTs to date, while not uniform in their results, provide indications that VD supplementation, taken daily or weekly without bolus, can lower the risk of severe ARTI in children with low baseline 25(OH)D (2).

There is a lack of evidence on administration of VD to infants during an ARTI, and the optimal dose and timing. A recent Cochrane review evaluated 4 studies involving 780 children with pneumonia and 3 studies including 749 children with severe or very severe pneumonia, all aged <5 years. Various doses and methods of administration of VD were used, but, because of low and very low-quality evidence, the reviewers remained uncertain as to whether oral vitamin D as an a adjunct to treatment of acute pneumonia in children <5 years has an effect on outcome (52).

Vitamin D and Primary Prevention of Respiratory Allergies

RW caused by respiratory viral and/or bacterial infections in infancy and early childhood often persists after the age of 7 years, and asthma becomes established. Interventional studies in pregnancy tend to support the value of maternal VD supplementation in reducing the prevalence of childhood asthma, in contrast to studies on supplementation in infancy, which show contradictory results. Once initiated, asthma appears to have an association with VD status. A systematic review identified 23 manuscripts (two case-control, 12 cohort and nine cross-sectional studies) and found that higher serum levels of VD are associated with a reduced risk of asthma exacerbations, but little evidence to suggest an association with asthma incidence, prevalence or severity (53).

VITAMIN D AS BIOMARKER

In local inflammation produced by respiratory viruses, the activity of enzymes responsible for synthesis [1α(OH)ase] and degradation [24(OH)ase] of the active vitamin D metabolite $1,25(OH)D_2$ is dysregulated. In order to exercise their antiviral role, local macrophage and other immune cells release antiviral proteins (cathelicidin, defensis and innate interferons) (9). It is possible that in more severe viral infections the higher release of antiviral proteins decreases the activity of inactivating 24(OH)ase and increases the activity of 1α(OH)ase. Consequently, the concentration of $1,25(OH)D_2$ is increased in extra-renal tissues, to the detriment of serum 25(OH)D from which it is synthesized. A severe viral infection during periods when VD intake and exposure to sunlight are reduced may thus result in low serum 25(OH)D. It has yet to be shown in the real-life situation whether or not VD level could be used as a biomarker for the severity of ARTIs. Current evidence suggests that VD supplementation may reduce the risk of severe ARTI in some clinical situations, depending on both host and virus characteristics. The changes at the molecular level may differ, depending on type of virus. Urashima and colleagues, studying the effect of 1,200 IU/day of vitamin D supplementation vs. placebo on the incidence of seasonal influenza A and B among children aged 6–15 years, showed reduced incidence of influenza A but not of influenza B infection (54). Production of active metabolite VD resulted in initial increase in 25(OH)D in blood, and consequently in the respiratory tract; sufficient VD increases the antiviral activity of respiratory epithelial cells (18).

As VD supplementation is not followed by reduction in RW or asthma prevalence, although VD deficiency is associated with both conditions, an inverse causal relationship could be hypothesized. In both asthma and in RW, local 25(OH)D is needed to produce $1,2(OH)_2D$. Recent studies showed that many innate immune cells can synthesize $1,2(OH)_2D$ from 25(OH)D (9). Whether low VD during ARTI is a co-factor in their appearance, or a result of local transformation to the active form to combat infection is unclear. Sophisticated determinations to conclude which children respond positively to intervention are not feasible in primary care, but it may be useful to measure VD during a new ARTI, and to correct deficiency, in children with RW.

CONCLUSIONS

New biomarkers are needed for early identification of those children with RW who are at increased risk of severe ARTI and require intensive treatment and close follow-up. VD status appears to be a suitable candidate in certain populations. As VD deficiency could be a risk factor for causing RW in children, measurement of their serum level of 25(OH)D is recommended. In the case of deficiency, VD should be administrated in doses

according to age for at least 6 weeks, until achievement of normal blood 25(OH)D level, followed by supplementation when exposure to sunlight is inadequate. Higher doses of VD in this group in an effort to influence the clinical course and prevent asthma appear to be of no additional benefit. In a new era of personalized medicine, decisions based on appropriate treatment for different wheezing phenotypes may be possible.

FURTHER RESEARCH

Further research is needed in this area, including well-designed RCT or longitudinal study, to confirm VD role in severe infection and analyze the risk factor in recurrent wheezing.

