SUMMARY

Background: Radiologically evident bronchiectasis is seen in 30% to 50% of patients with advanced chronic obstructive pulmonary disease (COPD). As COPD is now becoming more common around the world, bronchiectasis is as well.

Methods: We review pertinent articles published before May 2011 that were retrieved by a selective PubMed search.

Results: The principles of treatment of bronchiectasis in patients who do not have cystic fibrosis (“non-CF bronchiectasis”) are derived from the treatment of other diseases: secretolytic and anti-infectious treatment are given as in cystic fibrosis, while anti-obstructive treatment is given as in COPD. The few randomized trials of treatment for non-CF bronchiectasis that have been completed to date do not permit the formulation of any evidence-based recommendations. Many potential treatments are now under evaluation. Hypertonic saline is often used because of its demonstrated benefit in CF, even though no benefit has yet been shown for non-CF bronchiectasis. Phase II trials of inhaled mannitol have yielded promising results, leading to phase III trials that are now underway. There may be a future role for inhaled antibiotics, particularly in patients colonized with Gram-negative pathogens. Inhaled tobramycin and colistin are well established in clinical practice, though not approved for non-CF bronchiectasis; clinical trials of aztreonam, ciprofloxacin, and gentamicin are ongoing. Macrolides seem to bring an additional benefit, though the studies that documented this involved only small numbers of patients. Long-term treatment with inhaled antibiotics and/or macrolides is indicated only if a benefit is seen within three months of the start of treatment (less sputum, no exacerbations).

Conclusion: A national registry of patients with bronchiectasis should be established to help us gain better knowledge of its prognostic factors and treatment options.

Pathophysiology and etiology

Different mechanisms (Table 1) lead to the development of bronchiectasis, but the pathophysiological end stage is similar. In the beginning, patients usually have damaged bronchial epithelium as a result of inflammation; the surrounding parenchyma is infiltrated by inflammatory cells (Figure 1). The destruction of the neighboring tissues results in dilation in the form of cylindrical, varicose, or cystic distensions with destruction of the surrounding structures. This will in turn lead to deficient mucociliary clearance. The result is retention of secretions, which in turn attracts bacterial colonization with chronic inflammation (3). Furthermore, a thickening of the bronchial mucosa will ensue, which histologically shows notable metaplasias of the squamous epithelium, although an increased incidence in malignancies has not been observed.

Postinfectious causes

Different respiratory infections can cause bronchiectasis, including:
- Pertussis
- Gram negative bacteria (Pseudomonas aeruginosa, Haemophilus influenzae)
- Viruses (HIV, paramyxovirus, adenovirus, and flu)
- Tuberculosis
- Atypical mycobacteria.

Bronchiectasis subsequent to infection with Mycobacterium avium is a typical finding in Lady Windermere syndrome. Patients suffering from this syndrome are often older, immunocompetent women without a history of smoking or previous pulmonary pathologies (4).

Congenital causes

The most common congenital cause for non-CF bronchiectasis is a primary ciliary dyskinesia (PCD). Insufficient ciliary movement results in reduced clearance of secretions, triggering an increase in the rate of infections in turn. In combination with a situs inversus, the resultant pathology is known as Kartagener syndrome. Its prevalence is 1/20 000.

A more recently discovered congenital cause is a mutation of the ENaC gene, which results in a defective epithelial sodium channel. A hyperactive sodium channel triggers a disturbance to the salt and water homeostasis of the respiratory mucosa (5).

Chronic obstructive pulmonary disease

Patients with advanced chronic obstructive pulmonary disease (COPD) may have bronchiectasis; the literature reports rates between 30% and 50% (6). These patients more often suffer from dyspnea and show poorer lung function (6). CT-morphologically, bronchiectasis in COPD differs from classic bronchiectasis, since the ectasis is less pronounced but the peribronchial infiltration is more pronounced. With the rising global prevalence of COPD, bronchiectasis is of increasing importance.

Clinical features

Patients with bronchiectasis complain of chronic cough, sputum production, and lethargy. Hemoptyisis, chest pain, weight loss, bronchospasm, dyspnea, and impaired physical performance have also been observed (7). The often mentioned three-layer sputum consisting of a foamy upper layer, mucous middle layer, and viscous purulent bottom layer is pathognomonic, but does not always occur. Some patients are symptom free in everyday life and become clinically conspicuous only during exacerbations.

