Bronchiectasis – A clinical review

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Background (1/2)

- characterized by cough and sputum production + abnormal thickening and dilation of the bronchial wall
- First reported in 1819 by Rene Laennec
- Radiographically characterized with introduction of contrast bronchography in 1922
- 1950s: correlation between radiographic abnormalities and histopathological findings was confirmed
- Remarkable resurgence in its incidence and prevalence in the last 20 years
- Seitz et al.: increase of 8.7 percentage points in the diagnosis between 2000 and 2007 in the Medicare population in the United States
- 2018: Incidence in US 701 cases per 100,000 (higher among women, increased with age)
- Similar or higher rates in UK, Germany, Spain, Singapore and China (1.5% of women and 1.1% of men)
- Improved recognition because of increased use of CT + increase in underlying cause

Background (2/2)

- Heterogenous condition encountered as stand-alone pulmonary disease
- Sometimes complicates other pulmonary diseases: asthma, COPD
- Complication of many other disorders
- Coexist with a number of congenital and hereditary diseases: CF, primary ciliary dyskinesia, Mounier-Kuhn syndrome and alpha-1 antitrypsin deficiency
- Develop in patients with autoimmune disease: rheumatoid arthritis, Sjögren's syndrome, inflammatory bowel disease
- Develop in patients with immunodeficiency syndromes including common variable immunodeficiency and HIV infection
- In conjugation with chronic rhinosinusitis, GERD, dysphagia and aspiration syndromes
- Early recognition and initiating appropriate management improve patients' quality of life and overall prognosis
- Often misdiagnosed as COPD or asthma

Clinical presentation and course (1/2)

- Chronic cough and sputum production with intermittent exacerbations
- Sometimes just radiographic finding with few or no symptoms or exacerbations
- More common in women, non-smokers
- Cough range from dry to minimally productive to debilitating, with large volumes of purulent sputum
- Chest pain, shortness of breath, sometimes intermittent hemoptysis (not common)
- Systemic symptoms: intermittent fevers, night sweats, weight loss and fatigue
- DD: multiple other primary pulmonary disorders (distinguishing factor is a productive cough with a pattern of exacerbations), often fail diagnosed as chronic bronchitis, chronic rhinosinusitis and other causes of chronic cough
- Often therapied with antibiotics, inhaled glucocorticoids and bronchodilators
- CT is required for diagnosis of bronchiectasis

Clinical presentation and course (2/2)

- Consensus was published in 2017
- Three or more factors in following categories are present:
  - Deterioration in cough and sputum volume or consistency for at least 48h
  - Increase in sputum purulence, breathlessness or exercise intolerance, fatigue or malaise or hemoptysis for at least 48h
  - Determination by a clinician that a change in treatment is needed
- “frequent exacerbator” – most reliable phenotype, large multicenter cohort patients with three or more exacerbations per year had highest rate of future exacerbations and 5-year mortality
- *Pseudomonas aeruginosa* – marker of disease severity
- **Outcome:** scores on two severity scales – the Bronchiectasis Severity Index and FACED scale (measures combination of FEV1, age, chronic infection, extent and dyspnea) incorporates variables to predict short-term and long-term outcomes including mortality during a 15- year period

Prognosis scoring in patients with bronchiectasis

Table 1. Prognosis Scoring in Patients with Bronchiectasis, According to Two Scales.

Factor	Bronchiectasis Severity Index*		FACED Scale†	
	Value	Score	Value	Score
Forced expiratory velocity in 1 sec	>80% 50–80% 30–49% <30%	0 1 2 3	≥50% <50%	0 2
Age	<50 yr 50–69 yr 70–79 yr ≥80 yr	0 2 4 6	<70 yr ≥70 yr	0 2
Chronic *Pseudomonas aeruginosa* infection	No Yes	0 3	No Yes	0 1
No. of involved lobes	<3 ≥3	0 1	1 or 2 >2	0 1
Dyspnea scale‡	0 2 3	0 2 3	0, I, or II III or IV	0 1
Hospital admission	No Yes	0 5	—	—
Annual exacerbations	None 1 or 2 ≥3	0 0 2	—	—
Colonization with other organisms	No Yes	0 1	—	—
Body-mass index§	<18.5 18.5–25 26–29 ≥30	2 0 0 0	—	—
Total score range		0–26		0–7

