ACUTE EXACERBATION OF BRONCHIECTASIS (Non-Cystic Fibrosis)

CHI Formulary Indication Review

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INDICATION UPDATE

ADDENDUM- November 2023

To the CHI Acute Exacerbations of Bronchiectasis Clinical Guidance- Issued May 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

6MWT	6-Minute Walk Test
ACT	Airway clearance technique
CHI	Council of Health Insurance
COPD	Chronic Obstructive Pulmonary Disease
CPG	Clinical Practice Guideline
CT	Computed tomography
DPP1	Dipeptidyl Peptidase 1
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in the First Second
IDF	Insurance Drug Formulary
IgE	Immunoglobulin E
IMT	Inspiratory Muscle Training
ISWT	Incremental Shuttle Walk Test
NTM	Non-Tuberculous Mycobacterial
PCD	Primary Ciliary Dyskinesia
SFDA	Saudi Food and Drug Authority

Executive Summary

Bronchiectasis is a rare condition typically arising as a consequence of an infection, leading to the persistent and unusual deformation of one or multiple conducting bronchi or airways. There is currently a lack of comprehensive data regarding the occurrence or frequency of bronchiectasis. Bronchiectasis is not very prevalent in the United States, with an estimated 100,000 cases in the 1980s[1].

In Saudi Arabia, there is a lack of comprehensive national data regarding the prevalence and incidence of bronchiectasis. The available information primarily stems from studies conducted in hospitals, which are likely to provide an incomplete picture of the overall situation. For example, Al-Mobeireek et al. found that only 5% of adult cases with chronic persistent cough referred to pulmonary clinics were diagnosed with bronchiectasis, and *Pseudomonas aeruginosa* was the most identified pathogen in hospitalized patients in another study[2].

Diagnosis is based on a combination of radiological criteria and symptoms:

- Radiological criteria: either an inner airway – artery diameter ratio of ≥ 1 or an outer airway –artery diameter of ≥ 1 shown on CT scans
- Symptoms: patient have at least two of the followings:
    - A cough most days of the week
    - Sputum production most days of the week
    - A history of exacerbation[3].

Airway injury linked to acute infection can lead to the presence of blood-tinged sputum or hemoptysis. More general symptoms encompass shortness of breath, chest pain that worsens with breathing, wheezing, fever, fatigue, and a decrease in body weight[1].

An examination of sputum can be employed to provide additional support to the clinical suspicion[1].

After confirming the diagnosis, additional laboratory tests can be beneficial in identifying the root cause of the condition[1].

The objectives of treatment include enhancing symptoms, minimizing complications, managing flare-ups, and decreasing the overall burden of illness and the risk of death. Timely identification is crucial in the context of bronchiectasis and its related conditions. Furthermore, addressing the underlying conditions is a fundamental component of the overall treatment[1].

The primary treatment methods involve antibiotics and chest physiotherapy. In addition to treatments targeting specific associated conditions, other approaches might encompass bronchodilators, corticosteroid therapy, dietary supplementation, and the consideration of oxygen or surgical interventions[1].

Acute exacerbations are defined as:

- Worsening of symptoms greater than the normal day-to-day variation

  OR

- Specifically, deterioration in three or more of the following key signs or symptoms for 48 hours:
  - Cough;
  - Sputum volume and/or consistency; sputum purulence;
  - Breathlessness and/or exercise intolerance;
  - Fatigue and/or malaise; Hemoptysis;

  AND

- A clinician determines that a change in bronchiectasis treatment is required[4].

CHI issued an acute exacerbation of bronchiectasis (non-cystic fibrosis) guidance after thorough review of renowned international and national clinical guidelines in May 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an **addendum** to the prior CHI Acute exacerbation of bronchiectasis (non-cystic fibrosis) clinical guidance and seeks to offer guidance for the effective management of acute exacerbation of bronchiectasis (non-cystic fibrosis). It provides an update on the acute exacerbation of bronchiectasis (non-cystic fibrosis) guidelines for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing the **most updated best available clinical and economic evidence** related to drug therapies.

Main triggers for the update are summarized being the addition of **new guidelines and review articles** to the report such as **British Thoracic Society** guideline for bronchiectasis in adults **(2019)**, the **European Respiratory Society** guidelines for the management of adult bronchiectasis **(2017)** and **European Respiratory Society** guidelines for the management of children and adolescents with bronchiectasis **(2021)**, a **review article** on the exacerbation of bronchiectasis article **(2018),** a Cochrane review (2018) and a narrative review (2022) on the role of inhaled corticosteroids in bronchiectasis (2018), and finally a **narrative review** of bronchiectasis exacerbation causes, risk factors, management, and prevention **(2023).**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is recommended to remove **Clavulanic acid** and **INFLUENZA VACCINE SURFACE ANTIGEN NYMC X-181, NYMC X-187, AND NYMC BX-35** as they are no longer registered on the SFDA Drug List of September 2023. There have been no changes or updates made to any of the previously listed drugs in terms of drug information and prescribing edits since May 2020. Furthermore, there were no new drugs that were SFDA approved since then.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in acute exacerbation of bronchiectasis (non-cystic fibrosis) management.

Below is a table summarizing the major changes based on the acute exacerbation of bronchiectasis (non-cystic fibrosis) guidelines used to issue this report:

Table 1. General Recommendations for the Management of Acute Exacerbation of Bronchiectasis (Non-Cystic Fibrosis)

Management of Acute exacerbation of bronchiectasis (non-cystic fibrosis)		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
It is not recommended to use recombinant human DNase in adults who have bronchiectasis.	A	British Thoracic Society (2019)[5]
For specific individuals, like those facing elevated daily symptoms, frequent exacerbations, challenges in clearing sputum, and/or a diminished quality of life, it may be beneficial to contemplate the use of inhaled mannitol or a 6–7% hypertonic saline solution.	Not graded	European Respiratory Society (2021)[6]
Using inhaled corticosteroids for adults with bronchiectasis is not recommended.	Conditional recommendation, low quality of evidence	European Respiratory Society (2017)[7]
In certain cases, it is essential, advisable, or, at a minimum, not advisable to discontinue the prescription of inhaled	Not graded	Martinez-Garcia et al. (2022)[8]

corticosteroids (ICSs). This applies particularly to individuals with conditions such as asthma/bronchiectasis overlap, COPD/bronchiectasis overlap, allergic bronchopulmonary aspergillosis (ABPA), bronchiectasis featuring bronchial or peripheral eosinophilic components, or uncontrollable bronchorrhea.		
The routine use of long-acting bronchodilators for adults with bronchiectasis is discouraged.	Conditional recommendation, very low quality of evidence	European Respiratory Society (2017)[7]
Limited evidence exists to support the use of bronchodilators in individuals with bronchiectasis, even though both beta-2-agonists and anticholinergic bronchodilators are frequently employed in clinical practice.	Not graded	British Thoracic Society (2019)[5]
For individuals experiencing significant shortness of breath, it may be worth considering a trial of long-acting bronchodilator therapy.	D	British Thoracic Society (2019)[5]
We suggest a 14-day course of antibiotics as the treatment for acute bronchiectasis exacerbations.	Conditional recommendation, very low-quality evidence	European Respiratory Society (2017)[7]
Empirical antibiotic therapy should be based on previous sputum culture if known. If previous culture is not known, it should include coverage for pseudomonas pending the culture result.	Not graded	British Thoracic Society (2019)[5]
Route of administration of antibiotics: The choice between oral or intravenous antibiotics depends on severity and response to initial oral antibiotics.	Not graded	British Thoracic Society (2019)[5] European Respiratory Society (2017)[7]

Single or combined antibiotics: There is no evidence dual therapy is more effective, but it should be considered in patients with *Pseudomonas* organism or very severe cases		
Colonization with exacerbation less than 3 times (first growth or regrowth): The optimal eradication regime has not been determined, however common practice is to prescribe two weeks of oral antibiotics ciprofloxacin (pseudomonas) and then repeat the sputum culture. If the culture remains positive for *P. aeruginosa*, treatment may be escalated to intravenous for 14 days and inhaled antibiotics for 3 months.	Not graded	European Respiratory Society (2017)[7] British Thoracic Society (2019)[5]
Three exacerbation or more: An inhaled antibiotic should be first-line therapy: colistin, gentamycin or tobramycin. A follow-up should be done every 6 months for efficacy and tolerance.	Not graded	British Thoracic Society (2019)[5]
Long-term oral ciprofloxacin is not recommended due to concerns with resistance and potential side effects	Not graded	British Thoracic Society (2019)[5]
Combined Inhaled antibiotic and macrolide are recommended for severe cases	Not graded	British Thoracic Society (2019)[5]
Individuals with bronchiectasis who experience three or more exacerbations may want to contemplate the utilization of extended antibiotic treatment.	A	British Thoracic Society (2019)[5]
We advise contemplating the administration of eradication antibiotic therapy to adults with	Conditional recommendation,	European Respiratory Society (2017)[7]

bronchiectasis who have *Pseudomonas aeruginosa* colonization defined as isolation on 2 or more occasions, at least 3 months apart, within a 1-year period.	very low quality of evidence	
Offer pulmonary rehabilitation to those individuals with a Modified Medical Research Council (MMRC) Dyspnea Scale score of 1 or higher, indicating restricted functional capacity due to breathlessness.	B	British Thoracic Society (2019)[5]
Consider the possibility of lung resection for patients with localized disease if their symptoms persist, even after receiving optimized medical treatment from a specialist in bronchiectasis.	D	British Thoracic Society (2019)[5]
It is important to highlight that the occurrence of bronchiectasis substantially rises among the elderly. As a routine practice, it is advisable to administer vaccinations for both influenza and pneumococcal infections to individuals aged 65 and above, especially those with chronic respiratory conditions.	Not graded	Polverino et al. (2018)[9]
For children and adolescents with bronchiectasis, we suggest following their nation's immunization schedules, which may include receiving pneumococcal and annual seasonal influenza vaccines if these vaccines are not already integrated into the program.	Conditional recommendation, very low quality of evidence	European Respiratory Society (2021)[6]

At the end of the report, a **key recommendation synthesis** section is added highlighting the latest updates in the acute exacerbation of bronchiectasis clinical and therapeutic management.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: one part includes recommendations from **updated versions of guidelines** mentioned in the previous CHI *acute exacerbation of bronchiectasis (non-cystic fibrosis)* report, and another part includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

There are no guidelines that have been updated since May 2020.

Table 2. Clinical Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
The **Saudi Thoracic Society** Guidelines for Diagnosis and Management of Non-Cystic Fibrosis Bronchiectasis (**2017**)	Not available
NICE Guideline – Bronchiectasis (Non-Cystic Fibrosis), Acute Exacerbation: Antimicrobial Prescribing (**2018**)	Not available

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI acute exacerbation of bronchiectasis (non-cystic fibrosis) report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
British Thoracic Society guideline for bronchiectasis in adults **(2019)**
European Respiratory Society guidelines for the management of adult bronchiectasis **(2017)**
European Respiratory Society guidelines for the management of children and adolescents with bronchiectasis **(2021)**
Review Article: Exacerbation of Bronchiectasis **(Bronchiectasis, 2018)**
Cochrane Database of Systematic Reviews: Inhaled corticosteroids for bronchiectasis (**2018**)
Inhaled Corticosteroids in Adults with Non-Cystic Fibrosis Bronchiectasis: From Bench to Bedside. **A Narrative Review (2022)**

Bronchiectasis exacerbation: a narrative review of causes, risk factors, management, and prevention (Review article) **(2023)**

1.2.1 British Thoracic Society Guideline for Bronchiectasis in Adults (2019)

The British Thoracic Society published its clinical guidelines for the management of bronchiectasis in adults in 2019[5]. introduced a set of recommendations accompanied by a grading scheme, outlined as follows:

Table 4. Levels of Evidence

Levels of evidence	
1++	High quality meta-analyses, systematic reviews of randomized controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTS with a low risk of bias
1–	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is casual
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is casual
2–	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not casual
3	Nonanalytic studies, for example, case reports, case series
4	Expert opinion

Table 5. Grades of Recommendation

Grades of recommendation	
A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results

B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+directly applicable to the target population and demonstrating overall consistency of results or Extrapolated evidence from studies rated as 2++
D	Evidence of level 3 or four or Extrapolated evidence from studies rates as 2+
√	Important practical points for which there is no research evidence, nor is there likely to be any research evidence. The guideline committee wishes to emphasise these Good Practice Points

Essential for all patients

- Confirm the diagnosis Radiologically and clinically
- Identify the underlying cause and phenotyping
- Improve symptoms and keep the patient stable
    - Improve tracheobronchial clearance
    - Reverse airflow obstruction
    - Control infection
    - Eliminate colonization with *Pseudomonas*
- Address all comorbidities
- Serials sputum cultures- including ATM
- Treat and Prevent exacerbation
- Severity score: FACED, BSA

Diagnosis

- Chest radiography (CXR) is not very effective in accurately diagnosing bronchiectasis, especially in mild cases. (2+)
- In contrast, when compared to bronchography, thin-section CT scans performed with 10mm intervals are highly accurate in identifying bronchiectasis. (2+)
- Conduct an initial chest X-ray for individuals suspected of having bronchiectasis (D).
- Perform a thin-section CT scan to validate the diagnosis of bronchiectasis when there is clinical suspicion (C).

- Carry out baseline imaging when the disease is clinically stable, as this is the best time for diagnostic purposes and for subsequent comparisons (D).

Specific disease groups with associated bronchiectasis

- Research in non-affected populations does not yield a robust body of proof, but it indicates that the ongoing production of thick, pus-like sputum during stable health could be indicative of concealed bronchiectasis. This suspicion becomes even more significant if there is a history of significant respiratory infections (such as measles, whooping cough, pneumonia, tuberculosis) or persistent rhinosinusitis. (2-)
- Bronchiectasis has been observed in individuals with HIV infection more frequently than in the general population (2-).
- In patients with HTLV-1 infection, bronchiectasis with associated inflammatory complications has been reported at a rate higher than that of the general population (3).
- Contemplate evaluating patients for bronchiectasis when they have continuous production of thick or purulent sputum, especially if they have relevant associated risk factors. (D)
- Consider investigating bronchiectasis in patients with rheumatoid arthritis if they exhibit symptoms of a persistent productive cough or recurring chest infections. (C)
- Consider examining patients with COPD who experience frequent exacerbations (two or more per year) and have previously tested positive for *Pseudomonas aeruginosa* in their sputum when they are stable. (B)
- Consider investigating bronchiectasis in patients with inflammatory bowel disease who have a chronic productive cough. (C)

Investigations for causes of bronchiectasis

- To determine the underlying cause of bronchiectasis, a set of investigations should be conducted: (B)
    a. Patients diagnosed with bronchiectasis should have their co-morbidities and medical history documented to identify relevant and potentially causative conditions such as rheumatoid arthritis, COPD, asthma, gastro-esophageal reflux disease, and inflammatory bowel disease. (C)
    b. In all individuals with bronchiectasis, conduct a full blood count with differential, assess serum total IgE levels, sputum culture for bacteria

and mycobacterium and evaluate sensitization (specific IgE or a skin prick test) to Aspergillus fumigatus. (D)

c. Perform tests for serum Immunoglobulin G (IgG), Immunoglobulin A (IgA), and Immunoglobulin M (IgM) in all bronchiectasis patients. (C)

d. Consider measuring baseline levels of specific antibodies against Streptococcus pneumoniae's capsular polysaccharides in all patients to investigate specific antibody deficiencies. If pneumococcal antibodies are low, administer the 23-valent polysaccharide pneumococcal vaccine, followed by measuring specific antibody levels 4-8 weeks later. (D)

e. Further investigation should be conduct on based on clinical suspicion:

    i. Evaluate patients for cystic fibrosis, following the NICE Guidelines for Cystic Fibrosis, in cases where clinical features support it, such as early onset, male infertility, malabsorption, or pancreatitis. (B)

    ii. Assess patients for Primary Ciliary Dyskinesia (PCD) based on the ERS Guidelines for PCD Diagnosis if they exhibit corresponding clinical features, including a history of neonatal distress, childhood symptoms, recurrent otitis media, rhinosinusitis, or infertility. (A)

Severity scoring

- The presence of the two clinical scoring systems, namely the Bronchiectasis Severity Index (BSI) and FACED predict prospective mortality in bronchiectasis patients.
- Consider using the bronchiectasis severity index which may assist in directing the course of treatment.

