



REVIEW ARTICLE

## Chronic obstructive pulmonary diseases in children<sup>☆</sup>



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### KEYWORDS

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### Abstract

**Objectives:** To verify and describe the main events related to the diagnosis and management of chronic obstructive pulmonary diseases in children (COPDC) and adolescents, considering the interrelated physiopathology, genetic, and environmental characteristics.

**Sources:** Relevant literature from PubMed was selected and reviewed.

**Summary of the findings:** COPDC have an environmental and/or genetic origin and its manifestation has manifold genotypes, phenotypes, and endotypes. Although COPDC has no cure, it can be clinically controlled. Chronic cough is the main symptom and bronchiectasis can be present in several COPDC patients. The management of COPDC is more effective if based on guidelines and when treatment regimen adherence is promoted. Oral and inhaled corticosteroids, bronchodilators, inhaled antibiotics, and treatment of pulmonary exacerbation (PE) are the bases of COPDC management, and should be individualized for each patient.

**Conclusions:** Correct diagnosis and knowledge of risk factors and comorbidities are essential in COPDC management. Procedures and drugs used should be based on specific guidelines for each COPDC case. Treatment adherence is critical to obtain the benefits of management. COPDC clinical control must be evaluated by the decrease in PEs, improved quality of life, reduction of pulmonary function loss, and lung structural damage. For most cases of COPDC, monitoring by interdisciplinary teams in specialized reference centers with surveillance strategies and continuous care leads to better outcomes, which must be evaluated by decreasing pulmonary function damage and deterioration, better prognosis, better quality life, and increased life expectancy.

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**PALAVRAS-CHAVE**

Criança;  
Doença pulmonar  
obstrutiva crônica;  
Tosse crônica

**Doenças pulmonares obstrutivas crônicas na criança****Resumo**

**Objetivos:** Verificar e descrever os principais eventos relacionados ao diagnóstico e manejo das doenças pulmonares obstrutivas crônicas em crianças (DPOCC) e adolescentes, tendo em vista a fisiopatologia, características genéticas e ambientais inter-relacionadas.

**Fonte dos dados:** Revisão na base de dado PUBMED com seleção de referências relevantes.

**Síntese dos dados:** As DPOCC têm origem ambiental e/ou genética e se manifestam com diversos genótipos, fenótipos e endótipos e, embora possam ser controladas, não têm cura. O principal sintoma é a tosse crônica e muitas cursam com bronquiectasia. O manejo tem maior eficácia se baseado em *guidelines* e se a adesão ao regime terapêutico for estimulada e comprovada. Corticóides orais e inalatórios, broncodilatadores, antibióticos inalados e tratamento das exacerbações pulmonares (EP) são vigas mestras do manejo e devem ser individualizados para cada DPOCC.

**Conclusões:** Nas DPOCC é fundamental o diagnóstico correto, conhecer os fatores de risco e comorbidades. Os procedimentos e os medicamentos devem ser baseados em *guidelines* específicos para cada DPOCC. Adesão ao tratamento é fundamental para obter os benefícios do manejo. O controle deve ser avaliado pela diminuição das EP, melhora na qualidade de vida e redução da evolução da perda da função e dano estrutural pulmonar. Para a maioria das DPOCC, o acompanhamento por equipes interdisciplinares em centros de referência especializados, com estratégias de vigilância e acolhimento contínuos, conduz a melhores desfechos que devem ser avaliados pela diminuição da deterioração do dano e da função pulmonar, melhor prognóstico, melhor qualidade de vida e aumento da expectativa de vida.

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**Introduction**

Chronic obstructive pulmonary disease (COPD) is typically shown in the literature as evidence, in most cases, of the damage caused by smoking in adults older than 40 years. Without any direct and exclusive association with active long-term smoking, several chronic obstructive pulmonary diseases in children (COPDC) and adolescents progress with deterioration in lung structure and function, causing persistent (fixed) or intermittent (temporary) obstruction to pulmonary flow, secondary to genetic and/or environmental changes that cause airway inflammation and/or infection. Although the symptoms of COPDC are very similar, they have variable etiology, morbidity, physiopathology, prevalence, prognosis, genotypes, and phenotypes.<sup>1,2</sup>

While some COPDC have been the object of many studies, such as asthma, cystic fibrosis (CF), recurrent wheezing in infants (RWI), and bronchopulmonary dysplasia (BPD), others are known as “orphan diseases,” such as primary ciliary dyskinesia (PCD), non-cystic fibrosis bronchiectasis (NCFB), plastic bronchitis (PB), and bronchiolitis obliterans (BO).

COPDC are characterized by high prevalence of asthma, RWI, and BPD, or low prevalence of BO, CF, PB, PCD, and NCFB. They are noncommunicable diseases, of long duration and slow progression, showing episodes of pulmonary exacerbation (PE), acute or permanent airflow limitation, and significant quality of life impairment.<sup>3</sup> In all, the main pulmonary symptom is chronic cough, reflecting the presence of alterations in the airways, as there are no cough receptors in the alveoli. Another characteristic is the presence of bronchiectasis in many of them.<sup>4</sup>

Most of them, including some of the several clinical forms of asthma, course with neutrophilic airway inflammation,

which contributes to progressive worsening of pulmonary damage and function by releasing: (i) elastase: cleaves elastin and causes bronchiectasis, decreases opsonization and phagocytosis, increases secretion, decrease mucociliary clearance; (ii) DNA: increases the viscosity of secretions; (iii) hydrogen peroxide and other oxidants: causes tissue damage and inactivates  $\alpha$ -1-antitrypsin; (iv) IL-8 and LTB4: attract more neutrophils.<sup>5</sup>

Two aspects of COPDC have been thoroughly studied: the genetic component and environmental aggressions that initiate or exacerbate the diseases. Most COPDC show different genotypes, phenotypes, endotypes, and degrees of severity, require different types of management, and have no cure.<sup>6</sup>

Pneumonia, BPD, BO, and/or RWI in the first years of life constitute risk groups for COPD in the long term and should receive medical follow-up and interventions to prevent the potential impact on long-term respiratory sequelae.<sup>7-9</sup>

In all COPDC, PE is often triggered by viral and/or bacterial infections, pollution, and aeroallergens. The PE manifests as acute respiratory failure of varying intensity, both in asthma and RWI, and as increased cough and chronic infection in CF, BPD, NCFB, and PCD. The signs and symptoms of PE are more frequent and intense at nighttime.

While the majority of acute respiratory diseases can be diagnosed easily and efficiently through history and physical examination, those with a chronic nature may require sophisticated laboratory tests. Continuous and scheduled evaluations by interdisciplinary health teams in specialized centers are required for effective management, better prognosis, and improved quality of life in COPDC.

Establishing protocols based on systematic reviews, meta-analyses, and guidelines allows for gaining control of

the signs and symptoms of COPDC. Oral and (OC) inhaled corticosteroids (IC), mucolytics, bronchodilators, inhaled antibiotics, and other drugs should be used according to specific guidelines for each COPDC.

While some groups of drugs are widely used, with variable degree of scientific evidence, such as bronchodilators and IC, others, such as long-term macrolide use, are more controversial. The use of macrolides in COPDC have been justified by the anti-inflammatory and immunomodulatory effect, the decrease in mucus production, and neutrophil elastase inhibition, in addition to reducing the production of pro-inflammatory mediators (e.g. IL8) and stimulating phagocytosis of apoptotic cells.<sup>10-14</sup> Although macrolides have shown to be effective in patients with CF and other COPDC, and have shown encouraging *in vitro* effects, their use in other COPDC has shown to be less effective and requires further studies.<sup>14</sup>

The objective of this review was to assess and describe the main events related to the diagnosis and management of COPDC, considering the physiopathology and interrelated genetic and environmental characteristics.

## Data sources

Review of the PubMed databases with selection of relevant references. The following descriptors were used (according to the MeSH criteria) related to each COPD included in the study: asthma, CF, RWI, BPD, PCD, NCFB, BO, and PB.

## COPDC: an overview

The first important feature of COPDC is that their clinical manifestations and prevalence are more common in certain age groups, as shown in Fig. 1. The second is that interactions between the genetic component and environmental aggressions initiate or exacerbate them, as shown in Fig. 2. The main differences and similarities between the COPDC are shown in Table 1. The third characteristic of COPDC is that they evolve with PE, predominantly infectious (CF), inflammatory (asthma), and mixed (asthma and viruses/bacteria).

Infectious PE caused by bacteria are different in healthy children when compared with those with COPDC. *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Staphylococcus aureus*, which have high virulence, are common causes of pneumonia in previously healthy individuals without COPDC and require treatment with low-spectrum antibiotics (e.g., penicillin and amoxicillin), but cause short-term mortality. In contrast, many patients with COPDC, especially those with CF, PCD, and NCFB, have PE caused by low-virulence bacteria (*Pseudomonas aeruginosa* (PA), *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia* and *Achromobacter xylosoxidans*), which cause long-term mortality; however, they require broad-spectrum antibiotics such as aminoglycosides, meropenem, and third-generation cephalosporins (Fig. 3).