* On the Bronchiectasis Severity Index, a score of 0 to 4 indicates mild disease, a score of 5 to 8 indicates moderate disease, and a score of 9 or more indicates severe disease. The 4-year mortality associated with these scores is 0 to 5.3% for mild disease, 4 to 11.3% for moderate disease, and 9.9 to 29.2% for severe disease.[19]

† On the FACED scale (which measures the forced expiratory volume in one second, age, chronic infection, extent, and dyspnea), a score of 0 to 2 indicates mild disease, a score of 3 or 4 indicates moderate disease, and a score of 5 to 7 indicates severe disease. The 5-year mortality associated with these scores is 3.7% for mild disease, 20.5% for moderate disease, and 48.5% for severe disease.[19]

‡ The dyspnea scale of the Modified Medical Research Council ranges from 0 to 3 on the Bronchiectasis Severity Index and from 0 to IV on the FACED scale, with higher scores indicating worse dyspnea.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

Pathobiologic mechanisms (1/2)

- Multiple inciting factors lead to bronchiectasis – results in vicious cycle of remodeling and dilation of the airways
- Initial insult – airway dysfunction, inflammatory response and structural disease and infection
- Progressive process over time and overcomes local and systemic host protective factors
- Impaired mucocociliary clearance – mucus retention, airway distortion and vulnerability to infection
- Initial result varies and often unknown
- Expansion of NETs as marker for disease activity
- 433 patients in Scotland – NETs in sputum was associated with higher score on Bronchiectasis Severity Index, worse dyspnea scores, increased lung-function abnormalities and more extensive radiologic disease
- NETs increased with exacerbations and was responsive to antibiotic treatment – target for treatment?
- Another study – elevated eosinophils contribute to exacerbations when no asthma
- Role of microbiome is evaluated

Pathobiologic mechanisms (2/2)