Many patients have regular exacerbations, the average is 1.5 per year. Exacerbation is defined as the

### Table 1

<table>
<thead>
<tr>
<th>Category</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postinfectious</td>
<td>– Viral</td>
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<tr>
<td></td>
<td>– Bacterial</td>
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<td></td>
<td>– Fungal</td>
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<td></td>
<td>– Atypical mycobacteria</td>
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<tr>
<td>ABPA</td>
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<td>COPD</td>
<td>– Posttuberculous fibrosis</td>
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<td></td>
<td>– Radiation fibrosis</td>
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<td></td>
<td>– Pulmonary fibrosis</td>
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<tr>
<td>Idiopathic traction</td>
<td>– Foreign body aspiration</td>
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<tr>
<td>Aspiration</td>
<td>– Benign tumors</td>
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<tr>
<td>Obstruction</td>
<td>– Enlarged lymph nodes</td>
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<tr>
<td>Amyloidosis</td>
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<td>Celiac disease</td>
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<td>Yellow nail syndrome</td>
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<td>Young’s syndrome</td>
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<tr>
<td>Immunological defects</td>
<td>– CVID</td>
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<td></td>
<td>– Agammaglobulinemia</td>
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<td></td>
<td>– Hyper-IgE syndrome</td>
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<td></td>
<td>Secondary</td>
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<tr>
<td></td>
<td>– Chemotherapy</td>
</tr>
<tr>
<td></td>
<td>– Immunosuppressant therapy</td>
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<td></td>
<td>– Tumor</td>
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<tr>
<td>Congenital defects</td>
<td>Anatomical</td>
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<td></td>
<td>– Scoliosis</td>
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<td></td>
<td>– Marfan syndrome</td>
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<tr>
<td></td>
<td>– Tracheobronchomegaly</td>
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<tr>
<td></td>
<td>Others</td>
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<tr>
<td></td>
<td>– Primary ciliary dyskinesia</td>
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<tr>
<td></td>
<td>– Kartagener syndrome</td>
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<tr>
<td></td>
<td>– Alpha-1-antitrypsin deficiency</td>
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<tr>
<td></td>
<td>– defect ENaC protein</td>
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<tr>
<td>Diffuse panbronchiolitis</td>
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<tr>
<td>Rheumatoid arthritis</td>
<td></td>
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<tr>
<td>Systemic lupus erythematoses</td>
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<tr>
<td>Chronic bowel disease</td>
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presence of four or more of the symptoms listed in Box 1 (8). The loss of lung function in non-smokers with bronchiectasis has been reported to be about 50 mL/year. Factors that would imply disease progression are frequent exacerbations, chronic colonization with *Pseudomonas aeruginosa*, and confirmed systemic inflammation. In case of severe bronchiectasis, pulmonary hypertension and systolic and diastolic left ventricular dysfunction may develop.

**Diagnostic evaluation**

**Investigating the colonization**

Microbiological sputum analysis is a standard diagnostic procedure. Risk factors for colonization include varicose or cystic bronchiectasis, a forced expiratory volume in one second (FEV1) <80%, and age <14 years at first diagnosis (7). The most common pathogens are *Haemophilus influenzae*, *Pseudomonas spp.*, and *Streptococcus pneumoniae*. In progressive disease with recurring exacerbations and negative sputum results, bronchoscopy is indicated for the purpose of specimen sampling.

**Imaging**

The imaging method of choice is high-resolution computed tomography (Figure 2). Often the type and localization of the radiological changes can provide indications of the pathogenesis. Bronchiectasis in the proximal airways is typical of allergic bronchopulmonary aspergillosis; multiple nodular bronchiectasis may indicate infection with *Mycobacterium avium* complex.

**Therapy**

The treatment for bronchiectasis is mostly based on experiences gained from the treatment of COPD and CF (Figure 3). Whether these concepts actually translate has not been studied. Only few controlled studies exist, so that for non-CF bronchiectasis, hardly any evidence-based recommendations can be made. The aims of treatment for bronchiectasis are:

- Treating the underlying disease
- Improving mucociliary clearance or drainage of secretions
- Treating the infection
- Treating airway obstruction
- Treating the chronic inflammation that leads to disease progression.

