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Early View

Task force report

# European Respiratory Society guideline on long term management of children with bronchopulmonary dysplasia

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# European Respiratory Society guideline on long term management of children with bronchopulmonary dysplasia.

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**Key words:** Bronchopulmonary dysplasia, preterm birth, patient care management, imaging, lung function, day care, bronchodilators, corticosteroids, diuretics, oxygen.

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D. Rigau, R.L. Morgan, and T. Tonia acted as ERS Methodologists.

**ABSTRACT**

This document provides recommendations for monitoring and treatment of children in whom bronchopulmonary dysplasia (BPD) has been established and were discharged from the hospital, or who were older than 36 weeks of postmenstrual age. The guideline was based on pre-defined Population, Intervention, Comparison and Outcomes (PICO) questions relevant for clinical care, a systematic review of the literature, and assessment of the evidence using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. After considering the balance of desirable (benefits) and undesirable (burden, adverse effects) consequences of the intervention, the certainty of the evidence, and values, the Task Force made conditional recommendations for monitoring and treatment of BPD based on very low to low quality of evidence. We suggest monitoring with lung imaging using ionising radiation in a subgroup only, for example severe BPD or recurrent hospitalizations, and monitoring with lung function in all children. We suggest to give individual advice to parents regarding day care attendance. With regards to treatment, we suggest to use bronchodilators in a subgroup only, for example asthma-like symptoms, or reversibility in lung function, no treatment with inhaled or systemic corticosteroids, natural weaning of diuretics by the relative decrease in dose with increasing weight gain if diuretics are started in the neonatal period, and to treat with supplemental oxygen with a saturation target range of 90-95%. A multidisciplinary approach for children with established severe BPD after the neonatal period into adulthood is preferable. These recommendations should be considered until new and urgently needed evidence becomes available.

## INTRODUCTION

Bronchopulmonary dysplasia (BPD), also called chronic lung disease of prematurity, is a chronic respiratory disease that predominantly affects children born preterm. Advanced perinatal care has improved the survival of extremely preterm born children, however the incidence of BPD has not decreased (1). Improved survival is mainly due to the introduction of antenatal management, including maternal corticosteroid administration, intratracheal surfactant administration, less aggressive mechanical ventilation strategies and targeted oxygen therapy, which consequently led to a different form of BPD (2-26). Since 1999, BPD is defined as oxygen need for ≥28 days from birth until 36 weeks of postmenstrual age (PMA) (27, 28). Whilst in earlier years BPD was associated with aggressive mechanical ventilation, improved ventilation changed the histologic phenotype of BPD from a predominantly post-traumatic condition leading to the formation of hyaline membranes (old form of BPD), to one where pulmonary changes are characterized by a global alveolar development arrest (new form of BPD) (27, 29). The precise maturational trajectory of airways, lungs and related vessels in extreme preterm, early extra-uterine life is not fully known but is likely to comprise airway, lung, and vascular driven pathology leading to severe chronic respiratory and vascular diseases across the life course, and potentially shorten life expectancy. Once discharged from the neonatal unit, children with BPD are at a high risk of re-hospitalization due to higher susceptibility of viral infections, decreased nutritional state or poorer neurological outcome, leading to increased health care utilization and costs (30). Apart from advising on preventative measures, the application of supportive measures is paramount. Therefore, physicians and caretakers need to assess the disease progression and tailor treatment adequately. Also, previous studies showed that children with BPD have an impaired lung structure, lower lung function, including declining lung function over time, and increased risk of respiratory symptoms in later life (31-41). This suggests that BPD partly reflects an ongoing chronic respiratory disease with long-term consequences and not just stabilized structural lung damage after the neonatal period. BPD in childhood may form a new group of chronic obstructive pulmonary disease (COPD) in adulthood.

Although several tools have been studied for their utility in monitoring children with BPD, to date, there are no guidelines on comprehensive monitoring strategies for children in whom BPD has been established and who are discharged from the hospital (42, 43). Further, most studies have so far largely focused on preventing, rather than treating established BPD. Interventional studies beyond the neonatal period, such as use of inhaled or systemic corticosteroids, bronchodilators and long-term oxygen treatment, are far and few available. A clear consensus and recommendations with grading evidence on how to monitor and treat children with BPD at the long term is lacking.

Therefore, we undertook a systematic review of the literature and developed recommendations following the Grading of Recommendations Assessment, Development and Evaluation (GRADE)(44), to inform decisions regarding the monitoring and treatment of children with BPD. Specifically, we focused on those children with the new form of BPD in whom BPD already had been established *and* were discharged from the hospital, *or* who were older than 36 weeks of postmenstrual age. This population is meant when referring to children with BPD throughout this manuscript. The target audience of this guideline includes specialists in respiratory medicine, pediatricians and/or neonatologists who manage children with bronchopulmonary dysplasia. Other healthcare physicians such as respiratory nurses and policy makers may also benefit from this guideline. This guideline provides the basis for rational decisions in the monitoring and treatment of specifically children in whom BPD has been established and who were discharged from the hospital, or were older than 36 weeks of PMA. Clinicians, patients and their parents/care-givers, third-party payers, stakeholders or the courts should never view the recommendations contained in these guidelines as mandatory. Though evidence-based guidelines can summarize the best available evidence regarding the effects of an intervention in a given patient population, they cannot take into account all of the unique clinical circumstances that may arise when managing an individual patient.

## Methods

**Task Force composition** The chairs applied for a Task Force on BPD, which was approved and funded by the European Respiratory Society. The Task Force consisted of a multidisciplinary group of clinicians, scientific researchers, methodologists or patient representatives with expertise in the pediatric respiratory (n=11), neonatology (n=3), pediatric cardiology (n=1), adult respiratory (n=1), epidemiology (n=3), and patient involvement (n=4) field related to long term monitoring and treatment of children with BPD. All representatives had intensive experience in long term follow-up of children born preterm or with BPD. Task Force members were from Europe, the United States and Australia. Two junior members/trainees of the ERS, a parent of a patient with BPD, an adult patient with BPD, and national (Lung Foundation Netherlands) and international (European Lung Foundation) patient representatives were active members of the committee. Also, methodologists from the ERS provided expertise in guideline development following the GRADE approach. Potential conflicts of interest were disclosed and managed according to ERS policies.

**Formulation of the topics and questions** Task Force members compiled a list of topics that they considered important and relevant to the monitoring and treatment of children with established BPD after the neonatal period. Discussion among the Task Force members was applied to identify the eight most relevant and important questions to be addressed in this guideline. Questions related to the topics were phrased using the Population, Intervention, Comparison and Outcomes (PICO) format. The population (P) consisted specifically of children with the new form of BPD, in whom BPD had been established *and* who were discharged from the hospital, *or* were older than 36 weeks of PMA. The interventions (I) comprised monitoring with lung imaging or lung function, discouraging daycare attendance, and treatment with inhaled bronchodilators, inhaled corticosteroids, systemic corticosteroids, diuretics or oxygen. The comparison (C) were those without the intervention. Specific important and critical outcomes (O) defined for each question are presented in Table 1. The eight questions for children with BPD were:

1. Does monitoring with *lung imaging* versus no lung imaging; and
2. Does monitoring with *lung function* versus no lung function; and
3. Does discouraging *day care attendance* versus not discouraging day care attendance; and
4. Does treatment with *inhaled bronchodilators* versus no inhaled bronchodilators; and
5. Does treatment with *inhaled corticosteroids* versus no inhaled corticosteroids; and
6. Does treatment with *systemic corticosteroids* versus no systemic corticosteroids; and
7. Does treatment with *diuretics* versus no diuretics; and
8. Does treatment with *oxygen* versus no oxygen;

affect outcomes which are defined as important or critical? Thereafter, the questions 'Does treatment with *inhaled corticosteroids* versus no inhaled corticosteroids'; and 'Does treatment with *systemic corticosteroids* versus no inhaled corticosteroids affect important and critical defined outcomes' were combined for practical reasons. For each question, a PICO working group was composed with a leader and two to four members.

**Rating the importance of outcomes** The Task Force identified BPD morbidity and related outcomes after discharge or after 36 weeks of PMA that they considered relevant to each question. These comprised number and severity of respiratory symptoms, adverse growth, hospital admissions, CT abnormalities, reduced physical exercise capacity, pulmonary hypertension, use of inhaled bronchodilators, use of inhaled corticosteroids, use of systemic corticosteroids, use of diuretics, prolonged duration of supplemental oxygen need, side effects, adverse neurodevelopment, decreased quality of life, mortality, or impaired lung function, depending on each question under study. Task Force members rated the importance of each outcome a-priori, using a scale from 1 to 9. A rating of 1–3 was assigned to outcomes of low importance, 4–6 to outcomes important, and 7–9 to outcomes critical for decision-making. Individual ratings were summarized and evaluated by the co-chairs and an ERS methodologist. A final rating was proposed to all Task Force members, and approved. All outcomes were categorized as "not important", "important" or "critical" for decision-making

(Supplementary Table 1). Only “important” or “critical” outcomes were used in the literature search and decision making (45).

**Literature search methods** We conducted literature searches in Embase.com, Medline Ovid, Cochrane Central Registry of Trials, and Web of Science Core Collection until July 11th, 2018 (last data search). We included meta-analyses and systematic reviews of randomised trials, randomised trials, and retrospective or prospective cohort studies published from 1999, in which BPD was defined. Detailed scripts of the search terms created by a librarian (WB) are given in the methods part of the Supplementary Material and Supplementary table 1. Scripts were set broad to limit missing of relevant articles. Conference abstracts were omitted.

**Study selection** For each PICO question, working groups selected relevant articles in 3 stages by: 1) title screening and abstract screening, 2) full article screening, and 3) reading full articles to summarize findings related to the PICO. A minimum of 2 group members were required to independently review the relevant articles to minimize potential bias. Inclusion criteria were the study population of children in whom BPD had been established and who were discharged from the hospital, or were older than 36 weeks of PMA, and studying the specifically defined monitoring and treatment tools in relation to the defined outcomes of interest. Exclusion criteria were incorrect population under study (no children, no BPD only as second best), incorrect monitoring or treatment intervention, study focused on prevention instead of monitoring or treatment of BPD, outcomes of interest not reported, no abstract or full text available, or no English text available. When no articles for the PICO directly fulfilled these criteria, indirect articles that indirectly fulfilled these criteria were included using a less favourable study design, preterm born children (as opposed to children with BPD) or the old form of BPD (as opposed to the new form of BPD). A discussion was held between the independent PICO working group members when no consensus was reached to include or

exclude identified articles. Also, 1 physician-epidemiologist (LD), 1 junior ERS member-epidemiologist (EM), and 1 junior member-trainee (LM) read the identified articles, and discussed these to reach consensus on the selection of final articles if differences in opinion to in- or exclude the articles were present. When also no indirect articles for the PICO were found, experience of local, regional or national management of Task Force members was asked, summarized, and discussed if relevant.

**Evidence synthesis and grading** With guidance from the ERS methodologists, relevant data were extracted from the selected studies for each PICO taking the outcomes into account that were rated “important” or “critical” for decision-making. We graded the effect estimates for the body of the evidence for each outcome to determine our certainty in the evidence, and presented the findings using the GRADEpro Guideline Development Tool (http://gdt.gradepro.org/app/). We primarily used findings from only one type of study design, preferably observational studies for monitoring questions and randomized trials (RCT) for treatment questions, to create a summary of evidence, and where appropriate used findings of other types of study designs to complement recommendations. Data were not amenable to pooling.

**Formulating recommendations** The evidence profiles were sent to the Task Force members for review. Using an iterative consensus process conducted face to face and via email, recommendations were formulated on the basis of the balance of desirable (benefits) and undesirable (burden, adverse effect) consequences of the intervention, the certainty of the evidence, values, balance of effects, required resources, costs, equity, acceptability and feasibility, using the Evidence to Decision framework (46). Whether all domains could be assessed depended on the availability of the evidence per PICO. Recommendations could either be strong, or conditional (weak) (Table 2). A strong recommendation for an intervention was made when the Task Force was confident that the desirable effects outweighed the undesirable effects, while a strong recommendation against an intervention

was made when the Task Force was confident that the undesirable effects outweighed the desirable effects. A conditional recommendation for an intervention was made if the Task Force concluded that the desirable effects probably outweighed the undesirable effects, but was not confident, while a conditional recommendation against the intervention was made if the Task Force concluded that the undesirable effects probably outweighed the desirable effects, but was not confident.

Reasons for making a conditional recommendation included low or very low certainty in the quality of evidence, a close balance between the desirable and undesirable consequences, or underlying values and preferences, equity, acceptability or feasibility in the direction opposite to that of the desirable effects (e.g. the desirable consequences of an intervention clearly outweigh the undesirable consequences taking into account that in some healthcare systems or situations the intervention is not widely acceptable or feasible to implement).

**Manuscript preparation** The initial draft of the manuscript was prepared by the physician-epidemiologist (LD) and a junior ERS member-epidemiologist (EM), and reviewed by a methodologist. Thereafter, both the manuscript and the online supplement were reviewed, edited and approved by all Task Force members prior to submission.

## RESULTS

The results of the evidence assessment are presented in Supplementary Tables 3.1 to 3.4. A summary of the recommendations is presented in Table 3. For each question, the number of potentially relevant papers ranged from 197 to 4,329, and of final papers from four to none. When formulating the recommendations, required resources, costs, equity, acceptability and feasibility were not taken into account due to lack of evidence.

### *Review of evidence addressing the question on lung imaging*

*PICO 1* In children with BPD, does monitoring with lung imaging versus no lung imaging affect important and critical defined outcomes?

