Cystic Fibrosis

Care Guidelines for Pulmonary Exacerbations

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Authors

Ian Waters MD, past CF Clinic Director, Royal Jubilee Hospital (RJH), Victoria

Aaron Young MD, CF Clinic Director, RJH, Victoria

Grant Hoffert, RN, BSN, CF Nurse Clinic Coordinator, RJH, Victoria

Contributors

Pearce Wilcox, MD, CF Clinic Director, St. Paul's Hospital (SPH), Vancouver

Mark Chilvers MD, CF Clinic Director, B.C. Children's Hospital (BCCH), Vancouver

Robert Levy MD, Medical Director Lung Transplant Program, BC Transplant Society, Vancouver

Delane Peters, CF Dietitian, VGH, Victoria

Steve Kent MD, CF Clinic Director, Victoria General Hospital (VGH), Victoria

Brad Quon MD, CF Physician, SPH, Vancouver

Maggie McIlwaine PHD, CF Physiotherapist, BCCH, Vancouver

Anna Gravelle, RN, MSN, CF Nurse Clinician, BCCH, Vancouver

Vanessa McMahon, RN, BSN, CFNBS Nurse Clinician, BCCH, Vancouver

Hilary Vallance, MD, Medical Director, BC Newborn Screening Program, Department of Pathology and Laboratory Medicine, BCCH, Vancouver

Graham Sinclair, PhD, Laboratory Head, BC Newborn Screening Program, Department of Pathology and Laboratory Medicine, BCCH, Vancouver

Vilte Barakauskas, PhD, Clinical Scientist, Division of Clinical Biochemistry, Department of Pathology and Laboratory Medicine, BCCH, Vancouver

Benjamin Jung, PhD, Division Head, Division of Clinical Biochemistry, Department of Pathology and Laboratory Medicine, BCCH, Vancouver

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Table of Contents

General Age Range Guide

Infant	Preschool	Child	Adolescent	Adult
0 to 2 years	2 to 6 years	6 to 12 years	12 to 18 years	≥ 18 years

Abbreviation Guide

AC . . . . . Activity Coefficient
BMI . . . . . Body Mass Index
CF . . . . . Cystic Fibrosis
CFRD . . . . Cystic Fibrosis-Related Diabetes
CRP . . . . C-reactive protein
CXR . . . . Chest Xray
FEV1 . . . . Forced Expiratory Volume in 1 second
LGTH . . . . Length
mos. . . . . Months
PEx . . . . . Pulmonary Exacerbation
PCTL . . . . Percentile
PICC . . . . Peripherally inserted central catheter
Wt. . . . . Weight

Introduction

Cystic Fibrosis (CF) lung disease is marked by a progressive decline in lung function (FEV_1) with episodic acute worsening of symptoms termed a pulmonary exacerbation (PEx).

Incidence: Pulmonary exacerbations occur frequently in CF.

> In 2007, 38% of all patients followed in CF centers in the U.S. were treated with intravenous antibiotics for a PEx.[1]

Impact: Pulmonary exacerbations are associated with more rapid decline in lung function.

> A study from Toronto found more than 50% of the decline in FEV_1 (seen over a 10 year period) could be attributed to exacerbations.[2] This means recovery from a PEx is not always complete, leaving the patient with a new, lower baseline of lung function. Liou et al, using data from the CF Foundation Patient Registry, developed a 5-year survivorship model of CF.[3] They identified 8 characteristics, in addition to FEV_1, that accurately predict survival. Pulmonary exacerbations play an important part in the model with each PEx having a large negative impact on 5-year survival equivalent to reducing the FEV_1 by 12%. Therefore, PEx not only cause acute worsening of symptoms, they also lead to permanent loss of lung function with more rapid decline in functional capacity, quality of life, and survival.

For these reasons, the prevention and treatment of PEx is a major focus of CF care.