Table 6. Variables Involved in Calculating the Severity Score in the Bronchiectasis Severity Index (Adapted from the 2019 British Thoracic Society Guideline)

Factor and points for scoring system				
Age (years)	< 50 (0 points)	50-59 (2 points)	70-79 (4 points)	> 80 (6 points)
BMI (kg/m²)	< 18.5 (2 points)	18.5-25 (0 points)	26-30 (0 points)	> 30 (0 points)
FEV1 % predicted	> 80 (0 points)	50-80 (1 points)	30-49 (2 points)	< 30 (3 points)
Hospital admission within last 2 years	No (0 points)		Yes (5 points)	
Number of exacerbations in previous 12 months	0 (0 points)	1-2 (0 points)	≥ 3 (2 points)	
MRC breathlessness score	1-3 (0 points)	4 (2 points)	5 (3 points)	
***P. aeruginosa* colonization**	No (0 points)		Yes (3 points)	
Colonization with other organisms	No (0 points)		Yes (1 point)	
Radiological severity	< 3 lobes affected (0 points)		≥ 3 lobes or cystic bronchiectasis in any lobe (1 point)	
0-4 points = mild disease; 5-8 = moderate disease; 9 and over = severe disease				

Table 7. Variables Involved in Calculating Severity in the FACED Score (Adapted from the 2019 British Thoracic Society Guideline)

Factor and points for scoring system		
FEV1 % predicted	< 50 (2 points)	≥ 50 (0 points)
Age (years)	≤ 70 (0 points)	> 70 (2 points)
***P. aeruginosa* colonization**	No (0 points)	Yes (1 point)
Radiological extension of bronchiectasis	1-2 lobes (0 points)	> 2 lobes (1 point)

Modified MRC dyspnea scale	1-2 (0 points)	III-IV (1 point)
0-2 points = mild disease; 3-4 = moderate disease; 5-7 = severe disease		

Airway clearance techniques

- Using oscillating positive expiratory pressure (Acapella), along with postural drainage, is both effective and safe when applied during an acute exacerbation (1-).
- Manual techniques can be provided to improve sputum clearance when the patient is tired or experiencing exacerbation.
- Contemplate the use of intermittent positive pressure breathing or non-invasive ventilation during an acute exacerbation. This can help reduce the effort required for breathing, enabling fatigued or breathless patients to endure longer treatment sessions and assume postural drainage positions.
- The frequency and duration of the airway clearance method should be customized for each person and might change during exacerbations.
- Provide individuals diagnosed with bronchiectasis the option of using either the active cycle of breathing techniques or oscillating positive expiratory pressure (D).
- Consider employing gravity-assisted positioning (if there are no contraindications) to improve the efficacy of an airway clearance technique (D).

Mucoactives in bronchiectasis

- Recombinant human DNase should not be used in non-cystic fibrosis, as it increases the frequency of exacerbations and the risk of mortality (1+).
- Both isotonic and hypertonic saline have the potential to enhance cough-related quality of life (QoL) and health-related quality of life (HQoL) in bronchiectasis patients when combined with airway clearance (1-).
- Mannitol, while not reducing exacerbation frequency, was found to extend the time until the first exacerbation, bring about a slight improvement in QoL, and may help reduce sputum plugging (1+).
- Oral mucolytics have the potential to improve sputum expectoration (1-).
- It is not recommended to regularly employ recombinant human DNase in adults with bronchiectasis (A).

Treatments that improve outcomes for patients with stable bronchiectasis

- The use of long-term antibiotics leads to a reduction in exacerbations among bronchiectasis patients (1++).
- Inhaled colistin, administered at a dose of 1 MU twice daily through the I-neb, enhances the quality of life in bronchiectasis patients with chronic *Pseudomonas aeruginosa* infection and one or more exacerbations annually (1+). This treatment also extends the time until the next exacerbation in bronchiectasis patients with chronic *Pseudomonas aeruginosa* infection who are compliant with the treatment and experience one or more exacerbations per year (1+).
- Inhaled gentamicin prolongs the time to exacerbation, decreases the rate of exacerbations, and improves the quality of life in bronchiectasis patients with chronic infection from a potentially pathogenic microorganism and who suffer from two or more exacerbations each year (1+).
- Both azithromycin and erythromycin reduce the number of exacerbations and the proportion of patients who experience at least one exacerbation in bronchiectasis patients (1++).
- Tetracyclines may lead to a reduction in the number of exacerbations in bronchiectasis patients (2+).
- Participants in long-term antibiotic randomized controlled trials (RCTs) had experienced three or more exacerbations in the year preceding their enrollment, surpassing the inclusion criteria (1+).
- Inhaled aztreonam, administered twice daily for four weeks, does not demonstrate clinically significant benefits when assessed by changes in QOL-B-RSS (Quality of Life-Bronchiectasis Respiratory Symptoms Scale) and time until the first exacerbation. Moreover, aztreonam is associated with a higher incidence of treatment-related adverse events and discontinuation due to adverse events (1+).
- The use of cyclical intravenous antibiotics may lead to a reduction in the number of exacerbations and the number of hospital bed days in patients experiencing five or more exacerbations and subjective ill health between exacerbations (3).
- Patients with bronchiectasis who have 3 or more exacerbations should consider the use of prolonged antibiotic therapy. (A)

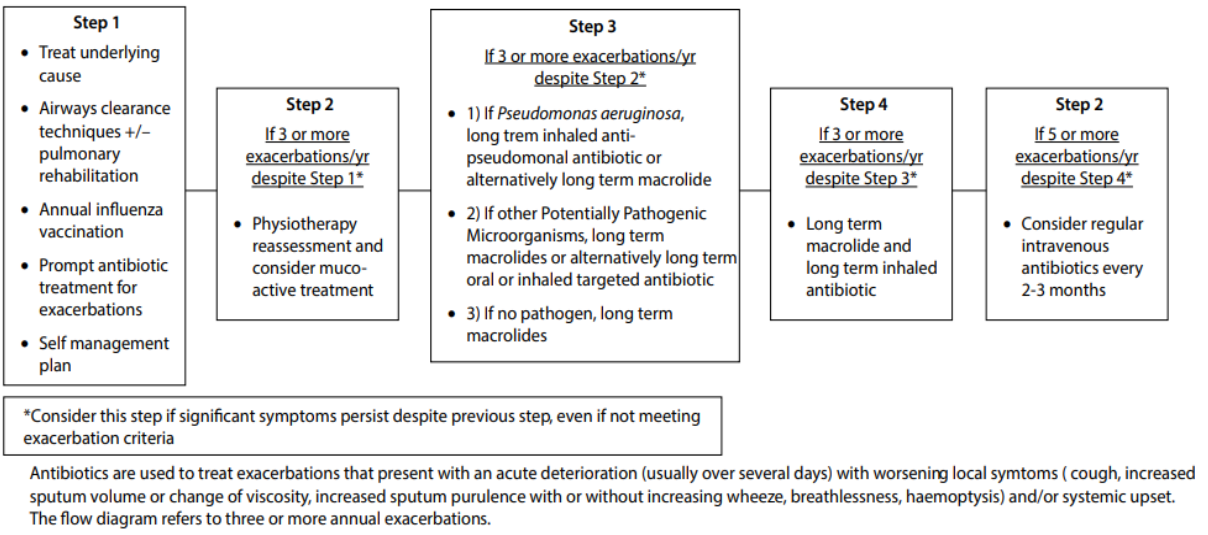


Figure 1. *Stepwise management (Retrieved from the 2019 British Thoracic Society Guideline)*

Table 8. Long Term Antibiotic Regimes (Adapted from the 2019 British Thoracic Society Guideline)

Agent	Route	Dose - Adults
Gentamicin	Nebulized	80 mg BD
Tobramycin	Nebulized	160 mg BD
Colomycin	Nebulized	300 mg BD
Tobi®	Nebulized	1MU BD or 2 MU BD
Promixin	iNEB Adaptive Aerosol Delivery (AAD) System	1MU BD
Erythromycin	Oral	250mg BD
Azithromycin	Oral	250mg Thrice weekly
Doxycycline	Oral	100mg OD
Amoxicillin	Oral	250mg BD
Amoxicillin with clavulanic acid	Oral	375 mg BD
OD Once a day, BD Twice a day		

P. aeruginosa colonized patients

- Use inhaled colistin for patients with bronchiectasis and chronic *P. aeruginosa* infection. (B)
- For individuals with bronchiectasis and chronic *P. aeruginosa* infection, contemplate the use of inhaled colistin. As a secondary option to colistin, think about employing inhaled gentamicin. (B)
- In cases of bronchiectasis with chronic *P. aeruginosa* infection, if inhaled antibiotics are not well-tolerated, consider azithromycin or erythromycin as an alternative treatment. (B)
- For patients with severe bronchiectasis and chronic *P. aeruginosa* colonization experiencing frequent exacerbations, or not tolerating inhaled therapy, consider adding azithromycin or erythromycin. (D)

Non-*P. aeruginosa* colonized patients

- Use azithromycin or erythromycin for bronchiectasis patients with 3 or more exacerbations. (A)
- Consider using inhaled gentamicin as a secondary choice to azithromycin or erythromycin. (B)
- In cases where macrolides are not well-tolerated or ineffective, consider doxycycline as an alternative for patients. (C)

Long term bronchodilators and anti-inflammatory therapies

- The routine use of long use of ICS or bronchodilators is not recommended.
- The BTS guidelines advise against long term oral corticosteroids, phosphodiesterase type 4 inhibitors, methylxanthines, leukotriene receptor antagonists. (D)
- There is limited supporting evidence for the use of bronchodilators, although both beta-2-agonists and anticholinergic bronchodilators are commonly used in clinical practice.
- Patients experiencing breathlessness may find long-acting beta-2-agonists to be advantageous. (4)
- In individuals with bronchiectasis who have breathlessness, long-acting anti-cholinergics may offer benefits. (4)
- No supporting evidence was found for the use of short-acting beta-2-agonists. (4)

- Bronchodilator therapy can encompass either short-acting or long-acting beta-agonists, short-acting or long-acting anti-cholinergic bronchodilators, or a combination of these. There is no conclusive evidence to determine the optimal bronchodilator strategy in bronchiectasis. (4)
- In patients with bronchiectasis who also have concurrent COPD or asthma, the administration of bronchodilators should adhere to the respective COPD or asthma guideline recommendations. (D)
- Consider initiating a trial of long-acting bronchodilator therapy in individuals experiencing significant breathlessness. (D)
- Conducting reversibility testing with beta-2-agonists or anticholinergic bronchodilators may aid in identifying patients with co-existing asthma, but there is no indication that a positive response is necessary to derive benefits from bronchodilators. (D)

Pulmonary Rehabilitation

- Participation in pulmonary rehabilitation can enhance exercise capacity and potentially lead to an improvement in the quality of life for individuals with bronchiectasis. (1+)
- Pulmonary rehabilitation may contribute to a reduction in the frequency of exacerbations over a 12-month period and an extension of the time to the first exacerbation. (1-)
- When integrated with pulmonary rehabilitation, the utilization of inspiratory muscle training (IMT) can extend the durability of training effects. (1+)
- IMT, when applied on its own, does not result in an increase in exercise capacity or improvements in the quality of life for individuals with bronchiectasis. (1-)
- Both the 6-Minute Walk Test (6MWT) and Incremental Shuttle Walk Test (ISWT) are reliable and responsive evaluation tools for measuring exercise capacity before and after pulmonary rehabilitation in bronchiectasis. (3)
- There is currently no available evidence addressing the risk of cross-infection of respiratory pathogens among individuals with bronchiectasis in a group exercise setting.
- Provide pulmonary rehabilitation to individuals whose functional capacity is restricted by breathlessness, as indicated by a Modified Medical Research Council (MMRC) Dyspnea Scale score of 1 or higher. (B)

- Consider incorporating inspiratory muscle training alongside standard pulmonary rehabilitation to improve the sustainability of the training benefits. (B)

Surgery

- In bronchiectasis, surgical intervention can be effective in reducing exacerbations and managing hemoptysis. (3)
- The characteristics of the ideal candidate(s) for surgery, the appropriate timing for the procedure, and the surgical approach to be employed are not well-established. (3)
- Using video-assisted thoracoscopic techniques can yield outcomes that are at least as favorable as traditional open surgery. (3)
- Surgical treatment for bilateral bronchiectasis can lead to improvements in bronchiectasis symptoms. (3)
- Contemplate the option of lung resection for patients with localized disease if their symptoms persist despite medical treatment that has been optimized by a bronchiectasis specialist. (D)
- Provide a multidisciplinary evaluation, including a bronchiectasis specialist, a thoracic surgeon, and a skilled anesthetist, to assess the suitability for surgery and to conduct a pre-operative assessment of cardiopulmonary reserve after the resection. (D)
- Consider nutritional support and pre-operative pulmonary rehabilitation before surgical referral.

Lung transplantation for bronchiectasis

- According to international guidelines on lung transplantation, it is generally recommended that individuals aged 65 years or younger be considered for the procedure, as post-transplant health issues and mortality rates tend to rise with age. (3)
- In specific cases involving patients with bronchiectasis, lung transplantation can enhance their quality of life and is linked to a post-transplant survival rate exceeding 60% at the five-year mark. (3)
- Patients with bronchiectasis face challenging outcomes while on lung transplant waiting lists, with mortality rates reaching up to 60% within two years. (3)
- Most lung transplant procedures conducted for bronchiectasis involve bilateral lung transplants and are typically reserved for individuals with

severely impaired quality of life or those experiencing rapid health deterioration. (3)

- Evaluate the possibility of referring bronchiectasis patients for transplantation if they are 65 years of age or younger, have an FEV1 of less than 30%, and exhibit significant clinical instability. Alternatively, consider referral in cases of rapid and progressive respiratory decline, even when optimal medical management is in place. (D)
- In bronchiectasis patients with compromised lung function, consider an earlier transplant referral when they present additional factors such as severe hemoptysis, significant secondary pulmonary hypertension, multiple ICU admissions, or respiratory failure, particularly if non-invasive ventilation (NIV) is required. (D)

Influenza and pneumococcal vaccination

- The potential advantages of influenza vaccination in lessening exacerbations and influenza infections are gleaned from studies involving individuals with COPD, some of whom may also have bronchiectasis. In cases where direct evidence is lacking, the decision to administer influenza vaccination can be justified based on individual patient considerations, such as the presence of COPD, immune deficiency, residing in nursing homes, patient preferences, and expert opinions, while adhering to national guidelines. (4)
- The combination of a 23-valent polysaccharide pneumococcal vaccination with influenza immunization may contribute to a reduction in bronchiectasis exacerbations. (1-)
- A meta-analysis of randomized controlled trials (RCTs) supports the use of the 23-valent pneumococcal vaccine in reducing the incidence of all-cause pneumonia in both healthy adults and those with chronic illnesses, although there was significant statistical variation. (1+)
- Provide yearly influenza vaccination to all individuals diagnosed with bronchiectasis. (D)
- Make the polysaccharide pneumococcal vaccine available to all patients with bronchiectasis. (D)

Treatment of respiratory failure

- While there are no dedicated studies on the use of long-term oxygen therapy (LTOT) for respiratory failure in bronchiectasis, expert consensus, drawing on COPD data, suggests that this intervention is likely to be advantageous. (4)

- The use of non-invasive ventilation (NIV) could potentially result in a decrease in the number of days of hospitalization for patients with bronchiectasis and hypercapnic respiratory failure. However, the percentage of patients continuing NIV therapy at the two-year mark is relatively limited. (3)
- Evaluate the potential use of long-term oxygen therapy in individuals with bronchiectasis who experience respiratory failure, employing eligibility criteria similar to those applied for COPD. (D)
- Contemplate the use of home-based non-invasive ventilation with added humidification for bronchiectasis patients facing respiratory failure linked to hypercapnia, particularly in cases where this condition relates to noticeable symptoms or recurring hospital admissions. (D)

Bronchiectasis and other treatments: cough suppression, nutritional supplements, complementary therapy/ homeopathy, supplemental treatments

- The available evidence for alternative treatments, including complementary therapy and homeopathy, as well as supplemental treatments, is limited.
- It is not advisable to routinely endorse alternative treatments, such as cough suppression, nutritional supplementation, complementary therapy/homeopathy, or supplemental treatments, as part of the overall care for individuals with bronchiectasis. Further interventional trials and randomized controlled studies are necessary to determine the potential role of alternative therapies in bronchiectasis management. (D)
- Research studies focusing on the advantages of nutritional supplementation in patients with bronchiectasis should be conducted.