*Summary of the evidence* No direct evidence that would answer this question in an appropriate way was identified. Indirect evidence was provided by four studies that examined the relation of lung imaging with lung function or duration of supplemental oxygen need (Supplementary Table 3.1)(47-50). Twenty-one school-children with BPD (mild, n = 9; moderate, n = 4; and severe, n = 8) were offered the opportunity to undergo high-resolution CT (HRCT) scans (47). The rate of severe BPD was higher compared to those not participating for scanning. Mean age of the children was 12.7 years (range: 8.7-16.7). Higher HRCT scores were related to lower Forced Expiratory Volume in 1 second ($FEV_1$) (β -4.23; 95% CI -6.97 to -1.49, p = 0.004) and Maximal Mid-Expiratory Flow (MMEF) (β -3.45; 95% CI -6.10 to -0.80, p = 0.013), but not to gas exchange as measured by CO diffusion capacity (DLCO). A retrospective study among 19 children with BPD observed that all children at a median age of 14.6 months (range 1.5-53.7) had CT abnormalities, which were not associated with clinical outcomes such as gestational age, type and duration of mechanical ventilation and BPD severity (48). In a retrospective review, 41 very low birthweight infants with BPD, who had exacerbations in the last 6 months at a mean age, underwent HRCT scans and lung function tests at a mean age of 16 months. Maximal expiratory flow at functional residual capacity (VmaxFRC) and functional residual capacity (FRC) were

measured by the squeeze technique (50). An increased number of triangular subpleural opacities and of limited linear opacities on CT were associated with a lower FRC (r -0.426 and -0.421 (p-value for both <0.02), respectively), but not VmaxFRC. A study among 40 preterm born children (median age 27 weeks (range 24-32 weeks) observed that those remaining oxygen dependent at a post-conceptional age of 36 weeks had significantly higher chest radiograph scores at one of month of age (median 9, range 7 to 20) than those not chronically oxygen dependent (median 3, range 0 to 13); p<0.05 (49).

*Certainty of the evidence* The certainty of the evidence was considered very low.

*Strength of the recommendation* Conditional for the intervention.

*Task Force recommendation* The Task Force suggests lung imaging to monitor children with BPD in subgroups only, for example children with severe BPD, severe respiratory symptoms, and/or recurrent hospital admissions due to respiratory morbidity (conditional recommendation based on very low certainty of evidence).

*Justification of recommendation* Among the presented studies with indirect evidence to use lung imaging as a monitor tool, the study population consisted of children defined with the old form of BPD (51), the studies used retrospective or cross-sectional data collection with potential risk of bias, or reported not enough numerical data to be able to judge imprecision. Therefore, the evidence was considered very low. In clinical practice, Task Force members agreed that given the low certainty of evidence and potential side effects of radiation, monitoring with lung imaging would be justified only in subgroup of children with severe BPD, severe respiratory symptoms, recurrent hospitalizations or equivalent. For example, a chest CT with intravenous contrast could be considered to exclude other diagnoses, which may affect treatment strategies.

*Other considerations* Almost all children with established BPD seem to have lung structure abnormalities measured by lung imaging (50, 52). However, studies are mostly among children from an outpatient clinic, and proper control groups are often lacking. Also, the natural course of lung structural abnormalities and of normal alveolarization in early life is not fully known.

*Suggestions for future research* Recently, nonionizing magnetic resonance imaging (MRI) scan protocols for children with BPD have been developed, and a quiet-breathing MRI scan independently assessed structural abnormalities of BPD, disease severity, and predicted short term outcomes at discharge from the neonatal intensive care unit (53, 54). This technique is a promising monitoring tool for long term outcomes. Further studies are warranted to examine the predictive value of lung imaging, preferably non-radiant, on long term outcomes of children with established BPD. Studies using lung imaging such as CT or MRI in the neonatal phase might be considered to better define the severity of BPD, or to diagnose or exclude other causes of BPD.

***Review of evidence addressing the question on lung function***

*PICO 2* In children with BPD, does monitoring with lung function versus no lung function affect important and critical defined outcomes?

*Summary of the evidence* No direct evidence that would answer this question in an appropriate way was identified. Indirect evidence was provided by two studies among preterm born children. The first study showed that among extremely preterm born children, the ratio of tidal expiratory flow at 50% of expired volume to peak tidal expiratory flow ($TEF_{50}$/PTEF), which reflects airway obstruction, measured by electromagnetic inductance plethysmography predicts respiratory morbidity in the first year of life (Area Under Curve (95% Confidence Interval): 0.723 (0.55, 0.86)) (Supplementary Table 3.2)(55). Also, $TEF_{50}$/PTEF was lower in the group with respiratory morbidity in the first year of life, than in

the group without (73.5 vs. 79.9, p-value = 0.03). Other tidal breathing lung function measures did not differ between those with and without respiratory morbidity. Another prospective cohort among 163 preterm born children measured tidal breathing and performed multiple breath washout measurements during sleep at the age of 44 weeks PMA (56). After adjustment for confounders, a higher respiratory rate and higher tidal volume were associated with a decreased and increased risk of wheeze, respectively, in the first year of life (OR (95% CI): 0.69 (0.50, 0.96) and 1.40 (1.04, 1.90), respectively), and a higher time to peak tidal expiratory flow expiratory time ratio (*t*PTEF/*t*E) with less bronchodilator inhalation therapy during the first year of life (OR (95% CI): 0.56 (0.35, 0.89)). Other lung function measures such as FRC and lung clearance index (LCI) were not associated with wheeze, inhalation therapy or re-hospitalization, and none of the lung function measures were associated with home oxygen therapy. The additional value of lung function tests was tested by adding them to prediction models for wheezing in the first year of life based on BPD classification, the clinical risk index for babies (CRIB) score, or clinical standard predictors such as sex, PMA and days of mechanical ventilation. Adding lung function to either of the three models however did not improve prediction of wheeze (AUC of model with vs. without added lung function (likelihood ratio test p-value) 0.63 vs 0.54 (0.15), 0.62 vs 0.52 (0.08) and 0.71 vs 0.68 (0.12)).

*Certainty of evidence* The certainty of the evidence was considered very low.

*Strength of the recommendation* Conditional for the intervention.

*Task Force recommendation* The Task Force suggests lung function to monitor children with BPD (conditional recommendation based on very low certainty of evidence).

*Justification of the recommendation* No studies have been performed that examined the potential beneficial effect of lung function monitoring on important and critical defined

outcomes in children with BPD. Among the presented studies with indirect evidence to use lung function as a monitoring tool, the study population consisted of preterm born children, not specifically children with BPD, or potential confounders were not taken into account. Therefore, the evidence was considered very low. No evidence was found that monitoring children with BPD with lung function reduces morbidity and related outcomes. However, for clinical practice, Task Force members agreed that monitoring with lung function would be justified despite the lack of evidence. Lung function, specifically spirometry and related bronchodilator response at older ages, is an objective measure, is associated with lung function in adulthood, and with increased risks of morbidity and mortality, has sex, age, height, and ethnicity adjusted reference ranges, and has no potential side effects. Lung function could also act as a potential indicator for the risk of lung- and related vascular diseases in adulthood.

*Other considerations* Many prospective and retrospective cohort studies have examined lung function at later ages among children with BPD (37, 57, 58), compared with preterm born children without BPD (37, 57, 58) or term born children (37). A recent meta-analysis of >50 studies showed that children who were born preterm and were diagnosed with BPD had a 16% lower $FEV_{1,}$ compared with children born at term (32). Similarly, a review of 18 studies showed that in those with BPD, compared with children born at term at age 6-19 years, $FEV_1$ was consistently lower (34). However, a large heterogeneity in results was observed suggesting variation in expression of the disease or differences in populations studied, with mostly diagnoses of the old form of BPD. Furthermore, also children born preterm without BPD or born preterm across the full gestational age range have a lower lung function at later age (32, 59), which suggests altered airway and lung maturation or mediation by specific ventilation strategies (60). Children with BPD often respond less to bronchodilators and have a lower fractional exhaled nitric oxide (FeNO), a measure of eosinophilic airway inflammation, compared with children with asthma (61, 62). This suggests that airway reactivity through eosinophilic airway inflammation is probably not involved in BPD. Previous

studies observed elevated neutrophils and oxidative stress in airways, measured by induced sputum and exhaled breath condensate respectively, in children aged 11 years or adolescents born preterm compared with children born term (63, 64). This suggests that BPD reflect an ongoing respiratory disease after birth with long-term consequences and not just stabilized structural lung damage after the neonatal period. The possible adverse effects of BPD on lung clearance index, a measure of ventilation heterogeneity of the lungs and a well-accepted and applicable lung function test for children aged <5 years, and on exercise capacity are not fully clear (65-68). Some differences in lung function in early life have shown to be persistent in adulthood (69), which suggests that the expected optimal peak in lung function development is not reached. The relation of lung function measures with lung structure and risk of respiratory morbidity in children with BPD is not fully clear.
Spirometry seems the most useful method for longitudinal follow up of lung growth and airway obstruction in school-age children with BPD. For preschool children (age <= 4 years) with BPD, the forced oscillation technique and multiple breath washout tests are the most applicable regarding technique and validity (43, 70). However, reported studies have small sample sizes and limitations, and the success rate in routine clinical practice without sedation is considered low.

*Suggestions for future research* Further studies, observational or RCT, are warranted to examine the predictive value of lung function on long term lung structure and respiratory morbidity of children with established BPD, and its value in monitoring responses to treatment.

***Review of evidence addressing the question on day care attendance***

*PICO 3* In children with BPD, does discouraging day care attendance versus not discouraging day care attendance affect important and critical defined outcomes?

*Summary of the evidence* This could not be given because no articles were available.

*Certainty of evidence* The certainty of the evidence was considered very low.

*Strength of the recommendation* Conditional for either the intervention or the comparison.

*Task Force recommendation* The Task Force suggests to give individual advice to parents regarding day care attendance for children with BPD (conditional recommendation based on very low certainty of evidence).

*Justification of the recommendation* Due to the lack of evidence, all Task Force members were asked what they would advise in their own clinical practice. Most do not discourage day care attendance, but do not encourage day care attendance either. The younger the child and the potentially higher prevalence of infectious diseases in specific seasons of the year, the more reluctant the Task Force members were to encourage day care attendance. The first winter in young, severely affected children with established BPD would be of most concern for attending day care. It was mentioned that day care attendance also has positive effects on e.g. social development. The Task Force group noted that parental leave regulations differ greatly among countries, for example 12 months in Scandinavian countries versus 3 months in The Netherlands, which could influence the decision to take the child to day care.

*Other considerations* Advice should be based on local experience, age of the child, season of the year, and parental wishes and possibilities.

*Suggestions for future research* Studies are needed to examine the effects of day care attendance on number and severity of respiratory symptoms, adverse growth, hospital admissions, duration of supplemental oxygen need, neurodevelopment and quality of life.

***Review of evidence addressing the question on inhaled bronchodilators***

*PICO 4* In children with BPD, does treatment with inhaled bronchodilators versus no inhaled bronchodilators affect important and critical defined outcomes?

*Summary of the evidence* This could not be given because no articles were available.

*Certainty of the evidence* The certainty of the evidence was considered very low.

*Strength of the recommendation* Conditional recommendation for the intervention.

*Task Force recommendation* The Task Force suggests treatment with bronchodilators for children with BPD in subgroups only, for example children with severe BPD, those with asthma-like symptoms, recurrent hospital admission due to respiratory morbidity, exercise intolerance, or reversibility in lung function (conditional recommendation based on very low certainty of evidence).

*Justification of the recommendation* Due to the lack of evidence, a discussion among the group members of the Task Forces was held on the use of inhaled bronchodilators in practice. It was suggested that treatment with inhaled bronchodilators is optional for subgroups only, e.g. for children with severe BPD, those with asthma-like symptoms, recurrent hospital admission due to respiratory morbidity, exercise intolerance, or bronchodilator reversibility in lung function. Potential benefits for some of these children have been experienced by Task Force group members. Some clinical practices start bronchodilators as a trial, and only continue if significant improvement in respiratory symptoms, lung function, if available, or number of hospitalizations or emergency visits is shown.

*Other considerations* Effects of treatment with inhaled bronchodilators should be carefully monitored by symptoms or lung function if applicable, or reduction of number of hospitalizations or emergency visits before chronically applied.

*Suggestions for future research* Most studies have focused on treatment with bronchodilators of children before 36 weeks of PMA (71). Further studies are urgently needed to examine the use of inhaled bronchodilators in children with BPD.

***Review of evidence addressing the question on the use of inhaled/systemic corticosteroids***

*PICO 5/6* In children in with BPD, does treatment with inhaled or systemic corticosteroids versus no inhaled or systemic corticosteroids affect important and critical defined outcomes?

*Summary of the evidence* No direct evidence that would answer this question in an appropriate way was identified. Indirect evidence was obtained from one study, a crossover RCT that recruited eighteen children born premature (mean gestational age 28 weeks) at the age of 10.5 months, who had symptoms that were not controlled despite regular use of bronchodilators (72) (Supplementary Table 3.3). Children received either 200 μg of beclomethasone dipropionate or placebo twice daily for two six week periods, separated by a two-week washout period. During the active period, as compared to the placebo period, respiratory symptoms decreased (37% improvement in symptom score, p-value <0.001). During the active period, FRC increased significantly (30 vs 36 ml/kg, $p < 0.002$), while there was no change in FRC during the placebo treatment period (31 vs 32 ml/kg).

*Certainty of the evidence* The certainty of the evidence was low.

*Strength of the recommendation* Conditional against the intervention.