AUTHOR CONTRIBUTIONS

GF and CB had the conception, designed the work, and collected the data. GF, CB, and LS contributed to the data analysis, its interpretation and to the article's writing and editing. AB and MZ made the critical revision of the article. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. Douros K, Everard ML. Time to say goodbye to bronchiolitis, viral wheeze, reactive airways disease, wheeze bronchitis and all that. *Front. Pediatr.* (2020) 8:218. doi: 10.3389/fped.2020.00218
2. Camargo CA. Chapter 112 - vitamin D, acute respiratory infection, and asthma/chronic obstructive pulmonary disease. In: Feldman D, editor. *Vitamin D (Fourth Edition)* London: Academic Press (2018) p. 1095–120.
3. Brand PLP, Baraldi E, Bisgaard H, Boner AL, Castro-Rodriguez JA, Custovic A, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Resp J.* (2008) 32:1096–110. doi: 10.1183/09031936.00002108
4. Report GM. *Global Strategy Forasthma Management and Prevention Updated 2020*. (2018) Available online at: https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf. (accessed May 14, 2020).
5. Brand PL, Caudri D, Eber E, Gaillard EA, Garcia-Marcos L, Hedlin G, et al. Classification and pharmacological treatment of preschool wheezing: changes since 2008. *Eur Respir J.* (2014) 43:1172–7. doi: 10.1183/09031936.00199913
6. Holick MF. Vitamin D deficiency. *N Engl J Med.* (2007) 357:266–81. doi: 10.1056/NEJMra070553
7. Holick MF. The vitamin D deficiency pandemic: approaches for diagnosis, treatment and prevention. *Rev Endocr Metab Disord.* (2017) 18:153–65. doi: 10.1007/s11154-017-9424-1
8. Jolliffe DA, Greiller CL, Mein CA, Hoti M, Bakhsoliani E, Telcian AG, et al. Vitamin D receptor genotype influences risk of upper respiratory infection. *Br J Nutr.* (2018) 120:891–900. doi: 10.1017/S000711451800209X
9. Zdrenghea MT, Makrinioti H, Bagacean C, Bush A, Johnston SL, Stanciu LA. Vitamin D modulation of innate immune responses to respiratory viral infections. *Rev Med Virol.* (2017) 27:e1909. doi: 10.1002/rmv.1909
10. Newton AH, Cardani A, Braciale TJ. The host immune response in respiratory virus infection: balancing virus clearance and immunopathology. *Semin Immunopathol.* (2016) 38:471–82. doi: 10.1007/s00281-016-0558-0
11. Bozzetto S, Carraro S, Giordano G, Boner A, Baraldi E. Asthma, allergy and respiratory infections: the vitamin D hypothesis. *Allergy.* (2012) 67:10–7. doi: 10.1111/j.1398-9995.2011.02711.x
12. Carlberg C. Vitamin D genomics: from *in vitro* to *in vivo*. *Front Endocrinol.* (2018) 9:250. doi: 10.3389/fendo.2018.00250
13. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HF, O'Garra A. 1alpha,25-Dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. *J Immunol.* (2001) 167:4974–80. doi: 10.4049/jimmunol.167.9.4974
14. Zhang Y, Leung DY, Richers BN, Liu Y, Remigio LK, Riches DW, et al. Vitamin D inhibits monocyte/macrophage proinflammatory cytokine production by targeting MAPK phosphatase-1. *J Immunol.* (2012) 188:2127–35. doi: 10.4049/jimmunol.1102412
15. Greiller CL, Martineau AR. Modulation of the immune response to respiratory viruses by vitamin D. *Nutrients.* (2015) 7:4240–70. doi: 10.3390/nu7064240
16. Douros K, Boutopoulou B, Fouzas S, Loukou I. Asthma and allergy "epidemic" and the role of vitamin D deficiency. *Adv Exp Med Biol.* (2017) 996:169–83. doi: 10.1007/978-3-319-56017-5_14
17. Hypponen E, Berry DJ, Wjst M, Power C. Serum 25-hydroxyvitamin D and IgE - a significant but nonlinear relationship. *Allergy.* (2009) 64:613–20. doi: 10.1111/j.1398-9995.2008.01865.x
18. Telcian AG, Zdrenghea MT, Edwards MR, Laza-Stanca V, Mallia P, Johnston SL, et al. Vitamin D increases the antiviral activity of bronchial epithelial cells *in vitro*. *Antiviral Res.* (2017) 137:93–101. doi: 10.1016/j.antiviral.2016.11.004
19. Song Y, Qi H, Wu C. Effect of 1,25-(OH)2D3 (a vitamin D analogue) on passively sensitized human airway smooth muscle cells. *Respirology.* (2007) 12:486–94. doi: 10.1111/j.1440-1843.2007.01099.x
20. Wang Z, Zhang H, Sun X, Ren L. The protective role of vitamin D3 in a murine model of asthma via the suppression of TGF-beta/Smad signaling and activation of the Nrf2/HO-1 pathway. *Mol Med Rep.* (2016) 14:2389–96. doi: 10.3892/mmr.2016.5563
21. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. *Mayo Clin Proc.* (2013) 88:720–55. doi: 10.1016/j.mayocp.2013.05.011
22. Mirzakhani H, Al-Garawi A, Weiss ST, Litonjua AA. Vitamin D and the development of allergic disease: how important is it? *Clin Exp Allergy.* (2015) 45:114–25. doi: 10.1111/cea.12430
23. Holick MF, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr.* (2008) 87:1080S–6S. doi: 10.1093/ajcn/87.4.1080S
24. Sacheck JM, Van Rompay MI, Chomitz VR, Economos CD, Eliasziw M, Goodman E, et al. Impact of three doses of vitamin D3 on serum 25(OH)D deficiency and insufficiency in at-risk schoolchildren. *J Clin Endocrinol Metab.* (2017) 102:4496–505. doi: 10.1210/jc.2017-01179
25. Grossman Z, Hadjipanayis A, Stiris T, Del Torso S, Mercier JC, Valiulis A, et al. Vitamin D in European children-statement from the European Academy of Paediatrics (EAP). *Eur J Pediatr.* (2017) 176:829–31. doi: 10.1007/s00431-017-2903-2
26. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* (2011) 96:1911–30. doi: 10.1210/jc.2011-0385
27. DelGiudice NJ, Street N, Torchia RJ, Sawyer SS, Bernard SA, Holick MF. Vitamin D prescribing practices in primary care pediatrics: underpinnings from the health belief model and use of web-based delphi technique for instrument validity. *J Pediatr Health Care.* (2018) 32:536–47. doi: 10.1016/j.pedhc.2018.03.003
28. Litonjua AA, Carey VJ, Laranjo N, Harshfield BJ, McElrath TF, O'Connor GT, et al. Effect of prenatal supplementation with vitamin D on asthma or recurrent wheezing in offspring by age 3 years: the vdaart randomized clinical trial. *JAMA.* (2016) 315:362–70. doi: 10.1001/jama.2015.18589
29. Braegger C, Campoy C, Colomb V, Decsi T, Domellof M, Fewtrell M, et al. Vitamin D in the healthy European paediatric population. *J Pediatr Gastroenterol Nutr.* (2013) 56:692–701. doi: 10.1097/MPG.0b013e31828f3c05

