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Recommendations for diagnostic approach and management of bronchiectasis

Recomendaciones para abordaje diagnóstico y tratamiento de las bronquiectasias

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ABSTRACT. Bronchiectasis is a syndrome of chronic cough and production of viscous sputum associated with dilation of the airways and thickening of the bronchial wall. Exacerbations are usually caused by bacterial infections. It is a chronic disease that requires rapid responses for the treatment of exacerbations. Bronchial secretions should be cultured. Evaluate and treat underlying diseases to interrupt progression. In patients who have recurrent exacerbations (two to three in the last year) and do not have *Pseudomonas aeruginosa* infection, preventive therapy with a macrolide is recommended, excluding nontuberculous mycobacterial infections. In patients with recurrent exacerbations, or significant morbidity, and *Pseudomonas aeruginosa* in sputum, a therapeutic trial of nebulized tobramycin is useful. Nebulized tobramycin may also be for patients not infected with *Pseudomonas aeruginosa* in whom oral antibiotic prophylaxis is contraindicated, not tolerated, or ineffective. Patients who have *Pseudomonas aeruginosa* but cannot receive a nebulized antibiotic may benefit from macrolides as an alternative. Inhaled glucocorticoids are only indicated in patients with asthma or COPD. For patients who respond to bronchodilators on spirometry, the use of inhaled beta-adrenergic agents is suggested. All patients are candidates for pulmonary rehabilitation and bronchial hygiene. The prognosis is influenced by the underlying disease process, the frequency of exacerbations, and comorbidities, but in general, age-adjusted mortality is increased compared with the general population.

Keywords: bronchiectasis, approach, diagnosis, treatment.

RESUMEN. Las bronquiectasias son un síndrome de tos crónica y producción de esputo viscoso asociado con la dilatación de las vías respiratorias y el engrosamiento de la pared bronquial. Las exacerbaciones casi siempre son causadas por infecciones bacterianas. Es una enfermedad crónica que requiere respuestas rápidas al tratamiento de las exacerbaciones. Se deben cultivar las secreciones bronquiales, evaluar y tratar las enfermedades subyacentes para interrumpir la progresión. En los pacientes que tienen exacerbaciones recurrentes (dos a tres en el último año), y no tienen infección por *Pseudomonas aeruginosa,* se recomienda terapia preventiva con un macrólido, excluyendo infecciones por micobacterias no tuberculosas. En pacientes con exacerbaciones recurrentes o morbilidad significativa y *Pseudomonas aeruginosa* en el esputo, es útil una prueba terapéutica con tobramicina nebulizada. La tobramicina nebulizada también puede ser para pacientes no infectados con *Pseudomonas aeruginosa* en quienes la profilaxis con antibióticos orales está contraindicada, no se tolera o no es efectiva. Los pacientes que tienen *Pseudomonas aeruginosa*, pero no pueden recibir un antibiótico nebulizado pueden beneficiarse de los macrólidos como alternativa. Los glucocorticoides inhalados sólo están indicados en pacientes con asma o enfermedad pulmonar obstructiva crónica. Para pacientes con respuesta a broncodilatador en la espirometría se sugiere uso de agentes beta-adrenérgicos inhalados. Todos los pacientes son candidatos a rehabilitación pulmonar e higiene bronquial. El pronóstico está influenciado por el proceso patológico subyacente, la frecuencia de las exacerbaciones y las comorbilidades pero, en general, la mortalidad ajustada por la edad aumenta en comparación con la población general.

Palabras clave: bronquiectasias, abordaje, diagnóstico, tratamiento.

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Abbreviations:

NSAI = Non-stereoidal anti-inflammatory NSAI.
BSI = bronchiectasis severity index.
CFTR = cystic fibrosis transmembrane conductance regulator.
CV = cardiovascular.
CVID = common variable immunodeficiency.
DLCO = diffusing capacity of the lungs for carbon monoxide.
COPD = Chronic obstructive pulmonary disease.
ERS = European Respiratory Society.
FACED score = FEV_1, Age, Chronic colonization, Extension, Dyspnea Score.
FEV_1 = forced expiratory volume at one second.
CF = Cystic fibrosis.
GC = Glucocorticoids.
IGC = Inhaled glucocorticoids.
IV = Intravenous.
LABA = long acting beta agonist.
mMRC = Modified Medical Research Council Scale
NET = neutrophil extracellular traps.
P. aeruginosa = *Pseudomonas aeruginosa*.
PEP = Positive Expiratory Pressure
PZP = pregnancy zone protein.
GER = Gastroesophageal reflux.
PR = Pulmonary rehabilitation.
RR = Relative risk.
SABA = short acting beta agonist.
SGRQ = Saint George Respiratory Questionnaire.
HRCTS = High resolution CT scan.
ICU = Intensive Care Unit.

INTRODUCTION

Bronchiectasis is an acquired disorder of bronchi and bronchioles, characterized by a permanent abnormal dilatation and destruction of their walls. Its induction requires an infectious insult plus drainage alteration, airway obstruction or defects in the defenses of the host. Bronchiectasis share many clinical presentations with chronic obstructive pulmonary disease (COPD), including collapsible airway inflammation, expiratory airflow obstruction, frequent exacerbations that require scheduled or unscheduled consultations or hospitalization. Diagnosis based on the clinical history (daily cough, tenacious discharge expectoration, recurrent expectorations and, by imaging, bronchial dilatations).[1]

Epidemiology, diagnostic approach, pharmacological and non-pharmacological management are the objective of this review that aims to be a proposal for recommendations.

