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The Saudi Thoracic Society guidelines for diagnosis and management of noncystic fibrosis bronchiectasis

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Abstract:

This is the first guideline developed by the Saudi Thoracic Society for the diagnosis and management of noncystic fibrosis bronchiectasis. Local experts including pulmonologists, infectious disease specialists, thoracic surgeons, respiratory therapists, and others from adult and pediatric departments provided the best practice evidence recommendations based on the available international and local literature. The main objective of this guideline is to utilize the current published evidence to develop recommendations about management of bronchiectasis suitable to our local health-care system and available resources. We aim to provide clinicians with tools to standardize the diagnosis and management of bronchiectasis. This guideline targets primary care physicians, family medicine practitioners, practicing internists and respiratory physicians, and all other health-care providers involved in the care of the patients with bronchiectasis.

Keywords:

Bronchiectasis, cystic fibrosis, Saudi

Recognizing the need for improved care for patients with bronchiectasis in Saudi Arabia, the Saudi Thoracic Society (STS) formed a task force committee to develop "Best Practice Guidelines for the Management of Bronchiectasis" to optimize prevention, early diagnosis, and effective management of this disease. The aim of this committee is to provide practical guidance for family physicians, specialists, and other health-care professionals involved in bronchiectasis management, as well as to patients and their families.

Here, I would like to thank all members of the task force for their dedication and great effort in producing these guidelines. I would also like to express my thanks to the administrative and the secretarial staffing of the STS for their continuous support to the members of this task force.

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Objectives of the Bronchiectasis Guidelines

Over the past few years, there have been new developments and increasing interest in the field of non-cystic fibrosis (CF) bronchiectasis (hereafter referred to as bronchiectasis). One of the major challenges, however, is conflicting results from published researches about bronchiectasis, which results in controversies in the interpretation of study outcomes and recommendations. This is related not only to diversity in study designs, site selection, patient inclusion/exclusion criteria, and definition of exacerbations,

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but also the variation in the dose, scheme, route of administration, and duration of treatment. In addition, there are differences in the outcome definition and measurements across published studies. For example, outcome measurements that have been commonly used include bacterial load reduction or eradication, clinical response, number of exacerbation, time to the first exacerbation, number of hospitalizations, and quality of life. Recent studies suggest that there is an increase in the incidence and prevalence of bronchiectasis and related hospitalization. Our intention in this guideline is to utilize the current published evidence to develop recommendations about the management of bronchiectasis suitable to our local health-care system and available resources. We aim to provide clinicians with tools to standardize the diagnosis and management of bronchiectasis. This guideline targets primary care physicians, family medicine practitioners, practicing internists and respiratory physicians, and all other health-care providers involved in the care of the patients with bronchiectasis.

Methods

The main task of the bronchiectasis group was to develop evidence-based guidelines that are more suitable to local practices and to improve the management of adults with bronchiectasis by health-care providers to optimize bronchiectasis patient care.

These are the first non-CF bronchiectasis guidelines developed by a panel of academics and practicing pulmonologists who are experienced in developing guidelines. The panel reviewed several existing global guidelines for the management of bronchiectasis. In addition, panel members held several reviews and discussions of the guidelines to include all published literature related to bronchiectasis and grading the evidence. These recommendations were reviewed twice by international experts in the development of bronchiectasis guidelines. Local and international literature citations were reviewed. Each member was assigned a specific task, which was reviewed and examined then by the group. Each member reviewed the evidence and graded the evidence. Any discordance in the grading required further discussion and final consensus agreement by majority. The final manuscript was reviewed by independent internal and external auditors.

Level of Evidence

The criteria used to weigh the evidence were as follows:

- Evidence Category A: Randomized controlled trials (RCTs) with a rich body of data or meta-analysis from RCTs
- Evidence Category B: RCTs with a limited body of data or meta-analysis from non-RCTs
- Evidence Category C: Non-randomized trials and observational studies
- Evidence Category D: Panel consensus agreement. This category is only used in cases where the provision of some guidance was deemed valuable, but the clinical literature addressing the subject was insufficient to justify placement in one of the other categories.

Introduction

Bronchiectasis is a chronic lung disease that is characterized by permanent dilatation of the bronchi of the lung. Increased understanding of the disease mechanisms and improvements in diagnosis have recently brought attention to its prevalence in pediatric and adult populations and in both developing and developed countries. The true incidence of bronchiectasis is difficult to determine due to several factors. One of these factors is the underinvestigation of the disease in patients with a known cause for chronic sputum production, for example, smokers, asthma, or chronic obstructive pulmonary disease (COPD). Traditionally, bronchiectasis has been regarded as an orphan disease, in part due to its relative rarity in developed nations. The large decline in bronchiectasis from the 1930s to 1950s is likely related to a combination of factors including the availability of effective antibiotic management, improvement of public health, reduction in tuberculosis (TB), and vaccinations. In addition to the possibility that its symptoms overlap heavily with other respiratory conditions, the diagnosis can easily be overlooked. This presumption, however, has been challenged recently and some experts believe rightly that bronchiectasis is not an orphan disease.^[1] Recent data from Western countries estimate a much higher prevalence and incidence of bronchiectasis than the threshold of 5/10,000 population for the definition of an orphan disease as defined by the European Union.^[1] A study from the United Kingdom showed an increase in the incidence from 21.2/100,000 person-years in 2004 to 35.2/100,000 person-years in 2013 in women and from 18.2/100,000 person-years in 2004 to 26.9/100,000 person-years in 2013 in men.^[2] A recent population-based estimation of bronchiectasis prevalence in Germany estimated an overall prevalence rate of 67/100,000 in 2013 and a higher prevalence in elderly men (75–84 years) of 228/100,000.^[3] The prevalence in the USA is even higher, with an overall annual prevalence of 370 cases per 100,000 person-years and 537 cases per 100,000 person-years in women aged 80–84 years.^[4] Moreover, there is a steadily increasing prevalence of bronchiectasis-associated hospitalizations. In Germany, bronchiectasis-related hospitalization rates

range from 9.4 to 39.4/100,000 population.^[5] In the USA, the average annual hospitalization rate from 1993 to 2006 was 16.5/100,000 populations.^[6] In New Zealand, a prevalence of 52 of 100,000 children has been reported and 1470–2000/100,000 among indigenous children living in Australia and Alaska, USA.^[7,8] This increase in the prevalence and incidence of bronchiectasis is attributed to many factors; particularly the increased utilization of chest computed tomography (CT) is being considered the most important factor. For example, a Japanese study using CT screening as part of a health screening program reported a high prevalence of bronchiectasis (11.5% in females and 7.9% in males).^[9]

There are no data available in Saudi Arabia on the national prevalence or incidence of bronchiectasis. What have been published are mainly hospital-based studies and the findings which are likely to underestimate the actual national figure. In a study by Al-Mobeireek *et al.*, bronchiectasis was found to represent only 5% of adult cases of chronic persistent cough referred to pulmonary clinics and *Pseudomonas aeruginosa* was found to be the most common pathogen in hospitalized patients in another study.^[10,11] Attar *et al.* reported a 35% prevalence of asymptomatic bronchiectasis in patients with rheumatoid arthritis.^[12] In 2007, a retrospective study conducted in a pediatric group (900 cases, age <14 years) at King Faisal Specialist Hospital, Saudi Arabia, reported that 1 in 4 (25%) children presenting with recurring respiratory infections were having evidence of bronchiectasis.^[13] Banjar^[14] reviewed the clinical profile of bronchiectasis in children from 1993 to 2005 and reported associated disease in 91 (60%) cases, including pulmonary diseases in 48 (32%), immunodeficiency in 27 (18%), neurological in 18 (12%), cardiac in 12 (8%), and asthma in 103 (68%) patients.

Summary

- We believe that the frequent use of high-resolution computed tomography (HRCT) and awareness of the diseases that coexist with bronchiectasis such as asthma and COPD will increase the detection and, therefore, the reported prevalence and incidence of bronchiectasis in Saudi Arabia
- Undertaking a national study to determine the incidence and prevalence of bronchiectasis and its burden in Saudi Arabia is highly needed.

Pathogenesis

The pathogenesis of bronchiectasis includes an initial insult to the lower airways, impaired mucociliary clearance, microbial colonization/infection, and bronchial obstruction that lead to normal or exaggerated inflammatory response. A current model for the

pathogenesis of bronchiectasis involves the combination of an external insult with the underlying impairment of mucociliary function.^[15] Infection with inflammation results in dysfunction of the mucociliary apparatus, which subsequently predisposes to further infections resulting in a “vicious cycle.”^[16–18] This is known as Cole’s “vicious cycle” hypothesis.^[17] Insults to the lungs, including infectious and noninfectious causes, are often associated with an inflammatory process that eventually leads to airway destruction and, consequently, dilation of the bronchial tree.^[16,19–23]

The combination of chronic inflammation, dilated airways, and dysfunctional ciliary apparatus results in impaired clearance of secretions and altered lung microbiome. These changes in pulmonary structure build a suitable environment for bacterial colonization and subsequent airway infections.^[19–21] The repeated cycles of infection lead to further airway damage and the vicious cycle continues. Bronchiectasis is characterized by irreversibly dilated and abnormally thickened bronchial walls. This appears to be a “pathological end point,” resulting from a number of interacting respiratory dysfunctions.^[15] Bronchiectasis may coexist with or result from other diseases, such as TB,^[24] asthma,^[25,26] COPD,^[27–29] and connective tissue disease causing lung fibrosis.^[30–32] Approximately 50%–70% of reported cases of bronchiectasis can be attributed to a specific cause most of which are attributed to previous infectious;^[33–35] however, identifying the etiology depends on the sampling frame and depth of investigations.^[36]

Classification

Bronchiectasis can be classified according to morphology, anatomy, hemodynamic function, etiology, and clinical presentation. Based on airway morphology as proposed by Reid,^[37] bronchiectasis is classified into cylindrical, varicose, and saccular morphological types. In cylindrical bronchiectasis, the bronchi have thick, straight, and uniform walls, in addition to dilation and reduction of bronchial subdivisions in some ways. The sagittal imaging section, in this type, shows the characteristic “train track” appearance, whereas in the coronal section, they have a “signet ring” appearance. In varicose bronchiectasis, the bronchi are not uniform in shape or size. Bronchi may have rounded and bulging ends with alternating areas of dilation and constriction. In saccular (cystic) bronchiectasis, the bronchi are severely dilated and form large cysts. Bronchiectasis can also be classified anatomically to either localized or diffuse or, based on a ventilation perfusion scan, to perfused or nonperfused bronchiectasis. Localized bronchiectasis results often from airway obstruction which is uncommon and may occur bilaterally or from childhood pneumonia

which is more common and generally confined to one area distal to the main segmental or lobar bronchus. Diffuse disease is often related to immune or congenital diseases and often affects both lungs which is typically multilobar.^[38] However, childhood pneumonia may also cause multilobar disease.^[8,39]

Etiology of Bronchiectasis

Numerous causes of bronchiectasis have been recognized which may differ between different ethnic societies. Table 1 lists the common recognized causes reported in literature. Unfortunately, there are no local epidemiological studies about the common causes of bronchiectasis in our community; though we believe that postinfectious bronchiectasis is still the most common cause. The etiologies of bronchiectasis can be categorized into the following pathophysiological groups.