*Task Force recommendation* The Task Force suggests not to treat with inhaled or systemic corticosteroids for children with BPD (conditional recommendation based on low certainty of evidence). If the treating physician considers the use of inhaled/systemic corticosteroids of additional value, for example children with severe BPD, severe respiratory symptoms, recurrent hospitalizations or equivalent, and not controlled with regular use of bronchodilators, the effects of treatment with inhaled/systemic corticosteroids should be carefully monitored during a trial period before chronically applied.

*Justification of the recommendation* Only one study was available, which was not specifically performed in children with the new form of BPD, but preterm born children who had uncontrolled respiratory symptoms. Additionally, loss to follow up was of methodological concern. Last, the use of corticosteroids may have side effects and/or can lead to adverse events, which need to be outweighed by the possible benefits. Therefore, the evidence was considered low. Since the use of corticosteroids may lead to side effects, the Task Force did not deem it justified to recommend treatment with inhaled corticosteroids.

*Other considerations* Other evidence is provided by a cohort of 63 preterm born children, followed for 4 months, with a median age of 10 years at the time of the study (73). Those with bronchial obstruction, increased responsiveness to inhaled bronchodilators and/or abnormal diurnal peak expiratory flow (PEF) variation were included. In total 18 children met these criteria and received inhaled budesonide 0.8 $mg^{-2}$ $day^{-1}$ in two doses for the first month, followed by 0.4 $mg^{-2}$ $day^{-1}$ in two doses for another 3 months. Lung function was measured by spirometry twice daily at home, and at the clinic at baseline, after 1 months and after 4 months of budesonide treatment. Additionally, children kept a record of any respiratory symptoms, defined as cough or wheezing. Budesonide treatment did not lead to any changes in lung function measures at the clinic, although there was a decrease in diurnal peak expiratory flow (PEF) variation at home both after 1 and 4 months of budesonide treatment. The symptom score after 1 month of budesonide, but not after 4 months, was

significantly lower. When the Task Force discussed the recommendations, it was taken into account that the indirect evidence for the use of corticosteroids was not strong, that there is a difference in using corticosteroids as standard treatment, or at the time of uncontrolled disease, and that corticosteroids should be used with caution, especially since the effects on preterm born, still growing lungs are not yet known. If the treating physician considers the use of inhaled/systemic corticosteroids of additional value, for example children with severe BPD, severe respiratory symptoms, recurrent hospitalizations or equivalent, and not controlled with regular use of bronchodilators, the effects of treatment with inhaled/systemic corticosteroids should be carefully monitored during a trial period before chronically applied. Monitoring could be by number and severity of symptoms, improvement of lung function, if applicable, or by number of hospitalizations or emergency visits.

*Suggestions for future research* Further studies are urgently needed to examine the use of inhaled or systemic corticosteroids in children with BPD.

***Review of evidence directly addressing the question on diuretics***

*PICO 7* In children in with BPD, does treatment with diuretics versus no diuretics affect important and critical defined outcomes?

*Summary of the evidence* No direct evidence that would answer this question in an appropriate way was identified. Indirect evidence was provided by one study (74) (Supplementary Table 3.4). An RCT showed that, among infants with oxygen-dependent BPD who were clinically stable, there were no differences in number of rehospitalizations for respiratory deterioration (diuretic group 22 of 14 patients vs. placebo group 19 of 6 patients), pulmonary function tests, or total duration of supplemental oxygen use (diuretic group 133+/- 53 days vs. placebo group 147 +/- 71 days), and no differences in side effects including nephrocalcinosis, supplemental electrolytes or hearing deficits between the groups after 36 weeks of PMA. Only FRC measured between 9 weeks after weaned from oxygen and

diuretics and 1 year of corrected age gestational age was increased in the diuretics group. At 1 year of corrected gestational age, the FRC/TGV had improved in both the diuretic group (0.89±0.18) and the placebo group (0.97±0.11).

*Certainty of the evidence* The certainty of the evidence was considered very low.

*Strength of the recommendation* Conditional for either the intervention or the comparison.

*Task Force recommendation* For those children with BPD who already received treatment with diuretics from the neonatal phase or neonatal intensive care unit onwards, the Task Force suggests natural weaning by the relative decrease in dose with increasing weight gain (conditional recommendation based on very low certainty of evidence). If the treating physician considers the use of diuretics of additional value, for example when clinical signs of fluid retention are present, the effects of treatment with diuretics should be carefully monitored during a trial period before chronically applied.

*Justification of the recommendation* No intervention studies examined the potential beneficial effect of diuretics on important and critical defined outcomes in children in whom BPD has been established and were discharged from the hospital, or who were older than 36 weeks of PMA. In the presented study, the exact method of randomization procedure was unclear, potential confounders were not taken into account, the intention to treat analysis was not fully clear, and additional furosemide supplementation differed between the groups (diuretic group 0/22 patients vs placebo group 5/21 patients; p-value <0.05). The study group did not contain children with the new form of BPD. Therefore, the evidence was considered very low.

*Other considerations* None.

*Suggestions for future research* Further studies are needed to examine the use of diuretics in children with BPD.

***Review of evidence directly addressing the question oxygen***

*PICO 8* In children with BPD, does treatment with oxygen versus no oxygen affect important and critical defined outcomes?

*Summary of the evidence* This could not be provided because no articles were available.

*Certainty of the evidence* The certainty of the evidence was considered very low.

*Strength of the recommendation* Conditional recommendation for the intervention

*Task Force recommendation* The Task Force suggests for children with BPD that supplemental oxygen with a minimum saturation target level of 90% should be maintained until further studies are performed (conditional recommendation based on very low certainty of evidence).

*Justification of the recommendation* In a study among children born <30 weeks of gestation who were still dependent on supplemental oxygen at 32 weeks of gestation were randomized into target saturation range 91-94% vs. 95-98% (75). This study found no difference in growth (weight, length, head circumference at 38 weeks PMA or corrected age of 12 months, or weight and length <10th percentile, or head circumference <3rd percentile), re-hospitalization rate, retinopathy of prematurity stage 3 or 4, major developmental abnormality (blindness, cerebral palsy, or general quotient on revised Griffiths Mental Developmental Scale <2 SD below mean), psychosocial measures or death. Children with higher target saturation did have longer duration of oxygen use, compared to children with lower target saturation. A review of the literature concluded that no studies showed a conclusive proof of

the optimal target saturation in post-term oxygen therapy in children born preterm on several outcomes (76). Saturation targets used were not uniform across different studies. The suggestion was that saturation levels below 90% should be avoided, and that levels above 92-94% might be protective against adverse effects. We consider a minimum threshold of 90% $SpO_2$, not lower, since a recent review of the literature found no studies that showed a conclusive proof of the optimal target saturation in post-term oxygen therapy in children born preterm for beneficial effects on several health outcomes (76). Our suggestion of using a cut-off value of 90% $SpO_2$ for considering home oxygen is based on low-grade evidence, as is the minimum threshold of 93% as stated in a recent ATS guideline (77). A cut-off value of 90% $SpO_2$ instead of 93% $SpO_2$ will require fewer infants to be discharged on home oxygen therapy, which alleviates a relative financial burden of health care systems' resources without running an unduly high risk of compromising patient outcomes. However, we do emphasize on the need of future studies to define the optimal saturation targets for children in whom BPD already has been established and are discharged from the hospital, or who were older than 36 weeks of PMA, also taking potential effects on non-pulmonary outcomes into account.

*Other considerations* The BOOST II trial, an international RCT comparing an oxygen saturation target of 85-89% with 91-95% for children born before 28 weeks of gestation, demonstrated that a saturation target below 90% was associated with an increased risk of death before discharge (78). This finding led to an early stop of the trial. Results of studies comparing different saturation targets on health outcomes after discharge are lacking. The recent published British Thoracic Society guideline on supplementary home oxygen found C and D levels of evidence (of A to D categories) for supplementary oxygen in children with chronic neonatal lung disease to reduce or prevent pulmonary hypertension, reduce intermittent desaturations, reduce airway resistance, promote growth and neurodevelopment, and to possible reduce associated risk of sudden unexplained death in infancy. Home oxygen treatment should be recommended as oxygen at home is preferable to a prolonged

hospital stay for both quality of life and psychological impact for the infant, parents and family, and as it saves days in hospital due to earlier discharge despite a significant readmission rate. Specific saturation targets are not provided. The American Thoracic Society guideline on home oxygen therapy for children recommends home oxygen therapy for patients with BPD complicated by chronic hypoxemia, based on very low-quality evidence (77). Home oxygen therapy seems to increase growth rate, short-term oxygen use decreased mean pulmonary artery pressure, and nocturnal oxygen use improved sleep duration and decreased arousal. The utility of home monitoring on informing temporary decline of BPD is not fully known.

*Suggestions for future research* Further studies are urgently needed to examine the optimal saturation targets of oxygen use in children with BPD.

**General considerations** The new form of BPD is characterized predominantly by an arrest in development of airways and lungs, specifically alveoli, pulmonary vascular development, and to a lesser extent by iatrogenic lung damage (27). Clinically, the new form of BPD is defined as oxygen need for ≥28 days from birth until 36 weeks of PMA (27). However, this definition of BPD is currently under debate as the pathological process of BPD is a sliding scale, may also be present in preterm born children without BPD, and does not seem to allow prediction of outcomes. In the future, potentially biomarkers in blood and exhaled breath, lung function in early life, clinical parameters and quiet-breathing MRI scan may all dependent or independent of each other help to better define BPD and predict short term outcomes, and additionally long-term outcomes and treatment responses (53). As a consequence of the initial for identifying monitoring and treatment strategies for the current ERS guideline, not every new and promising avenue of monitoring or treatment could ultimately be pursued. It may therefore require future updates to integrate new emerging monitoring and treatment strategies, as for example long term monitoring and treatment of pulmonary hypertension in children with BPD, which is suggested to be an underdiagnosed

condition (79-82). Pediatric cardiologists should therefore be more intensively involved in multi-disciplinary follow-up of children with BPD from discharge into adulthood. Future research should not be limited to children with BPD but should also include children born across the full range of gestational age.

For children born <32 weeks of gestational age, BPD severity is based on the amount of oxygen need at 36 weeks of PMA, or discharge to home (28, 83). An objective, reliable and safe test for BPD severity is the 'oxygen reduction test', a standardized assessment of oxygen saturation during a timed stepwise reduction of administered oxygen to room air (84). Objectively determining the severity of BPD may be important for identifying children most at risk for later lung, pulmonary vascular, or other sequelae, implying that more close monitoring and treatment might be needed.

Additionally to the considered and rated outcomes, extremely preterm born children are at increased risks of adverse ophthalmologic and renal outcomes. The development or deterioration of retinopathy of prematurity in our defined population was considered very small but cannot be excluded for late-onset retinopathy. Therefore, retinopathy of prematurity warrants close monitoring specifically when discussing saturation limits if supplemental oxygen is needed. Future studies are warranted to examine interventions related to monitoring and treatment of adverse rental outcomes (85). Additionally, the incidence of chronic pulmonary vascular disease in children and adults born preterm in the new BPD era are not fully clear. Results from studies among children born within the old and new BPD era suggest that they have an increased risk of subclinical pulmonary hypertensive vascular disease, exercise induced pulmonary hypertension, right ventricular dysfunction, and autonomic dysfunction (81, 86-89). Protocols for screening and diagnosing these adverse health outcomes, specifically pulmonary hypertensive vascular diseases have recently been suggested (80, 82, 90). As with any lung disease or general health, exposure to smoking should be strongly discouraged and omitted.

In line with this Task Force, a workgroup among experts held by the National Institute of Child Health and Human Development in the US concluded that there is an urgent need of

studies on postnatal management to decrease the severity of BPD, improve respiratory and medication management of established BPD including BPD associated pulmonary hypertension, and to obtain more information on the long term outcomes of BPD (91). Prospective, structured, standardized and multi-disciplinary follow-up of children with BPD from discharge into adulthood is needed, and may help to generate important data for future monitoring and treatment studies. It depends on the (regions) of countries if neonatologists alone monitor and treat children with BPD for much longer than immediately after discharge. Some countries have set-up a multidisciplinary outpatient clinic for children with severe BPD with equally and important involvement of subspecialists, including pediatric-pulmonologists, neonatologists, pediatric-cardiologists, ear-nose-throat physicians, physiotherapists, psychologists, and social workers/case managers. Transition of such care systems into adulthood is needed, and research related to these multidisciplinary clinics may lead to new insights and improve long-term outcomes (92, 93).

Studies on monitoring or treatment of children with BPD are challenging. BPD is a rare disease, and preterm born children are a vulnerable group of children hampering clinical trials. Also, relevant health outcomes at a young age are difficult to define, and long-term follow up studies are ideally needed. Similarly, studies on the long term airway, lung, and vascular driven pathophysiology related to gestational age at birth, ventilation and oxygen concentration strategies leading to potential BPD subtypes in older children or adults are lacking. According to the Task Force members, all efforts should be made to design and perform studies in children with BPD to improve quality of life and prevent short- and long-term consequences across the life course.

**SUMMARY**

The Task Force utilized comprehensive syntheses to inform its judgments regarding the balance of desirable (benefits) and undesirable (burden, adverse effects) consequences of the intervention, certainty of the evidence, and values, and made conditional recommendations for all interventions. We suggest monitoring with lung imaging using ionising radiation in a subgroup only, for example severe BPD, severe symptoms, recurrent hospitalizations (conditional recommendation based on very low certainty of evidence), and monitoring with lung function in all children (conditional recommendation based on very low certainty of evidence). The Task Force suggests to give individual advice to parents regarding day care attendance (conditional recommendation based on very low certainty of evidence). With regards to treatment, the Task Force suggests treatment with bronchodilators in a subgroup only, for example children with severe BPD, asthma-like symptoms, and/or recurrent hospital admissions due to respiratory morbidity (conditional recommendation based on very low certainty of evidence), while treatment with inhaled or systemic corticosteroids is not suggested (conditional recommendation based on low certainty of evidence). The Task Force suggests not to start diuretics in children with BPD unless clinical signs for fluid retention are present, and for those children with BPD who already received treatment with diuretics from the neonatal phase or neonatal intensive care unit onwards, the Task Force suggests natural weaning by the relative decrease in dose with increasing weight gain (conditional recommendation based on very low certainty of evidence). The Task Force suggests supplemental oxygen with a minimum saturation target of 90% (conditional recommendation based on very low certainty of evidence). A multidisciplinary approach for children with established severe BPD with involvement of subspecialists from discharge after the neonatal period into adulthood is desirable. These recommendations should be considered until new and urgently needed evidence becomes available.