30. Gupta A, Bush A, Hawrylowicz C, Saglani S. Vitamin D and asthma in children. *Paediatr Respir Rev*. (2012) 13:236–43. doi: 10.1016/j.prrv.2011.07.003
31. Rusinska A, Pludowski P, Walczak M, Borszewska-Kornacka MK, Bossowski A, Chlebna-Sokol D, et al. Vitamin D Supplementation guidelines for general population and groups at risk of vitamin d deficiency in poland-recommendations of the polish society of pediatric endocrinology and diabetes and the expert panel with participation of national specialist consultants and representatives of scientific societies-2018 update. *Front Endocrinol*. (2018) 9:246. doi: 10.3389/fendo.2018.00246
32. Uysalol M, Uysalol EP, Yilmaz Y, Parlakgul G, Ozden TA, Ertem HV, et al. Serum level of vitamin D and trace elements in children with recurrent wheezing: a cross-sectional study. *BMC Pediatr*. (2014) 14:270. doi: 10.1186/1471-2431-14-270
33. Eroglu C, Demir F, Erge D, Uysal P, Kirdar S, Yilmaz M, et al. The relation between serum vitamin D levels, viral infections and severity of attacks in children with recurrent wheezing. *Allergol Immunopathol*. (2019) 47:591–7. doi: 10.1016/j.aller.2019.05.002
34. Dogru M, Seren LP. Serum 25-hydroxyvitamin D levels in children with recurrent wheezing and relation to the phenotypes and frequency of wheezing. *Eur Ann Allergy Clin Immunol*. (2017) 49:257–62. doi: 10.23822/EurAnnACI.1764-1489.14
35. Pecanha MB, Freitas RB, Moreira TR, Silva LS, Oliveira LL, Cardoso SA. Prevalence of vitamin D deficiency and its relationship with factors associated with recurrent wheezing. *J Bras Pneumol*. (2019) 45:e20170431. doi: 10.1590/1806-3713/e20170431
36. McNally JD, Leis K, Matheson LA, Karuananyake C, Sankaran K, Rosenberg AM. Vitamin D deficiency in young children with severe acute lower respiratory infection. *Pediatr Pulmonol*. (2009) 44:981–8. doi: 10.1002/ppul.21089
37. Vo P, Koppel C, Espinola JA, Mansbach JM, Celedon JC, Hasegawa K, et al. Vitamin D Status at the time of hospitalization for bronchiolitis and its association with disease severity. *J Pediatr*. (2018) 203:416–22.e1. doi: 10.1016/j.jpeds.2018.07.097
38. Roth DE, Jones AB, Prosser C, Robinson JL, Vohra S. Vitamin D status is not associated with the risk of hospitalization for acute bronchiolitis in early childhood. *Eur J Clin Nutr*. (2009) 63:297–9. doi: 10.1038/sj.ejcn.1602946
39. Jat KR. Vitamin D deficiency and lower respiratory tract infections in children: a systematic review and meta-analysis of observational studies. *Trop Doct*. (2017) 47:77–84. doi: 10.1177/0049475516644141
40. Wei Z, Zhang J, Yu X. Maternal vitamin D status and childhood asthma, wheeze, and eczema: A systematic review and meta-analysis. *Pediatr Allergy Immunol*. (2016) 27:612–9. doi: 10.1111/pai.12593
41. Christensen N, Sondergaard J, Fisker N, Christesen HT. Infant respiratory tract infections or wheeze and maternal vitamin D in pregnancy: a systematic review. *Pediatr Infect Dis J*. (2017) 36:384–91. doi: 10.1097/INF.0000000000001452
42. Pacheco-Gonzalez RM, Garcia-Marcos L, Morales E. Prenatal vitamin D status and respiratory and allergic outcomes in childhood: a meta-analysis of observational studies. *Pediatr Allergy Immunol*. (2018) 29:243–53. doi: 10.1111/pai.12876
43. Feng H, Xun P, Pike K, Wills AK, Chawes BL, Bisgaard H, et al. *In utero* exposure to 25-hydroxyvitamin D and risk of childhood asthma, wheeze, and respiratory tract infections: a meta-analysis of birth cohort studies. *J Allergy Clin Immunol*. (2017) 139:1508–17. doi: 10.1016/j.jaci.2016.06.065
44. Litonjua AA, Carey VJ, Laranjo N, Stubbs BJ, Mirzakhani H, O'Connor GT, et al. Six-year follow-up of a trial of antenatal vitamin D for asthma reduction. *N Engl J Med*. (2020) 382:525–33. doi: 10.1056/NEJMoa1906137
45. Aglipay M, Birken CS, Parkin PC, Loeb MB, Thorpe K, Chen Y, et al. Effect of high-dose vs standard-dose wintertime vitamin d supplementation on viral upper respiratory tract infections in young healthy children. *JAMA*. (2017) 318:245–54. doi: 10.1001/jama.2017.8708
46. Hueniken K, Aglipay M, Birken CS, Parkin PC, Loeb MB, Thorpe KE, et al. Effect of high-dose vitamin D supplementation on upper respiratory tract infection symptom severity in healthy children. *Pediatr Infect Dis J*. (2019) 38:564–8. doi: 10.1097/INF.0000000000002225
47. Aglipay M, Maguire JL. Vitamin D supplementation and upper respiratory tract infections in children-reply. *JAMA*. (2017) 318:2139–40. doi: 10.1001/jama.2017.15154
48. Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ*. (2017) 356:i6583. doi: 10.1136/bmj.i6583
49. Hibbs AM, Ross K, Kerns LA, Wagner C, Fuloria M, Groh-Wargo S, et al. Effect of vitamin D supplementation on recurrent wheezing in black infants who were born preterm: the D-wheeze randomized clinical trial. *JAMA*. (2018) 319:2086–94. doi: 10.1001/jama.2018.5729
50. Loeb M, Dang AD, Thiem VD, Thanabalan V, Wang B, Nguyen NB, et al. Effect of vitamin D supplementation to reduce respiratory infections in children and adolescents in Vietnam: a randomized controlled trial. *Influenza Other Respir Viruses*. (2019) 13:176–83. doi: 10.1111/irv.12615
51. Hong M, Xiong T, Huang J, Wu Y, Lin L, Zhang Z, et al. Association of vitamin D supplementation with respiratory tract infection in infants. *Matern Child Nutr*. (2020) 2020:e12987. doi: 10.1111/mcn.12987
52. Das RR, Singh M, Naik SS. Vitamin D as an adjunct to antibiotics for the treatment of acute childhood pneumonia. *Cochrane Database Syst Rev*. (2018) 7:Cd011597. doi: 10.1002/14651858.CD011597.pub2
53. Cassim R, Russell MA, Lodge CJ, Lowe AJ, Koplin JJ, Dharmage SC. The role of circulating 25 hydroxyvitamin D in asthma: a systematic review. *Allergy*. (2015) 70:339–54. doi: 10.1111/all.12583
54. Urashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. *Am J Clin Nutr*. (2010) 91:1255–60. doi: 10.3945/ajcn.2009.29094.

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OPINION
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Pulmonary Function Testing in Asthmatic Children. Tests to Assess Outpatients During the Covid-19 Pandemic

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INTRODUCTION

The worldwide Covid-19 outbreak has challenged our rules to manage pediatric patients with chronic respiratory diseases, particularly asthma. The spread of the novel coronavirus causing severe acute respiratory syndrome (SARS-Cov-2) constrained most countries to adopt drastic infection control strategies for health-care facilities (1, 2). Several Respiratory Societies have developed recommendations to protect patients and health-care staff in pulmonary function laboratories (3–6). These documents advise restriction of pulmonary function tests (PFTs) to those deemed essential, namely, spirometry and diffusion capacity measurements, in line with their clinical relevance and the epidemic phase. When testing is pertinent, infection prevention and control measures in the laboratory are required, including the disinfection of instruments, room cleaning, ventilation, and protective measures for patients and health personnel (3–6).

Notwithstanding the preceding measures, the risk of exposure to viral loads of SARS-Cov-2 following active respiratory maneuvers is not negligible. Consequently, all aerosol-generating procedures (AGPs) are discouraged, and no bronchial provocation tests are allowed.

Recommendations prevent spirometry in any child with suspected/confirmed Covid-19 (4, 6); on the other hand, the clinical picture of worsening asthma or an asthma exacerbation substantially overlaps with Covid-19 (7).

A recent consensus suggests screening patients for high-risk exposures, fever, and symptoms suggestive of COVID-19, ideally in two phases: within 3 days and upon arrival for medical visits when PFTs are due to be carried out. Alternatively, testing for SARS-CoV-2 patients within 72 h of their appointment (8). Patients reporting new symptoms upon arrival (even if previously tested negative for SARS-CoV-2) should be considered as suspected cases of COVID-19. In confirmed or suspected cases of COVID-19, resolution of symptoms and two negative tests for SARS-CoV-2 collected $\geq$24 h apart are required (6, 8). These patients could be rescheduled for PFTs after an interval without symptoms and fever since at least 10 days from their onset or, if asymptomatic, at least 10 days from their first positive test (8).