The impact of pathogens on prognosis in bronchiectasis

- Patients with chronic colonization of *Pseudomonas aeruginosa* should be regarded as having an elevated risk of experiencing complications related to bronchiectasis. (B)
- Conduct routine sputum microbiology screening for individuals with clinically substantial bronchiectasis to track the presence of pathogens and to identify any new instances of *Pseudomonas aeruginosa* isolation. (C)

The role of eradication of potentially pathogenic microorganisms in improving outcomes in patients with stable bronchiectasis

- For individuals with bronchiectasis who experience their initial *Pseudomonas aeruginosa* growth, a regimen consisting of two weeks of intravenous ceftazidime and tobramycin, followed by three months of nebulized

tobramycin (marketed as Tobi), leads to a longer median duration until *Pseudomonas aeruginosa* recurrence, a decrease in exacerbation frequency, and fewer hospital admissions and reduced days of hospital stay, as compared to a treatment course involving two weeks of intravenous antibiotics followed by three months of nebulized 0.9% saline. (1-)

- Provide individuals with bronchiectasis who exhibit clinical deterioration and experience a new emergence of *Pseudomonas aeruginosa* (either as a first occurrence or regrowth, considering previous intermittently positive cultures) with eradication antibiotic treatment. The initial treatment option involves ciprofloxacin at a dosage of 500-750mg twice daily for a two-week duration. If needed, a secondary treatment choice entails intravenous anti-pseudomonal beta-lactam along with or without an intravenous aminoglycoside for two weeks, followed by a three-month regimen of nebulized colistin, gentamicin, or tobramycin. (D)
- Engage in a dialogue with patients to explore the potential advantages and disadvantages of initiating eradication antibiotic treatment versus merely observing the situation clinically upon the detection of a new growth of *Pseudomonas aeruginosa*, especially in the context of stable bronchiectasis. This conversation should encompass considerations regarding the likelihood of achieving lasting eradication, the risk of developing chronic infection, and the potential for adverse events linked to each management approach. (D)
- For patients with bronchiectasis accompanied by clinical decline and the identification of a new occurrence or regrowth of methicillin-resistant S. aureus (MRSA) in the context of previous intermittently positive cultures, make efforts to eradicate MRSA. This is especially pertinent in view of infection control concerns. (D)

Acute Exacerbations

✓ **Antibiotics**

- Antibiotics are employed to address exacerbations characterized by a sudden decline in health, typically occurring over several days.
- These exacerbations are marked by deteriorating local symptoms, including increased cough, changes in sputum characteristics such as volume and thickness, heightened sputum purulence, and, in some cases, increased wheezing, breathlessness, and hemoptysis.
- Systemic symptoms like feeling unwell may also be present.
- Randomized, placebo-controlled studies assessing the effectiveness of antibiotics in adult exacerbations are lacking.

- There is a lack of adequate evidence to assess the effectiveness of antibiotics in adult bronchiectasis exacerbations. (2-)
- Consider the implementation of a patient self-management plan.
- Exacerbations should be promptly treated, and appropriate patients may have antibiotics readily available at home.
- Past sputum bacteriology results can be valuable in selecting the appropriate antibiotic. Table 9 outlines the primary and alternative treatments for the typical bacterial pathogens associated with bronchiectasis exacerbations.

Table 9. Common Organisms Associated with Acute Exacerbation of Bronchiectasis and Suggested Antimicrobial Agents in Adults (Adapted from the 2019 British Thoracic Society Guideline)

Organism	Recommended first-line treatment	Length of treatment	Recommended second-line treatment	Length of treatment
Streptococcus pneumoniae	Amoxicillin 500mg three times a day	14 days	Doxycycline 100mg BD	14 days
Haemophilus influenzae- beta lactamase negative	Amoxicillin 500mg three times a day Or Amoxicillin 1G three times a day Or Amoxicillin 3G BD	14 days	Doxycycline 100mg BD Or Ciprofloxacin 500mg or 750mg BD Or Ceftriaxone 2G OD (IV)	14 days
Haemophilus influenzae- beta lactamase positive	Amoxicillin with clavulanic acid 625 one tablet three times a day	14 days	Doxycycline 100mg bd Or Ciprofloxacin 500mg or 750mg BD Or Ceftriaxone 2G OD (IV)	14 days
Moraxella catarrhalis	Amoxicillin with clavulanic acid 625 one tablet three times a day	14 days	Clarithromycin 500mg BD Or Doxycycline 100mg BD Or Ciprofloxacin 500mg or 750mg BD	14 days
Staphylococcus aureus (MSSA)	Flucloxacillin 500mg four times a day	14 days	Clarithromycin 500mg BD Or Doxycycline 100mg BD Or Amoxicillin with clavulanic acid 625 one tablet three times a day	14 days
Staphylococcus aureus (MRSA)	Doxycycline 100mg BD Rifampicin (50Kg)	14 days	Third line Linezolid 600mg BD	14 days

Oral preparations	600mg OD Trimethoprim 200mg BD			
Staphylococcus aureus (MRSA) Intravenous preparations	Vancomycin 1 gm BD* (monitor serum levels and adjust dose accordingly) or Teicoplanin 400mg OD	14 days	Linezolid 600mg BD	14 days
Coliforms for example, Klebsiella, enterobacter	Oral Ciprofloxacin 500mg or 750mg BD	14 days	Intravenous Ceftriaxone 2G OD	14 days
Pseudomonas aeruginosa	Oral Ciprofloxacin 500mg bd (750mg bd in more severe infections)	14 days	Monotherapy: Intravenous Ceftazidime 2G TDS or Piperacillin with tazobactam 4.5G TDS or Aztreonam 2G TDS or Meropenem 2G TDS Combination therapy. The above can be combined with gentamicin or tobramycin or Colistin 2MU TDS (under 60 kg, 50 000–75 000 Units/kg daily in 3 divided doses) Patients can have an in vivo response despite in vitro resistance. Caution with aminoglycosides as highlighted below but also if previous adverse events, particularly previous ototoxicity/acute kidney injury due to aminoglycosides	14 days

OD once daily; BD, twice daily; IV intravenous. Caution with aminoglycosides in pregnancy, renal failure, elderly or on multiple other drugs. *Elderly (over 65 years), 500mg Vancomycin every 12 hours or 1 g once daily.

- Whenever feasible, obtain sputum samples, either spontaneously or through induced methods, for culture and sensitivity testing before initiating antibiotic treatment.
- While waiting for sputum microbiology results, empirical antibiotics can be initiated.
- Once a pathogen is identified, antibiotic adjustments can be made if there is no clinical improvement, with treatment decisions guided by antibiotic sensitivity test results.
- As a rule, standard antibiotic courses lasting 14 days are recommended and should be consistently employed for patients with *Pseudomonas aeruginosa* infections. For individuals with mild bronchiectasis, shorter courses may be adequate.
- When patients are in a severe state of illness, have infections caused by drug-resistant organisms, or do not show improvement with oral therapy (which is more common in cases involving *Pseudomonas aeruginosa*), intravenous antibiotics should be considered.

1.2.2 European Respiratory Society Guidelines for the Management of Adult Bronchiectasis (2017)

The European Respiratory Society (ERS) guidelines published in 2017 address the investigation of underlying causes of bronchiectasis, treatment of exacerbations, pathogen eradication, long term antibiotic treatment, anti-inflammatories, mucoactive drugs, bronchodilators, surgical treatment, and respiratory physiotherapy[7]. The main recommendations are summarized below.

Table 10. ERS Strength of Recommendations

Target group	Strong recommendations#	Conditional (weak) recommendations
Patients	All or almost all informed people would choose the recommended choice for or against an intervention.	Most informed people would choose the recommended course of action, but a substantial number would not.

Clinicians	Most patients should receive the recommended course of action.	Recognize that different choices will be appropriate for different patients. Clinicians and other healthcare providers need to devote more time to the process of shared decision making by which they ensure that the informed choice reflects individual values and preferences; decision aids and shared decision making are particularly useful.
Policy makers	The recommendation can be adopted as a policy in most situations.	Policy making will require substantial debate and involvement of many stakeholders.

#: strong recommendations based on high quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions; no recommendation can take into account all of the unique features of individual patients and clinical circumstances.

Table 11. ERS Levels of Evidence

Rank	Explanation	Examples
High	Further research is very unlikely to change our confidence in the estimate of effect	Randomized trials without serious limitations Well-performed observational studies with very large effects (or other qualifying factors)
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	Randomized trials with serious limitations Well-performed observational studies yielding large effects
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	Randomized trials with very serious limitations Observational studies without special strengths or important limitations

Very low	Any estimate of effect is very uncertain	Randomized trials with very serious limitations and inconsistent results Observational studies with serious limitations Unsystematic clinical observations (e.g., case series or case reports

Systemic antibiotic therapy for treating adult bronchiectasis patients with an acute exacerbation

- We recommend a 14-day course of antibiotics for the treatment of acute bronchiectasis exacerbations (Conditional recommendation, very low quality of evidence).
- Shorter antibiotic courses could be considered in certain situations. The panel of experts proposes that milder exacerbations, those in patients with mild bronchiectasis, episodes involving pathogens highly susceptible to antibiotics (e.g., Streptococcus pneumoniae), or instances where patients swiftly return to their baseline condition may potentially benefit from shorter treatment durations. However, it's important to note that there is limited evidence supporting the efficacy of shorter courses in these scenarios.
- In cases where patients do not show signs of improvement after a 14-day antibiotic course, we recommend reassessing the patient's clinical status and conducting a fresh microbiological analysis.
- Collecting a sputum sample at the onset of an exacerbation can be beneficial in guiding antibiotic selection if the initial treatment does not yield the desired response.
- Further research studies assessing the optimal duration of antibiotics are recommended.

Eradication treatment

- Eradication treatment encompasses any antibiotic therapy administered with the specific goal of eliminating the pathogen from the airways.
- It is recommended to consider the provision of eradication antibiotic treatment to adults with bronchiectasis who have recently isolated *Pseudomonas aeruginosa* (conditional recommendation, very low quality of evidence).
- It is recommended against providing eradication antibiotic treatment to adults with bronchiectasis when newly isolated pathogens other than

Pseudomonas aeruginosa are involved (conditional recommendation, very low quality of evidence).

- In the context of bronchiectasis, there is variability in eradication treatment regimens. However, there is some evidence suggesting that treatment regimens involving nebulized antibiotics result in higher rates of pathogen clearance and clinical benefits compared to intravenous treatment alone, particularly in the context of achieving *Pseudomonas aeruginosa* clearance.
- There is no clear evidence to support one regimen over another; figure 2 illustrates some commonly used regimes.

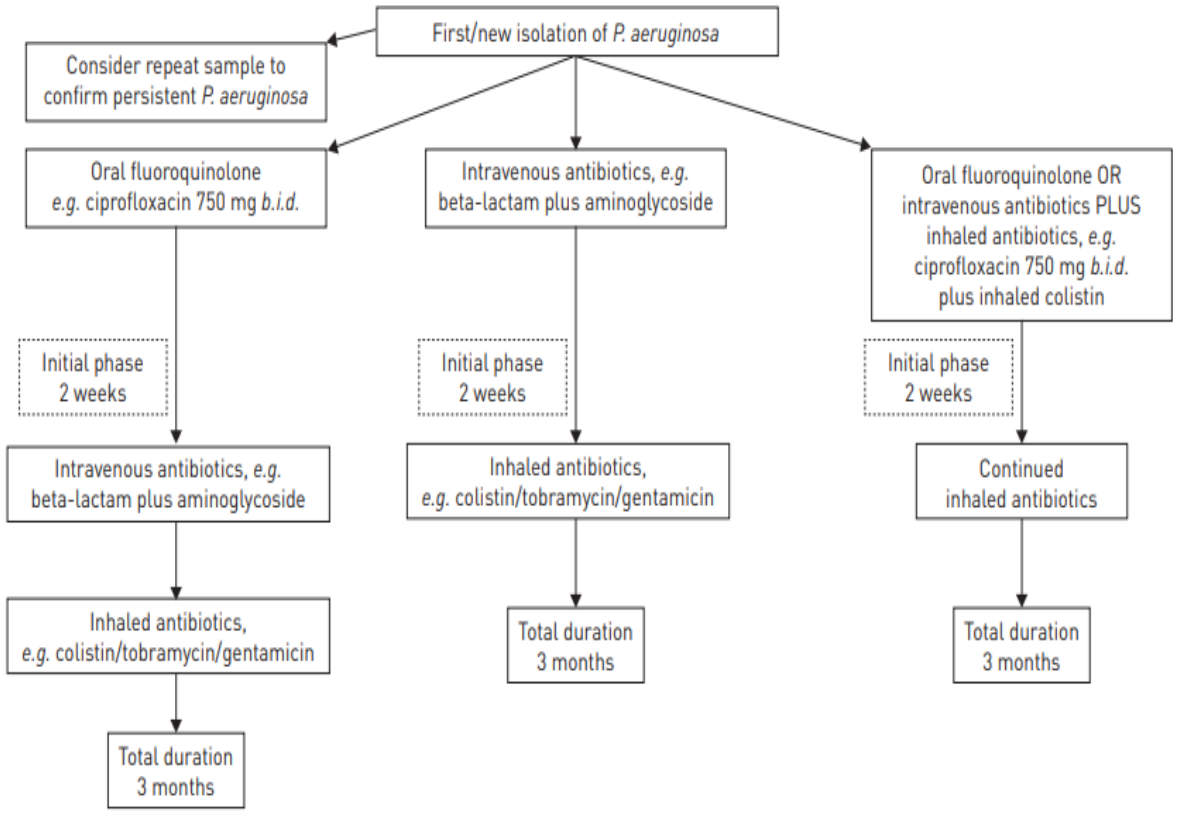


Figure 2. *Three possible and alternative eradication treatment pathways based on what is commonly used in clinical practice (Retrieved from The European Respiratory Society 2017 guidelines)*

- We recommend, at a minimum, that patients have an annual sputum sample collected when they are in a clinically stable condition.
- In cases where it is unclear when *Pseudomonas aeruginosa* was acquired, a clinical assessment should be conducted to determine the likely success or failure of an eradication attempt.

Long-term anti-inflammatory agents

- Providing inhaled corticosteroid treatment is not recommended to adults with bronchiectasis (conditional recommendation, low quality of evidence).
- The use of statins for treating bronchiectasis is not recommended (strong recommendation, low quality of evidence).
- We suggest that the diagnosis of bronchiectasis should not influence the utilization of inhaled corticosteroids in patients with concurrent asthma or COPD (best practice advice, indirect evidence).