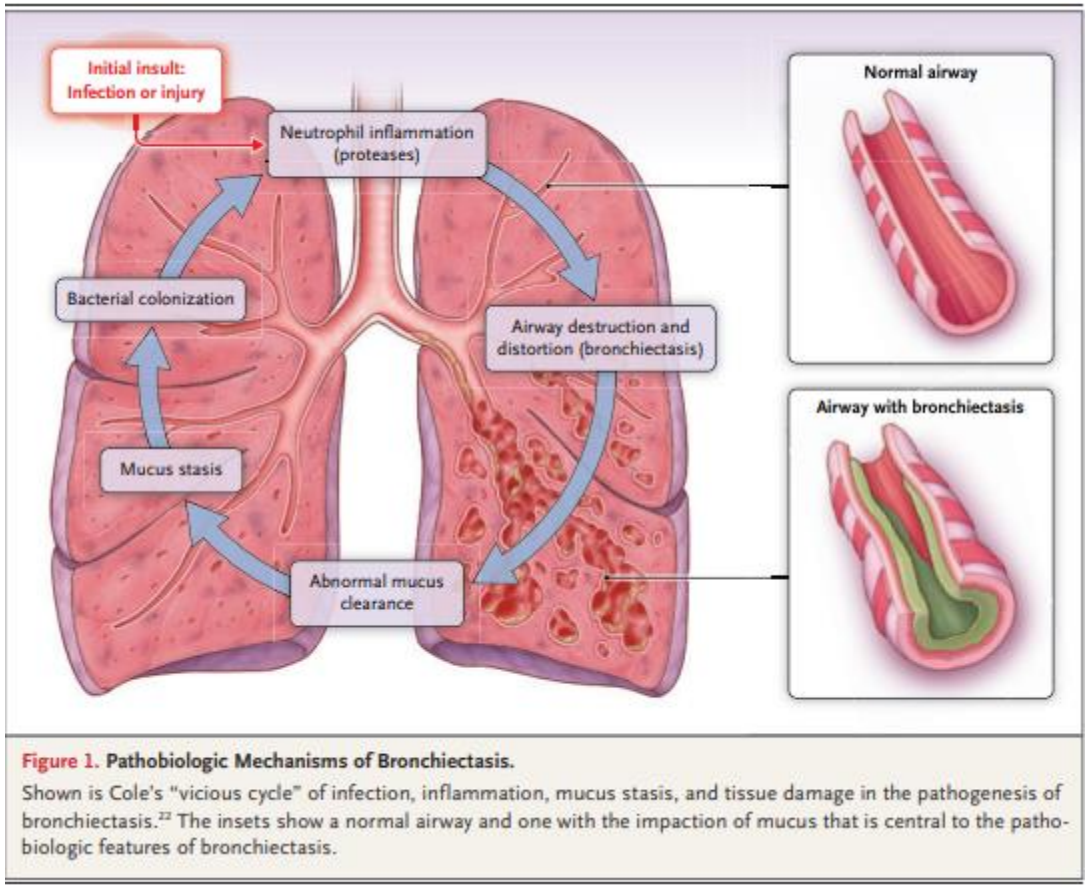

Figure 1. Pathobiologic Mechanisms of Bronchiectasis.

Shown is Cole's "vicious cycle" of infection, inflammation, mucus stasis, and tissue damage in the pathogenesis of bronchiectasis.[22] The insets show a normal airway and one with the impaction of mucus that is central to the pathobiologic features of bronchiectasis.