Table 1: List of causes of noncystic fibrosis bronchiectasis

Autoimmune disease/connective tissue diseases
Rheumatoid arthritis
Sjogren's syndrome
Ankylosing spondylitis
Relapsing polychondritis
Tracheobronchomegaly (Mounier–Kuhn syndrome)
Marfan's disease
Cartilage deficiency (Williams–Campbell syndrome)
Cilia abnormalities
Primary ciliary dyskinesia
Hypersensitivity
Allergic bronchopulmonary aspergillosis
Immune deficiency
Immunoglobulin deficiency
HIV infection
Job's syndrome (hyper-immunoglobulin E syndrome)
Inflammatory bowel disease
Ulcerative colitis
Crohn's disease
Injury
Pneumonia/childhood infections
Aspiration
Smoke inhalation
Malignancy
Chronic lymphocytic lymphoma
Stem cell transplantation; graft-versus-host disease
Obstruction
Tumor
Foreign body
Lymphadenopathy
Traction
Pulmonary fibrosis
Other
Alpha 1-antitrypsin deficiency
Yellow nail syndrome

Postinfectious bronchiectasis

Some infectious agents associated with postinfectious bronchiectasis such as measles, pertussis, adenovirus 21, and TB are the principal causative agents of respiratory damage in bronchiectasis.^[40-45] Others are concurrent infections with bronchiectasis such as allergic bronchopulmonary aspergillosis (ABPA), *P. aeruginosa*, human immunodeficiency virus, and atypical mycobacteria.^[41-45]

Airway damage in bronchiectasis compromises the normal pulmonary defense, thereby paving the way for pathogenic microbial colonization and subsequent new and/or recurrent infections. Patients with bronchiectasis, particularly adults, are often colonized with potentially pathogenic organisms.^[46] This colonization predisposes to lung infections which activate inflammatory process and the release of inflammatory mediators that cause progressive tissue damage. In severe bronchiectasis, lower airways are usually colonized with pathogens that increase in density leading to infection during the periods of exacerbation.^[17,47] The glycoprotein constituents of the bacterial cell wall attract immune defense cells such as neutrophils, macrophages, and lymphocytes, with neutrophils being the most important response element. The outer covering of Gram-negative bacteria (e.g., *P. aeruginosa*) is composed of complex lipopolysaccharides.^[43] *Haemophilus influenzae*, mainly nontypeable, is the most frequently isolated pathogen (34%–64%) in patients with bronchiectasis followed by *Pseudomonas*, *Streptococcus* species, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Mycobacterium avium* complex (MAC).^[47-49] Factors that influence the frequency of isolated pathogens include patient's age and disease severity.^[50] *Mycobacterium* species and *Aspergillosis* are rare in children and *Pseudomonas* is associated with more severe bronchiectasis.^[51,52] In children, the presence of *P. aeruginosa* should raise a suspicion of cystic fibrosis (CF). Table 2 lists the commonly isolated pathogens in patients with bronchiectasis. The growth of specific pathogens in culture from expectorated sputum does not provide direct evidence of an ongoing infection, especially during early bronchiectasis.^[49] Sputum culture in up to 24% of bronchiectasis cases was negative, especially in milder forms of the disease.^[49]

Pathogens, especially *P. aeruginosa*, which are associated with poor prognosis directly compromise mucociliary clearance through the release of inflammatory mediators that erode the epithelial layer of each cilium.^[53] The presence of these pathogens was shown to increase the inflammatory response significantly, even in clinically stable patients.^[54-56] Furthermore, a strong correlation was observed between bacterial count and the intensity of the inflammatory response. Chronic colonization with *P. aeruginosa* is associated with an accelerated decline of

Table 2: Microbes associated with bronchiectasis

<i>Haemophilus influenzae</i>
<i>Pseudomonas aeruginosa</i>
<i>Streptococcus pneumoniae</i>
<i>Staphylococcus aureus</i>
<i>Mycobacterium tuberculosis</i>
<i>Escherichia coli</i>
<i>Burkholderia cepacia</i>
<i>Alcaligenes xylosoxidans</i>
<i>Mycoplasma pneumoniae</i>
<i>Branhamella catarrhalis</i>
<i>Stenotrophomonas maltophilia</i>
<i>Acinetobacter baumannii</i>
<i>Aspergillus</i> spp.

lung function, more systematic inflammation, frequent severe exacerbations, hospitalization, and 3-fold increased risk of death.^[54,55] Therapeutic interventions geared toward reducing the airway bacterial population are likely to improve patient's symptoms and the quality of life (QoL). Chronic colonization with *S. aureus* should raise suspicion of either ABPA or CF. A repeat sputum culture is recommended when symptoms fail to respond to antibiotic therapy directed against an identified pathogen. In certain cases, severe infections that occur during early childhood, such as pertussis and measles, permanently modify the pulmonary architecture and render the airways continually vulnerable to microbial infections.

Inheritable causes associated with abnormal mucociliary clearance

Disorders associated with impaired clearance of secretions from airways can lead to bronchiectasis due to predisposition to recurrent pulmonary infections. Examples of such disorders include primary ciliary dyskinesia (PCD). PCD is a relatively rare disorder and has been determined as the cause of bronchiectasis in 9%–21% of children and up to 13% of adults with bronchiectasis.^[57-59] Another rare congenital abnormality of mucus clearance which accounts for <3% of bronchiectasis in adults is Young's syndrome. It is defined as a clinical triad of bronchiectasis, chronic rhinosinusitis, and obstructive azoospermia. Young's syndrome is characterized by abnormally viscous secretions that lead to reduced mucus clearance of the airway secretion and obstructive azoospermia. In Young's syndrome, sweat gland, pancreatic function, and ciliary activity are normal.^[60]

Immunodeficiency syndromes

By predisposing to recurrent pulmonary infections, congenital and acquired immunodeficiency syndromes can lead to bronchiectasis. Underlying immune-related causes include chronic granulomatous disorders and deficiencies of inflammatory complements or immunoglobulins (Igs) (IgG, IgA, or IgM).^[23,61,62] Early

diagnosis and treatment of primary immunodeficiency disorders, however, prevent the development or at least the progression of bronchiectasis in children.^[63-66]

Bronchial obstruction

Bronchial obstruction leads to the accumulation of airway secretions which predispose to pulmonary infection. Bronchial obstruction can be due to intraluminal obstruction by foreign bodies, carcinoid tumor, or other primary or secondary malignancy, or due to extraluminal compression from adjacent enlarged lymph nodes.^[23,67-69]

Other disorders

Bronchiectasis is associated with other disorders such as inflammatory bowel disease;^[70-73] α 1-antitrypsin deficiency;^[74,75] Marfan's syndrome;^[76] Hyper-IgE syndrome ("Job's syndrome");^[77] Swyer-James syndrome;^[78] asthma;^[25,26] COPD;^[27-29] lung fibrosis;^[30-32] and connective tissue diseases, especially rheumatoid arthritis^[79,80] and bronchiolitis obliterans.^[35,81] In addition, recurrent aspiration^[35,82] and exposure to toxins^[83,84] may cause bronchiectasis. Idiopathic bronchiectasis, after excluding secondary causes, accounts for <50% of cases.^[32]

Recommendations

- All patients with bronchiectasis should be assessed for underlying cause (s) (A)
- All patients with bronchiectasis should be assessed for a history of previous lower respiratory infection (D)
- All patients with bronchiectasis should undergo microbiological evaluation (C)
- Congenital defects should be considered in all patients with bronchiectasis (D)
- Gastric aspiration should be considered in all patients with bronchiectasis (D)
- Immune deficiency should be considered in all patients with bronchiectasis, especially those with severe, persistent, or recurrent infections involving multiple sites (B)
- Asthma or COPD should be considered as potential associated diseases if no other cause can be identified (D)
- The possibility of CF should be considered in all patients with bronchiectasis. (D).
- Bronchiectasis should be considered in patients with rheumatoid arthritis and inflammatory bowel disease (D)
- PCD should be considered in patients with bronchiectasis and a history of recurrent upper respiratory tract infections or infertility (D)
- Airway obstruction should be excluded in patients presenting with localized bronchiectasis (D)
- Sputum culture should be done for patients with bronchiectasis. It is very crucial in management and future prognosis of bronchiectasis. Chronic colonization with *P. aeruginosa* is associated with an

accelerated decline of lung function, frequent severe exacerbations and hospitalization, and a 3-fold increased risk of death (A)

- A national study is needed to determine the common underlying etiologies among our population and about TB, genetic disease, and other contributing causes of bronchiectasis (D).

Clinical Features of Bronchiectasis

Disease presentation depends on the severity of the disease; however, the most common and the most characteristic symptom is chronic productive cough with mucopurulent secretion.^[85] In children, productive or wet cough may only be present during periods of exacerbation.^[86-88] In some cases, expectoration is initially scanty, but becomes progressively more copious as the disease progresses and pulmonary function worsens. Other symptoms include dyspnea, wheezing, pleuritic chest pain, and hemoptysis.^[85] Symptoms may also include systemic symptoms such as fever, fatigue, and weight loss, which occur in up to 73% of patients with bronchiectasis exacerbation.^[85]

Symptoms can vary depending on the involved predisposing factors. A definitive diagnosis is required since many other respiratory conditions may present with similar clinical features. The presence of persistent or intermittent chronic cough accompanied by purulent sputum is the most common reason reported in hospital referrals which should raise the suspicion and initiation of confirmatory investigations for early diagnosis of bronchiectasis.