Execution of PFTs in patients coming from high prevalence settings [i.e., high-risk patients, require a negative pressure room (4, 8)]. The staff should wear an N95 mask, face shield, gown, and gloves; consumables must be managed within the risk area. Patients should wear a surgical mask between measures; both patients and staff should follow protocols on safe distance and hand washing. Metered dose inhalers (MDI) must replace nebulizers for assessing the bronchodilator response. Room and equipment disinfection, ventilation, and timing between patients are compulsory (4, 8).

Optional home spirometry can be useful for children needing close surveillance of pulmonary function (discussed in the last section).

QUESTIONS ON THE NEED FOR ALTERNATIVE TESTS

While restrictions in the pulmonary function laboratory will change as the disease prevalence changes, several questions remain: shall we continue monitoring airway patency/responsiveness (i.e., bronchodilation with beta-agonists) with spirometry as the sole measurement tool? Could we offer alternative PFTs to asthmatic children? If so, what is the rationale for considering this alternative?

Small airways dysfunction in asthma is now widely recognized (9–11). Spirometric variables such as FEV_1 are affected by flow resistance at the large airways. This fact may explain why spirometry poorly correlates with symptoms and why only markedly decreased FEV_1 values (<60%) predict disease exacerbations (12). On the other hand, visual inspection of flow-volume curves and assessment of bronchodilation help clinical decisions (12, 13).

Spirometry is effort dependent and requires expertise (13). However, it is just the "forced" nature of spirometry that allows enhancing viral diffusion nearby from a potentially infected patient. The maneuver itself, which involves a maximum inspiration followed by an explosive and prolonged expiration, induces cough and the release of droplets in the environment (4). To note, young patients often require a high number of attempts to achieve a reliable flow-volume curve (13, 14).

MEASUREMENTS OF RESPIRATORY RESISTANCE

Alternative tests are already available in many pulmonary function laboratories. The forced oscillation technique (FOT) provides information on airway patency/responsiveness in terms of respiratory system impedance (Z_{rs}) and its components, respiratory resistance (R_{rs}) and reactance (X_{rs}), during the patient's quiet breathing. Small oscillations are applied passively with a wave-emitting source (a loudspeaker) connected to the patient's mouth opening while cheeks are supported by the child or an operator. The pressure and flow relationship are then used to calculate R_{rs}, X_{rs}, the resonant frequency (F_{res}), and the area under the reactance curve (AX) (15). Waves can be delivered as a single frequency or multiple-single frequencies; another delivery method employs a train of pulses, the so-called impulse oscillometry (IOs) (15–17). Among the Z_{rs} components, X_{rs} represents counteracting inertial and elastic forces of the respiratory system (chest wall, lung, airway tissues, and gas column moving inside). Both R_{rs} and X_{rs} are frequency-dependent; thus, frequencies >4 HZ can easily reach the peripheral airways whereas high frequencies (>20 HZ) reflect frictional forces of the proximal airways and surrounding tissues (15, 16). Frequencies between 4 and 10 Hz are retained clinically relevant for children (16). For these frequencies, the within-subject coefficient of variation in R_{rs} (CV = SD/mean × 100) varies between 6.2 and 8.0% for children aged 3–16 years (14). Both R_{rs} and X_{rs} measures are repeatable over 2 weeks (18). Day-to-day R_{rs} variability is higher in asthmatic children than in healthy controls; this variability is associated with disease severity and symptom control (19).

The clinical utility of FOT measurements for assessing airway obstruction and bronchial response to bronchodilators has been recently summarized (15, 16, 20). Differences between techniques and patients' selection criteria lead to contrasting results when airway patency of healthy and wheezy children is compared at baseline; instead, most studies agree in the ability of FOT for assessing changes in the airway caliber (**Table 1**). The entity of Z_{rs} largely depends on standing height; thus, laboratories need to construct their reference values or to adopt those appropriated to their population (15). A decrease of at least −40% in R_{rs} and an increase of at least +50% in X_{rs} are considered thresholds for a bronchodilator response (15). Still, bronchodilator doses differ between studies (15, 20). Though several reference values have been provided for the different techniques, a call for standardization of these techniques is still evident (15–17, 20). The use of reference equations from studies whose population and devices most closely approximate the local situation has been recommended (15). In the absence of appropriated reference equations, the "personal best" measurement could be recorded as a reference point for the individual patient, to guide therapeutic decisions.

A modified FOT method that measures the tidal volume dependence on airway resistance has been recently described (21). This method, based on the change of within-breath R_{rs} at zero flow (end-expiration vs. end-inspiration), improves the ability to detect acute airway obstruction in young children (21). Advantages of FOT over spirometry and other tests of airway resistance have been described recently (9). Yet, a systematic review could not disclose enough evidence to place FOT as an adjunct or as a substituent of spirometry (10). Despite the FOT gaining interest, the lack of familiarity with the technique, lack of equipment, and complexity of analysis still limit its wider adoption.

Estimates of airway resistance can be also obtained with the interrupter technique (Rint). The child is invited to sit with the neck in a neutral position, to wear a nose clip, and to breathe normally through a mouthpiece and microbial filter. An automated valve briefly occludes the airway opening at the end-expiratory phase, lasting 100 ms; the resultant pressure is divided by the flow immediately preceding the interruption to estimate airway resistance (14). As for the oscillometer, cheek support is required. The assumption is that alveolar and mouth pressure equilibrate after occlusion. This technique is simple, quick to perform, and suitable in younger children. Rint measurements mostly represent airway resistance but also a small resistance from lung tissues and chest wall (14). The within-subject variability in healthy children is close to 12% (14, 18). However, the wide between-subject CV in health leads to overlap values with those obtained in children with recurrent wheeze (18). Baseline Rint measurements have low sensitivity to detect

TABLE 1 | Alternative pulmonary function tests (PFTs) for asthmatic children during the Covid-19 pandemic.