Due to the characteristics of COPDC, several guidelines and systematic reviews for the diagnosis and management of the disease have been proposed for both periods between crises and PE of most COPDC, aiming to prevent further deterioration of pulmonary function and damage (Fig. 4).<sup>6,15-27</sup>

## Asthma

Asthmatic individuals who manifested the disease early in life persist with symptoms, and evidence suggests that asthma severity in childhood predicts the disease severity in adulthood.<sup>28</sup> Recent guidelines emphasize difficulties for the definitive diagnosis of asthma in children younger than 5 years, where several COPDC phenotypes have been identified.

For children older than 5 years, asthma diagnosis is based on: (1) a history of acute respiratory failure crises that improve with short-acting bronchodilators (SABA); (2) increased serum IgE in the absence of parasitic diseases, eosinophilia, and positive immediate hypersensitivity skin tests for airborne allergens; (3) spirometry and measurement of bronchial hyperresponsiveness (BHR) to methacholine challenge. The diagnosis can be made with the isolated presence and/or combination of the above items 1; 1+2; 1+3; or 1+2+3.

Numerous factors have been associated with increased risk of developing asthma in adolescence, of which the following should be mentioned: personal or family history of allergy, male gender, obesity, pollution, exposure to cigarette smoke, RWI, severe infection by respiratory syncytial virus (RSV), pneumonia in the first year of life, RWI severity, altered pulmonary function, and BHR.<sup>8,29-31</sup>

There is no specific treatment for asthma, and it is preferable to use the term management for the tools used to attain disease control. The main objectives for outpatient management are: (i) make chronic symptoms minimal or nonexistent; (ii) decrease the intensity and the number of PE; (iii) maintain lung function as close as possible to normal levels; (iv) maintain normal levels of daily activities, including physical exercises; (v) prevent the adverse effects of anti-asthmatic drugs; (vi) prevent disease progression to irreversible airflow limitation; (vii) prevent asthma mortality.<sup>6,15-20</sup> The main medications to control asthma are inhaled corticosteroids (IC).

The classification of the clinical pictures and respective treatment steps are listed below:

### Steps in the treatment of asthma

(Step 1) Individuals with intermittent asthma, characterized by normal spirometry and periods between crises lasting longer than 1 month without exacerbations in the last year, should receive SABA. (Step 2) Continued use of IC at low doses and rescue SABA during crisis. (Step 3) Continued use of low doses of IC + long-acting beta agonists (LABA) with SABA for crises or IC + formoterol for both maintenance and control. (Step 4) IC + formoterol for maintenance and crises or medium or high doses of IC + LABA and SABA, if necessary. (Step 5) Refer patient to a center specialized in asthma treatment for difficult-to-control disease: consider oral steroids and anti-IgE (omalizumab). Consider oral corticosteroids in severe PE and if the patient had previous severe PE.<sup>6,15-20</sup>

Medications and steps are modified to the next step or revert to the previous step, depending on whether or not the asthma is controlled. A decrease in management steps must occur if the asthma is well controlled for at least 3 months.

**Table 1** Main clinical and pathophysiological characteristics of COPDC *versus* COPD in adults.

COPDC characteristics	ASTHMA	RWIs	BPD	BO and PIBO	CF	BP	PCD	NCFB	Classic adult COPD
Symptom onset	Before 5 years of life	<2 years	Newborn	<3 years	<2 years in classical forms	CHD: <5 years Asthma: >5 years	First year of life	After the second year of life	Adults >40 years
Age of higher prevalence	Childhood	1–2 years	First year of life	Childhood and adolescence	Up to 30 years	CHD: <5 years Asthma: >5 years	Childhood and adolescence	Childhood and adolescence	After 40 years
Main clinical marker	Family history of asthma, personal atopy and positive response to BD	Infection by respiratory viruses (RSV and RV)	Prematurity Oxygen use	Virus	Chronic colonization of the airways by <i>Pseudomonas aeruginosa</i> and pancreatic failure	Elimination of bronchial casts with sputum	Suppurative infections of the upper and lower airways	Recurrent infections and chronic cough	Smoking, emphysema, and biomass smoke
Prevalence	High (5–30%)	High (15–60%)	High; 26% in VLBW infants	Low ?	Low. Classified as rare disease. 1:2500–1:10,000 live births	Low ?	Low ?	Low ?	6–15.8% of the population older >40 years
Bases for diagnosis	Spirometry, positive response to BD, IgE, and skin prick test	>3 episodes of wheezing in infancy and positive API	Prematurity and oxygen therapy for more than 28 days in early life	Lung biopsy, HRCT and lung perfusion scintigraphy	NBS with a positive IRT, chloride >60 mEq/L in sweat, two mutations in the CFTR gene	Airway cast expectoration and bronchoscopy	Dextrocardia, chronic sinusitis, pneumonia and recurrent URTIs	HRCT	Smoking, emphysema and alpha1 antitrypsin deficiency
Genotype	Many chromosomes and polymorphisms	Many chromosomes and polymorphisms	Little known	Little known	Autosomal recessive with alterations in CFTR gene located on chromosome 7. 6 classes of mutations. Many polymorphisms	Unknown	Autosomal recessive	Depends on the etiology	–
Phenotype	Several	Several	M, Mo, S	Constrictive proliferative	Many. With and without pancreatic failure	Depending on the etiology, the bronchial mold has a different composition	With and without dextrocardia	Depends on the etiology	With and without asthma

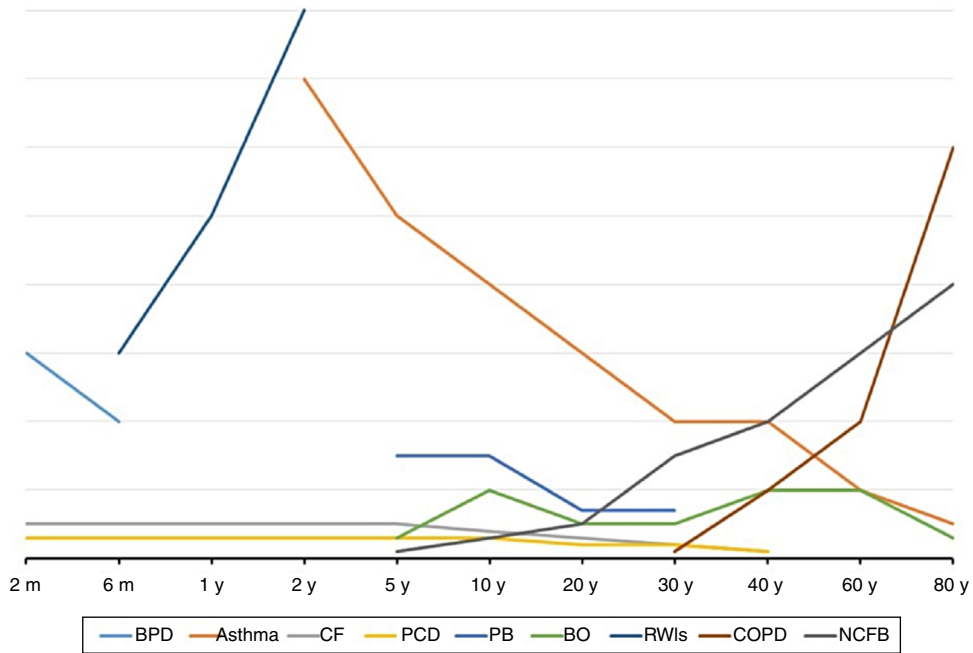
Table 1 (Continued)

COPDC characteristics	ASTHMA	RWIs	BPD	BO and PIBO	CF	BP	PCD	NCFB	Classic adult COPD
BAL	Eosinophils	Neutrophils and/or eosinophils	Neutrophils	Neutrophils	Neutrophils	Mucin and fibrin	Neutrophils	Neutrophils	Neutrophils and macrophages
Markers in lymphocytes	High CD4/CD8	Varies whether the BAL is eosinophilic or neutrophilic	?	?	?	?	?	Depends on the etiology	High CD8/CD4
Inflammatory mediators	IL4, IL5, IL9, IL13, TNF- $\alpha$ , GM-CSF	Varies whether the BAL is eosinophilic or neutrophilic	TNF- $\alpha$ , IL-1, IL-6, IL-10	IL1 $\beta$ , IL6, IL8, TNF- $\alpha$ , and NFk $\beta$	IL8	?	?	Depends on the etiology	IL8, LTB4, proteases, MMP9, TNF- $\alpha$ , TGF- $\beta$ 1
Main causes of PE	Viruses and aero-allergens	Viruses	Viruses	Viruses	Gram-negative bacteria	Influenza H1N1 ?	Viruses and bacteria	Bacteria and viruses	Viruses and bacteria
Response to BD Obstruction	Yes Intermittent in the mild cases and fixed in severe cases	Little known Intermittent	Unknown Fixed	Rare Fixed	Rare Fixed	? Intermittent	? Fixed	No Fixed	Low Fixed
Survival/ Mortality	Long/low	Long/low	Depends on the severity and gestational age	Depends on severity	<40 years – class I–III mutations. >40 years – class IV–VI mutations	Low/high	<40 years	Depends on the age of onset and etiology	Depends on the severity. High mortality in the elderly
Evolution to restrictive lung diseases	Rare	Rare	Rare	Frequent	Frequent	Rare	Frequent	Frequent	Frequent
Evolution to lung transplantation	No	No	No	Rare	Yes	No	Yes	Yes	No
Comorbidities	Allergic rhinitis, atopic dermatitis and GERD	GERD	GERD and prematurity	Severe adenovirus infection	Pancreatic failure, depression, diabetes, and osteoporosis	CHD, asthma, lymphatic disease, ABPA	Azoospermia and chronic rhinosinusitis	?	Asthma and GERD