EPIDEMIOLOGY

Prevalence increases with age eight to 10 times after the 60 years of age (300-500/100,000) when compared to < 40-50 years of age (40-50/100,000).[2] In United States a prevalence of 350,000-500,000 is estimated in adults.[3] Medicare (≥ 65 years of age) has an annual prevalence of 701/100,000 inhabitants.[4]

The greatest risk factor for chronic cough in the non-smoking population is bronchiectasis (OR = 5), among the former smokers it is OR = 7. It is more common in women, they make an extensive use of health resources (consultations, antibiotics, CT scans and hospitalization),[2,4] its prevalence is higher in the marginalized population, affects young people and impacts survival.[5,6] Social and environmental factors undoubtedly play a rol, including smoke exposition, limited access to health services and delayed antibiotic prescription.

Mortality: some small studies have described mortality rate of 16-20% at five years, which increase with the hospitalization in the Intensive Care Unit (ICU) and comorbidity. A study in United Kingdom found that mortality adjusted by age for adults with bronchiectasis was approximately twice that of the general population, regardless of age difference.[7] A report of 48 patients from France found 19% mortality in the ICU and 40% mortality per year.[8] In one series of 57 patients in Singapur a 26% general hospitalization mortality was reported without difference if the patients received non-invasive ventilation or intubation with mechanical ventilation.[9] Severe hypoxemia and high APACHE II scores were the worst prognosis factors.

In one series of 245 patients with bronchiectasis in Belgium between 2006 and 2013, mortality was 20%, increasing to 55% among those with COPD.[10] The cause of death was mainly respiratory (58%).

Pathophysiology: the consequent host response, immune effector cells (mainly neutrophils), neutrophils proteases (elastase), oxidative stress (hydrogen peroxide, H_2O_2) and inflammatory cytokines create a transmural inflammation, mucosa edema, ulceration and neovascularization in the airways.[11] The following factors may contribute to the physiopathology of bronchiectasis:

1. **Neutrophils effects and neutrophil elastase:** progressive destruction of airways. Serum and local neutrophils have increased variability (reduced apoptosis), reduced phagocytosis, increased release of myeloperoxidase and damaged bactericidal activity (for *Pseudomonas*).[12] Pregnancy zone protein (PZP) correlates with exacerbations, worsening and the presence of Pseudomonas aeruginosa *(P. aeruginosa)*.[13] Neutrophil extracellular traps (NETs) are networks of strings of DNA that contain histone, elastase, PZP and other inflammatory mediators that are formed as part of a cellular death process of neutrophils, which also contributes to anormal and permanent destruction and dilatation of the bronchial and bronchiole walls.[14]
2. **Physical properties of the sputum/mucus:** it is more tenacious, viscous and less elastic, contains concentration of DNA, mucin (mainly MUC5B), and other solid components.[15] These differences may explain divergent responses to bronchial hygiene.

3. **Atopy as conductive of inflammation:** it leads to a worse course, allergen test and serum inmunoglobulin E are associated with reduced pulmonary function and worse bronchiectasis severity index (BSI) score.[16]
4. **Variants of heterozygous of the cystic fibrosis transmembrane regulator (CFTR):** contributes to the development of bronchiectasis through dysfunction of sodium and chloride channels.[17] There are one to two CFTR mutations.
5. **Vitamin D deficiency:** potential role in vicious cycle of the recurrences and more probability to have *Pseudomonas* colonization, worse respiratory symptoms and greater inflammation.[5]
6. **Common variable immunodeficiency (CVID):** it is associated with small airway damage (air entrapped) as incipient and potentially reversible damage.[5]
7. **Gastroesophageal reflux (GER):** there is great concern about this association.[18,19] Among patients with advanced pulmonary disease that were waiting lung transplant, patients with bronchiectasis had higher prevalence of GER (50%).[20] In a retrospective study of 81 patients with bronchiectasis in a center in Irland, 36% had a hiatal hernia and 62% had symptomatic GER. There was no predilection for any affectation of a particular lobe, the severity of the bronchiectasis was greater in subjects with hiatal hernia.[21]

RISK FACTORS

History of pneumonia (in childhood), alcoholism (bronchoaspiration, GER), pertussis, measles, tuberculosis (and granulomatosis), asthma, allergies, rheumatism, infertility, inhaled agents.[22-24] In *Table 1* shows the causes grouped by etiology and their diagnostic approach base on studies.[22-24]

IMPLICATIONS AND COMPLICATIONS

Decreased pulmonary function: patients with bronchiectasis have a mean annual decrease in forced expired volume in the first second (FEV_1) of 50-55 mL/year.[25] This is higher than in normal individuals (20-30 mL/year), but similar to patients with COPD (approximately 60 mL/year). Among patients with bronchiectasis, FEV_1 decrease accelerates when there is *Pseudomonas* colonization, frequent exacerbations, or increased inflammatory markers (e.g., C reactive protein).

Pulmonary vascular disease: an observational study evaluated 94 patients with bronchiectasis by echocardiography.[26] There was evidence of pulmonary hypertension (defined as an estimated systolic pulmonary arterial pressure > 40 mmHg) in 33% of patients and right ventricular systolic dysfunction in 13%. Right ventricular dysfunction was correlated with low FEV_1, low diffusing capacity for carbon monoxide (DLCO), hypercapnia and hypoxemia. Only 15% of patients had evidence of left ventricular dysfunction.