Long-term antibiotic treatment (≥ 3 months)

- We recommend considering long-term antibiotic treatment for adults with bronchiectasis who experience three or more exacerbations per year (conditional recommendation, moderate quality of evidence).
- All subsequent recommendations pertain to patients with three or more exacerbations per year.
- We recommend long-term treatment with an inhaled antibiotic for adults with bronchiectasis and chronic *Pseudomonas aeruginosa* infection (conditional recommendation, moderate quality of evidence).
- We recommend long-term treatment with macrolides (azithromycin, erythromycin) for adults with bronchiectasis and chronic *Pseudomonas aeruginosa* infection when inhaled antibiotics are contraindicated, not well-tolerated, or impractical (conditional recommendation, low quality of evidence).
- We recommend long-term treatment with macrolides (azithromycin, erythromycin) either in addition to or as a substitute for inhaled antibiotics for adults with bronchiectasis and chronic *Pseudomonas aeruginosa* infection who experience frequent exacerbations despite inhaled antibiotic therapy (conditional recommendation, low quality of evidence).
- We recommend long-term treatment with macrolides (azithromycin, erythromycin) for adults with bronchiectasis who are not infected with *Pseudomonas aeruginosa* (conditional recommendation, moderate quality of evidence).
- We recommend long-term treatment with an oral antibiotic (choice based on antibiotic susceptibility and patient tolerance) for adults with bronchiectasis who are not infected with *Pseudomonas aeruginosa* when macrolides are contraindicated, not tolerated, or ineffective (conditional recommendation, low quality of evidence).

- We recommend long-term treatment with an inhaled antibiotic for adults with bronchiectasis who are not infected with *Pseudomonas aeruginosa* when oral antibiotic prophylaxis is contraindicated, not tolerated, or ineffective (conditional recommendation, low quality of evidence).

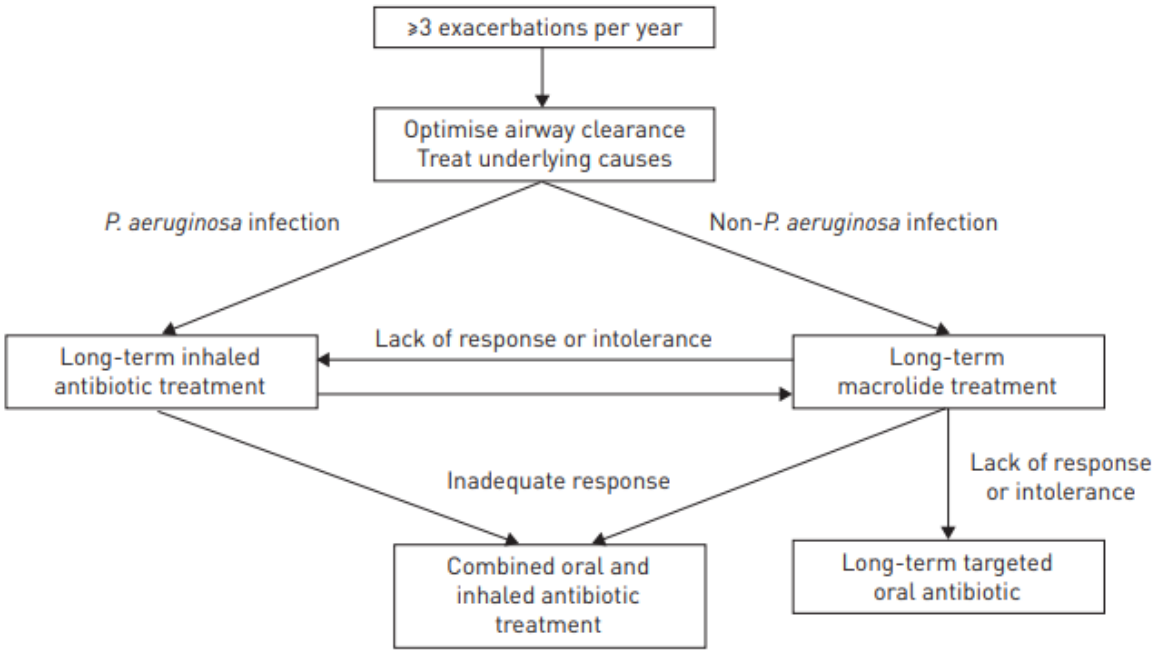


Figure 3. *Summary of recommendations for long-term antibiotic treatment (Retrieved from The European Respiratory Society 2017 guidelines)*

Long-term mucoactive treatment (≥ 3 months)

- Consider providing long-term mucoactive treatment (lasting at least three months) to adult bronchiectasis patients who struggle with sputum clearance and experience a reduced quality of life, particularly when standard airway clearance techniques have proven ineffective (weak recommendation, low quality of evidence).
- We strongly advise against offering recombinant human DNase to adult bronchiectasis patients (strong recommendation, moderate quality of evidence).

Long-term bronchodilator treatment (≥ 3 months)

- We do not recommend routinely providing long-acting bronchodilators for adult bronchiectasis patients (conditional recommendation, very low quality of evidence).

- Consider offering long-acting bronchodilators to patients with significant breathlessness on an individual basis (weak recommendation, very low quality of evidence).
- It is advisable to administer bronchodilators before physiotherapy, inhaled mucoactive drugs, and inhaled antibiotics to enhance tolerability and optimize the delivery of medication to affected lung areas (good practice advice, supported by indirect evidence).
- The presence of a bronchiectasis diagnosis should not influence the use of long-acting bronchodilators in patients with concurrent asthma or COPD (good practice advice, supported by indirect evidence).
- When multiple inhaled therapies are used in the same patient, the sequence of treatments illustrated in figure 7 is commonly employed by members of the task force.

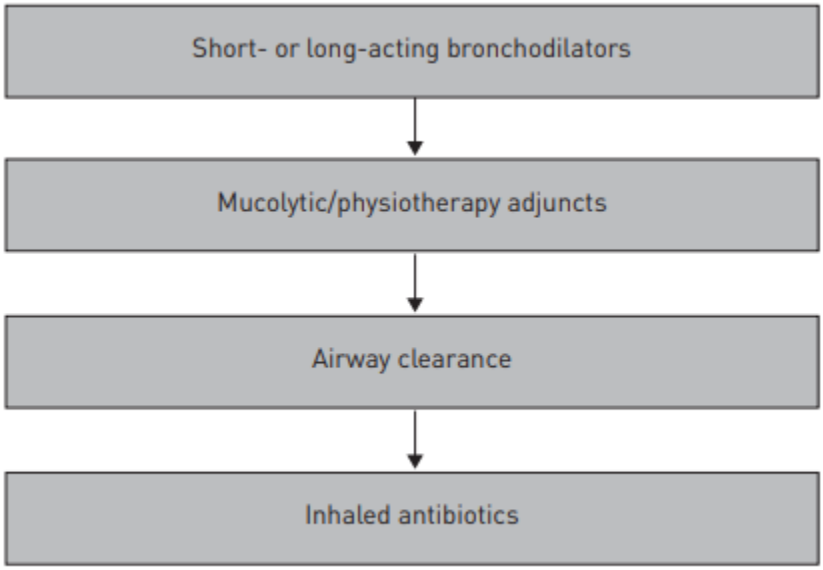


Figure 4. *Flowchart of multiple sequential airways treatment administration in adult patients with bronchiectasis (Retrieved from The European Respiratory Society 2017 guidelines)*

Surgical interventions

- We recommend against providing surgical interventions for adult bronchiectasis patients, except in cases involving patients with localized disease who experience frequent exacerbations despite optimizing all other aspects of their bronchiectasis management (weak recommendation, very low quality of evidence).

Regular physiotherapy (airway clearance and/or pulmonary rehabilitation)

- Consider instructing patients with persistent productive cough or sputum clearance difficulties to learn an airway clearance technique (ACT) from a qualified respiratory physiotherapist and perform it once or twice daily (weak recommendation, low quality of evidence).
- We strongly recommend that adult bronchiectasis patients with reduced exercise capacity should engage in a pulmonary rehabilitation program and engage in regular physical activity. All interventions should be customized to the patient's symptoms, physical abilities, and disease-specific characteristics (strong recommendation, high quality of evidence).

1.2.3 European Respiratory Society Guidelines for the Management of Children and Adolescents with Bronchiectasis (2021)

There is increasing awareness of bronchiectasis in children and adolescents, a chronic pulmonary disorder associated with poor quality of life for the child/adolescent and their parents, recurrent exacerbations, and costs to the family and health systems. Optimal treatment improves clinical outcomes. The European Respiratory Society (ERS) Task Force for the management of pediatric bronchiectasis sought to identify evidence-based management (investigation and treatment) strategies. This guideline addresses the definition, diagnostic approach and antibiotic treatment of exacerbations, pathogen eradication, long-term antibiotic therapy, asthma-type therapies (inhaled corticosteroids and bronchodilators), mucoactive drugs, airway clearance, investigation of underlying causes of bronchiectasis, disease monitoring, factors to consider before surgical treatment, and the reversibility and prevention of bronchiectasis in children/adolescents[6].

Strengths of recommendations and levels of evidence are similar to those outlined in tables 10 and 11 above.

Diagnosis

- When diagnosing bronchiectasis in **children or adolescents** suspected of having the condition, it is recommended to employ high-resolution MDCT scans with HRCT rather than conventional HRCT (conditional recommendation, very low quality of evidence).
- For children and adolescents suspected of bronchiectasis, consider using a pediatric-derived BAR (Barometric Airway Ratio), with an abnormality defined as a BAR ratio greater than 0.8, instead of using the adult threshold of greater than 1–1.5 (Conditional recommendation, very low quality of evidence stemming from the narrative review).

- For children and adolescents suspected or diagnosed with bronchiectasis, it is advisable to conduct a minimum set of tests, in line with the current practice of most experts in the field. This minimum panel of tests should encompass the following:
    1. chest CT scan (for bronchiectasis diagnosis)
    2. sweat test
    3. lung function tests (for those who can undergo spirometry)
    4. complete blood count
    5. immunological assessments (total IgG, IgA, IgM, IgE, and specific antibodies to vaccine antigens), and
    6. bacteriological analysis of lower airway samples (conditional recommendation, very low-quality evidence based on narrative review).
- In specific cases involving children and adolescents with bronchiectasis, consider the inclusion of additional tests based on their clinical presentation. These may encompass more extensive immunological evaluations (in collaboration with a pediatric immunologist), diagnostic bronchoscopy with bronchoalveolar lavage analysis for microbiology, and assessments for airway aspiration, primary ciliary dyskinesia, and gastroesophageal reflux disease (Conditional recommendation, low quality of evidence stemming from the narrative review)

Definition of exacerbation

- In children and adolescents with bronchiectasis, it is recommended to define a respiratory exacerbation when a child/adolescent experience heightened respiratory symptoms, mainly marked by an increased cough, with or without increased sputum quantity and/or purulence, lasting for three or more days (conditional recommendation, low quality of evidence stemming from the narrative review).
- For children and adolescents with bronchiectasis, consider the presence of dyspnea (increased work of breathing) and/or hypoxia as indicative of a severe exacerbation, regardless of its duration Strong recommendation, low quality of evidence stemming from the narrative review)

Management

1- Airway clearance

- Children and adolescents with bronchiectasis should be instructed in and regularly practice airway clearance techniques or maneuvers (strong recommendation, low quality of evidence).

2- Mucoactive agents

- Routine use of recombinant human DNase (rhDNase) is not recommended for children and adolescents with bronchiectasis (strong recommendation, very low quality of evidence).
- Routine use of bromhexine is not advised for children and adolescents with bronchiectasis (conditional recommendation, very low quality of evidence).
- Routine use of inhaled mannitol or hypertonic saline is not suggested for children and adolescents with bronchiectasis. (Conditional recommendation, very low quality of evidence).
- In selected patients, such as those experiencing high daily symptoms, frequent exacerbations, difficulty in sputum clearance, and/or poor quality of life, it may be worth considering the use of inhaled mannitol or 6–7% hypertonic saline.
- If well-tolerated, these interventions could potentially enhance quality of life and facilitate sputum clearance.
- For hypertonic saline and mannitol, it is advisable for children to be of an age where they can comfortably tolerate these treatments, and it is recommended to administer short-acting β2-agonists prior to inhaling either hypertonic saline or mannitol.
- The initial dose of hypertonic saline or mannitol should be administered under the supervision of a healthcare professional.
- It is important to bear in mind that mannitol is considerably more expensive than hypertonic saline.

3- Use of antibiotics in acute exacerbations

- For children and adolescents experiencing an acute respiratory exacerbation in the context of bronchiectasis, we recommend employing an adequate antibiotic via systemic administration for a duration of 14 days. (Strong recommendation, moderate quality of evidence)
- The preferred empirical antibiotic is amoxicillin-clavulanate, although the selection of antibiotics should be guided by the patient's airway culture results, with different treatment regimens for those with *Pseudomonas*

aeruginosa as opposed to those without and considering the patient's history of antibiotic hypersensitivity reactions.

- In cases of severe exacerbation, such as when the child or adolescent is experiencing hypoxia, or if the initial response to oral antibiotics is inadequate, intravenous antibiotics will be required.
- The evidence summary indicates that there is a single, high-quality randomized controlled trial (RCT) supporting the use of antibiotics to treat exacerbations.
- In this trial, it was found that amoxicillin-clavulanate was more effective than a placebo in resolving symptoms after a 14-day treatment. While azithromycin did show some improvement, it did not reach statistical significance in terms of being superior to a placebo.
- Additionally, amoxicillin-clavulanate significantly reduced the duration of exacerbations, whereas this duration was similar between azithromycin and the placebo among those whose symptoms resolved by day 14.

4- Long-term (≥ 2 months) antibiotics

- For children and adolescents with bronchiectasis and recurrent exacerbations, it is recommended to consider long-term macrolide antibiotic treatment as a measure to reduce the frequency of exacerbations (Strong recommendation, low quality of evidence).
- Based on the collective experience of the panel, it is recommended to consider long-term macrolide antibiotics only for individuals who have a history of either more than one hospital admission or three or more non-hospitalized exacerbations in the preceding 12 months.
- The duration of such treatment should be a minimum of 6 months, with periodic assessments to ascertain whether the antibiotic continues to yield clinical benefits. In the case of children and adolescents undergoing extended treatment courses (exceeding 24 months), ongoing evaluation of the risk-benefit ratio is essential.
- It is important to note that this recommendation is made within the context of limited available data regarding the optimal timing for initiating long-term azithromycin treatment, and it underscores the need for caution due to the growing issue of antibiotic resistance among bacterial pathogens both in patients and the wider community.

5- Eradication treatment

- In children and adolescents with bronchiectasis, it is advised to consider eradication therapy when *Pseudomonas aeruginosa* is initially detected or upon new detection of the pathogen (Conditional recommendation for the intervention, very low quality of evidence).
- Despite the limited evidence, we suggest that the initiation of eradication therapy should occur promptly upon confirmation of the presence of *Pseudomonas aeruginosa* (figure 5).