Table 1 (Continued)

COPDC characteristics	ASTHMA	RWIs	BPD	BO and PIBO	CF	BP	PCD	NCFB	Classic adult COPD
Treatment	IC; SABA; LABA; Montelukast; omalizumab	IC; SABA; Montelukast	IC; SABA; Sildenafil and PH Diuretics	IC; SABA; LABA; corticoids; oxygen; tiotropium bromide	Mucolytics; IA; digestive enzymes, IC; SABA; LABA; corticosteroids; tiotropium; Oxygen	bronchoscopy; mucolytics and antifibrinolytics	Mucolytics, IA; IC; SABA; LABA; corticosteroids and oxygen	Mucolytics; IA; IC; SABA; LABA; corticosteroids; oxygen; macrolides	IC; SABA; LABA; corticosteroids; Tiotropium and oxygen
Perspectives	Early intervention <i>in utero</i> and early in life at risk populations. Prophylaxis against RSV and RV. Immunomodulation with prebiotics, probiotics and bacterial lysates. Prevention of allergic sensitization.	Permissive hypercapnia and improved care to VLBW infants	Palivizumab; genes and polymorphisms; respiratory virus vaccines	Corrections by potentiators and carriers of CFTR protein and new tests for the diagnosis of atypical forms	Multicenter studies, national registries	Genetic studies and early diagnosis	Prophylaxis against viruses	Avoid smoking Asthma control	

?, unknown; ABPA, allergic bronchopulmonary aspergillosis; IA, inhaled antibiotics; BD, bronchodilator; NCFB, non-cystic fibrosis bronchiectasis; BO, bronchiolitis obliterans; PIBO, post-infectious bronchiolitis obliterans; PB, plastic bronchitis; CHD, congenital heart disease; IC, inhaled corticosteroids; CD4, CD4 molecule; CD8, CD8 molecule; CFTR, cystic fibrosis transmembrane regulator; BPD, bronchopulmonary dysplasia; PCD, primary ciliary dyskinesia; COPD, chronic obstructive pulmonary disease; COPDC, chronic obstructive pulmonary disease in childhood; GERD, gastroesophageal reflux disease; PE, pulmonary exacerbation; CF, cystic fibrosis; GM-CSF, granulocyte macrophage-colony stimulating factor; PH, pulmonary hypertension; IgE immunoglobulin E; IL, interleukin; API, asthma predictor index; URTI, upper respiratory tract infection; LABA, long-acting beta-agonists; BAL, bronchoalveolar lavage; LTB4 leukotriene B4; M, mild; Mo, moderate; S, severe; MMP, matrix metalloproteinase; NF- $\kappa$ B, NF-kappaB; VLBW, very low birth weight; RSV, respiratory syncytial virus; RV, rhinovirus; SABA, short-acting beta agonists; RWI, recurrent wheezing in infants; HRCT, high-resolution computed tomography; SPT, skin prick test; TGF, transforming growth factor; IRT, immunoreactive trypsinogen; NBS, newborn screening test; TNF, tumor necrosis factor; RSV, respiratory syncytial virus.

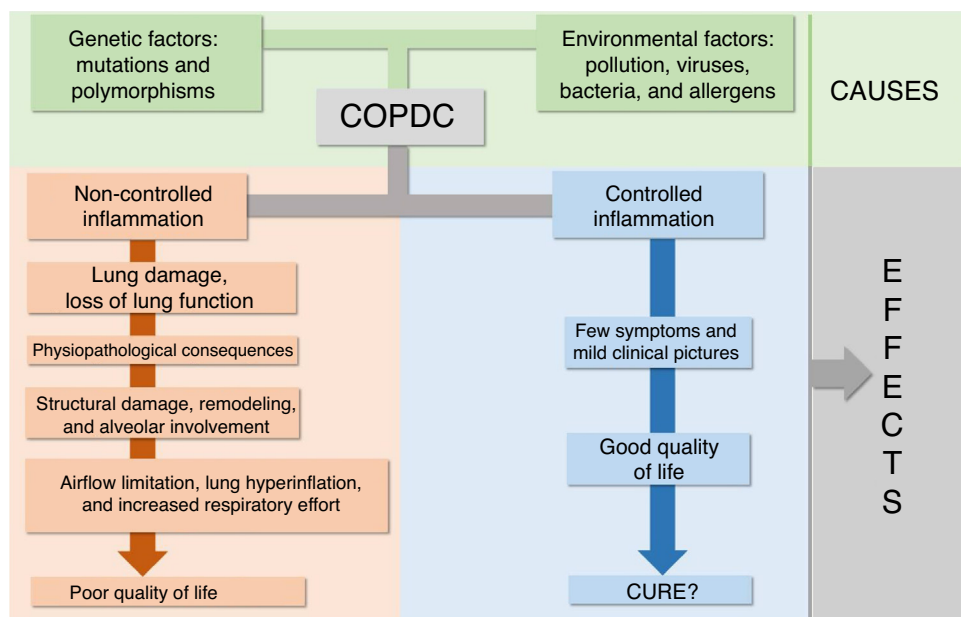


**Figure 1** Age of onset and higher prevalence of major chronic obstructive pulmonary disease in children (COPDC) compared with chronic obstructive pulmonary disease (COPD) in adults. CF, cystic fibrosis; RWIs, recurrent wheezing in infants; BPD, bronchopulmonary dysplasia; PCD, primary ciliary dyskinesia; NCFB, non-cystic fibrosis bronchiectasis; PB, plastic bronchitis; BO, bronchiolitis obliterans; m, month; y, year.

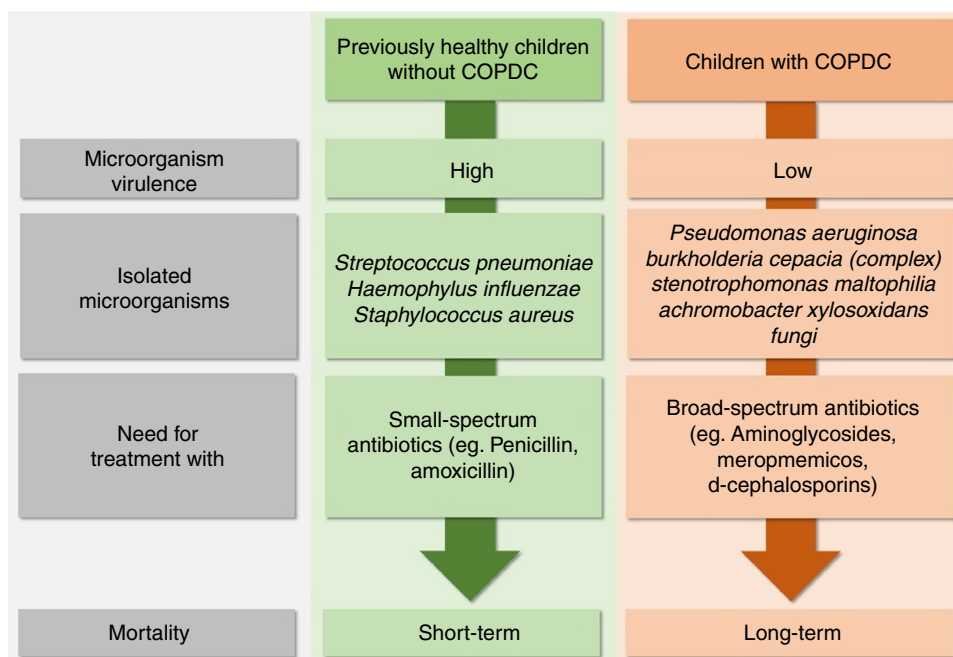
It is essential to verify at all consultations, whether the asthma is controlled or not, from the clinical and/or functional point of view, based on six parameters: (i) nocturnal signs and symptoms; (ii) daytime signals and symptoms; (iii) signs and symptoms with physical exercise or limitation in daily activities; (iv) PE; (v) need for relief medication (SABA); (vi) changes in lung function. Hence, asthma is considered controlled when all parameters are normal; it should be classified as partially controlled in the

presence of one or two altered parameters; and finally, non-controlled asthma should be considered when three or more parameters are altered.

The absence of control of signs and symptoms, frequent exacerbations, previous admission to an intensive care unit (ICU), low values of forced expiratory volume in 1 s (FEV1), exposure to tobacco smoke, and need to use high-dose medications are characteristics associated with increased risk of adverse events in the future. By definition, an



**Figure 2** Interactions of causes, effects, and clinical outcomes of chronic obstructive pulmonary disease in children (COPDC).

