Current and future best practice for the management of non-cystic fibrosis bronchiectasis

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Agenda

- Disease prevalence and risk factors for acute exacerbations
- Management of chronic infection
- Available and emerging pharmacotherapeutic strategies

Disease prevalence and risk factors for acute exacerbations

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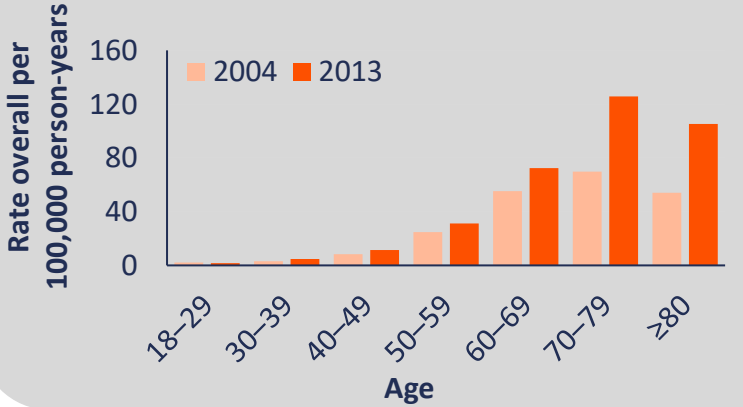
Incidence and prevalence of non-CF bronchiectasis

- **Prevalence** and **incidence** increase with age and are increasing over time, although recent data are lacking[1–4]

- **Incidence:** 29 cases/100,000 adults aged ≥18 years in 2013[2]
- **Prevalence:** 139 cases/100,000 adults aged ≥18 years in 2013[2]
  - 8.7% per year increase in US Medicare outpatient claims database from 2000–2007[3*]

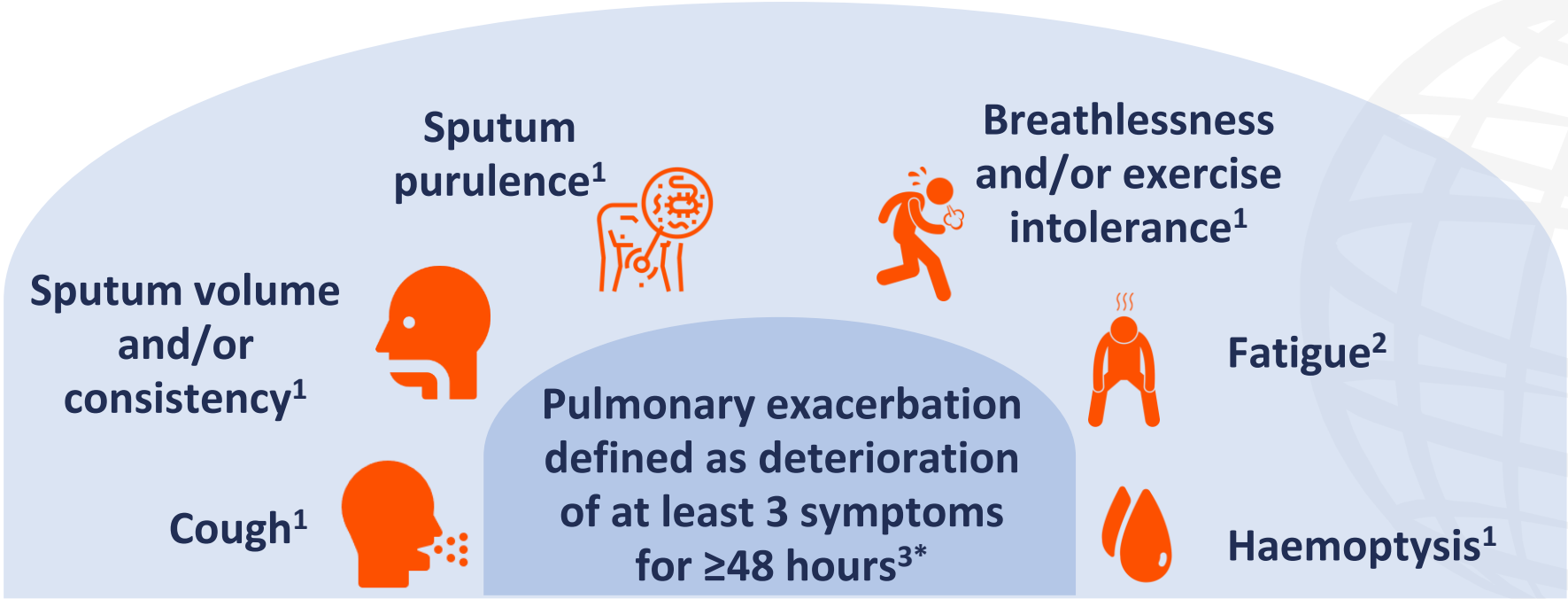
UK incidence of non-CF bronchiectasis[4]



*Analysis of Medicare outpatient claims database of patients with non-CF bronchiectasis.
CF, cystic fibrosis.

