Non-cystic fibrosis bronchiectasis

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Originally described by Laennac in 1819,[1] bronchiectasis is a chronic, debilitating condition characterised by persistent cough, excessive sputum production and recurrent chest infections. The precise prevalence is unknown, but figures quoted vary from about 4×10^5 aged 18–34 years to 272×10^5 aged 75 years and over.[2,3]

Pathologically, there is abnormal permanent dilatation of the airways. This leads to impaired mucociliary clearance, which in turn leads to a vicious cycle of bacterial colonisation in normally sterile airways and excessive bronchial inflammation. This review explores current clinical practice for this complex condition.

Key Points

- **Bronchiectasis should be considered in patients with a chronic, productive cough and a history of recurrent chest infections**
- **The gold standard for diagnosis is computed tomography of the chest**
- **The aetiology is unknown in up to 50% of cases and post-infective in up to 42%**
- **The mainstays of treatment are regular chest physiotherapy, annual influenza vaccination and prompt administration of antibiotics for exacerbations**
- **Long-term antibiotics should be considered for patients with recurrent chest infections impacting on their health-related quality of life**

KEY WORDS: bronchiectasis, exacerbations, investigations, management

Diagnosis

There is usually a history of a chronic productive cough and recurrent chest infections. There may be symptoms related to airways obstruction (wheeze and breathlessness), mucus plugging (chest pain) and also systemic symptoms.[4] The diagnosis of bronchiectasis is confirmed radiologically with computed tomography of the chest. The defining characteristic is bronchial dilatation with the internal diameter of the bronchial lumen greater than that of the adjacent artery, categorised as tubular, varicose or cystic (Figs 1(a), 1(b) and 1(c)).[5]

Aetiology

No underlying cause is identified in up to 50% of cases and is post-infective in up to 42%.[6,7] The common causes, appropriate investigations and expected abnormal findings are listed in Table 1.[6,7]

Assessment of severity

Clinical, radiological and microbiological features guide clinicians to the severity of bronchiectasis. These investigations not only provide clinicians with a quantitative assessment of disease severity but may also help in the management of both stable disease and exacerbations.

- *Sputum colour and volume.* Colour is graded as mucoid, mucopurulent or purulent (Fig 2) and volume is measured over a 24-hour collection period. Patients with severe bronchiectasis usually have purulent sputum and volumes that may exceed 25 ml/day, even when stable.
- *Exacerbation frequency.* In severe disease there are often multiple exacerbations (usually ≥3 a year) and inpatient management may be necessary.

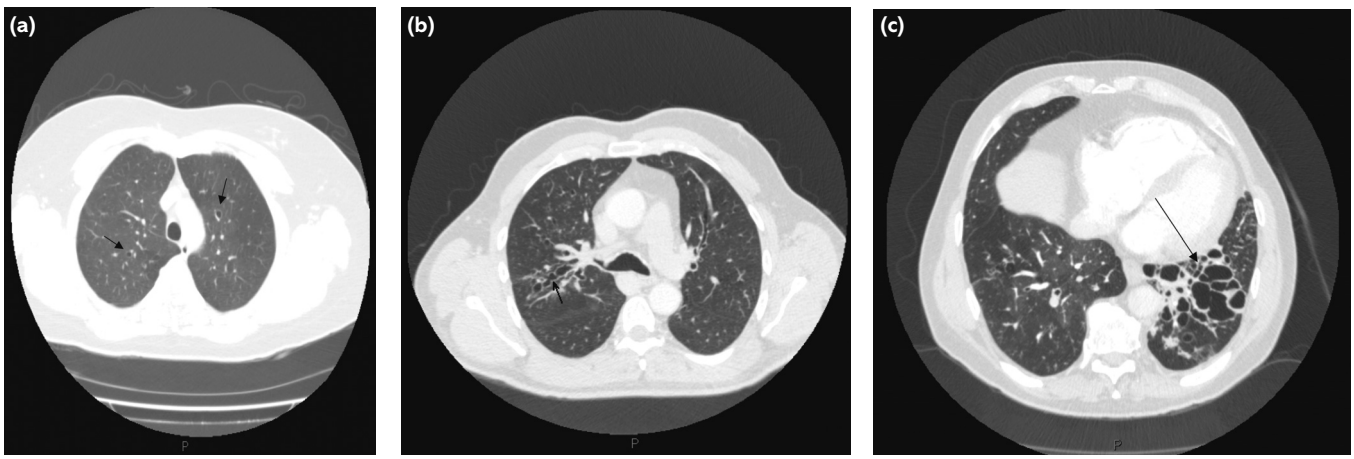


Fig 1. (a) Tubular dilation of airways (see arrow); (b) varicose dilatation of airways (arrow shows irregular, dilated airway); (c) cystic dilatation of airways with thickened bronchi and mucus plugging (see arrow).