**Treating the underlying disease**

If possible, the underlying disease should be treated first. This primarily applies to immunodeficiency syndromes. In hypogammaglobulinemia, substitution treatment with immunoglobulins can be given (0.4 g/kg body weight every 4–6 weeks).

**Draining secretions**

Breathing therapy and physiotherapeutic measures are the basic treatments for bronchiectasis, to improve drainage of secretions and deal with dyspnea. The mainstay of treatment is sufficient administration of fluids for secretolytic purposes. This can be supported by inhalation of hypertonic saline solution. Especially inhaling hyperosmolar solutions has been found to be beneficial. The raised salt concentration results in an osmotic penetration of fluid into the secretions, thus improving their rheological properties, which in turn results in faster and more effective clearance. Studies using 7% saline for inhalation by CF patients have shown improved lung function and secretion clearance (9). In non-CF bronchiectasis, reduced sputum viscosity was found in a small number of patients (n=24) during a non-exacerbation period (10).

In contrast to other hyperosmolar solutions, mannitol has the advantage of a longer half life within the airways. In an open label, non-controlled study over 12 days, quality of life, lung function, and sputum viscosity were notably improved (11). A disadvantage of mannitol is the fact that hyperresponsiveness increases during inhalation. Currently, further studies are being conducted.
conducted in order to gain licensing approval for the substance.

**Vaccinations**

No randomized studies of vaccinations exist for this group of patients. The effect of annual flu vaccination has been proved for other chronic airway disorders, such as COPD, and translates to patients with bronchiectasis. Data from smaller cohort have shown that the pneumococcal vaccine is beneficial, although a final conclusion cannot currently be drawn. In principle, the recommendation is to follow the vaccination guidelines issued by Germany’s Standing Vaccination Committee (STIKO) for patients with chronic pulmonary disorders.

**Antibiotics**

In an acute exacerbation of bronchiectasis, antibiotics should be given if an increase in dyspnea and sputum volume is observed and the sputum has assumed a yellow-green or green tinge.

If the patient is known to have chronic colonization with respiratory pathogens, targeted treatment should be started while taking into consideration the latest antibiogram. If no microbiological result is available then a broad spectrum antibiotic should be selected for initial treatment. This should include treatment for *Pseudomonas* strains, since these range among the pathogens particularly in severely ill patients and determine the prognosis.

In the outpatient setting, the fluoroquinolones levofloxacin or ciprofloxacin are the only available options. It needs to be borne in mind, however, that ciprofloxacin is not sufficiently effective against *Pneumococci*, the most common pathogens in community acquired pneumonia. Pletz et al. reported the case of a patient with bronchiectasis in whom consecutive courses of treatment failed in the presence of ciprofloxacin resistant *Pneumococci* (e1).

In hospital inpatients, the range of substances that are effective against *Pseudomonas* spp is wider (carbapenem, cephalosporins with activity against *Pseudomonas*, ureidopenicillins). Whether combination therapy using a beta-lactam with an aminoglycoside or fluoroquinolone is superior to monotherapy with a substance that is active against *Pseudomonas* is the subject of controversial debate. *Pseudomonas* infections should be treated for 10–14 days. In patients not at risk from *Pseudomonas aeruginosa*, treatment with aminopenicillin/inhibitor or third-generation cephalosporins is recommended. The duration of treatment is usually seven days. Attempts to diagnose the pathogen should be made before antibiotics are given, and the antibiotic treatment should be tailored accordingly.

The importance of antibiotics treatment outside exacerbations is the subject of controversy. Thus far, attempts to reduce the amount of pathogens by means of long-term oral antibiotic treatment, and to lower the rate of exacerbations, have remained unsuccessful. The development of resistance patterns in patients receiving long-term therapy may be important in this context.

Inhaled antibiotics are standard treatment for patients with CF who have been colonized with *Pseudomonas aeruginosa* (12). Since 25% of patients with non-CF bronchiectasis are colonized with *Pseudomonas aeruginosa*, this therapeutic principle may offer an advantage in this setting. In the meantime, smaller studies have shown the importance of inhaled antibiotics in non-CF bronchiectasis. Significant clinical improvement has been shown, with a reduced density of pathogens and eradication of *Pseudomonas aeruginosa* in up to 35% of cases (13). Patients receiving treatment with inhaled tobramycin had fewer symptoms and an improved quality of life (14). Inhaled colistin led to improvements in lung function and quality of life (15); furthermore, a reduction in inpatient admissions and exacerbations has been reported (16). Inhaled aztreonam lowered the rate of

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**Box 1**

**Symptoms of exacerbation**

- Increase of sputum with cough
- Increased dyspnea
- Raised temperature >38°C
- Increased wheezing
- Lowered physical resilience
- Fatigue
- Deterioration in lung function
- Radiological signs of infection

A minimum of 4 symptoms are the defining criteria for an exacerbation

(modified from [8])
exacerbations, reduced symptoms, and improved lung function in patients with CF (17). A study of inhaled aztreonam in non-CF bronchiectasis is in the planning stages.