Laboratory (References)	Advantages	Limitations
FOT (9, 10, 14–21)	• Assess respiratory mechanics and airway resistance during tidal breathing. Help to detect peripheral airway obstruction. • Brief, feasible for children who are unable to cooperate with spirometry. • Baseline outcomes fairly distinguish subjects with recurrent wheeze/asthma from those healthy (see limitations). • Best utility, to assess the BDR and AHR. • Help overtime assessment and prediction of loss of asthma control.	• Outcomes depend on patient selection and diagnostic criteria. • Sensitive to upper airway shunting. • Multi-ethnic normative values are lacking. • Usefulness for long-term monitoring of patients, further studies needed. • Standardization of the technique and response to bronchodilators (type, drug dose, and timing), should be improved.
Rint (9, 14, 18, 22–25)	• Assess respiratory resistance during tidal breathing. Simple, quick, adapted for toddlers. • Reported high values in young children with persistent wheeze as compared with transient wheezers or never wheezers. • Assess the BDR with good sensitivity and specificity. • Relatively useful to assess AHR to cold air or exercise challenge (see limitations).	• Low sensitivity to detect peripheral airway obstruction. • Sensitive to upper airway shunting. • Does not discriminate well between children with recurrent wheeze and those healthy. • May underestimate resistance in children with severe airway obstruction. • Unclear utility for asthma monitoring.
FE_{NO} (26–33)	• Assess TH2-type airway inflammation during slow exhalation maneuvers. • Moderate accuracy for asthma diagnosis in subjects 5 yrs. and older. • Patients with FE_{NO} >35 ppb are likely to benefit from inhaled corticosteroids (ICs). • Assist correct use of ICs, therapy compliance, and resistance to ICs. • Help to monitor biological therapy. • Raising levels predict disease exacerbations.	• Positively skewed levels; overlapping between asthmatic and healthy subjects. Low FE_{NO} does not exclude asthma. • The optimization of therapy based on FE_{NO} has not proven better outcomes. • Several factors can affect its levels (e.g., atopy, infections, comorbidities, age, height, sex, and smoking exposure). • Needs coaching, especially in young children.
MBW (18, 34–40)	• Inert gas clearance technique. Assess ventilation distribution inhomogeneity during tidal breathing. Also measures the functional residual capacity (FRC). • Feasible for young children, reproducible. • Useful in severe or uncontrolled asthma. • More sensitive than spirometry to detect small airway disease. • Both MBW and FE_{NO} indices can help to assess disease exacerbations and EIB.	• Prolonged testing, especially in patients with uneven ventilation. • Requires experienced personnel. Preparation of the equipment and data processing is complex. • Insensitive to detect small airway dysfunction in mild asthma. • Multi-ethnic normative values are lacking. • Expensive devices, scarce accessibility.
Home (References)		
PEF (41–45)	• Assess airflow limitation during maximal expiratory maneuvers. Hand-held devices.	• Effort dependent. Do not enhance self-management during asthma flare-ups.
	• Assessment of diurnal variation or changes between visits; variability weakly correlates with asthma symptoms and AHR. • New electronic devices with smartphone applications are feasible for children.	• Written records are unreliable. • Compliance decreases after 4 weeks. • Often disagrees with spirometric records. • Electronic PEF meters with automatic teletransmission still need validation.
Spirometry (13, 46–50)	• Assess maximal inspiratory and expiratory volumes; estimate the baseline airway patency and its changes (BDR and AHR). • Flow-volume curves can be evaluated remotely, by an operator. • Acceptability and reproducibility criteria (with instructions to subjects if criterion not met) are available. • Portable devices.	• Effort dependent; underestimated data. Data quality decreases with younger age, lack of controller therapy, and FEV_1 < 80%. • Daily FEV_1 telemonitoring does not lead to better symptom control or fewer attacks. • Devices often lack instructive videos and maneuver's quality feedback. • Variable accuracy. Expensive. • Smartphone spirometers need validation.
FOT (51)	• As above (Laboratory). Useful for assessing day-to-day variability.	• Expensive. Requires more evidence for long-term monitoring.
FE_{NO} (52, 53)	• As above (Laboratory). Improves with mobile direct observation of therapy (MDOT).	• Expensive. Needs good quality control, instructions, and online feedback.

FOT, forced oscillation technique; Rint, respiratory resistance measured with the interrupter technique; FE_{NO}, fractional exhaled nitric oxide concentration; MBW, multiple breath washout; PEF, peak expiratory flow; BDR, bronchodilator response; AHR, airway hyperresponsiveness; ICs, inhaled corticosteroids.

bronchial obstruction but perform better for assessing bronchial response to bronchodilators (BDR) (14, 22, 23). A reliable BDR has been reported for a decrease in Rint $\geq$ 0.26 kPa L^{-1}s from baseline or −1.25 Z-scores (22).

Measurements of respiratory resistance have a long history (14, 54); still, they must gain a wider consensus among general practitioners and pulmonologists. While airway resistance could be measured with body plethysmography, it has inconvenience in the pandemic context such as the need for thorough disinfection of the box and execution difficulties for younger children. Instead, oscillometry and Rint techniques are available with smaller devices and are simple to perform in the Lab. Another advantage of these procedures is that the operator can be placed behind the child during the breathing maneuvers and his participation to support the child's cheeks is required only for toddlers. Acquisition time is also reduced for these tests. For instance, during oscillometry, the minimal acquisition time for children under 12 years of age is 16 s (15). Both FOT and Rint devices are small and supplied with appropriated in-line antimicrobial filters. Some instruments (e.g., Resmon Pro Full) store outcomes automatically in a pen drive, so the operator can evaluate the results safely, outside the laboratory. The advantages and limitations of FOT and Rint are reported in **Table 1**.

EXHALED NITRIC OXIDE (NO)

The fractional concentration of exhaled nitric oxide (FE_{NO}) has been studied in the last decades for assessing asthmatic patients, including children; guidelines on standardized methods are still valid (26). This free radical is a helpful non-invasive biomarker of the atopic-eosinophilic (Th2-type) airway inflammation (26, 27). A robust model with FE_{NO}, together with blood eosinophil counts and other biomarkers of IL-13–driven gene expression (serum CCL17 and CCL26), has been recently developed; this model identifies Type 2-high asthma patients with positive and negative predictive values of 100 y and 87%, respectively (28).

The test requires a deep inspiration followed by a constant slow exhalation into the analyzer across an in-line microbial filter. A target expiratory flow rate of 50 ml/s, against an expiratory resistance between 5 and 20 cmH_2O, is required to close the soft palate and to exclude contamination from nasal NO. Exhalations of at least 4 s can be sufficient to achieve a NO plateau. Schoolchildren usually can perform the classic maneuver; toddlers need audiovisual coaching and the use of dynamic flow restrictors to maintain a constant expiratory flow rate (26).

FE_{NO} measurements help in asthma diagnosis if taken together with the clinical history; FE_{NO} also assists in evaluating the therapeutic response to oral or inhaled corticosteroids and predicts disease exacerbations after treatment withdrawal (29). Because FE_{NO} is a phenotype-linked biomarker, it is suited for monitoring children on biological therapy (30). A recent systematic review and meta-analysis support the diagnostic accuracy of FE_{NO} testing in pediatric asthma (31). Overall, FE_{NO} levels over 35 ppb in children indicate eosinophilic airway inflammation and changes below or above 20% between visits are consistent with either response to anti-inflammatory therapy or with a need for adjusting therapy, respectively (29).