Hemoptysis: the origin of bleeding in bronchiectasis is due to the rupture of a tortuous bronchial artery or submucosal capillary plexus. It is a frequent and serious complication of the bronchiectasis. Hemoptoics are common in stable patients, while, the occurrence of increased amount of fresh blood or clots during an acute exacerbation is less common; bronchiectasis is a common cause of life-threatening bleeding. The most common causes of hemoptysis in bronchiectasis are mycobacteria and fungi. When bleeding is present, the time, amount and condition of the patient should be evaluated. The approach to bronchiectasis based on hemoptysis escapes the approach of these recommendations.

Cardiovascular morbidity: respiratory tract infections are associated with increased cardiovascular events (CV): myocardial infarction, stroke.[27] In a revision of patients with bronchiectasis from primary care practices in the United Kingdom, an increase in CV events was observed in the first 90 days after higher relative risk (RR) respiratory infection in the first three days.[28] In a separated study, bronchiectasis was an independent risk factor for the coronary artery disease and strokes after the adjustment for age, sex, smoking and other known CV risk factors.[29] Serum desmosine, is a marker of elastin degradation, it may be a marker of CV mortality.[30]

Classification of severity and prognosis

Few studies have examined the frequency of exacerbations, the hospitalization, comorbidities and mortality, as well as the rate of pulmonary decline function among patients with bronchiectasis; long-term outcome studies are limited.[8,25,31] Score systems have been propose to help guide prognosis assessment and identify patients who exacerbate frequently.[32,33] The bronchiectasis severity index (BSI) *(Table 2)*, was derived from 608 patients with bronchiectasis in a center in Scotland and was validated in 597 patients in other centers of the United Kingdom and Europe.[32] The predictors of hospitalization included prior hospitalization high index of dyspnea, low FEV_1, presence of *Pseudomonas* in the sputum and more extensive involvement (> 3 lobes) in high Resolution CT Scan. Mortality was correlated with advanced age, low FEV_1, prior hospitalization and three or more exacerbations in the last year. This score system presented a prognosis capacity for all the causes of mortality at four year of diagnosis, it also presented value for future hospitalization.[34]

FACED score *(Table 3)* is an easy scale to use composed by five variables and 10 points (**F**EV_1, **A**ge, presence or not of

Table 1: Diagnostic approach: characteristic causes and tests.[22-24]

Category	Specific examples/traits	Diagnostic test
Acquired bronchial obstruction (several produce localized bronchiectasis)		
Foreign body suction	Peanuts, bone, tooth, etc.	X-ray, CT scan; FBC
Tumors	Laryngeal papillomatosis; adenoma, endobronchial teratomas	X-ray, CT scan; FBC
Adenopathy	Tuberculosis; histoplasmosis; sarcoidosis	PPD; X-ray, CT scan; FBC
COPD	Chronic bronchitis	PFT, symptoms
Connectivopathies	Polychondritis, amyloidosis	Cartilage biopsy
Mucoid impaction	ABPA; bronchocentric granulomatosis; post-surgical	Total and specific IgE aspergillosis; skin reaction, X-ray, CT scan; bronchial biopsy
Congenital anatomical defects causing bronchial obstruction		
Tracheo-bronchial	Bronchomalacia; bronchial cyst; cartilaginous deficiency (Sx Williams-Campbell); tracheobroncomegaly (Sx Mounier-Kuhn); ectopic bronchus; tracheoesophageal fistula	X-ray, CT scan
Vascular	Intralobar sequestration, pulmonary arterial aneurysm	X-ray, CT scan
Lymphatics	yellow nail syndrome	History of dystrophy, slow-growing nails
Immunodeficiencies		
IgG	Congenital (Bruton type), agammaglobulinemia; selective deficiency (IgG2, IgG4); acquired Ig deficiency; variable common hypogammaglobulinemia; Nezelof Syndrome; «Naked lymphocyte syndrome»	Quantitative Ig and subclasses; damaged response to pneumococcal vaccine
IgA	Selective deficiency with or without ataxia-telangiectasia syndrome	Quantitative Ig
Leukocyte dysfunction	Chronic granulomatous disease (NADPH oxidase dysfunction)	Dihydrorhodamine 123; oxidation test; tetrazolium nitroblue test, genetic testing
Humoral immunodeficiencies (CXCR4 mutation, CD40 and ligand deficiency)	WHIM syndrome; hypergammaglobulinemia M	Neutrophil count; Ig levels
Abnormal clearance of secretions		
Mucociliary defects	Kartagener syndrome; ciliary dyskinesias	X-ray, CT scan (situs inversus); bronchial biopsy; ciliary motility; electron microscopy of sperm or respiratory mucosa
Cystic fibrosis	Typical early infantile LH; late presentation with sinopulmonary symptoms	Chlorine in sweat; genetic testing
Young syndrome	Obstructive azoospermia with sinopulmonary infections	Spermatocrit
Miscellaneous disorders		
Alpha-1 antitrypsina deficiency	Absence or synthesis/abnormal function	Alpha-1 antitrypsin levels
Recurrent bronchoaspiration pneumonia	Alcoholism; neurological disorders; lipoid pneumonia	Medical record; X-ray, CT scan
Connectivopathies	Sjogren syndrome and Rheumatoid Arthritis	Rheumatoid factor; antiSSA/antiSSB; salivary gland biopsy
Toxic inhalation of fumes and dusts	Ammonium; nitrogen dioxide, irritant gases; fumes; talc; silicates	Medical record; X-ray, CT scan

Table 1 continues: Diagnostic approach: characteristic causes and tests.[22-24]