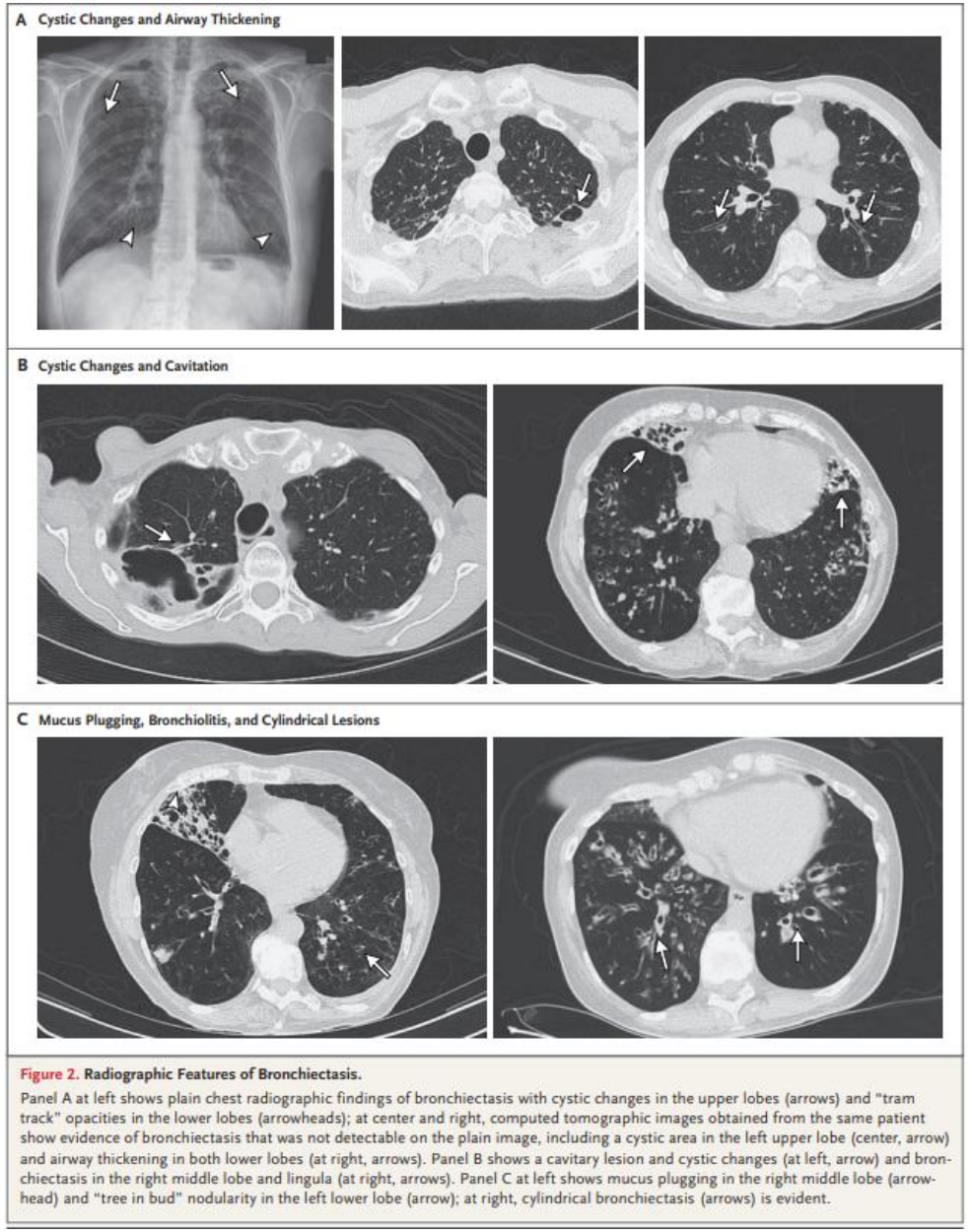

Figure 2. Radiographic Features of Bronchiectasis.

Panel A at left shows plain chest radiographic findings of bronchiectasis with cystic changes in the upper lobes (arrows) and "tram track" opacities in the lower lobes (arrowheads); at center and right, computed tomographic images obtained from the same patient show evidence of bronchiectasis that was not detectable on the plain image, including a cystic area in the left upper lobe (center, arrow) and airway thickening in both lower lobes (at right, arrows). Panel B shows a cavitary lesion and cystic changes (at left, arrow) and bronchiectasis in the right middle lobe and lingula (at right, arrows). Panel C at left shows mucus plugging in the right middle lobe (arrowhead) and "tree in bud" nodularity in the left lower lobe (arrow); at right, cylindrical bronchiectasis (arrows) is evident.

Evaluation of patients with bronchiectasis (1/4)

- Productive cough on most days of the week + history of exacerbation + at least one of the following findings in high-resolution CT (slice thickness of 1mm or less):
  - Ratio of the inner and outer airway diameter to the artery diameter of 1.0 or more
  - Lack of tapering of the airways
- Presence of radiographically visible airways in the perimeter
- Other CT findings:
  - Mucus plugging
  - “tree in bud” nodularity
  - Waxing and waning pattern to the nodules
  - In more advanced bronchiectasis – cystic changes and cavitation
- CT findings are never pathognomonic of particular cause or microbial pathogen but certain findings: right middle lobe and lingular disease – nontuberculous mycobacterial infection; predominantly upper lobe disease due to CF and central bronchiectasis is often caused by allergic bronchopulmonary aspergillosis

Evaluation of patients with bronchiectasis (2/4)

- Once confirmed by CT – systemic workup based on patient's history and clinical symptoms should be undertaken, Basic components of the evaluation include:
  - testing for underlying cause of disease
  - Performing pulmonary-function testing
  - Obtaining respiratory cultures
- Assessment of all patients for current coexisting illness and history of predisposing disorders: COPD, asthma, GERD, aspiration, rheumatologic diseases, inflammatory bowel disease
- Complete blood count with differential und immunoglobulin levels (IgG, IgM, IgA and IgE) are required for all patients
- More advanced testing for congenital or acquired disorders on the basis of patients' disease features
- Reduced immunoglobulin levels (including subclasses) – assessment of antibody response to vaccinations
- Testing for CF is a consideration especially for early-onset bronchiectasis or in patients with bronchiectasis with other disorders such as male infertility, malabsorption or pancreatitis
- Ciliary evaluation in patients with early onset particularly with history of neonatal respiratory distress, otitis media, rhinosinusitis or infertility
- Alpha-1 antitrypsin deficiency is a rare cause of bronchiectasis and can be assessed with measurement of levels of phentotypical analysis

Evaluation of patients with bronchiectasis (3/4)

- No specific cause may be found – bronchiectasis is sometimes idiopathic or due to suspected but difficult-to-prove infections in childhood
- Geographic differences in underlying causes
- Data from US Bronchiectasis Research Registry (published in 2017) showed that 68% of 1826 patients had history of pneumonia, 20% COPD, 29% had received a diagnosis of asthma and 47% had GERD
- 8% had a history of rheumatologic diseases, 3% had inflammatory bowel disease, 5% had an immunodeficiency disease and 3% had primary ciliary dyskinesia
- In a study with 1258 patients with bronchiectasis, investigators with the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) network found a cause of disease was determined in 60% of the patients, including previous infection (20%), COPD (15%), connective-tissue disease (10%), immunodeficiency (5.8%) and asthma (3.3%)
- In Asia-Pacific region post-tuberculous disease and idiopathic bronchiectasis are more common than in other regions
- Even with extensive testing, no specific identifiable cause is determined in up to 40% of patients with bronchiectasis