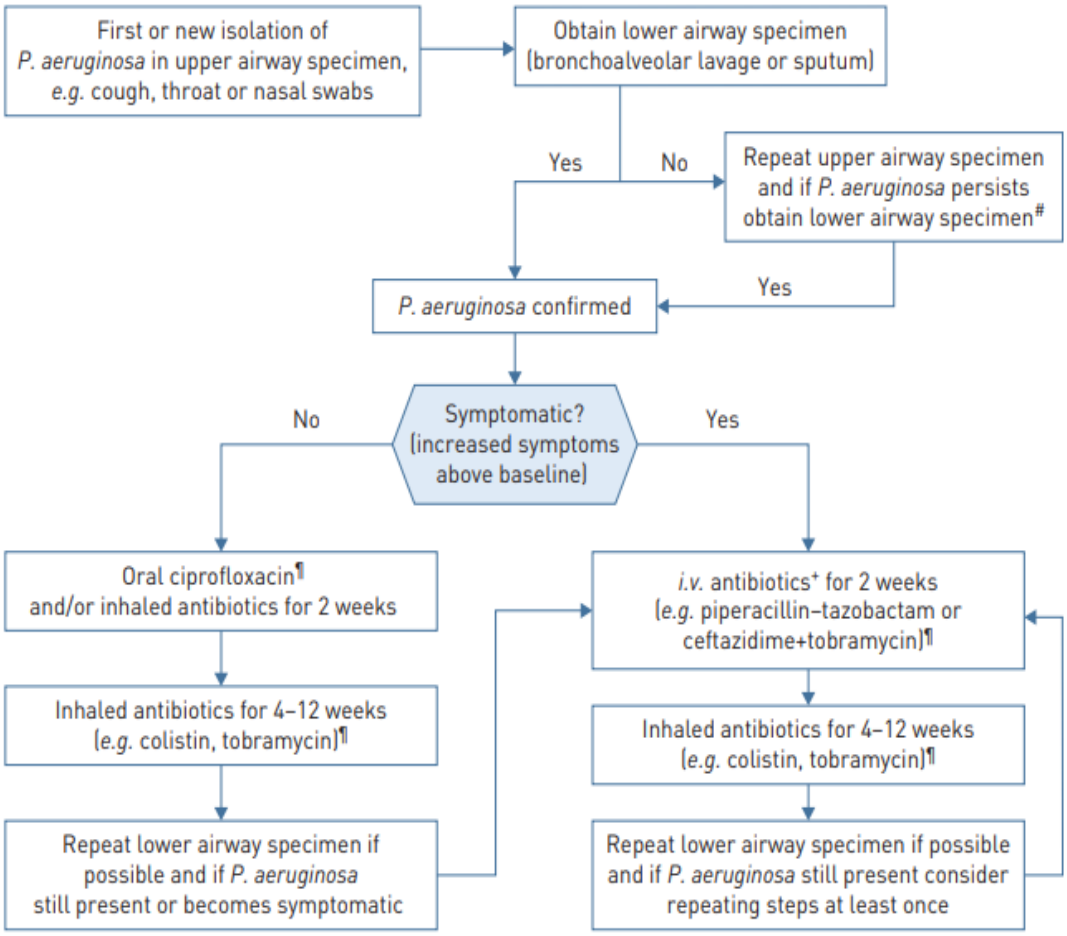


Figure 5. *Suggested management approach used by the panel when Pseudomonas aeruginosa is first or newly isolated in a child with bronchiectasis (Retrieved from the European Respiratory Society 2021 guidelines)*

- However, it is important to acknowledge that there is insufficient evidence to make a recommendation regarding eradication treatment for pathogens other than *Pseudomonas aeruginosa*. This decision should be made on a case-by-case basis, considering the child's clinical condition and the type of pathogen involved.

6- Inhaled corticosteroids (ICS), short-acting β2-agonists (SABA), long-acting β2-agonists (LABA)

- In the case of children and adolescents diagnosed with bronchiectasis, we advise against the routine use of inhaled corticosteroids (ICS) with or without long-acting beta-agonists (LABA) in both the short-term and long-term, regardless of their condition being stable or experiencing exacerbations (Conditional recommendation, very low quality of evidence).
- It is worth noting that ICS could be potentially helpful for those individuals who have eosinophilic airway inflammation.
- However, since there is a lack of studies examining the use of short-acting beta-agonists (SABA) in bronchiectasis, we are unable to provide a specific recommendation for their use. We recommend a thorough assessment be conducted if asthma-type medications like SABA are being considered. In some cases, SABA may offer benefits as a pre-treatment before airway clearance procedures.

7- Surgery

- In the case of children and adolescents with bronchiectasis, we strongly recommend that several factors should be carefully considered when contemplating surgery. These factors include the patient's age, the severity of their symptoms and disease burden, the specific location of bronchiectatic areas as revealed by chest CT scans, the underlying cause of the condition (which can influence the likelihood of disease recurrence), the surgical facility's expertise and the availability of pre- and post-surgical care, as well as the overall health and clinical condition of the child (Strong recommendation, very low quality of evidence stemming from the narrative review).
- It is important to note that the benefits of surgery are more significant for individuals with localized disease that can be completely removed, and especially when the disease is not expected to recur (no underlying cause, such as immunodeficiency).

8- Other pediatric systematic care issues (nutrition, aerobic and non-aerobic exercise, psychological support, equipment care, vaccinations, etc.)

- In the case of children and adolescents with bronchiectasis, we propose the optimization of their nutrition, which should include the assessment and improvement of their vitamin D status (Conditional recommendation, very low quality of evidence stemming from the narrative review). It is worth noting that there is insufficient evidence to support the recommendation of additional nutritional supplements.

- Furthermore, we recommend that children and adolescents with bronchiectasis should engage in ongoing exercise, as short periods of exercise training are unlikely to yield long-term benefits (Conditional recommendation, very low quality of evidence stemming from the narrative review). However, there is currently insufficient evidence to make a recommendation regarding the establishment of formal exercise and rehabilitation programs for this group.
- Additionally, we suggest that children and adolescents with bronchiectasis should follow their national immunization programs, including the administration of pneumococcal and annual seasonal influenza vaccines if they are not already included in the program (Conditional recommendation, very low quality of evidence stemming from the narrative review).
- It is recommended that children and adolescents with bronchiectasis receive psychological support and education regarding the proper use and care of equipment (Conditional recommendation, very low quality of evidence stemming from the narrative review).

Prevention of cross-infection

- For children and adolescents diagnosed with bronchiectasis, it is advisable to provide counseling to both the affected individuals and their families regarding proper coughing techniques and hand hygiene. Additionally, whenever feasible, they should steer clear of individuals displaying symptoms of viral respiratory infections. For children and adolescents under the care of a cystic fibrosis (CF) clinic, it is imperative to adhere to the clinic's infection control policies (Conditional recommendation, very low quality of evidence stemming from the narrative review).

Monitoring

- For children and adolescents with bronchiectasis, it is recommended that they undergo regular evaluations in outpatient clinics every 3 to 6 months. These check-ups are important for monitoring their overall health, assessing their respiratory condition, which may include lung function assessments when appropriate for their age, and identifying any potential complications (Conditional recommendation, very low quality of evidence stemming from the narrative review).
- For children and adolescents who can expel sputum, it is recommended that regular, scheduled sputum samples be obtained every 6 to 12 months. This practice is aimed at detecting new pathogens, particularly *Pseudomonas aeruginosa*, and assisting in determining the appropriate initial antibiotic treatment for any potential future exacerbations (Conditional

recommendation, very low quality of evidence stemming from the narrative review).

1.2.4 Review Article: Exacerbation of Bronchiectasis (*Bronchiectasis*, 2018)

This review article published by Polverino et al in *Bronchiectasis* in 2016 provides a concise overview on the treatment of acute exacerbations of bronchiectasis[9]. The main findings are summarized below:

Treatment of exacerbations

- Since most exacerbations are generally attributed to bacterial infections, current guidelines advocate antibiotic therapy.
- The selection of the appropriate antibiotic is contingent on several factors, including prior airway infections, allergies, intolerances, individual preferences, concurrent medical conditions (such as renal or hepatic failure), and any ongoing medications. Furthermore, when available, microbiological data also play a role in the decision.
- Currently, systemic antibiotics are the recommended treatment for exacerbations, as inhaled antibiotics may have potential side effects or limited tolerability in these conditions, which can include symptoms like bronchospasm, wheezing, and coughing.
- The choice between oral or intravenous administration varies according to the severity of the exacerbation, the availability of the drug, pharmacokinetics, and the patient's specific characteristics.
- For H. influenzae infections, the typical recommendations include the use of amoxicillin-clavulanic acid, doxycycline, or a fluoroquinolone like levofloxacin or ciprofloxacin.
- In the case of *P. aeruginosa*, regrettably, ciprofloxacin is the only effective oral antibiotic, generally administered at a dosage of 750 mg twice a day (BID). Alternatively, depending on antibiogram data, intravenous options such as ceftazidime, carbapenem, piperacillin-tazobactam, or cefepime should be considered.
- Although there is a lack of scientific evidence regarding the use of combination antibiotic therapy in bronchiectasis, it could be considered in situations involving severe exacerbations or when dealing with mucoid or multidrug-resistant strains of *P. aeruginosa*. Specifically, a combination therapy involving tobramycin, colistin, gentamycin, or amikacin should be contemplated.

- If there is suspicion of treatment failure (clinical deterioration despite antibiotic therapy or inadequate improvement at the end of the antibiotic course), a new microbiological evaluation should be conducted.
- Additionally, investigations into other non-infectious factors contributing to clinical deterioration, such as pulmonary embolism or heart failure, should also be considered.

Table 12. Recommended Antibiotic Treatment According to the Most Common Microbiology Isolates in Exacerbations of Bronchiectasis (Adapted from Poverino et al., 2018)

Microorganism	Chosen treatment	Alternative
Mild outpatient exacerbation		
Hemophilus influenzae	Amoxicillin/clavulanic acid 875/125 mg c/8 h oral or doxycycline 100 mg/12–24 h	Amoxicillin 1–2 g c/8 h oral ciprofloxacin 750 mg c/12 h oral
Pseudomonas aeruginosa	Ciprofloxacin 750 mg c/12 h oral	Levofloxacin 500 mg c/12 h oral
Staphylococcus aureus	Cloxacillin 500–1000 mg c/6 h oral	Amoxicillin/clavulanic acid 875/125 mg c/8 h oral + or levofloxacin 500 mg c/12 h oral
Moderate-to-severe exacerbation		
Hemophilus influenzae	Amoxicillin/clavulanic acid 1–2 g c/8 h IV	Ceftriaxone 2 g c/24 h IV
Pseudomonas aeruginosa	Ceftazidime 2 g c/8 h IV + amikacin 15–20 mg/kg c/24 h IV, or tobramycin 5–10 mg/kg c/24 h IV	Imipenem 1 g c/8 h IV, or meropenem 2 g c/8 h IV, or piperacillin/ tazobactam 4 g c/8 h IV, or cefepime 2 g c/8 h IV, or aztreonam 2 g c/8 h IV, or ciprofloxacin 400 mg c/12 h IV + amikacin 15–20 mg/kg c/24 h IV
Staphylococcus aureus	Vancomycin 1 g c/12 h IV	Linezolid 600 mg c/12 h, or sodium colistimethate 1–2 mU c/12 h IV

- If a patient presents with a high fever, a C-reactive protein level exceeding 5 mg/dl, and atypical findings during a chest examination, it's essential to investigate for pneumonia by performing a chest X-ray or CT scan. In such cases, it's important to consider the risk of S. pneumoniae, but it's also crucial to consider the microorganisms responsible for pre-existing chronic bronchial infections.
- Specific recommendations for corticosteroids or inhaled bronchodilators during bronchiectasis exacerbations are not available. Their use typically follows general indications for these medications.
- Regarding inhaled hyperosmolar agents like hypertonic saline or mannitol, there is scientific evidence supporting their use during exacerbations. However, it is worth noting that the risk of side effects, such as bronchospasm, may be elevated during exacerbations due to increased airway inflammation.

Prevention of Exacerbations

✓ **Antibiotics**

- The primary focus of long-term management for bronchiectasis aims to prevent exacerbations. Consequently, several recommendations are outlined in both Spanish and British guidelines.
- Notably, the utilization of chronic oral macrolides and inhaled antibiotics has received widespread endorsement from experts globally.
- Over time, numerous intriguing trials have provided mounting scientific support for these treatment approaches. Particularly noteworthy are three significant randomized clinical trials (BLESS, EMBRACE, and BAT) that have clearly demonstrated a reduction in exacerbations, whether measured in terms of the time until the first exacerbation or the frequency of exacerbations. This reduction was achieved through the ongoing use of azithromycin (with dosages ranging from 250 mg daily to 500 mg three times a week) or erythromycin (at a dosage of 400 mg twice daily).

Table 13. Prevention of Exacerbations (Adapted from Poverino et al., 2018)

Intervention	Drug	Target population	Note
Oral antibiotics	Azithromycin, erythromycin	> 3 exacerbations per year	Discard NTM infection, QTc prolongation
Inhaled antibiotics	Colistin, tobramycin,	> 3 exacerbations per year	Use bronchodilators before antibiotic administration A

	ciprofloxacin, gentamycin		supervised challenge test is recommended for first use
Hyperosmolar agents	Hypertonic saline (7%), mannitol	Abundant or difficult expectoration, poor quality of life, > 3 exacerbations per year	Use bronchodilators prior to antibiotic administration A supervised challenge test is recommended on first use
Respiratory physiotherapy	Airway clearance techniques, pulmonary rehabilitation	Abundant or difficult expectoration; poor quality of life; dyspnea and or fatigue	Personalized intervention according to patient characteristics, needs, preferences, and availability of physiotherapist, devices, etc.
Vaccines	Anti-influenza, pneumococcal (PPSV23 or PCV13)	All patients with bronchiectasis	If PPSV23 has been administered in the past, wait 1 year before administering PCV13

- It is important to reiterate that there have been notable adverse events associated with these treatments. In particular, diarrhea and an increase in the presence of macrolide-resistant microorganisms (like Streptococci) in the oropharyngeal mucosa are relatively common.
- Although less frequent, other potential treatment-related adverse effects, including QTc prolongation, tinnitus/hearing loss, and the selection of macrolide-resistant non-tuberculous mycobacteria (NTM), should be carefully taken into account when initiating long-term macrolide therapy.
- Specifically, it is recommended that individuals undergo 2 to 3 sputum cultures to confirm the absence of NTM before starting macrolides, as infections caused by macrolide-resistant strains of NTM tend to be more challenging to treat.

- On the other hand, various chronic regimens involving oral antibiotics, such as amoxicillin or tetracycline, have been observed to improve sputum purulence. However, they do not demonstrate such clear advantages in terms of reducing exacerbations as macrolides do.
- Many experts in the field of bronchiectasis believe that inhaled antibiotics offer the best potential for reducing exacerbations due to their ability to achieve high concentrations locally in the airways, minimal systemic side effects, and a lower likelihood of antibiotic resistance development. In recent years, numerous antibiotics have been developed for inhaled administration, including ciprofloxacin, aztreonam, colistin, and tobramycin in various forms such as dry powder and nebulized solutions. However, the level of evidence supporting their use in clinical practice remains controversial, as some unexpected results in clinical trials have not met primary outcome expectations.

✓ **Mucolytic and Hyperosmolar Agents**

- While hypertonic saline has been shown to enhance airway clearance, quality of life, and FEV1 in bronchiectasis when used in conjunction with respiratory physiotherapy, there is currently no supporting evidence for its ability to prevent exacerbations. Given the promising outcomes observed and the cost-effectiveness of this approach, it is imperative that further research is conducted to address this gap in knowledge.
- Alternative hyperosmolar agents, like mannitol, which are more expensive, did not demonstrate a significant reduction in the annual exacerbation frequency.
- Deoxyribonuclease (RhDNase) is currently not recommended for use in bronchiectasis. This is due to the results of the only randomized controlled trial (RCT) that revealed an increased exacerbation rate when this mucolytic agent, which is frequently employed in cystic fibrosis (CF) treatment, was used in conjunction with bronchiectasis.

✓ **Vaccines**

- There is a lack of specific data concerning the effectiveness of influenza and pneumococcal vaccines in individuals with bronchiectasis.
- However, it is important to note that the prevalence of bronchiectasis significantly rises among the elderly population, and as a general practice, it is advisable to administer vaccines for both influenza and pneumococcal infections to individuals aged over 65 years, especially those with chronic respiratory conditions.

- The 23-valent polysaccharide vaccine has been traditionally employed in bronchiectasis for assessing the immune response, specifically the production of antibodies.
- In contrast, the 13-valent conjugate vaccine has only been introduced in recent years. This introduction was prompted by its acknowledged superiority in terms of lowering the risk of pneumococcal pneumonia and extending the duration of protection through T-cell-mediated immunological memory.
- However, further targeted research is necessary in the future to refine strategies for preventing infections in this particular segment of the bronchiectasis population.