Peripheral and proximal airway contributions of exhaled NO can be calculated from exhalations at several flow rates, using the two-compartment model (55). Their employ has been reported useful to distinguish disease patterns in asthmatic patients (32). However, most studies agree on the role of partitioned-NO airway parameters to assess exercise-induced bronchoconstriction (EIB), a hint of poor disease control (34, 56, 57). Recently, we found that increased concentrations of both alveolar NO (CaNO) and urinary adenosine predicted EIB in atopic asthmatic children (33). Because exercise bronchial challenge is an AGP, surrogates of EIB such as partitioned-NO parameters could replace the traditional challenge at this time.

An advantage of FE_{NO} testing is the low-target expiratory flow rate that needs only slow exhalation maneuvers. FE_{NO} analyzers are small; also, handheld devices help for daily home monitoring (**Table 1**).

MULTIPLE BREATH WASHOUT (MBW)

Small airway dysfunction and ventilation heterogeneity are relevant in asthma (11, 18, 35–37). Uneven ventilation can be assessed through inert gas dilution during tidal breathing: washout of the resident nitrogen with 100% oxygen, or initial wash-in of an exogenous gas (e.g., sulfur hexafluoride, SF_6), and washout thereafter. Initial and final tracer gas concentrations allow measuring the resting volume [i.e., the functional residual capacity (FRC)]. When the dilution process achieves 1/40th of the initial gas concentration, the "Lung clearance index" (LCI) is then calculated as the cumulative expired volume (CEV) during the procedure divided by the FRC:

$$LCI = CEV/FRC.$$

This index means how many "turnovers" are required to clear the subject's FRC and reflects the extent of its ventilation distribution inhomogeneity. Young children usually cooperate with the test; they need coaching to breath normally while seated, wearing a mouthpiece with in-line microbial filter. Gas leaks should be avoided during the process (11, 38).

There is a slight inverse relationship between LCI and age in schoolchildren. Reports on upper limits for normal LCI vary between 7.0 and 7.9 in subjects aged 6–18 years, depending on the technique (39). Children with severe asthma have elevated LCI values as compared to those with a mild-to-moderate disease or healthy controls. However, many patients with severe disease yield LCI values within the normal range (11, 36).

Presence of high LCI values in subjects whose FEV_1 is normal suggests ongoing small airway dysfunction (37). A recent study shows that both LCI and FE_{NO} (but not FEV_1) concordantly improved 4 weeks after a systemic steroid dose in children with severe therapy-resistant asthma (35).

Some devices can analyze the phase III of each tidal breath to estimate the conductive (Scond) and acinar (Sacin) contributions to inhomogeneity. Scond better correlates with LCI than Sacin (11, 37).

The clinical application of these indexes still needs to be established. See also in **Table 1**. Using the MBW technique during this pandemic requires caution. Tidal breathing PFTs generate small particles ($\leq$0.5 μm) at the equipment inhalation port, even if at lower amounts than forced expiratory maneuvers (58). The main concerns with MBW testing are prolonged breathing (and room stay) and possible gas leaks. Requirements for testing high-risk patients (see Introduction) are advisable.

HOME PFT MEASUREMENTS

Several home PFTs have been developed with the aim to enhance patients' self-management (41, 47). Their use helps to overcome the infection control issues, as compared with laboratory tests. Most of these PFTs regard PEF and spirometry (13, 41–47, 51–53). Unsupervised measurements tend to be lower at home than in the laboratory, suggesting the need for patients' coaching (59, 60). Telemonitoring with visual coaching and automatic feedback for outcomes is promising, but its clinical utility remains unclear (13, 49). Daily home FEV_1 telemonitoring did not reduce exacerbations in children with severe asthma (49). A recent Cochrane review found no additional benefits of telemonitoring for asthma control or exacerbations, over usual asthma care (50). Devices differ widely on their inclusion of instructive videos, graphical descriptions, and immediate feedback on the quality of the breathing maneuver (47) (**Table 1**).

CONCLUSION

The unpredictable duration of the Covid-19 pandemic imposes infection prevention and control measures in ambulatory settings with a pulmonary function. In keeping with these preventive actions, pulmonary function procedures offering quiet breathing or slow expiration are suitable for testing asthmatic children. Measurements of airway resistance (Oscillometry, Rint), and FE_{NO}, can help respiratory physicians to manage their patients until spirometry and bronchoprovocation tests can be resumed. The MBW test relies on the need to evaluate ventilation inhomogeneity in children with severe disease. Standardization of these PFTs and improvement of home telemonitoring are priorities, given this and other infectious community threats.

AUTHOR CONTRIBUTIONS

MB and MV conceived and designed the text body. MB wrote the manuscript. ME, MM, and SM helped for searching the literature and reviewed critically the manuscript. All authors contributed to the article and approved the submitted version.

REFERENCES

1. World Health Organization. *Infection prevention and control during health care when COVID-19 is suspected: interim guidance, 19 March*. (2020). World Health Organization. (2020). Available online at: https://apps.who.int/iris/handle/10665/331495 (accessed April 25, 2020).
2. CDC - Centers for Disease Control and Prevention. *Outpatient and Ambulatory Care Settings: Responding to Community Transmission of COVID-19 in the United States*. (2020). Available online at: https://www.cdc.gov/coronavirus/2019-ncov/hcp/ambulatory-care-settings.html (accessed June 06, 2020).
3. McCormack MC, Kaminsky DA. *2020 members of the ATS Proficiency Standards for Pulmonary Function Testing Committee. Advice Regarding COVID 19 for Pulmonary Function Laboratories*. (2020). Available online at: www.thoracic.org/professionals/clinical-resources/disease-relatedresources/pulmonary-function-laboratories.php (accessed May 31, 2020).
4. European Respiratory Society Groups 9.1 and 4.1. *Recommendation from ERS Group 9.1 (Respiratory function technologists /Scientists). Lung function testing during COVID-19 pandemic and beyond*. (2020). Available online at: https://ers.app.box.com/s/zs1uu88wy51monr0ewd990itoz4tsn2h (accessed May 31, 2020).
5. ARTP and British Thoracic Society. *Respiratory Function Testing During Endemic COVID-19. Version 1.5*. (2020). Available online at: https://www.artp.org.uk/COVID19 (accessed May 31, 2020).
6. Bignamini E, Cazzato S, Cutrera R, Ferrante G, La Grutta S, Licari A, et al. Italian pediatric respiratory society recommendations on pediatric pulmonary function testing during COVID-19 pandemic. *Ital J Pediatr*. (2020) 46:68. doi: 10.1186/s13052-020-00829-0
7. Abrams EM, Szefler SJ. Managing asthma during coronavirus disease-2019: an example for other chronic conditions in children and adolescents. *J Pediatr*. (2020) 222:221–6. doi: 10.1016/j.jpeds.2020.04.049
8. Wilson KC, Kaminsky DA, Michaud G, Sharma S, Nici L, Folz RJ, et al. Restoring pulmonary and sleep services as the COVID-19 pandemic lessens: from an association of pulmonary, critical care, and sleep division directors and American thoracic society-coordinated task force. *Ann Am Thorac Soc*. (2020). doi: 10.1513/AnnalsATS.202005-514ST. [Epub ahead of print].
9. Kaminski DA. What does airway resistance tell us about lung function? *Respir Care*. (2012) 57:85–96. doi: 10.4187/respcare.01411
10. Dos Santos K, Fausto LL, Camargos PAM, Kviecinski MR, da Silva J. Impulse oscillometry in the assessment of asthmatic children and adolescents: from a narrative to a systematic review. *Paediatr Respir Rev*. (2017) 23:61–7. doi: 10.1016/j.prrv.2016.09.002
11. Nuttall AGL, Velásquez W, Beardsmore CS, Gaillard EA. Lung clearance index: assessment and utility in children with asthma. *Eur Respir Rev*. (2019) 28:190046. doi: 10.1183/16000617.0046-2019
12. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, (2020). Available online at: www.ginasthma.org (accessed May 11, 2020).
13. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 update. An official american thoracic society and european respiratory society technical statement. *Am J Respir Crit Care Med*. (2019) 200:e70–88. doi: 10.1164/rccm.201908-1590ST
14. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HG, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. *Am J Respir Crit Care Med*. (2007) 175:1304–45. doi: 10.1164/rccm.200605-642ST
15. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, et al. Technical standards for respiratory oscillometry. *Eur Respir J*. (2020) 55:1900753 doi: 10.1183/13993003.00753-2019
16. Skylogianni E, Douros K, Anthracopoulos MB, Fouzas S. The forced oscillation technique in paediatric respiratory practice. *Paediatr Respir Rev*. (2016) 18:46–51. doi: 10.1016/j.prrv.2015.11.001
17. Soares M, Richardson M, Thorpe J, Owers-Bradley J, Siddiqui S. Comparison of forced and impulse oscillometry measurements: a clinical population and printed airway model study. *Sci Rep*. (2019) 9:2130. doi: 10.1038/s41598-019-38513-x
18. Rosenfeld M, Allen J, Arets BH, Aurora P, Beydon N, Calogero C, et al. An official American Thoracic Society workshop report: optimal lung function tests for monitoring cystic fibrosis, bronchopulmonary dysplasia,