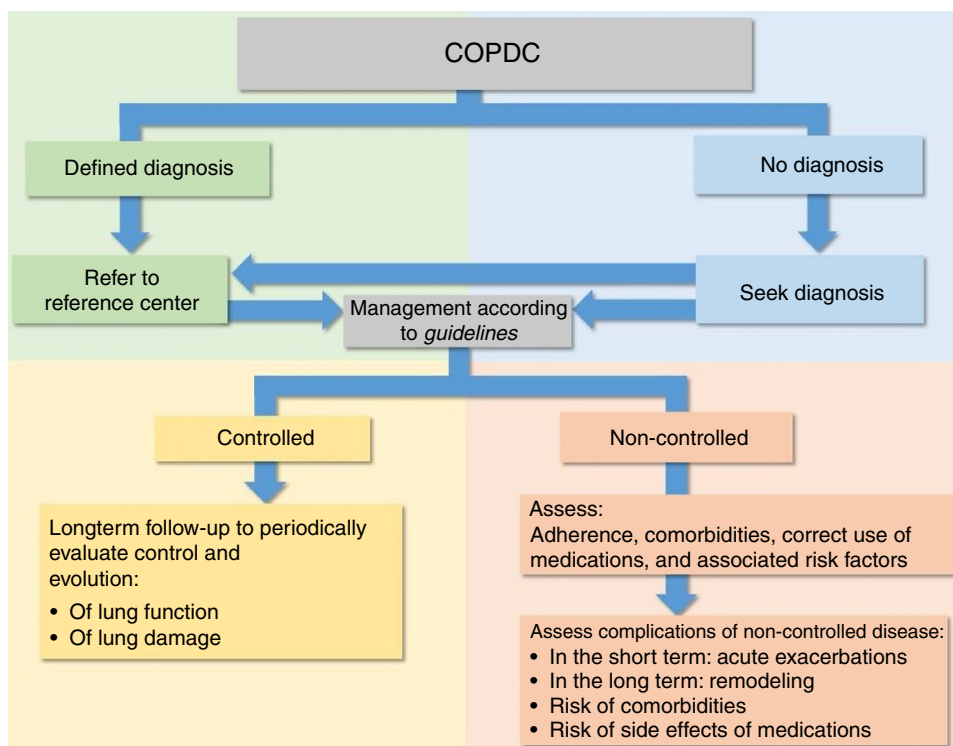


**Figure 3** Bacterial acute pulmonary exacerbations in chronic obstructive pulmonary disease in children (COPDC) and pneumonia in previously healthy children.

exacerbation at any week is indicative of non-controlled asthma and also of the need for review of the maintenance treatment.<sup>16,17</sup>

In the management of patients with asthma, the following are essential: (i) management supported by evidence-based medicine; (ii) to perform the diagnosis and,

if possible, the phenotype (e.g., allergic and non-allergic); (iii) to exclude and treat comorbidities; (iv) to assess and recommend the adequate use of prescribed drugs; (v) to assess, advise, and encourage treatment adherence; (vi) to assess and advise about environmental prophylaxis; (vii) to assess and advise on the triggering factors; (viii) to educate



**Figure 4** Control or non-control of chronic obstructive pulmonary disease in children (COPDC) based on diagnosis.



patient's caregivers about asthma and the factors influencing it; (ix) to give instructions on the adequate use of devices for administration of metered-dose and dry powder inhalers; (x) instructions for patients to be able to recognize when asthma control is deteriorating and what medications to use, when it occurs; (xi) to identify non-controlled patients and causes of lack of control; (xii) to advise that inhaled medications should be used with spacers; (xiii) to advise on the hygiene of spacers, which must be washed and left to soak in water with detergent; (xiv) LABA must not be used in children younger than 4 years; (xv) SABA are the agents of choice in PE; (xvi) IC alone or associated with bronchodilators are the basis of asthma treatment; (xvii) children younger than 6 years can use inhaled medication with spacer and those older than 6 years can use dry powder inhalers; (xviii) to assess pulmonary function regularly; (xix) to advise on the need for long-term medical care; (xx) omalizumab should be prescribed in reference centers for the management of patients with difficult-to-control asthma.

### Recurrent wheezing in infants (RWI)

There are several phenotypes and risk factors (RF) for RWI, creating difficulties for asthma diagnosis and resulting in an excessive assessment for comorbidities.<sup>32–37</sup> The main RF include: presence of familial and/or personal allergy, early sensitization, severe RSV infection, maternal smoking during pregnancy, and unfavorable airway geometry. Other implicated RF are: genetic variants, excessive hygiene, Western lifestyle, pollution, gastroesophageal reflux disease (GERD), low socioeconomic status, urban environment, antibiotic use, diet, few siblings, ethnicity, male gender, and attendance of daycare.<sup>38</sup>

Exposure to maternal smoking, both intrauterine and in the early years of life, has contributed to increased incidence and severity of childhood and adult asthma, COPD in adults, lung function deficits, lung hypoplasia, respiratory tract infections, and higher predisposition to sudden death syndrome.<sup>39–41</sup> Respiratory viruses are the main RF for asthma and RWI initiation or exacerbation: (i) some viruses

initiate asthma; (ii) the more severe the respiratory infection, the higher the likelihood of developing asthma; (iii) viruses cause PE in children and adults with established asthma.<sup>42</sup>

The diagnosis of asthma in infants is a major challenge for clinicians; to attain a diagnosis with a high degree of suspicion, the presence of allergy should be investigated, as it is a persistent asthma predictor. The investigation of severe COPDC in children younger than 5 years may require many tests, including high-resolution computed tomography (HRCT), lung function assessment, cellular and humoral immunity evaluation, bronchoscopy, bronchoalveolar lavage, 24-h esophageal pH-metry, endo-bronchial biopsy, mutation screening, and sodium and chloride sweat measurements.<sup>35</sup> In contrast, no investigation is necessary for most of RWI, because it cannot be differentiated with certainty whether the future course of the RWI will be persistent asthma or transient wheezing.<sup>43</sup>

Some asthma predictive indices (APIs) have been developed to identify children with RWI and at risk for asthma after 6 years of age (Table 2).<sup>38,44</sup> Some authors have mentioned methodological and practical limitations of APIs, suggesting that they have low capacity and poor sensitivity to predict asthma at school age,<sup>45,46</sup> and that although they are simple and easy-to-apply tools, they have not been sufficiently validated. According to these authors, predicting asthma using simple clinical models is virtually impossible.<sup>45,46</sup>

Although most of the scientific community is favorable to the use of APIs,<sup>47,48</sup> the search for clinical and/or laboratory markers for the diagnosis of asthma in RWI and children younger than 5 years remains a rich area for future studies. Infants and preschoolers with RWI or asthma have less PE, and show symptom and lung function improvement when treated with IC.<sup>49–51</sup>

The dosages of the main IC used in COPDC are shown in Table 3.

### Bronchiolitis obliterans (BO)

Bronchiolitis obliterans (BO) is a predominantly neutrophilic COPDC with high levels of proinflammatory cytokines,

**Table 2** Asthma Predictive Index (API) by Castro-Rodriguez et al.<sup>44</sup> and Guilbert et al.<sup>38</sup>

API criteria	Original API <sup>1</sup>	Modified API <sup>38</sup>
General	<p>Convincing API: more than three episodes of wheezing/year during the first 3 years of life with a major criterion or two minor.</p> <p>Less convincing API: less than three episodes of wheezing/year during the first 3 years of life with a major criterion or two minor.</p>	The child must have a history of four or more episodes of wheezing. At least one episode verified and confirmed by a physician.
Major	<p>History of parental asthma</p> <p>Atopic dermatitis</p>	<p>History of parental asthma</p> <p>Atopic dermatitis diagnosed by physician</p> <p>Allergic sensitization to one or more aeroallergens</p>
Minor	<p>Allergic rhinitis diagnosed by physician</p> <p>Wheezing unrelated to colds</p> <p>Eosinophilia <math>\geq 4\%</math></p>	<p>Sensitization to cow's milk, egg, or peanut</p> <p>Wheezing unrelated to colds</p> <p>Eosinophilia <math>\geq 4\%</math></p>

API, asthma predictive index.

**Table 3** Low, medium, and high daily doses of inhaled corticosteroids (IC) in asthma (Global Initiative for Asthma – GINA) and in chronic obstructive pulmonary disease in childhood.

Inhaled corticosteroids	Daily doses in children younger than 5 years			Daily doses (6–11 years)		
	Low	Medium	High	Low	Medium	High
Beclomethasone Dipropionate HFA	100			50–100	>100–200	>200
Budesonide spray	200			100–200	>200–400	>400
Nebulized budesonide	250–500	> 500–1000	> 1000	250–500	>500–1000	>1000
Fluticasone propionate HFA spray	100			100–200	>250–500	>500
Fluticasone propionate dry powder				100–200	>250–400	>400
Ciclesonide	160			80	>80–160	>160
Mometasone	There are no studies			110	220 ≤ 440	440 or more
Triamcinolone	There are no studies			400–800	>800–1200	>1200

bronchial remodeling, and fibrosis in the small airways. When the etiology is infectious, it is called post-infectious BO (PIBO). Most often, PIBO is caused by previous infection caused by adenovirus, but influenza, measles, RSV, and *Mycoplasma pneumoniae* are also observed. Latin American countries have the highest rates of this disease.<sup>27,52–62</sup>

Studies have shown that lung function remains altered with an obstructive pattern and air trapping during childhood. These patients are often hospitalized due to recurrent respiratory infections. Patients show slight improvement over the years.<sup>54,62</sup>

Five criteria are essential for the diagnosis of PIBO: (i) history of acute viral bronchiolitis and viral pneumonia before the age of 3; (ii) evidence of persistent airway obstruction after the acute event, identified by physical examination and/or lung function, which is not responsive to at least 2 weeks of systemic corticosteroids associated with bronchodilator; (iii) radiological findings of obstruction such as hyperinflation, atelectasis, bronchial wall thickening, and bronchiectasis; (iv) mosaic perfusion and air trapping on HRCT; (v) exclusion of other COPDC.<sup>27,60</sup>

Among the causes of BO are: drugs, association with Stevens–Johnson syndrome, collagenoses, irradiation, foreign body or gastric content aspiration, and graft vs. host disease after transplantation.