1.2.5 Review Article: Inhaled Corticosteroids for Bronchiectasis (*Cochrane Database of Systematic Reviews*, 2018)

This review article published in May 2018 by Kapur et al. in the Cochrane Database of Systemic Reviews aimed to evaluate the efficacy and safety of inhaled corticosteroids (ICS) in children and adults with stable bronchiectasis, specifically to assess whether ICS reduces the severity and frequency of acute exacerbations or affects long-term pulmonary function decline[10].

- The studies selected were all randomized controlled trials (RCTs) comparing ICS with a placebo or no medication. children and adults with clinical or radiographic evidence of bronchiectasis were include, but people with cystic fibrosis were excluded.
- In the short-term group (using ICS for six months or less) during stable periods, data from two included studies revealed no significant differences from baseline values in forced expiratory volume in the first second (FEV1) at the study conclusion (mean difference (MD) -0.09, 95% confidence interval (CI) -0.26 to 0.09) and forced vital capacity (FVC) (MD 0.01 L, 95% CI -0.16 to 0.17) among adults using ICS compared to those not using ICS.
- Similarly, no significant differences were observed in average exacerbation frequency (MD 0.09, 95% CI -0.61 to 0.79) or health-related quality of life (HRQoL) total scores in adults using ICS compared to those not using ICS, although the available data were limited.
- Regarding a single non-placebo-controlled study with extracted clinical data, there was a marginal, though statistically significant, improvement in sputum volume and dyspnea scores with ICS.

- The sole study focusing on long-term outcomes (over 6 months) that examined lung function and other clinical outcomes showed no significant effect of ICS on any of the outcomes.
- Conclusions on adverse effects could not be drawn due to limited available data.

In summary, the analysis determined insufficient evidence to support the regular utilization of inhaled corticosteroids (ICS) in adults experiencing stable bronchiectasis. No conclusions can be drawn regarding the use of ICS during bronchiectasis flare-ups or their application in children due to the absence of relevant studies.

1.2.6 Narrative Review: Inhaled Corticosteroids in Adults with Non-cystic Fibrosis Bronchiectasis: From Bench to Bedside (*Drugs*, 2022)

The objectives of this review were to examine the basic properties of ICSs, how they impact bronchiectasis in adults, the current position of international guidelines on this treatment, and the current indications and future challenges related to ICS use in bronchiectasis[8]. The main findings are summarized below:

- According to international guidelines, there is a consensus that inhaled corticosteroids (ICSs) are not routinely recommended for the treatment of bronchiectasis, as outlined in the information provided in this review. However, the guidelines acknowledge that the scientific evidence supporting this recommendation is limited.
- However, various guidelines make exceptions, suggesting instances where the prescription of inhaled corticosteroids (ICSs) is necessary, recommended, or at the very least, should not be discontinued.
- The exceptions include asthma/bronchiectasis overlap, COPD/bronchiectasis overlap, allergic bronchopulmonary aspergillosis (ABPA), bronchiectasis with bronchial or peripheral eosinophilic component and uncontrollable bronchorrhea.

1.2.7 Review Article: Bronchiectasis Exacerbation: A Narrative Review of Causes, Risk Factors, Management and Prevention (*Ann Transl Med*., 2023)

Bronchiectasis exacerbations are significant events in the natural course of the disease and determine long-term clinical outcomes. This review aims to discuss the definition, causes, risk factors, management, and prevention of bronchiectasis exacerbations[11]. The main findings are summarized below:

Definition

- The experts agreed on the final definition of bronchiectasis exacerbation as follows: a person with bronchiectasis with a deterioration of three or more key symptoms for at least 48 hours, in addition to a clinician's decision that a change in bronchiectasis treatment is required.
- The main symptoms include:
    1. Cough
    2. Sputum volume and/or consistency
    3. Sputum purulence
    4. Breathlessness and/or exercise intolerance
    5. Fatigue and/or malaise
    6. Hemoptysis

Causes of exacerbations

- The understanding of bronchiectasis pathophysiology is limited, and this extends to a shortage of studies investigating the mechanisms behind exacerbations.
- Current guidelines advise using antibiotics to manage exacerbations, and patient experiences often indicate symptom improvement after antibiotic treatment.
- However, available data indicates that several other factors, such as viral infections, inflammation, and external environmental factors, can influence the risk of exacerbation.

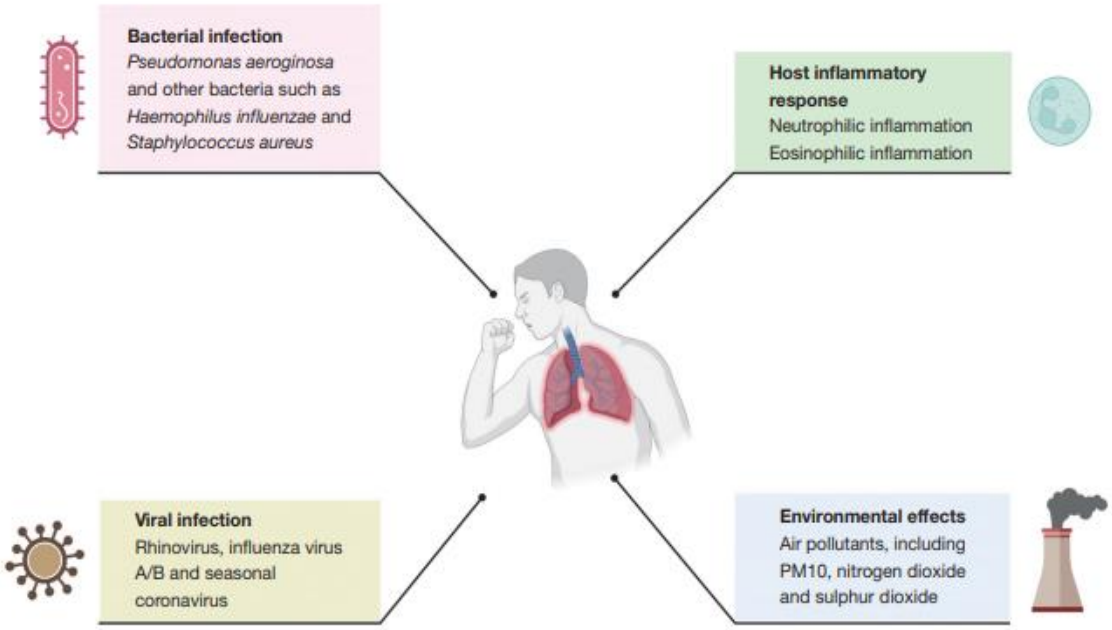


Figure 6. *Causes of bronchiectasis exacerbations (Retrieved from Choi et al., 2023)*

Risk factors and the "frequent exacerbator phenotype"

- Given that exacerbations are pivotal events in the progression of bronchiectasis, it is important to identify particular populations that are at a higher risk of experiencing exacerbations.
- The notion of a "frequent exacerbator phenotype" in bronchiectasis is akin to a similar concept in COPD, where it characterizes a group of patients who are more prone to experiencing recurrent pulmonary exacerbations, irrespective of their lung function.
- In addition to the frequent exacerbator phenotype, the *P. aeruginosa* phenotype in bronchiectasis is renowned for its unique clinical presentation.
- Since the colonization of *P. aeruginosa* is linked to frequent exacerbations and other indicators of disease severity, global guidelines have placed their emphasis on eliminating and controlling this pathogen.
- The presence of airway disease alongside bronchiectasis raises the likelihood of experiencing an exacerbation.
- Bronchiectasis patients are frequently elderly and have multiple concurrent medical conditions, and research has revealed a link between a higher rate of exacerbations and a greater occurrence of coexisting illnesses.

Management of acute exacerbations

✓ **Antibiotic treatment**

- Antibiotics are the primary treatment for managing bronchiectasis exacerbations and are in line with the recommendations provided by international bronchiectasis guidelines.
- The reason for employing antibiotics is that their use lowers the bacterial burden, subsequently alleviating symptoms and decreasing airway and systemic inflammation in bronchiectasis.
- An investigation conducted in the United Kingdom, which assessed the effects of a 14-day course of intravenous antibiotics, demonstrated that this treatment leads to a reduction in 24-hour sputum production, improvements in exercise capacity, alleviation of symptoms as indicated by the St. George's Respiratory Questionnaire (SGRQ) score, and a decrease in systemic inflammation.
- According to the guidance of experts, it is recommended to prescribe a 14-day course of antibiotics.
- For patients with a *P. aeruginosa* infection, a full 14-day antibiotic course is always advisable.
- However, in situations of mild exacerbations or when a rapid return to the baseline condition is observed, shorter courses of antibiotics may be adequate.
- Further studies are needed to elucidate the optimal duration of antibiotics in bronchiectasis exacerbations.
- Three factors should be considered regarding antibiotics:
    1. Antibiotic selection should be based on sputum cultures obtained either at the onset of an exacerbation or from previous isolates. In cases where sputum microbiology information is not available, clinicians can initiate empirical antibiotics while awaiting these results. Additionally, if no specific sputum microbiology data is accessible, healthcare providers can choose antibiotics according to local data regarding common pathogens typically encountered in patients with bronchiectasis.
    2. The British Thoracic Society Guideline for adult bronchiectasis advises that eligible patients should possess a supply of antibiotics at home as a component of their self-management plan. This approach ensures the rapid treatment of exacerbations but may not be universally adopted because of apprehensions regarding antibiotic overuse.

3. It's probable that not all exacerbations necessitate antibiotic treatment, as molecular methods may not detect bacteria in every case. In some instances, the exacerbation of symptoms could potentially be managed through more rigorous airway clearance techniques. Additional research is required to establish whether certain exacerbation episodes could be addressed without the use of antibiotics.

✓ **Other measures**

1- Airway clearance technique (ACT)

- A randomized controlled trial (RCT) investigating the long-term advantages of airway clearance techniques (ACT) in bronchiectasis has suggested its potential role in managing acute exacerbations, but it's worth noting that only one study extended for 12 months.
- While there is no definitive evidence on this matter, several systematic reviews are worth considering.
- One systematic review, which included six studies involving 120 patients, indicated that all ACT methods were safe for adult bronchiectasis patients during an acute exacerbation, with no reported adverse effects.
- Another systematic review, comprising seven studies with 105 patients, concluded that the role of ACT in acute exacerbations of bronchiectasis remains uncertain in terms of its clinical effects.
- However, given the chronic nature of bronchiectasis, more data may be necessary to accurately determine its impact.
- Airway clearance techniques (ACT) may have restricted functions in the treatment of acute exacerbations of bronchiectasis. Nonetheless, these techniques can be safely continued in bronchiectasis patients, even during exacerbations.

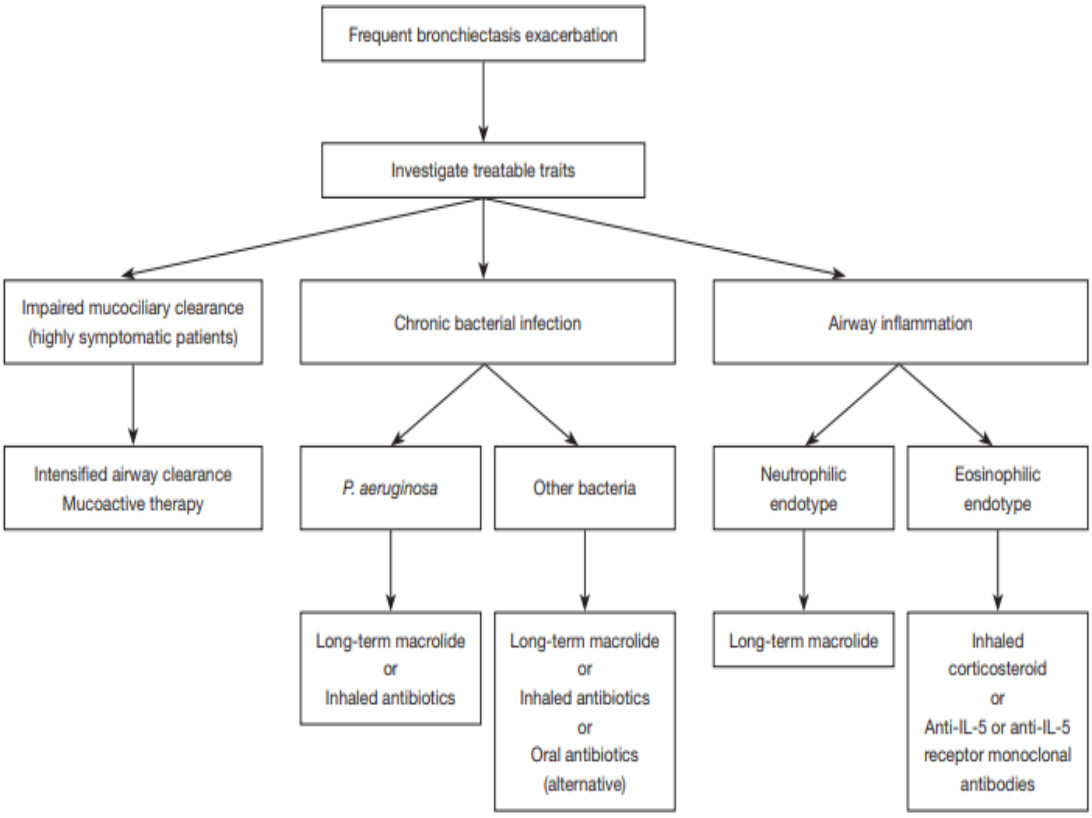
2- Pulmonary rehabilitation

- In relation to pulmonary rehabilitation, a preliminary randomized controlled trial (RCT) compared pulmonary rehabilitation involving 9 participants to standard care involving 18 participants in individuals who had experienced exacerbations after completing antibiotic treatment.
- The findings of this study indicated that there was no significant difference in the time to the next exacerbation between the two groups (HR, 0.83; 95% CI, 0.31–2.19; P=0.7).
- The role of pulmonary rehabilitation in the management of acute exacerbation of bronchiectasis is limited.

Prevention

1- Concept of vicious vortex and treatable traits

- The three primary factors - impaired mucociliary clearance, airway infection, and inflammation contribute to the gradual and ongoing structural damage to the airways over time. Consequently, frequent exacerbations are linked to disease progression and a high risk of mortality.
- Therefore, it is essential for healthcare professionals to intervene in one or more of these key factors with the aim of reducing exacerbations.
- Patients may exhibit multiple risk factors for exacerbations, many of which are amenable to treatment. These characteristics are collectively known as "treatable traits," which encompass both pulmonary and non-pulmonary traits.
- The most effective approach involves addressing all potential risk factors in a multidisciplinary manner. Figure 10 provides an overview of management strategies that target treatable traits in order to prevent exacerbations in bronchiectasis.



IL, interleukin

Figure 7. *Management targeting treatable traits to prevent bronchiectasis exacerbations (Retrieved from Choi et al., 2023)*

2- Mucoactive therapy

- Consistent airway clearance practices have been demonstrated to decrease the frequency of exacerbations, as evidenced by a recent 12-month randomized controlled trial (RCT).
- Therefore, it is advisable to promote airway clearance techniques for all individuals diagnosed with bronchiectasis.

3- Inhaled antibiotics

- Persistent infection, especially involving *Pseudomonas aeruginosa*, is linked to poorer prognoses.
- Consequently, international guidelines advise the use of inhaled antibiotics to eliminate and control *P. aeruginosa* in individuals who frequently experience exacerbations.
- There is conflicting data on the efficacy of inhaled antibiotics.