Category	Specific examples/traits	Diagnostic test
Miscellaneous disorders		
Post-transplant rejection	Bone marrow, bronchiolitis obliterans (lung transplant)	PFT; X-ray, CT scan
Childhood infections	Pertussis; measles	Medical record
Bacterial Infections	Staphylococcus aureus, Klebsiella, Pseudomonas aeruginosa	Medical history; cultures
Viral Infections	Adenovirus (types 7 and 21), influenza, herpes simplex	Medical history, evidence of infection
Other infections	Histoplasmosis; Mycobacterium tuberculosis, non-tuberculous mycobacterium; mycoplasma	Cultures; stains

X-ray = simple chest X-ray. CT scan=computed tomography of the chest. FBC = fibrobronchoscopy. COPD = chronic obstructive pulmonary disease. ABPA = allergic broncho pulmonary aspergillosis. Ig = immunoglobulin. PFT = pulmonary function tests. Sx =syndrome. NADPH = nicotinamide adenine dinucleotide phosphate. Whim = warts, hypogammaglobulinemia, infections and myelocatexis. PPD = purified protein derivative. antiSSA =antibody Sjögren'ssyndrome A/Ro. antiSSB = antibody Sjögren's syndrome B/La.

Colonization/ chronic bronchial infection for *Pseudomonas*, radiological **E**xtension in the high resolution CT Scan mentioning the number of lobes affected and Dyspnoea measured by the modified Medical Research Council scale [mMRC] dichotomized in 0-II and III-IV, the higher score the more dyspnoea). It was developed in 397 subjects from a multi center cohort of 819 patients from Spain.[33] This scale presented an excellent predictive capacity for all causes of mortality five years after diagnosis and for respiratory causes.[34]

The BSI and FACED were evaluated retrospectively over 19 years with respect to mortality estimates in 91 patients followed at the Royal Brompton Hospital in London. Both scores gave equally mortality estimates at five years, with the FACED slightly higher at 15 years.[35] Regarding, other clinical results, in an additional analysis of 1,612 subjects of seven European cohorts, the BSI more accurately predicted exacerbations, hospitalizations, respiratory symptoms, and quality of life than the FACED score.[36]

Daily sputum production and the presence of *Pseudomonas* or other potential infectious pathogens in sputum culture were the main characteristics related to quality of life (QoL = *quality of life*), inflammatory markers and the clinical results at three years.[37]

Clinical criteria to guide management

1. Criteria for close or specialized monitoring:
   a. Congenital/genetic bronchiectasis (cystic fibrosis [CF], dyskinesias and immunodeficiencies).
   b. BSI score ≥ 9 points.
   c. Diffuse multilobe (multi-segmental) bronchiectasis with extensive involvement in pulmonary function tests ($FEV1_1$ < 50%p).
   d. Recurrent relapses ≥ 3 times/year.
   e. History of multiple hospitalizations.
   f. Chronic infection by *Pseudomonas*, *Staphylococcus aureus* or others.
   g. Candidate for eradication treatment (*Pseudomonas* or others).
   h. Candidate for resection for localized bronchiectasis.
2. Criteria for prophylactic outpatient antibiotic treatment:
   a. Unexacerbated patient (stable and without respiratory compromise) with positive isolation culture (chronic infection) or empirical.
3. Criteria for acute antibiotic treatment (exacerbation):
   a. Stable exacerbated patient without respiratory compromise for ambulatory management, or unstable, or with respiratory compromise for hospitalization, with positive cultures or empirical.
4. Criteria for eradication treatment *(Pseudomonas)*:
   a. New isolation of *Pseudomonas* in exacerbated or non-exacerbated patients.
5. Criteria for hospitalization:
   a. Unstable exacerbated patient or with respiratory compromise.
   b. Intravenous (IV) eradication treatment.

TREATMENT

The goals of bronchiectasis treatment are to prevent exacerbations, reduce symptoms, improve quality of life, and stop disease progression.

The underlying cause should be treated specifically, CFTR (cystic fibrosis transmembrane conductance regulator) modulators in CF; DNase in primary ciliary dyskinesia; antibiotics for non-tuberculous mycobacterial infections; macrolides in diffuse panbronchiolitis; intravenous or subcutaneous immunoglobulins in immunodeficiencies; inhibitors of acid secretion in gastroesophageal reflux (GER); oral and antifungal corticosteroids in allergic broncho pulmonary aspergillosis; smoking withdrawal; intravenous

alpha 1 antitrypsin in PIZZ phenotypes, management of associated diseases (COPD, asthma, inflammatory bowel disease, systemic diseases);and surgery or bronchial dilatation in bronchial obstruction.

An exacerbation of bronchiectasis is defined as a deterioration in three or more of the following symptoms: cough, sputum volume or consistency, sputum purulence, shortness of breath or exercise intolerance, fatigue or malaise, hemoptysis lasting at least 48 hours, accompanied by a change in the treatment of bronchiectasis, and exclusion of other possible causes of clinical deterioration.[38] It may be accompanied by changes in respiratory examination, deterioration of lung function, or increased markers of inflammation. The pathogens that are most often isolated in an exacerbation are: *P. aeruginosa, H. influenzae, S. pneumoniae, S. aureus, Moraxella catarrhalis* and enterobacteria.[39] Viruses are isolated in 25% of cases (coronavirus, rhinovirus, influenza, SARS-CoV-2).[25]

Table 2: Bronchiectasis Severity Index (BSI).[32,34]

	Score
Age (years)	
< 50	0
50-69	2
70-79	4
> 80	6
Body mass index	
< 18.5	2
18.5-25	0
26-29	0
≥ 30	0
FEV_1 (% of predicted value)	
> 80	0
50-80	1
30-49	2
< 30	3
Medical research council dyspnea scale	
1-3	0
4	2
5	3
Colonization by *Pseudomonas aeruginosa*	
No	0
Yes	3
Colonization by other organisms	
No	0
Yes	1
Radiological severity > 3 lobes or cystic bronchiectasis	
No	0
Yes	1
Hospitalization in the last year	
No	0
Yes	5
Exacerbations in the last year	
0	0
1-2	0
≥ 3	2

Score: mild 0-4 points, moderate 5-8 points, severe ≥ 9 points.