1. Eralp EE, et al. *BMC Pulm Med*. 2020;20:172; 2. Weycker D, et al. *Chron Respir Dis*. 2017;14:377–84; 3. Seitz AE, et al. *Chest*. 2012;142:432–9;
4. Quint JK, et al. *Eur Respir J*. 2016;47:186–93.

Acute exacerbations in non-CF bronchiectasis



*Definition from European Multicentre Bronchiectasis Research Collaboration (EMBARC) and US Bronchiectasis Research Registry (BRR) definitions working group.
CF, cystic fibrosis.

1. Macfarlane L, et al. *Clin Med (Lond)*. 2021;21:e571–7; 2. Delestre-Levai I, et al. *ERJ Open Res.* 2021;7:00096–2021; 3. Hill AT, et al. *Eur Respir J*. 2017;49:1700051.

Management of chronic infection

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Chronic infection in patients with non-CF bronchiectasis

- Most studies report up to 60% of patients with non-CF bronchiectasis have a chronic infection[1]
- No current standardized definition for chronic infection[1]
- **General definition: Two or more consecutive positive cultures or >50% of cultures positive for the same pathogen within 6–12 months, in samples taken at least 1 month apart[1–3]**

CF, cystic fibrosis.

1. Di Pasquale M, et al. *Expert Opin Pharmacother.* 2020:21:1975–90; 2. Martínez-García MÁ, et al. *Arch Bronconeumol (Engl Ed).* 2018;54:88–98;
3. Pressler T, et al. *J Cyst Fibros.* 2011;10(Suppl. 2):S75–8.

Treatments for chronic infection in patients with non-CF bronchiectasis

- **Mechanical airway clearance**[1]
- **Mucolytic agents** (nebulized saline solution)[2]
- **Oral/IV antibiotics** (macrolides)[2]

- **Long-term inhaled antibiotics** (gentamicin, tobramycin, colistin, ciprofloxacin, aztreonam)[2,3]
- **Mucolytic agents** (bromhexine)[4]

- **Long-term bronchodilators and corticosteroids**[2]
- **Mucolytic agents** (rhDNase, acetylcysteine)[2]

CF, cystic fibrosis; IV, intravenous; rhDNase, recombinant human deoxyribonuclease.

1. Severiche-Bueno D, et al. *Breathe.* 2019;15:286–95; 2. Imam JS, Duarte AG. *Respir Med*. 2020;166:105940;
3. Martínez-García M-G, et al. *Arch Bronconeumol.* 2018;54:88–98; 4. Hill AT, et al. *Thorax.* 2019;74(Suppl. 1):1–69.

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Eradication protocol guidance for the management of non-CF bronchiectasis

- Some clinical guidelines recommend **inhaled antibiotics** for the treatment of early infection with *Pseudomonas aeruginosa*[1–3]
- ERS guidelines suggest not to use eradication protocols for other organisms[3]

CF, cystic fibrosis; ERS, European Respiratory Society.

1. Martínez-García M-G, et al. *Arch Bronconeumol*. 2018;54:88–98; 2. Pasteur MC, et al. *Thorax*. 2010;65 (Suppl. 1):i1–58; 3. Polverino E, et al. *Eur Respir J*. 2017;50:1700629.

Available and emerging pharmacotherapeutic strategies

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Stepwise management of stable non-CF bronchiectasis

British Thoracic Society Guidelines

Step 1

- Treat underlying cause
- Airway clearance techniques ± pulmonary rehabilitation
- Annual influenza vaccination
- Prompt antibiotic treatment for exacerbations
- Self-management plan

≥3 exacerbations/year

Step 2

- Physiotherapy reassessment and consider muco-active treatment

≥3 exacerbations/year

Step 3

- For *P. aeruginosa:* long-term inhaled antipseudomonal antibiotic or long-term macrolide
- For other pathogens: long-term macrolide/ long-term oral or inhaled targeted antibiotic
- If no pathogen: long-term macrolide

≥3 exacerbations/year

Step 4

- Long-term macrolide and long-term inhaled antibiotic

≥5 exacerbations/year

Step 5

- Consider regular IV antibiotics every 2–3 months

The next step in the management pathway should be considered if significant symptoms persist, even if patients do not meet exacerbation criteria

CF, cystic fibrosis; IV, intravenous.