- *Lung function*. There can be advanced airflow obstruction in severe bronchiectasis, but there may also be restrictive or normal patterns.
- *Radiological findings*. In severe disease bronchial dilatation is usually varicose or cystic with multiple lobes affected. There may be associated bronchial wall thickening, mucus plugging and subsegmental, segmental or lobar collapse.
- *Sputum microbiology*. Most patients with severe bronchiectasis are chronically colonised with pathogenic organisms in their sputum when stable.[8] Typical organisms include *Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus,*

Table 1. Investigating the aetiology of non-cystic fibrosis (CF) bronchiectasis.

Aetiology	Incidence (%)	Investigations	Expected abnormal findings
Post-infectious (eg pneumonia, pertussis, *Mycobacterium tuberculosis*)	29–42	• History of previous infection • Radiological evidence of previous infection	Radiological evidence of previous infection (eg old, healed TB etc)
CTD (commonly RA, also systemic sclerosis, SLE, relapsing polyarthritis, ankylosing spondylitis)	3–6	• History of CTD ± vasculitis • Autoimmune screen, including RF, ANAs, ANCAs	Positive autoantibody screen may occur with or without clinical evidence of CTD
ABPA	1–7	• Full blood count • Total IgE • Specific IgE and IgG to *Aspergillus fumigatus* • *A. fumigatus* skin-prick test • Spirometry (FEV_1, FVC) • HRCT	Criteria to diagnose ABPA in patients with bronchiectasis include: • history of asthma • peripheral blood eosinophlia • ↑total IgE • central bronchiectasis on HRCT • +ve skin test reactivity to *A. fumigatus* • ↑specific serum IgE and IgG to *A. fumigatus*
Immunodeficiency (typically CVI, X-linked agammaglobulinaemia, IgA deficiency)	1–8	• IgG, IgA, IgM • IgG subclasses • Baseline specific antibody levels against tetanus toxoid and polysaccharide capsules of *Streptococcus pneumoniae* and *Haemophilus influenzae type B*	• Deficiencies as per condition • Low levels of IgG subclass 2 associated with recurrent infections with Gram +ve encapsulated organisms • Low baseline antibody response; should be immunised with the appropriate vaccine and antibody response rechecked at 21 days
CF	3–4	• Cytogenetics for CFTR receptor mutations • Sweat test	• Positive CFTR mutations • Positive sweat test • Should be reserved for patients ≤40 years, clinical features of malabsorption, history of male infertility, upper lobe bronchiectasis on HRCT, recurrent *Staphylococcus aureus* in sputum or other organisms typically identified in CF
Ciliary defect (eg primary ciliary dyskinesia)	2–4	• History of chronic upper respiratory tract problems, otitis media, male infertility • Referral for specialist investigations: direct examination of cilia, saccharin test etc	• Abnormal ciliary beat pattern ± frequency • Saccharin taste test (saccharin not tasted after 60 min)
IBD	1	• History • GI opinion and specialist investigations	NA
Aspiration/inhalation of foreign body	4	• Bronchoscopy if history of aspiration or localised (single lobe) bronchiectasis	• Foreign body in airway(s)
Idiopathic	30–35	• Above causes excluded	• Diagnosis of exclusion

ABPA = allergic bronchopulmonary aspergillosis; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; CF = cystic fibrosis; CFTR = CF transmembrane regulator; CTD = connective tissue disease; CVI = common variable immunodeficiency; GI = gastrointestinal; HRCT = high-resolution computed tomography; IBD = inflammatory bowel disease; Ig =immunoglobulin; NA = not applicable; RA = rheumatoid arthritis; RF = rheumatoid factor; SLE = systemic lupus erythematosus; TB = tuberculosis.

Moraxella catarrhalis and, in patients with advanced bronchiectasis, *Pseudomonas aeruginosa*. Patients colonised with *P. aeruginosa* have a poor health-related quality of life (HRQL), more severe airways obstruction and perhaps an accelerated decline in FEV_1.[9,10]

Management of stable disease

Management aims to reduce symptoms, limit exacerbations, preserve lung function and improve HRQL.

Patient education

Patients should be advised on smoking cessation, chest clearance techniques and long-term treatments. They should receive annual influenza vaccinations, the pneumococcal vaccination and prompt antibiotic treatment for infections.

Physiotherapy

The normal mucociliary clearance mechanism is impaired in bronchiectasis. Although randomised controlled trials (RCTs) assessing the efficacy of sputum clearance are lacking, physiotherapy is advised to promote clearance. Traditional postural drainage exercises can be difficult; newer techniques such as the active cycle breathing technique and assisted devices (eg the flutter) have been developed for patient ease. These have similar outcomes to postural drainage but are associated with greater patient preference.[11,12] All patients should be reviewed by a specialist chest physiotherapist.