The definitive diagnosis of BO is made through anatomicopathological examination of fragments obtained from lung biopsy. BO is classified as: (i) proliferative BO, characterized by airway obstruction by polyps and/or granulation tissue in the lumen of bronchioles; or (ii) constrictive BO, characterized by peribronchial inflammation and fibrosis.<sup>58</sup> As the lung biopsy is an invasive test, most studies perform the diagnosis based on clinical history and HRCT, spirometry, and perfusion scintigraphy with technetium. Alterations in HRCT include wall thickening and bronchiole obliteration and, with the disease progression, bronchiectasis, bronchial wall thickening, mosaic perfusion, air trapping, reduced lung volume, and decreased diameter of hilar and peripheral vessels are observed.<sup>27,59</sup>

There is no specific treatment for BO. Oxygen therapy is essential in some patients, mainly after ICU discharge for severe acute viral bronchiolitis (AVB) and in patients who develop chronic hypoxemia. Contact prophylaxis with

intra and extra-domestic pollutants, reduction of exposure to active and passive smoking, and anti-pneumococcal and influenza vaccination are important steps for BO management. In the early phases of the disease, some patients may benefit from systemic corticosteroid therapy. Bronchodilators, antibiotics in infectious exacerbations, surgery for resection of fixed collapsed lung, and lung transplant have also been used.<sup>27</sup>

### Primary ciliary dyskinesia (PCD)

Primary ciliary dyskinesia (PCD) is an autosomal recessive COPDC caused by several alterations in airway cilia anatomical and functional structure, resulting in inflammation and infection, with an incidence of 1:4000–40,000 live births. Laterality defects in the thoraco-abdominal organs occur in about 50% of patients with PCD, and most have *situs inversus totalis* (Kartagener syndrome).<sup>24,63–66</sup>

PCD should be suspected in children with: (i) *situs inversus totalis* or other laterality defect in thoraco-abdominal organs; (ii) recurrent upper (otitis, sinusitis) and lower respiratory tract infections (pneumonia, abscesses) and chronic respiratory tract diseases of undefined etiology (bronchiectasis, chronic cough, atelectasis, and middle lobe syndrome); (iii) neonatal respiratory distress syndrome of undefined causes; (iv) diagnosis of PCD in other family members; (v) congenital heart disease, especially if associated with heterotaxia, and with chronic and repeated infections of the lower and upper airways.<sup>24,67</sup>

Clinical manifestations and alterations in PCD vary according to age<sup>25</sup>: in the prenatal period, ultrasound may reveal mild fetal cerebral ventriculomegaly, heterotaxia and *situs inversus totalis* (approximately 25% of individuals with *situs inversus totalis* have PCD). PCD prevalence in patients with heterotaxia remains unknown. In the neonatal period, 75% of full-term newborns with PCD have respiratory distress, requiring supplemental oxygen for days or weeks. Some have continuous rhinorrhea, heterotaxia, and hydrocephalus.

During childhood, chronic productive cough is observed, in association with atelectasis and/or recurrent pneumonia, atypical asthma that does not respond to treatment, bronchiectasis, NCFB, nasal polyps, chronic rhinosinusitis,

hearing impairment, and chronic otitis. In adolescence and adulthood, bronchiectasis, chronic mucopurulent sputum, digital clubbing, spirometry with progressive or mixed obstructive ventilatory pattern, nasal polyposis, and halitosis can be observed, as well as infertility in men (50%) and ectopic pregnancy in women.

Diagnosis is based on clinical and radiological alterations, nasal nitric oxide levels, ciliary beat pattern at video microscopy, structural alterations of the cilia by electron microscopy, and detection of mutations. Only 50–60% of PCD patients have a known mutation.<sup>25,68,69</sup>

CF evolves with secondary ciliary dyskinesia, whereas in PCD it is primary; the management of pulmonary disease in these two diseases is virtually identical.<sup>25</sup>

## Cystic fibrosis (CF)

CF is an autosomal recessive disease caused by mutations in the CFTR (cystic fibrosis transmembrane regulator) gene, 7q31.2 region, which has more than 2000 identified mutations, divided into six classes regarding the production and function of the CFTR protein. The qualitative or quantitative absence or dysfunction of CFTR causes physiopathological changes in several organs. Most of CF morbidity and mortality is caused by manifestations in the respiratory and digestive tracts.<sup>70–73</sup>

It is currently known that in Class I, II, and III mutations, the disease starts before symptom onset, constituting a major factor for early intervention and more aggressive treatments, showing promising results in reducing lung function damage and deterioration, with consequent increased survival.<sup>70–73</sup>

Availability of newborn screening, sweat testing, CFTR gene mutation screening, medications, and possible use of correctors, enhancers, and stabilizers (for some mutations) of the CFTR protein are concrete facts in the last decade. The consequence is that the survival of these patients is increasingly higher.<sup>73</sup> Lung damage and decreased lung function are progressive, and depend on the mutation, gender, polymorphisms, treatment availability and adherence, early treatment, comorbidities, and care in reference centers.<sup>74–76</sup>

The physiopathology of COPD in CF can be understood with the following six events (6D): (i) defect in the CFTR gene; (ii) impairment or absence of the CFTR protein; (iii) dehydration of the airway surface liquid; (iv) defect in bacterial clearance in the airways; (v) secondary ciliary dyskinesia; (vi) destruction of the airway epithelium.<sup>77</sup>

To attain the diagnosis of CF after neonatal screening, alterations in the gene and or CFTR protein should be verified. The CFTR gene is studied through the analysis of mutations and polymorphisms. The CFTR protein function and/or presence can be assessed in the sweat glands (sweat test, evaporimetry, difference of potential, and pH) nasal epithelium, salivary glands, and digestive tract.<sup>78,79</sup>

Diagnosing or ruling out CF is not always easy, even after comprehensive testing, particularly in adolescents and adults with classes IV, V, and VI mutations, which cause non-classical forms and are often associated with rare mutations, threshold levels of chloride in sweat, late-onset clinical manifestations, and atypical symptoms.<sup>80</sup>

As CF affects many organs, its management is complex. The service must have interdisciplinary teams with several health care professionals, physical therapy, medical examinations, frequent visits to the hospital, and use of daily, repetitive medications, which are sometimes complicated and costly.<sup>81</sup>

Patients with CF are highly susceptible to chronic lung infection by PA. PA acquisition occurs very early and is related to lung function deterioration and worse CF prognosis; hence, intensive treatment against PA is crucial in the management of CF.

Other bacteria frequently found in the airways of CF patients and that determine the lung function damage and deterioration include *S. aureus*, *H. influenzae*, PA, *B. cepacia* complex, *S. maltophilia*, and *Achromobacter species*. Non-tuberculous *Mycobacteria* (NTM) and other anaerobic bacteria and fungi are found less frequently, and tend to appear at the more advanced stages of lung disease.<sup>82,83</sup>

Inhaled antibiotics (IA) are essential for the treatment of chronic lung infections in CF. The increased survival in patients with CF in recent decades can be partly attributed to the use of IA. They have higher deposition at the infection site and less risk of systemic side effects than parenteral therapy, decrease PE, and improve quality of life and spirometry.<sup>84,85</sup>

CF patients with chronic lung infection by PA should receive long-term, nebulized anti-pseudomonal therapy, unless there is contraindication. Among the IA, tobramycin and colistin are currently available, while aztreonam, levofloxacin, and liposomal amikacin will soon be available.<sup>86</sup> The administration of IA is time-consuming and is a heavy burden for patients. Treatment adherence is a significant challenge.<sup>87</sup>

The treatment of the first acquisition episode, from infection to chronic infection and PE due to PA, are reasons for debates and controversies in the literature.<sup>88</sup>

PA eradication protocols have demonstrated antibiotic efficacy in the first bacterial isolation; intensive treatment with intravenous antibiotics in PE and IA in the periods between crises.<sup>89–91</sup>

It is advisable to perform lung damage assessment by HRCT at least every 2 years, and pulmonary function assessment by spirometry at least twice a year.

IA, anti-inflammatory drugs, corticosteroids, bronchodilators, and mucolytics may be necessary for the management of lung disease in CF. Auxiliary measures have shown benefits with respiratory physical therapy, regular exercise, avoiding indoor and outdoor pollution, and active and passive smoking. It is crucial to include treatment adherence measures and continuity of care for life. Visits to the reference center must be monthly during the first year and at least four times a year until adulthood.