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**Table 1.** Outcomes defined as “important” or “critical” for decision-making for each PICO question related to the intervention for children with BPD.

| Intervention | Outcome |
|---|---|
| Monitoring with lung imaging | Number and severity of respiratory symptoms, adverse growth, hospital admissions, reduced physical exercise capacity, prolonged duration of supplemental oxygen need, side effects, adverse neurodevelopment, decreased quality of life, mortality, or impaired lung function |
| Monitoring with lung function | Number and severity of respiratory symptoms, hospital admissions, CT abnormalities, reduced physical exercise capacity, use of inhaled bronchodilators, use of inhaled corticosteroids, use of systemic corticosteroids, prolonged duration of supplemental oxygen need, adverse neurodevelopment, quality of life, or mortality |
| Discourage daycare attendance | Number and severity of respiratory symptoms, adverse growth, hospital admissions, prolonged duration of supplemental oxygen need, adverse neurodevelopment, quality of life, or mortality |
| Treatment with inhaled bronchodilators | Number and severity of respiratory symptoms, hospital admissions, reduced physical exercise capacity, prolonged duration of supplemental oxygen need, quality of life, mortality, or impaired lung function |
| Treatment with inhaled/systemic corticosteroids | Number and severity of respiratory symptoms, adverse growth, hospital admissions, reduced physical exercise capacity, pulmonary hypertension, prolonged duration of supplemental oxygen need, side effects, adverse neurodevelopment, quality of life, mortality, or impaired lung function |
| Treatment with diuretics | Number and severity of respiratory symptoms, hospital admissions, pulmonary hypertension, prolonged duration of supplemental oxygen need, side effects, adverse neurodevelopment, quality of life, mortality, or impaired lung function |
| Treatment with oxygen | Number and severity of respiratory symptoms, adverse growth, hospital admissions, reduced physical exercise capacity, pulmonary hypertension, prolonged duration of supplemental oxygen need, side effects, adverse neurodevelopment, quality of life, mortality, or impaired lung function |

**Table 2.** Interpretation of the strength of the recommendations (94)

| Implications | Strong recommendation | Conditional (weak) recommendation |
|---|---|---|
| For patients | Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. | The majority of individuals in this situation would want the suggested course of action, but many would not. |
| For clinicians | Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. | Recognize that different choices will be appropriate for individual patients and that clinicians must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences. |
| For policy makers | The recommendation can be adapted as policy in most situations | Policy making will require substantial debate and involvement of various stakeholders. |

**Table 3.** Recommendations for the monitoring and treatment of children with BPD (details of the recommendations are provided in main text).

| Question | Recommendation | Strength | Quality of evidence |
|---|---|---|---|
| **1** | We suggest monitoring with lung imaging using ionising radiation in a subgroup only (e.g. children with severe course of BPD, severe respiratory symptoms, and/or recurrent hospital admissions due to respiratory morbidity). | Conditional | Very low |
| **2** | We suggest monitoring with lung function. | Conditional | Very low |
| **3** | We suggest to give individual advice to parents regarding day care attendance. | Conditional | Very low |
| **4** | We suggest that treatment with bronchodilators could be optional for subgroups (e.g. children with severe course of BPD, severe respiratory or asthma-like symptoms, recurrent hospital admission due to respiratory morbidity, exercise intolerance, or reversibility in lung function). | Conditional | Very low |
| **5/6** | We suggest no treatment with inhaled or systemic corticosteroids. | Conditional | Low |
| **7** | We suggest natural weaning of diuretics by the relative decrease in dose with increasing weight gain. | Conditional | Very low |
| **8** | We suggest supplemental oxygen with saturation target range of 90-95%. | Conditional | Very low |

**Supplementary material**

# European Respiratory Society guideline on long term management of children with bronchopulmonary dysplasia.

## Supplementary Methods

The first kick-off meeting with European Respiratory Society (ERS) Task Force members was held in April, 2016, at the Erasmus University Medical Center Rotterdam, The Netherlands, to define strict goals, methodology of assessing evidence, formation of subgroups and tasks, and determine time-lines for a relevant paper. After formulation of the topics and questions, we aimed to identify systematic reviews of randomized trials, randomized controlled trials, and retrospective or prospective cohort studies published from 1999 ('new' BPD defined) until July 2016 through Embase.com, Medline Ovid, Cochrane Central Registry of Trials, and Web of Science Core Collections and where appropriate add relevant individual studies or expert based opinions. A first broad literature search was performed using scripts defined by a librarian according to the research questions. Thereafter, the Task Force members selected the relevant studies themselves. A minimum of 2 independent PICO working group members were required to review the articles to minimize potential bias. Inclusion criteria were the study population of children in whom BPD had been established and were discharged from the hospital, or who were older than 36 weeks of PMA, studying the specifically defined monitoring and treatment tools in relation to the defined outcomes of interest. Exclusion criteria were incorrect population under study (no children, no BPD only as second best), incorrect monitoring or treatment intervention, study focused on prevention instead of monitoring or treatment of BPD, outcomes of interest not reported, no abstract or full text available, no English text available. When no articles for the PICO directly fulfilled these criteria, indirect articles that indirectly fulfilled these criteria were included using a less favourable study design, preterm born children (as opposed to children with BPD) or the old form of BPD (as opposed to the new form of BPD). When also no indirect articles for the PICO were found, experience of local, regional or national management of Task Force members was asked, summarized, and discussed if relevant. When there was no consensus on whether to include one of the identified articles, this was discussed between the independent PICO working group. Initial results of the literature search were discussed during a meeting at the ERS Congress, London, in September, 2016.

Thereafter, finalisation of the rating of the importance of outcomes and final study selection were performed. Because of extended duration of the Task Force, an update of the literature search was performed on July 11th, 2018. No additional relevant articles were observed. During a meeting at the ERS Congress, Paris, in September, 2018, draft recommendations were discussed.

**Supplementary Table 1.** Scripts used in the first phase of the literature search strategy.

| | Database | | | |
|---|---|---|---|---|
| | **Embase** | **Medline Ovid** | **Cochrane** | **Web of Science** |
| Lung imaging (n=2,120) | ('lung dysplasia'/de OR 'chronic lung disease'/de OR 'chronic respiratory tract disease'/de OR 'lung disease'/de OR (((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ('prematurity'/de OR 'premature labor'/de OR 'extremely low birth weight'/de OR 'very low birth weight'/de OR 'gestational age'/de OR (((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND [english]/lim NOT [Conference Abstract]/lim NOT ([animals]/lim NOT [humans]/lim) AND ('imaging'/exp OR 'radiodiagnosis'/exp OR 'nuclear magnetic resonance imaging'/exp OR 'nuclear magnetic resonance'/exp OR (imag* OR radiodiagnos* OR (comput* NEAR/3 tomography*) OR (magnetic NEAR/3 resonance ) OR mri OR radiogra* OR x-ray*):ab,ti)<br>(n=795) | ("Bronchopulmonary Dysplasia"/ OR "Lung Diseases"/ OR (((lung OR bronchopulmon* OR pulmon*) ADJ3 dysplasi*) OR ((lung OR pulmonar*) ADJ3 (disease*)) OR bpd OR (oxygen ADJ3 dependen*)).ab,ti.) AND (exp "Infant, Premature"/ OR exp "Obstetric Labor, Premature"/ OR exp "Infant, Very Low Birth Weight"/ OR "Gestational Age"/ OR (((prematur* OR pre-matur*) ADJ3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) ADJ3 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age").ab,ti.) AND english.la. NOT (exp animals/ NOT humans/) AND (exp "Diagnostic Imaging"/ OR "radiodiagnosis"/ OR (imag* OR radiodiagnos* OR (comput* ADJ3 tomography*) OR (magnetic ADJ3 resonance ) OR mri OR radiogra* OR x-ray*).ab,ti.)<br>(n=923) | ((((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ((((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND ((imag* OR radiodiagnos* OR (comput* NEAR/3 tomography*) OR (magnetic NEAR/3 resonance ) OR mri OR radiogra* OR x-ray*):ab,ti)<br>(n=35) | TS=(((((lung OR bronchopulmon* OR pulmon*) NEAR/2 dysplasi*) OR ((lung OR pulmonar*) NEAR/2 (disease*)) OR bpd OR (oxygen NEAR/2 dependen*))) AND ((((prematur* OR pre-matur*) NEAR/2 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/2 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age")) AND ((imag* OR radiodiagnos* OR (comput* NEAR/3 tomography*) OR (magnetic NEAR/2 resonance ) OR mri OR radiogra* OR x-ray*))) AND DT=(article) AND LA=(english)<br>(n=367) |
| Lung function (n=2,301) | ('lung dysplasia'/de OR 'chronic lung disease'/de OR 'chronic respiratory tract disease'/de OR 'lung disease'/de OR (((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ('prematurity'/de OR 'premature labor'/de OR 'extremely low birth weight'/de OR 'very low birth weight'/de OR 'gestational age'/de OR (((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND [english]/lim NOT [Conference Abstract]/lim NOT ([animals]/lim NOT [humans]/lim) AND ('lung function'/exp OR 'lung clearance'/de OR 'lung diffusion'/de OR 'body plethysmography'/de OR plethysmography/de OR 'airway resistance'/de OR (((lung OR pulmonar*) NEAR/3 function*) OR (cardiopulmon* NEAR/3 exercis* | ("Bronchopulmonary Dysplasia"/ OR "Lung Diseases"/ OR (((lung OR bronchopulmon* OR pulmon*) ADJ3 dysplasi*) OR ((lung OR pulmonar*) ADJ3 (disease*)) OR bpd OR (oxygen ADJ3 dependen*)).ab,ti.) AND (exp "Infant, Premature"/ OR exp "Obstetric Labor, Premature"/ OR exp "Infant, Very Low Birth Weight"/ OR "Gestational Age"/ OR (((prematur* OR pre-matur*) ADJ3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) ADJ3 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age").ab,ti.) AND english.la. NOT (exp animals/ NOT humans/) AND ("Respiratory Function Tests"/ OR "Plethysmography, Whole Body"/ OR Plethysmography/ OR "Airway | ((((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ((((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND ((((lung OR pulmonar*) NEAR/3 function*) OR (cardiopulmon* NEAR/3 exercis* NEAR/3 test*) OR ((nitrogen* OR breath*) NEAR/3 (washout* OR test*)) OR spirometr* OR ((lung OR pulmonar*) NEAR/3 (clearance* OR diffusion*)) OR plethysmogra* OR | TS=(((((lung OR bronchopulmon* OR pulmon*) NEAR/2 dysplasi*) OR ((lung OR pulmonar*) NEAR/2 (disease*)) OR bpd OR (oxygen NEAR/2 dependen*))) AND ((((prematur* OR pre-matur*) NEAR/2 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/2 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age")) ) AND DT=(article) AND LA=(english) AND TS=((((lung OR pulmonar*) NEAR/2 function*) OR (cardiopulmon* NEAR/2 exercis* NEAR/2 test*) OR ((nitrogen* OR breath*) NEAR/2 (washout* OR test*)) OR spirometr* OR ((lung OR pulmonar*) NEAR/2 (clearance* OR diffusion*)) OR plethysmogra* OR (forced NEAR/2 oscillat*) OR rint OR (airway NEAR/2 resistance*)))<br>(n=659) |