Evaluation of patients with bronchiectasis (4/4)

Table 2. Causes of Disease in the Diagnosis of Bronchiectasis.*

Cause	Associated Findings	Evaluation
Airway abnormality		
After bacterial or viral pneumonia or tuberculosis; airway obstruction by tumor or foreign body	Usually none	Patient history, prior imaging review, bronchoscopy in focal disease
Congenital disorder		
Cystic fibrosis	Early onset of disease, sinusitis, pancreatitis or malabsorption, male infertility	Sweat chloride testing, CFTR mutations
Primary ciliary dyskinesia	Early onset of disease, sinusitis, male or female infertility, neonatal respiratory distress, otitis media, situs abnormalities	Reduced nasal nitric oxide, genetic testing, ciliary-function evaluation
Alpha-1 antitrypsin deficiency	Emphysema	Alpha-1 antitrypsin levels and phenotyping
Congenital tracheobronchial abnormalities		
Mounier–Kuhn, Williams–Campbell, and Ehlers–Danlos syndromes	—	CT findings
Immunodeficiency		
Common variable immunodeficiency; acquired immunodeficiency; HIV infection; hematologic cancer	Sinusitis, inadequate vaccine response	Immunoglobulin levels, HIV antibody and viral load, antibody tests before and after vaccination
Autoimmune disorder		
Rheumatoid arthritis	Joint stiffness	Rheumatoid factor
Sjögren's syndrome	Dysphagia	Anti–cyclic citrullinated peptide
Scleroderma	Reflux	Antinuclear antibody
Inflammatory bowel disease	Diarrhea, hematochezia	Bowel biopsy
Aspiration syndrome		
Vocal cord disease or dysfunction; esophageal disease or dysmotility	Head and neck cancer, prior radiation treatment, neurologic disease, esophageal motility disorder, gastroesophageal-junction abnormality	Modified barium swallow, esophagram, pH testing, esophageal motility testing
Allergic bronchopulmonary aspergillosis	Asthma symptoms	Aspergillus-specific IgE, aspergillus skin-prick testing, IgE level
Chronic obstructive pulmonary disease or asthma	Chronic purulent sputum production	Pulmonary-function testing, CT imaging

* CFTR denotes cystic fibrosis transmembrane conductance regulator, CT computed tomography, and HIV human immunodeficiency virus.

Microbiologic features (1/2)

- obtain cultures of respiratory secretions at the time of diagnosis, at regular intervals after that for surveillance and ideally at the time of exacerbations
- Sputum can be collected and submitted for culture by the patients – bronchoscopy is not routinely required for collection of respiratory cultures
- Sputum is tested for bacterial organisms including acid-fast bacteria, in some patients also fungal cultures and viral testing may be indicated
- Data from Bronchiectasis Research Registry showed approximately one third of patients positive for P. aeruginosa, 12% positive for Staph. Aureus, 8% in H. influenza
- Other organisms that are seen in lesser frequency in all cohorts include: Streptococcus pneumoniae, Stenotrophomonas maltophilia, Klebsiella pneumoniae, Moraxella catarrhalis, E. coli and achromobacter species

Microbiologic features (2/2)

- Chronic infection with P. aeruginosa - marker for severity of disease and frequency of exacerbations
- Comprehensive analysis of data from 21 observational cohort studies:
  - P. aeruginosa infection was associated with increased mortality, hospital admissions, number of exacerbations, worse quality of life and deterioration in pulmonary function and radiographic findings
- In US and other countries non-tuberculous mycobacterial infections are common in patients with bronchiectasis, in Bronchiectasis Research Registry 50% of enrolled patients had growth of nontuberculous mycobacterial organisms in any culture – have been reported in increasing number of patients with bronchiectasis in the US – nontuberculous mycobacterial infection may be a causative agent in bronchiectasis development
- Fungal cultures from patients yield most commonly aspergillus (especially bronchiectasis caused by allergic bronchopulmonary aspergillosis) and candida species
- Study of 119 patients in China: presence of viral infection detected by PCR was more frequent during exacerbation period than during steady-state (Coronaviruses, Rhinovirus and Influenza)
- EMBARC investigators found marked reduction in exacerbations in UK during lockdown although chronic symptoms were unchanged – attributed to social-distancing measures