Adherence to CF management varies between 35 and 75% and is lower in adolescence. Poor adherence to medication worsens lung function, increases the frequency of PE, and results in a larger number of consultations, hospitalizations, and costs. Therefore, interventions are necessary to improve medication adherence.<sup>81</sup>

Many international organizations have proposed that the management of lung disease in CF should be directed by guidelines based on scientific evidence. Thus, recent

publications on the management of COPD in CF can be found, and represent the "state-of-the-art" for CF reference centers.<sup>82,83,91,92</sup>

Recently, advances in the treatment of CF have gained prominence. Mutations in the CFTR gene have been widely identified, and the highest prevalence of the F508del mutation has been emphasized. Treatment for the specific mutation and/or class of mutations has focused on the study of new drugs. Two drugs have been used in studies considering the F508del mutation in homozygous form, and results of the association of ivacaftor (increases opening of the chloride channel – potentiator) and lumacaftor (increases protein number in the epithelium – potentiator) have shown increased chloride transport when compared with the values of the individual drugs.<sup>93</sup>

### Bronchopulmonary dysplasia (BPD)

BPD is a secondary COPDC, and is associated with prematurity and risk factors (RF) related to it. Low birth weight, high fraction of inspired oxygen, patent ductus arteriosus, high intravenous fluid volume values, mechanical ventilation with high pressures, genetic susceptibility, and infection in the neonatal period contribute to the prevalence and severity of BPD. This disease affects approximately 30% of newborns with birth weight less than 1500 g.<sup>94,95</sup>

Several studies have shown that most infants who develop BPD evolve with lung function alterations throughout life.<sup>9,96–101</sup>

Similar to all COPDC, BPD has no specific treatment. Regarding the advances to reduce mortality in the neonatal period, in recent decades, three factors have clearly proven to be effective: (i) corticosteroid administration to pregnant women with high-risk pregnancies; (ii) administration of surfactants to premature infants; (iii) less aggressive ventilation strategies.<sup>102,103</sup>

The following have also been used: diuretics (furosemide); bronchodilators; systemic corticosteroids and IC; vitamin A; methylxanthines (pentoxifylline, caffeine); pulmonary vasodilators (sildenafil, inhaled nitric oxide); late surfactant administration; and antioxidants (superoxide dismutase), with varying degrees of efficacy in the management of acute and/or chronic BPD. However, there is little evidence of the beneficial actions of most of these agents when used in short- or long-term management of BPD.<sup>102,103</sup>

BPD is associated with a high incidence of pulmonary arterial hypertension (PAH). Treatment with sildenafil has been associated with significant improvement in echocardiographic markers of PAH and reduced need for oxygen. The drug is well tolerated.<sup>104</sup>

### Bronchiectasis related to diseases other than CF (NCFB)

Bronchiectasis is an alteration that accompanies many COPDC. It may be associated with and complicate asthma, PCD, CF, BO, and NCFB, and be consequent to measles, pertussis, immunodeficiency, allergic bronchopulmonary aspergillosis, inflammatory bowel disease, rheumatoid arthritis, foreign body inhalation, PCD, BO, respiratory

tract malformation (e.g.: tracheoesophageal fistula, congenital cystic adenomatoid malformation) and result from inflammatory and infectious diseases to the airways. NCFB encompasses several etiologies and degrees of severity; a clear cause cannot be established in many patients.<sup>105,106</sup>

Pulmonary disease in NCFB is very similar to CF, BO, and PCD. The challenge a child with NCFB faces is the pursuit of a diagnosis. The management is very similar to that of most COPDC and should be considered on a case-by-case basis, aiming at patient comfort and clinical response.<sup>107</sup>

Although some randomized, controlled, double-blind trials have shown that prolonged use of macrolides in patients with NCFB improves quality of life and reduces PE rates, the role of macrolides in NCFB management remains unclear and they cannot be recommended for routine use. Until very recently, these drugs were investigated in small trials of short duration, which did not evaluate relevant clinical outcomes, such as PE and quality of life.

Long-term oral antibiotics should not be routinely prescribed. Macrolides (or other antibiotics) can be considered for a limited period of 12–24 months, especially in patients with frequent exacerbations.<sup>4,108,109</sup>

### Plastic bronchitis (PB)

PB is a rare COPDC with unknown prevalence and etiology, with formation of bronchial molds of gelatinous or solid appearance in the large airways, whose composition varies, consisting of mucins, fibrin, DNA, or eosinophils, depending on the PB etiology. The diseases most often associated with PB are congenital heart disease and asthma. It has also been described in infection by influenza virus, H1N1, lymphatic diseases, allergic bronchopulmonary aspergillosis, and sickle-cell disease.<sup>109</sup> Although bronchodilators, corticosteroids, antibiotics, mucolytics, physical therapy, antifibrinolytic therapy with heparin, and urokinase have been used, single or repeat bronchoscopy is essential for diagnosis and treatment.

### Final considerations

The pediatrician's actions are vital for the management of COPDC. The clinician should suspect the disease in the presence of signs and symptoms in order to attain an early and accurate diagnosis, know the risk factors and associated comorbidities, and assess treatment adherence, the correct use of prescribed drugs, and their side effects based on well-defined management protocols, preferably based on specific guidelines.

Management benefits should be assessed through the reduction in acute pulmonary exacerbations, increased quality of life, and decreased evolution of lung function loss (spirometry, measurement of oxygen saturation, lung clearance index) and lung damage (HRCT every 2 years, if necessary). Therefore, the sequential evaluation of lung function and damage should be standardized and continuous, throughout life. For most COPDC, monitoring in specialized reference centers by interdisciplinary teams leads to better outcomes.

## Conflicts of interest

The authors declare no conflicts of interest.

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## References

- Duijts L, Reiss IK, Brusselle G, Jongste JC. Early origins of chronic obstructive lung diseases across the life course. *Eur J Epidemiol.* 2014;29:871–85.
- Braman SS. The chronic obstructive pulmonary disease–asthma overlap syndrome. *Allergy Asthma Proc.* 2015;36:112–8.
- Bousquet J, Jorgensen C, Dauzat M, Cesario A, Camuzat T, Bourret R, et al. Systems medicine approaches for the definition of complex phenotypes in chronic diseases and ageing. From concept to implementation and policies. *Curr Pharm Des.* 2014;20:1–17.
- 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;202:21–3.
- Chmiel JF, Berger M, Konstan MW. The role of inflammation in the pathophysiology of CF lung disease. *Clin Rev Allergy Immunol.* 2002;23:5–23.
- Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Götz M, et al. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy.* 2008;63:5–34.
- Edmond K, Scott S, Korczak V, Ward C, Sanderson C, Theodoratou E, et al. Long term sequelae from childhood pneumonia; systematic review and meta analysis. *PLoS ONE.* 2012;7:e31239.
- Chan JY, Stern DA, Guerra S, Wright AL, Morgan WJ, Martinez FD. Pneumonia in childhood and impaired lung function in adults: a longitudinal study. *Pediatrics.* 2015;135:607–16.
- Ronkainen E, Dunder T, Peltoniemi O, Kaukola T, Marttila R, Hallman M. New BPD predicts lung function at school age: follow-up study and meta-analysis. *Pediatr Pulmonol.* 2015;50:1090–8.
- Spagnolo P, Fabbri LM, Bush A. Long-term macrolide treatment for chronic respiratory disease. *Eur Respir J.* 2013;42:239–51.
- Parnham MJ, Erakovic Haber V, Giamarellos-Bourboulis EJ, Perletti G, Verleden GM, Vos R. Azithromycin: mechanisms of action and their relevance for clinical applications. *Pharmacol Ther.* 2014;143:225–45.
- Brusselle GG, Joos G. Is there a role for macrolides in severe asthma? *Curr Opin Pulm Med.* 2014;20:95–102.
- Simpson JL, Phipps S, Gibson PG. Inflammatory mechanisms and treatment of obstructive airway diseases with neutrophilic bronchitis. *Pharmacol Ther.* 2009;124:86–95.
- Brusselle GG, Vander CS, Jordens P, Deman R, Slabbynck H, Ringoet V, et al. Azithromycin for prevention of exacerbations in severe asthma (AZISAST): a multicentre randomised double-blind placebo-controlled trial. *Thorax.* 2013;68:322–9.
- Bousquet J, Khaltaev N, Cruz A, Yorgancioglu A, Chuchalin A. International European Respiratory Society/American Thoracic Society guidelines on severe asthma. *Eur Respir J.* 2014;44:1377–8.
- Global Strategy for Asthma Management and Prevention. Available from: [http://www.ginasthma.org/local/uploads/files/GINA\\_Report\\_2014\\_Aug12.pdf](http://www.ginasthma.org/local/uploads/files/GINA_Report_2014_Aug12.pdf) [cited 26.03.15].
- Sociedade Brasileira de Pneumologia e Tisiologia. Diretrizes da Sociedade Brasileira de Pneumologia e Tisiologia para o manejo da asma. *J Bras Pneumol.* 2012;38:S1–46.
- British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma – a national clinical guideline [Revised]; 2014. Available from: [www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk) [cited 16.03.15].
- British Thoracic Society, Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. *Thorax.* 2014;69:S1–192.
- Diagnosis and management of asthma in children 5 years and younger. A guide for health care professionals [Revised]; 2014. Available from: [http://www.ginasthma.org/local/uploads/files/GINA\\_Pediatric\\_Pocket\\_2014.pdf](http://www.ginasthma.org/local/uploads/files/GINA_Pediatric_Pocket_2014.pdf) [cited 28.03.15].
- Clinical guidelines for the care of children with cystic fibrosis 2014 – Royal Brompton Hospital. 6th ed; 2014. Available on: [www.rbht.nhs.uk/childrenrcf](http://www.rbht.nhs.uk/childrenrcf) [cited 28.03.15].
- Flume PA, Mogayzel PJ Jr, Robinson KA, Goss CH, Rosenblatt RL, Kuhn RJ, et al. Clinical Practice Guidelines for Pulmonary Therapies Committee. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med.* 2009;180:802–8.
- Rabin HR, Butler SM, Wohl ME, Geller DE, Colin AA, Schidlow DV, et al. Pulmonary exacerbations in cystic fibrosis. *Pediatr Pulmonol.* 2004;37:400–6.
- Werner C, Onnebrink JG, Omran H. Diagnosis and management of primary ciliary dyskinesia. *Cilia.* 2015;4:2.
- Barbato A, Frischer T, Kuehni CE, Snijders D, Azevedo I, Baktai G, et al. Primary ciliary dyskinesia: a consensus statement on diagnostic and treatment approaches in children. *Eur Respir J.* 2009;34:1264–76.
- Iyengar A, Davis JM. Drug therapy for the prevention and treatment of bronchopulmonary dysplasia. *Front Pharmacol.* 2015;6:12.
- Champs NS, Lasmar LM, Camargos PA, Marguet C, Fischer GB, Mocelin HT. Post-infectious bronchiolitis obliterans in children. *J Pediatr (Rio J).* 2011;87:187–98.
- James AL, Knuiman MW, Divitini ML, Hui J, Hunter M, Palmer LJ, et al. Changes in the prevalence of asthma in adults since 1966: the Busselton health study. *Eur Respir J.* 2010;35:273–8.
- Martinez FD. The origins of asthma and chronic obstructive pulmonary disease in early life. *Proc Am Thorac Soc.* 2009;6:272–7.
- Edmond K, Scott S, Korczak V, Ward C, Sanderson C, Theodoratou E, et al. Long term sequelae from childhood pneumonia; systematic review and metaanalysis. *PLoS ONE.* 2012;7:e31239.
- Guilbert TW, Denlinger LC. Role of infection in the development and exacerbation of asthma. *Expert Rev Respir Med.* 2010;4:71–83.
- Chippes BE, Bacharier LB, Harder JM. Phenotypic expressions of childhood wheezing and asthma: implications for therapy. *J Pediatrics.* 2011;158:878–84.
- Just J, Saint Pierre P, Amat F, et al. What lessons can be learned about asthma phenotypes in children from cohort studies? *Pediatr Allergy Immunol.* 2015;26:300–5.