Bronchiectasis may present with symptoms commonly identified in other airway diseases such as asthma or COPD, which may cause delay in the diagnosis of bronchiectasis. Despite the similarity symptoms, these airway diseases have different pathophysiological and prognostic characteristics; therefore, early differentiation between them is crucial for effective treatment. The pattern of symptom presentation is often relevant to diagnosis. For example, patients with asthma or COPD who have chronic sputum production of purulent sputum should be investigated for possible bronchiectasis.^[25-29]

History should also include neonatal symptoms, previous pulmonary infection in childhood, gastric aspiration, smoking history, asthma, connective tissue or autoimmune symptoms, and infertility. Family history is also important to identify genetic causes such as CF, PCD, and immunodeficiency. Recently, multidimensional clinical prediction tools, including the Bronchiectasis Severity Index (BSI)^[89] and the FACED score,^[90] have been developed to assess disease severity and future mortality in adults. Indicators of "FACED" prediction tool are summarized by its letter as "F" for forced expiratory

volume in 1 second (FEV₁); A for age, C for colonization with *Pseudomonas*, E for extent of bronchiectasis based on the number of lobes involved, and D for the Medical Research Council's dyspnea score. The ranges of score which predict the 5-year all-cause mortality are 0–2 for mild, 3–4 for moderate, and 5–7 for severe diseases [Table 3]. The BSI, on the other hand, is based on nine score parameters that are categorized as mild when ≤ 4 , moderate when 5–8, and severe when ≥ 9 [Table 4]. A recent study which included 1612 patients across seven European cohorts showed similar accuracy between both FACED and BSI tools for predicting mortality. Although FACED scoring tool is easy to use, BSI was superior to FACED in predicting multiple clinically useful outcomes including respiratory symptoms, exercise capacity and lung function decline, exacerbations leading to hospital admissions, and QoL.^[91] Unfortunately, both scoring tools are not validated in our patient population and children.

Children with bronchiectasis who present with chronic cough should be referred to a specialist when there are features suggestive of underlying bronchiectasis, for example, a chronic productive cough that does not resolve after 4 weeks of antibiotics.^[86,92]

Recommendations

- Adult patients who have the following clinical features should be investigated for bronchiectasis (D for all of the following)
 1. Persistent chronic productive cough on daily basis, especially
 - a. In younger age at presentation
 - b. An absence of smoking history
 - c. Sputum colonization with *P. aeruginosa*
 - d. Family history suggestive of an underlying

Table 3: Noncystic fibrosis bronchiectasis severity score: The FACED score

	Points
Chronic colonization by <i>Pseudomonas aeruginosa</i>	
No	0
Yes	1
Dyspnea mMRC score	
0-2	0
3-4	1
FEV ₁ percentage predicted	
≥ 50	0
< 50	2
Age (years)	
< 70	0
≥ 70	2
Number of lobes	
1-2	0
> 2	1

Maximum score: 7 points. 0-2 mild, 3-4 moderate, and 5-7 severe disease. mMRC = Modified Medical Research Council, FEV₁ = Forced expiratory volume in 1 s

- inherited disease (such as CF, dextrocardia, immunodeficiency disease).
- Unexplained hemoptysis
 - Patients diagnosed with COPD who have an increasing number of exacerbations and worsening lung function, especially if there is no history of smoking
 - Patients with bronchial asthma or COPD who have large amounts of purulent sputum
 - Recurrent lower respiratory tract infections (more than three times per year)
- The number of infective exacerbations and hospital admissions per year and the type of used antibiotics should be recorded (D)
 - BSI scoring [Table 4] should be used as a multidimensional clinical prediction to assess disease severity (B)

- Children who have the following clinical features should be investigated for bronchiectasis:
- Chronic moist/wet/productive cough that do not resolve after 4 weeks of antibiotics (B)
- Chronic respiratory symptoms with finger clubbing and/or failure to thrive (D)
- An episode of severe or incompletely resolving pneumonia (D)
- Recurrent pneumonia (D)
- Localized chronic bronchial obstruction (D)
- Respiratory symptoms in children with risk for aspiration or recurrent sinusitis (D)
- Unexplained hemoptysis (D)
- Respiratory symptoms with any clinical features of CF, PCD, or immunodeficiency (D).

Investigations

In all cases, unless the underlying cause is very well documented, investigations of patients with bronchiectasis are performed to identify the underlying etiology and assess disease severity. Studies have shown that prior knowledge of the underlying etiology of bronchiectasis leads usually to changes in the disease management plan.^[93] For example, a positive sputum culture for *S. aureus*, *P. aeruginosa*, or nontuberculous mycobacteria may indicate CF or primary cilia dyskinesia as potential underlying etiologies. *Burkholderia cepacia* complex, on the other hand, may indicate chronic granulomatous disease or CF.^[35,53,94,95] Diagnostic investigations also help physicians in making informed decisions such as the choice of antibiotic regimen.

Blood Tests

Although routine blood tests such as complete blood count (CBC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) do not help in establishing a diagnosis of bronchiectasis, they are useful inflammation markers for assessment of disease severity and exacerbation. Other specific tests should include serum Igs (IgG, IgA, IgM, and IgE) which should be measured in all patients to determine the unrecognized etiology of bronchiectasis. The yield of measuring of IgG subclasses in bronchiectasis is very low and therefore is not recommended.^[95-97] If specific antibody levels to pneumococcal and tetanus antigens are low, these should be repeated 6 weeks after vaccination.^[33,35]

Specific blood investigations also include *Aspergillus fumigatus* radioallergosorbent (RAST) test and IgG precipitins, serum protein electrophoresis strip and urine electrophoresis, and autoantibodies, which include α 1-antitrypsin and its phenotypes in case of low blood level. Autoimmune diseases including connective tissue diseases may also cause bronchiectasis in particular rheumatoid arthritis and patients with Sjogren's

Table 4: The bronchiectasis severity index

	Points
Age (year)	
<50	0
50-69	2
70-79	4
>80	6
BMI	
<18.5	2
18.5-25	0
26-29	0
≥30	0
FEV ₁ , percentage of predicted	
>80	0
50-80	1
30-49	2
<30	3
Hospital admission	
No	0
Yes	5
Exacerbations before the study	
0	0
1-2	0
≥3	2
MRC dyspnea score	
1-3	0
4	2
5	3
<i>Pseudomonas</i> colonization	
No	0
Yes	3
Colonization with other organisms	
No	0
Yes	1
Radiological severity: >3 lobes involved or cystic bronchiectasis	
No	0
Yes	1

Mild BSI score (0-4), moderate BSI score (5-8), severe BSI score (>9).
mMRC = Modified Medical Research Council, FEV₁ = Forced expiratory volume in 1 s, BSI = Bronchiectasis Severity Index, BMI = Body mass index

syndrome. Rheumatoid factor (RF) and antinuclear antibody (ANA) although are not specific, if RF or ANA is highly positive, further investigation should be considered. Autoimmune disease screening should include antinuclear factor (ANA), RF, aCCP, SSA, and SSB antibodies.^[35,98] Bronchiectasis may be a consequence of emphysema rather than a primary effect,^[99] hence α 1-antitrypsin is not recommended except in patients with radiological evidence of emphysema.

Recommendations

The following blood tests should be ordered in patients with no obvious cause for bronchiectasis:

1. CBC, ESR, and CRP should be ordered in all patients with bronchiectasis and during exacerbation (D)
2. Serum Igs (IgG, IgA, and IgM) and serum protein electrophoresis should be measured (A)
3. All adult patients should be investigated for ABPA, serum IgE, *Aspergillus fumigatus* RAST/CAP, *Aspergillus* precipitins, and peripheral eosinophils (C)
4. Specific baseline antibody levels to pneumococcal and tetanus antigens should be measured; if low, the tests should be repeated 6 weeks after vaccination (D)
5. If autoimmune or connective tissue disease is suspected, initial screening tests should include RF and ANA (D)
6. Patients with bronchiectasis who have radiological evidence of basal emphysema should be investigated for α 1-antitrypsin deficiency (D).

Radiology

Chest X-ray (CXR) is usually the initial imaging study performed in patients with suspected bronchiectasis, although is very insensitive. CXR findings in patients with bronchiectasis vary considerably, but may raise a suspicion of bronchiectasis, and trigger further definitive imaging. These findings include prominence of bronchial markings, rounded or cystic areas of increased radiance, parallel linear densities, tram-track opacities, and lobar/lobular atelectasis. The presence of chronic pulmonary infiltrates on repeated CXR should also raise the suspicion of bronchiectasis.^[100] Normal CXR has been reported in 7.1% of patients with bronchiectasis.^[100] This is due to the limited sensitivity and specificity of CXR for the diagnosis of bronchiectasis, particularly in mild disease, ranging from 13% to 47% of confirmed bronchiectasis cases.^[100,101] Thus, a normal CXR does not exclude the presence of bronchiectasis.

HRCT is more sensitive and remains the gold standard test for diagnosis of bronchiectasis.^[102] Addition of multiple detection computed tomography to HRCT further increases the diagnostic accuracy.^[101] Diagnostic features of CT scan include the absence of normal bronchi

tapering toward distal airways and increase of the size of inner bronchial walls compared to adjacent arteries by more than 1–1.5 times in adults.

A lower bronchoarterial ratio should be used in children. In young children (<5 years of age), the normal bronchoarterial ratio is around 0.5, and in older children (<18 years of age), the upper limit is <0.8.

Bronchi are visible within 1–2 cm of the “lung fields.”^[65,100,103-106] In addition to confirming the diagnosis of bronchiectasis, an HRCT scan helps in the classification and staging of airway morphology and, in certain cases, identification of probable underlying pathogenesis and etiology.^[100,103,104,107-109]

The high sensitivity of HRCT for the detection of bronchiectasis makes it the method of choice for definitive diagnosis of bronchiectasis. HRCT scan findings have been linked to specific underlying disease pathophysiology in some studies.^[109-111] Other studies showed limited value of HRCT patterns of bronchiectasis in distinguishing between idiopathic form and specific disease etiologies.^[107,109] For example, HRCT scan may also reveal features suggestive of underlying disease etiology, such as ABPA, tracheobronchomegaly, endobronchial obstruction, and CF.^[106,111-113] Ventilation perfusion scan (VQ) may help to identify areas of cystic bronchiectasis that are irreversibly damaged as they are nonperfused and can play a role in surgical resection in multisegmental bronchiectasis.

Recommendations

- CXR have very low sensitivity in diagnosing bronchiectasis except in advanced cases (C)
- All patients with bronchiectasis should have a baseline CXR and during follow-up when indicated (D)
- A HRCT scan of the chest is the method of choice for a definitive diagnosis of bronchiectasis (A)
- HRCT of the chest may suggest the underlying cause of bronchiectasis, for example, ABPA and tracheomegaly (C)
- Patients with bronchiectasis do not need routine follow-up HRCT of the chest except in patients with immune deficiency syndromes to evaluate for disease progression (D)
- VQscan may be indicated prior to surgical treatment (C).