| | | | | |
|---|---|---|---|---|
| | NEAR/3 test*) OR ((nitrogen* OR breath*) NEAR/3 (washout* OR test*)) OR spirometr* OR ((lung OR pulmonar*) NEAR/3 (clearance* OR diffusion*)) OR plethysmogra* OR (forced NEAR/3 oscillat*) OR rint OR (airway NEAR/3 resistance*)):ab,ti)<br>(n=936) | Resistance"/ OR (((lung OR pulmonar*) ADJ3 function*) OR (cardiopulmon* ADJ3 exercis* ADJ3 test*) OR ((nitrogen* OR breath*) ADJ3 (washout* OR test*)) OR spirometr* OR ((lung OR pulmonar*) ADJ3 (clearance* OR diffusion*)) OR plethysmogra* OR (forced ADJ3 oscillat*) OR rint OR (airway ADJ3 resistance*)).ab,ti.)<br>(n=633) | (forced NEAR/3 oscillat*) OR rint OR (airway NEAR/3 resistance*)):ab,ti)<br>(n=74) | |
| Daycare attendance (n=197) | ('lung dysplasia'/de OR 'chronic lung disease'/de OR 'chronic respiratory tract disease'/de OR 'lung disease'/de OR (((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ('prematurity'/de OR 'premature labor'/de OR 'extremely low birth weight'/de OR 'very low birth weight'/de OR 'gestational age'/de OR (((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND [english]/lim NOT [Conference Abstract]/lim NOT ([animals]/lim NOT [humans]/lim) AND ('day care'/de OR 'child care'/de OR 'kindergarten'/de OR ('day care' OR daycare OR kindergarten* OR 'child care' OR 'childcare' OR 'centre care' OR 'center care'):ab,ti)<br>(n=108) | ("Bronchopulmonary Dysplasia"/ OR "Lung Diseases"/ OR (((lung OR bronchopulmon* OR pulmon*) ADJ3 dysplasi*) OR ((lung OR pulmonar*) ADJ3 (disease*)) OR bpd OR (oxygen ADJ3 dependen*)).ab,ti.) AND (exp "Infant, Premature"/ OR exp "Obstetric Labor, Premature"/ OR exp "Infant, Very Low Birth Weight"/ OR "Gestational Age"/ OR (((prematur* OR pre-matur*) ADJ3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) ADJ3 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age").ab,ti.) AND english.la. NOT (exp animals/ NOT humans/) AND ("Child Day Care Centers"/ OR "child care"/ OR ("day care" OR daycare OR kindergarten* OR "child care" OR "childcare" OR "centre care" OR "center care").ab,ti.)<br>(n=16) | ((((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ((((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND (('day care' OR daycare OR kindergarten* OR 'child care' OR 'childcare' OR 'centre care' OR 'center care'):ab,ti)<br>(n=57) | TS=(((((lung OR bronchopulmon* OR pulmon*) NEAR/2 dysplasi*) OR ((lung OR pulmonar*) NEAR/2 (disease*)) OR bpd OR (oxygen NEAR/2 dependen*))) AND ((((prematur* OR pre-matur*) NEAR/2 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/2 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age")) AND (("day care" OR daycare OR kindergarten* OR "child care" OR "childcare" ))) AND DT=(article) AND LA=(english)<br>(n=19) |
| Inhaled bronchodilators (n=902) | ('lung dysplasia'/de OR 'chronic lung disease'/de OR 'chronic respiratory tract disease'/de OR 'lung disease'/de OR (((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ('prematurity'/de OR 'premature labor'/de OR 'extremely low birth weight'/de OR 'very low birth weight'/de OR 'gestational age'/de OR (((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND [english]/lim NOT [Conference Abstract]/lim NOT ([animals]/lim NOT [humans]/lim) AND ('bronchodilating agent'/exp OR 'beta adrenergic stimulation'/de OR 'beta adrenergic receptor stimulating agent'/exp OR (bronchodilat* OR | ("Bronchopulmonary Dysplasia"/ OR "Lung Diseases"/ OR (((lung OR bronchopulmon* OR pulmon*) ADJ3 dysplasi*) OR ((lung OR pulmonar*) ADJ3 (disease*)) OR bpd OR (oxygen ADJ3 dependen*)).ab,ti.) AND (exp "Infant, Premature"/ OR exp "Obstetric Labor, Premature"/ OR exp "Infant, Very Low Birth Weight"/ OR "Gestational Age"/ OR (((prematur* OR pre-matur*) ADJ3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) ADJ3 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age").ab,ti.) AND english.la. NOT (exp animals/ NOT humans/) AND (exp "Bronchodilator | ((((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ((((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND ((bronchodilat* OR beta2mimetic* OR betamimetic* OR salbutamol OR terbutaline OR ipratropium-bromide OR formoterol OR beta-2-agonist* OR beta-adrenerg*-stimulat*):ab,ti) | TS=(((((lung OR bronchopulmon* OR pulmon*) NEAR/2 dysplasi*) OR ((lung OR pulmonar*) NEAR/2 (disease*)) OR bpd OR (oxygen NEAR/2 dependen*))) AND ((((prematur* OR pre-matur*) NEAR/2 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/2 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age")) AND ((bronchodilat* OR beta2mimetic* OR betamimetic* OR salbutamol OR terbutaline OR ipratropium-bromide OR formoterol OR beta-2-agonist* OR beta-adrenerg*-stimulat*)) ) AND DT=(article) AND LA=(english)<br>(n=100) |

| | | | | |
|---|---|---|---|---|
| | beta2mimetic* OR betamimetic* OR salbutamol OR terbutaline OR ipratropium-bromide OR formoterol OR beta-2-agonist* OR beta-adrenerg*-stimulat*):ab,ti)<br>(n=447) | Agents"/ OR exp "Adrenergic beta-Agonists"/ OR (bronchodilat* OR beta2mimetic* OR betamimetic* OR salbutamol OR terbutaline OR ipratropium-bromide OR formoterol OR beta-2-agonist* OR beta-adrenerg*-stimulat*).ab,ti.)<br>(n=337) | (n=18) | |
| Inhaled/systemic corticosteroids<br>(n=4,329) | ('lung dysplasia'/de OR 'chronic lung disease'/de OR 'chronic respiratory tract disease'/de OR 'lung disease'/de OR (((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ('prematurity'/de OR 'premature labor'/de OR 'extremely low birth weight'/de OR 'very low birth weight'/de OR 'gestational age'/de OR (((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND [english]/lim NOT [Conference Abstract]/lim NOT ([animals]/lim NOT [humans]/lim) AND ('corticosteroid'/exp OR (corticosteroid* OR adrenal-cort*-hormone* OR adrenocort*-hormone* OR steroid* OR fluticasone OR beclomethasone OR budesonide OR prednisolon* OR prednison* OR glucocorticoid* OR dexamethason* OR hydrocortison*):ab,ti)<br>(n=1,806) | ("Bronchopulmonary Dysplasia"/ OR "Lung Diseases"/ OR (((lung OR bronchopulmon* OR pulmon*) ADJ3 dysplasi*) OR ((lung OR pulmonar*) ADJ3 (disease*)) OR bpd OR (oxygen ADJ3 dependen*)).ab,ti.) AND (exp "Infant, Premature"/ OR exp "Obstetric Labor, Premature"/ OR exp "Infant, Very Low Birth Weight"/ OR "Gestational Age"/ OR (((prematur* OR pre-matur*) ADJ3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) ADJ3 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age").ab,ti.) AND english.la. NOT (exp animals/ NOT humans/) AND (exp "Adrenal Cortex Hormones"/ OR (corticosteroid* OR adrenal-cort*-hormone* OR adrenocort*-hormone* OR steroid* OR fluticasone OR beclomethasone OR budesonide OR prednisolon* OR prednison* OR glucocorticoid* OR dexamethason* OR hydrocortison*).ab,ti.)<br>(n=1,148) | ((((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ((((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND ((corticosteroid* OR adrenal-cort*-hormone* OR adrenocort*-hormone* OR steroid* OR fluticasone OR beclomethasone OR budesonide OR prednisolon* OR prednison* OR glucocorticoid* OR dexamethason* OR hydrocortison*):ab,ti)<br>(n=231) | TS=(((((lung OR bronchopulmon* OR pulmon*) NEAR/2 dysplasi*) OR ((lung OR pulmonar*) NEAR/2 (disease*)) OR bpd OR (oxygen NEAR/2 dependen*))) AND ((((prematur* OR pre-matur*) NEAR/2 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/2 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age")) AND ((corticosteroid* OR adrenal-cort*-hormone* OR adrenocort*-hormone* OR steroid* OR fluticasone OR beclomethasone OR budesonide OR prednisolon* OR prednison* OR glucocorticoid* OR dexamethason* OR hydrocortison*)) ) AND DT=(article) AND LA=(english)<br>(n=1,144) |
| Diuretics<br>(n=670) | ('lung dysplasia'/de OR 'chronic lung disease'/de OR 'chronic respiratory tract disease'/de OR 'lung disease'/de OR (((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ('prematurity'/de OR 'premature labor'/de OR 'extremely low birth weight'/de OR 'very low birth weight'/de OR 'gestational age'/de OR (((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND [english]/lim NOT [Conference Abstract]/lim NOT ([animals]/lim NOT [humans]/lim) AND ('diuretic agent'/exp OR (diuretic* OR chlorothiazide OR hydrochlorothiazide OR furosemide OR bumetanide OR triamterene OR | ("Bronchopulmonary Dysplasia"/ OR "Lung Diseases"/ OR (((lung OR bronchopulmon* OR pulmon*) ADJ3 dysplasi*) OR ((lung OR pulmonar*) ADJ3 (disease*)) OR bpd OR (oxygen ADJ3 dependen*)).ab,ti.) AND (exp "Infant, Premature"/ OR exp "Obstetric Labor, Premature"/ OR exp "Infant, Very Low Birth Weight"/ OR "Gestational Age"/ OR (((prematur* OR pre-matur*) ADJ3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) ADJ3 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age").ab,ti.) AND english.la. NOT (exp animals/ NOT humans/) AND (exp "diuretics"/ OR | ((((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ((((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND ((diuretic* OR chlorothiazide OR hydrochlorothiazide OR furosemide OR bumetanide OR triamterene OR spironolactone):ab,ti)<br>(n=29) | TS=(((((lung OR bronchopulmon* OR pulmon*) NEAR/2 dysplasi*) OR ((lung OR pulmonar*) NEAR/2 (disease*)) OR bpd OR (oxygen NEAR/2 dependen*))) AND ((((prematur* OR pre-matur*) NEAR/2 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/2 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age")) AND ((diuretic* OR chlorothiazide OR hydrochlorothiazide OR furosemide OR bumetanide OR triamterene OR spironolactone))) AND DT=(article) AND LA=(english) |

| | | | | |
|---|---|---|---|---|
| | spironolactone):ab,ti)<br>(n=407) | (diuretic* OR chlorothiazide OR hydrochlorothiazide OR furosemide OR bumetanide OR triamterene OR spironolactone).ab,ti.)<br>(n=151) | | (n=83) |
| Oxygen duration (n=1,815) | ('lung dysplasia'/de OR 'chronic lung disease'/de OR 'chronic respiratory tract disease'/de OR 'lung disease'/de OR (((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ('prematurity'/de OR 'premature labor'/de OR 'extremely low birth weight'/de OR 'very low birth weight'/de OR 'gestational age'/de OR (((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND [english]/lim NOT [Conference Abstract]/lim NOT ([animals]/lim NOT [humans]/lim) AND ('oxygen therapy'/de OR 'home oxygen therapy'/de OR (((oxygen OR o2 OR o-2) NEAR/3 (therap* OR treat*))):ab,ti)<br>(n=902) | ("Bronchopulmonary Dysplasia"/ OR "Lung Diseases"/ OR (((lung OR bronchopulmon* OR pulmon*) ADJ3 dysplasi*) OR ((lung OR pulmonar*) ADJ3 (disease*)) OR bpd OR (oxygen ADJ3 dependen*)).ab,ti.) AND (exp "Infant, Premature"/ OR exp "Obstetric Labor, Premature"/ OR exp "Infant, Very Low Birth Weight"/ OR "Gestational Age"/ OR (((prematur* OR pre-matur*) ADJ3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) ADJ3 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age").ab,ti.) AND english.la. NOT (exp animals/ NOT humans/) AND ("Oxygen Inhalation Therapy"/ OR (((oxygen OR o2 OR o-2) ADJ3 (therap* OR treat*))).ab,ti.)<br>(n=578) | ((((lung OR bronchopulmon* OR pulmon*) NEAR/3 dysplasi*) OR ((lung OR pulmonar*) NEAR/3 (disease*)) OR bpd OR (oxygen NEAR/3 dependen*)):ab,ti) AND ((((prematur* OR pre-matur*) NEAR/3 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/3 (birth-weight OR birthweight)) OR elbw OR vlbw OR 'gestational age'):ab,ti) AND ((((oxygen OR o2 OR o-2) NEAR/3 (therap* OR treat*))):ab,ti)<br>(n=55) | TS=(((((lung OR bronchopulmon* OR pulmon*) NEAR/2 dysplasi*) OR ((lung OR pulmonar*) NEAR/2 (disease*)) OR bpd OR (oxygen NEAR/2 dependen*))) AND ((((prematur* OR pre-matur*) NEAR/2 (birth* OR child* OR born OR newborn OR neonat* OR infan* OR labor)) OR preterm* OR pre-term* OR ((extreme* OR very) NEAR/2 (birth-weight OR birthweight)) OR elbw OR vlbw OR "gestational age")) AND ((((oxygen OR o2 OR o-2) NEAR/3 (therap* OR treat*))))) AND DT=(article) AND LA=(english)<br>(n=280) |

Rows represent the topic of the research question ('What is the evidence for *lung imaging* to monitor patients to reduce morbidity and related outcomes?', 'What is the evidence for *lung function testing* to monitor patients to reduce morbidity and related outcomes?', 'What is the evidence for *discouragement of daycare attendance* to reduce morbidity and related outcomes?', What is the evidence for *the use of inhaled bronchodilators* to reduce morbidity and related outcomes?'', 'What is the evidence for *the use of inhaled or systemic corticosteroids* to reduce morbidity and related outcomes?', 'What is the evidence for *the use of systemic diuretics* to reduce morbidity and related outcomes?', and 'What is the evidence for *oxygen use* to reduce morbidity and related outcomes?'. Columns represent the data base in which the literature search was performed. Cells represent the used scripts.