A liposomal preparation of inhaled ciprofloxacin confirmed the reduced pathogenic load of Pseudomonas aeruginosa (e3); the same was confirmed for powder inhalation of ciprofloxacin (e4). Further studies of inhaled amikacin and intratracheal instillation of fosfomycintobramycin are expected.

In a randomized controlled study, inhaled gentamycin led to eradication of Pseudomonas aeruginosa in 30.8% of cases and prolonged the interval to the next exacerbation (120 days versus 61.5 days) (18). Another study of inhaled gentamycin found a lowered rate of exacerbations and improved quality of life (19). Table 2 provides an overview of inhaled antibiotics.

### Anti-obstructive therapy

If a patient’s airways are obstructed, anti-obstructive treatment similar to COPD should be considered. Parasympatholytics and β-sympathomimetics constitute the treatment of choice. Long-acting substances (tiotropium bromide or salmeterol/formoterol) seem superior to short-acting substances. Proof of superiority is lacking for inhalation therapy with compression or ultrasound nebulizers (both of which are popular in Germany) compared with conventional treatment with metered-dose aerosol inhalers or powder inhalers.

#### Inhibiting inflammation

Oral corticosteroids are often administered in acute exacerbations of bronchiectasis, in analogy to acute exacerbations of COPD. For inhaled steroids, long-term usage seems to confer benefits. Tsang et al. showed in a study of 73 patients with non-CF bronchiectasis a reduction in the exacerbation rate and sputum production when using inhaled steroids (20). Randomized studies are, however, lacking.

Macrolide antibiotics such as azithromycin have a potent anti-inflammatory effect in addition to their antibacterial effects. They reduce the production of proinflammatory cytokines. The cytokines act as chemoattractants for neutrophils and effect an expression of adhesion molecules, which neutrophils require for their migration from the bloodstream to the interstitium. Furthermore, in addition to their regular bacteriostatic effects, macrolides inhibit the production of biofilms by Pseudomonas aeruginosa (independently of their antibiotic effectiveness) (21).

In the therapy of neutrophil-dominated, chronic inflammatory pulmonary disorders, such as diffuse panbronchiolitis (DPB) or CF, macrolides are already in use, successfully and without notable side effects.

The treatment with macrolide antibiotics has led to a reduction in the amount of sputum and improved 5-year survival in patients with non-CF bronchiectasis too (22). At this point in time, however, neither inhaled antibiotics nor macrolides are licensed for the treatment of patients with non-CF bronchiectasis.

#### Allergic bronchopulmonary aspergillosis

Allergic bronchopulmonary aspergillosis (ABPA) is a rare but typical complication in bronchiectasis. The

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**TABLE 2**

<table>
<thead>
<tr>
<th>Substance</th>
<th>Results</th>
<th>Source</th>
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</thead>
<tbody>
<tr>
<td>Tobramycin</td>
<td>Eradication in 13–35%, reduction of pathogenic load, improved lung function</td>
<td>(13)</td>
</tr>
<tr>
<td>Colistin</td>
<td>Rise in FEV1, eradication in 3 of 18 cases, fewer exacerbations, reduction of pathogenic load</td>
<td>(15)</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>CF: improved lung function, longer interval to exacerbation</td>
<td>(17)</td>
</tr>
<tr>
<td>Liposomal ciprofloxacin</td>
<td>Reduction of pathogenic load</td>
<td>(e3)</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Reduction of pathogenic load</td>
<td>(e4)</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>Fewer exacerbations, improved quality of life</td>
<td>(19)</td>
</tr>
</tbody>
</table>

**CF, cystic fibrosis; P. a., Pseudomonas aeruginosa; FEV, forced expiratory volume in one second**

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**FIGURE 3**

**Therapeutic scheme for bronchiectasis (modified from [e2])**
underlying pathophysiology is a sensitization to Aspergillus fumigatus, which leads to a CD4+/TH2 mediated inflammatory reaction. Typical symptoms include a raised body temperature, weight loss, a drop in FEV1, and pulmonary infiltrates on the radiograph. Bronchiectasis can be a sequela of ABPA, but it can also predispose to ABPA. The clinical diagnosis is difficult and is based on criteria set out by Greenberger (overview in Agarwal [23]) (Box 2).