and recurrent wheezing in children less than 6 years of age. *Ann Am Thorac Soc.* (2013) 10:S1–11. doi: 10.1513/AnnalsATS.201301-017ST
19. Robinson PD, Brown NJ, Turner M, Van Asperen P, Selvadurai H, King GG. Increased day-to-day variability of forced oscillatory resistance in poorly controlled or persistent pediatric asthma. *Chest.* (2014) 146:974–81. doi: 10.1378/chest.14-0288
20. Alblooshi A, Alkalbani A, Albadi G, Narchi H, Hall G. Is forced oscillation technique the next respiratory function test of choice in childhood asthma. *World J Methodol.* (2017) 7:129–38. doi: 10.5662/wjm.v7.i4.129
21. Czövek D, Shackleton C, Hantos Z, Taylor K, Kumar A, Chacko A, et al. Tidal changes in respiratory resistance are sensitive indicators of airway obstruction in children. *Thorax.* (2016) 71:907–15. doi: 10.1136/thoraxjnl-2015-208182
22. Mele L, Sly PD, Calogero C, Bernardini R, Novembre E, Azzari C, et al. Assessment and validation of bronchodilation using the interrupter technique in preschool children. *Pediatr Pulmonol.* (2010) 45:633–8. doi: 10.1002/ppul.21210
23. Beydon N, Mahut B, Maingot L, Guillo H, La Rocca MC, Medjahdi N, et al. Baseline and postbronchodilator interrupter resistance and spirometry in asthmatic children. *Pediatr Pulmonol.* (2012) 47:987–93. doi: 10.1002/ppul.22526
24. Delacourt C, Lorino H, Fuhrman C, Herve-Guillot M, Reinert P, Harf A, et al. Comparison of the forced oscillation technique and the interrupter technique for assessing airway obstruction and its reversibility in children. *Am J Respir Crit Care Med.* (2001) 164:965–72. doi: 10.1164/ajrccm.164.6.2010153
25. Caudri D, Wijga AH, Hoekstra MO, Kerkhof M, Koppelman GH, Brunekreef B, et al. Prediction of asthma in symptomatic preschool children using exhaled nitric oxide, Rint and specific IgE. *Thorax.* (2010) 65:801–7. doi: 10.1136/thx.2009.126912
26. American Thoracic Society, European Respiratory Society. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med.* (2005). 171:912–30. doi: 10.1164/rccm.200406-710ST
27. Barreto M, Villa MP, Monti F, Bohmerova Z, Martella S, Montesano M et al. Additive effect of eosinophilia and atopy on exhaled nitric oxide levels in children with or without a history of respiratory symptoms. *Pediatr Allergy Immunol.* (2005) 16:52–8. doi: 10.1111/j.1399-3038.2005.00220.x
28. Silkoff PE, Laviolette M, Singh D, FitzGerald JM, Kelsen S, Backer V, et al. Identification of airway mucosal type 2 inflammation by using clinical biomarkers in asthmatic patients. *J Allergy Clin Immunol.* (2017) 140:710–9. doi: 10.1016/j.jaci.2016.11.038
29. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, et al. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FeNO) for clinical applications. *Am J Respir Crit Care Med.* (2011) 184:602–15. doi: 10.1164/rccm.9120-11ST
30. Amat F, Labbé A. Biomarkers for severe allergic asthma in children: could they be useful to guide disease control and use of omalizumab? *Expert Rev Respir Med.* (2018) 12:475–82. doi: 10.1080/17476348.2018.1475233
31. Wang Z, Pianosi PT, Keogh KA, Zaiem F, Alsawas M, Alahdab F, et al. The diagnostic accuracy of fractional exhaled nitric oxide testing in asthma: a systematic review and meta-analyses. *Mayo Clin Proc.* (2018) 93:191–8. doi: 10.1016/j.mayocp.2017.11.012
32. Puckett JL, Taylor RWE, Leu S-Y, Guijon OL, Aledia AS, Galant SP, et al. Clinical patterns in asthma based on proximal and distal airway nitric oxide categories. *Respir Res.* (2010) 11:47. doi: 10.1186/1465-9921-11-47
33. Barreto M, Capi M, Lionetto L, Caiazzo I, Salerno G, Cardelli P, et al. Urinary and exhaled biomarkers of exercise-induced bronchoconstriction in atopic asthmatic children. *Pediatr Pulmonol.* (2019) 54:1447–56. doi: 10.1002/ppul.24419
34. Knihtilä H, Kotaniemi-Syrjänen A, Pelkonen AS, Mäkelä MJ, Malmberg LP. Small airway function in children with mild to moderate asthmatic symptoms. *Ann Allergy Asthma Immunol.* (2018) 121:451–57. doi: 10.1016/j.anai.2018.07.026
35. Irving S, Fleming L, Ahmad F, Biggart E, Bingham Y, Cook J, et al. Lung clearance index and steroid response in pediatric severe asthma. *Pediatr Pulmonol.* (2020) 55:890–8. doi: 10.1002/ppul.24675
36. Keen C, Olin AC, Wennergren G, Gustafsson P. Small airway function, exhaled NO and airway hyper-responsiveness in paediatric asthma. *Respir Med.* (2011) 105:1476–84. doi: 10.1016/j.rmed.2011.04.004
37. Macleod KA, Horsley AR, Bell NJ, Greening AP, Innes JA, Cunningham S. Ventilation heterogeneity in children with well-controlled asthma with normal spirometry indicates residual airways disease. *Thorax.* (2009) 64:33–7. doi: 10.1136/thx.2007.095018
38. Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, Gappa M, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath test. *Eur Respir J.* (2013) 41:507–22. doi: 10.1183/09031936.00069712
39. Anagnostopoulou P, Latzin P, Jensen R, Stahl M, Harper A, Yammine S, et al. Normative data for multiple breath washout outcomes in school-aged Caucasian children. *Eur Respir J.* (2020) 55:1901302. doi: 10.1183/13993003.01302-2019
40. Arianto L, Hallas H, Stokholm J, Bønnelykke K, Bisgaard H, Chawes BL. Multiple breath washout for diagnosing asthma and persistent wheeze in young children. *Ann Am Thorac Soc.* (2019) 16:599–605. doi: 10.1513/AnnalsATS.201807-503OC
41. Mikalsen IB, Nassehi D, Øymar K. Vortex whistle and smart phone application for peak flow recordings in asthmatic children: a feasibility study. *Telemed J E Health.* (2019) 25:1077–82. doi: 10.1089/tmj.2018.0270
42. Sly PD, Flack F. Is home monitoring of lung function worthwhile for children with asthma? *Thorax.* (2001) 56:164–5. doi: 10.1136/thorax.56.3.164
43. Wensley D, Silverman M. Peak flow monitoring for guided self-management in childhood asthma: a randomized controlled trial. *Am J Respir Crit Care Med.* (2004) 170:606–12. doi: 10.1164/rccm.200307-1025OC
44. Brand PL, Duiverman EJ, Postma DS, Waalkens HJ, Kerrebijn KF, van Essen-Zandvliet EE. Peak flow variation in childhood asthma: relationship to symptoms, atopy, airways obstruction and hyperresponsiveness. Dutch CNSLD study group. *Eur Respir J.* (1997) 10:1242–7. doi: 10.1183/09031936.97.10061242
45. Kamps AW, Roorda RJ, Brand PL. Peak flow diaries in childhood asthma are unreliable. *Thorax.* (2001) 56:180–2. doi: 10.1136/thorax.56.3.180
46. Mortimer KM, Fallot A, Balmes JR, Tager IB. Evaluating the use of a portable spirometer in a study of pediatric asthma. *Chest.* (2003) 123:1899–907. doi: 10.1378/chest.123.6.1899
47. Carpenter DM, Jurdi R, Roberts CA, Hernandez M, Horne R, Chan A. A review of portable electronic spirometers: implications for asthma self-management. *Curr Allergy Asthma Rep.* (2018) 18:53. doi: 10.1007/s11882-018-0809-3
48. Thompson R, Delfino RJ, Tjoa T, Nussbaum E, Cooper D. Evaluation of daily home spirometry for school children with asthma: new insights. *Pediatr Pulmonol.* (2006) 41:819–28. doi: 10.1002/ppul.20449
49. Deschildre A, Béghin L, Salleron J, Iliescu C, Thumerelle C, Santos C, et al. Home telemonitoring (forced expiratory volume in 1 s) in children with severe asthma does not reduce exacerbations. *Eur Respir J.* (2012) 39:290–6. doi: 10.1183/09031936.00185310
50. Kew KM, Cates CJ. Home telemonitoring and remote feedback between clinic visits for asthma. *Cochrane Database Syst Rev.* (2016) 2016:CD011714. doi: 10.1002/14651858.CD011714.pub2
51. Wong A, Hardaker K, Field P, Huvanandana J, King GG, Reddel H, et al. Home-based forced oscillation technique day-to-day variability in pediatric asthma. *Am J Respir Crit Care Med.* (2019) 199:1156–60. doi: 10.1164/rccm.201809-1659LE
52. van der Valk RJ, Baraldi E, Stern G, Frey U, de Jongste JC. Daily exhaled nitric oxide measurements and asthma exacerbations in children. *Allergy.* (2012) 67:265–71. doi: 10.1111/j.1398-9995.2011.02734.x
53. Shields MD, ALQahtani F, Rivey MP, McElnay JC. Mobile direct observation of therapy (MDOT) - a rapid systematic review and pilot study in children with asthma. *PLoS ONE.* (2018) 13:e0190031. doi: 10.1371/journal.pone.0190031
54. Dubois A, Brody A, Lewis D, Burgess BF. Oscillation mechanics of lungs and chest in man. *J Appl Physiol.* (1956) 8:587–94. doi: 10.1152/jappl.1956.8.6.587
55. Tsoukias NM, George SC. A two-compartment model of pulmonary nitric oxide exchange dynamics. *J Appl Physiol.* (1998) 85:653–66. doi: 10.1152/jappl.1998.85.2.653