Adjuncts to physiotherapy. Several adjuncts have been proposed, including bronchodilator therapy, inhaled hyperosmolar agents (nebulised hypertonic saline, inhaled mannitol) and inhaled mucolytics (recombinant human DNase). Bronchodilator therapy (see below) may be used prior to chest physiotherapy to minimise bronchial hyperreactivity and improve airway clearance. Nebulised hypertonic 7% saline has been shown to yield greater sputum weights with greater ease and less viscosity, and small studies have shown that inhaled mannitol improves mucociliary clearance.[13,14] Further studies are needed, but currently the latter two agents are not used in routine clinical practice.

Recombinant human DNase aims to reduce sputum viscosity, but a Cochrane review[15] did not find enough evidence to support its regular use in bronchiectasis, and a multicentre study found it had a significant negative impact on FEV_1.[16]

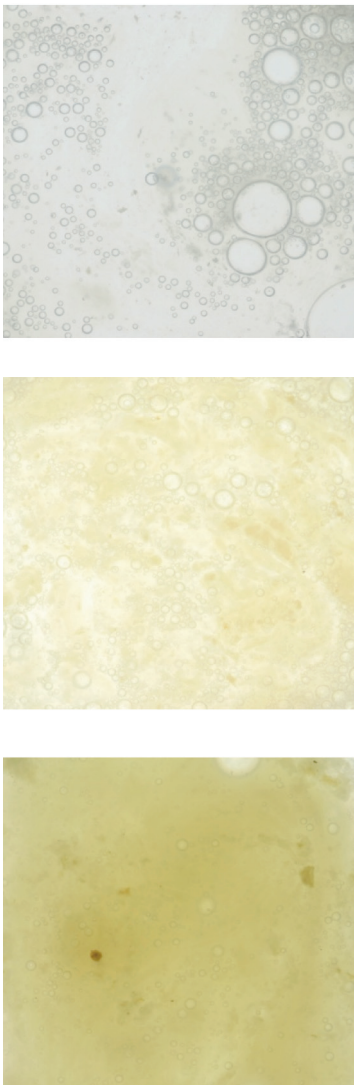
Bronchodilators

The role of bronchodilator therapy is yet to be established, but may be used as an adjunct to physiotherapy and to relieve breathlessness. If there is evidence of airways obstruction, reversibility testing should be performed to determine whether the patient could benefit from inhaled β_2-agonists and/or anticholinergics. Both, however, may provide symptomatic relief of breathlessness, with or without an objective improvement in FEV_1. A trial of the short-acting agents is recommended in the first instance in patients with impaired lung function and consideration of long-acting agents if clinical improvement.[17,18]

Inhaled corticosteroids

To date, RCTs of inhaled corticosteroids have shown a reduction in 24-hour sputum volume and improvement in HRQL, but no impact on FEV_1 or exacerbation frequency.[19–21] These studies used high-dose inhaled corticosteroids (fluticasone 500 μg bd or beclometasone

Fig 2. Sputum chart. Sputum is graded as mucoid, mucopurulent or purulent.



750 μg bd) but the optimal dose needs further clarification. A six-month trial of inhaled corticosteroids may be warranted, particularly for patients with evidence of airway obstruction and reversibility or with severe bronchiectasis.

Long-term antibiotics

The rationale for prescribing long-term antibiotics (oral or nebulised) is to reduce the bacterial burden in the airways, limiting inflammation and promoting healing of the bronchial tree.

Oral antibiotics. RCTs of long-term oral antibiotics for bronchiectasis are limited. In a 12-month Medical Research Council randomised placebo-controlled trial of tetracycline there was reduction in sputum volume, purulence and the number of days absent from work due to ill health.[22] An eight-month randomised placebo-controlled trial of high-dose daily oral amoxicillin (3 g BD) found clinical improvement, reduction in 24-hour sputum volume, purulence and days absent from work, with the treatment well tolerated.[23] Open label studies (≥6 months) assessing the role of macrolides have shown a reduction in exacerbation frequency.[24,25] Oral treatment is inexpensive but systemic side effects are common.

Nebulised antibiotics. These offer a targeted therapy with limited systemic side effects. However, they are expensive and may be less well tolerated due to bronchospasm, even with adjunctive treatment with a β_2-agonist. To date, the RCTs of long-term nebulised antibiotics have included only patients chronically colonised with *P. aeruginosa*. Two studies compared twice daily nebulised tobramycin with placebo, one cyclically (4 weeks treatment, 2 weeks off) and the other daily for six months.[26,27] In both studies there was a reduction in bacterial density in the sputum but a small increased incidence of bronchospasm in the treatment arms. Another study compared nebulised ceftazidime and tobramycin with placebo for 12 months. Although there was no reduction in overall exacerbation frequency in the active group, the number and duration of hospital admissions for exacerbations were reduced.[28]

Further studies are needed to define who would benefit from long-term antibiotics and to determine the optimum treatment. Currently, long-

Table 2. Recommended antibiotic therapy for exacerbations of bronchiectasis based on previous sputum microbiology.