Hill AT, et al. *Thorax.* 2019;74(Suppl. 1):1–69.

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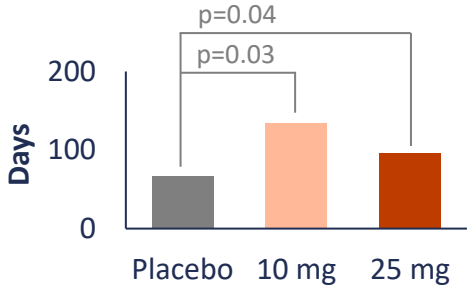
Key clinical trials in non-CF bronchiectasis

Brensocatib (WILLOW)[1]

N=256

Phase II study of adult patients with ≥2 exacerbations in past 12 months

25th percentile of time to first exacerbation



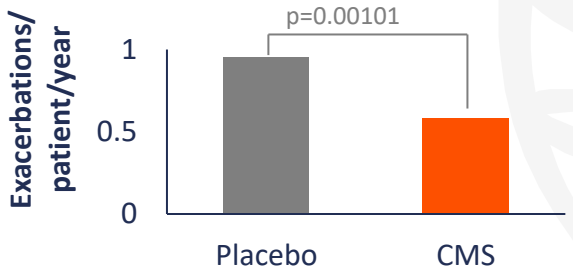
Higher incidence of dental and skin AESIs for 10 mg and 25 mg brensocatib doses, respectively, vs placebo

Colistimethate sodium (PROMIS-I)[2,3]

N=377

Phase III study of adult patients with *P. aeruginosa* in sputum and ≥2 exacerbations or 1 requiring IV antibiotics in past 12 months

Annual exacerbation rate



Similar proportion of patients with AEs between treatment arms

AE, adverse event; AESI, AE of special interest; CF, cystic fibrosis; CMS, colistimethate sodium; IV, intravenous.

1. Chalmers J, et al. *N Engl J Med*. 2020;383:2127–37; 2. Haworth CS, et al. *Eur Respir J*. 2021;58:RCT4267;
3. NCT03093974. Available at: https://clinicaltrials.gov/ct2/show/NCT03093974 (accessed 5 April 2022).

Clinical trials in non-CF bronchiectasis in progress

Brensocatib (oral DPP-1 inhibitor)[1]
- ASPEN phase III trial
  - Estimated completion: March 2024

Benralizumab (subcutaneous anti-IL-5R)[4]
- MAHALE phase III trial
  - Estimated completion: January 2026

Colistimethate sodium (inhaled antibiotic)[2]
- PROMIS II phase III trial
  - Estimated completion: February 2022

Roflumilast (oral anti-inflammatory)[5]
- NCT04322929 phase II trial
  - Estimated completion: February 2022

Melphalan (inhaled alkylating agent)[3]
- SEADIB1 phase II trial
  - Estimated completion: December 2021

CSL787 (inhaled immunoglobulin)[6]
- NCT04643587 phase I trial
  - Estimated completion: May 2022

CF, cystic fibrosis; DPP, dipeptidyl peptidase; IL-5R, interleukin 5 receptor.

1. NCT04594369. Available at: https://clinicaltrials.gov/ct2/show/NCT04594369 (accessed 23 March 2022); 2. NCT03460704. Available at: https://clinicaltrials.gov/ct2/show/record/NCT03460704 (accessed 23 March 2022); 3. NCT04278040. Available at: https://clinicaltrials.gov/ct2/show/NCT04278040 (accessed 23 March 2022); 4. NCT04278040. Available at: https://clinicaltrials.gov/ct2/show/NCT05006573 (accessed 23 March 2022); 5. NCT04322929. Available at: https://clinicaltrials.gov/ct2/show/record/NCT04322929 (accessed 23 March 2022); 6. NCT04643587. Available at: https://clinicaltrials.gov/ct2/show/NCT04643587 (accessed 23 March 2022).

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