Prevention of Pulmonary Exacerbations

Given the negative consequences of PEx, every effort should be made at prevention. A number of strategies have been proven to reduce exacerbations and many more are believed to have a positive impact on preserving lung function.

Best practices recommended by or delivered through the multi-disciplinary CF Clinics:

- A smoke free environment, including no second-hand smoke exposure early in life.[4]
- Multi-disciplinary care provided through an accredited CF care centre.[4, 5]
- Chest clearance therapy initiated in the first few months after diagnosis and maintained throughout life with appropriate age-related adjustments.
- Age-related and pancreatic-function specific nutritional recommendations.
- Infection control, surveillance and treatment:
  - Separation of patients and their care-givers from others with CF
  - Annual influenza vaccination beginning at 6 months of age for those with CF and to include all of their health care providers and care givers
  - Pneumococcal conjugate (PCV 13) vaccine at age 2, 4, 6 and 12 months
  - Pneumococcal polysaccharide vaccine at age 2 years or older with a possible repeat 5-10 years later
  - All other age appropriate vaccinations
- Medications proven to reduce PEx:
  - Mucolytics
    - Currently only dornase alfa has been shown to reduce the decline in lung function and reduce PEx.[6]
    - Recommended for use in symptomatic infants.[4]
  - Hydrator therapy
    - Hypertonic saline (7%) has been shown to reduce PEx and marginally improve lung function.[7]
    - Hypertonic saline is recommended for use in symptomatic infants.[4]
  - Pseudomonas eradication treatment
    - On first culture from airway secretions.
  - Macrolides

- Azithromycin taken 3 times per week has improved lung function and reduced PEx in chronically infected patients.[8] It should not be given to those colonized with an nontuberculous mycobacteria (NTM) organism and currently there is insufficient data to recommend for or against its use in those under 2 years of age.[9]

- Inhaled antibiotics
  - When targeted at chronic Pseudomonas aeruginosa airway colonization, inhaled antibiotics have been proven to reduce PEx, improve lung function, and reduce respiratory symptoms.[1, 10]
  - Tobramycin by inhalation is recommended for those chronically colonized with Pseudomonas aeruginosa under 2 years of age.[11]
- Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) modulator Therapy
  - CFTR pharmacotherapy aims to increase protein expression or its function at the cell surface. These drugs are targeted at individual or class-specific CFTR mutations.
  - Currently Ivacaftor, a CFTR potentiator, is approved for treatment of those carrying the G551D gating mutation and may soon be approved for a larger group of mutations. It has been shown to have a wide range of benefits in affected individuals including reducing PEx.[12]

Diagnosis of Pulmonary Exacerbations

Currently, there is no universally accepted definition of a PEx. However, the clinical features common to most and across all age groups include some combination of the following:

- increased cough and/or sputum production
- increased shortness of breath
- fever
- hemoptysis
- weight loss or loss of appetite
- increased fatigue
- reduced exercise tolerance
- reduced lung function (FEV_1)
- oxygen desaturation
- a change in physical findings (e.g. new lung crackles or wheezes)
- changes on chest X-ray

Most studies that have demonstrated a more rapid decline in lung function related to PEx used these common clinical features to define a PEx based on the need to administer antibiotics, usually intravenously.[13] However, the role of milder exacerbations (e.g. those treated with oral antibiotics) on decline in lung function, especially in younger children, remains unclear.[14] Also, the optimal treatment of these milder PEx remains uncertain.

In addition, not all PEx are acute events. An individual with CF may have a gradually decline in lung function over several weeks which is only picked up at their next clinic visit. As with acute events, treatment usually results in improvement but the long term impact on lung function is unknown.

Children, especially young children, may present with signs and symptoms of PEx different from adult patients.[14] Viral infections are particularly common in children and may play a role in the development of bacterial infections. Influenza viruses, rhinoviruses, and respiratory syncytial virus (RSV) are amongst the most frequently identified from individuals with CF. As a result, defining a PEx is even more difficult in young children.