4- Long-term macrolide treatment

- The bronchiectasis guidelines on a global scale suggest the extended use of macrolides for individuals who experience frequent exacerbations and do not have chronic *Pseudomonas aeruginosa* infection.
- These recommendations are grounded in three randomized controlled trials (RCTs) that have demonstrated the effectiveness of long-term macrolide treatment in reducing the occurrence of bronchiectasis exacerbations.
- In upcoming bronchiectasis guidelines, there is a possibility of designating macrolides as the primary medication for individuals who frequently experience exacerbations, regardless of whether they have a *Pseudomonas aeruginosa* infection.
- However, it is essential to bear in mind the potential adverse effects associated with macrolides, such as an elevated risk of cardiovascular complications and the development of macrolide-resistant non-tuberculous mycobacterial (NTM) infections.
- Given the challenging nature of treating macrolide-resistant NTM pulmonary disease, it is crucial to obtain sputum samples for NTM culture from patients with bronchiectasis who are being considered for long-term macrolide therapy.

5- Anti-inflammatory therapy

- Brensocatib is an oral drug that acts as a reversible inhibitor of dipeptidyl peptidase 1 (DPP1). By blocking DPP1, it leads to the release of neutrophils from the bone marrow with decreased levels of active neutrophil elastase and other neutrophil serine proteases, resulting in reduced inflammation.
- In the WILLOW phase II randomized controlled trial (RCT), individuals with bronchiectasis were enrolled in a 1:1:1 ratio to receive either a placebo (n=87), 10 mg of brensocatib (n=82), or 25 mg of brensocatib (n=87) over a 24-week period. The primary outcome assessed was the time it took for the first exacerbation to occur, and brensocatib demonstrated a significant increase in the time to first exacerbation at both the 10-mg (HR, 0.58; 95% CI, 0.35–0.95; P=0.03) and 25-mg (HR, 0.62; 95% CI, 0.38–0.99; P=0.046) dosages when compared to the placebo (as reported in source 81). Additionally, noteworthy reductions in sputum neutrophil elastase were observed. Presently, this therapy is progressing to phase III clinical trials.
- In current clinical practice, inhaled corticosteroids (ICS) are the most commonly employed anti-inflammatory medications.
- Nevertheless, international guidelines do not advise the use of ICS for the entire population with bronchiectasis; rather, they recommend ICS specifically for patients with bronchiectasis who have certain coexisting conditions, such as asthma or allergic bronchopulmonary aspergillosis.

Section 2.0 Drug Therapy in Acute Exacerbation of Bronchiectasis

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth summarizes drugs that are in the pipeline for the management of bronchiectasis.

2.1 Additions

Medications such as antibiotics, vaccines and hypertonic saline that are routinely used for this indication were added to the drug summary spreadsheet and include:

1. Amikacin
2. Teicoplanin
3. Linezolid
4. Vancomycin
5. Cefepime hydrochloride
6. Meropenem
7. Imipenem/Cilastatin
8. INFLUENZA A VIRUS A/INDONESIA/5/2005 (H5N1) ANTIGEN (UV, FORMALDEHYDE INACTIVATED)
9. A/Brisbane/02/2018 (H1N1), A/Kansas/14/2017 (H3N2), B/Colorado/06/2017, B/Phuket/3073/2013
10. INFLUENZA VIRUS INACTIVATED SPLIT
11. Sodium Chloride

2.2 Modifications

Table 14 details the prescribing edits modifications that were made for various medications included in the previous CHI report.

Table 14. Prescribing Edits Modifications

Medications	Modifications
Amoxicillin	PA was removed
Amoxicillin/Clavulanic Acid	PA was removed
Azithromycin	PA was removed
Cefotaxime	PA was removed
Ceftazidime	PA was removed. MD was added: Should be prescribed by an infectious diseases specialized physician.
Ceftriaxone	PA was removed
Ciprofloxacin	PA was removed
Clarithromycin	PA was removed
Colistimethate sodium	PA was removed
Doxycycline	PA was removed
Erythromycin	PA was removed
Flucloxacillin	PA was removed
Gentamicin	PA was removed
Levofloxacin	PA was removed
Piperacillin/Tazobactam	PA was removed. MD was added: Should be prescribed by an infectious diseases specialized physician.
Tobramycin	PA was removed

PA: prior authorization; MD: medical doctor

2.3 Delisting

The medications below are no longer SFDA registered[12], therefore, it is advisable to delist the following drugs from CHI formulary.

1. Clavulanic acid
2. INFLUENZA VACCINE SURFACE ANTIGEN NYMC X-181, NYMC X-187, AND NYMC BX-35

2.4 Other Drugs

In 2020, the WILLOW phase 2 trial demonstrated that **brensocatib** effectively reduces the risk and frequency of bronchiectasis exacerbations within 24 weeks. This positive outcome is attributed to its inhibition of dipeptidyl peptidase I and the reduction in the activation of neutrophil serine proteases. Building on these promising results, several other noteworthy trials are currently in progress. The phase 3 ASPEN study is set to assess the efficacy of **brensocatib** over a 52-week period (NCT04594369)[13].

Additionally, a phase 2 study is underway to influence the respiratory microbiome using **BI1291583, a novel selective inhibitor of cathepsin C** (NCT05238675)[13].

Furthermore, there is ongoing research on **alpha 1-proteinase inhibitors** due to their potential to reduce airway inflammation and enhance neutrophil function (NCT05582798)[13].

Section 3.0 Key Recommendations Synthesis

- Contemplate the use of the bronchiectasis severity index as it can help guide the choice of treatment approach[5].
- It is discouraged to routinely use recombinant human DNase in adults who have bronchiectasis (A)[5].
- For specific individuals, like those facing elevated daily symptoms, frequent exacerbations, challenges in clearing sputum, and/or a diminished quality of life, it may be beneficial to contemplate the use of inhaled mannitol or a 6–7% hypertonic saline solution[6].
- Routine use of bromhexine is not recommended for children and adolescents with bronchiectasis (conditional recommendation, very low quality of evidence)[6].
- Routine use of inhaled mannitol or hypertonic saline is not advised for children and adolescents with bronchiectasis. (Conditional recommendation, very low quality of evidence)[6].
- We advise against administering inhaled corticosteroids to adults with bronchiectasis (conditional recommendation, low quality of evidence)[7].
- We strongly discourage the use of statins as a treatment for bronchiectasis (strong recommendation, low quality of evidence)[7].
- We do not advise the routine prescription of long-acting bronchodilators for adult patients with bronchiectasis (conditional recommendation, very low quality of evidence)[7].
- Consider starting a trial of long-acting bronchodilator treatment for those individuals who are dealing with notable shortness of breath (D)[5].
- A 14-day antibiotics course for the treatment of acute bronchiectasis exacerbations is recommended (Conditional recommendation, very low quality of evidence)[7].
- In cases of mild exacerbations or when a swift return to the usual baseline state is evident, shorter antibiotic regimens may suffice[11].
- The choice of antibiotics should rely on sputum cultures collected either at the start of an exacerbation or from earlier samples. When sputum microbiological details are not accessible, clinicians can begin empirical antibiotic treatment while awaiting these results. Furthermore, if specific sputum microbiological information is not at hand, healthcare professionals can make antibiotic selections based on local data pertaining to the usual pathogens encountered in bronchiectasis patients[11].

- Individuals with bronchiectasis who experience three or more exacerbations may want to contemplate the utilization of extended antibiotic treatment (A)[5].
- We advise contemplating the administration of eradication antibiotic therapy to adults with bronchiectasis who have recently identified *Pseudomonas aeruginosa* (conditional recommendation, very low quality of evidence)[7].
- Offering eradication antibiotic therapy to adults with bronchiectasis when isolated pathogens other than *Pseudomonas aeruginosa* are implicated is not recommended (conditional recommendation, very low quality of evidence)[7].
- It is strongly recommended that children and adolescents with bronchiectasis receive instruction in airway clearance techniques and perform them regularly (strong recommendation, low quality of evidence)[6].
- Offer pulmonary rehabilitation to those individuals with a Modified Medical Research Council (MMRC) Dyspnea Scale score of 1 or higher, indicating restricted functional capacity due to breathlessness (B)[5].
- Consider the possibility of lung resection for patients with localized disease if their symptoms persist, even after receiving optimized medical treatment from a specialist in bronchiectasis (D)[5].
- It is worth emphasizing that the incidence of bronchiectasis significantly increases in the elderly population. As a standard procedure, it is recommended to provide vaccinations for both influenza and pneumococcal infections to individuals over the age of 65, particularly those with chronic respiratory conditions[9].
- We recommend that children and adolescents with bronchiectasis adhere to their country's immunization schedules, which may involve receiving pneumococcal and yearly seasonal influenza vaccines if these vaccines are not already part of the program (Conditional recommendation, very low quality of evidence stemming from the narrative review)[6].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Acute exacerbation of bronchiectasis (non-cystic fibrosis) report** and aims to provide recommendations to aid in the management of Acute exacerbation of bronchiectasis (non-cystic fibrosis). It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Acute exacerbation of bronchiectasis (non-cystic fibrosis). Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Acute Exacerbation on Bronchiectasis Scope

2020	Changes	2023	Rationale
Section 1.0 Acute exacerbation of bronchiectasis (non-cystic fibrosis) Clinical Guidelines			
The Saudi Thoracic Society guidelines for diagnosis and management of Non-Cystic Fibrosis Bronchiectasis 2017	N/A		
Bronchiectasis (non-cystic fibrosis), acute exacerbation: antimicrobial prescribing NICE guideline NICE guideline July 2018	N/A		
	Missing	British Thoracic Society Guideline for bronchiectasis in adults (2019)[5]	**Diagnosis** **Specific disease groups with associated bronchiectasis** **Investigations for causes of bronchiectasis** **Severity Scoring** The presence of the two clinical scoring systems, namely the Bronchiectasis Severity Index (BSI) and FACED has enhanced our capacity to forecast prospective mortality in bronchiectasis patients. **Airway clearance techniques**

			• Using oscillating positive expiratory pressure (Acapella), along with postural drainage, is both effective and safe when applied during an acute exacerbation (1-). **Mucoactives in bronchiectasis** • It is not recommended to regularly employ recombinant human DNase in adults with bronchiectasis (A). • Consider the use of humidification with sterile water or normal saline to aid in airway clearance (D). **Treatments that improve outcomes for patients with stable bronchiectasis** • Patients with bronchiectasis who have 3 or more exacerbations should consider the use of prolonged antibiotic therapy. (A) **P. Aeruginosa colonized patients** **Non-P. aeruginosa colonized patients** **Long term bronchodilators** • In patients with bronchiectasis who also have concurrent COPD or asthma, the administration of bronchodilators should adhere to the respective COPD or asthma guideline recommendations. (D) • Consider initiating a trial of long-acting bronchodilator therapy in individuals experiencing significant breathlessness. (D) **Pulmonary Rehabilitation** • Provide pulmonary rehabilitation to individuals whose functional capacity is restricted by breathlessness, as indicated by a Modified Medical Research Council (MMRC) Dyspnea Scale score of 1 or higher. (B) • Consider incorporating inspiratory muscle training alongside standard pulmonary rehabilitation to improve the sustainability of the training benefits. (B)

			Surgery • Contemplate the option of lung resection for patients with localized disease if their symptoms persist despite medical treatment that has been optimized by a bronchiectasis specialist. (D) • Provide a multidisciplinary evaluation, including a bronchiectasis specialist, a thoracic surgeon, and a skilled anesthetist, to assess the suitability for surgery and to conduct a pre-operative assessment of cardiopulmonary reserve after the resection. (D) **Lung transplantation for bronchiectasis** • Evaluate the possibility of referring bronchiectasis patients for transplantation if they are 65 years of age or younger, have an FEV1 of less than 30%, and exhibit significant clinical instability. Alternatively, consider referral in cases of rapid and progressive respiratory decline, even when optimal medical management is in place. (D) • In bronchiectasis patients with compromised lung function, consider an earlier transplant referral when they present additional factors such as severe hemoptysis, significant secondary pulmonary hypertension, multiple ICU admissions, or respiratory failure, particularly if non-invasive ventilation (NIV) is required. (D) **Influenza and pneumococcal vaccination** • Provide yearly influenza vaccination to all individuals diagnosed with bronchiectasis. (D) • Make the polysaccharide pneumococcal vaccine available to all patients with bronchiectasis. (D) **Treatment of respiratory failure**

			• Evaluate the potential use of long-term oxygen therapy in individuals with bronchiectasis who experience respiratory failure, employing eligibility criteria similar to those applied for COPD. (D) • Contemplate the use of home-based non-invasive ventilation with added humidification for bronchiectasis patients facing respiratory failure linked to hypercapnia, particularly in cases where this condition relates to noticeable symptoms or recurring hospital admissions. (D) **Bronchiectasis and other treatments: cough suppression, nutritional supplements, complementary therapy/ homeopathy, supplemental treatments** • It is not advisable to routinely endorse alternative treatments, such as cough suppression, nutritional supplementation, complementary therapy/homeopathy, or supplemental treatments, as part of the overall care for individuals with bronchiectasis. Further interventional trials and randomized controlled studies are necessary to determine the potential role of alternative therapies in bronchiectasis management. (D) **The impact of pathogens on prognosis in bronchiectasis** • Patients with chronic colonization of Pseudomonas aeruginosa should be regarded as having an elevated risk of experiencing complications related to bronchiectasis. (B) • Conduct routine sputum microbiology screening for individuals with clinically substantial bronchiectasis to track the presence of pathogens and to identify any new instances of Pseudomonas aeruginosa isolation. (C) **The role of eradication of potentially pathogenic microorganisms in improving outcomes in patients with stable bronchiectasis**

			Acute Exacerbations ✓ **Antibiotics** • There is a lack of adequate evidence to assess the effectiveness of antibiotics in adult bronchiectasis exacerbations. (2-) • Past sputum bacteriology results can be valuable in selecting the appropriate antibiotic. Figure 1 outlines the primary and alternative treatments for the typical bacterial pathogens associated with bronchiectasis exacerbations. • While waiting for sputum microbiology results, empirical antibiotics can be initiated. • Once a pathogen is identified, antibiotic adjustments can be made if there is no clinical improvement, with treatment decisions guided by antibiotic sensitivity test results. • As a rule, standard antibiotic courses lasting 14 days are recommended and should be consistently employed for patients with Pseudomonas aeruginosa infections. For individuals with mild bronchiectasis, shorter courses may be adequate. • When patients are in a severe state of illness, have infections caused by drug-resistant organisms, or do not show improvement with oral therapy (which is more common in cases involving Pseudomonas aeruginosa), intravenous antibiotics should be considered.
	Missing	European Respiratory Society guidelines for the management of adult	**Testing for Bronchiectasis** • We recommend conducting a basic set of diagnostic tests in adults newly diagnosed with bronchiectasis (conditional recommendation, very low quality of evidence) 1. differential blood count 2. serum immunoglobulins (total IgG, IgA and IgM); and

		bronchiectasis (2017)[7]	3. testing for allergic bronchopulmonary aspergillosis (ABPA). **Systemic antibiotic therapy for treating adult bronchiectasis patients with an acute exacerbation** • We recommend a 14-day course of antibiotics for the treatment of acute bronchiectasis exacerbations (Conditional recommendation, very low quality of evidence). **Eradication treatment** • Eradication treatment encompasses any antibiotic therapy administered with the specific goal of completely eliminating the pathogen from the airways. • We recommend considering the provision of eradication antibiotic treatment to adults with bronchiectasis who have recently isolated Pseudomonas aeruginosa (conditional recommendation, very low quality of evidence). • We recommend against providing eradication antibiotic treatment to adults with bronchiectasis when newly isolated pathogens other than Pseudomonas aeruginosa are involved (conditional recommendation, very low quality of evidence). **Long-term anti-inflammatory agents** • We recommend against providing inhaled corticosteroid treatment to adults with bronchiectasis (conditional recommendation, low quality of evidence). • We strongly recommend against the use of statins for treating bronchiectasis (strong recommendation, low quality of evidence). • We suggest that the diagnosis of bronchiectasis should not influence the utilization of inhaled corticosteroids in patients with concurrent asthma or COPD (best practice advice, indirect evidence).