Spirometry

In patients with bronchiectasis, lung function impairment might be heterogeneous. Spirometry is not specific or sensitive in the diagnosis of bronchiectasis and can be entirely normal even when bronchiectasis is determined by HRCT scans, especially in children.^[63,64,114] However, it is regarded as a complementary test that may aid in monitoring and assessing disease severity. Studies

have shown deterioration of lung function, including carbon monoxide diffusion capacity (DLCO) during bronchiectasis exacerbation which improves after antibiotics.^[63,64,90,115-117] Risk factors for the accelerated decline in lung function may include colonization with *P. aeruginosa* and frequent exacerbations.^[90,115,116] Obstructive pattern with low FEV₁/forced vital capacity (FVC) ratio is the most frequent finding. However, in a severe disease with destruction of the lungs, a low FVC, indicating an additional restrictive defect, can also be seen. FEV₁ and the FEV₁/FVC ratio predict the degree of functional compromise^[64] and disease stability and progressions in patients with bronchiectasis.^[63,64,118] In a recent study enrolling 61 patients with bronchiectasis, both lung volume (FEV₁ and FEV₁/FVC) and DLCO and DLCO/VA were decreased considerably during the follow-up period.^[117]

A lack of response during the bronchodilator test should alert the physician to the possibility of underlying bronchiectasis.^[119] In patients with mild-to-moderate bronchiectasis, significant lung function impairment should prompt further investigations including sputum culture to rule out *P. aeruginosa* colonization which is known to cause further disease progression.^[115]

Recommendations

- All patients with bronchiectasis should have spirometry performed initially and annually during follow-up (C)
- Patients suspected to have bronchial asthma require spirometry and pre- and post-bronchodilator therapy may be used to diagnose associated asthma (D)
- Pulmonary function impairment should prompt to further investigations, including sputum culture to rule out *P. aeruginosa* colonization (C)
- Full pulmonary function tests (PFTs) including DLCO may help identify other disorders such as COPD and emphysema (D).

Sputum Culture

In adults with bronchiectasis, *H. influenzae* is the most frequently isolated pathogen (35%–47%) followed by *P. aeruginosa* in up to 31% of cases in adults, but not in children.^[35,49] In Saudi Arabia, *P. aeruginosa* was the most common isolated organism among hospitalized patients with bronchiectasis^[10] and among those who have chronic lung disease.^[120] Among children with bronchiectasis, *H. influenzae* is the most commonly isolated (37%), followed by *S. pneumoniae* (17%) and *P. aeruginosa* (16%).^[14] However, the relative frequency of isolated pathogens is influenced by many factors such as the setting, patient age, disease severity, and underlying disease etiology.^[51,121] The relative frequencies of pathogens depend on the setting, age, severity, and

underlying cause of disease.^[51,120] Sputum specimens that are reflective of lower respiratory tract bacterial flora should be sent always for culture whenever possible. Routine sputum samples can be obtained through spontaneous coughing, sputum induction with hypertonic saline, or through chest physiotherapy. Three sputum samples may improve the diagnostic yield, especially in patients without prior sputum culture results. The specimen should preferably be obtained before starting antibiotic therapy, especially during infective exacerbations, and should be delivered to the microbiology laboratory within 3 h of collection as *S. pneumoniae* and *H. influenzae* microbes may not be cultured if specimens are kept in the heat for longer period.^[122] Antibiotic choice should preferably be guided by knowledge of previous sputum or lower airway microbiology.^[121] Deep throat swab may be useful to replace sputum in nonexpectorating children <10 years of age, especially for *S. aureus* and *P. aeruginosa*.^[122]

Routine testing for mycobacteria is not needed unless suggestive clinical features are present such as unexplained systemic symptoms and new CXR infiltrates or cavities that are not responding to treatment with antibiotics. If *S. aureus* is persistently grown from sputum cultures in adults, ABPA or CF should be suspected,^[123] although they may also be isolated in bronchiectasis from other etiologies.^[52]

Recommendations

- All patients with bronchiectasis should have microbiological sputum analysis (D)
- To maximize the yield of culture sample, sputum specimens, unless kept frozen, should reach to the microbiology laboratory within few hours of collection and should be protected from heat (D)
- Isolation of *S. aureus* from patients with bronchiectasis should raise the possibility of ABPA or CF (D).
- During exacerbation, sputum samples should be obtained prior to the commencement of antibiotic treatment (D)
- *Mycobacterium tuberculosis* infection is not uncommonly associated as a cause or complication of bronchiectasis; therefore, the initial evaluation should involve at least one sputum culture for mycobacteria (D)
- Repeated testing for mycobacteria should be performed when there are suggestive clinical or radiologic features of mycobacterial infection including the following situations (D):
 - Unexplained fever, night sweats, or weight loss
 - New infiltrates or cavities not responding to antibiotic treatment
 - Deterioration in clinical condition of the patient despite appropriate antibiotics.
- A national study to determine the incidence and the most common pathogens among our patients with bronchiectasis (D).

Investigations to Exclude Cystic Fibrosis

The diagnosis of CF has important prognostic and therapeutic implications in patients with bronchiectasis features. CF should be excluded in children and young adults aged <40 years and patients who have diffuse bronchiectasis and in all patients, regardless of age, with features suggestive of CF. The diagnosis of CF is confirmed by either a sweat chloride level ≥ 60 mmol/L or by the identification of two or more CFTR mutations detected in genomic DNA located in *trans* on two separate chromosomes or in *cis* on the same chromosome.^[124] Sweat chloride levels >60 mmol/L make CF a likely diagnosis.^[125] The most common CF genotypes in Saudi Arabia are the 1548delG and I1234V, which are different from CF genotypes encountered among Caucasians.^[126]

Recommendations

- The possibility of CF should be considered in all children and adult patients with diffuse bronchiectasis and no obvious cause (D)
- Regardless of the age, all patients with bronchiectasis should be investigated for CF if one or more of the following features are present (D):
 1. Persistent isolation of *S. aureus* or *P. aeruginosa* in the sputum
 2. Male infertility
 3. Features of malabsorption or history of childhood steatorrhea.
- Patients in whom CF is suspected should undergo two sweat chloride tests at an accredited laboratory (D).

Bronchoscopy

With the availability of chest CT, fiber-optic bronchoscopy is not recommended routinely for the diagnosis of bronchiectasis. Bronchoscopy is indicated if the CT scan suggests the presence of an obstructing lesion, foreign body, or tumor causing distally located bronchiectasis or in young children (who cannot expectorate) to obtain a microbiological specimen. A foreign body as a cause of bronchiectasis is not always apparent in a CT scan; therefore, bronchoscopy should be considered for localized bronchiectasis or with a history suggestive of foreign body aspiration.^[127] Bronchoscopy is indicated in all patients with right middle lobe syndrome to evaluate for a compressing or obstructing lesion or TB infection.^[128-131] It can be used also to obtain additional samples for microbiological investigation in acutely ill patients, patients not responding to antibiotic treatment, or if TB is suspected. Patients with bronchiectasis presenting with hemoptysis may need bronchoscopy to identify the location of bleeding for further interventional procedures.

Recommendations

- Bronchoscopy is indicated in patients with bronchiectasis in the following situations (all D):
 1. Children with localized bronchiectasis (to exclude foreign body)
 2. Adults with localized bronchiectasis (to exclude obstruction or tumor)
 3. Patients not responding to antibiotic treatment
 4. Patients presenting with severe hemoptysis to localize the site of bleeding for further management
 5. If *M. tuberculosis* complex or atypical *Mycobacterium* is suspected and repeated sputum samples are negative.

Ciliary Function Tests

PCD syndrome is an uncommon genetic disease inherited in an autosomal recessive manner that causes bronchiectasis. The major abnormality in PCD is a defect of the structure and/or function of motile cilia/flagella, causing chronic upper and lower respiratory tract infections and infertility.^[132] The prevalence of PCD is estimated to be 1 in 20,000 live births.^[133] PCD is usually associated with productive cough, chronic rhinosinusitis, otitis media, and infertility. When it is associated with dextrocardia, known as “Kartagener’s syndrome,” the diagnosis is usually not difficult. However, in the absence of dextrocardia, the diagnosis may be difficult and requires a high index of suspicion.^[133] PCD should be suspected in any patient without an identified cause of bronchiectasis and those with a history of chronic rhinitis or otitis media since the neonatal period or infertility.^[95,132,134] Saccharin and nasal nitric oxide tests, if available, should be used as screening tools to measure the nasal mucociliary clearance for ciliary function. This test, however, has a limited usefulness in children because the patient must lie still with no sneezing, sniffing, or coughing for up to 1 h. Alsaadi *et al.* suggest that FNO can be used as a useful screening tool for PCD in Saudi children.^[135] Nasal NO is extremely low (5%–15% of normal) in PCD patients and hence it is a useful for screening for PCD.^[136]

If these test results are abnormal, confirmation should be done by nasal mucosal biopsy and examination of cilia by electronic microscopy, if available. Cilia ultrastructure should be studied for beat frequency and pattern.^[132,133,137] Genetic testing may be useful in diagnosing PCD. More than 30 genes were able to identify approximately 60% of PCD cases.^[138] As more genes were discovered, the sensitivity of genetic testing will improve. Therefore, genetic testing for PCD mutation is recommended if PCD is suspected and other tests for PCD are not available or not conclusive.^[138]

Recommendations

Patients with bronchiectasis should be investigated for primary ciliary disorder if they have one or more of the following features (all D).

- Persistent productive cough, persistent rhinitis, or chronic middle ear disease with or without situs anomalies
- Siblings of patients with PCD, particularly if they have symptoms suggestive of PCD
- If available, a saccharin test and nasal nitric oxide should be performed in each patient as screening tests
- If these test results are abnormal, assessment for cilia ultrastructure and motility through a nasal brush biopsy should be made or the patient should be referred to another higher tertiary care hospital
- Genetic testing for PCD mutation is recommended if PCD is suspected and other tests for PCD are not available or not conclusive.

Other Tests

Table 5 lists the common tests that may be indicated for the investigation of patients with bronchiectasis. Gastro-esophageal reflux disease (GERD) and gastric aspiration are common in patient with CF, but its association with bronchiectasis is not established.^[139,140] Other tests may be done to rule out other congenital defects or underlying etiology such as inflammatory bowel disease or associated symptoms such as sinusitis.

Recommendations

- Patients with bronchiectasis should be investigated for GERD and gastric aspiration if the presentation is suggestive or if there is no identified underlying etiology (D)
- Patients with bronchiectasis should be investigated for other congenital defects if suspected or other symptoms of underlying etiologies (D).