An analysis of the Epidemiologic Study of CF (ESCF) by Rabin and colleagues[15] identified findings of new crackles, increased cough, increased sputum, and weight loss during a clinic visit as the four clinical findings most likely to result in treatment for a PEx in young CF patients. In a follow-up review of the ESCF data, Regelmann et al[8] found that the presence of one or more of these findings identified young children having a PEx whose signs and symptoms are likely to improve with a course of

antibiotics. In addition, treatment reduces the proportion with Pseudomonas aeruginosa detected at the next clinic visit. However, treatment did not reduce hospitalizations in the following year.

With the advent of newborn screening, the diagnosis of CF is being made shortly after birth. These infants are being followed monthly in the first year of life and present new problems in defining a PEx, though the constellation of findings used to define a PEx in infants is similar to those used in preschool-aged children.

The early development of lung infection was demonstrated in a study of infants less than 6 months of age, identified by newborn screening, who underwent bronchoalveolar lavage. In this study, Stafler et al[16] found 27% had unsuspected positive bacterial cultures and all had evidence of airway inflammation manifest by airway neutrophilia. Whether early treatment will result in improved outcomes awaits further study.

Current options for diagnosis

a. Children, adolescents, and adults

- Two of the more frequently used definitions are those of the European Consensus Group and Fuchs et al.[17]

  1. The European Consensus Group defines a PEx as the presence of any 2 of the above symptoms which results in treatment with an antibiotic.[18]

  2. The modified Fuch's criteria, which were used in the hypertonic saline trial[19] and the Azithromycin study[20], delineate symptoms into major or minor categories.

Fuchs major criteria:	Fuchs minor criteria:
■ decrease in FEV_1 ≥ 10% ■ O2 saturation < 90% or ≥ 5% drop ■ new infiltrate on chest X-ray	■ hemoptysis ■ increased work of breathing ■ increased adventitial sounds ■ 5% or greater weight loss ■ increased cough ■ decreased exercise tolerance ■ increased chest congestion ■ change in sputum

- An exacerbation is defined as the presence of any one of the major criteria or any 2 of the minor criteria lasting longer than 3 days.

b. Pre-school children and infants

- The US Cystic Fibrosis Foundation has recently published two sets of Clinical Practice Guidelines, one for infants[4] and one for pre-school aged children[5]. In both age groups, the same criteria, based on consensus recommendations, are used to define a PEx:
  - increased cough
  - increased sputum production
  - new crackles
  - oxygen desaturation
  - wheezing
  - hemoptysis
- A mild-to-moderate exacerbation is further defined as:
  - 1 to 2 signs or symptoms present or that the symptom severity is mild
- A moderate-to-severe exacerbation is:
  - More than 3 new findings or 1 to 2 severe findings (e.g. oxygen desaturation, new crackles)

    or
  - A mild-to-moderate exacerbation unresponsive to oral of inhaled antibiotics

Treatment of Pulmonary Exacerbations

CF lung disease begins early in life with impaired mucociliary clearance, inflammation and chronic bacterial infection. Although CF is a complex disorder involving many organ systems, 85% of mortality is due to lung disease and PEx play a major role in the decline of lung function as well as having an adverse effect on patient's quality of life. Therefore, effective treatment of PEx is a critical part of optimal care for those with CF.

Unfortunately, for many of the key questions regarding management of PEx, there is insufficient evidence to make definitive recommendations. This is particularly true for infants and children where treatment decisions often must be extrapolated from studies performed in adults. As a result, most of the recommendations regarding the treatment of PEx are based on consensus opinion and may require considerable individual adaptation.