Table 3: FACED Score.[33,34]

Variable	Values	Scores
Exacerbations with hospital admission (previous year)	No	0
	At least 1	2
FEV_1 (% of predicted)	At least 50%	0
	Less than 50%	2
Age (years)	Under 70 years of age	0
	At least 70 years of age	2
Chronic bronchial infection (colonization) by *Pseudomonas aeruginosa*	No	0
	Yes	1
Radiological extension (number of lobes)	1-2	0
	More than 2	1
Dyspnoea (modified mMRC scale)	0-II	0
	III-IV	1

FACED = FEV_1 Age, Chronic colonization, Extension, Dyspnea. FEV_1 = expiratory volume in the first second. mMRC = modified Medical Research Council. Score: mild 0-2 points, moderate 3-4 points, severe 5-7 points.

Exacerbations

Antibiotic therapy is the cornerstone of treatment because it reduces the bacterial load and systemic and airway inflammatory mediators.[40] Ideally, it should initially be adapted to previous sputum cultures and sensitivities, where possible rather than chosen empirically. Other factors in antibiotic selection are the route of administration, oral or parenteral, the history of success or failure, and the presence of allergy or intolerance. Do not use nebulizad antibiotics as single agents in an acute exacerbation.[41]

Mild exacerbation: most afebrile and clinically stable patients (mild exacerbation) can be treated on an outpatient basis with an oral antibiotic guided by the most recent sputum culture results, and by the patient's experience with previous regimens. In the absence of culture, a respiratory fluoroquinolone (e.g., levofloxacin, moxifloxacin)is a reasonable and broad-spectrum option. In cultures without positive beta-lactamases (*H. influenzae* or *Pseudomonas*), the options are amoxicillin or macrolide. It can be modified based on response to therapy and culture results and sputum sensitivity. In beta-

lactamase positive culture (*M. catarrhalis* or *H. influenzae*) the options are amoxicillin-clavulanate, second or third generation cephalosporin, azithromycin or clarithromycin, doxycycline or a fluoroquinolone.[41] In positive culture of *P. aeruginosa*, the initial selection is ciprofloxacin. Given previous courses of antipseudomonal, resistance to quinolones often requires IV. Due to the propensity of *P. aeruginosa*, it is recommended to add nebulized tobramycin to ciprofloxacin.[42,43]

Clinical experience favors a duration of 10-14 days for patients with a first time or few exacerbations. The European Respiratory Society (ERS, 2017) guidelines suggest a 14-day cycle. When there is no response or relapses in a short time, repeat culture them *(Table 4)*.[44]

Severe exacerbation: when there is increased respiratory rate ≥ 25/minute, hypotension, temperature ≥ 38 °C, hypoxemia (pulse oxygen saturation < 92%) or lack of improvement after oral antibiotics (no intravenous therapy at home), hemoptysis, severe cardiopulmonary instability, or the presence of resistance to available oral agents, initial intravenous and hospital treatment is appropriate.[45]

Always obtain sputum culture before starting antibiotics. A significant number of severe exacerbations are by *Pseudomonas* and if they are resistant to oral quinolones, antipseudomonas penicillin can usually be used as ceftazidime; in case the patient looks seriously ill or has incipient *Pseudomonas* pneumonia a second agent (e.g. fluoroquinolone, aminoglycoside) can be added *(Table 5)*.[45]

Treatment of severe exacerbation should be 14-21 days; a short treatment of seven days will depend on exacerbation severity, patient conditions, and expectoration cultures.[41]

Antivirals are indicated when the etiology is due to influenza virus (oseltamivir or oral baloxavir). For SARS-CoV-2 should be individualized based on symptoms, risk factors and severity of disease.

Eradication of P. aeruginosa

When there is evidence of new isolation and clinical deterioration. Multiple treatments have been suggested. A practical way is as seen in *Figure 1*.

Table 4: Treatment of mild exacerbation.

Agent	Selection	Alternative	Duration (days)
Haemophilus influenzae	Amoxicillin/clavulanate 875/125 mg every 8 h	Amoxicillin 1-2 g every 8 h Ciprofloxacin 750 mg every 8 h Azithromycin 500 mg every 24 hours	10-21 Azithromycin 3-5
Staphylococcus aureus	Amoxicillin/clavulanate 875/125 mg every 8 h	Amoxicillin/clavulanate 875/125 mg every 8 h	10-21
MRS	Linezolid 600 mg every 12 h PO	Clindamycin 300-450 mg every 8 h	10-21
Pseudomonas	Ciprofloxacin 750 mg every 12 h PO	Levofloxacin 750 mg every 24 h PO	14-21

MRS = Methicillin-resistant *Staphylococcus aureus*. PO = PER OS (orally).

Table 5: Treatment of severe exacerbation.