34. He XY, Simpson JL, Wang F. Inflammatory phenotypes in stable and acute childhood asthma. *Paediatr Respir Rev*. 2011;12:165–9.
35. Saglani S, Nicholson AG, Scallan M, Balfour-Lynn I, Rosenthal M, Payne DN, et al. Investigation of young children with severe recurrent wheeze: any clinical benefit? *Eur Respir J*. 2006;27:29–35.
36. Fogaça HR, Marson FA, Toro AA, Solé D, Ribeiro JD. Epidemiological aspects of and risk factors for wheezing in the first year of life. *J Bras Pneumol*. 2014;40:617–25.
37. Mallol J, García-Marcos L, Solé D, Brand P. EISL Study Group. International prevalence of recurrent wheezing during the first year of life: variability, treatment patterns and use of health resources. *Thorax*. 2010;65:1004–9.
38. Guilbert TW, Morgan WJ, Zeiger RS, Bacharier LB, Boehmer SJ, Krawiec M, et al. Atopic characteristics of children with recurrent wheezing at high risk for the development of childhood asthma. *J Allergy Clin Immunol*. 2004;114:6.
39. Stapleton M, Howard-Thompson A, George C, Hoover RM, Self TH. Smoking and asthma. Review. *J Am Board Fam Med*. 2011;24:313–22.
40. Stocks J, Dezateux C. The effect of parental smoking on lung function and development during infancy. *Respirology*. 2003;8:266–85.
41. Oberg M, Jaakkola MS, Woodward A, Peruga A, Prüss-Ustün A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. *Lancet*. 2011;377:139–46.
42. Busse WW, Lemanske RF Jr, Gern JE. Role of viral respiratory infections in asthma and asthma exacerbations. *Lancet*. 2010;376:826–34.
43. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ, et al. Asthma and wheezing in the first six years of life. *N Engl J Med*. 1995;332:133–8.
44. 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.
45. Fouzas S, Brand PLP. Predicting persistence of asthma in preschool wheezers: crystal balls or muddy waters? *Paediatr Respir Rev*. 2013;14:46–52.
46. Brand PL. The asthma predictive index: not a useful tool in clinical practice. *J Allergy Clin Immunol*. 2010;127:293–4.
47. Huffaker MF, Phipatanakul W. Utility of the Asthma Predictive Index in predicting childhood asthma and identifying disease-modifying interventions. *Ann Allergy Asthma Immunol*. 2014;112:188–90.
48. Castro-Rodriguez JA. The necessity of having asthma predictive scores in children. *J Allergy Clin Immunol*. 2013;132:1311–3.
49. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefer SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med*. 2006;354:1985–97.
50. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in infants and preschoolers with recurrent wheezing and asthma: a systematic review with meta-analysis. *Pediatrics*. 2009;123:e519–25.
51. Castro-Rodriguez JA, Rodrigo GJ. Efficacy of inhaled corticosteroids in wheezy infants/preschoolers. *Respir Med*. 2013;107:153–4.
52. Colom AJ, Teper AM, Vollmer WM, Diette GB. Risk factors for the development of bronchiolitis obliterans in children with bronchiolitis. *Thorax*. 2006;61:503–6.
53. Castro-Rodriguez JA, Daszencies C, Garcia M, Meyer R, Gonzales R. Adenovirus pneumonia in infants and factors for developing bronchiolitis obliterans: a 5-year follow-up. *Pediatr Pulmonol*. 2006;41:947–53.
54. Colom AJ, Maffey A, Bournissen FG, Teper A. Pulmonary function of a paediatric cohort of patients with post infectious bronchiolitis obliterans. A long term follow-up. *Thorax*. 2015;70:169–74.
55. Rosewich M, Zissler UM, Kheiri T, Voss S, Eickmeier O, Schulze J, et al. Airway inflammation in children and adolescents with bronchiolitis obliterans. *Cytokine*. 2015;73:156–62.
56. Colom AJ, Teper AM. Clinical prediction rule to diagnose post-infectious bronchiolitis obliterans in children. *Pediatr Pulmonol*. 2009;44:1065–9.
57. Mauad T, Dolhnikoff M, Bronchiolitis Obliterans Study Group. Histology of childhood bronchiolitis obliterans. *Pediatr Pulmonol*. 2002;33:466–74.
58. Myers JL, Colby TV. Pathologic manifestations of bronchiolitis, constrictive bronchiolitis, cryptogenic organizing pneumonia and diffuse panbronchiolitis. *Clin Chest Med*. 1993;14:611–22.
59. Zhang L, Irion K, da Silva Porto N, Abreu e Silva F. High-resolution computed tomography in pediatric patients with postinfectious bronchiolitis obliterans. *J Thorac Imaging*. 1999;14:85–9.
60. Fischer GB, Sarria EE, Mattiello R, Mocelin HT, Castro-Rodriguez JA. Post infectious bronchiolitis obliterans in children. *Paediatr Respir Rev*. 2010;11:233–9.
61. Vega-Briceno LE, Zenteno AD. Clinical guide for diagnosis and care of children and adolescents with post-infectious bronchiolitis obliterans. *Rev Chil Enf Respir*. 2009;25:141–63.
62. Mattiello R, Mallol J, Fischer GB, Mocelin HT, Rueda B, Sarria EE. Pulmonary function in children and adolescents with postinfectious bronchiolitis obliterans. *J Bras Pneumol*. 2010;36:453–9.
63. Noone PG, Leigh MW, Sannuti A, Minnix SL, Carson JL, Hazucha M, et al. Primary ciliary dyskinesia: diagnostic and phenotypic features. *Am J Respir Crit Care Med*. 2004;169:459–67.
64. O’Callaghan C, Chetcuti P, Moya E. High prevalence of primary ciliary dyskinesia in a British Asian population. *Arch Dis Child*. 2010;95:51–2.
65. Knowles MR, Daniels LA, Davis SD, Zariwala MA, Leigh MW. Primary ciliary dyskinesia: recent advances in diagnostics, genetics, and characterization of clinical disease. *Am J Respir Crit Care Med*. 2013;188:913–22.
66. Hosie PH, Fitzgerald DA, Jaffe A, Birman CS, Rutland J, Morgan LC. Presentation of primary ciliary dyskinesia in children: 30 years’ experience. *J Paediatr Child Health*. 2015;51:722–6.
67. Brown DE, Pittman JE, Leigh MW, Fordham L, Davis SD. Early lung disease in young children with primary ciliary dyskinesia. *Pediatr Pulmonol*. 2008;43:514–6.
68. Horani A, Brody SL, Ferkol TW. Picking up speed: advances in the genetics of primary ciliary dyskinesia. *Pediatr Res*. 2014;75:158–64.
69. Leigh MW, Hazucha MJ, Chawla KK, Baker BR, Shapiro AJ, Brown DE, et al. Standardizing nasal nitric oxide measurement as a test for primary ciliary dyskinesia. *Ann Am Thorac Soc*. 2013;10:574–81.
70. Stoltz DA, Meyerholz DK, Welsh MJ. Origins of cystic fibrosis lung disease. *N Engl J Med*. 2015;372:351–62.
71. Goss CH, MacNeill SJ, Quinton HB, Marshall BC, Elbert A, Knapp EA, et al. Children and young adults with CF in the USA have better lung function compared with the UK. *Thorax*. 2015;70:229–36.
72. Marson FA, Hortencio TD, Aguiar KC, Ribeiro JD. Demographic, clinical, and laboratory parameters of cystic fibrosis during the last two decades: a comparative analysis. *BMC Pulm Med*. 2015;15:3.
73. Hoo AF, Thia LP, Nguyen TT, et al. Lung function is abnormal in 3-month-old infants with cystic fibrosis diagnosed by newborn screening. *Thorax*. 2012;67:874–81.