Treatment (1/6)

- Educating the patient about disease with providing information regarding coexisting illnesses and associated chronic infections
- Microbiologic data should be monitored on a regular basis
- Treatment goals:
  - Symptom reduction
  - Improvement in quality of life
  - Preservation of lung function
  - Reduction of overall morbidity and mortality
- Careful monitoring with respect to clinical symptoms, radiographic progression and functional change
- asymptomatic or minimally symptomatic disease may have disease progression that entail lifelong care
- Goal is to reduce frequency of exacerbations – high frequency of exacerbations is associated with worse outcomes including cardiovascular complications

Treatment (2/6)

- Treatable underlying conditions should be addressed in order to prevent disease progression and potentially reverse bronchiectasis
- CF can be treated with modulators of CF transmembrane conductance regulator, allergic bronchopulmonary aspergillosis – glucocorticoids and antifungal therapy
- Likely that mitigation of GERD and aspiration helps disease control
- Lacking data for effect of replacement therapy in alpha-1 antitrypsin deficiency and potential for primary ciliary dyskinesia
- Treatment of chronic rhinosinusitis may have a salutary effect on symptoms – recent retrospective review showed sinus surgery in patients with rhinosinusitis and bronchiectasis dis not reduce overall frequency of exacerbations
- Airway-clearance therapies include nonpharmacologic strategies, mucoactive treatments and pulmonary rehabilitation and exercise – aim: mobilize secretions to reduce cough and dyspnea and prevent further airway damage
- Guidelines endorse airway clearance as key therapy – weak evidence
- Nonpharmacologic airway-clearance options include an active cycle of breathing techniques, autogenic drainage (controlling speed and depth of exhalation to mobilize secretions), slow exhalation with glottis open in the lateral decubitus position, use of positive-expiratory-pressure oscillating devices and high-frequency chest-wall oscillation

Treatment (3/6)

- Nebulized hypertonic saline is a mucoactive treatment that has shown promise in patients with bronchiectasis – small study investigators found that daily nebulization of 7% saline solution showed benefit in lung function and quality of life
- Observational studies conducted in Australia and Italy showed improvements in physiological measures, including the 6-minute-walk distance and health-related quality of life
- Challenges with these treatments include time commitment, expense and availability of therapy
- Other personalized therapeutic options: bronchodilator treatment (in airflow obstruction), caution with use of inhaled glucocorticoids – promote infections including nontuberculous mycobacteria
- Routine vaccinations and nutritional counseling are recommended for all patients
- In case of hemoptysis – treatment depends on severity of bleeding (temporary cessation of airway clearance may be needed and bronchial-artery embolization is an option for severe bleeding

Treatment (4/6)

- Patients with substantial daily symptoms and frequent exacerbations (3 or more per year) need additional therapies
- Meta-analysis of three randomized trials – investigators found use of macrolide antibiotics reduced frequency of exacerbations and increased time until next exacerbation + improvement of life quality
- Mechanism is unclear, although macrolides may inhibit quorum sensing by P. aeruginosa
- Dosing: 500mg 3x per week or 250mg daily (macrolides are generally safe and have an acceptable side-effect profile over longer durations)
- Caution in prescribing given the risk of resistance and gastrointestinal, cardiac and auditory side effects
- No Macrolide monotherapy when nontuberculous mycobacterial infection is present or has not been ruled out
- Since 2000, several studies investigated use of inhaled antibiotics as treatment for patients who have frequent exacerbations – results have been disappointing
- Inhaled gentamicin and inhaled colistin have shown promise, although inhaled tobramycin, aztreonam and ciprofloxacin have not met predetermined end points in clinical trials
- Patients with high bacterial load my be the most likely to have good response to inhaled antibiotic therapy
- Guidelines of British Thoracic Society and European Respiratory Society recommend use of long-term inhaled antibiotics in patients with chronic P. aeruginosa infection with 3 or more exacerbations per year, although none of these treatments are currently approved by regulatory agencies

Treatment (5/6)