General Recommendations

- Patients experiencing a change in symptoms that could represent a PEx should have access to a CF clinic as soon as possible.[21]
- Most PEx are treated with antibiotics which can be given orally or intravenously and occasionally by inhalation. However, treatment of a PEx does not rely on antibiotics alone.[21]

  Recent studies using culture-independent methods, such as polymerase chain reaction (PCR) techniques, have demonstrated large numbers of bacterial species in high concentrations in the airways of those with CF. As a result, there is growing evidence questioning the usefulness of treatment based on standard antibiotic susceptibility testing.[22] However, until further evidence is available antibiotic treatment of a PEx is usually based on airway culture results.

- Cultures of airway secretions should be done in a laboratory familiar with the kinds of bacteria found in those with CF.

  Where reliable culture results are not available, treatment should be targeted at the most likely pathogen.

  a. Infants and children with mild to moderate exacerbations:

     - Treatment would usually target Staphylococcus aureus and possibly Haemophilus influenza. Antibiotic treatment options include oral agents such as cloxacillin, a cephalosporin, or trimethoprim-sulfa.

  b. Children and adults with a more severe exacerbation:

     - Antibiotic coverage should include Pseudomonas aeruginosa, the most common CF pathogen.

- Increased airway clearance activities and optimization of aerosol routines are often indicated along with attention to increased nutritional requirements.
- Evaluation should be carried out for glucose intolerance which may develop during an exacerbation. Those with CF related diabetes (CFRD) will need adjustments to their insulin regimens.
- Those with CF related liver disease or renal impairment may need adjustments to their treatment regimens.

Note: Flow charts outlining the recommended management in each age group are included in Figures 1, 2 and 3 in the APPENDIX

Oral versus intravenous antibiotics

- For milder exacerbations, outpatient therapy using oral antibiotics may be appropriate. However, it requires that the patient (or family) must be able to provide treatment in the home, including other important aspects of the treatment of a PEx, such as increased airway clearance activities.
- Consider recent and past history of oral antibiotic treatment.
- Consider patient preference – some patients might prefer intravenous antibiotics to oral.
- Intravenous antibiotics might be the only option even if the PEx is mild if there are no oral antibiotic options for certain bacteria.

Hospital versus Home Intravenous Therapy

- Many factors go into the decision on home versus hospital treatment of a PEx including patient and/or family choice. While consensus guidelines generally recommend hospital treatment as the standard of care for those requiring IV antibiotics[1, 23] in selected patients, Home IV Therapy may be appropriate.
- Home IV Therapy can either follow treatment initiated as an inpatient or can be done totally through the outpatient department.
- For Home IV Therapy to be an option, consider:
  - available and adequately resourced home IV program
  - the ability to place an appropriate IV access device, usually a peripherally inserted central catheter (PICC)
  - available outpatient laboratory and clinical follow-up
- Given these limitations, Home IV Therapy should be considered for those with:
  - a mild exacerbation
  - no significant complications (such as poorly-controlled CFRD or renal insufficiency)
  - an uncomplicated antibiotic routine
  - adequate home resources and supports

Single versus double antibiotic coverage for Pseudomonas aeruginosa (PA)

- Although data is limited, the general consensus is to use two antibiotic classes when treating a PA infection.[1, 21]
- Once daily dosing of aminoglycosides is preferable to multiple doses[1, 23] and those receiving multiple courses of an aminoglycoside should have intermittent monitoring of drug concentration and renal function.
- Periodic audiograms, if available, are also recommended[1] for early detection of hearing damage.