74. 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.
75. Meyerholz DK, Stoltz DA, Namati E, Ramachandran S, Pezzulo AA, Smith AR, et al. Loss of cystic fibrosis transmembrane conductance regulator function produces abnormalities in tracheal development in neonatal pigs and young children. *Am J Respir Crit Care Med.* 2010;182:1251–61.
76. Regamey N, Jeffery PK, Alton EW, Bush A, Davies JC. Airway remodelling and its relationship to inflammation in cystic fibrosis. *Thorax.* 2011;66:624–9.
77. Peterson-Carmichael SL, Harris WT, Goel R, Noah TL, Johnson R, Leigh MW, et al. Association of lower airway inflammation with physiologic findings in young children with cystic fibrosis. *Pediatr Pulmonol.* 2009;44:503–11.
78. Servidoni MF, Sousa M, Vinagre AM, Cardoso SR, Ribeiro MA, Meirelles LR, et al. Rectal forceps biopsy procedure in cystic fibrosis: technical aspects and patients perspective for clinical trials feasibility. *BMC Gastroenterol.* 2013;13:91.
79. Sousa M, Servidoni MF, Vinagre AM, Ramalho AS, Bonadia LC, Felício V, et al. Measurements of CFTR-mediated Cl-secretion in human rectal biopsies constitute a robust biomarker for cystic fibrosis diagnosis and prognosis. *PLoS ONE.* 2012;7:e47708.
80. Ooi CY, Dupuis A, Ellis L, Jarvi K, Martin S, Ray PN, et al. Does extensive genotyping and nasal potential difference testing clarify the diagnosis of cystic fibrosis among patients with single-organ manifestations of cystic fibrosis? *Thorax.* 2014;69:254–60.
81. Eakin MN, Riekert KA. The impact of medication adherence on lung health outcomes in cystic fibrosis. *Curr Opin Pulm Med.* 2013;19:687–91.
82. Chmiel JF, Aksamit TR, Chotirmall SH, Dasenbrook EC, Elborn JS, LiPuma JJ, et al. Antibiotic management of lung infections in cystic fibrosis. II. Nontuberculous mycobacteria, anaerobic bacteria, and fungi. *Ann Am Thorac Soc.* 2014;11:1298–306.
83. Chmiel JF, Aksamit TR, Chotirmall SH, Dasenbrook EC, Elborn JS, LiPuma JJ, et al. Antibiotic management of lung infections in cystic fibrosis. I. The microbiome, methicillin-resistant *Staphylococcus aureus*, Gram-negative bacteria, and multiple infections. *Ann Am Thorac Soc.* 2014;11:1120–9.
84. Flume PA, O'Sullivan BP, Robinson KA, Goss CH, Mogayzel PJ Jr, Willey-Courand DB, et al. CF pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med.* 2007;176:957–69.
85. Döring G, Hoiby N, Consensus Study Group. Early intervention and prevention of lung disease in CF: a European consensus. *J Cyst Fibros.* 2004;3:67–91.
86. Waters V, Smyth A. Cystic fibrosis microbiology: advances in antimicrobial therapy. *J Cyst Fibros.* 2015;14:551–60.
87. Konstan MW, Flume PA, Kappler M, Chiron R, Higgins M, Brockhaus F, et al. Safety, efficacy and convenience of tobramycin inhalation powder (TIP™) in CF patients. The EAGER trial. *J Cyst Fibros.* 2011;10:54–61.
88. Knudsen PK, Olesen HV, Høiby N, Johannesson M, Karpati F, Laerum BN, et al. Differences in prevalence and treatment of *Pseudomonas aeruginosa* in cystic fibrosis centers in Denmark, Norway and Sweden. *J Cyst Fibros.* 2009;8:135–42.
89. Treggiari MM, Retsch-Bogart G, Mayer-Hamblett N, Khan U, Kulich M, Kronmal R, et al. Comparative efficacy and safety of 4 randomized regimens to treat early *Pseudomonas aeruginosa* infection in children with cystic fibrosis. *Arch Pediatr Adolesc Med.* 2011;165:847–56.
90. Ratjen F, Munck A, Kho P, Angyalosi G, ELITE Study Group. Treatment of early *Pseudomonas aeruginosa* infection in patients with cystic fibrosis: the ELITE trial. *Thorax.* 2010;65:286–91.
91. Mogayzel PJ Jr, Naureckas ET, Robinson KA, Brady C, Guill M, Lahiri T, Cystic Fibrosis Foundation Pulmonary Clinical Practice. Guidelines committee cystic fibrosis foundation pulmonary guideline – pharmacologic approaches to prevention and eradication of initial *Pseudomonas aeruginosa* infection. *Ann Am Thorac Soc.* 2014;11:1640–50.
92. Mogayzel PJ Jr, Naureckas ET, Robinson KA, Mueller G, Hadjilias D, Hoag JB, et al. Cystic fibrosis pulmonary guidelines chronic medications for maintenance of lung health. *Am J Respir Crit Care Med.* 2013;187:680–9.
93. 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.
94. Cunha GS, Mezzacappa Filho F, Ribeiro JD. Maternal and neonatal factors affecting the incidence of bronchopulmonary dysplasia in very low birth weight newborns. *J Pediatr (Rio J).* 2003;79:550–6.
95. Cunha GS, Mezzacappa-Filho F, Ribeiro JD. Risk factors for bronchopulmonary dysplasia in very low birth weight newborns treated with mechanical ventilation in the first week of life. *J Trop Pediatr.* 2005;51:334–40.
96. Sanchez-Solis M, Garcia-Marcos L, Bosch-Gimenez V, Pérez-Fernandez V, Pastor-Vivero MD, Mondéjar-Lopez P. Lung function among infants born preterm, with or without bronchopulmonary dysplasia. *Pediatr Pulmonol.* 2012;47:674–81.
97. Palta M, Sadek-Badawi M, Sheehy M, Albanese A, Weinstein M, McGuinness G, et al. Respiratory symptoms at age 8 years in a cohort of very low birth weight children. *Am J Epidemiol.* 2001;154:521–9.
98. Fawke J, Lum S, Kirkby J, Hennessy E, Marlow N, Rowell V, et al. Lung function and respiratory symptoms at 11 years in children born extremely preterm: the EPICure study. *Am J Respir Crit Care Med.* 2010;182:237–45.
99. Broström EB, Akre O, Katz-Salamon M, Jaraj D, Kaijser M. Obstructive pulmonary disease in old age among individuals born preterm. *Eur J Epidemiol.* 2013;28:79–85.
100. 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.
101. Gough A, Linden M, Spence D, Patterson CC, Halliday HL, Mc Garvey LP. Impaired lung function and health status in adult survivors of bronchopulmonary dysplasia. *Eur Respir J.* 2014;43:808–16.
102. Iyengar A, Davis JM. Drug therapy for the prevention and treatment of associated pulmonary hypertension: a retrospective study of efficacy and safety. *Eur J Pediatr.* 2015;6:1–7.
103. Iyengar A, Davis JM. Drug therapy for the prevention and treatment of bronchopulmonary dysplasia. Review. *Front Pharmacol.* 2015;16:12.
104. Tan K, Krishnamurthy MB, O'Henev JL, Paul E, Sehgal A. Sildenafil therapy in bronchopulmonary dysplasia-associated pulmonary hypertension: a retrospective study of efficacy and safety. *Eur J Pediatr.* 2015;174:1109–15.
105. Brower KS, Del Vecchio MT, Aronoff SC. The etiologies of non-CF bronchiectasis in childhood: a systematic review of 989 subjects. *BMC Pediatrics.* 2014;14:1–8.
106. Chang AB, Masel JP, Boyce NC, Wheaton G, Torzillo PJ. Non-CF bronchiectasis: clinical and HRCT evaluation. *Pediatr Pulmonol.* 2003;35:477–83.
107. Yap VL, Metersky ML. New therapeutic options for non-cystic fibrosis bronchiectasis. *Curr Opin Infect Dis.* 2015;28:171–6.
108. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2012;380:660–7.
109. Madsen P, Shah SA, Rubin BK. Plastic bronchitis: new insights and a classification scheme. *Paediatr Respir Rev.* 2005;6:292–300.