Acute exacerbation of ABPA usually requires treatment with systemic steroids for a long period of time (23). In order to prevent recurrence, long-term oral therapy with itraconazole is indicated in patients with pulmonary colonization; several studies have shown the effectiveness of this treatment in CF. Inhaled amphotericin B is the subject of studies. Individual reports have documented successful treatment with a monoclonal antibody against IgE (omaluzimab).

**Surgical therapy**
Surgery is the method of choice in unilateral and localized bronchiectasis. Several studies have shown that resection of the bronchiectasis improved symptoms (24). In the different studies, mortality varied from 1% to 8.6% (e5, e6), the rate of surgical complications was 8.8–25% (e7). Complications included pneumonias, postoperative hemorrhage, atelectasis, bronchopulmonary fistula, and wound infection. In particular cases, the resection of bilateral bronchiectasis may be the aim, but the lesions should be limited and completely resectable (24). In severe complications, such as life threatening hemorrhage or fungal infection, surgical therapy can be used as the method of last resort.

Hemoptysis, which is mostly caused by bleeds from hypertrophied vessels of the inflamed mucosa, can be controlled by bronchial artery embolization (coiling) if required. This should only be done in specialized centers.

**Lung transplantation in advanced disease**
Lung transplantation can be a useful intervention in very advanced non-CF bronchiectasis. It is of vital importance to identify the right time for putting the patient on the transplant list. In accordance to the guidelines, the following criteria should be met:

* FEV1 < 30% and an exacerbation with inpatient admission to intensive care, or
* More than three exacerbations per year, or
* Recurrent pneumothorax, or
* Hemoptysis requiring—and receiving—intervention (25).

A double lung transplant is the method of choice in more than 90% of cases. In case only one lung is transplanted, there is a risk that pathogens are transferred from the native lung into the transplanted lung. Experiences from large centers have shown that he long-term prognosis does not differ much from that of other indications, with 5-year survival rates between 55% and 60% (e8).

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**Conflict of interest statement**
Dr. Rademacher has received honoraria for speaking from Forest and MSD. Professor Welte has received honoraria for acting as an adviser from Novartis, Bayer Pharma, and Gilead.

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**REFERENCES**


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For eReferences please refer to:
www.aerzteblatt-international.de/ref4811
Bronchiectasis—Diagnosis and Treatment

Jessica Rademacher, Tobias Welte

References


BOX 2

**Diagnostic criteria for allergic bronchopulmonary aspergillosis**

1. Asthma
2. Skin reactions*1
3. Raised total IgE in serum (> 1 000 ng/L)*1
4. Raised specific IgE and/or IgE to Aspergillus fumigatus in serum*1
5. Bronchiectasis*1 *2
6. Radiologically confirmed infiltrate
7. Eosinophilia in blood (> 500/µL)
8. Precipitating antibodies to Aspergillus fumigatus

(modified from Agarwal [23])

*1 Obligatory criterion for defining the diagnosis.
*2 If criteria 1–4 are met but no bronchiectasis is found, the finding is taken to be seropositive allergic bronchopulmonary aspergillosis.

KEY MESSAGES

- Thanks to improved antibiotic treatments and vaccination programs, more congenital than postinfectious causes of bronchiectasis have been observed.
- Different mechanisms lead to bronchiectasis, but the pathophysiological end stage of inflammation and destruction is the same.
- For diagnostic purposes, a sputum specimen should be sampled. If imaging is used then high-resolution computed tomography is the method of choice.
- The treatment of the underlying disease should always be considered. The basics of treatment include breathing measures and physiotherapeutic measures. Treatment of exacerbations should be based on the diagnostic test results for the pathogen and the antibiogram. Additional administration of inhaled antibiotics or macrolides should be considered in the individual case scenario.
- Surgical measures are available for circumscribed bronchiectasis.