Other considerations in antibiotic treatment

- Continuous infusions of B-lactam antibiotics are not recommended for the treatment of PEx and antibiotic synergy testing is not routinely recommended for those with multi-drug resistant bacteria.[1]
- Currently, there is insufficient data to recommend an optimal duration of treatment[1] though a 14-day course of IV antibiotics is generally considered routine.[24] In some cases, a 10-day course may be adequate, and in others, 3 weeks or more may be needed, depending on the clinical and laboratory response to treatment.
- The pharmacokinetics of antibiotics in those with CF differ compared to non-CF individuals. Therefore, when treating a PEx, dosages and frequency of administration may need to be altered.[24]

Continuation of chronic therapies during treatment of a PEx

- While there is no good data on what should be done with most chronic treatments during a PEx, the consensus recommendation is they should be continued.[1]
- One proviso is that, due to concerns regarding increased toxicity and interference with the assessment of serum drug levels, inhaled anti-Pseudomonas treatment should be discontinued when the same antibiotic is used intravenously.[21]
- Airway clearance therapy should be increased during an exacerbation and may be one of the reasons for recommending hospital versus home treatment, at least initially.
- Those with CFRD may need adjustments to their insulin routine and those who have demonstrated glucose intolerance during exacerbations may need insulin treatment temporarily.

Diagnosis and treatment of other causes of PEx

a. Viruses

- Viruses can cause PEx independent of a bacterial infection. This is particularly true in children and during epidemics of influenza and RSV.
- Viral-type symptoms persisting for more than a few days, if accompanied by persistent cough or other symptoms of an exacerbation, will usually be treated with an antibiotic aimed at covering the bacteria from a recent respiratory culture.

b. Allergy

- Allergic bronchopulmonary aspergillosis (ABPA) or other triggers for asthma should be considered when there is:
  - a past history of these disorders
  - poor response to anti-bacterial treatment, or
  - new onset of wheezing
- The diagnosis should be confirmed with appropriate chest imaging, laboratory and lung function tests.
- Treatment involves corticosteroids (inhaled or oral) and, in some cases, antifungal agents. However, except when a significant allergy component is present, routine use of corticosteroids is not recommended in the treatment of an acute exacerbation.[1]

c. Nontuberculous mycobacteria

- CF patients colonized with nontuberculous mycobacteria (NTM) can present difficulty in determining the cause of a PEx, especially when there is an unexpected decline in lung function or a lack of improvement with standard antibiotic treatment. However, decisions regarding when to treat NTM disease in CF and the treatment routines are complex and require involvement of those with expertise in these disorders.

d. New acquisition of bacteria

- New acquisition of bacteria, such as Burkholderia species, can also lead to a PEx especially in adults and should be considered when there is an inadequate response to standard treatment.

Follow-up care

- Ongoing monitoring is based on overall clinical response including:
  - resolution or improvement of symptoms
  - improvement in weight and lung function, and
  - resolution or improvement in laboratory markers of inflammation
- The C-reactive protein or CRP may be a useful marker of the level of inflammation in CF and therefore helpful in assessing the response to treatment.[11]
- Lung function should be assessed by performing measurements of FEV_1 at the start and end of treatment. However, it is important to remember that about 25% patients will not full recover to their baseline FEV_1.[21]
- Since most of the trials conducted on the treatment of PEx have included mainly adults, considerable extrapolation is needed when treating younger individuals with CF. Fortunately, there are recently published guidelines on the management of infants[4] and preschoolers[5] with CF. These guidelines contain consensus recommendations for the treatment of worsening pulmonary symptoms, such as PEx.

Note: Flow charts outlining the recommended management in each age group are included in Figures 1, 2 and 3 in the APPENDIX

Appendix

Figure 1: Care of infants with a change in respiratory status[4]