			Long-term antibiotic treatment (⩾3 months) • We recommend considering long-term antibiotic treatment for adults with bronchiectasis who experience three or more exacerbations per year (conditional recommendation, moderate quality of evidence). **Long-term mucoactive treatment (⩾3 months)** • Consider providing long-term mucoactive treatment (lasting at least three months) to adult bronchiectasis patients who struggle with sputum clearance and experience a reduced quality of life, particularly when standard airway clearance techniques have proven ineffective (weak recommendation, low quality of evidence). • We strongly advise against offering recombinant human DNase to adult bronchiectasis patients (strong recommendation, moderate quality of evidence). **Long-term bronchodilator treatment (⩾3 months)** • We do not recommend routinely providing long-acting bronchodilators for adult bronchiectasis patients (conditional recommendation, very low quality of evidence). • Consider offering long-acting bronchodilators to patients with significant breathlessness on an individual basis (weak recommendation, very low quality of evidence). **Surgical interventions** • We recommend against providing surgical interventions for adult bronchiectasis patients, except in cases involving patients with localized disease who experience frequent exacerbations despite optimizing all other aspects of their bronchiectasis management (weak recommendation, very low quality of evidence).

			Regular physiotherapy (airway clearance and/or pulmonary rehabilitation) • Consider instructing patients with persistent productive cough or sputum clearance difficulties to learn an airway clearance technique (ACT) from a qualified respiratory physiotherapist and perform it once or twice daily (weak recommendation, low quality of evidence). • We strongly recommend that adult bronchiectasis patients with reduced exercise capacity should engage in a pulmonary rehabilitation program and engage in regular physical activity. All interventions should be customized to the patient's symptoms, physical abilities, and disease-specific characteristics (strong recommendation, high quality of evidence).
	Missing	European Respiratory Society guidelines for the management of children and adolescents with bronchiectasis (2021)[6]	**Diagnosis** **Definition of exacerbation** **Management** • **Airway clearance** • Children and adolescents with bronchiectasis should be instructed in and regularly practice airway clearance techniques or maneuvers (strong recommendation, low quality of evidence). • **Mucoactive agents** • Routine use of recombinant human DNase (rhDNase) is not recommended for children and adolescents with bronchiectasis (strong recommendation, very low quality of evidence).

			• Routine use of bromhexine is not advised for children and adolescents with bronchiectasis (conditional recommendation, very low quality of evidence). • Routine use of inhaled mannitol or hypertonic saline is not suggested for children and adolescents with bronchiectasis. (Conditional recommendation, very low quality of evidence). • **Use of antibiotics in acute exacerbations** • For children and adolescents experiencing an acute respiratory exacerbation in the context of bronchiectasis, we recommend employing an adequate antibiotic via systemic administration for a duration of 14 days. (Strong recommendation, moderate quality of evidence) • **Long-term (⩾2 months) antibiotics** • For children and adolescents with bronchiectasis and recurrent exacerbations, it is recommended to consider long-term macrolide antibiotic treatment as a measure to reduce the frequency of exacerbations (Strong recommendation, low quality of evidence). • **Eradication treatment** • In children and adolescents with bronchiectasis, it is advised to consider eradication therapy when Pseudomonas aeruginosa is initially detected or upon new detection of the pathogen (Conditional recommendation for the intervention, very low quality of evidence). • **Inhaled corticosteroids (ICS), short-acting β2-agonists (SABA), long-acting β2-agonists (LABA)** • In the case of children and adolescents diagnosed with bronchiectasis, we advise against the routine use of inhaled corticosteroids (ICS) with or without long-acting beta-agonists

			(LABA) in both the short-term and long-term, regardless of their condition being stable or experiencing exacerbations (Conditional recommendation, very low quality of evidence). • **Surgery** • In the case of children and adolescents with bronchiectasis, we strongly recommend that several factors should be carefully considered when contemplating surgery. These factors include the patient's age, the severity of their symptoms and disease burden, the specific location of bronchiectatic areas as revealed by chest CT scans, the underlying cause of the condition (which can influence the likelihood of disease recurrence), the surgical facility's expertise and the availability of pre- and post-surgical care, as well as the overall health and clinical condition of the child (Strong recommendation, very low quality of evidence stemming from the narrative review). • **Other pediatric systematic care issues (nutrition, aerobic and non-aerobic exercise, psychological support, equipment care, vaccinations, etc.)** • In the case of children and adolescents with bronchiectasis, we propose the optimization of their nutrition, which should include the assessment and improvement of their vitamin D status (Conditional recommendation, very low quality of evidence stemming from the narrative review). **Prevention of cross-infection** **Monitoring**
	Missing	Exacerbation of Bronchiectasis Article (2018)[9]	**Definition** **Risk Factors** **Etiology of Exacerbations** **Treatment of Exacerbations**

			Prevention of Exacerbations ✓ **Antibiotics** • The primary focus of long-term management for bronchiectasis aims to prevent exacerbations. Consequently, several recommendations are outlined in both Spanish and British guidelines. ✓ **Mucolytic and Hyperosmolar Agents** • Alternative hyperosmolar agents, like mannitol, which are more expensive, did not demonstrate a significant reduction in the annual exacerbation frequency. • Deoxyribonuclease (RhDNase) is currently not recommended for use in bronchiectasis. This is due to the results of the only randomized controlled trial (RCT) that revealed an increased exacerbation rate when this mucolytic agent, which is frequently employed in cystic fibrosis (CF) treatment, was used in conjunction with bronchiectasis. ✓ **Vaccines** • However, it is important to note that the prevalence of bronchiectasis significantly rises among the elderly population, and as a general practice, it is advisable to administer vaccines for both influenza and pneumococcal infections to individuals aged over 65 years, especially those with chronic respiratory conditions.
	Missing	Cochrane Database of Systematic Reviews: Inhaled corticosteroids for bronchiectasis (Review) 2018[10]	• Regarding a single non-placebo-controlled study with extracted clinical data, there was a marginal, though statistically significant, improvement in sputum volume and dyspnea scores with ICS. • The sole study focusing on long-term outcomes (over 6 months) that examined lung function and other clinical

			outcomes showed no significant effect of ICS on any of the outcomes. • Conclusions on adverse effects could not be drawn due to limited available data. - In summary, the analysis determined insufficient evidence to support the regular utilization of inhaled corticosteroids (ICS) in adults experiencing stable bronchiectasis. - No conclusions can be drawn regarding the use of ICS during bronchiectasis flare-ups or their application in children due to the absence of relevant studies.
	Missing	Inhaled Corticosteroids in Adults with Non-cystic Fibrosis Bronchiectasis: From Bench to Bedside. A Narrative Review (2022)[8]	• According to international guidelines, there is a consensus that inhaled corticosteroids (ICSs) are not routinely recommended for the treatment of bronchiectasis, as outlined in the information provided in this review. However, the guidelines acknowledge that the scientific evidence supporting this recommendation is limited. • However, various guidelines make exceptions, suggesting instances where the prescription of inhaled corticosteroids (ICSs) is necessary, recommended, or at the very least, should not be discontinued. • The exceptions include asthma/bronchiectasis overlap, COPD/bronchiectasis overlap, allergic bronchopulmonary aspergillosis (ABPA), bronchiectasis with bronchial or peripheral eosinophilic component and uncontrollable bronchorrhea.
	Missing	Bronchiectasis exacerbation: a narrative review of causes, risk factors, management and	**Definition** **Causes of exacerbations** **Risk factors and the "frequent exacerbator phenotype"** **Management of acute exacerbations** • **Antibiotic treatment**

		prevention (Review article) (2023)[11]	• Antibiotics are the primary treatment for managing bronchiectasis exacerbations and are in line with the recommendations provided by international bronchiectasis guidelines. • According to the guidance of experts, it is recommended to prescribe a 14-day course of antibiotics. **Other measures** • **Airway clearance technique (ACT)** A randomized controlled trial (RCT) investigating the long-term advantages of airway clearance techniques (ACT) in bronchiectasis has suggested its potential role in managing acute exacerbations, but it's worth noting that only one study extended for 12 months. • **Pulmonary rehabilitation** The role of pulmonary rehabilitation in the management of acute exacerbation of bronchiectasis is limited. **Prevention** **1- Concept of vicious vortex and treatable traits** **2- Mucoactive therapy** • Consistent airway clearance practices have been demonstrated to decrease the frequency of exacerbations, as evidenced by a recent 12-month randomized controlled trial (RCT). • Therefore, it is advisable to promote airway clearance techniques for all individuals diagnosed with bronchiectasis. **3- Inhaled antibiotics** • Consequently, international guidelines advise the use of inhaled antibiotics to eliminate and control P. aeruginosa in individuals who frequently experience exacerbations.

			• There is conflicting data on the efficacy of inhaled antibiotics. **4- Long-term macrolide treatment** • The bronchiectasis guidelines on a global scale suggest the extended use of macrolides for individuals who experience frequent exacerbations and do not have chronic Pseudomonas aeruginosa infection. **5- Anti-inflammatory therapy** • Brensocatib is an oral drug that acts as a reversible inhibitor of dipeptidyl peptidase 1 (DPP1). By blocking DPP1, it leads to the release of neutrophils from the bone marrow with decreased levels of active neutrophil elastase and other neutrophil serine proteases, resulting in reduced inflammation. • In current clinical practice, inhaled corticosteroids (ICS) are the most commonly employed anti-inflammatory medications. • Nevertheless, international guidelines do not advise the use of ICS for the entire population with bronchiectasis; rather, they recommend ICS specifically for patients with bronchiectasis who have certain coexisting conditions, such as asthma or allergic bronchopulmonary aspergillosis.

Appendix C. MeSH Terms PubMed

C.1 Pubmed Search for Bronchiectasis

The following is the result of the PubMed search conducted for bronchiectasis guideline search:

Query	Filters	Search Details	Results
((((((((((((Bronchiectasis[MeSH Terms]) OR (Bronchiectases[Title/Abstract])) OR (Saccular Bronchiectasis[Title/Abstract])) OR (Bronchiectasis, Saccular[Title/Abstract])) OR (Saccular Bronchiectases[Title/Abstract])) OR (Cystic Bronchiectasis[Title/Abstract])) OR (Bronchiectasis, Cystic[Title/Abstract])) OR (Cystic Bronchiectases[Title/Abstract])) OR (Cylindrical Bronchiectasis[Title/Abstract])) OR (Bronchiectasis, Cylindrical[Title/Abstract])) OR (Cylindrical Bronchiectases[Title/Abstract])) OR (Varicose Bronchiectasis[Title/Abstract])) OR (Bronchiectasis, Varicose[Title/Abstract])) OR (Varicose Bronchiectases[Title/Abstract])	Guideline, in the last 5 years	("Bronchiectasis"[MeSH Terms] OR "Bronchiectases"[Title/Abstract] OR "saccular bronchiectasis"[Title/Abstract] OR "bronchiectasis saccular"[Title/Abstract] OR ("Saccular"[All Fields] AND "Bronchiectases"[Title/Abstract]) OR "cystic bronchiectasis"[Title/Abstract] OR "bronchiectasis cystic"[Title/Abstract] OR "cystic bronchiectases"[Title/Abstract] OR "cylindrical bronchiectasis"[Title/Abstract] OR "bronchiectasis cylindrical"[Title/Abstract] OR (("cylindric"[All Fields] OR "Cylindrical"[All Fields] OR "cylindrically"[All Fields]) AND "Bronchiectases"[Title/Abstract]) OR "varicose bronchiectasis"[Title/Abstract] OR (("bronchiectasies"[All Fields] OR "Bronchiectasis"[MeSH Terms] OR "Bronchiectasis"[All Fields] OR "Bronchiectases"[All Fields]) AND "Varicose"[Title/Abstract]) OR "varicose bronchiectases"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	6

Appendix D. Treatment Algorithm for Bronchiectasis

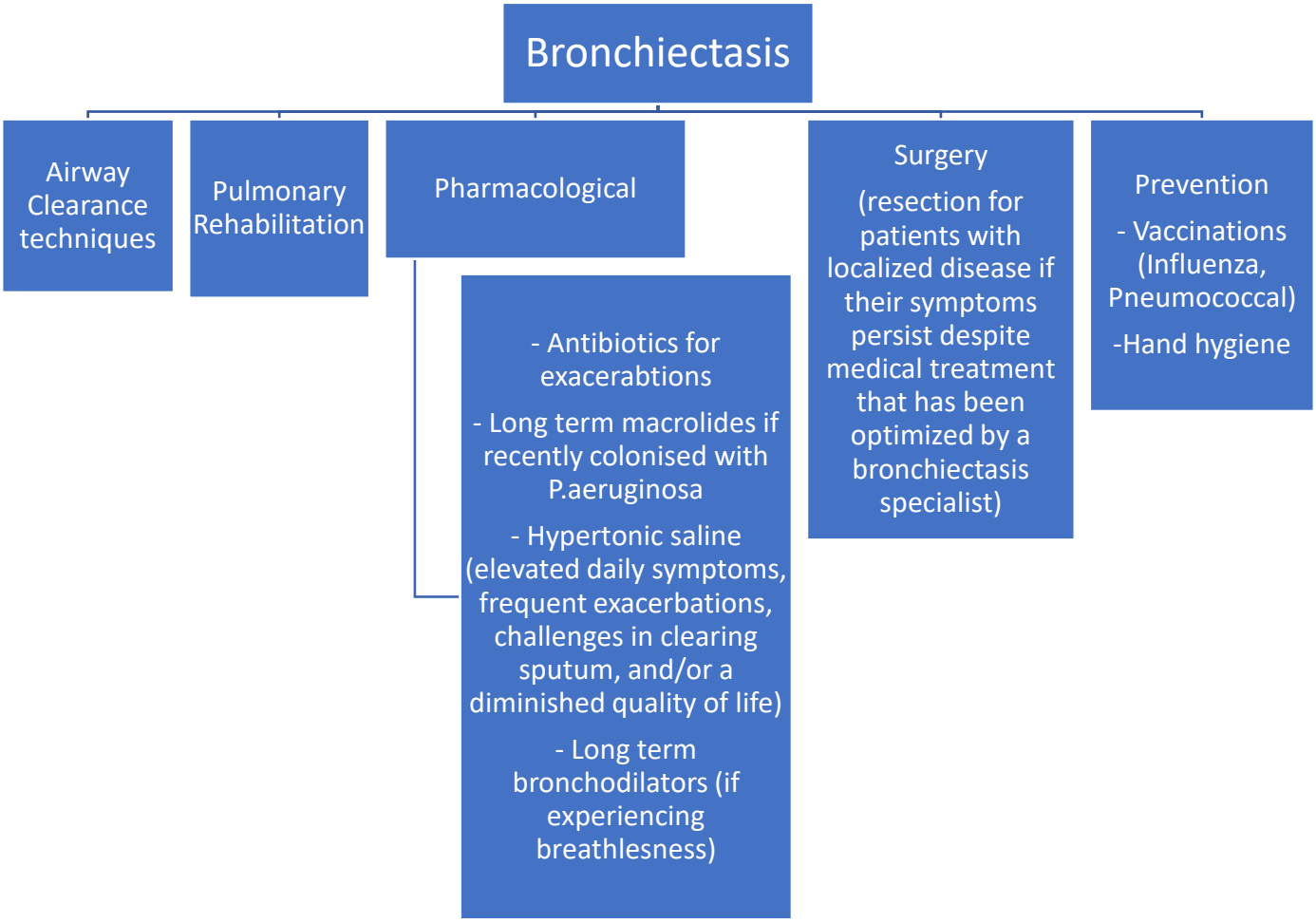

Figure 8. *Treatment Algorithm for the Management of Bronchiectasis*[5–7,9,11]