Agent	Selection	Alternative	Duration (days)
Haemophilus influenzae	Ceftriaxone 2 g/24 h IV	Amoxicillin/clavulanate 500/125 mg 2 tab every 8 h PO	14-21
Staphylococcus aureus	Vancomycin 15-20 mg/kg/8 - 12 h IV	Vancomycin 15-20 mg/kg/8-12 h IV	14-21
MRS	Linezolid 600 mg/12 h IV	Vancomycin 15-20 mg/kg/8-12 h IV Ceftriaxone 600 mg every 12 h IV	14-21
Pseudomonas	Ceftazidime 2 g every 8 h IV + tobramycin 5-10 mg/kg every 24 h IV	Imipenem 1 g every 8 h or piperacillin/tazobactam 4-8 g every 24 h or cefepime 2 g every 8 h or meropenem 2 g every 8 h or ciprofloxacin 400 mg every 12 h + amikacin 15-20 mg/kg every 24 h or gentamicin 5-7 mg/kg every 24 h	14-21

MRS = Methicillin-resistant *Staphylococcus aureus*. PO = PER OS (orally). IV = intravenous.

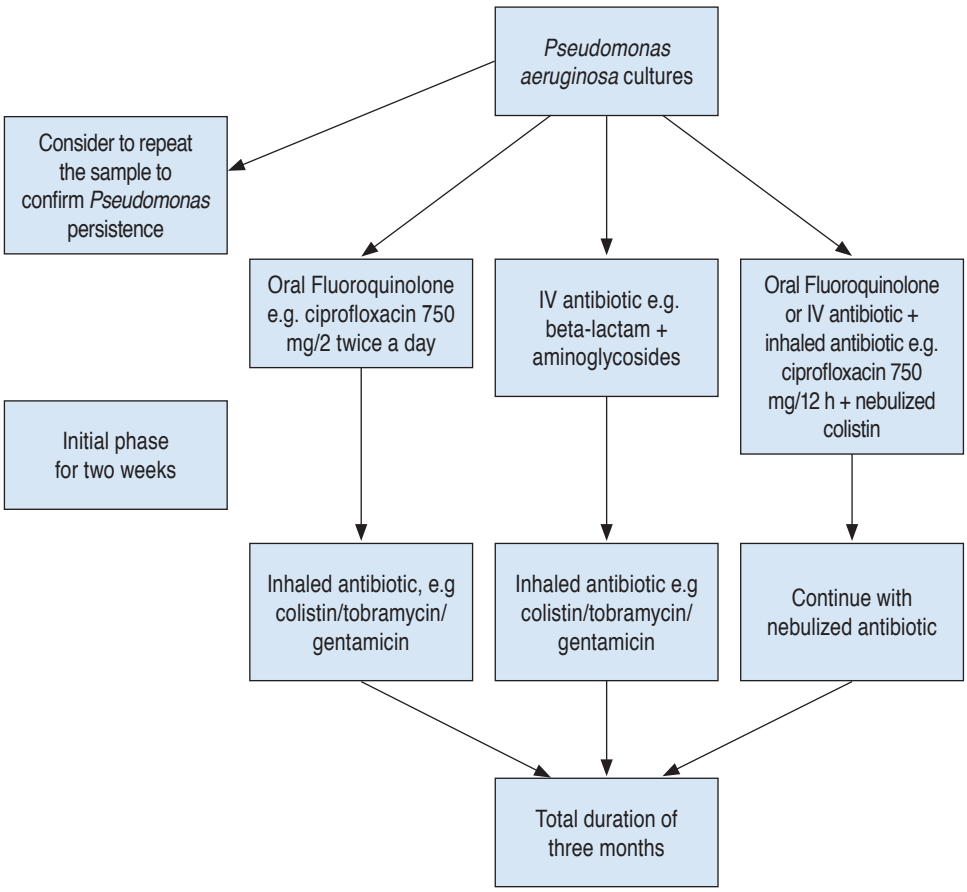

Figure 1:

Schematic eradication of *P. aeruginosa*.

After completing the eradication treatment, a monthly sputum culture must be performed for the first three months and then every two months for a year. It would be a failure of eradication if a positive culture returned during the first year. We will add a nebulized treatment if it had not been added initially, if it had been added we must repeat the same regimen of ciprofloxacin plus nebulized antibiotic, or change the nebulized treatment used in the first regimen. If at least two strategies with nebulized and oral antibiotics fail, the use of nebulized plus IV treatment is recommended. If at least three strategies fail, it should be considered a chronic infection.[46]

Treatment of chronic infection

It is defined as having two or more isolates of the same organism at least three months apart in a year.[11] The most commonly associated germs are *Haemophilus influenzae* and *P. aeruginosa*, less commonly *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Moraxella catarrhalis*.[46,47]

Chronic infections, particularly *P. aeruginosa*, potentiate airway inflammation and are associated with increased frequency of exacerbations, hospitalizations, reduced quality of life, increased mortality, and increased health care costs.

For treatment, the nebulized route is recommended because it reduces exacerbations and decreased lung function, possibly by reducing bacterial load and airway inflammation. It has also been shown to provide consistent antibiotic deposition, high concentrations in ventilated areas of the lung with a lower risk of toxicity or systemic adverse effects versus other routes. A systematic review and meta-analysis of 16 studies, with a treatment duration between four weeks to 12 months demonstrated significant reduction in the number of exacerbations with nebulized treatment. It was well tolerated with low proportions of adverse effects (bronchospasm), which disapeared with drug discontinuation. There was an increase in antimicrobial resistance at the end of the study, but it appeared to decrease after discontinuation. Nebulized antibiotics did not improve quality of life.[48]

Spanish regulations *(Table 6)*[44] recommend maintaining the nebulized route for long periods of time according to risk/benefit and depending on the selection of the antibiotic with continuous or intermittent guidelines. If with the intermittent form there is clinical worsening, it may be considered to alternate with another nebulized antibiotic without rest periods

Table 6: Treatment of chronic infection.