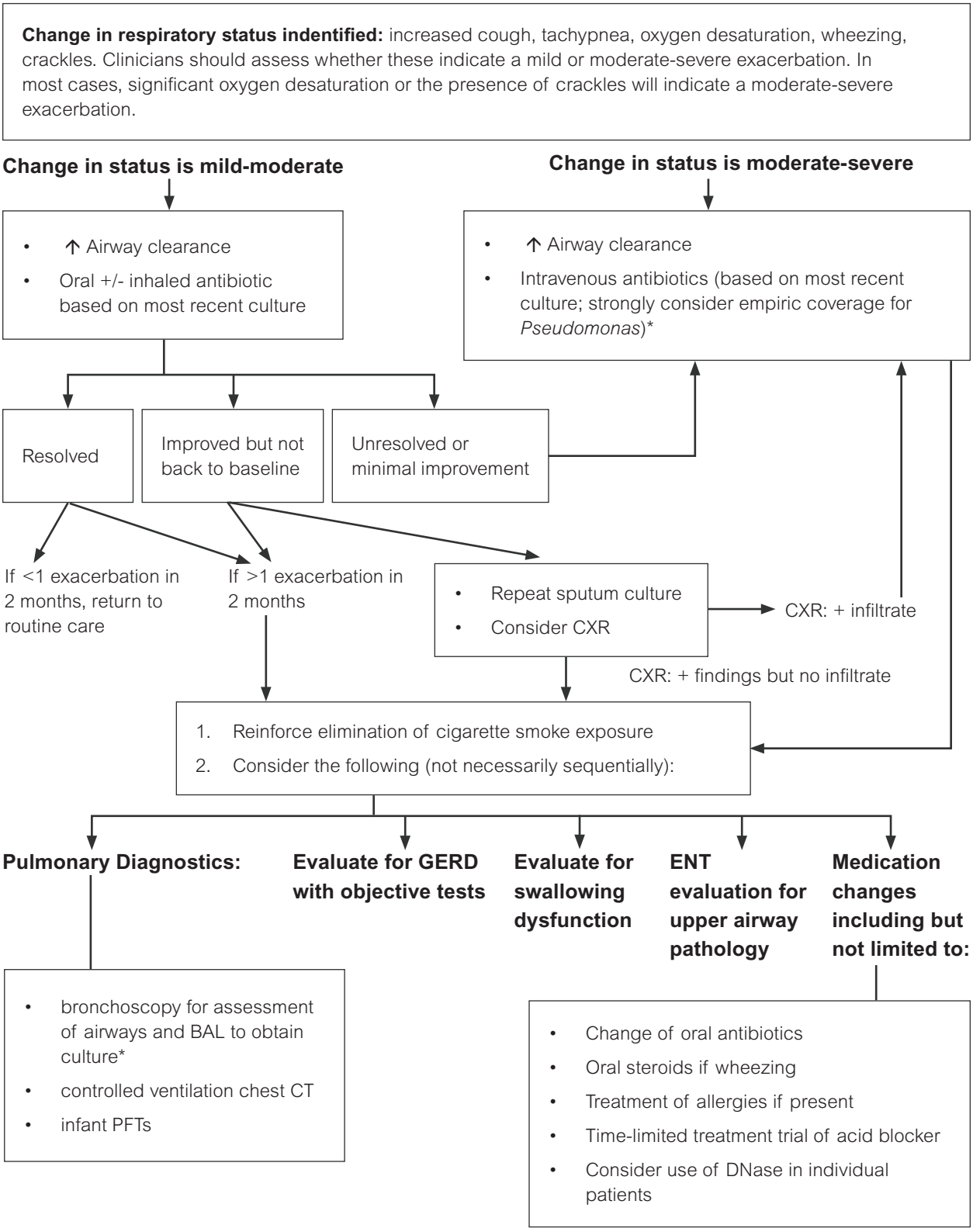


Figure 2: Care of preschool children with a change in respiratory status[5]