- Decision between long-term macrolide therapy as compared with inhaled antibiotics should be based on the disease features of individual patients, including contraindications and adverse effects of medications
- Small subgroup of patients with localized or predominant area of bronchiectasis may be candidates for surgery to extirpate the worst area of disease
- Endstage patients – LuTX
- In one small randomized, controlled trial involving 35 patients, the eradication of either first or new growth of P. aeruginosa was shown to be effective
- Two weeks of iv ceftazidime or tobramycin followed by nebulized tobramycin for 3 months resulted in 55% sustained culture negativity at 1 year
- Exacerbations generally warrant the addition of targeted systemic antibiotics – oral or iv route is determined by severity of exacerbation and antibiotic susceptibility of the pathogen as well as the side-effect profile of the specific antibiotic
- Appropriate duration has not been clearly defined, guidelines generally suggest a 14-day course of therapy

Treatment (6/6)

Table 3. Algorithm for the Treatment of Bronchiectasis.*

Goal	Action	Outcome Measurement
All patients		
Patient education	Basic disease education, CT image review, provision of patient-friendly educational materials	Patient understands options for diagnosis and treatment
General health care	Vaccinations, nutritional support, smoking cessation	Pneumococcal, influenza, and Covid-19 vaccines; maintaining healthy weight; lung-function improvement
Address treatable causes		
Obstructed airway	Bronchoscopy	Removal of foreign body or tumor
Cystic fibrosis	CFTR modulators	Improvement in lung function, overall health
Immunoglobulin deficiency	Immunoglobulin replacement	Reduction in infectious exacerbations
Recurrent aspiration	Aspiration precautions	Reduction in exacerbations
Esophageal dysfunction	Aspiration precautions	Reduction in exacerbations
Allergic bronchopulmonary aspergillosis	Systemic glucocorticoids, antifungal therapy	Improved bronchiectasis
Airway clearance therapy	Exercise, huff coughing, active cycle of breathing techniques, autogenic drainage, slow expiration with ELTGOL	Improved endurance, improved mucus clearance, reduced cough
Targeted patients		
Airway clearance techniques for bothersome symptoms and exacerbations	Oscillatory positive-expiratory-pressure devices, high-frequency chest-wall oscillation devices, pulmonary rehabilitation, hypertonic sodium chloride nebulization	Improved mucus clearance, reduced cough, reduction in exacerbations
Oral antibiotics for maintenance in patients with ≥3 exacerbations per year	Long-term macrolide treatment, azithromycin (500 mg three times per wk or 250 mg daily)	Reduction in exacerbations; need to monitor for adverse effects, including antibiotic resistance, gastrointestinal effects, hearing loss, cardiac electrophysiological derangements, and drug–drug interactions
Nebulized antibiotics for maintenance in patients with ≥3 exacerbations per year	Inhaled aminoglycosides (tobramycin, gentamicin, amikacin), inhaled fluoroquinolones (ciprofloxacin, levofloxacin), inhaled aztreonam, inhaled colistin	Reduction in exacerbations; need to monitor because none of these drugs have been approved by regulatory authorities for this use; clinical trials have shown mixed results
Eradication of specific organisms, targeted to new growth of *P. aeruginosa*	Antibiotics targeted to known pathogen; intravenous antibiotic for 2 wk, plus nebulized antibiotic for 3 mo	Eradication for ≥6–12 mo
Surgical therapy	Resection of most involved section of lobe or lobes, lung transplantation	Reduction of infectious or inflammatory burden, treatment of advanced disease with poor prognosis
Acute illness		
Treatment of exacerbations	Antibiotic targeted to known pathogen (oral if pathogen is susceptible, intravenous for severe exacerbations or resistant pathogens)	Resolution of exacerbation, shorter duration of symptoms

* Covid-19 denotes coronavirus disease 2019 and ELTGOL expiratory reserve volume during slow expiration with glottis opened in infralateral decubitus position.

Future directions

- Treatments that target neutrophils may have an important role to play in bronchiectasis
- Recent phase 2 trial of brensocatib, oral reversible inhibitor of dipeptidyl peptidase 1 showed promising results in patients with history of 2 or more exacerbations in the year before trial enrollment
- Time to next exacerbation was longer with brensocatib than with placebo with an acceptable side-effect profile – phase 3 trial is on the way
- Other potential therapeutics being considered in bronchiectasis include novel inhibitors of dipeptidyl peptidase 1, antagonism of CXC chemokine receptor 2 und immunomodulatory drugs, including those that target eosinophils

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