**Supplementary Table 3.** Evidence profiles of monitoring and treatment for children with BPD.

**Table 3.1.** Evidence for children with BPD if monitoring with *lung imaging* versus no lung imaging affect important and critical defined outcomes.

| Certainty assessment | | | | | | | Impact | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | |
| **Impaired lung function** | | | | | | | | | |
| 2 [1,2] | observational studies | serious [a] | not serious | serious [b] | serious [c] | none | In 21 schoolchildren with a history of new BPD (mild, n = 9; moderate, n = 4; and severe, n = 8) with a mean age of 12.7 years (range: 8.7-16.7). HRCT scores were inversely related to FEV1 (β -4.23; 95% CI -6.97 to -1.49, p = 0.004) and MMEF (β -3.45; 95% CI -6.10 to -0.80, p = 0.013) but not to DLCO. In a retrospective review of 41 very low birthweight infants with BPD, who had exacerbations in the last 6 months at a mean age of 16 months, underwent HRCT scans and lung function tests. Forced expiration (VmaxFRC) and functional residual capacity (FRC) was measured by the squeeze technique. CT abnormalities such as an increased number of triangular subpleural opacities and of limited linear opacities were associated with a lower FRC (r -0.426 and -0.421 (p-value for both <0.02), respectively), but not VmaxFRC. | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Prolonged duration of supplemental oxygen need** | | | | | | | | | |
| 2 [3,4] | observational studies | serious [d] | not serious | serious [e] | serious [f] | none | No association between oxygen supplementation and chest CT during their first year of life among children with moderate to severe BPD. No association between neonatal or 40-month chest X-ray severity scores and duration of oxygen therapy. Infants who remained oxygen dependent at a post-conceptional age of 36 weeks had significantly higher scores (median 9, range 7 to 20) than those not chronically oxygen dependent (median 3, range 0 to 13); p<0.05 | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Adverse growth, reduced physical exercise capacity, adverse neurodevelopment, , and side effects** | | | | | | | | | |
| | | | | | | | These outcomes were assessed as important, however no articles were found. | - | IMPORTANT |
| **Number and severity of respiratory symptoms, hospital admissions, decreased quality of life, and mortality** | | | | | | | | | |
| | | | | | | | These outcomes were assessed as critical, however no articles were found. | - | CRITICAL |

**CI:** Confidence interval

**Explanations**

a. In the second study (Mahut et al), correlations between CT abnormalities and lung function was measured only, and there was no adjustment for confounders.

b. Cross-sectional measures of lung imaging and lung function. Prognostic/longitudinal value cannot be determined.

c. Low number of patients for each BPD severity group (Ronkainen et al)

d. Retrospective data collection

e. Indirect study population

f. Not enough numerical data reported to be able to judge imprecision

**References**

1. Ronkainen E, Perhomaa M,Mattila L,Hallman M,Dunder T. Structural Pulmonary Abnormalities Still Evident in Schoolchildren with New Bronchopulmonary Dysplasia. Neonatology; 2018.

2. Mahut B, de Blic J,Emond S,Benoist MR,Jarreau PH,Lacaze-Masmonteil T,Magny JF,Delacourt C. Chest computed tomography findings in bronchopulmonary dysplasia and correlation with lung function.. Arch Dis Child Fetal Neonatal Ed; 2007.

3. Tonson la Tour A, Spadola L,Sayegh Y,Combescure C,Pfister R,Argiroffo CB,et al. Chest CT in bronchopulmonary dysplasia: clinical and radiological correlations. Pediatr Pulmonol; 2013.

4. Maconochie I, Greenough A,Yuksel B,Page A,Karani J.. A chest radiograph scoring system to predict chronic oxygen dependency in low birth weight infants. Early Hum Dev; 1991.

**Table 3.2.** Evidence for children with BPD if monitoring with *lung function* versus no lung function affect important and critical defined outcomes.

| Certainty assessment | | | | | | | Impact | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | |
| **Number and severity of respiratory symptoms** | | | | | | | | | |
| 2 [1,2] | observational studies | serious [a] | not serious | serious [b] | not serious | none | Lung function was measured at discharge or term age (whichever came first) in 35 children born before 28 weeks gestational age. TEF50/PTEF was lower in the group with respiratory morbidity (defined as need for hospital readmission for respiratory symptoms and/or parental report of treatment with inhaled asthma medication) in the first year of life, than in the group without (73.5 vs 79.9, p-value = 0.03). Other tidal breathing lung function measures did not differ between the two groups. Another prospective cohort among 163 preterm born children measured tidal breathing and performed multiple breath washout measurements during sleep at the age of 44 weeks PMA. After adjustment for confounders, a higher respiratory rate and tidal volume were associated with a decreased and increased risk of wheeze in the first year of life (OR (95% CI): 0.69 (0.50, 0.96) and 1.40 (1.04, 1.90), respectively). Other measures, such as FRC and LCI showed no associations with wheeze. The additional value of lung function tests was tested by adding them to prediction models for wheezing in the first year of life based on BPD classification, the clinical risk index for babies (CRIB) score, or clinical standard predictors such as sex, PMA and days of mechanical ventilation. Adding lung function to either of the three models however did not improve prediction of wheeze (AUC (likelihood ratio test p-value) 0.63 vs 0.54 (0.15), 0.62 vs 0.52 (0.08) and 0.71 vs 0.68 (0.12)). | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Use of bronchodilators** | | | | | | | | | |
| 1 [2] | observational studies | not serious | not serious | serious [b] | not serious | none | In the cohort among 163 preterm born children, a higher tPTEF/tE was associated with a decreased risk of β2-agonist inhalation therapy during the first year of life after adjustment for confounders (OR (95% CI): 0.56 (0.35, 0.89)). | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Hospital admissions** | | | | | | | | | |
| 1 [2] | observational studies | not serious | not serious | serious [b] | not serious | none | In the cohort among 163 children born preterm, a higher moment 1 ratio from multiple breath washout was associated with a decreased risk of re-hospitalization in the first year of life after adjustment for confounders (OR (95% CI): 0.15 (0.02, 0.96)). | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Prolonged duration of supplemental oxygen need** | | | | | | | | | |

| Certainty assessment | | | | | | | Impact | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | |
| 1 [2] | observational studies | not serious | not serious | serious [b] | not serious | none | In the cohort among 163 children born preterm, none of the tidal breathing measurements, nor multiple breath washout measurements were associated with home oxygen therapy. | ⨁◯◯◯ VERY LOW | IMPORTANT |

**Reduced physical exercise capacity, and decreased quality of life**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | These outcomes were assessed as critical, however no articles were found. | - | CRITICAL |

**Adverse growth, CT abnormalities, use of inhaled/systemic corticosteroids, use of diuretics, side effects, adverse neurodevelopment, and mortality**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | These outcomes were assessed as important, however no articles were found. | - | IMPORTANT |

**CI:** Confidence interval

**Explanations**

a. Difference in lung function measurement was assesed by t-test and no adjustment for confounders (Bentsen). No group where lung function was not measured (Bentsen and Proietti).

b. Indirect population (preterm born children, not specifically BPD)

**References**

1. Bentsen MH, Markestad T,Oymar K,Halvorsen T. Lung function at term in extremely preterm-born infants: a regional prospective cohort study. BMJ Open; 2017.

2. Proietti E, Riedel T,Fuchs O,Pramana I,Singer F,Schmidt A,Kuehni C,Latzin P,Frey U. Can infant lung function predict respiratory morbidity during the first year of life in preterm infants?. Eur Respir J; 2014.

**Table 3.3.** Evidence for children with BPD if treatment with *inhaled/systemic corticosteroids* versus no inhaled/systemic corticosteroids affect important and critical defined outcomes.

| Certainty assessment | | | | | | | Impact | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | |
| **Number and severity of respiratory symptoms** | | | | | | | | | |
| 1 [1] | randomised trials | serious [a] | not serious | serious [b] | not serious | none | The difference in symptom score (cough, wheeze), was 59 points (confidence interval ranging from 24.1 to 92.9), in favour of treatment, which is a 37% improvement. | ⨁⨁◯◯ LOW | CRITICAL |
| **Impaired lung function** | | | | | | | | | |
| 1 [1] | randomised trials | serious [a] | not serious | serious [b] | not serious | none | During the active period, FRC increased significantly (30 vs 36 ml/kg, p < 0.002), while there was no change in FRC during the placebo treatment period (31 vs 32 ml/kg). | ⨁⨁◯◯ LOW | IMPORTANT |
| **Hospital admission, mortality, decreased quality of life, reduced physical exercise capacity, neurodevelopment and pulmonary hypertension** | | | | | | | | | |
| | | | | | | | These outcomes were assessed as critical, however no articles were found. | - | CRITICAL |
| **Prolonged duration of supplemental oxygen and adverse growth** | | | | | | | | | |
| | | | | | | | These outcomes were assessed as important, however no articles were found. | - | IMPORTANT |

**CI:** Confidence interval

**Explanations** a. High loss to follow up; possible bias. b. Indirect study population (preterm born children, not within 'new' BPD era)

**References** 1. B Yuksel, A Greenough. Randomised trial of inhaled steroids in preterm infants with respiratory symptoms at follow up. Thorax; 1992.

**Table 3.4.** Evidence for children with BPD if treatment with *diuretics* versus no diuretics affect important and critical defined outcomes.

| Certainty assessment | | | | | | | Impact | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | |
| **Hospital admissions** | | | | | | | | | |
| 1 [1] | randomised trials | very serious [a] | not serious | serious [b] | serious [c] | none | After discharge until age 1 year of corrected age no difference in number of rehospitalizations for respiratory deterioration (diuretic group 22 of 14 patients vs placebo group 19 of 6 patients) | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Impaired lung function** | | | | | | | | | |
| 1 [1] | randomised trials | very serious [a] | not serious | serious [b] | serious [c] | none | Pulmonary function tests (PFT) were performed at baseline (1), 4 weeks after start RCT (2), 1 and 8 weeks after weaned from oxygen (3,4), and 1 year at corrected age (5). Between PFT 1 and 2, infants in the diuretic group had improvement in dynamic pulmonary compliance (46%; p <0.001) and airway resistance (31%; p<0.05), while the placebo group did not. No changes in TGV or FRC in the groups. No differences in PFT after discontinuation of diurectics/placebo. Comparison within groups but not between groups are given. | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Prolonged duration of supplemental oxygen need** | | | | | | | | | |
| 1 [1] | randomised trials | very serious [a] | not serious | serious [b] | serious [c] | none | No difference in total duration of supplemental oxygen use (diuretic group 133+/-53 days vs. placebo group 147 +/- 71 days) | ⨁◯◯◯ VERY LOW | CRITICAL |
| **Side effects** | | | | | | | | | |
| 1 [1] | randomised trials | very serious [a] | not serious | serious [b] | serious [c] | none | No difference in number of infants with nephrocalcinosis (diuretic group 7/22 patients vs placebo group 5/21 patients), supplemental electrolytes (diuretic group 2/22 patients vs placebo group 0/21) or hearing deficit (diuretic group 2/22 patients vs placebo group 1/21 patients). Note: Difference in supplemental furosemide (diuretic group 0/22 patients vs placebo group 5/21 patients, p<0.05) | ⨁◯◯◯ VERY LOW | IMPORTANT |
| **Number and severity of respiratory symptoms, pulmonary hypertension, and reduced physical exercise capacity** | | | | | | | | | |

| Certainty assessment | | | | | | | Impact | Certainty | Importance |
|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | | | |
| | | | | | | | These outcomes were assessed as important, however no articles were found. | - | IMPORTANT |

**Adverse neurodevelopment, decreased quality of life, and mortality**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | These outcomes were assessed as critical, however no articles were found. | - | CRITICAL |

**CI:** Confidence interval

**Explanations** a. Exact method of randomization procedure unclear, not stated whether patients were treated equally except for the intervention (but could be assumed), potential confounders were not taken into account, intention to treat analysis not fully clear, additional furosemide supplementation differed between the groups (diuretic group 0/22 patients vs placebo group 5/21 patients; p-value <0.05). b. Indirect study population of infants with oxygen-dependent BPD after extubation, clinically stable for at least 3 weeks before enrolment (gestational age and definition of BPD not specified). c. Differences between the intervention and placebo groups not examined but changes in lung function per group are described. Number of subjects small.

**References** 1. Kao LC, Durand DJ,McCrea RC,Birch M,Powers RJ,Nickerson BG.. Randomized trial of long-term diuretic therapy for infants with oxygen-dependent bronchopulmonary dysplasia.. May; 1994.

**Supplementary table 4.** Evidence to decision tables of monitoring and treatment for children with BPD.

**Table 4.1** Evidence to decision tables for children with BPD if monitoring with *lung imaging* versus no lung imaging affect important and critical defined outcomes.