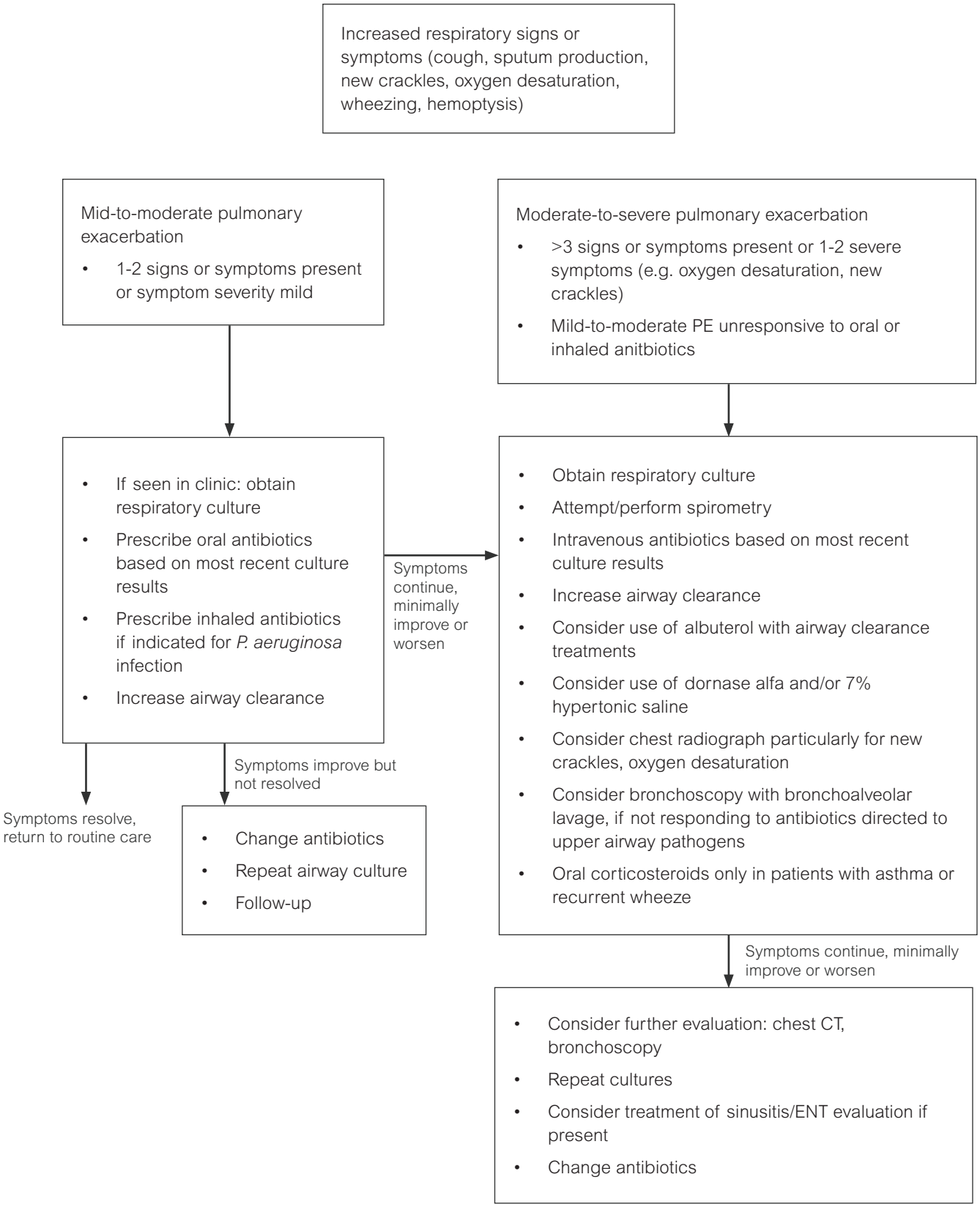


Figure 3: Care of school-aged children and adults with a change in respiratory status