56. Barreto M, Zambardi R, Villa MP. Exhaled nitric oxide and other exhaled biomarkers in bronchial challenge with exercise in asthmatic children: current knowledge. *Paediatr Respir Rev.* (2015) 16:68–74. doi: 10.1016/j.prrv.2013.11.006
57. Paraskakis E, Brindicci C, Fleming L, Krol R, Kharitonov SA, Wilson NM, et al. Measurement of bronchial and alveolar nitric oxide production in normal children and children with asthma. *Am J Respir Crit Care Med.* (2006) 174:260–7. doi: 10.1164/rccm.200506-962OC
58. Helgeson SA, Lim KG, Lee AS, Niven AS, Patel NM. Aerosol generation during spirometry. *Ann Am Thorac Soc.* (2020). doi: 10.1513/AnnalsATS.202005-569RL. [Epub ahead of print].
59. van Vliet D, van Horck M, van de Kant K, Vaassen S, Gulikers S, Winkens B, et al. Electronic monitoring of symptoms and lung function to assess asthma control in children. *Ann Allergy Asthma Immunol.* (2014) 113:257–62.e1. doi: 10.1016/j.anai.2014.05.015
60. Gerzon FLGR, Jöbsis Q, Bannier MAGE, Winkens B, Dompeling E. Discrepancy between lung function measurements at home and in the hospital in children with asthma and CF. *J Clin Med.* (2020) 9:1617. doi: 10.3390/jcm9061617

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