Management

Acute exacerbation

Once bronchiectasis has developed, the aim of management is to limit the cycle of infection and inflammation and, hence, improving QoL, reducing disease advancement, and preventing acute exacerbations and hospitalizations. Exacerbations are associated with disease progression, frequent hospitalization, poor QoL, and high mortality.^[6] Therefore, regardless of the specific cause of bronchiectasis, the first step in its management is to treat and prevent the frequency of exacerbations and complications. The diagnosis of bronchiectasis exacerbation is purely clinical. Kapur *et al.* identified that changes in cough frequency or character, fever, and increase in purulent sputum are the most common

features of bronchiectasis exacerbation.^[88] Bronchiectasis exacerbation in children, may manifest by increased sputum expectoration; cough severity; change in cough quality (dry to wet); or sputum purulence, and reduction in exercise tolerance. Fever and hemoptysis are uncommon in exacerbations of pediatric bronchiectasis. However, the presence of productive cough and increased cough severity (score ≥ 2) over 72 h with or without elevated serum biomarkers (e.g., CRP) was the best predictor of an exacerbation.^[87] Other studies have defined an exacerbation as an increase or new onset of more than one of the following pulmonary symptoms: sputum volume, sputum purulence, and dyspnea.^[141] In the largest prospective study of patients with bronchiectasis by O'Donnell *et al.*,^[142] an exacerbation was defined as the presence of four out of nine symptoms. In children, exacerbations are defined clinically with or without elevated serum biomarkers (e.g., CRP).^[87] Table 6 summarizes the clinical features of bronchiectasis exacerbation in adults and children. The second important step in the management of acute exacerbation is deciding whether the patient should be admitted to hospital or treated as an outpatient.

The criteria for hospital admission include dyspnea with a raised respiratory rate (>25 /min) and increased

Table 5: Criteria for surgical resection of bronchiectasis

Adequate cardiopulmonary reserve
Localized bronchiectasis
Symptomatic bronchiectasis failed to respond to medical therapy
Development of complications in cylindrical or diffuse bronchiectasis
Failure to thrive (children)
Poor academic performance (children)
Frequent admission or hospitalization >3 years

Table 6: Clinical features of bronchiectasis exacerbation in adults

A: In adults
1. Change in sputum production (consistency, color, volume, or hemoptysis)
2. Increased dyspnea (chest congestion or shortness of breath)
3. Increased cough
4. Fever (38°C)
5. Increased wheezing
6. Decreased exercise tolerance, malaise, fatigue, or lethargy
7. FEV ₁ or FVC decreased 10% from a previously recorded value
8. Radiographic changes indicative of a new pulmonary process
9. Changes in chest sounds
Note: Presence of four of these symptoms was defined as having an acute exacerbation
B: In children
Exacerbations are defined clinically (increased cough, altered cough and/or sputum characteristics) with or without elevated serum biomarkers (e.g. C-reactive protein)

work of breathing, hypotension, respiratory failure, oxygen saturation $<92\%$, temperature $\geq 38^{\circ}\text{C}$, and failure to improve after oral antibiotics or to take oral therapy.^[95] When possible, sputum samples should always be obtained for bacteriologic culture prior to initiation of antibiotics and blood cultures should be performed if the body temperature is $\geq 38^{\circ}\text{C}$ or more and among patients with evidence of respiratory distress.

Recommendations

- The most important step in the management of bronchiectasis is to recognize symptoms of exacerbation and to promptly start appropriate therapies (D)
- The definition of bronchiectasis exacerbation is based predominantly on clinical features. In adults, if they have at least four of the following nine symptoms (C):
 1. Change in sputum production (consistency, color, volume, or hemoptysis)
 2. Increased dyspnea (chest congestion or shortness of breath)
 3. Increased cough
 4. Fever ($>38^{\circ}\text{C}$)
 5. Increased wheezing
 6. Decreased exercise tolerance, malaise, fatigue, or lethargy
 7. FEV₁ or FVC decreased by 10% from previously recorded value
 8. Radiographic changes indicative of a new pulmonary process
 9. Changes in chest breath sounds.
- In children, exacerbations are defined clinically by increased cough, altered cough, and/or sputum characteristics with or without elevated serum biomarkers (e.g., CRP). (D), D is a separate it indicate grading of evidence
- The second step in the management of an exacerbation is to decide whether the patient needs hospitalization or can be treated at an outpatient department (D).

Management of acute exacerbation

The treatment and prevention of bronchiectasis exacerbation is an important step in the management of bronchiectasis. A number of options are currently available, but the choice of treatment depends commonly on factors such as the underlying etiologies, individual case assessments, prognosis, whether the disease is diffuse or localized, and the acceptability of management plans by the patient. As bronchiectasis is a chronic disease, cost may be a crucial factor in decisions that must be made by patients and their families regarding disease management options on a long-term basis.

The management of bronchiectasis exacerbations is multifaceted and should include, besides patient education, the use of appropriate antibiotic therapy,

measures to improve airway clearance, prescription of airway drug therapy such as bronchodilators and anti-inflammatory drugs, prevention of future exacerbation, identification of candidates for surgical intervention, and dealing with the acute and chronic disease complications.

Pharmacotherapeutic Interventions

Challenges encountered by clinicians in the management of bronchiectasis include the absence of drugs that are primarily designed for treating bronchiectasis and the lack of well-designed randomized controlled studies about the best antibiotic therapy for acute exacerbation.

Antibiotic Therapy

Antibiotics are indicated in the management of all patients with bronchiectasis exacerbations. The choice of antibiotics and treatment regimen depends on many factors, including disease severity and patient-specific considerations, such as the presence of other concurrent conditions that could preclude certain treatment options. For example, caution is recommended when selecting macrolides and fluoroquinolones in cases of concurrent MAC infection as there is a heightened chance of selecting resistant strains of MAC when macrolide is used as a single agent. Furthermore, the duration of treatment is important in optimizing clinical outcome in certain cases.

The antibiotics should be selected based on the most likely causative organism of exacerbation and guided by sputum analysis, if available. It is advisable that sputum samples are sent for microbiological testing prior to the initiation of antibacterial treatment to initiate pathogen-specific antibiotic treatment. Nevertheless, in practical terms, antibiotic treatments can typically be based on suspected pathogens derived either from a patient's medical history or from the prevalence pattern of infectious agents in the immediate community. Antibiotics should be selected so as to cover the most likely suspected pathogens, particularly when co-infections are suspected.

The choice of antibiotics for an acute exacerbation is dependent on many factors, which include disease severity, availability of sputum culture analysis and drug sensitivity results, patient's tolerance to oral therapy, and the need for hospital admission. Unfortunately, there is no good evidence about the best choice of antibiotics or duration of therapy in acute exacerbation.^[95,143,144] In addition, patients enrolled in most of the published studies are partially representative of the patients seen in clinical practice.^[145] The majority of mortality and morbidity in bronchiectasis cases occur in patients who

are not eligible for many current trials. Due to the paucity of more inclusive studies, a recent Cochrane review about short courses of antibiotics for children and adults with bronchiectasis did not provide enough evidence to make a recommendation about the choice of antibiotics or duration for treatment of acute exacerbation.^[146]

Oral antibiotics

Oral therapy is recommended for clinically stable patients if it can be tolerated. Based on expert's opinion, antibiotic therapy should be started according to culture and drug sensitivity results if available. If sputum culture results are not available or not done, or in case of high risk of *P. aeruginosa* colonization, it is better to use anti-pseudomonas agents (e.g., fluoroquinolone). If the organism is not beta-lactamase-positive *H. influenzae*, amoxicillin 500 mg administered orally every 8 h for 14 days is the recommended first-line option as its antibiotic coverage includes *H. influenzae*, which is the most common organism in the lower airways of patients with postinfectious bronchiectasis. If beta-lactamase-producing *H. influenzae* or *M. catarrhalis* is isolated or suspected, beta-lactamase inhibitors such as clavulanate should be concurrently administered with amoxicillin, typically as amoxicillin-clavulanate in a dose of 625 mg 8 hourly for 14 days in adults (in children, use the adjusted doses for weight). Alternatively, a second- or third-generation cephalosporin can be used. These regimens cover *M. catarrhalis* infections as well. The option of clarithromycin (500 mg 12 hourly for 14 days) is only recommended for patients who are allergic to penicillin.^[95,144]

The local concentration of antibiotics is an important issue in the treatment of *P. aeruginosa* infections as the bacterium is intrinsically resistant to the usually administered doses of antibiotics due to a variety of reasons including the production of biofilm. For this reason, much higher concentrations of antibiotics may be required. For patients with positive *Pseudomonas* culture, the initial antibiotic selection depends on the sensitivity patterns of the isolated organisms. In the absence of resistance to quinolones, the usual drug of choice is ciprofloxacin 500 mg (or 750 mg, depending on disease severity) every 12 h for 14 days as a first-line treatment. The first-line treatment of methicillin-sensitive *S. aureus* (MSSA) infections involves flucloxacillin 500 mg every 6 h for 14 days. For methicillin-resistant *S. aureus* (MRSA) or *M. tuberculosis*, we recommend seeking for specialist and expert advice.

Duration of Therapy

There is no consensus or rigorous medical evidence about the best duration of antibiotics. Most experts recommend therapy for 10–14 days.^[147] The presence of co-infections

is often considered as a justification for instituting combination of antibiotic therapy, but a single agent with an antibacterial profile that covers all suspected pathogens, when available, is preferred. In certain cases, however, the antibiotic resistance profile of the infection will require a combination of antibiotic therapy.