Agent	Nebulized	Oral or intravenous
Pseudomonas	Tobramycin (solution for nebulization): 300 mg/5 mL twice daily 28 days of treatment followed by 28 days of rest in e-Flow®, Pari LC plus® Gentamicin (inhaled intravenous formulation): 80 mg twice daily continuous treatment	If despite nebulized treatment poor clinical control persists, associate an oral or intravenous antibiotic with activity according to antibiogram, on demand or in cycles
MRS	Vancomycin (intravenous formulation administered by nebulized route): 250 mg/2 times a day continuous treatment	If the response is insufficient or there is intolerance, add or replace vancomycin with IV linezolid
Other germs	Gentamicin: 80 mg/2 times daily or any of those used for pseudomone continuous treatment	If the response is insufficient or there is intolerance, consider adding (or replacing) the nebulized antibiotic with an oral one according to sensitivity

MRS = Methicillin-resistant *Staphylococcus aureus*.

between them. If poor control persists, oral or intravenous antibiotic therapy should be associated every 1-2 months.

Long-term treatment (prophylactic)

To those who have ≥ 3 exacerbations per year (frequent exacerbators), to prevent exacerbation. Macrolides (azithromycin, erythromycin) are suggested as the first line due to the high quality, evidence in decreasing exacerbations and acceptable side effect profile. In the case of *P. aeruginosa* infection add a long-term nebulized treatment.

British Thoracic Society (BTS) guidelines suggest for colonization by *P. aeruginosa*:[49]

1. Nebulized colistin.
2. Nebulized gentamicin as a second-line alternative to colistin.
3. Azithromycin/erythromycin as an alternative (intolerance to nebulized antibiotics).
4. Azithromycin/erythromycin as an add-on treatment to a nebulized antibiotic in chronic *P. aeruginosa* infection with frequent exacerbations.

No colonization by *P. aeruginosa*:[49]

1. Azithromycin/erythromycin.
2. Nebulized gentamicin as a second-line alternative to azithromycin/erythromycin.
3. Doxycycline as an alternative to macrolide intolerance/ineffectiveness.

Muco active and mucolytic treatment

In those who frequently have difficulty in expectorating, or abundant secretions where standard airway cleaning techniques have failed to control symptoms, hypertonic substances and mannitol can be used long-term (≥ 3 months).[49]

Nebulized hypertonic saline (6-7%) is related to improved mucus clearance, increased ciliary motility, and improved cough clearance. Low mucus salinity contributes to mucus retention. It may improve FEV_1 combined with chest physiotherapy and is not superior to 0.9% saline.[50,51]

Mannitol is a hyperosmolar agent that is believed to hydrate secretions, improving mucus clearance. There is insufficient evidence. In a therapeutic multicenter trial (the largest in bronchiectasis) 461 patients inhaled mannitol dry powder 400 mg or mannitol 50 mg (control) twice daily for 52 weeks, showed only modest significant improvements in time to first exacerbation, antibiotic days and quality of life according to St. George Respiratory Questionnaire (SGRQ). A post hoc analysis of 333 patients showed that the greater the burden of symptoms, the time to first exacerbation and fewer exacerbations against placebo were reduced.[52,53]

Aerosolized dornase alpha (recombinant deoxyribonuclease, also called DNase), which breaks down DNA (gelatinous product of neutrophils), improves FEV_1 and reduces hospitalizations in CF patients,[53] but is not effective in another etiology and is potentially harmful.[54]

Mucolytics, essentially N-acetylcysteine, for one year were associated with a reduction in exacerbations and sputum volume, and also improved quality of life.[55]

Other medical therapies

Bronchodilators: should be used in patients with asthma or COPD[49,56] or with significant dyspnea. Airflow obstruction should be assessed by pre- and post-bronchodilator spirometry. If there is reversibility inspirometry, a trial with short-acting beta agonist (SABA) is almost always initiated.[46] If symptoms improve, continue with SABA or prolonged

(LABA). If no airway obstruction is demonstrated, they are not indicated. Information is missing in this context.

Oral glucocorticoids (GC): their use is reserved. In other types of patients, it is suggested to avoid this treatment because they can depress the immunity of the host, promote bacterial and fungal colonization, which perpetuates the infection. Only in patients with asthma or allergic bronchopulmonary aspergillosis it may be used.

Inhaled glucocorticoids (ICGs): there is no evidence for their use when they do not coexist with asthma or COPD as a concomitant disease.[45,57] The ERS guidelines recommend it only in such a situation.[10] They show no significant effect on spirometry, exacerbation rate or sputum volume. Patients with serum eosinophils > 3% improved quality of life (SGRQ) at six months.[58] Although its use was associated with an increased likelihood of *P. aeruginosa*[59] infection and adrenal insufficiency in 48%.[60]

NSAIDs: there is not enough information to support their role.[61,62]

Statins: they have anti-inflammatory properties, but there is not enough information either.[63]

Non-pharmacological treatment

Avoid lung irritants: avoid lung irritants: exposure to respiratory irritants should be avoided as far as possible, e.g. smoking and vaping, cleaning agents, dusts, fumes, gases, etc.