Organism	First-line treatment*	Second-line treatment*
Streptococcus pneumoniae or *Haemophilus influenzae* (β-lactamase-negative)	Amoxicillin 500 mg TDS or Amoxicillin 1 g TDS or 3 g BD in severe disease	Clarithromycin 500 mg BD
Haemophilus influenzae (β-lactamase-positive) or *Moraxella catarrhalis*	Co-amoxiclav 625 mg TDS	Doxycycline 100 mg BD or Clarithromycin 500 mg BD or Ciprofloxacin 500 mg BD or Ceftriaxone 1–2 g OD (iv)
Staphylococcus aureus	Flucloxacillin 500 mg QDS	Clarithromycin 500 mg BD
MRSA oral therapy	<50 kg: Rifampicin 450 mg OD + trimethoprim 200 mg BD ≥50 kg: Rifampicin 600 mg OD + trimethoprim 200 mg BD	<50 kg: Rifampicin 450 mg OD+ doxycycline 200 mg OD ≥50 kg: Rifampicin 600 mg OD + doxycycline 200 mg OD
MRSA	Vancomycin (iv**) or Teicoplanin (iv**)	Linezolid** (oral or iv)
Coliforms (eg *Klebsiella, Enterobacter*)	Ciprofloxacin 500 mg BD	Ceftriaxone 1–2 g OD (iv)
Pseudomonas aeruginosa	Ciprofloxacin 500 mg BD (or, in severe infections Ciprofloxacin 750 mg BD)	Monotherapy: ceftazidime 2 g (iv) TDS or tazocin 4.5 g (iv) TDS or aztreonam 2 g (iv) TDS or meropenem 1 g (iv) TDS Dual therapy**: Each of the above may be combined with either: gentamicin (iv) or tobramycin (iv) or colomycin (iv)
If no previous sputum samples or if previous sputum microbiology shows mixed normal flora or no pathogens	Amoxicillin 500 mg TDS	Clarithromycin 500 mg BD

* All treatments are given for 10–14 days.
** See *British National Formulary* for doses.
iv = intravenous; MRSA = methicillin-resistant *Staphylococcus aureus*.

term antibiotics may be indicated in those who have frequent exacerbations (usually ≥3/year) that impact on their HRQL.

Surgery

Indications for surgery include major haemoptysis or localised disease causing significant morbidity not responsive to medical management. Reported outcomes from surgery are good but studies were not randomised and in practice referral for surgical intervention is rare.[29]

Management of exacerbations

Prompt antibiotic treatment is recommended for patients presenting with increasing cough, sputum volume and purulence. There are many unanswered questions, including mode, choice and duration of antibiotic, monotherapy or dual agents and how best to assess response to treatment.

Antimicrobial agents

Sputum should be sent for microbiological culture at the start of all exacerbations and empirical treatment commenced immediately based on previous sputum microbiology, if available (see Table 2). Treatment should only be adjusted if there is no clinical response and should then be guided by the sputum culture and sensitivity results.

Oral versus intravenous treatment

Oral antibiotic therapy should be used as first-line management unless:

- the culture of pathogenic organisms sensitive only to intravenous agents
- patients have clinical sepsis necessitating acute inpatient admission
- there has been a failure of response to oral antimicrobials.

Monotherapy or dual antibiotic therapy?

Monotherapy is recommended for exacerbations due to *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, or methicillin-sensitive *S. aureus* (MSSA). To prevent further resistance emerging, two antibiotics are recommended for patients colonised with methicillin-resistant *S. aureus* (MRSA) and in patients with *P. aeruginosa* with multiple frequent exacerbations.

Duration

The optimum duration of treatment is unknown. In one study, inflammatory response returned to normal within a week of antimicrobial therapy, but symptomatic improvement has generally been seen in studies employing 10–14 days of treatment.[30] At present, antibiotics are recommended for 10–14 days.

Other adjuncts to treatment

Regular chest physiotherapy is recommended. Patients with increased wheeze and dyspnoea may require optimisation of their bronchodilator therapy, including steroids.

Assessing response

It is helpful for clinicians to have endpoints to assess response to treatment. Bacterial clearance, 24-hour sputum volume, C-reactive protein and the St George's Respiratory Questionnaire (an HRQL questionnaire) are useful markers of treatment response, although the latter questionnaire is predominantly a research tool.[31,32]

Conclusions

There has been a resurgence of interest in the previously neglected condition of bronchiectasis. Ongoing and future RCTs will provide stronger evidence-based treatment for this chronic disabling disease.

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