Intravenous antibiotics

Intravenous (IV) antibiotics are indicated for treatment of bronchiectasis exacerbation in the following situations; severe exacerbation, critically ill patients, and patients who are unable to tolerate an oral regimen, have an antibiotic-resistant organism, or did not respond to oral antibiotics. As with oral antibiotics, the choice should be guided by previous or current knowledge of sputum culture and sensitivity. If resistant organism is not expected, third-generation cephalosporins, such as cefotaxime, are sufficient to cover *H. influenzae* and other respiratory pathogens. If *Pseudomonas* species is suspected, ceftazidime at a dose of 2,000 mg 8 hourly for 2 weeks is recommended. Dual therapy, i.e., beta-lactam plus aminoglycoside or quinolones is controversial and is not recommended unless *Pseudomonas* is isolated in a critically ill patient.^[95] There is currently no published evidence supporting the addition of inhaled aminoglycoside (tobramycin or gentamicin) to IV antibiotics in acute exacerbations due to *Pseudomonas* infection and, therefore, it is not recommended.^[95,144]

Duration of Therapy

There is no consensus or rigorous evidence about adequate duration of antibiotic treatment or the proper time to switch IV to oral therapy. Once the culture results are available, the choice of antibiotics should be adjusted accordingly. Switching to oral therapy could be justified if the organism is sensitive and the patients show clinical improvement and can take oral medication. If the patient has a resistant organism or no oral alternatives, it is preferable to continue IV antibiotics for a total of 10–14 days.^[148,149]

Recommendations of antibiotic regimens

- Patients with bronchiectasis who present with infective exacerbation should be assessed for the need for admission depending on severity and the route of antibiotics (D)
- Sputum sample should always be sent for culture before commencing empiric antibiotic treatment (D):
 - Once the sputum culture is ready, the antibiotic regimen can be modified according to sensitivity
 - Sputum culture should be repeated if there is no response to the initial antibiotic treatment.
- If the patient is a candidate for oral antibiotics, we recommend the following:
 - If the organism is not beta-lactamase-positive

H. influenzae or *Pseudomonas*, amoxicillin 500 mg administered orally every 8 h for 14 days is recommended as the first-line option for adults. The dose needs to be adjusted for children (B)

- If beta-lactamase-producing *H. influenzae* or *M. catarrhalis* is confirmed or suspected, beta-lactamase inhibitors such as clavulanate should be concurrently administered with amoxicillin, typically as amoxicillin-clavulanate at a dose of 625 mg 8 hourly for 14 days for adults (this dosage needs to be adjusted for children) (B).
- Alternatively, second- or third-generation cephalosporin, (B), or
- Clarithromycin (500 mg 12 hourly for 14 days in adults [this dosage needs to be adjusted for children]) is recommended for patients who are allergic to penicillin (B).
 - If the suspicion of *Pseudomonas* is high, a fluoroquinolone (e.g., ciprofloxacin) is recommended (B)
 - In patients are colonized with *Pseudomonas*, the initial antibiotic selection should be based on the sensitivity patterns, if available.
- If there is no resistance to quinolones, ciprofloxacin 500 mg (or 750 mg, depending on disease severity) every 12 h for 14 days should be considered. The dose needs to be adjusted for children (B)
- In patients not responding to oral ciprofloxacin, monotherapy with an antipseudomonal IV antibiotic should be considered (B)
 - The first-line treatment of MSSA infections includes flucloxacillin 500 mg every 6 h for 14 days for adults (needs to be adjusted for children) (C)
 - For methicillin-resistant MRSA or *M. tuberculosis*, we recommended to seek specialist/expert advice (D).
- If the patient requires IV antibiotics, we recommend the following:
 - The choice of IV antibiotic should always be guided by previous knowledge of the sputum culture and sensitivity (D)
 - If no resistant organism is expected, third-generation cephalosporins, such as cefotaxime or ceftriaxone, for adults should be considered (needs to be adjusted for children) (B).
- Dual therapy (i.e., beta-lactam plus aminoglycoside, or quinolone) is controversial and is not recommended unless the patient has *Pseudomonas* and is critically ill (D).
 - Aminoglycoside may cause nephrotoxicity and hearing loss; therefore, it should be used only where facilities to monitor the serum level are available and patients should be monitored frequently
- Addition of inhaled aminoglycoside (tobramycin or gentamicin) to IV antibiotics in acute

exacerbations due to *Pseudomonas* organism is not recommended (D)

- Patients infected with *P. aeruginosa* who do not respond to oral ciprofloxacin should be treated with IV antipseudomonal antibiotics (D)
- If fluoroquinolone resistance is suspected or the patient is critically ill, combined anti-pseudomonas antibiotic is recommended (D)
- We do not recommend the use of inhaled antibiotics (tobramycin, gentamicin, or colistin) except in very selected cases with chronic *Pseudomonas* colonization and frequent exacerbation and hospitalization (D).

Long-term Management of Bronchiectasis

Role of short- and long-term inhaled antibiotics

Inhaled antibiotics have been increasingly used in the management of bronchiectasis to target the infection source directly and to minimize the systemic side effects. The rationale for using inhaled antibiotics is to deliver a relatively high dose of drugs by directly releasing the antibiotic into the infected area to achieve high concentrations at the site while minimizing systemic absorption and toxicity.^[150] Studies in patients with CF colonized with *P. aeruginosa* in sputum showed a reduction in sputum *Pseudomonas* density, decreased hospitalizations, and improved lung function. The evidence base of the clinical efficacy of inhaled antibiotics in bronchiectasis is modest and conflicting and not sustained beyond 3 months.^[151-156]

A Cochrane systematic review in 2011 did not come to a solid conclusion regarding inhaled antibiotics due to the paucity of the evidence.^[146] Yang *et al.* recently published a meta-analysis that included eight randomized controlled trials (RCTs) comprising 539 adults that studied the efficacy and safety of long-term inhaled antibiotics for patients with bronchiectasis. That meta-analysis concluded that inhaled antibiotics are effective in reducing the sputum bacterial density, attenuating the risk of exacerbation increase and the eradication of *Pseudomonas*.^[157]

A recent systematic review that included 12 randomized trials and 8 meta-analyses involving 1854 participants showed that inhaled antibiotics are more effective than placebo in reducing sputum bacterial load, eradicating the bacteria from sputum, and reducing the risk of acute exacerbations in stable bronchiectasis. However, there was no significant benefit in reducing the risk of unscheduled hospitalizations or in improving health-related QoL. Moreover, the use of inhaled antibiotics was associated with a small, but statistically significant, reduction in predicted FEV₁%, increase in cough, wheezing, and dyspnea.^[155,158] Based on the

existing data, we do not recommend routine use of inhaled antibiotics (tobramycin, gentamicin, or colistin) except in very selected cases with chronic *Pseudomonas* colonization, frequent exacerbation, and significant morbidity.^[159,160]

Recommendation

- Benefits of long-term inhaled antibiotics are not clear and we do not recommend their use (D).

Macrolides and Long-term Oral Antibiotic Treatments

The purpose of long-term antibiotic treatment of infections in bronchiectasis is to reduce exacerbations and improve patients' QoL. It aims to reduce the microbial load and/or ameliorate airway inflammation and, thus, break the vicious cycle of infection–inflammation–impaired mucociliary clearance. Antibiotics, particularly macrolides, have immune modulatory effects even at doses below those required for antimicrobial effects and have been used in several chronic airway diseases.^[161-163] Even though it is reported that macrolides can penetrate through the mucoid matrix of the small airways and into intraluminal regions, their observed efficacy in bronchiectasis has been attributed to immunomodulatory effects, such as their ability to prevent inflammatory cell mobilization, cytokine production, and a sputum secretion-reducing effect through the modulation of chloride diffusion.^[164] Macrolides lack direct activity against *P. aeruginosa*, but can prevent the synthesis of its protective biofilm. In addition, they have activity against *H. influenzae* and *S. pneumoniae*. Recently, meta-analyses studies concluded that the long-term use of macrolides is a treatment option for stable bronchiectasis, both in adults and children. Macrolides were shown to be effective and safe in reducing bronchiectasis exacerbations, improving lung function in adults, and decreasing sputum volume but did not reduce hospital admissions for exacerbations or improve QoL.^[141,165-169] In adults, the duration of treatment varied from 6 to 52 weeks; the most tried macrolide was azithromycin 250–500 mg 2–3/times/week. In children, the duration of therapy in two published studies was 12–24 months.^[170,171]

Other long-term antibiotics used in patients with frequent exacerbation should be based on previous sputum culture. A recent Cochrane review^[172] showed how long-term antibiotics, in rotation or continuous, may reduce bronchiectasis exacerbation and hospitalization. However, drug resistance is increased more than threefold. Recent guidelines recommend long-term antibiotics only for patients who have three or more exacerbations per year, or where the risk of developing severe morbidity is high.^[160] Long-term quinolones should

not be used in patients colonized with *P. aeruginosa* due to the high risk of antibiotic resistance.^[173-175]

Recommendations

- Long-term, low-dose macrolide therapy reduces the frequency of exacerbations and sputum volume, attenuates the decline in pulmonary function, and improves QoL in patients with bronchiectasis, but at a cost of increased risk of side effects and antibiotic resistance (A)
- Macrolides are recommended in patients with moderate-to-severe bronchiectasis with three or more exacerbations and/or two hospitalizations in the previous year causing significant morbidity (A)
- The advantages of long-term macrolides therapy need to be balanced against the risks, which include the emergence of bacterial resistance and cardiotoxicity (D).
- Prerequisite to start macrolides includes: (D)
 - A sputum culture should be obtained to document MAC is not present
 - An ECG should be obtained in adults to rule out prolonged QT prior to starting long-term macrolides.
- Long-term antibiotics (rotational or continuous) should be guided by sputum culture results and considered in patients with three or more exacerbations and/or two hospitalizations in the previous year causing significant morbidity (D)
- Long-term antibiotics therapy should be assessed for efficacy, development of resistance and side effects frequently, and should not exceed 1 year in duration (D).

Eradication of Chronic Colonization with *Pseudomonas aeruginosa*

Colonization with *P. aeruginosa* is associated with increased airway inflammation, more frequent exacerbations, worse QoL, greater risk of hospitalization, and increased mortality is one of the major risk factors for accelerated decline in lung function and frequent exacerbations.^[54,115,116,176,177] Unfortunately, there are no national studies about the prevalence of *P. aeruginosa* among bronchiectasis. In one study among adult hospitalized patients with bronchiectasis, it was found that *P. aeruginosa* was the most common organism.^[10] Another study found that *P. aeruginosa* was a common pathogen among patients with bronchiectasis who have associated chronic lung disease.^[178] *P. aeruginosa* accounts for only 16% of children <14 years with bronchiectasis in one tertiary center.^[14] Studies in patients with CF colonized with *P. aeruginosa* in sputum showed reduction in sputum *Pseudomonas* density which led to decreased hospitalizations but did not affect lung function.^[154] The evidence base of the clinical

efficacy of eradication of *P. aeruginosa* in bronchiectasis is modest, not sustained and conflicting.^[151-156] A Cochrane systematic review, 2011, did not come to solid conclusion regarding inhaled antibiotics due to paucity of the evidence.^[146] Yang *et al.*^[157] recently published a meta-analysis which included eight RCTs recruiting 539 adults about the efficacy and safety of long-term inhaled antibiotics for patients with bronchiectasis and concluded that inhaled antibiotics are effective in reducing the sputum bacterial density, attenuating the risk of exacerbation and increasing the eradication of *Pseudomonas*. A recent systematic review including 12 randomized trials and 8 meta-analyses involving 1854 participants showed that inhaled antibiotics are more effective than placebo in reducing sputum bacterial load, eradicating the bacteria from sputum, and reducing the risk of acute exacerbations in stable bronchiectasis. However, there was no significant benefit in reducing the risk of unscheduled hospitalizations or in improving health-related QoL. Moreover, use of inhaled antibiotics was associated with a small, but statistically significant, reduction in FEV₁% predicted, increase in cough, wheezing, and dyspnea.^[155,158] Based on the existing data, we do not recommend routine use of inhaled antibiotics (tobramycin, gentamicin, or colistin) except in very selected cases with chronic *Pseudomonas* colonization and frequent exacerbation and significant morbidity.^[159,160]

Recommendations

- Patients with frequent exacerbation and colonized with *P. aeruginosa* should be referred to a specialist (D)
- There is a need to do more studies about the effectiveness of eradication in our population (D)
- There is a need to do studies about eradication of *P. aeruginosa* in patients with bronchiectasis versus CF (D).