Systemic hydration: maintaining hydration is important to help decrease thick secretions.

Pulmonary rehabilitation (PR): undoubtedly brings benefit.[64] Indicated for patients with diminished exercise capacity.[65] Aerobic exercise (cycloergometer, elliptical) is recommended in stable patients with dyspnea mMRC = 2-4.[45] To deepen into the subject, we suggest going to the pulmonary rehabilitation guidelines.

Airway clearance therapy: all patients should undergo physiotherapy regularly to remove airway secretions *(Table 4)*.[66]

Bronchial hygiene improves cough[67] by adequately expelling secretions and mucous plugs from the airway with manual techniques or devices *(Table 7)*.[68] The choice of a technique or device should be based on the amount and characteristics of the secretions, patient comfort, cost, and ability to use the device.[69] The drainage of secretions is contraindicated in unstable situations.

Oscillatory positive expiratory pressure (PEP) devices combine with high-frequency oscillations to release secretions and move them into the mouth. Schemes of 6-10 deep inhalation cycles, 2-3 second breath hold, exhalation through the device creating oscillations and coughing. Oscillatory PEP improves quality of life, but not the amount of sputum, dyspnea, or lung function.[70] Information about PEP during exacerbations or long-term use is missing.

Nutritional support. The protein-rich nutritional supplement enriched with hydroxy-beta-methylbutyrate (anti-catabolic and anti-inflammatory effect) showed a greater improvement in strength and physical functioning.[71]

Other medical therapies

Anti-GER: Suppression of gastric acid by use of H2 blocker or proton pump inhibitor is indicated in persistent

Table 7: Airway cleaning /bronchial hygiene.

Technique	Advantages	Comment/disadvantage
Directed cough	Cheap, simple	Chest pain may limit
Regular exercise	Economical, strengthens respiratory and peripheral muscles	
Autogenous breathing	Control your breathing	Requires patient cooperation
Forced expiration	Helps control breathing	Requires patient learning
Thoracic physiotherapy (CPT; postural drainage, mechanical or manual thoracic percussions)	Most tested in cystic fibrosis	Needs assistant, difficult to place, hypoxemia, sometimes worsens gastroesophageal reflux
Positive expiratory pressure (PEP)	Easy, cheap	Device needs cleaning
Oscillatory PEP (e.g., acapella device with flutter valve)	Easy, economical, adds vibration to the airways	Device needs cleaning
High frequency chest wall oscillation vest with inflatable bladder	Extensive experience	Pain may limit; needs power outlet
High frequency chest wall oscillation vest with mechanical oscillators	Doesn't hurt compared to inflatable bladder	May be mobile; small batteries in vest; closest to CPT

CPT = chest physical therapy.

and unexplained symptomatic patients or in those with ≥ 2 exacerbations/year. Anti-reflux measures must also be carried out.

Vaccines: review missing immunizations and promote the application of influenza vaccine (live attenuated viruses except in immunodeficiency). Pneumococcal polysaccharide vaccine or conjugate must be present.[72] Both vaccines significantly reduce the number of acute infectious exacerbations during the first year compared to the influenza vaccine alone.[73]

Lung surgery and transplantation

Surgery (lobectomy or segmentectomy) is indicated in case of localized bronchiectasis or severe hemoptysis that does not respond to conventional treatment. Lung transplantation is the only solution in patients with advanced disease, whose survival is estimated to be < 2 years, once all available treatments have been used without obtaining a response.

Follow-up: patients should be asked at each visit about dyspnea and exercise tolerance, color, consistency, and estimated amount of sputum, as this information is useful in determining if a patient has an exacerbation.

Exacerbations, emergency department visits or hospitalizations, or if they were given antibiotics, including dose and frequency, should be recorded. Must have supervision in pulmonary rehabilitation programs.

CONCLUSIONS

1. Bronchiectasis is a chronic syndrome characterized by irreversible distortion of bronchi and bronchioles, characterized by productive cough and exacerbations, with risk factors and multiple etiology.
2. It is quite common with considerable mortality.
3. It has a complex pathophysiology with many mechanisms.
4. It shares many similarities with COPD because it affects pulmonary function, quality of life, and survival.
5. Exacerbations are usually caused by acute bacterial infections.
6. Always culturing bronchial secretions.
7. Its severity is evaluated through validated questionnaires with predictive value.
8. We recommend clinical criteria to facilitate the way to follow for management.
9. The mainstay of treatment is to treat exacerbations mainly of infectious origin, since they are the cause of pulmonary deterioration, greater symptoms, worse quality of life and increased mortality.
10. Antibiotherapy is the basis for the treatment of exacerbations supplemented with physiotherapy and pulmonary rehabilitation.
11. The most frequent cause of severe exacerbations is *P. aeruginosa*.
12. It is important to culture secretions.
13. In recurrent exacerbations (≥ 2/year) without *P. aeruginosa* or nebulization intolerance, preventive macrolide therapy. Exclude non-tuberculous mycobacteria.
14. In recurrent exacerbations or significant morbidity and *P. aeruginosa* or intolerance/contraindication/ineffectiveness of the oral route inhaled tobramycin is suggested. Requires bronchodilator premedication.
15. More information on benefits of hypertonic solution, mannitol, N-acetylcysteine and DNase is missing. Inhaled glucocorticoids and systemic glucocorticoids only in concomitant asthma or COPD.
16. Other medical therapies in selected patients are inhaled bronchodilators, anti-reflux therapy, and immunization.

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