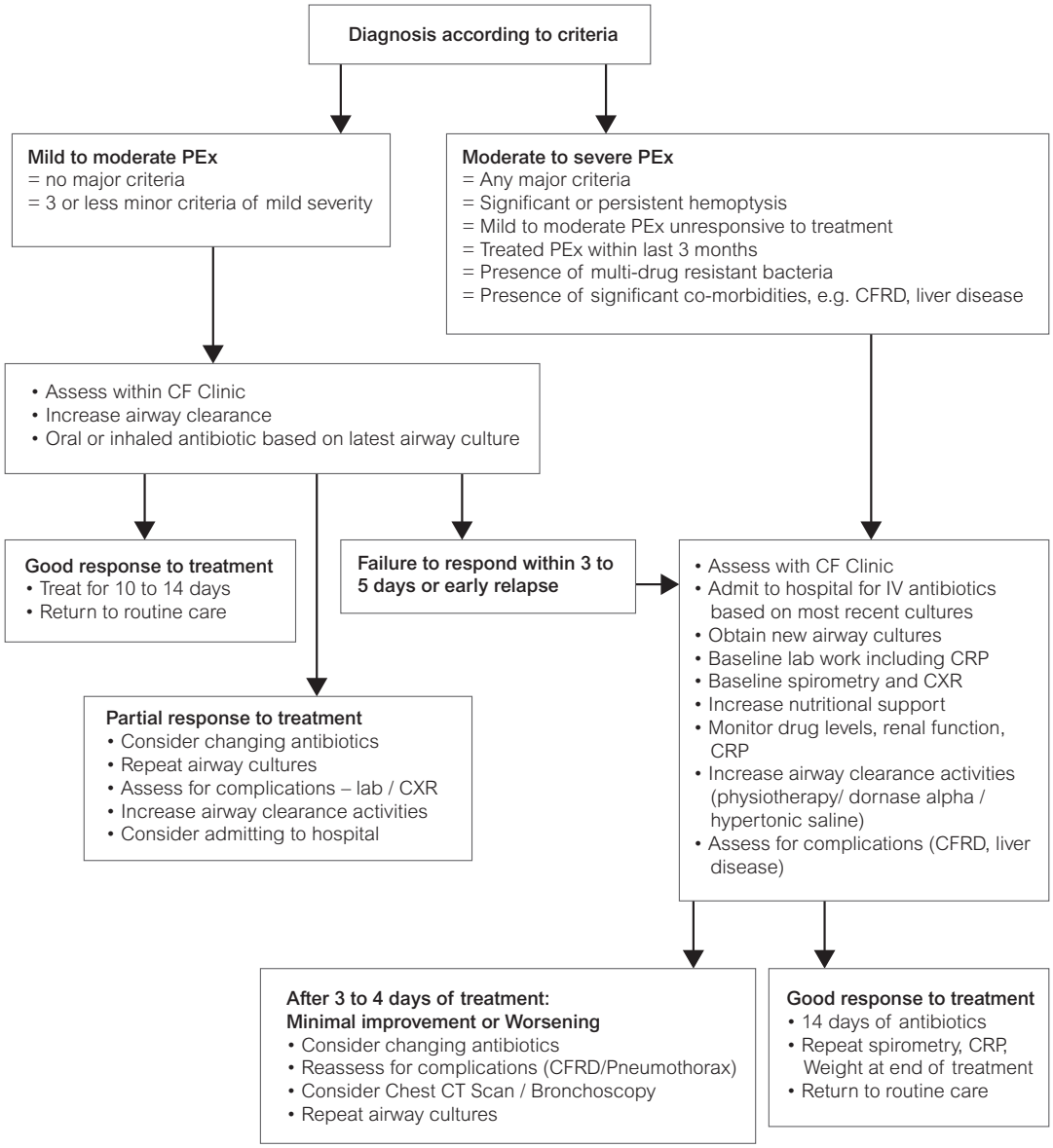
1 or more major criteria

- decrease in FEV1 > 10%
- O2 saturation < 90% or > 5% drop
- new infiltrate on chest X-ray

OR

At least 2 minor criteria lasting longer than 3 days

- hemoptysis
- increased work of breathing
- increased adventitial sounds
- 5% or greater weight loss
- increased cough
- decreased exercise tolerance
- increased chest congestion
- change in sputum



Endnotes

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