Bronchodilators

Increased airway hyper-responsiveness, increased airway smooth muscle mass, and bronchospasm are the likely explanations for airway obstruction usually observed in bronchiectasis.^[54,179,180] Some patients exhibit hyper-responsiveness or recurrent bronchospasm due to concurrent asthma or COPD or because the bronchiectasis is secondary to ABPA or post-TB: these conditions are likely to respond to bronchodilators.^[54,180-185] Due to a lack of RCTs, the Cochrane review did not recommend the routine use of bronchodilator short-acting β 2-agonist,^[186-188] anticholinergic,^[189] or oral methylxanthines^[186] pending availability of further evidence. Therefore, there is no strong evidence to recommend routine bronchodilators, including β 2-adrenoceptor agonists, anticholinergic agents, or oral xanthines, in the treatment of bronchiectasis. There is a subset of patients who may benefit from

β 2-agonist therapy.^[180-185,190] The use of anticholinergics has to be balanced with the theoretical risk of influencing sputum viscosity. Therefore, assessment of airflow obstruction reversibility in response to beta-agonist is important and should be done prior to starting bronchodilators in all patients with bronchiectasis.

Recommendations

- There are subsets of patients with bronchiectasis who may benefit from β 2-agonists or anticholinergic bronchodilators:
 1. Spirometry and bronchodilator response should be requested in bronchiectasis patients. Those who demonstrate a response can be started on β 2 agonist and/or anticholinergic inhalers (D)
 2. If facilities for performing spirometry are not available, an empirical trial of bronchodilator is justified in selected patients such as those with an asthma phenotype; however, patients should be assessed clinically for improvement (D)
 3. We do not recommend the use of methylxanthines in patients with bronchiectasis (D).

Anti-inflammatory Agents

The main essence of bronchiectasis is inflammatory changes and continuous damage of the airway.^[17] Biopsies from airways, bronchoalveolar lavage (BAL) analysis, and sputum analysis can confirm the presence of multiple pro-inflammatory mediators. Studies confirm the presence of tumor necrosis factor- α (TNF- α), elastase, myeloperoxidase, interleukins (IL)-8 and IL-6 in BAL, endobronchial biopsies, an increase in adhesion molecules such as E-selectin, intercellular adhesion molecule-1, and vascular adhesion molecule-1 level in serum, and TNF- α , IL-8, and neutrophil elastase in sputum.^[47,191-193] This persistent inflammation plays a role in the progressive deterioration of lung function and frequent exacerbation.^[194] The identification of the cardinal role of inflammatory mediators in the pathogenesis of bronchiectasis has suggested that efforts to control associated inflammatory responses are likely to yield desirable clinical outcomes. Antibiotics to treat the underlying cause of infection are the cornerstone of bronchiectasis management and well established.

The Cochrane review concluded that current evidence is insufficient to support or refute the use of inhaled or oral NSAIDs for the management of bronchiectasis in adults or children^[195] and there are not enough studies to recommend oral NSAIDs in the management of bronchiectasis in adults or children.^[196]

An older Cochrane review (2001) on the use of oral steroids in patients with stable bronchiectasis and patients in acute exacerbation described the absence

of any randomized trial and, hence, reached no firm conclusions.^[197] However, systemic corticosteroids should not be used for patients with non-CF bronchiectasis except in the subset of patients with ABPA or associated bronchial asthma, particularly when there is a poor response to inhaled steroids.

Tsang *et al.* conducted a double-blind, placebo-controlled trial that followed the use of inhaled steroids (inhaled corticosteroid [ICS]) in adults (73 cases) over 12 months. They concluded that ICS treatment is beneficial to patients with bronchiectasis, particularly those with *P. aeruginosa* infection.^[198] Elborn *et al.* studied the effect of inhaled beclomethasone dipropionate (1500 µg/day) on symptoms, lung function, and sputum production in a double-blind, placebo-controlled, crossover study in twenty patients with bronchiectasis and concluded that ICS treatment is beneficial to patients with bronchiectasis, resulting in an 18% reduction in daily sputum production, decreased cough score, and improvement in PEF and FEV₁.^[199] Another prospective, randomized, double-blind study by Martínez-García *et al.* using fluticasone (250 mg or 500 mg bid for 6 months) in 93 adults with bronchiectasis found improvement in the dyspnea score, sputum production, and cough, but only for high doses of ICS.^[200]

The Cochrane review concluded that there is insufficient evidence to recommend the routine use of inhaled steroids in adults with stable state bronchiectasis.^[201] However, ICS treatment may improve lung function but the effect is small. Long-acting β₂ agonist/ICS combination therapy may reduce dyspnea, wheeze, and cough.^[202]

Therefore, a therapeutic trial may be justified in adults with difficult-to-control symptoms and in the subset of patients who show evidence of airway hypersensitivity, asthma, COPD, or ABPA. No recommendation can be made for the use of ICS in adults during an acute exacerbation or in stable bronchiectasis unless they have evidence of reversible airway disease. Similarly, in children (for any state), ICS are not recommended as there are no related studies.^[203]

Leukotrienes, particularly LTB₄, are an important group of mediators released by mast cells at the site of inflammation. LTB₄ and IL-8 are perhaps the most important of these and their inhibition is likely to yield beneficial results in bronchiectasis. Antagonists of leukotriene receptors (LRAs) are licensed for the treatment of acute episodes in patients with asthma as they can inhibit the inflammatory, chemotactic, and bronchoconstriction properties of leukotrienes. However, there is no evidence supporting the routine use of LRAs in bronchiectasis patients.^[204] Furthermore,

a Cochrane review of the available clinical studies has suggested that there may be a theoretical basis for the use of LRAs in bronchiectasis, but the absence of data from controlled trials suggests that their routine use in bronchiectasis is not recommended at present.^[205]

Recommendations

- Inhaled or oral NSAIDs are not recommended for acute exacerbation or in stable bronchiectasis patients unless there is co-existing airway hyper-responsiveness (D)
- Systemic corticosteroids should not be used for patients with bronchiectasis except in the subset of patients with ABPA (D)
- Decisions to use or discontinue combined ICS-long-acting beta-2 agonist should be individualized based on the presence or absence of co-existing airway hyper-responsiveness and considering side effects associated with the therapy (D)
- Routine use of LRAs in patients with bronchiectasis is not currently supported by evidence (D).

Airway Clearance

The main pathophysiology of bronchiectasis is a vicious circle of airway infection and inflammation, leading to alteration of the cilia and impairing mucociliary clearance. Therefore, the main principle of management, in addition to antibiotics, is to improve mucus clearance, which is considered essential in optimizing respiratory function, facilitating expectoration of sputum, and reducing the progression of lung disease. There are a variety of pharmacological and nonpharmacological techniques used to clear the airway from secretions. Pharmacological agents include nebulized hypertonic saline solution, mannitol, and mucolytic agents while nonpharmacological agents include airway clearance techniques (ACTs).

Airway Clearance Technique

ACTs include respiratory exercises, directed cough, forced expiration, chest physical therapy with postural drainage, hand or mechanical chest-clapping, positive expiratory pressure (PEP), oscillatory PEP (e.g., flutter valve device), and high-frequency chest wall compression [Table 7]. These ACT techniques can be used in isolation or in combination. There is limited evidence that the active breathing cycles and flutter are superior in the gravity-assisted position compared with the sitting position.^[206-208]

A recent Cochrane review (2015) concluded that the role of ACT in acute exacerbation is unclear; however, for stable patients with bronchiectasis, it is safe and may improve sputum expectoration, lung function, and health-related QoL.^[209] Mazzocco *et al.* studied stable bronchiectasis patients and found that chest physiotherapy increased the

Table 7: Various maneuvers of physiotherapy for bronchiectasis

Physiotherapy maneuvers	Techniques
Assistive components to techniques	Manual techniques
	Chest percussion/clapping
	Chest wall vibrations
	Overpressure
	Postural drainage
Device-dependent techniques	Gravity-assisted positioning if no contraindication
	Positive expiratory pressure
	Oscillating positive expiratory pressure
	Intrathoracic: Flutter
	Extrathoracic: High-frequency chest wall oscillations
	Intermittent positive pressure breathing
	Noninvasive ventilation
	Test of incremental respiratory endurance
Adjuncts to assist techniques	Humidification
	Nebulized therapy
	β ₂ -agonists
	Mucolytics
	Saline (0.9%)
Hypertonic saline 7%	
Mannitol	

mobilization of sputum, was well-tolerated and safe, and had no immediate or delayed effects on pulmonary function or oxygen saturation.^[210] Furthermore, it does not induce or increase the incidence of gastroesophageal reflux.^[211] Physicians and chest physiotherapists should review CT scans to confirm the location of the disease to determine the appropriate ACT. Patients should be taught and encouraged in the chosen ACT exercise while taking into account patient's preference and adherence to treatment.^[207]

Recommendations

- There is lack of data about the role of ACT in the management of acute bronchiectasis exacerbation; thus, it may be used if there are no contraindications (D)
- ACT is safe and recommended as it may improve sputum expectoration, lung function, and health-related QoL in stable bronchiectasis patients (C)
- Taking in account patient's preference and adherence to treatment, the patient or their caregiver should be taught and encouraged to use ACT and appropriate device (D).