## ASSESSMENT

| ***Problem*** Is the problem a priority? | | |
|---|---|---|
| ***JUDGEMENT*** | ***RESEARCH EVIDENCE*** | ***ADDITIONAL CONSIDERATIONS*** |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Based on clinical experts opinion it is of relevance to have evidence on monitoring with chest imaging in children with established BPD | |
| ***Desirable Effects*** How substantial are the desirable anticipated effects? | | |
| ***JUDGEMENT*** | ***RESEARCH EVIDENCE*** | ***ADDITIONAL CONSIDERATIONS*** |
| ○ Trivial<br>○ Small<br>● Moderate<br>○ Large<br>○ Varies<br>○ Don't know | No direct evidence that would answer this question in an appropriate way was identified. Indirect evidence was provided by four studies that examined the relation of lung imaging with lung function or duration of supplemental oxygen need.. Twenty-one school-children with BPD (mild, n = 9; moderate, n = 4; and severe, n = 8) were offered the opportunity to undergo high-resolution CT (HRCT) scans. The rate of severe BPD was higher compared to those not participating for scanning. Mean age of the children was 12.7 years (range: 8.7-16.7). Higher HRCT scores were related to lower Forced Expiratory Volume in 1 second (FEV1) (β -4.23; 95% CI -6.97 to -1.49, p = 0.004) and Maximal Mid-Expiratory Flow (MMEF) (β -3.45; 95% CI -6.10 to -0.80, p = 0.013), but not to gas exchange as measured by CO diffusion capacity (DLCO). A retrospective study among 19 children with BPD observed that all children at a median age of 14.6 months (range 1.5-53.7) had CT abnormalities, which were not associated with clinical outcomes such as gestational age, type and duration of mechanical ventilation and BPD severity. In a retrospective review, 41 very low birthweight infants with BPD, who had exacerbations in the last 6 months at a mean age, | |

| | | |
|---|---|---|
| | underwent HRCT scans and lung function tests at a mean age of 16 months. Maximal expiratory flow at functional residual capacity (VmaxFRC) and functional residual capacity (FRC) were measured by the squeeze technique. An increased number of triangular subpleural opacities and of limited linear opacities on CT were associated with a lower FRC (r -0.426 and -0.421 (p-value for both <0.02), respectively), but not VmaxFRC. A study among 40 preterm born children (median age 27 weeks (range 24-32 weeks) observed that those remaining oxygen dependent at a post-conceptional age of 36 weeks had significantly higher chest radiograph scores at one of month of age (median 9, range 7 to 20) than those not chronically oxygen dependent (median 3, range 0 to 13); p<0.05. | |

## *Undesirable Effects*

How substantial are the undesirable anticipated effects?

| ***JUDGEMENT*** | ***RESEARCH EVIDENCE*** | ***ADDITIONAL CONSIDERATIONS*** |
|---|---|---|
| ○ Large<br>● Moderate<br>○ Small<br>○ Trivial<br>○ Varies<br>○ Don't know | Lung imaging with CT or chest X-ray implies the use of radiation. | |

## *Certainty of evidence*

What is the overall certainty of the evidence of effects?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | | |

## *Values*

Is there important uncertainty about or variability in how much people value the main outcomes?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | | |

## *Balance of effects*

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Among the presented studies with indirect evidence to use lung imaging as a monitor tool, the study population consisted of children defined with the old form of BPD, the studies used retrospective or cross-sectional data collection with potential risk of bias, or reported not enough numerical data to be able to judge imprecision. Therefore, the evidence was considered very low. In clinical practice, Task Force members agreed that given the low certainty of evidence and potential side effects of radiation, monitoring with lung imaging would be justified only in subgroup of children with severe BPD, severe symptoms, recurrent hospitalizations or equivalent. For example, a chest CT with intravenous contrast could be considered to exclude other diagnoses, which may affect treatment strategies. | |

## *Resources required*

How large are the resource requirements (costs)?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>● Don't know | | |

## *Certainty of evidence of required resources*

What is the certainty of the evidence of resource requirements (costs)?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | | |

## *Cost effectiveness*

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | | Not studied. |

## *Equity*

What would be the impact on health equity?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | | |

## *Acceptability*

Is the intervention acceptable to key stakeholders?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>● Don't know | | |

## *Feasibility*

Is the intervention feasible to implement?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | | |

| | | |
|---|---|---|
| | | |

## SUMMARY OF JUDGEMENTS

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |
| **DESIRABLE EFFECTS** | Trivial | Small | **Moderate** | Large | | Varies | Don't know |
| **UNDESIRABLE EFFECTS** | Large | **Moderate** | Small | Trivial | | Varies | Don't know |
| **CERTAINTY OF EVIDENCE** | **Very low** | Low | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **RESOURCES REQUIRED** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |
| **ACCEPTABILITY** | No | Probably no | Probably yes | Yes | | Varies | **Don't know** |
| **FEASIBILITY** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |

## TYPE OF RECOMMENDATION

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

## CONCLUSIONS

### *Recommendation*

The Task Force suggests lung imaging to monitor children with BPD in subgroups only, for example children with severe BPD, severe respiratory symptoms, and/or recurrent hospitalizations (Conditional recommendation based on very low certainty of evidence).

### *Justification*

Among the presented studies with indirect evidence to use lung imaging as a monitor tool, the study population consisted of children defined with the old form of BPD, the studies used retrospective or cross-sectional data collection with potential risk of bias, or reported not enough numerical data to be able to judge imprecision. Therefore, the evidence was considered very low. In clinical practice, Task Force members agreed that given the low certainty of evidence and potential side effects of radiation, monitoring with lung imaging would be justified only in subgroup of children with severe or an atypical course of BPD, severe symptoms, recurrent hospitalizations or equivalent. For example, a chest CT with intravenous contrast could be considered to exclude other diagnoses, which may affect treatment strategies.

### *Subgroup considerations*

The Task Force suggests lung imaging for monitoring in subgroups only, for example children with severe  BPD, sever respiratory symptoms, recurrent hospitalization or equivalent.

## *Implementation considerations*

Implementation depends on expert knowledge of the center/country, availability (CT, MRI), and costs.

## *Monitoring and evaluation*

None.

## *Research priorities*

Recently, nonionizing magnetic resonance imaging (MRI) scan protocols for children with BPD have been developed, and a quite-breathing MRI scan independently assessed structural abnormalities of BPD, disease severity, and predicted short term outcomes at discharge from the neonatal intensive care unit. This technique is a promising monitoring tool for long term outcomes. Further studies are warranted to examine the predictive value of lung imaging, preferably non-radiant, on long term outcomes of children with established BPD. Studies using lung imaging such as computer tomography (CT) or MRI in the neonatal phase might be considered to better define the severity of BPD, or to diagnose or exclude other causes of BPD.

**Table 4.2** Evidence to decision tables for children with BPD if monitoring with *lung function* versus no lung function affect important and critical defined outcomes.

## ASSESSMENT

| ***Problem*** Is the problem a priority? | | |
|---|---|---|
| ***JUDGEMENT*** | ***RESEARCH EVIDENCE*** | ***ADDITIONAL CONSIDERATIONS*** |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Based on clinical experts opinion it is of utmost relevance to have evidence on monitoring with lung function in children with established BPD | |
| ***Desirable Effects*** How substantial are the desirable anticipated effects? | | |
| ***JUDGEMENT*** | ***RESEARCH EVIDENCE*** | ***ADDITIONAL CONSIDERATIONS*** |
| ○ Trivial<br>● Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | No direct evidence that would answer this question in an appropriate way was identified. Indirect evidence was provided by two studies among preterm born children. The first study showed that among extremely preterm born children, the ratio of tidal expiratory flow at 50% of expired volume to peak tidal expiratory flow (TEF50/PTEF), which reflects airway obstruction, measured by electromagnetic inductance plethysmography predicts respiratory morbidity in the first year of life (Area Under Curve (95% Confidence Interval: 0.723 (0.55, 0.86)). Also, TEF50/PTEF was lower in the group with respiratory morbidity in the first year of life, than in the group without (73.5 vs. 79.9, p-value = 0.03). Other tidal breathing lung function measures did not differ between those with and without respiratory morbidity. Another prospective cohort among 163 preterm born children measured tidal breathing and performed multiple breath washout measurements during sleep at the age of 44 weeks PMA. After adjustment for confounders, a higher respiratory rate and | |

| | | |
|---|---|---|
| | higher tidal volume were associated with a decreased and increased wheeze in the first year of life (OR (95% CI): 0.69 (0.50, 0.96) and 1.40 (1.04, 1.90), respectively), and a higher time to peak tidal expiratory flow expiratory time ratio (*t*PTEF/*t*E) with less bronchodilator inhalation therapy during the first year of life (OR (95% CI): 0.56 (0.35, 0.89)). A higher moment ratio 1 (representing the mean alveolar flow volume distribution) was associated with a decreased risk of re-hospitalization in the first year of life (OR (95% CI): 0.15 (0.02, 0.96)). Other lung function measures such as FRC and lung clearance index (LCI) were not associated with wheeze, inhalation therapy or re-hospitalization, and none of the lung function measures were associated with home oxygen therapy. The additional value of lung function tests was tested by adding them to prediction models for wheezing in the first year of life based on BPD classification, the clinical risk index for babies (CRIB) score, or clinical standard predictors such as sex, PMA and days of mechanical ventilation. Adding lung function to either of the three models however did not improve prediction of wheeze (AUC (likelihood ratio test p-value) 0.63 vs 0.54 (0.15), 0.62 vs 0.52 (0.08) and 0.71 vs 0.68 (0.12)). | |

## *Undesirable Effects*

How substantial are the undesirable anticipated effects?

| ***JUDGEMENT*** | ***RESEARCH EVIDENCE*** | ***ADDITIONAL CONSIDERATIONS*** |
|---|---|---|
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | Undesirable effects are not studied, however, since monitoring with lung function is non-invasive and performed often, undesirable effects are most likely small. | |

## *Certainty of evidence*

What is the overall certainty of the evidence of effects?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Very low<br>● Low<br>○ Moderate<br>○ High<br>○ No included studies | | |

## *Values*

Is there important uncertainty about or variability in how much people value the main outcomes?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Important uncertainty or variability<br>○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | | |

## *Balance of effects*

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | No studies have been performed that examined the potential beneficial effect of lung function monitoring on important and critical defined outcomes in children with BPD. Among the presented studies with indirect evidence to use lung function as a monitor tool, the study population consisted of preterm born children, not specifically children with BPD, or potential confounders were not taken into account. Therefore, the evidence was considered very low. No evidence was found that monitoring children with BPD with lung function reduces morbidity and related outcomes. However, for clinical practice, Task Force members agreed that monitoring with lung function would be justified despite the lack of evidence. Lung function, specifically spirometry and related bronchodilator response at older ages, is an objective measure, is associated with lung function in adulthood, and with increased risks of morbidity and mortality, has sex, age, height, and ethnicity adjusted reference ranges, and has no potential side effects. Lung function could also act as a potential indicator for the risk of lung- and related vascular diseases in childhood. | |

## *Resources required*

How large are the resource requirements (costs)?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>● Don't know | | |

## *Certainty of evidence of required resources*

What is the certainty of the evidence of resource requirements (costs)?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | | |

## *Cost effectiveness*

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | | |

## *Equity*

What would be the impact on health equity?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | | |

## *Acceptability*

Is the intervention acceptable to key stakeholders?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>● Don't know | | |

## *Feasibility*

Is the intervention feasible to implement?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Spirometry seems the most useful method for longitudinal follow up of lung growth and airway obstruction in school-age children with BPD. For preschool children (age <= 4 years) with BPD, the forced oscillation technique and multiple breath washout tests are the most applicable regarding technique and validity. However, reported studies have small sample sizes and limitations, and the success rate in routine clinical practice without sedation is considered low. | |

| | | |
|---|---|---|
| | | |

## SUMMARY OF JUDGEMENTS

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |
| **DESIRABLE EFFECTS** | Trivial | **Small** | Moderate | Large | | Varies | Don't know |
| **UNDESIRABLE EFFECTS** | Large | Moderate | **Small** | Trivial | | Varies | Don't know |
| **CERTAINTY OF EVIDENCE** | Very low | **Low** | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **RESOURCES REQUIRED** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |
| **ACCEPTABILITY** | No | Probably no | Probably yes | Yes | | Varies | **Don't know** |
| **FEASIBILITY** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |

# TYPE OF RECOMMENDATION

| Strong recommendation against the intervention | Conditional recommendation against the intervention | Conditional recommendation for either the intervention or the comparison | **Conditional recommendation for the intervention** | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ○ | ● | ○ |

# CONCLUSIONS

## *Recommendation*

The Task Force suggests lung function to monitor with BPD (Conditional recommendation based on very low certainty of evidence).

## *Justification*

No direct evidence that would answer this question in an appropriate way was identified. Indirect evidence was provided by two studies among preterm born children. The first study showed that among extremely preterm born children, the ratio of tidal expiratory flow at 50% of expired volume to peak tidal expiratory flow (TEF50/PTEF), which reflects airway obstruction, measured by electromagnetic inductance plethysmography predicts respiratory morbidity in the first year of life (Area Under Curve (95% Confidence Interval: 0.723 (0.55, 0.86)). Also, TEF50/PTEF was lower in the group with respiratory morbidity in the first year of life, than in the group without (73.5 vs. 79.9, p-value = 0.03). Other tidal breathing lung function measures did not differ between those with and without respiratory morbidity. Another prospective cohort among 163 preterm born children measured tidal breathing and performed multiple breath washout measurements during sleep at the age of 44 weeks PMA. After adjustment for confounders, a higher respiratory rate and higher tidal volume were associated with a decreased and increased wheeze in the first year of life (OR (95% CI): 0.69 (0.50, 0.96) and 1.40 (1.04, 1.90), respectively), and a higher time to peak tidal expiratory flow expiratory time ratio (*t*PTEF/*t*E) with less bronchodilator inhalation therapy during the first year of life (OR (95% CI): 0.56 (0.35, 0.89)). A higher moment ratio 1 (representing the mean alveolar flow volume distribution) was associated with a decreased risk of re-hospitalization in the first year of life (OR (95% CI): 0.15 (0.02, 0.96)). Other lung function measures such as FRC and lung clearance index (LCI) were not associated with wheeze, inhalation therapy or re-hospitalization, and none of the lung function measures were associated with home oxygen therapy. The additional value of lung function tests was tested by adding them to prediction models for wheezing in the first year of life based on BPD classification, the clinical risk index for babies (CRIB) score, or clinical standard predictors such as sex, PMA and days of mechanical ventilation. Adding lung function to either of the three models however did not improve prediction of wheeze (AUC (likelihood ratio test p-value) 0.63 vs 0.54 (0.15), 0.62 vs 0.52 (0.08) and 0.71 vs 0.68 (0.12)). No evidence was found that monitoring children in whom BPD has been established and were discharged from the hospital, or who were older than 36 weeks of PMA with lung function reduces morbidity and related outcomes. However, for clinical practice, Task Force members agreed that monitoring with lung function would be justified despite the lack of evidence. Lung function, specifically spirometry and related bronchodilator response at older ages, is an objective measure, is associated with lung function in adulthood, and subsequently increased risks of morbidity and mortality, has sex, age, height, and ethnicity adjusted reference ranges to compare with, and has no potential side effects. Lung function could also act as a potential indicator for the risk of lung- and related vascular diseases in adulthood. Spirometry seems the most useful method to longitudinally examine lung growth and airway obstruction in school-age children with BPD. For preschool children (age <= 4 years) with BPD, the forced oscillation technique and multiple breath washout tests are the most applicable regarding technique and validity. However, reported studies have small sample sizes and limitations, and the success rate in routine clinical practice without sedation is considered low.