Inhaled Hyperosmolar Agents for Bronchiectasis

Hypertonic saline inhalation is known to accelerate tracheobronchial clearance by potentially altering the physical properties of mucus and facilitating its clearance by increasing the water in the airway lumen and by reducing the entanglements of the mucin network.^[212]

In Kellett *et al.*'s study, regular use of 7% hypertonic saline improved lung function, QoL, and health-care utilization compared with normal saline.^[213] However, Nicolson *et al.*'s 12-month trial comparing normal saline and 6% hypertonic saline in stable bronchiectasis patients found no difference between the groups based on the outcomes of exacerbations, sputum colonization, QoL, and lung function.^[214]

Nebulized mannitol is expected to have a longer retention time in the local airways than hypertonic saline. In a recent Cochrane review, the use of mannitol in patients with bronchiectasis increased the time to first exacerbation and was found safe. The review concluded that mannitol has a role in reducing exacerbations and antibiotic use in patients with normal or mild-to-moderately impaired spirometry. A Phase 3 randomized study of the efficacy and safety of inhaled dry powder mannitol for the symptomatic treatment of non-CF bronchiectasis by Bilton *et al.* showed that inhaled mannitol was safe, but did not significantly reduce exacerbation rates.^[215] A recent Cochrane review concluded that hypertonic saline is unlikely to have benefit over isotonic saline in bronchiectasis patients.^[216]

The main problem with hypertonic saline and inhaled mannitol is their tendency to induce bronchospasm. In recent studies, 12% of patients treated with inhaled mannitol had airway hyper-responsiveness.^[217,218] A recent systematic review and meta-analysis including thirty studies which showed hypertonic saline was not more effective than normal saline for lung function, QoL, and hospitalization in bronchiectasis, while the effects of N-acetylcysteine were unclear. Mannitol also improve mucus clearance, sputum load, and exacerbation rate, but lacks evidence over long periods.^[219]

Recommendations

- Nebulized saline or mannitol may be useful in patients with bronchiectasis to increase the ease of sputum expectoration and decrease its viscosity (B)
- Airway hyper-responsiveness occurs in approximately 12% of patients; therefore, the physician should be aware of this side effect (D).

Recombinant Human DNase

Deoxyribonucleic acid (DNA) induces the necrotizing activity of neutrophils, which thickens sputum viscosity and makes it increasingly difficult to clear. A number of recombinant human DNases, such as pulmozyme, dornase α , and recombinant human DNase, have been used in this respect to break down the DNA content in the mucus of patients with CF. Indications from randomized investigations, however, have suggested that the use of rhDNase (which is approved for the management of CF)

in adult patients with bronchiectasis is associated with deteriorating respiratory function and rapidly declining FEV₁.^[142] A recent systematic review and meta-analysis included thirty studies confirming the risk of lung function decline and increase in exacerbation with DNase 1 use.^[219]

Recommendation

- DNase 1 in the treatment of bronchiectasis is potentially harmful and, therefore, is not recommended (A).

Mucolytic/Mucoactive Agents

Mucolytics are indicated for the facilitation of tracheobronchial clearance through modifications to the physicochemical properties of the sputum. However, data are only available on the proven efficacy of bromhexine in the management of bronchiectasis. Bromhexine disrupts the structure of mucopolysaccharide fibers in sputum and, therefore, reduces the viscosity of sputum and improves ciliary clearance.^[220] A double-blind RCT that compared bromhexine 30 mg three times daily to placebo in conjunction with antibiotics showed that bromhexine improved expectoration, sputum clearance, auscultatory findings, and the FEV₁.^[221]

Two other inhalational agents target the basic chemistry of the bronchial content and have been investigated in relation to bronchiectasis management. While N-acetylcysteine loosens the mucus matrix by disrupting disulfide bonds and pulmozyme dissolves the cysteine bonds of leukocytic DNA remnants present in the airway. However, undesirable side effects that involve the inflammatory response associated with these agents have precluded their routine use in the treatment of bronchiectasis. There are no data about the use of other mucolytics in non-CF bronchiectasis or in children in general. A recent Cochrane review (2014) about mucolytics in bronchiectasis concluded that bromhexine, coupled with antibiotics, may help with sputum production and clearance. Similarly, erdosteine may be a useful adjunct to physiotherapy for sputum clearance in stable patients.^[222]

Recommendation

- Bromhexine is the only mucolytic agent shown to be beneficial (coupled with antibiotics) in reducing sputum and expectoration in patients with bronchiectasis (B).

Pulmonary Rehabilitation

Patients with severe bronchiectasis, similar to other chronic pulmonary diseases, suffer from a marked decrease in exercise tolerance due to many factors including impaired muscle function and decreased physical activity levels in daily life, poor nutrition, the

ongoing inflammation due to active bronchiectasis, and reduction in lung function. There are limited data about the role of rehabilitation in bronchiectasis patients. However, many societies now recommend pulmonary rehabilitation as an essential component in the management of chronic disease and, therefore, bronchiectasis patients might be excellent candidates for pulmonary rehabilitation.^[223-225] There is evidence, though not very strong and needing better study conditions, indicating that pulmonary rehabilitation improves exercise tolerance and inspiratory muscle strength in patients with bronchiectasis.^[226-230] A recent systematic review by Lee *et al.* about pulmonary rehabilitation in bronchiectasis reported a reduced frequency of exacerbations and improvements in exercise capacity and QoL.^[231]

Recommendation

- Pulmonary rehabilitation is recommended as a potential complementary management option in patients with moderate-to-severe disease (C).

Vaccination

The multifactorial etiology of postinfectious bronchiectasis suggests that a combined vaccination approach is required to obtain effective antimicrobial coverage against all potential infectious agents. Vaccinations against influenza A and B viruses have been reported to reduce morbidity and mortality by up to 85% in the general population, particularly among elderly patients. It has also been recommended for routine use in chronic pulmonary illnesses such as bronchiectasis.^[232-234] Furthermore, patients with bronchiectasis have a high risk of contracting pneumococcal diseases and pneumococcal vaccination has been demonstrated to reduce the incidence of pneumococcal infections by up to 32% in adults.^[234] We recommend to follow the Saudi Guideline for Influenza and Pneumococcal Vaccination.^[235,236]

Recommendation

- Patients with bronchiectasis should receive pneumococcal and annual influenza vaccines as per the STS guidelines (D).

Surgical versus Nonsurgical Treatment for Bronchiectasis

The surgical management of bronchiectasis depends mainly on the distribution of disease, clinical presentation, and patient's suitability for surgery; morphology itself is not essential in terms of deciding surgery. However, it is helpful to define more precisely the patient selection criteria for surgery and areas to resect or preserve, particularly with diffuse or bilateral bronchiectasis.^[237,238]

The rationale for surgery is removal of diseased segments that are no longer functional and to prevent the infectious contamination of healthy lung tissue.^[238] Patients with localized areas of bronchiectasis in the presence of normal lung parenchyma should be assessed carefully. If these areas (lobar or multi segmental, unilateral or bilateral) are cystic, nonperfused, surgical resection is recommended early if the patient has satisfactory respiratory reserve. Early intervention can provide cure and prevent infection to the nonaffected areas secondary to spillage.

The initial management of patients with cylindrical and mixed bronchiectasis should be conservative, with the aim of controlling infection and improving bronchial hygiene with the aid of bronchodilatation and active physiotherapy. Associated medical conditions, such as GERD, Ig deficiencies, or sinusitis, should be identified and aggressively treated. Indications for surgical resection are reserved for irreversible, localized bronchiectasis that failed to respond to medical therapy [Table 5]. The Cochrane review did not identify any RCTs that address this issue despite it being a common practice to manage bronchiectasis surgically.^[239] The general indications for patients who failed initial medical treatments include recurrent chest infections, recurrent hemoptysis (failed embolization), lung abscess, failure to thrive due to the disease (children), and localized disease even if bilateral.^[237,238,240-246] Clinical and radiologic assessment should be conducted by the pulmonologist before surgery regarding safety of surgery and candidacy of patient for lung resection.

Preoperative Assessment

Before considering surgery for patients with bronchiectasis, radiological assessment in the form of plain radiography, PFTs, CT chest scan, and, in some cases, ventilation/perfusion lung scan also should be completed. The aims of diagnostic evaluation are radiologic confirmation, assessment of the extent of the disease, and the identification of any treatable causes. The pulmonologist should be consulted always and engaged in the management of the patient before the patient goes for surgery.

Prior to surgery, intraoperative flexible bronchoscopy is mandatory to identify possible etiologies, provide bronchial toilette, to obtain samples from the bronchial secretions that may guide antimicrobial treatment, chest physiotherapy, and for postural drainage.

Palliative Surgery

Palliative surgery is also indicated on the rare occasion of recurrent or massive hemoptysis in the context of diffuse disease, when bronchial artery embolization fails to control bleeding or when hemoptysis recurs following embolization.^[245,247] The exact site of bleeding must be

identified by bronchoscopy and angiography. Surgery in these cases carries higher mortality and morbidity risks. As a result, every effort should be made to control bleeding by conservative measures before surgery is considered.^[245]

Lung Transplantation

For end-stage bronchiectasis, bilateral lung transplantation is now an established and successful palliative treatment.^[248] Criteria for referral for lung transplantation include postbronchodilatation FEV₁ <30% and the threshold for transplant should be lowered in patients with pulmonary hypertension, respiratory failure, or pulmonary hypertension.^[160]

Recommendations

Surgery is indicated for patients with localized disease (even if bilateral) if symptoms fail to be controlled medically (D).

Patients should be evaluated by chest HRCT, PFT, and ventilation perfusion scan and should be referred to a chest physician or discussed through multidisciplinary meetings to assess patient candidacy of surgery before resection, or transfer to a specialized center (D).

Palliative surgery carries a high risk for morbidity and mortality and should be considered only in life-threatening situations of hemoptysis and after obtaining patient consent (D).

Follow-up of Patients with Bronchiectasis

Most patients with bronchiectasis could be followed up successfully through primary care or community medicine clinics. Guidelines help the treating physician to implement minimal standards for managing stable patients with bronchiectasis. Certain patients with bronchiectasis need to be followed up by a specialist pulmonary or infectious disease specialist at a secondary or tertiary care hospital. The criteria for specialist referral include all pediatrics with bronchiectasis, frequent exacerbation, respiratory failure, rapid deterioration in pulmonary physiology, patients colonized with chronic *P. aeruginosa*, or MRSA colonization or atypical mycobacteria, and patients who need surgical resection.^[160]

Routine follow-up for bronchiectasis includes clinic visits according to disease severity and annual PFTs, CXR, and influenza vaccine. The regular assessment of patients with bronchiectasis also includes education, counseling about smoking cessation, and assessment of nutrition status, exercise capacity, and referral for rehabilitation if needed.

Recommendation

- Patients should be referred to a specialist if they meet any of the following criteria (D):
 - All children with bronchiectasis for diagnosis and initial treatment
 - Frequent exacerbation or hospitalization (>2/year)
 - Respiratory failure
 - Rapid decline in pulmonary physiology or FEV₁/FVC decreased 10% from previous recorded value
 - Patients colonized with chronic *P. aeruginosa* or MRSA colonization
 - Patients who need surgical resection.

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