## *Subgroup considerations*

None.

## *Implementation considerations*

None.

## *Monitoring and evaluation*

None.

## *Research priorities*

Further studies, observational or RCT, are warranted to examine the predictive value of lung function on long term lung structure and respiratory morbidity of children with established BPD, and its value in monitoring responses to treatment.

**Table 4.3** Evidence to decision tables for children with BPD if treatment with *corticosteroids* versus no corticosteroids affect important and critical defined outcomes.

## ASSESSMENT

| ***Problem*** Is the problem a priority? | | |
|---|---|---|
| ***JUDGEMENT*** | ***RESEARCH EVIDENCE*** | ***ADDITIONAL CONSIDERATIONS*** |
| ○ No<br>○ Probably no<br>○ Probably yes<br>● Yes<br>○ Varies<br>○ Don't know | | |
| ***Desirable Effects*** How substantial are the desirable anticipated effects? | | |
| ***JUDGEMENT*** | ***RESEARCH EVIDENCE*** | ***ADDITIONAL CONSIDERATIONS*** |
| ○ Trivial<br>● Small<br>○ Moderate<br>○ Large<br>○ Varies<br>○ Don't know | No direct evidence that would answer this question in an appropriate way was identified. Indirect evidence was obtained from one study, a crossover RCT that recruited eighteen children born premature (mean gestational age 28 weeks) at the age of 10.5 months, who had symptoms that were not controlled despite regular use of bronchodilators. Children received either 200 µg of beclomethasone dipropionate or placebo twice daily for two six week periods, separated by a two-week washout period. During the active period, as compared to the placebo period, respiratory symptoms decreased (37% improvement in symptom score, p-value <0.001). During the active period, FRC increased significantly (30 vs 36 ml/kg, $p < 0.002$), while there was no change in FRC during the placebo treatment period (31 vs 32 ml/kg). | |

## *Undesirable Effects*

How substantial are the undesirable anticipated effects?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Large<br>○ Moderate<br>○ Small<br>○ Trivial<br>○ Varies<br>● Don't know | Side-effects are not specifically studied. One study mentions that none of the children developed oral candidiasis, but also mentions that there might be side effects and therefore monitoring is needed during treatment. | |

## *Certainty of evidence*

What is the overall certainty of the evidence of effects?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Very low<br>● Low<br>○ Moderate<br>○ High<br>○ No included studies | | |

## *Values*

Is there important uncertainty about or variability in how much people value the main outcomes?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Important uncertainty or variability | | |

| | | |
|---|---|---|
| ● Possibly important uncertainty or variability<br>○ Probably no important uncertainty or variability<br>○ No important uncertainty or variability | | |

## *Balance of effects*

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Favors the comparison<br>● Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | Only one study was available and not specifically performed in children with the new form of BPD. Additionally, loss to follow up was of methodological concern. Last, the use of corticosteroids may have side effects and/or can lead to adverse events, which need to be outweighed by the possible benefits. Therefore, the evidence was considered low. Since the use of corticosteroids may lead to side effects, the Task Force did not deem it justified to recommend treatment with inhaled corticosteroids. | |

## *Resources required*

How large are the resource requirements (costs)?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>● Don't know | | |

## *Certainty of evidence of required resources*

What is the certainty of the evidence of resource requirements (costs)?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | | |

## *Cost effectiveness*

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | | |

## *Equity*

What would be the impact on health equity?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Reduced<br>○ Probably reduced<br>○ Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>● Don't know | | |

## *Acceptability*

Is the intervention acceptable to key stakeholders?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>● Don't know | | |

## *Feasibility*

Is the intervention feasible to implement?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>● Don't know | | |

| | | |
|---|---|---|
| | | |

## SUMMARY OF JUDGEMENTS

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | Probably yes | **Yes** | | Varies | Don't know |
| **DESIRABLE EFFECTS** | Trivial | **Small** | Moderate | Large | | Varies | Don't know |
| **UNDESIRABLE EFFECTS** | Large | Moderate | Small | Trivial | | Varies | **Don't know** |
| **CERTAINTY OF EVIDENCE** | Very low | **Low** | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | **Possibly important uncertainty or variability** | Probably no important uncertainty or variability | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | **Probably favors the comparison** | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **RESOURCES REQUIRED** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | Probably reduced | Probably no impact | Probably increased | Increased | Varies | **Don't know** |
| **ACCEPTABILITY** | No | Probably no | Probably yes | Yes | | Varies | **Don't know** |
| **FEASIBILITY** | No | Probably no | Probably yes | Yes | | Varies | **Don't know** |

## TYPE OF RECOMMENDATION

| Strong recommendation against the intervention | **Conditional recommendation against the intervention** | Conditional recommendation for either the intervention or the comparison | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ● | ○ | ○ | ○ |

## CONCLUSIONS

### *Recommendation*

The Task Force suggests not to treat with inhaled or systemic corticosteroids for children with BPD (conditional recommendation based on low certainty of evidence). If the treating physician considers it of additional value, the effects of treatment with inhaled/systemic corticosteroids should be carefully monitored by symptoms, lung function, if applicable, or of hospitalizations or emergency visits before chronically applied.

### *Justification*

Only one study was available and not specifically performed in children with the new form of BPD. Additionally, loss to follow up was of methodological concern. Last, the use of corticosteroids may have side effects and/or can lead to adverse events, which need to be outweighed by the possible benefits. Therefore, the evidence was considered low. Since the use of corticosteroids may lead to side effects, the Task Force did not deem it justified to recommend treatment with inhaled corticosteroids.

### *Subgroup considerations*

### *Implementation considerations*

## *Monitoring and evaluation*

If the treating physician considers it of additional value, the effects of treatment with inhaled/systemic corticosteroids should be carefully monitored by symptoms, lung function, if applicable, or reduction of number of hospitalizations or emergency visits before chronically applied.

## *Research priorities*

Further studies are urgently needed to examine the use of inhaled or systemic corticosteroids for children with BPD.

**Table 4.4.** Evidence to decision tables for children with BPD if treatment with *diuretics* versus no diuretics affect important and critical defined outcomes.

## ASSESSMENT

| ***Problem***<br>Is the problem a priority? | | |
|---|---|---|
| ***JUDGEMENT*** | ***RESEARCH EVIDENCE*** | ***ADDITIONAL CONSIDERATIONS*** |
| ○ No<br>○ Probably no<br>● Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | Based on clinical experts opinion it is of utmost relevance to have evidence on diuretic use in children with established BPD | |
| ***Desirable Effects***<br>How substantial are the desirable anticipated effects? | | |
| ***JUDGEMENT*** | ***RESEARCH EVIDENCE*** | ***ADDITIONAL CONSIDERATIONS*** |
| ○ Trivial<br>○ Small<br>● Moderate<br>○ Large<br>○ Varies<br>○ Don't know | No direct evidence that would answer this question in an appropriate way was identified. Indirect evidence was provided by one study. A randomized trial showed that, among infants with oxygen-dependent BPD-who were clinically stable, there were no differences in number of rehospitalizations for respiratory deterioration (diuretic group 22 of 14 patients vs placebo group 19 of 6 patients), pulmonary function tests, or total duration of supplemental oxygen use (diuretic group 133+/-53 days vs. placebo group 147 +/- 71 days) after 36 weeks of PMA Only FRC measured between 9 weeks after weaned from oxygen and diuretics and 1 year of corrected gestational age was increased in the diuretics group. At 1 year of corrected age, the FRC/TGV had improved in both the diuretic group (0.98±0.18) and the placebo group (0.97±0.11). | |

## *Undesirable Effects*

How substantial are the undesirable anticipated effects?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Large<br>○ Moderate<br>● Small<br>○ Trivial<br>○ Varies<br>○ Don't know | The above mentioned randomized trial found no differences in side effects including nephrocalcinosis, supplemental electrolytes or hearing deficits between the groups. | |

## *Certainty of evidence*

What is the overall certainty of the evidence of effects?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ● Very low<br>○ Low<br>○ Moderate<br>○ High<br>○ No included studies | | |

## *Values*

Is there important uncertainty about or variability in how much people value the main outcomes?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Important uncertainty or variability | | |

| | | |
|---|---|---|
| ○ Possibly important uncertainty or variability<br>● Probably no important uncertainty or variability<br>○ No important uncertainty or variability | | |

## *Balance of effects*

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>● Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>○ Don't know | No intervention studies examined the potential beneficial effect of diuretics on important and critical defined outcomes in children in whom BPD has been established and were discharged from the hospital, or who were older than 36 weeks of PMA. In the presented study, the exact method of randomization procedure was unclear, potential confounders were not taken into account, the intention to treat analysis was not fully clear, and additional furosemide supplementation differed between the groups (diuretic group 0/22 patients vs placebo group 5/21 patients; p-value <0.05). They study group did not contain children with the new form of BPD. Therefore, the evidence was considered very low. | |

## *Resources required*

How large are the resource requirements (costs)?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Large costs<br>○ Moderate costs<br>○ Negligible costs and savings<br>○ Moderate savings<br>○ Large savings<br>○ Varies<br>● Don't know | | |

## *Certainty of evidence of required resources*

What is the certainty of the evidence of resource requirements (costs)?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Very low<br>○ Low<br>○ Moderate<br>○ High<br>● No included studies | | |

## *Cost effectiveness*

Does the cost-effectiveness of the intervention favor the intervention or the comparison?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Favors the comparison<br>○ Probably favors the comparison<br>○ Does not favor either the intervention or the comparison<br>○ Probably favors the intervention<br>○ Favors the intervention<br>○ Varies<br>● No included studies | | |

## *Equity*

What would be the impact on health equity?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ Reduced<br>○ Probably reduced<br>● Probably no impact<br>○ Probably increased<br>○ Increased<br>○ Varies<br>○ Don't know | | |

## *Acceptability*

Is the intervention acceptable to key stakeholders?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ No<br>○ Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>● Don't know | | |

## *Feasibility*

Is the intervention feasible to implement?

| *JUDGEMENT* | *RESEARCH EVIDENCE* | *ADDITIONAL CONSIDERATIONS* |
|---|---|---|
| ○ No<br>● Probably no<br>○ Probably yes<br>○ Yes<br>○ Varies<br>○ Don't know | | |

| | | |
|---|---|---|
| | | |

## SUMMARY OF JUDGEMENTS

| | JUDGEMENT | | | | | | |
|---|---|---|---|---|---|---|---|
| **PROBLEM** | No | Probably no | **Probably yes** | Yes | | Varies | Don't know |
| **DESIRABLE EFFECTS** | Trivial | Small | **Moderate** | Large | | Varies | Don't know |
| **UNDESIRABLE EFFECTS** | Large | Moderate | **Small** | Trivial | | Varies | Don't know |
| **CERTAINTY OF EVIDENCE** | **Very low** | Low | Moderate | High | | | No included studies |
| **VALUES** | Important uncertainty or variability | Possibly important uncertainty or variability | **Probably no important uncertainty or variability** | No important uncertainty or variability | | | |
| **BALANCE OF EFFECTS** | Favors the comparison | Probably favors the comparison | **Does not favor either the intervention or the comparison** | Probably favors the intervention | Favors the intervention | Varies | Don't know |
| **RESOURCES REQUIRED** | Large costs | Moderate costs | Negligible costs and savings | Moderate savings | Large savings | Varies | **Don't know** |
| **CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES** | Very low | Low | Moderate | High | | | **No included studies** |
| **COST EFFECTIVENESS** | Favors the comparison | Probably favors the comparison | Does not favor either the intervention or the comparison | Probably favors the intervention | Favors the intervention | Varies | **No included studies** |
| **EQUITY** | Reduced | Probably reduced | **Probably no impact** | Probably increased | Increased | Varies | Don't know |
| **ACCEPTABILITY** | No | Probably no | Probably yes | Yes | | Varies | **Don't know** |
| **FEASIBILITY** | No | **Probably no** | Probably yes | Yes | | Varies | Don't know |

## TYPE OF RECOMMENDATION

| Strong recommendation against the intervention | Conditional recommendation against the intervention | **Conditional recommendation for either the intervention or the comparison** | Conditional recommendation for the intervention | Strong recommendation for the intervention |
|---|---|---|---|---|
| ○ | ○ | ● | ○ | ○ |

## CONCLUSIONS

### *Recommendation*

For those children with BPD who already received treatment with diuretics from the neonatal phase or neonatal intensive care unit onwards, the Task Force suggests natural weaning by the relative decrease in dose with increasing weight gain (conditional recommendation based on very low certainty of evidence). If the treating physician considers the use of diuretics of additional value, for example when clinical sign of fluid retention are present, the effects of treatment with diuretics should be carefully monitored during a trial period before chronically applied.

### *Justification*

No intervention studies examined the potential beneficial effect of diuretics on important and critical defined outcomes in children in whom BPD has been established and were discharged from the hospital, or who were older than 36 weeks of PMA. In the presented study, the exact method of randomization procedure was unclear, potential confounders were not taken into account, the intention to treat analysis was not fully clear, and additional furosemide supplementation differed between the groups (diuretic group 0/22 patients vs placebo group 5/21 patients; p-value <0.05),. The study group did not contain children with the new form of BPD. Therefore, the evidence was considered very low.

### *Subgroup considerations*

None

### *Implementation considerations*

None

## *Monitoring and evaluation*

None

## *Research priorities*

Further studies are urgently needed to examine the use of diuretics in children in whom BPD has been established and were discharged from the hospital, or who were older than 36 weeks of PMA with diuretics to reduce morbidity and related outcomes.